BEHAVIORAL AND BRAIN SCIENCES (2000) **23,** 793–1121
Printed in the United States of America

Dreaming and the brain: Toward a cognitive neuroscience of conscious states

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Abstract: Sleep researchers in different disciplines disagree about how fully dreaming can be explained in terms of brain physiology. Debate has focused on whether REM sleep dreaming is qualitatively different from nonREM (NREM) sleep and waking. A review of psychophysiological studies shows clear quantitative differences between REM and NREM mentation and between REM and waking mentation. Recent neuroimaging and neurophysiological studies also differentiate REM, NREM, and waking in features with phenomenological implications. Both evidence and theory suggest that there are isomorphisms between the phenomenology and the physiology of dreams. We present a three-dimensional model with specific examples from normally and abnormally changing conscious states.

Keywords: consciousness, dreaming, neuroimaging, neuromodulation, NREM, phenomenology, qualia, REM, sleep

1. Introduction

Dreaming is a universal human experience that offers a unique view of consciousness and cognition. It has been studied from the vantage points of philosophy (e.g., Flanagan 1997), psychiatry (e.g., Freud 1900), psychology (e.g., Foulkes 1985), artificial intelligence (e.g., Crick 1994), neural network modeling (Antrobus 1991; 1993b; Fookson & Antrobus 1992), psychophysiology (e.g., Dement & Kleitman 1957b), neurobiology (e.g., Jouvet 1962) and even clinical medicine (e.g., Mahowald & Schenck 1999; Mahowald et al. 1998; Schenck et al. 1993). Because of its broad reach, dream research offers the possibility of bridging the gaps in these fields.

We strongly believe that advances in all these domains make this a propitious time to review and further develop these bridges. It is our goal in this target article to do so. We will study dreams (defined in the American Heritage Dictionary [1992] as "a series of images, ideas, emotions, and sensations occurring involuntarily in the mind during certain stages of sleep") and REM sleep, as well as the numerous forms of wake-state and sleep-state mentation. We will also review polysomnographically defined wake and sleep states. Our analyses will be based on comparisons and correlations among these various mental and physiological states.

1.1. An integrative strategy

Three major questions seem to us to be ripe for resolution through constructive debate:

1. Are the similarities and differences in the conscious experiences of waking, NREM, and REM sleep defined with sufficient clarity that they can be measured objectively? If so, do the measures establish clear-cut and major differences between the phenomenological experience of these three physiological states?
2. Are the similarities and differences between the brain

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 0140-525X/00 $12.50

substrates of the states of waking, NREM, and REM sleep defined with sufficient clarity that they can be measured objectively? If so, do the measures establish clear-cut differences between these states at the level of brain regions, as well as at the cellular and molecular levels?

3. To the extent that affirmative answers can be given to the two preceding questions, can a tentative integration of the phenomenological and physiological data be made? Can models account for the current results and suggest experiments to clarify remaining issues?

Hoping to stimulate a useful debate, we will answer all three of the preceding questions affirmatively, documenting our responses with appropriate data drawn from our own work and from that of our colleagues. Referring to this ample literature, one can now identify numerous operationally defined psychological and physiological parameters with which to make such conscious state comparisons. In developing our answers, we will advance the thesis that the conscious states of waking, NREM, and REM sleep differ in three clear and important ways which are measurable at both the psychological and physiological levels. The three parameters will become the axes of a state space model that we introduce only briefly here but discuss in more detail in concluding this article.

1.2. A state space model of the brain-mind

In essence, our view is that the brain-mind is a unified system whose complex components dynamically interact so as to produce a continuously changing state. As such, any accurate characterization of the system must be multidimensional and dynamic and must be integrated across the neurobiological and psychological domains. Both neurobiological and psychological probes of the system must therefore be designed, applied and interpreted so as to recognize and clarify these features.

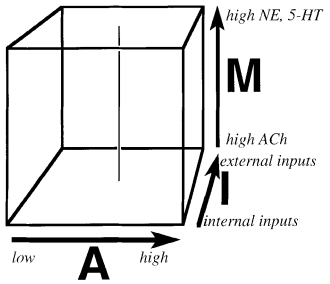
As a first step in that direction, we have created a three-dimensional state space model (AIM) that allows us to represent the system according to variables with referents in both the neurobiological and psychological domains as is shown in Figure 1. They are activation (A), information flow (I), and mode of information processing (M). Each of these terms has meaning both at the cognitive and neurobiological levels.

Roughly speaking, these dimensions are meant to capture respectively: (1) the information processing capacity of the system (activation); (2) the degree to which the information processed comes from the outside world and is or is not reflected in behavior (information flow); and (3) the way in which the information in the system is processed (mode).

The resulting state space model, while still necessarily overly simplistic, is nonetheless a powerful tool for studies of consciousness. It captures many aspects of the neurobiological, cognitive, and psychological dynamics of wake-sleep states, and is unique in several important respects that we will discuss in light of the controversial conceptual and empirical issues that have stymied the study of waking, sleeping, and dreaming.

1.3. Caveat lector

In setting the stage for a full explication of our integrative AIM model (sect. 4), we will review the evidence regarding the differentiation of brain-mind states at the levels of psychophysiology (sect. 2) and basic and clinical neuroscience



Model Factor	Psychological	Neurobiological
A-Activation: Level of energy processing capacity	•Word count •Cognitive complexity e.g., perceptual vividness, emotional intensity, narrative	•EEG activation •Firing level and synchrony of reticular, thalamic and cortical neurons
I-Information Source internal or external.	•Real world space, time and person referents and their stability •Real vs. imagined action	•Level of presynaptic and postsynaptic inhibition. •Excitability of sensorimotor pattern generators.
M-Mode: Organization of data.	•Internal consistency? •Physical possibility? •Linear logic?	•Activity level of aminergic neurons

Figure 1. The Activation-Input Source-Neuromodulation model (AIM). Illustration of three dimensional state space and the psychological neurobiological correlates of each dimension. See section 4 and also Hobson (1990; 1992a; 1997a).

(sect. 3). Although these reviews are extensive, they do not broach many of the fundamental questions of sleep research. For example, we do not consider the biological functions of REM sleep as we do elsewhere (Hobson 1988a) nor do we address the equally interesting question of how psychological and cognitive factors impinge upon sleep neurobiology, a subject which has been the focus of our most recent work (Stickgold et al. 1998a; 1999a; 2000a; Xie et al. 1996). As has often been shown, cognitive activity affects sleep as well as vice versa (e.g., Smith & Lapp 1991) reflecting, certainly, a reciprocal effect of psychological factors and their neural substrates. Additionally, we sidestep entirely the intriguing but difficult issue of whether dreaming itself, as a conscious experience, has a psychological function over and above the postulated benefits of sleep to homeostasis and heteroplasticity (Hobson 1988a). Finally, it is important to note that we deal here exclusively with what Chalmers (1995b) has termed the "easy problem" of consciousness, that is, the mechanisms of the cognitive components of consciousness, rather than the "hard problem" of how consciousness itself could arise from a neural system (see, e.g., Tononi & Edelman 1998; Woolf 1997).

2. The phenomenology and psychophysiology of waking, sleeping, and dreaming

In this section we discuss the evidence which has been gathered over the past 40 years in an effort to define the conscious states of waking, sleeping, and dreaming and to measure their formal features quantitatively. With respect to the first question raised by us in the introduction, we will defend the position that these three states *can* be defined, that their components can be analyzed and measured, and that they *are* significantly different from one another.

After presenting our justification for this claim, we will

address the claim made by many psychologists that differences between REM and NREM mentation – and even differences between REM and waking mentation – are much smaller than we believe. In the course of this discussion, we will identify several areas of disagreement and then suggest some new approaches to their resolution.

Definitions of dreaming have ranged from the broadest "any mental activity occurring in sleep" to the narrower one that we prefer:

> Mental activity occurring in sleep characterized by vivid sensorimotor imagery that is experienced as waking reality despite such distinctive cognitive features as impossibility or improbability of time, place, person and actions; emotions, especially fear, elation, and anger predominate over sadness, shame, and guilt and sometimes reach sufficient strength to cause awakening; memory for even very vivid dreams is evanescent and tends to fade quickly upon awakening unless special steps are taken to retain it.

We believe that this highly specified definition serves both folk psychology and cognitive neuroscience equally well. It captures what most people mean when they talk about dreams and it lends itself admirably to neurocognitive analysis as we now intend to show.

2.1. Early findings of distinct differences between REM and NREM mentation

Before proceeding, we provide definitions of "REM" and "NREM" sleep for those readers unfamiliar with these terms. These two clearly distinguishable types of sleep are defined, by convention, in terms of electrophysiological signs detected with a combination of electroencephalography (EEG), electroculography (EOG), and electromyography (EMG) whose measurement is collectively termed "polysomnography" (see Rechtschaffen & Kales 1968). First described by Aserinsky and Kleitmann in 1953, REM sleep (also known as "paradoxical," "active" or "desynchronized" sleep) is characterized by: (1) wake-like and "activated" (high frequency, low amplitude or "desynchronized") activity in the EEG; (2) singlets and clusters of rapid eye movements (REMs) in the EOG channel; and (3) very low levels of muscle tone (atonia) in the EMG channel. NonREM (NREM) sleep includes all sleep apart from REM and is, by convention, divided into four stages corresponding to increasing depth of sleep as indicated by the progressive dominance of the EEG by high-voltage, low-frequency (also termed "synchronized") wave activity. Such low frequency waves dominate the deepest stages of NREM (stages 3 and 4) which are also termed "slow-wave" or "delta" sleep. We refer the reader to Hobson (1989) for a comprehensive primer on sleep physiology.

Aserinsky and Kleitman's (1953) report of the correlation of REM sleep with dreaming began an intense period of research on the relation of brain to mind that lasted well into the 1970s. In the early days of the human sleep-dream laboratory era, much attention was paid to the specificity, or lack thereof, of the REM-dream correlation using the newly available sleep laboratory paradigm. Normal subjects, usually students, were awakened from either the NREM or REM phase of sleep in the sleep laboratory and asked to report their recollection of any mental experience preceding the awakening.

During this period, the similarities and differences in mentation between the brain states of waking, NREM, and REM sleep were lavishly documented (e.g., Foulkes 1962; Foulkes & Fleisher 1975; Goodenough et al. 1959; Herman et al. 1978; Monroe et al. 1965; Nielsen 1999; Pivik & Foulkes 1968; Rechtschaffen 1973; Rechtschaffen et al. 1963; Vogel 1991). We have summarized these REM-NREM differences in Table 1. Some of the important conclusions from this cross-sectional normative paradigm are:

1. Following REM sleep awakenings, variously defined dream reports are obtained much more frequently (Aserinsky & Kleitman 1953; 1955; Dement 1955; Dement & Kleitman 1957b; Kales et al. 1967; Wolpert & Trosman 1958) or at least substantially more frequently (Foulkes 1962; Goodenough et al. 1965a; Hobson et al. 1965; Molinari & Foulkes 1969; Rechtschaffen et al. 1963; Stoyva 1965) than after NREM awakenings. For reviews of this early work see Foulkes (1966; 1967), Herman et al. (1978), Nielsen (1999), Pivik (1991), Rechtschaffen (1973), and Snyder (1967). In an extensive review of 29 REM and 33 NREM recall rate studies, Nielsen (1999) found an average REM recall rate of 81.8 (±8.7)% compared to an average rate for NREM of 42.5 (±21.0)%.

2. The frequency of dream recall rapidly drops off as awakenings are delayed beyond the end of a REM period (Dement & Kleitman 1957b; Goodenough et al. 1965b; Wolpert & Trosman 1958), a finding which has recently been both supported (Stickgold et al. 1994a) and challenged (Rosenlicht et al. 1994). Subjects who are able to indicate that they are dreaming during sleep more often indicate dreaming during REM than during NREM (Antrobus et al. 1965).

3. There exists a positive relationship of both report word count and subjectively estimated dream duration with the length of preceding REM sleep (Dement & Kleitman 1957b) and this relationship has been recently replicated for word count (Stickgold et al. 1994a). Moreover, stimulus-incorporation studies suggest that there exists a positive relationship between the length of time dream events would occupy in real time and the duration of the preceding REM sleep epoch (Dement & Wolpert 1958).

4. Judges are able to distinguish unaltered REM mentation reports from NREM reports (Monroe et al. 1965), a finding that has been recently replicated (e.g., Herman et al. 1978; Reinsel et al. 1992). Furthermore, some dreamers can subjectively determine whether they themselves had been awakened from REM or from NREM (Antrobus & Antrobus 1967).

5. Reports from REM sleep awakenings are typically longer (Antrobus 1983; Casagrande et al. 1990; 1996b; Foulkes & Rechtschaffen 1964; Foulkes & Schmidt 1983; Stickgold et al. 1994a; Waterman et al. 1993), more perceptually vivid, more motorically animated, more emotionally charged, and less related to waking life than NREM reports (Antrobus et al. 1987; Cavallero et al. 1992; Foulkes 1962; Herman et al. 1978; Ogilvie et al. 1982; Rechtschaffen et al. 1963; see Nielsen, 1999 and Table 1 for summaries). In addition, there is linguistic evidence for greater consolidation of dream elements in REM (Salzarulo & Cipolli 1979).

6. In contrast to REM reports, NREM reports contain thought-like mentation and representations of current concerns more often than do REM sleep reports (Foulkes 1962; Rechtschaffen et al. 1963).

In a review of early data, Monroe et al. (1965) stated that "the high degree of success attained by the judges [in dis-

Table 1. *Phenomenological differences between REM and NREM dream reports*

Study Sleep Stage	# S's	# S's x # nights	# awak- enings	% recall (any content)	% using more strict criteria	report length	bizarreness	visual vividness	emotionality	movement
Antrobus (1983)	73	73			not compared	no data given	not compared	REM vs St. 2	not compared	not compared
REM			73	no report		REM >St.2		n.s. when length		
St. 2 NREM			73	no report		p<.01		controlled		
Aserinsky & Kleitman (1953)	10	14			"dreaming"					
REM			27	74	74					
NREM			19	22	11					
Casagrande et al. (1996)	20	40			"≥1 sentence	*using word*	*w. Antrobus et*	*w. Antrobus et*	not compared	not compared
REM				REM	& ≥1 action"	*count indices:*	*al., 1976 index:*	*al., 1976 index:*		
early (in night)			40	early	75	early:	early:	early:		
late (in night)			40	late	75	REM> 2 & SO	REM> 2 & SO	REM> 2 & SO		
NREM (St. 2 abbreviated "2")				NREM (2)		late:	late:	late:		
early			40	early	50	REM & 2> SO	REM & 2> SO	REM & 2> SO		
late			40	late	70		*using a global*	*using a global*		
Sleep onset NREM St. 2 (SO)				NREM (SO)			*rating:*	*rating:*		
early			40	early	50		REM always >	REM always >		
late			40	late	55		2 & SO	2 & SO		
Cavallero et al. (1992)	60	120			not compared	temporal units	implausibility	not compared	% containing	not compared
REM			60	89.2		5.1 p<.0001	34 n.s.		62 p<.01	
St. 3&4 NREM			60	64.5		1.88	50		34	
Cicogna et al., 1998					not compared	temporal units	implausibility*	not compared	number reported	body feelings
late spontaneous REM	36	72	144	95		7.3	84.2%		.76	21.1%
late spontaneous St. 2			144	91		6.0	79.6%		.60	10.2%
Dement (1955)	13	?		not compared	"dreaming"	not compared	not compared	not compared	not compared	not compared
REM			51		88.2					
NREM			19		0					
Dement & Kleitman (1957)	9	61		not compared	"dreaming"	not compared	not compared	not compared	not compared	not compared
REM			191		79.6					
NREM			160		6.9%					

Foulkes (1962)	8	56			“vs. thinking”		judged scene	judged visual	judged present	judged present
REM			108	87	82		shift:REM>	vs. not:REM>	/absent: REM>	/absent: REM>
NREM			136	74	54		NREM $p<.02$	NREM $p<.02$	NREM $p<.02$	NREM $p<.01$
St. 1 NREM			32	69	56	subject-judged:	subject-judged	subject-judged	subject-judged	subject-judged
St. 2 NREM			32	74	51	REM>NREM	“distortion”:	“% visible”:	“present”:	“activity”:
St. 3&4 NREM			32	70	51	$p<.05$	R>N $p<.05$	R>N $p<.05$	R>N $p<.05$	R>N $p<.05$
Foulkes & Rechtschaffen (1964)	24	48			not compared	word count	subject-judged	subject-judged	subject-judged	subject-judged
REM			143	88.8		229.2	REM>NREM	REM>NREM	REM>NREM	REM>NREM
NREM			84	61.9		158.6	$p=.01$	$p=.01$	$p=.01$	$p=.01$
Foulkes & Schmidt (1983)	23	69			>1 temporal unit	temporal units	not compared	not compared	not compared	not compared
REM			82	93	80	5.5				
NREM			78	67	40	1.33 $p<.01$				
Goodenough et al. (1959)	16	48			not compared	not compared	not compared	not compared	not compared	not compared
REM			91	69.2						
NREM			99	34.3						
Goodenough et al. (1965a)	10	98			“dreaming”	word count	judged:	judged visual	not compared	judged activity:
REM			120	84	76	115	REM > NREM	imagery:REM		REM > NREM
NREM			240	45	21	34	$p<.02$	>NREM $p<.01$		$p<.01$
Hobson et al. (1965)	10	40–60			“dreaming”	not compared	not compared	not compared	not compared	not compared
REM			195	87.2	76.4					
NREM			102	37.2	13.7					
Kales et al. (1967)	3	40		dream+thinking	“dreaming”	not compared	not compared	not compared	not compared	not compared
REM			134	83	81					
NREM			108	35	7					
Kamiya (1961)	25	250			“dreaming”	not compared	not compared	not compared	not compared	not compared
REM			?	?	85					
NREM			400	46	27					
Molinari & Foulkes (1969)	10	40		tonic / phasic	not compared	not compared	not compared	subject judged	not compared	not compared
REM			40	80 100				tonic / phasic		
				descend / ascend				60 100		
NREM			79	72 75				79–80		
Ogilvie et al. (1982)	9	27		not reported	not reported	not compared	judged: REM>	judged: REM>	judged: REM>	not compared
REM			54				St. 2 NREM	St. 2 NREM	St. 2 NREM	
NREM			54				$p<.05$	“marginally”	“tendency”	

(*continued*)

Table 1. (*Continued*)

Study Sleep Stage	# S's	# S's x # nights	# awak- enings	% recall (any content)	% using more strict criteria	report length	bizarreness	visual vividness	emotionality	movement
Pivik & Foulkes (1968)	20	40			not compared	not compared	not compared	not compared	not compared	not compared
NREM total			158	64.6						
NREM St. 2			74	71.6						
NREM St. 3			56	64.3						
NREM St. 4			28	46.4						
Rechtschaffen et al. (1963)	17	30			Ss say dreaming	not compared	subject judged	subject judged	subject judged	not compared
REM				86	87		37% bizarre	74% vivid	74% emotional	
NREM				23	41		6% bizarre	24% vivid	24% emotional	
Salzarulo & Cipolli (1979)	8	80			"contentful"	# sentences	not compared	not compared	not compared	not compared
REM			240		95	4.22				
NREM			240		85	3.48				
Stickgold et al. (1994) Nightcap	11	110	(spont.)		> 100 words		not compared	not compared	not compared	not compared
REM			88	83	62	314				
NREM			61	54	18	65				
Stoyva (1965)	7 (deaf)	28			not compared	not compared	not compared	not compared	not compared	not compared
REM			51	73						
NREM			68	38						
Waterman et al. (1993)	12	24	72	not reported	not reported	REM>NREM	not compared	*w.Antrobus et al., 1976 index and length partialed out: REM>NREM*	not compared	not compared
Wolpert & Trosman (1958)	10	51			"dreaming"	not compared	not compared	not compared	not compared	not compared
REM			54	90.8	85.2					
NREM St. 2			26	3.8	0					

*Cicogna et al. 1998 actually found significantly more "space-time distortions" and a trend toward more "dimensional distortions" in Stage 2 versus REM reports, while the trend in global bizarreness (implausibility) went in the usual REM>Stage 2 direction. R = REM, N = NREM, spont. = spontaneous awakenings from identified sleep stage.

tinguishing REM from NREM reports] indicates that physiological sleep phase, REM or NREM, is highly diagnostic of the presence, amount, and quality of reported sleep mentation" (p. 456). In discussing the findings of this study, Rechtschaffen (1973) concluded that "these figures – discriminability ranging from about 70 to 90% – probably represent one of the best correlations ever discovered between psychological and physiological variables" (p. 163).

In REM sleep, the integrated conscious experience that is commonly referred to as dreaming is characterized by the following remarkably consistent set of features (see Hobson 1988b; 1994 for reviews):

1. Dreams contain formed hallucinatory perceptions, especially visual and motoric, but occasionally in any and all sensory modalities (Hobson 1988b; McCarley & Hoffman 1981; Snyder 1970; Zadra et al. 1998).

2. Dream imagery can change rapidly, and is often bizarre in nature (Hobson 1988b; 1997b; Hobson & Stickgold 1994a; Hobson et al. 1987; Mamelak & Hobson 1989a; McCarley & Hoffman 1981; Porte & Hobson 1986; Reinsel et al. 1992; Revonsuo & Salmivalli 1995; Williams et al. 1992). It has also been noted that dream reports contain a great many images and events which are relatively commonplace in everyday life (Dorus et al. 1971; Snyder 1970).

3. Dreams are delusional; we are consistently duped into believing that we are awake unless we cultivate lucidity (Barrett 1992; Hobson 1997b; Kahan 1994; LaBerge 1990; 1992; Purcell et al. 1986).

4. Self-reflection in dreams is generally found to be absent (Rechtschaffen 1978) or greatly reduced (Bradley et al. 1992) relative to waking and, when present, often involves weak, post hoc, and logically flawed explanations of improbable or impossible events and plots (Hobson 1988b; Hobson et al. 1987; Williams et al. 1992). It has been recently asserted, however, that self-reflection, self control and other forms of metacognition are more common in dreams than previously thought (Kahan 1994; Kahan & LaBerge 1994).

5. Dreams lack orientational stability; persons, times, and places are fused, plastic, incongruous and discontinuous (Hobson 1988b; 1997b; Hobson et al. 1987; McCarley & Hoffman 1981; Revonsuo & Salmivalli 1995; Rittenhouse et al. 1994; Stickgold et al. 1994b; 1997b; Williams et al. 1992).

6. Dreams create story lines to explain and integrate all the dream elements in a single confabulatory narrative (Blagrove 1992b; Cipolli & Poli 1992; Cipolli et al. 1998; Foulkes 1985; Hobson 1988b; Hunt 1991; Montangero 1991).

7. Dreams show increased and intensified emotions, especially fear-anxiety (Domhoff 1996; Merritt et al. 1994; Nielsen et al. 1991), which appear to integrate bizarre dream features (Merritt et al. 1994), and may even shape the narrative process (Seligman & Yellin 1987). Although the trend toward a predominance of negative emotion is prominent in most studies, other workers have found more balanced amounts of positive and negative emotion (for a good review, see Schredl & Doll 1998). Emotion also ranks as a prominent explanatory focus in functional theories of dreaming (e.g., Cartwright et al. 1998a; Greenberg et al. 1972; Kramer 1993; Perlis & Nielsen 1993).

8. Dreams show increased incorporation of instinctual programs (especially fight-flight), which also may act as powerful organizers of dream cognition (Hobson 1988b; Hobson & McCarley 1977; Jouvet 1973; 1999).

9. Volitional control is greatly attenuated in dreams (Hartmann 1966b). The dreamer rarely considers the possibility of actually controlling the flow of dream events (Purcell et al. 1986) and, on those infrequent occasions when this does occur, the dreamer can only gain lucidity with its concomitant control of dream events for a few seconds (LaBerge 1990). Unlike the rarer form of dream control offered by lucidity, however, the more mundane self-control of thoughts, feelings and behavior may be fairly common in dreams (Kahan 1994).

All of these features can be found in REM dreams, and most REM dreams contain a majority of these features. Contrastingly, they are found relatively rarely in NREM reports (see Nielsen 1999). This is the empirical basis of our contention that all of these features will eventually be explainable in terms of the distinctive physiology of REM sleep.

We interpret the foregoing evidence as strongly supporting our conclusion that there are clear-cut and major differences among the states of waking, sleeping (NREM) and dreaming (REM) at the phenomenological level. We take the robust evidence for quantitative differences in amount of NREM and REM sleep mentation as convincing proof of the validity of an important role for not only activation (factor A) but for the two other factors, information source (I) and modulation (M) in our AIM model. In addition, we take the evidence that state transitions are gradual rather than discontinuous and the evidence that correlations between phenomenology and physiology are statistical rather than absolute as further support of this model.

2.2. Overview of the NREM-REM sleep mentation controversy

Although the discovery of REM sleep and its strong correlation with dreaming (Aserinsky & Kleitman 1953) initially led to the strong hypothesis that dreaming occurred *only* during REM sleep (Dement & Kleitman 1957b), this hypothesis was clearly refuted by the discovery that reports of dreaming could be elicited from NREM sleep (Foulkes 1962) and that reports of dream-like mentation could also be obtained at sleep onset (Foulkes & Vogel 1965) and even from quiet waking (Foulkes & Fleischer 1975; Foulkes & Scott 1973). Given dreaming's lack of absolute state specificity, some investigators sought the psychophysiological correlates of specific dream features in the phasic events of REM and NREM sleep (Molinari & Foulkes 1969; see Kahn et al. 1997 and Pivik 1991 for reviews). Again, weak but consistently positive quantitative relationships were found (Kahn et al. 1997; Pivik 1991).

This lack of specificity led at least some investigators ultimately to conclude that investigations of REM sleep neurophysiology could provide no data helpful to understanding the genesis of dreaming (e.g., Bosinelli 1995; Foulkes 1990; 1991; 1993b; 1995; 1996a; 1997; Moffitt 1995). Such a view was encouraged by reports suggesting that in fact the differences between REM and NREM mentation were not nearly as great as had first been reported (e.g., Cavallero et al. 1992). In this section, we will present our reasons for rejecting these conclusions (see also Nielsen, target article).

How could the firm conclusions of the pioneer era (1955–1975) have apparently dissolved in the subsequent era of growing controversy (1975–1999)? In this section, we will analyze some of the scientific problems that led to the decline of the sleep-laboratory paradigm as this psy-

chophysiological approach lost much of its initially enthusiastic support. In the subsequent section we will turn our attention to the concomitant development of cellular and molecular neurobiology and show how the findings of basic research provided an alternative approach.

2.2.1. REM sleep dreaming is not qualitatively unique. While dream studies generally agree that REM reports are more frequent, longer, more bizarre, more visual, more animated and more emotional than NREM reports (Table 1), a pair of papers published in 1983 (Antrobus 1983; Foulkes & Schmidt 1983) led some researchers to the remarkable conclusion that the "characteristics [of dreaming] are pretty much the same throughout sleep" (Moffitt 1995) and that "dreaming in other sleep stages is not qualitatively different from REM dreaming" (Foulkes 1995). Because these papers are so central to the REM-NREM dreaming debate, we now offer a detailed review and critique of their findings and interpretations.

At the outset, it is important to point out that neither article actually concluded that REM and NREM dreams are indistinguishable, or even substantially the same, in either their quantitative or their qualitative features. In regard to qualitative features, Antrobus (1983) reported that when judges rated 154 REM and NREM reports for their relative "dreaminess" (using scales based on "visual imagery, bizarreness, hallucinatory quality and storylike quality"), they correctly identified 93% of the reports as either REM or NREM, indicating that REM dream reports were much more dreamlike than NREM reports. Similarly, Foulkes and Schmidt (1983, p. 276) concluded that "REM reports are likely to be significantly more dreamlike qualitatively (e.g., in character density, setting clarity) than typical NREM" reports, even when elicited after only five minutes of stage REM.

In regard to quantitative features, when Foulkes and Schmidt (1983) looked at 160 REM and NREM reports and characterized their lengths by the number of "temporal units" (narrative events), their data showed that temporal sequences (sequential events = temporal units − 1) were 14 times more common in REM reports than in NREM reports. In a similar way, Antrobus analyzed total recall frequency (TRF), which reflects the number of words in a report used to describe sleep mentation, and reported that word count significantly distinguished REM from NREM reports ($F = 95.52$). Using the same reports (J. Antrobus, personal communication), we have determined that the REM reports collected by Antrobus had a median length 6.4 times longer than their matched NREM reports, a number similar to the ratio of 7.0 obtained in a home study using reports from spontaneous awakenings (Stickgold et al. 1994a).

Since both Foulkes and Schmidt (1983) and Antrobus (1983) report such impressive differences between REM and NREM reports, one might wonder how and why these very authors have come to argue so strongly for a phenomenological sameness of these states. The critical question, raised by Foulkes and Schmidt and by Antrobus, pertains to the origin of the differences between REM and NREM reports, "whether there are . . . qualitative . . . differences as well as quantitative ones, and . . . whether such differences are merely attendant upon or are independent of the quantitative ones" (Foulkes & Schmidt 1983, p. 269). Or, as Antrobus wonders, whether "judges of Dreaming [dreaminess] implicitly rely on a dimension similar to the Total Recall Freq." (p. 562). It is this analysis that has led subsequent writers to claim that "when the quantitative characteristics of reports . . . from REM and nonREM . . . sleep are adjusted for length there are no differences in the characteristics of the reports" (Moffitt 1995, p. 19).

The normalization-for-length technique has been subsequently used to argue that bizarreness differences between REM and slow wave sleep (SWS) reports (Colace & Natale 1997), the number of dream-like features in a report (Fein et al. 1985; Rosenlicht & Feinberg 1997), memory sources of dreams (Cavallero et al. 1990) and even dream bizarreness itself (Bonato et al. 1991) are all directly and causally dependent on report length independent of sleep stage. Similar arguments have been advanced to explain correlations between dream bizarreness and creativity (Livingston & Levin 1991).

We will shortly reiterate our introductory arguments against this line of reasoning. Meanwhile, we emphasize some of these authors' own data that favor placing a strategic emphasis on the *differences* between REM and NREM mentation rather than using the similarities as a rationale for rejecting the cognitive neuroscience paradigm in favor of a purely cognitive description of mental states. (A similar critique of purely cognitive descriptions can be found in Nielsen 1999; and his target article.)

For example, Antrobus has recently shown that the REM/NREM distinction exerts a far greater effect on bizarreness than diurnal activation (Antrobus et al. 1995). He attributed the observed increase in bizarreness in REM reports to the increased activation seen in that state (Antrobus et al. 1995). It is also noteworthy that purely visual (versus verbal) imagery gave robust REM/NREM differences suggesting a differential sensory activation between the two states (Antrobus et al. 1995). And even when REM and NREM dreams were adjusted for length (a procedure we will shortly argue to be invalid), both Antrobus (1983) and Foulkes and Schmidt (1983) still found significant differences (e.g., in character density and setting clarity) between the two states. Notably, the persistence of a REM/NREM effect on bizarreness, visual imagery, and several other dream features in spite of normalization for report length has recently been confirmed (Casagrande et al. 1996b; Faucher et al. 1999; Nielsen 1999; and his target article; Raymond et al. 1999; Waterman et al. 1993). For example, when analysis of covariance (with report length as the covariate) is used to partial out the effect of report length on dream features, REM reports were still judged significantly more visual and bizarre than sleep onset or stage 2 reports (Casagrande et al. 1996b) and more visual than NREM reports (Waterman et al. 1993).

Even when dream features appear to be specifically linked to distinctive REM physiology, interpretations can still be cast toward either camp. Hong et al. (1997) reported an impressive correlation between visual imagery and REM density ($r = 0.8$), which we would argue as evidence for a dependence of dream imagery on a qualitative feature of REM sleep. But Antrobus et al. (1995) consider this to be another example of the simple dependence of dream content on levels of brain activation, arguing that rapid eye movements are not under strict brainstem cholinergic control, but come increasingly under the control of the frontal eye fields as general cortical activation increases.

Whatever one's assessment of the similarity versus difference argument, it is clear that none of the analyses in these two papers can distinguish between two competing

hypotheses: (1) that dream features are dependent on report length; and its simpler converse (2) that report length is dependent on dream features. We now consider the arguments in favor of the second hypothesis, which we have adopted in our own work.

2.2.2. The relationship between dream features and dream report length. That report length depends on dream features was first implied by Hunt (1982) in his analysis of dreaming as fundamentally visuospatial versus verbal-propositional and was then explicitly proposed by Hunt et al. (1993). We agree with their logical assumption that reports with more dream features will require more words to describe them. For example, a report with such dream features as self-representation, visual hallucination, emotion, narrative plot, and bizarreness will almost certainly be longer than a report with none of these features. Similarly, it is highly unlikely that a report with a word count of only seven words, the median length of the Antrobus (1983) NREM reports (J. Antrobus, personal communication), could possibly have more than one of the above features.

Inexplicably, Antrobus (1983) and Foulkes and Schmidt (1983) both seem to regard word count and content as independent of each other. In doing so, each has emphasized a very different explanation. Although conceding that alternative explanations were "in no way excluded by these findings," Antrobus (1983) concluded that the NREM reports were shorter due to a defect in "the ability of the subject to recall and describe the [dream] events" (p. 567). In this view, the shorter reports failed to include dream features which were nonetheless present in the NREM dream itself. To us this seems, at best, a risky assumption. In contrast, Foulkes and Schmidt (1983) concluded that the shortened reports and the rarity of dream features reported resulted from differences in dream production. On this view, the differences reflected "the relative paucity and superficiality of mnemonic units active during NREM sleep" (p. 279) compared to REM sleep. The conclusion of Foulkes and Schmidt (1983) is strikingly similar to our position, which is that the relative brevity of NREM reports reflects a decrease in the types (superficiality) and number (paucity) of dream features present in the conscious experience reported in them. If Foulkes really agrees with us on this point, he cannot then also countenance controlling for word count in evaluating reports.

Analyzing the same data set used by Antrobus (1983) we have shown that REM/NREM differences can not be explained simply in terms of report length (Porte & Hobson 1986). Thus we agree with Antrobus when he pointed out that there is still a part of the REM/NREM variance that Dreaming (i.e., judges' idiosyncratic scales for "dreaminess") picks up better than a Total Recall Frequency factor.[1] Similarly, Foulkes and Schmidt (1983) reported that some residual REM/NREM differences in temporal unit composition (e.g., in character density) persist even after report length is controlled. Residual stage differences following normalization for report length in these as well as additional studies have recently been reviewed by Nielsen (1999).

In the face of such unambiguous statements, it is critical to try to understand why these results have been so frequently and so passionately misinterpreted. In part, the erroneous interpretations were encouraged by the original authors. For example, Antrobus (1983, p. 567) concluded that "although there are slight differences . . . it is quite clear that the global judgment of Dreaming adds little, if anything, to Total Recall [Frequency] with respect to the association with the sleep stages REM and NREM." Similarly, Foulkes and Schmidt (1983; p. 279) concluded that "*most* typically observed inter-stage differences in dream reports stem from different lengths rather than the different stages of the reports" (emphasis added). Because they have conflated causality with correlation, both Antrobus and Foulkes and Schmidt unjustifiably assume that most of the differences seen can be explained as correlates of report length. We disagree on the basis of the following studies.

Recent evidence provides strong support for Hunt's proposition that report length reflects the number and intensity of dreamlike features prior to awakening. Hunt et al. (1993) have argued "it is not the length of the dream that somehow makes bizarreness more likely, but . . . it is more parsimonious to conclude that episodes of bizarreness within the dream are one major determinant of overall dream length . . . making length a necessary consequence of bizarreness and not the other way around" (p. 180). In addition, Hunt et al. (1993) note that Hauri et al.'s (1967) factor analysis of dreams found that bizarreness and report length significantly load on the same factor (and therefore strongly co-vary), "which would make their enforced statistical separation highly questionable" (Hunt et al. 1993, p. 181). In other words, if quantity follows quality and is, in fact, caused by it, then longer reports are needed to describe dreamier dreams. On this view, word count is perhaps even a direct measure of dreaminess and might well be taken as such.

To support their position, Hunt et al. (1993) first demonstrated that awake subjects used more words to describe a visually bizarre picture than a mundane picture. They then showed that the bizarreness scores correlated positively with the number of words devoted to describing the bizarre episodes. Finally, they showed that normalizing dream features for report length actually eliminated the correlations of bizarreness with non-verbal imagination test scores. Hunt et al. therefore concluded that bizarreness directly determines a major component of report length and that controlling for total word count introduces an artifactual dilution of bizarreness scores.

In summary, a critical review of the papers of Antrobus (1983) and Foulkes and Schmidt (1983) reveals that these papers report significant quantitative differences in the features of REM and NREM dreams. Both papers also find features such as dreaminess or character density to differ significantly between REM and NREM dreams *even when report length is unjustifiably normalized.* Neither study reports data that argue against the contention that the strong correlation between report length and dream features occurs because reports with more dream features require more words to describe them (Hunt et al. 1993; Nielsen 1999). We urge the collection of additional data to further clarify the nature of these REM/NREM differences. Such data should include ample numbers of reports, collected longitudinally in naturalistic settings, which are obtained from home awakenings physiologically monitored with unintrusive devices such as the Nightcap (e.g., Rowley et al. 1998).

2.3. Methodological considerations in the study of dreaming

The study of mental states is replete with methodological shortcomings and conceptual confusions. We believe that

some of these areas of confusion can be clarified in a manner that could increase consensus. In what follows, we address five methodological issues to point out the nature of the problems, offer clarifications, and suggest possible resolutions.

2.3.1. The reduction of psychological states to narrative reports. The most profound problem in studying conscious states is the necessity of reliance on verbal reports. This method is problematic because these accounts are just *reports,* not the subject's experience of the states themselves. This reduction of conscious experience to prose has at least three important ramifications:

(1) A multimodal conscious experience including pseudosensory perceptual, emotional, and motoric dimensions is reduced to only one mode, that of narration. (To emphasize this point, we merely point out that if a picture is worth a thousand words, we certainly are not getting the whole picture with a seven-word report!)

(2) The narratives describing sleep state mentation are all generated during the waking state and are thus likely to mix, if not contaminate, the dreaming phenomenology with the phenomenology of waking (for a discussion of this point relative to dream meaning, see Hunt 1989, p. 9).

(3) Analysis of narrative dream reports is extremely limited in its power to recreate or model the true underlying mechanism of dream production at any fundamental, primordial level of explanation (be it cognitive-mnemonic, linguistic or neuropsychological) because narratives about experience display a high degree of what Pylyshyn (1989) terms "cognitive penetrability."

Pylyshyn's point can be applied to dreaming as follows. The behavior of the dream production system is highly malleable using the same cognitive processes invoked to explain its behavior such as the dreamer's goals and beliefs (see Pylyshyn 1989). For example, in the case of the dreamer's goals, the frequency of overall dream recall as well as lucidity can be greatly increased by auto-suggestion techniques that employ many of the same cognitive abilities (e.g., imagination and visualization) that most theorists believe contribute to dream production itself (see sect. 3.3). In the case of beliefs, the meaning of a dream experience *while it is occurring* is highly dependent on the dreamer's personal (and changeable) philosophy of what dreaming is (e.g., a message from a deity, a psychopathomimetic experience, "travel outside the body," etc.). According to Pylyshn (1989) such highly penetrable experiences, rather than illustrating primordial cognitive mechanisms, instead reflect "the nature of the representations and . . . cognitive processes operating over these representations" (p. 81), which, in the case of dream reports, is language itself. Given that Pylyshn (1989) asserts that cognitive penetrability can affect even highly objective and replicable psychological data (such as the visualized-image-size/image-scanning-time relationships described by Kosslyn & Koenig 1992), penetrability is all the more likely to influence the highly elaborated and individualistic phenomenon of dream reporting. The rendering of dream reports in conventional (wake state) grammar and syntax may, therefore, tend to obscure important differences between the actual experiences of waking and dreaming.

These considerations raise the concern that using the sentence or the word as a unit for quantifying mental activity may say more about language than about the multimodal nature of conscious experience. This is important because so many researchers consider the quantification of report length as the single most salient feature of a dream. In this context, it is also worth noting that verbal retrospective reports are often considered inadequate to describe mental states that are closer to dreaming than to waking mentation. These states include religious conversion, near-death experience, functional psychosis, delirium, drug-induced conditions, and other altered states of consciousness.

This aspect of the REM physiology-dream mentation controversy may be particularly relevant to the current debate about self-representation and bizarreness in dreams of children aged 3 to 8 (see Foulkes 1990; 1993b; 1996a; 1996b; 1997; Resnick et al. 1994). Based upon an extensive longitudinal study (Foulkes 1982b) and a later cross-sectional study (Foulkes et al. 1990), Foulkes asserted that "dreaming is absent until ages 3 to 5 and does not assume the form of adult dreaming until ages 6 to 7" (Foulkes 1997, p. 4). Foulkes hypothesizes that, lacking or being deficient in their ability to consciously mentally represent their perceptuo-behavioral experience, young children (like animals) may not experience dreaming in spite of having an abundance of REM (Foulkes 1990; 1993c). He argues further that dreaming is "a high-level symbolic skill, a form of intelligent behavior with cognitive prerequisites and showing systematic development over time" (Foulkes 1993c, p. 120), and that dreaming has, as its prerequisite, conscious representational competence (Foulkes 1990; Foulkes et al. 1990). As evidence to support this, he cites studies in which he finds very low recall of dreaming and little bizarreness prior to age 5 (Foulkes 1982b; Foulkes et al. 1979), low rates of reporting at ages 5–8 (Foulkes 1982b; Foulkes et al. 1990), acquisition of kinetic versus static imagery only after age 6 (Foulkes et al. 1990), and acquisition of self-representation as an active dream participant as well as narrative continuity only after age 7 (Foulkes et al. 1990; 1991). Further, from his data showing correlation of report rate with measures of visuospatial versus verbal skills (Foulkes et al. 1990), Foulkes (1993b) suggests that "young children may fail to report dreams because they are not having them, rather than because they have forgotten them or are unable to verbalize their contents" (p. 201). For a recent review see Foulkes (1999).

Subsequent studies have shown that dream bizarreness does indeed increase over ages 3 to 8 (Colace et al. 1993; 1997; Colace & Tuci 1996; Resnick et al. 1994). However, other of Foulkes's findings have not been supported. For example, dream reporting rates in 4- to 5-year olds has been reported to be almost identical to that in 8- to 10-year olds (Resnick et al. 1994). In addition, active self representation in dreams of 4- to 5-year olds has been reported to occur in over 80% of their dream reports (Colace et al. 1995; Resnick et al. 1994). Finally, substantial occurrence rates for bizarre elements have been reported in the dreams of both 4- to 5-year olds (0.45 per 100 words) and 8- to 10-year olds (0.71 per 100 words) (Resnick et al. 1994).

Moreover, although rates of adult dream recall have been related to performance on tests of visuospatial skill (Butler & Watson 1985), rates of dream recall have also been correlated with individual differences in visual memory (Schredl et al. 1995). Therefore, any ontogenetic changes in visual memory would confound the effects of developmental changes in higher order visuospatial skills on dream reporting rates in children.

Overarching these conflicting data, however, is the theoretical point bearing on the current discussion: that is, that

dream reports are given in waking and thus, of necessity, must be constrained by an organism's waking cognitive and linguistic abilities. At one extreme, it must be conceded that even if a cat had the most vivid of "dreams," it would not be able to report it. Similarly, if a toddler is variously unable (or unwilling) to conceive and verbalize a complex perceptual-emotional-motor REM experience, it does not mean it was not originally experienced in some form which, later in life, might be reported as a dream. In other words, we challenge here the assumption by Foulkes (e.g., 1990) and others (e.g., Bosinelli 1995) that "dreaming" is an experience that can occur only if it can be later reported by an organism possessing linguistic abilities. We recognize that verification of oneiric activity in organisms that are unable to report (or even, possibly, reflect upon) their experiences is currently impossible, although we do not rule out the possibility that new methods may someday provide hints as to the conscious experiences of nonverbal beings (e.g., see Marten & Psarakos 1995).

Nevertheless, as with many other psychological constructs such as emotional expression (e.g., Darwin 1873) or behavioral inhibition (e.g., Goldman-Rakic 1986), such inferences drawn between human developmental as well as mammalian phylogenetic levels has a long scientific tradition. It is, therefore, not inherently invalid to cautiously speculate from adult human oneiric experience to observed REM behavior in infants and animals, especially given the abundant behavioral correlates (e.g., ethologically meaningful oneiric behavior; for a full discussion see Jouvet 1999). Similarly, we specifically suggest that the human neonate, spending as it does more than 50% of its time in REM sleep (Hobson 1989), is having indescribable but nevertheless real oneiric experiences. An infant's waking experience remains essentially indescribable and speculative to us older persons but we do not doubt that infants enjoy some sort of waking conscious experience. For us, it is not at all difficult to imagine that an infant might be experiencing hallucinosis, emotions, and fictive kinesthetic sensations during REM sleep.

Given these caveats, we suggest that more effort be put into the development and use of other methodologies and scales such as the photo-response visual brightness and clarity scale (Antrobus et al. 1987; 1995; Rechtschaffen & Buchignani 1992), temporal unit analysis (Cavallero et al. 1990; Foulkes & Schmidt 1983), computerized content analyses (Gottschalk 1999), the analysis of dream drawings (Hobson 1988b), or the use of affirmative probes (e.g., Herman 1992; Merritt et al. 1994; Pace-Schott et al. 1997a; Stickgold et al. 1997a; see Herman 1992 and Hobson & Stickgold 1994a for further discussion). In other words, we need recourse to more diverse means to elicit detailed descriptions of salient aspects of conscious experience.

2.3.2. The sleep laboratory environment. The sleep laboratory itself constitutes a second major methodological problem. Anyone who has ever slept in a sleep laboratory (as all of us have!) knows that it is an inhospitable and unnatural setting that makes sleep more difficult and less deep than is possible in more naturalistic settings. To appreciate this point, the reader need only imagine going to an unfamiliar place in an inner city neighborhood of dubious safety, encountering a technician who is a stranger and often of the opposite sex, having ten electrodes affixed to the scalp with cement that smells like airplane dope and then being bid "goodnight" and "pleasant dreams." Hence the famous first night effect (objectively poor sleep owing to discomfort and anxiety) often extends to a second night, and may contribute to a constriction of dream experience (as in dreams of the sleep lab setting) over even longer times. The laboratory environment may even alter the content of dreams recalled from spontaneous awakenings in the laboratory at the end of a night's sleep as evidenced by the high frequency of laboratory references in morning spontaneous awakening REM and NREM laboratory dream reports (Cicogna et al. 1998).

Studies such as those of Dement et al. (1965), Domhoff and Kamiya (1964), Okuma et al. (1975) and Whitman et al. (1962) have shown substantial incorporation of the experimental situation into laboratory dream reports particularly on the first night in the laboratory but persisting, at a lower level, into subsequent laboratory nights (Dement et al. 1965; Domhoff & Kamiya 1964). Similarly, content differences have been noted between laboratory and home dreaming (Domhoff & Kamiya 1964; Domhoff & Schneider 1999; Hall & Van de Castle 1966), although it has been argued that these differences are very small (Domhoff & Schneider 1999). Although these early studies were confounded by spontaneous (home) versus instrumental (laboratory) awakening conditions (as has been noted by Foulkes 1979), later studies controlling for reporting conditions (Lloyd & Cartwright 1991; Weisz & Foulkes 1970) still found some content differences between the home and laboratory dreams of adults. Waterman et al. (1993) emphasize that home-laboratory differences can arise from both environmental factors and factors related to investigator expectancies and, therefore, both should be controlled. In our view, full adaptation to the sleep lab may take four days or longer (see Domhoff & Kamiya 1964) exceeding the length of most laboratory studies.

As in the case of NREM compared to REM dreaming, we are not arguing for a gross, qualitative distinction between home and laboratory dreams. Laboratory dreams are, undoubtedly, largely representative of many of the formal and content features of dreaming in naturalistic settings. Nevertheless, we suggest that quantitative constraints on the dreaming experience may be imposed by the laboratory setting so that the full potential expression of certain dream features is limited. Of additional concern is the finding by Antrobus et al. (1991) that REM-NREM differences in both word count and global judgment of dreamlike quality diminish over 14 nights in the sleep laboratory, an effect they attribute largely to motivational factors in dream reporting. Minimizing any such "laboratory-fatigue" confound constitutes further argument for longitudinal awakenings to be performed in the more comfortable environs of the home.

To overcome these problems, several options are possible. First, laboratory studies can simply be extended in time, perhaps recording each subject for a full week. This has obvious disadvantages including inconvenience, high cost, and the above noted motivational effects. A second option is to continue to run relatively short (1–4 night) paradigms, and accept the suppressive effects on sleep architecture and dream content. While perhaps no longer normatively valid, the data obtained would still be at least reliable. A third option, and the one that we have chosen, is to move recording into the home for extended longitudinal studies using the Nightcap (Ajilore et al. 1995; Mamelak & Hobson 1989b; Pace-Schott et al. 1994; Rowley et al. 1998; Stickgold et al. 1994a; 1998b).

2.3.3. The question of "similarity" and "difference." We have long thought that the argument over whether mentation in two states like REM and NREM sleep is more similar or different was specious. Thinking the dilemma to be false, we have ignored or minimized it in our previous writings. However, we now feel obliged to clarify for the reader how the debate over REM and NREM mentation has become inextricably entangled with the larger and more general question of the mind-brain problem. In doing so, we hope to elevate the debate from the parochial to the general level and to make our own position on mind-brain issues crystal clear.

In some ways, understanding the conflicting opinions that swirl around the sleep and dream mental content debate is relatively straightforward. One group of psychologists, exemplified by David Foulkes and the late Alan Moffitt, hypothesizes that the brain and the mind are so loosely linked that the study of the mind need not be constrained – or even informed – by the study of the brain (e.g., Bosinelli 1995; Foulkes 1991; 1993b; 1996a; 1997; Moffitt 1995). This group interprets the empirical data as indicating that mental content does not differ qualitatively across brain states. There is only one dream mentation production system that is more or less active during waking and sleep. In such theories, termed "One-Generator" models of sleep mentation by Nielsen (1999), it is only the fluctuating level of cognitive activation that determines differences between REM and NREM sleep in report length as well as in the broad range of dream features that co-vary with report length. By taking this position, these psychologists minimize the importance of physiology, which they assert to be irrelevant to the understanding of dreaming. How cognitive activation could be independent of brain activation is a question not addressed by these scientists.

Another group, consisting largely of psychophysiologists, holds that the mind and the brain form an integrated system, so tightly linked within and across states that detailed qualitative and quantitative distinctions at either level of analysis imply the existence of isomorphic distinctions at the other. This is the position that we take. For us, the cognition production system *is* the brain. And, of course, it is always the *same* brain. But we know that the brain's mode of information processing changes radically across states. So, therefore, must its mental products. Nielsen (1999) terms this point of view a "Two-Generator" model of sleep mentation. For us, the state-specific changes in brain function virtually guarantee concomitant changes in mental function, even if our psychological methodology may still be inadequate to identify these changes (just as for many years the physiological changes also eluded us!).

With respect, we suggest that the failure to demonstrate psychological differences concomitant with physiological ones must be laid at the door of inadequate psychological methodology. If psychology has so far failed to document the robust phenomenological differences between waking and dreaming that most people experience every day of their lives, then more vigorous and more creative psychological research is needed. Otherwise we are faced with the absurd and unacceptable conclusion that brain and mind have nothing to do with each other.

That even a single, "One-Generator" system (i.e., a "dream mentation production system") may show dramatically different features in different states is in no way a self-contradiction. To our way of thinking, states of the brain are analogous to other dynamic states of matter. Consider, for example, the way that liquid water changes state with changes in temperature: above 100° C it is steam; below 0° C it is ice. These states are analogous to the states of waking, NREM sleep, and REM sleep in the brain (as well as to less common mental states such as coma, hypnosis, and mania). No one would say that in the frozen state (ice) or in the vapor state (steam) that the material is not still water. Nor could any sentient person ignore the obvious differences in the properties and behavior of water across states. We believe that it is equally inappropriate to argue that since there is a single dream production system (i.e., the brain-mind), that the properties and behavior of its products, for example, dreams, must be identical or even similar across different states. Such an important error in scientific thinking would lead to minimizing or missing entirely the change in matter (in this case the brain) that underlies the change in its state-dependent properties (in this case, consciousness).

The question of whether REM and NREM mentation are the same or different has often devolved into a search for characteristics of mentation that are absolutely unique to REM sleep. We consider this quest to be a fool's errand and indeed no absolute qualitative distinction between the two states has yet been documented. Since the late 1950s, many sleep laboratory studies have shown substantial recall of mentation from NREM, thereby obviating an exclusive association of sleep mentation with REM (Cicogna et al. 1998; Foulkes 1962; 1966; Foulkes & Rechtschaffen 1964; Goodenough et al. 1959; 1965b; Kamiya 1961; Molinari & Foulkes 1969; Pivik & Foulkes 1968; Rechtschaffen et al. 1963; Salzarulo & Cipolli 1979; Stoyva 1965; Zimmerman 1970; see Foulkes 1967, Herman et al. 1978, and Nielsen 1999 for reviews). For example, among nine studies, the percentage of NREM awakenings yielding at least minimal recall varied from 23 to 74% (Foulkes 1967) and, as noted, Nielsen (1999) has found an average NREM recall rate of 42.5% over 33 published studies. Recall rates similar to those of NREM in general have even been obtained from stages III and IV of NREM (e.g., Bosinelli 1995; Cavallero et al. 1992; Goodenough et al. 1965b; Herman et al. 1978; Nielsen 1999; Pivik & Foulkes 1968; Salzarulo & Cipolli 1979; Tracy & Tracy 1974). In a review of eight studies of stages III and IV mentation, Nielsen (1999) found an average recall rate of 52.5 (+18.6)%, but also notes that a substantial percentage of subjects never recall stage III and IV mentation or require several nights of awakenings before reporting such mentation.

The findings of several studies have countered the hypothesis that NREM mentation is simply recall from previous REM (Foulkes 1962; 1967; Foulkes & Rechtschaffen 1964; Goodenough et al. 1965b; Rechtschaffen et al. 1963), although report length does drop precipitously following the end of REM periods (Stickgold et al. 1994a).

The fact that differences are *not absolute* does not mean however that *no* differences exist. Indeed, all the evidence shows that such differences *do* exist and we have already advanced good reasons to believe that these may have been seriously underestimated. For example, similarities in dream features such as bizarreness may be inflated when report length is controlled in REM and NREM reports (Hunt et al. 1993) and REM-NREM bizarreness differences may persist even when report length is partialled out (Casagrande et al. 1996b; Nielsen 1999; Waterman et al. 1993). In addition, recent work comparing sleep onset REM and NREM dreams using an experimental protocol which controlled for previ-

ous sleep and waking time has shown that sleep onset REM periods are specifically related to physiological signs of REM whereas NREM dreams were related to intrusions of waking into NREM (Takeuchi et al. 1999b). These authors conclude that the mechanisms underlying REM and NREM dreaming must, therefore, differ (Takeuchi et al. 1999b). We thus conclude that while *some* NREM dreams approach REM dreams in length, vividness, dreaminess, and bizarreness (Cicogna et al. 1998; Foulkes & Schmidt 1983; Herman et al. 1978; Nielsen 1999) and while "dreamlike" versus "thought-like" mentation may predominate in some NREM reports (Foulkes 1962; Nielsen 1999; Rechtschaffen et al. 1963; Zimmerman 1970), NREM reports are far more likely than REM reports to be short, dull, and undreamlike (Nielsen 1999; Rechtschaffen et al. 1963).

Many of the above-noted problems inherent in assessing the similarity versus difference of two phenomena can be addressed with improved methodologies. For example, when two states (such as REM and NREM) are being compared in terms of specific parameters (such as bizarreness) to a third state (such as waking), the question of the similarity versus difference between the two states becomes much more tractable.

2.3.4. The source and fate of dream memory. A tendency to emphasize psychological similarity has also characterized recent studies on the memory sources of REM and NREM dreams. Using a modification of Tulving and Thomson's (1973) classification of memory sources and an experimental free association technique, Cavallero and his colleagues initially found a distinct difference in memory sources between early-night REM and NREM mentation (Bosinelli 1991; Cavallero & Cicogna 1993; Cicogna et al. 1986). Early-night NREM sources consisted primarily of discrete biographical episodes while REM sources were a mixture of episodic, abstract self-referential and semantic sources (Bosinelli 1991; Cavallero & Cicogna 1993; Cicogna et al. 1986). This observation fits with the commonly accepted distinction between NREM dreaming as a simpler and REM dreaming as a more complex state of consciousness.

However, when REM and NREM reports were collected later in the night and matched for "temporal unit composition" (a procedure akin to diluting bizarreness by controlling for word count), the same researchers emphasized the similarity of memory sources between REM and NREM (Bosinelli 1991; Cavallero & Cicogna 1993; Cavallero et al. 1988; 1990; 1992; Cicogna et al. 1991; Fagioli et al. 1989). Likewise, Cicogna et al. (1991) reported few REM/Stage 2 differences in number of temporal units, implausibility, self presence, settings or characters. Nonetheless, as in the case of dream content (Antrobus 1983; Foulkes & Schmidt 1983), some residual state-related memory source differences continued to be reported (Cavallero & Cicogna 1993; Cavallero et al. 1990; 1992; Cicogna et al. 1991) and these need to be explained.

The research on memory sources for mentation among the different behavioral states overlooks the far more robust difference in the overall functioning of memory processes that distinguishes sleep from waking. This is the notorious difficulty of recalling dreams or any other mental content following either instrumental laboratory or spontaneous awakening. Many dreamers are aware that recall actively eludes them as they awaken. And even when dream recall is confident and detailed, it is common for subjects to assert that they are sure that there was much more antecedent dreaming that could not be recalled. One reason for the neglect of this robust phenomenon is that it is difficult to study something, in this case memory, that isn't there! But the very absence of recall is a datum which any dream theory must explain, especially in the face of the robust brain activation in REM sleep!

Freud's famous explanation was that dream forgetting was an active function of repression. We have instead attributed this prominent failure of recall to a state dependent amnesia caused by aminergic demodulation of the sleeping brain (Hobson 1988b). The waking level of aminergic modulation falls to 50% in NREM sleep and to nearly zero in REM (Hobson & Steriade 1986; Steriade & McCarley 1990a). It would appear that the intense activation of REM must overcome this demodulation and persist into subsequent waking in order for very vivid dreams to be remembered. In our view, the low level of production and recall of NREM mentation is due to the additive effects of inactivation and demodulation.

This hypothesis is consonant with subjective experience. For example, when one introspectively compares recall of a night's dreaming with that of a corresponding waking epoch, one of the most obvious differences lies in the far greater amount of detail that can be recalled in waking. Moreover, it is commonplace for long dreams to have complete scene shifts of which the dreamer takes no significant cognitive account. If such orientational translocations occurred in waking, memory would immediately note the discontinuity and seek an explanation for it. This intuitively convincing difference between memory for dreaming and memory of waking mentation is confirmed by several empirical studies (see below).

Although the frequent inability to recall dreamed experience in subsequent waking has been a robust finding in dream research (Goodenough 1991), there is also strong evidence of deficient memory for prior waking experience in subsequent sleep. For example, little continuity has been shown between pre-sleep stimuli and the content of REM dreaming when this phenomenon has been probed using the following paradigms:

1. Specific experimental pre-sleep stimuli in the form of films have little effect on dream content (Cartwright et al. 1969; DeKoninck & Koulack 1975; Foulkes et al. 1967; Foulkes & Rechtschaffen 1964; Goodenough et al. 1975; Karacan et al. 1966; Witkin 1969; Witkin & Lewis 1967).

2. Specific experimental pre-sleep stimuli such as static visual images or altered social milieu are rarely incorporated into dreams (Carpenter 1987; Orr et al. 1968; Shevrin & Fisher 1967).

3. Specific pre-sleep waking behavioral or thought experiences are not easily detectable in subsequent dreams (Bakeland 1971; Bakeland et al. 1968; Breger et al. 1971; Cartwright 1974b; Hauri 1970).

4. Presleep mentation is infrequently picked up by the dream process (Rados & Cartwright 1982; Roussy et al. 1996; 1997).

5. Naturalistic daytime events rarely enter dream content, casting grave doubt on the classical psychoanalytic concept of day residue as dream instigator (Epstein 1985; Harlow & Roll 1992).

6. Pre-sleep modification of biological drives or perceptual experience has very weak effects on dreaming (Baldridge et al. 1965; Bokert 1968; Dement & Wolpert 1958;

Roffwarg et al. 1978). (For reviews see Arkin & Antrobus 1978 and Cavallero & Cicogna 1993.)

It must, therefore, be concluded that because dreaming is so little shaped by pre-sleep experience, memory systems active during REM sleep have extremely poor access to recent waking memories. Even if dreaming is concerned far more with emotionally salient content than with current events, it is remarkable that the dream construction process fails to incorporate recent episodic memories, including emotionally salient ones, to any significant extent. Two experimental exceptions to this generality, however, should be noted. The first involves the practice of dream incubation whereby focused pre-sleep attention on a specific concern has been shown to increase its rate of occurrence in subsequent dreaming (Saredi et al. 1997). Dream incubation techniques, however, introduce substantial confounds in the form of artificially imposed practice effects as well as the focus on emotionally salient issues. The second involves the finding by Rosenblatt et al. (1992) that significantly more of cartoon segments viewed prior to sleep were recalled following REM versus Stage 2 NREM awakenings, a difference which disappears if a 30 second pre-reporting waking delay is interposed after awakening. Following the arousal-retrieval model of Goodenough (1991), Rosenblatt et al. attribute this REM-NREM difference to greater mnemonic capacity immediately following post-REM versus post-NREM awakenings resulting from greater immediately pre-awakening cortical arousal in REM versus NREM. Using the semantic priming task, we have recently reported a similarly positive mnemonic effect of pre-awakening REM versus NREM for associative memory processes (Stickgold et al. 1999b). Certain forms of memory, such as generating associations to weakly related word primes, may, in fact, be preferentially enhanced by both the activation and the neuromodulatory differences (see sect. 4) between REM and NREM (Stickgold et al. 1999b). In contrast, greater sleep inertia (Dinges 1990) following NREM awakenings (a phenomenon undoubtedly reflecting low pre-awakening brain activation) may less selectively impair a wide spectrum of mnemonic processes.

Even within sleep, memory appears impaired. If episodic experiences within sleep were to persist in the sleeper's memory, one would expect greater content and thematic continuity between contiguous REM periods than more distant REM periods. But despite the fact that content and thematic continuity of successive dreams is greater within the same night than across nights, continuity does not differ between contiguous and noncontiguous REM periods of the same night (Cipolli et al. 1987; Fagioli et al. 1989).

We have recently completed three preliminary studies that seek to quantify aspects of memory within sleep and to compare sleep memory to waking memory. In the first study, 27 subjects became aware of and could later recall three aspects of their memory functioning (semantic, recent, and remote episodic) more often during two waking experiences than during dreaming. Since both types of waking experience sampled were much shorter than the duration of a night's dreaming, results further support the concept of a mnemonic deficiency in dreaming compared to waking (Pace-Schott et al. 1997a).

A second study examined perceived duration of dreaming. The 22.5 minute median perceived duration of dreams by 54 subjects was associated with an unexpectedly large variation. Even ignoring the highest and lowest 10% still left a 24-fold variation. Such wide variance in a basic memory function further suggests a profound alteration of memory processes in dreaming as compared to waking (Stickgold et al. 1997a).

In the third study, 11 subjects recorded the processes by which a total of 103 dreams were recalled. Fifty-two reports (50%) were recalled in "chunks" (i.e., entire dream segments were recalled as units). Another 38 reports (37%) were recalled all at once upon waking and 13 reports (13%) were recalled gradually. Nine of the 11 subjects reported at least one dream recalled in chunks, and there were often significant delays between the recall of different "chunks." These results point strongly to the presence of stored dream memories which cannot be readily accessed on awakening and further suggests both qualitative and quantitative alterations in basic memory processes during and after dreaming (Stickgold 1998; Stickgold et al. 1997a).

All of the above findings can be regarded as being caused by the failure of recent episodic memory (as defined by Tulving 1994) in sleep. And as we have noted, recent episodic memory is weak across wake-sleep and sleep-wake transitions as well as within sleep itself (Pace-Schott et al. 1997b). We believe that a deficiency of memory in dreaming may go a long way toward explaining such distinctive and robust dream phenomena as orientational instability, loss of self-reflective awareness, and failure of directed thought and attention.

2.3.5. Type I versus Type II statistical analyses. In analyzing studies of dream mentation, it is important to understand the nature of the statistical tests employed. In general, such tests calculate the probability that a specific null hypothesis – normally that there is no difference between two population samples – is or is not true. The most common statistical tests, that is, Student's t-test and ANOVA, measure Type I error, which determines the probability that the obtained results could be explained by the null hypothesis. When the probability is sufficiently low, normally less than 0.05, the null hypothesis is rejected and one concludes that the populations are different. Such analyses, however, provide no information on whether or not the null hypothesis is true. Thus, while a low p-value provides strong evidence that the null hypothesis is false, a high p-value does not necessarily indicate that it is true.

This is relevant to the conclusion of both of the papers we critiqued above. Antrobus (1983) concluded that "the global judgment of Dreaming adds little, if anything, to Total Recall Content with respect to the association with the sleep stages REM and NREM" (p. 567), although his statistics did confirm a significant contribution ($F(1,71) = 15.9$, $p < 0.01$). Nevertheless, this conclusion formed the basis of the wider interpretation that the differences between REM and NREM reports are merely a consequence of enhanced recall in REM.

In the second paper critiqued, Foulkes and Schmidt (1983) concluded that global discontinuity "is stage-invariant [and] *never* significantly discriminated reports from different stages of sleep, even in length-uncontrolled comparisons" (p. 277). Although this was true, it was also true that sleep onset reports contained 2.3 times more global discontinuity than NREM reports, a ratio that increased to more than 3 to 1 when normalized for report length (measured in "temporal units"), a fact that could lead to a conclusion quite different from the one drawn by the authors.

It thus appears premature to conclude, based on these early studies, that robust differences between REM and NREM sleep mentation do not exist. Until studies are carried out that measure Type II error and determine the likelihood that the null hypothesis is correct, it is only safe to say that these studies have failed to demonstrate either the presence or absence of differences between REM and NREM mentation. Under the circumstances, more recent studies reporting the presence of significant differences would appear more easily interpreted.

2.3.6. The need for new approaches. The conclusion that we draw from all these studies is that there are significant differences between the formal aspects of the states of consciousness associated with waking, NREM, and REM sleep. These differences, which are quantitative not qualitative, have not yet been adequately characterized for a variety of methodological reasons. Instead of continuing to argue over this issue, we urge our colleagues to join us in a more creative attempt to capture and measure the dimensions of conscious experience.

Basing the attempt to characterize dreaming solely on verbal reports of the poorly recalled subjective experience of subjects sleeping in unfamiliar, non-natural settings has led, not surprisingly, to a sterile and nonproductive controversy about whether the conscious correlates of waking, NREM sleep, and REM sleep are more similar or different, and to a very unfortunate split in what was once a unified field.

This mind-brain split is akin to the gulf that opened between psychiatry and neurology after Sigmund Freud abandoned the goals of his brain-based Project for a Scientific Psychology and declared brain science off limits to his psychology. To reunify two approaches that belong together, we call for a new neuropsychology of conscious states that integrates from the level of cellular-molecular events to the formal features of the mental states of which they form the substrate.

3. The cognitive neuroscience of waking, sleeping, and dreaming

We now turn our attention to the shifts in activation level, input-output gating processes, and the neuromodulatory balance of the brain that underlie the ultradian REM/NREM cycle in humans and in animals. We first enumerate the profound physiological differences that distinctively differentiate waking, NREM, and REM sleep and show that these differences are as robust as those shown above in the phenomenology of waking, sleeping, and dreaming. Then, we point out relationships between the physiological and phenomenological changes seen as the brain-mind shifts from one state to another, as a prelude to integrative modeling. Our overarching hypothesis is that for each phenomenological difference seen between conscious states it is possible to identify a specific physiological counterpart. The end result is a first approximation of a cognitive neuroscience of brain-mind states.

3.1. Recent findings in human neurobiology

3.1.1. Neuroimaging studies. The experimental study of human REM sleep dreaming has until recently 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 us to analyze and compare REM sleep physiology with that of waking in an effective way. This limitation has probably helped reinforce the erroneous idea that the brain activation of REM sleep and waking are identical or at least, very similar. However, recent technological advances in the field of human brain imaging have made it possible to document a highly selective regional activation pattern of the brain in REM sleep (Braun et al. 1997; 1998; Maquet et al. 1996; Nofzinger et al. 1997). At the same time, experiments of nature – in the form of strokes – have allowed a correlation of the locale of brain lesions with deficits or accentuations of dream experience in patients (Doricchi & Violani 1992; Solms 1997a).

Before discussing these intriguing new results, it is important to stress the methodological limitations of both the brain lesion and imaging techniques. We know from our long and relevant experience in basic sleep research that neither method can capture many significant mechanistic and functional details that emerge from cellular and molecular level neurophysiology (see Hobson et al. 1986 and Steriade & Hobson 1976 for a full discussion of these issues). For example, it is now clear that the lesion method, applied to the pontine brain stem, gave misleading results regarding both the general role of that region in state control and failed even to hint at the specific functions of its subcomponent nuclei. This is because the lesion method cannot discriminate between the effects of destruction and disconnection and cannot target specific neuronal groups in heterogeneous regions like the brain stem.

It is important to note that the preliminary regional functional neuroimaging studies that we review below suffer from such unavoidable limitations of new technologies as the following (see Rauch & Renshaw 1995 for a more complete discussion). First, one must consider whether or not more efficient functioning of an area might result in less versus more observed metabolism or whether glucose or oxygen uptake by inhibitory interneurons may produce local maxima in areas that are, in fact, less active due to inhibition. Second, there are statistical problems inherent in the small sample sizes used in some of these sleep studies (e.g., Braun et al. 1998; Nofzinger et al. 1997) as well as the repeated comparisons employed by the statistical parametric mapping technique (Friston et al. 1991), which is used by all these investigators. Third, global activation measures like electroencephalographic voltage averaging or cerebral blood flow cannot be expected to reveal mechanistic and functional details because they cannot identify small but influential neuronal populations like the locus coeruleus, the raphe nuclei and the pedunculopontine tegmental nucleus. Fourth, there is the potential of altered sleep physiology due to the sleep deprivation (Maquet et al. 1996) or REM deprivation (Braun et al. 1997; 1998) procedures used to maximize sleep stability and stimulate REM in these studies. And fifth, the functional activity of a brain area may vary with changes in its inputs as most dramatically illustrated by neuroplasticity involving recruitment of dedicated brain areas to subserve new modalities such as the visual cortex in Braille learning (e.g., Pascual-Leone 1999) or the reorganization of visual association cortex following V1 damage (e.g., Baeseler et al. 1999). Additionally, it is possible that normal functional disconnections, as occurs between V1 and visual association cortices in REM (Braun et al. 1998), result in the same neural structures performing differing, state-specific functional tasks.

In spite of these caveats, the widespread use of this tech-

nology and the broad agreement of the data with clinical neuropsychological findings argues strongly for the basic validity of neuroimaging as a tool in cognitive neuroscience (Cabeza & Nyberg 1997; 2000). Specifically in response to the fifth caveat above, strong suggestion that the functions of specific brain areas are similar between REM and wake is provided by the observable enactment of experienced dream movement in the REM sleep behavior disorder (Schenck et al. 1993). Moreover, wake-like function of regional brain areas is preserved in many abnormal states such as focal motor activity during seizures (Adams et al. 1997) or the recruitment of visual association cortex during visual hallucinations (Ffytche et al. 1998; Silbersweig et al. 1995). In future sleep research, many of these limitations may be overcome by the finer temporal and spatial resolution offered by functional MRI (fMRI) imaging (e.g., Ellis et al. 1999; Huang-Hellinger et al. 1995; Ives et al. 1997; Sutton et al. 1996; 1997; 1998; Lovblad et al 1999).

Our review of this new literature is undertaken with these shortcomings in mind. Three factors weighed heavily in our evaluation of these data: (1) their novelty and uniqueness in beginning to describe the role of forebrain subsystems; (2) the surprising concordance in the neuroimaging results that emerged from studies carried out simultaneously by three independent groups; and (3) the complementarity between the lesion and imaging studies that confer the value of a double dissociation on the validity of the inferences drawn.

3.1.2. PET studies indicating regional activation differences between REM sleep and waking. Two very recent and entirely independent PET studies confirm the importance of the pontine brain stem in REM sleep brain activation (Braun et al. 1997; Maquet et al. 1996). 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 has been suggested by EEG studies, all of these new imaging studies indicate a preferential activation of limbic and paralimbic regions of the forebrain in REM compared to waking (Braun et al. 1997; 1998; Maquet et al. 1996; Nofzinger et al. 1997). One implication of these discoveries is that dream emotion may be a primary shaper of dream plots rather than playing a secondary role in dream plot instigation.

3.1.2.1. The PET imaging findings of the Maquet group. Maquet et al. (1996) used an $H_2{}^{15}O$ positron source to study REM sleep activation in their subjects who were then 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 2). Significantly, despite the general deactivation in much of the parietal cortex, Maquet et al. (1996) reported activation of the right inferior parietal lobe (Bredman area 40) – a brain region thought to be important for spatial imagery construction, an important aspect of dream cognition. The authors interpreted their data in terms of the selective processing, in REM, of emotionally influenced memories (see also Braun et al. 1997; Maquet & Franck 1997).

3.1.2.2. The PET imaging findings of the Braun group. In another $H_2{}^{15}0$ PET study, Braun et al. (1997) largely replicated the Maquet group's findings of a consistent REM-related brainstem, limbic, and paralimbic activation. In REM compared *individually* to delta NREM and to pre- and post-sleep waking (see Table 2), these authors showed relative activation of the pons, midbrain, anterior hypothalamus, hippocampus, caudate, and medial prefrontal, caudal orbital, anterior cingulate, parahippocampal, and inferior temporal cortices (Braun et al. 1997). Based on their observations, the Braun group then offered the following speculations which are relevant to the neurology of dreaming:

(1) Ascending reticular activation during REM as compared to waking may favor a more ventral cholinergic route leading from the brainstem to the basal forebrain over a more dorsal route via the thalamus.

(2) Activation of the cerebellar vermis in REM may reflect input to this structure from the brainstem vestibular nuclei. We note that these nuclei also constitute an important potential source of neuronal activation causing the unique vestibular features of fictive movement in dreams (Hobson et al. 1998c; Leslie & Ogilvie 1996; Sauvageau et al. 1998).

(3) Noting both a particularly strong REM sleep-related activation of the basal ganglia and the known connectivity of these subcortical structures, Braun et al. suggest that the basal ganglia may play an important role in an ascending thalamocortical activation network. They suggest that this network extends successively from the brainstem to the intralaminar thalamic nuclei, then to the basal ganglia, and back to the ventral anterior and ventromedial thalamic nuclei, and thence to the cortex.

This network contains multiple regulatory back projections including interconnections between the pedunculopontine tegmentum and the striatum further suggesting a possible role for the basal ganglia in the rostral transmission of PGO waves and the modulation of REM sleep phenomena. The extensive interconnections of the basal ganglia and the pedunculopontine area have recently been reviewed by Rye (1997) and Inglis and Winn (1995). The role of the basal ganglia in the initiation of motor activity may, in turn, be related to the ubiquity of motion in dreams (Hobson 1988b; Porte & Hobson 1996).

(4) The REM-associated increase in activation of unimodal associative visual (Brodmann areas 19 and 37) and auditory (Brodmann area 22) cortices contrasted with the maintained (NREM and REM) sleep-related deactivation of heteromodal association areas in the frontal and parietal cortex. Combined with findings of striate cortex deactivation in REM, this group (Braun et al. 1998) has subsequently theorized that, during REM, internal information is being processed between extrastriate and limbic cortices while they are functionally isolated from the external world both in terms of input (from the striate cortex) and output (via the frontal cortex).

(5) The prominent decrease in the executive portions of the frontal cortex (dorsolateral and orbital prefrontal cortices) contrasts with the REM-associated increase in activation of the limbic associated medial prefrontal area. This medial area region has the most abundant limbic connections in the prefrontal cortex, has been associated with arousal and attention, and disruption of this area has been shown to cause confabulatory syndromes formally similar to dreaming. (Note also the dream-wake confusional syndrome associated with anterior limbic cortical lesions reported by Solms 1997a.)

3.1.2.3. The PET imaging findings of the Nofzinger group. Also confirming widespread limbic activation in REM

sleep, Nofzinger et al. (1997) described increased glucose utilization in the lateral hypothalamic area and the amygdaloid complex using an 18F-fluoro-deoxyglucose (FDG) PET technique (Table 2). The largest area of activation was, in their own words, " . . . an extensive confluent area along the midline that includes the lateral hypothalamic area, septal area, ventral striatum-substantia innominata, infralimbic cortex, prelimbic and orbitofrontal and the anterior cingulate cortex . . . Much of this is bilateral" (p. 198). The authors suggest that an important function of REM sleep is the integration of neocortical function with basal forebrain and hypothalamic motivational and reward mechanisms.

3.1.3. Selective deactivation of the dorsolateral prefrontal cortex in REM sleep. Relevant to the cognitive deficits in self-reflective awareness, orientation, and memory during dreaming was the $H_2{}^{15}O$ PET finding of significant deactivation, in REM, of a vast area of dorsolateral prefrontal cortex (Braun et al. 1997; Maquet et al. 1996). A similar decrease in cerebral blood flow to frontal areas during REM has been noted by Madsen et al. (1991a) using single photon emission computed tomography (SPECT) and by Lovblad et al. (1999) using fMRI. Dorsolateral prefrontal deactivation during REM, however, was not replicated by an FDG PET study (Nofzinger et al. 1997) and this discrepancy, therefore, remains to be clarified by other FDG as well as $H_2{}^{15}O$ studies. (A potential cause of this discrepancy arising from differences between FDG and $H_2{}^{15}O$ methods is discussed further in sect. 3.3.5.2.)

Nevertheless, it seems likely that considerable portions of executive and association cortex active in waking may be far less active in REM, leading Braun et al. (1997) 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" (p. 1190).

Taken together, these results 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 is associated with selective activation of the subcortical and cortical limbic structures (which mediate emotion) and with relative inactivation of the lateral prefrontal cortex (which mediates directed thought). 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.

The Maquet et al. (Maquet et al. 1996; Maquet & Franck 1997), Nofzinger et al. (1997), and Braun et al. (1997) groups all stress that their findings suggest assigning REM sleep a role in the processing of emotion (along with its cognitive and autonomic correlates) in memory systems via a limbic-cortical interplay. Additionally, PET researchers suggest the possible origin of dream emotionality in REM-associated limbic activation (Braun et al. 1997; Maquet & Franck 1997) and dream-associated executive deficiencies in REM-associated frontal deactivation (Braun et al. 1997; Maquet & Franck 1997). Although tantalizing correlations such as: (1) limbic activation and dream emotionality, (2) dream emotionality and affect-congruent dream narratives, and (3) frontal deactivation and dream bizarreness, are now becoming apparent in the sleep and dream literature, the precise causal sequence among these phenomena remains to be established by future research.

Two additional findings support this proposed corticolimbic interaction. First, the anterior cingulate cortex has consistently shown increased activation in REM in other PET studies (e.g., Bootzin et al. 1998; Buchsbaum et al. 1989; Hong et al. 1995). Second, recent studies of human limbic structures with depth electrodes during REM sleep have shown distinctive rhythmic EEG patterns possibly related to the REM-associated hippocampal theta rhythms seen in animals (Mann et al. 1997; Staba et al. 1998). Human frontal midline theta has also been detected using scalp electrodes (Inanaga 1998).

3.1.4. Global and regional decreases in activation level in NREM sleep. Neuroimaging studies also strongly support a distinction between REM and NREM sleep as states whose differing neuroanatomical activation patterns predict their observed phenomenological differences (Table 2). PET studies of NREM sleep generally show a decrease in global cerebral energy metabolism (i.e., O_2 or glucose utilization) relative to waking and REM (Buchsbaum et al. 1989; Heiss et al. 1985; Madsen & Vorstup 1991; Madsen et al. 1991b; 1999b; Maquet 1995; Maquet et al. 1990; 1992; 1997). The magnitude of this decline relative to waking has varied from 11% glucose utilization in stage 2 (Maquet et al. 1992) to 40% glucose utilization in stages 3 and 4 (Maquet et al. 1990). A similar pattern has usually been reported for global cerebral blood flow as measured by $H_2{}^{15}O$ PET, SPECT, near infrared spectroscopy or a modification of the Kety-Schmidt O_2 uptake technique (Braun et al. 1997; Hoshi et al. 1994; Madsen et al. 1991a; 1991b; Maquet et al. 1997; Meyer et al. 1987; Sakai et al. 1980), although some studies have failed to show this global hemodynamic change (Andersson et al. 1995; 1998; Hofle et al. 1997). In addition, cerebral energy metabolism decreases with progressively greater depth of NREM sleep (Maquet 1995) a result recently replicated with fMRI (Sutton et al. 1997). By contrast, in REM, global cerebral energy metabolism tends to be equal to (Asenbaum et al. 1995; Braun et al. 1997; Madsen et al. 1991b; Maquet et al. 1990) or greater than (Buchsbaum et al. 1989; Heiss et al. 1985) that of waking. Cerebral blood flow velocity measured in the middle cerebral artery similarly shows a slowing during NREM followed by values similar to waking during REM (Droste et al. 1993; Haiak et al. 1994; Klingelhofer et al. 1995; Kuboyama et al. 1997).

More striking than global patterns are the now well-replicated regional variations in cerebral energy metabolism over the wake-NREM-REM sleep cycle (Table 2). Earlier studies showing specific declines in thalamic glucose utilization in NREM relative to waking (Buchsbaum et al. 1989; Maquet et al. 1990; 1992) have been confirmed by recent oxygen utilization studies (Andersson et al. 1998; Braun et al. 1997; Hofle et al. 1997; Maquet et al. 1997). In addition to prominent thalamic deactivation, all three recent studies have found regional deactivation during NREM in the pontine brain stem, orbitofrontal cortex, and anterior cingulate cortex (Braun et al. 1997; Hofle et al. 1997; Maquet et al. 1997). NREM deactivation of lateral prefrontal cortex was also observed in some studies (Andersson et al. 1998; Braun et al. 1997). Thalamic activation was found to decline significantly concomitant with increased delta EEG activity and there was an additional decline associated with increased spindle-frequency activity when the decrements associated with delta were subtracted (Hofle et al. 1997). (For a very recent review see Maquet 2000.)

Table 2. *Review of relative activation of cortical and subcortical areas in REM and SWS noted in four recent PET studies (from Hobson 1998a; 2000)*

SLEEP STAGE	REM	REM	REM	REM	NREM (3&4)	NREM (delta)	NREM (3&4)
STUDY	Maquet et al. 1996	Nofzinger et al. 1996	Braun et al. 1997	Braun et al. 1997	Maquet et al. 1997	Hofle et al. 1997	Braun et al. 1997
TECHNIQUE	$H_2{}^{15}O$	^{18}FDG	$H_2{}^{15}O$	$H_2{}^{15}O$	$H_2{}^{15}O$	$H_2{}^{15}O$	$H_2{}^{15}O$
RELATIVE TO	all other stages	waking	pre- (& post*)-sleep waking	NREM 3&4	all other stages	change with increased delta	pre- or post-sleep waking
SUBCORTICAL AREAS							
brainstem							
pontine tegmentum	increase		increase (R*)	increase	decrease	decrease:R	decrease
midbrain			increase*	increase			decrease
dorsal mesencephalon	increase				decrease		
diencephalon							
thalamus	increase: L			increase	decrease	decrease: M	decrease
hypothalamus		increase: R, Lat.	increase: A-POA	increase: A-POA	decrease		decrease: A-POA
basal forebrain					decrease		
limbic system							
left amygdala	increase	increase					
right amygdala	increase						
septal nuclei		increase					
hippocampus			increase*	increase			
basal ganglia/striatum							
caudate		increase: A, I, L	increase*	increase	decrease		decrease
putamen				increase			decrease: P
ventral striatum (n. accumbens, sub.innominata)		increase		increase			decrease
lenticular nuclei					decrease		
cerebellum			incr. (vermis)*	increase (vermis)		decrease	decrease: I

SLEEP STAGE	REM	REM	REM	REM	NREM (3&4)	NREM (delta)	NREM (3&4)
STUDY	Maquet et al. 1996 $H_2{}^{15}O$	Nofzinger et al. 1996 ^{18}FDG	Braun et al. 1997 $H_2{}^{15}O$	Braun et al. 1997 $H_2{}^{15}O$	Maquet et al. 1997 $H_2{}^{15}O$	Hofle et al. 1997 $H_2{}^{15}O$	Braun et al. 1997 $H_2{}^{15}O$
TECHNIQUE RELATIVE TO	all other stages	waking	pre or post-sleep waking	NREM 3&4	all other stages	change with increase delta	pre or post-sleep waking
CORTICAL AREAS							
FRONTAL		decrease: L, small areas increase: R					
dorsolateral prefrontal	decrease: L: 10,11,46,47 R: 8,9,10,11,46	increase	decrease: 46*				decrease: 46
opercular			decrease: 45*				decrease: 45
paraolfactory		increase					
lateral orbital		increase: 11,12	decrease: 11*		decrease: 11,25	decrease: R 11	decrease: 11
medial orbital							decrease: R
caudal orbital			increase	increase			decrease
gyrus rectus		increase					
PARIETAL							
Brodmann area 40 (supramarginal gyrus)	increase: R A 40 decrease: L 40		decrease: 40*			increase: L 40	decrease: 40
angular gyrus			decrease: 39*				decrease: 39
precuneus	decrease				decrease: 7		
cuneus					decrease: 19		
pericentral						increase: L 3/4	
TEMPORAL							
mesiotemporal					decrease: R 28		
middle		increase R				incr: A R,L 21	
posterior superior				increase: 22		increase: L 22	
inferior/fusiform			increase: 37,19 (post-sleep only)	increase 37,19			
OCCIPITAL		decrease: L, small areas					
medial						incr: R 17/18 incr: L 17	
post-rolandic sensory			increase				
LIMBIC ASSOCIATED							
medial (prelimbic) prefrontal		increase: R 32	increase: 10	increase: 10			decrease: 10
anterior cingulate	increase: 24	increase: 24	increase: 32*	increase: 32	decrease: 24,32	decrease: 24/32	decrease: 32
posterior cingulate	decrease: 31	dec.: R sm. areas	decrease*				
infralimbic		increase: 25					
insula		increase: L	decrease: P	increase: A I			decrease: A
parahippocampal		increase	increase: 37*	increase: 37			
entorhinal	increase	increase (in fusiform)					
temporal pole				increase: 38			decrease: 38

Abbr: L-left hemisphere; R-right hemisphere; A-anterior; P-posterior; C-caudal; M-medial; Lat.-lateral; I-inferior; S-superior; A-POA-anterior preoptic area; all numerals = Brodmann's area; sm.-small, dec.-decrease, inc.-increase.

Hofle et al. (1997) and Maquet et al. (1997) both interpret this pattern of decline as reflecting the progressive deactivation of the reticular activating system (RAS) that accompanies deepening NREM sleep. This deactivation leads to dysfacilitation of thalamocortical relay neurons, which allows the emergence of underlying thalamocortical oscillatory rhythms (Steriade & McCarley 1990a; Steriade et al. 1993a; 1993b; 1993c; 1993d; 1994; for recent reviews see Steriade 1997; 1999; 2000). GABAergic neurons of the thalamic reticular nucleus then further hyperpolarize and dysfacilitate thalamic relay neurons as NREM deepens (Steriade et al. 1994). In this hyperpolarized condition, thalamic neurons become constrained to burst firing patterns first in spindle (12–14 Hz) and later in delta (1–4 Hz) frequencies as NREM deepens from Stage 2 to delta sleep (Steriade et al. 1993a; 1993d). The cortex may further constrain these spindle and delta-wave-generating thalamocortical bursts within a newly described slow (<1 Hz) oscillation seen in cats (Steriade et al. 1993a; 1993b; 1993c; 1993d) and humans (Achermann & Borbely 1997). In conclusion, the metabolic decline seen during NREM is centered on the central core structures (brain stem, thalamus) which are known to play a role in generation of the slow oscillations of NREM sleep (Maquet 2000; Maquet et al. 1997).

The regional pattern of deactivation in NREM, therefore, sharply contrasts with the regional *activation* of these same regions (i.e., thalamus, pontine brain stem, anterior cingulate cortex) in REM (Braun et al. 1997; Maquet et al. 1996; Nofzinger et al. 1997). Details of these stage-related differences are shown in Table 2. Note that a recent cat study has shown a similar pattern of brain glucose metabolism in REM (Lydic et al. 1991a).

3.1.5. Interpreting the PET imaging results with respect to the psychophysiology of dreaming. According to PET researchers, regional activation during REM may reflect a specific activation of subcortical and cortical arousal and limbic structures for the adaptive processing of emotional and motivational learning (Maquet et al. 1996; Nofzinger et al. 1997). Such processing may, in turn, account for the emotionality and psychological salience of REM dreaming (Braun et al. 1997). Some support for this comes from a PET (glucose) study showing correlation between content-analyzed dream anxiety and medial frontal activation (Gottschalk et al. 1991a).

In summary, the markedly differing physiology of wake, NREM, and REM cerebral activation should be reflected in the respective phenomenology of mentation reported from these three conscious states. More particularly, the specific phenomenology of REM mentation may reflect the neurobiologically specific brain activation pattern. Nofzinger et al. (1997) conclude that "the current findings of increased limbic and paralimbic activation during REM sleep . . . as well as global, regionally nonselective cortical deactivation and decreased metabolism during NREM sleep, are generally supportive of the traditional notion that more story-like affect-laden dreams are more attributable to the REM sleep, than NREM sleep behavioral state" (p. 199).

3.1.6. Brain lesions resulting in loss or alteration of dreaming.

3.1.6.1. Solms's nosology for lesion-related disorders of dreaming. A set of findings and conclusions which have proved remarkably complementary to the neuroimaging results have been reached following a neuropsychological survey of 332 clinical cases of cerebral lesions as well as a review of 73 extant publications on the dreaming-related sequelae of cerebral injury (Solms 1997a). Using these welcome and long overdue neuropsychological data, Solms proposes a new nosology for the brain-lesion related disorders of dreaming.

In one syndrome, "global anoneria," total cessation of dreaming in patients (whose normal waking vision is preserved) results from either posterior cortical or deep bilateral frontal lesions. The posterior global anoneria syndrome results from lesions of the inferior parietal lobes in either hemisphere, with lesions to Brodmann's areas 39 and 40 being the most restricted damage sufficient to produce the syndrome. The anterior variant of global anoneria results from deep medial frontal damage resulting in the disconnection of the mediobasal frontal cortex from the brain stem and diencephalic limbic regions. In this syndrome, bilateral damage to white matter in the vicinity of the frontal horns of the lateral ventricles was the most restricted site causing the syndrome.

The nosological distinction of a second syndrome, non-visual dreaming, from syndromes of global cessation of dreaming, was first systematically formulated by Doricchi and Violani (1992). In this syndrome, termed "visual anoneria" by Solms (1997a), bilateral medial occipito-temporal lesions produce full or partial loss of dream visual imagery (again with normal waking vision). Among his own patients, 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 V3, V3a, and V4 but not V1, V5, or V6). Notably, a correlate of visual anoneria was visual irreminiscence, the inability to produce mental imagery in waking. In addition, partial variants of visual anoneria exist which involve selective loss of particular visual elements (e.g., "kinematic anoneria" or "facial anoneria").

In addition to these two disorders of attenuated dreaming, Solms reported another interrelated pair of symptom complexes that combined increased frequency and intensity of dreaming. He suggested that increased vivacity and frequency of dreaming was associated with anterior limbic lesions while recurring nightmares are associated with temporal seizures.

3.1.6.2. Conclusions suggested by convergent PET and lesion findings. We believe that these findings map particularly well onto the neuroimaging findings on REM. For example, extrastriate visual cortex is activated during REM (Braun et al. 1997; 1998) and lesions to this region produce the distinctive dream deficits of full or partial visual anoneria (Solms 1997a). In contrast, the striate visual cortex is deactivated during REM (Braun et al. 1998) while lesions to this region do not affect dreaming (Solms 1997a). Similarly, the seat of spatial cognition in the inferior parietal cortex (BA 40) is activated in the right (but not the left) hemisphere during REM (Maquet et al. 1996) while damage to this region, especially on the right, is sufficient to produce global anoneria (Solms 1997a). Moreover, much of the lateral prefrontal area is deactivated during REM (Braun et al. 1997; Maquet et al. 1996), while lesions to this region do not affect dreaming (Doricchi & Violani 1992; Solms 1997a).

Two exceptions to this general correspondence involve lesions of the brainstem (for which Solms reports no attenuation of dreaming) and lesions of the rostral limbic system (for which Solms reports an accentuation of dreaming). In

the case of pontine lesions, we suggest that any lesion capable of destroying the pontine REM sleep generator mechanism would have to be so extensive as to eliminate consciousness altogether. We base this caveat upon the difficulty of suppressing REM by experimental lesions of the pons in animals. In the case of the rostral limbic system, we caution that lesions there could as well be irritative as destructive and that lesions in different areas of this functionally highly heterogeneous region (Devinsky et al. 1995) could produce dramatically different effects.

3.2. Reciprocal interaction: A neurobiological update

The discovery of the ubiquity of REM sleep in mammals provided the brain side of the brain-mind state question with an animal model (Dallaire et al. 1974; Dement 1958; Jouvet & Michel 1959; Jouvet 1962; 1999; Snyder 1966). 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 concept of a brain stem reticular activating system (Moruzzi & Magoun 1949) required extension and modification to account for the differences between the behavioral and subjective concomitants of waking and those of REM sleep (see Hobson & Brazier 1981).

3.2.1. Implications for dream theory. We take the theoretical position that it is the cellular and molecular level brain events to be discussed that bias the brain to produce the conscious state differences that contrast waking, NREM, and REM sleep. As we will point out in detail in section 4 when we develop the AIM model, the shift from aminergic dominance in waking to cholinergic dominance in REM lowers the probability that consciousness will be exteroreceptive, logical, and mnemonic while correspondingly raising the probability that consciousness will be interoceptive, illogical, and amnesic.

3.2.2. Behavioral state-dependent variations in neuromodulation. A conceptual breakthrough was made possible by the discovery of the chemically specific neuromodulatory subsystems of the brain stem (e.g., Dahlstrom & Fuxe 1964; for reviews see Foote et al. 1983; Gottesmann 1999; Hobson & Steriade 1986; Hobson et al. 1998; Jacobs & Azmita 1992; Lydic & Baghdoyan 1999; Mallick & Inoue 1999; Rye 1997; Steriade & McCarley 1990a) and of their differential activity in waking (noradrenergic and serotonergic systems on, cholinergic system damped) and REM sleep (noradrenergic and serotonergic systems off, cholinergic system undamped) (Aston-Jones & Bloom 1981; Cespuglio et al. 1981; Chu & Bloom 1973; 1974; Hobson et al. 1975; Jacobs 1986; Lydic et al. 1983; 1987; McCarley & Hobson 1975; McGinty & Harper 1976; Rasmussen et al. 1986; Reiner 1986; Steriade & McCarley 1990a; Trulson & Jacobs 1979).

3.2.2.1. The original reciprocal interaction model: an aminergic-cholinergic interplay. The model of reciprocal interaction (McCarley & Hobson 1975) 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. 2). The reciprocal interaction hypothesis (McCarley & Hobson 1975) provided a description of the aminergic-cholinergic interplay at the

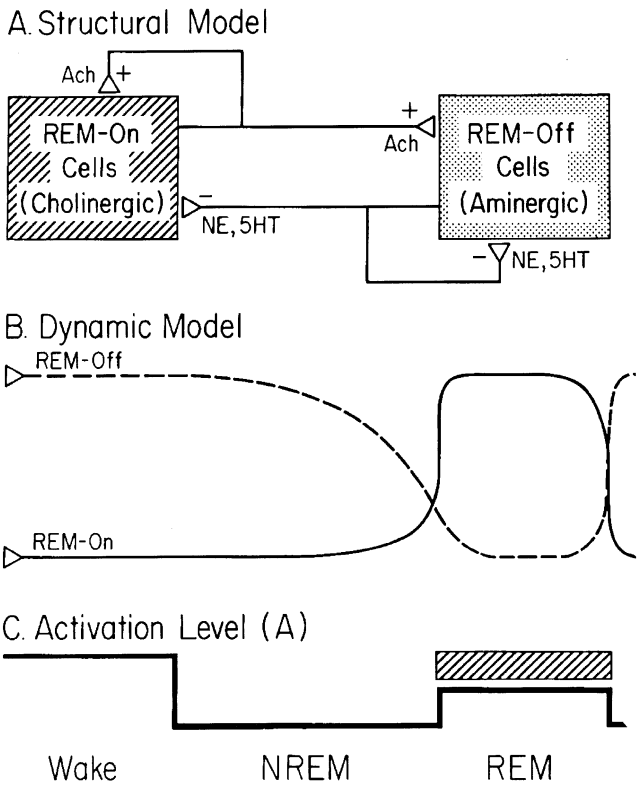


Figure 2. The original Reciprocal Interaction Model of physiological mechanisms determining alterations in activation level. A: Structural model of Reciprocal Interaction. REM-on cells of the pontine reticular formation are cholinoceptively excited and/or cholinergically excitatory (ACH+) at their synaptic endings. Pontine REM-off cells 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 (A) is at equally high levels in waking and REM sleep and at about half this peak level in NREM sleep. (Taken from Hobson 1992a.)

synaptic level and a mathematical analysis of the dynamics of the neurobiological control system (Figs. 2 and 3A). In this section we review subsequent work that has led to the alteration (Fig. 3B) and elaboration (Fig. 4) of the model.

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 Datta 1995; 1997b; 1999; Hobson 1992b; Hobson et al. 1993; Lydic & Baghdoyan 1999; Rye 1997), not all pontine PPT and LDT neurons are cholinergic (Kamodi et al. 1992; Kang & Kitai 1990; Leonard & Llinas 1990; 1994; Sakai & Koyama 1996; Steriade et al. 1988) and cortical acetylcholine release may be as high during wakefulness as during sleep (e.g., Jasper & Tessier 1971; Jimenez-Capdeville & Dykes 1996; Marrosu et al. 1995).

Recently, reciprocal interaction (McCarley & Hobson 1975) and reciprocal inhibition (Sakai 1988) models for control of the REM sleep cycle by brain stem cholinergic

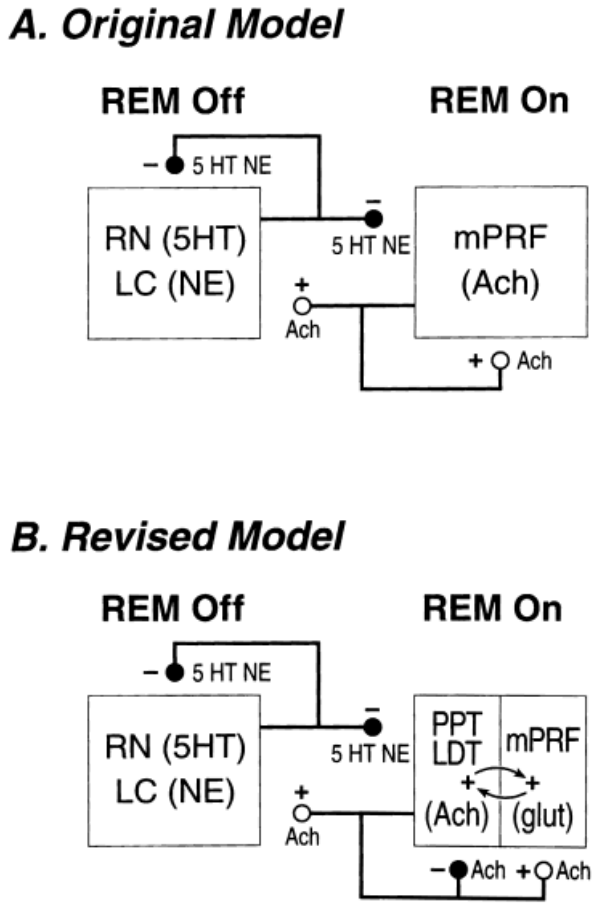


Figure 3. Synaptic modifications of the original reciprocal interaction model based upon recent findings. A: The original model proposed by McCarley and Hobson (1975) and detailed in Figure 2. B: Synaptic modifications of the original reciprocal interaction model based upon recent findings of self-inhibitory cholinergic autoreceptors in mesopontine cholinergic nuclei and excitatory interactions between mesopontine cholinergic and noncholinergic neurons (see Fig. 4 for more detail and references). Note that the exponential magnification of cholinergic output predicted by the original model (Fig. 2) can also occur in this model with mutually excitatory cholinergic-noncholinergic interactions taking the place of the previously postulated, mutually excitatory cholinergic-cholinergic interactions. In the revised model, inhibitory cholinergic autoreceptors would contribute to the inhibition of LDT and PPT cholinergic neurons, which is also caused by noradrenergic and serotonergic inputs to these nuclei. Therefore the basic shape of reciprocal interaction's dynamic model (illustrated in Fig. 2B) and its resultant alternation of behavioral state (illustrated in Fig. 2C) could also result from the revised model. *Abbreviations:* open circles, excitatory postsynaptic potentials; closed circles, inhibitory postsynaptic potentials; RN, dorsal raphe nucleus; LC, locus coeruleus; mPRF, medial pontine reticular formation; PPT, pedunculopontine tegmental nucleus; LDT, laterodorsal tegmental nucleus; 5HT, serotonin; NE, norepinephrine; Ach, acetylcholine; glut, glutamate.

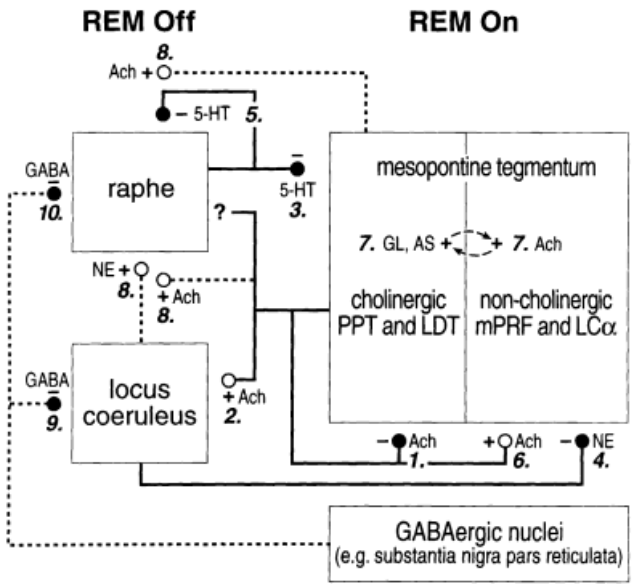


Figure 4. Additional synaptic details of the revised reciprocal interaction model shown in Figure 3B derived from data reported (solid lines) and hypothesized relationships suggested (dotted lines) in recent experimental studies (numbered on Figure and below). See text for discussion of these findings. Additional synaptic details can be superimposed on the revised reciprocal interaction model without altering the basic effects of aminergic and cholinergic influences on the REM sleep cycle. 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. 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). 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. *Abbreviations:* open circles, excitatory postsynaptic potentials; closed circles, inhibitory postsynaptic potentials; mPRF, medial pontine reticular formation; PPT, pedunculopontine tegmental nucleus; LDT, laterodorsal tegmental nucleus; LCα peri-locus coeruleus α; 5HT, serotonin; NE, norepinephrine; Ach, acetylcholine; GL, glutamate; AS, aspartate; GABA, gamma-aminobutyric acid. *References:* (1) Baghdoyan et al. 1997; El Manseri et al. 1990; Kodama & Honda 1996; Leonard & Llinas 1990; 1994; Luebke et al. 1993; Roth et al. 1996; Sakai & Koyama 1996; Sakai et al. 1990. (2) Egan & North 1985; 1986b. (3) Horner et al. 1997; Leonard & Llinas 1994; Luebke et al. 1992; Thakkar et al. 1997. (4) Sakai & Koyama 1996. (5) Portas et al. 1996. (6) Sakai & Koyama 1996; Sakai & Onoe 1997; Vanni-Mercier et al. 1989; Yamamoto et al. 1990a; 1990b. (7) Greene & McCarley 1990; Leonard & Llinas 1994; Sakai & Koyama 1996. (8) Li et al. 1997. (9) Nitz & Siegel 1997; Datta 1997b; Datta et al. 1991. (10) Porkka-Heiskanen et al. 1997a (from Hobson et al. 1998b).

and aminergic neurons have been questioned (Leonard & Llinas 1994). Specifically, the self-stimulatory role of acetylcholine on pontine PGO-bursting neurons has not been confirmed in *in vitro* slice preparations (Leonard & Llinas 1994). For example, ACh has been shown to hyperpolarize cell membranes in slice preparations of the rodent parabrachial nucleus (Egan & North 1986a), LDT (Leonard & Llinas 1994; Luebke et al. 1993), and PPT (Leonard & Llinas 1994). 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 (Leonard & Llinas 1990). 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 (Fig. 3B).

3.2.2.2. New findings supporting the cholinergic enhancement of REM sleep. Numerous findings confirm the hypothesis that cholinergic mechanisms are essential to the generation of REM sleep and its physiological signs (for recent reviews see Capece et al. 1999; Datta 1995; 1997;1999; Gottesmann 1999; Hobson 1992b; Hobson et al. 1986; 1993; Hobson & Steriade 1986; Lydic & Baghdoyan 1999; Jones 1991; 1998; Mallick & Inoue 1999; McCarley et al. 1995; 1997; Rye 1997; Sakai 1988; Semba 1999; Steriade & McCarley 1990a). A selection of the many recent examples follows:

1. Microinjection of cholinergic agonist or cholinesterase inhibitor into many areas of the paramedian pontine reticular formation induces REM sleep (Baghdoyan et al. 1987; 1989; Hobson et al. 1993; Vanni-Mercier et al. 1989; Velazquez-Moctezuma et al. 1989; 1991; Yamamoto et al. 1990a; 1990b). 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 (Calvo et al. 1992; Datta et al. 1992; 1993).

2. Cholinergic (type II and III) PPT and LDT neurons have firing properties which make them well suited for the tonic maintenance of REM (Leonard & Llinas 1990).

3. PGO input to the LGB is cholinergic (Steriade et al. 1988) and can be antidromically traced to pontine PGO-burst neurons (Sakai & Jouvet 1980). Retrograde tracers injected into the thalamus label 50% or more of cholinergic PPT/LDT neurons (Oakman et al. 1999; Rye 1997). Moreover, stimulation of mesopontine neurons induces depolarization of cortically projecting thalamic neurons (Curro-Dossi et al. 1991).

4. PGO waves can be blocked by cholinergic antagonists (Hu et al. 1989) and neurotoxic lesions of pontomesencephalic cholinergic neurons reduce the rate of PGO spiking (Webster & Jones 1988).

5. PPT and LDT neurons show specifically c-fos and fos-like immunoreactivity following carbachol-induced REM sleep (Shiromani et al. 1995; 1996).

6. Low amplitude electrical stimulation of the LDT enhances subsequent REM sleep (Thakkar et al. 1996).

7. Electrical stimulation of the cholinergic LDT evokes excitatory post synaptic potentials (EPSPs) in pontine reticular formation neurons which can be blocked by scopolamine (Imon et al. 1996).

8. The excitatory amino acid, glutamate, when microinjected into the PPT dose-dependently increases REM sleep (Datta 1997a; Datta & Siwek 1997).

9. Microdialysis studies showed enhanced release of endogenous acetylcholine in the medial pontine reticular formation during natural (Kodama et al. 1990) and carbachol-induced (Lydic et al. 1991b) REM sleep.

10. Thalamic ACh concentration of mesopontine origin is higher in wake and REM than in NREM (Williams et al. 1994), a REM-specific increase of ACh in the lateral geniculate body has been observed (Kodama & Honda 1996), and both muscarinic and nicotinic receptors participate in the depolarization of thalamic nuclei by the cholinergic brainstem (Curro-Dossi et al. 1991).

11. Although *in vivo* cholinergic REM enhancement has been difficult to demonstrate in rats (Deurveiller et al. 1997), such enhancement has recently been reported (Datta et al. 1998; Marks & Birabil 1998) and a specific carbachol-sensitive site in the dorsal locus subcoeruleus of rats has recently been described (Datta et al. 1998). Moreover, rats that are genetically supersensitive to ACh show enhanced REM sleep (Benca et al. 1996).

12. The new presynaptic anticholinergic agents have been shown to block REM (Capece et al. 1997: Salin-Pascual et al. 1995).

13. Muscarinic activation by carbachol has been shown to increase G-protein binding in brainstem nuclei associated with REM sleep (Capece et al. 1998).

14. Cholinergic PPT neurons have now been quantitatively mapped in the human pontine brainstem (Manaye et al. 1999).

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. (For a recent review see Semba 1999.)

3.2.2.3. New findings supporting the serotonergic and noradrenergic suppression of REM sleep. But what about the essence of the theory: the idea that cholinergic REM sleep generation can only occur when the noradrenergic and serotonergic mediators of waking release their inhibitory constraint? The evidence for inhibitory serotonergic and noradrenergic influences on cholinergic neurons and REM sleep is now also quite strong. For example:

1. Serotonergic neurons have been shown to project to the LDT and PPT (Honda & Semba 1994; Steininger et al. 1997) and serotonin has been shown to hyperpolarize rat cholinergic LDT cells *in vitro* (Leonard & Llinas 1994; Luebke et al. 1992) and to reduce REM sleep percent *in vivo* (Horner et al. 1997).

2. Serotonin has been shown to counteract the REM-like carbachol-induced atonia of hypoglossal motoneurons (Kubin et al. 1994; 1996; Okabe & Kubin 1997).

3. Extracellular levels of serotonin are higher in waking than in NREM and higher in NREM than REM in the hypothalamus (Auerbach et al. 1989; Imeri et al. 1994), dorsal raphe (Portas et al. 1998) and frontal cortex (Portas et al. 1998) of rats, as well as the dorsal raphe (Portas & McCarley 1994) and medial pontine reticular formation (Iwakiri et al. 1993) of cats. And, the same pattern of extracellular serotonin concentration change over the sleep-wake cycle has recently been demonstrated in the human amygdala, hippocampus, orbitofrontal cortex, and cingulate cortex (Wilson et al. 1997).

4. Microinjection of the serotonin agonist 8-OH-DPAT into the peribrachial region impeded REM initiation in cats (Sanford et al. 1994b) and systemic injection of 8-OH-DPAT into serotonin-depleted rats also suppressed REM (Monti et al. 1994). However, localization of the serotonergic REM suppressive effect to the PPT/LDT has recently been challenged in favor of an amygdalar-pontine interaction (Morrison et al. 1999; Sanford et al. 1996; 1998b).

5. Microinjection with simultaneous unit recording has shown that 8-OH-DPAT suppresses the firing of REM-on but not REM-and-Wake-on cells of the cholinergic LDT and PPT (Thakkar et al. 1997; 1998).

6. *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 REM sleep percent (Portas et al. 1996; Thakkar et al. 1998).

7. Electrical stimulation of the pons in the vicinity of the

(noradrenergic) locus coeruleus reduced REM sleep in rats (Singh & Mallick 1996) and locus coeruleus neurons have been shown to become quiescent during REM in the monkey (Rajkowski et al. 1997).

8. The alpha-2 noradrenergic agonist clonidine suppresses REM in human subjects (Gentili et al. 1996; Nicholson & Pascoe 1991) and the cat (Tononi et al. 1991) while the noradrenergic antagonist idazoxan increases REM when injected into the pontine reticular formation of cats (Bier & McCarley 1994).

9. There is near universal suppression of REM sleep in humans by acute dosage of serotonin and norepinephrine reuptake-inhibiting antidepressants (Gaillard et al. 1994; Nicholson et al. 1989; Vogel 1975; Vogel et al. 1990).

10. Mesopontine injection of a serotonin agonist depressed ACh release in the lateral geniculate body (Kodama & Honda 1996).

It can therefore also be stated that aminergic suppression of REM sleep is now an established principle (for recent reviews see Monti & Monti 1999 and Luppi et al. 1999a; 1999b).

3.2.2.4. Modification of the original reciprocal interaction hypothesis to accommodate new findings. Modifications of simple reciprocal inhibition or interaction models, which are consonant with recent findings, have been proposed for the brain stem control of REM sleep. For example, Leonard and Llinas (1994) suggest in regard to the McCarley and Hobson (1975) 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" (p. 327). A similar mutually excitatory or mutually inhibitory interaction between REM-on cholinergic and REM-on noncholinergic mesopontine neurons has also been proposed in the cat (Sakai & Koyama 1996). Such a mechanism is depicted in Figures 3B and 4.

From recent *in vitro* studies in the rat, the following modification of reciprocal interaction has been proposed proposed by Li et al. 1997 (see Fig. 4). 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, the same presynaptic nicotinic input may facilitate serotonergic self-inhibition by raphe neurons themselves. *In vivo* microdialysis studies of GABA in the cat further suggests selective suppression of noradrenergic locus coeruleus neurons by GABAergic inhibition during REM (Nitz & Siegel 1997) as can be seen in Figure 4. Both of these modifications retain one or both of the major tenets of the reciprocal interaction model: cholinergic facilitation and aminergic inhibition of REM.

It is important to realize that many of the studies questioning reciprocal interaction or reciprocal inhibition (e.g., Egan & North 1986a; 1986b; Leonard & Llinas 1990; 1994; Luebke et al. 1993) have been carried out on *in vitro* rodent models, and the relationship of these findings to findings on the *in vivo* generation of REM sleep signs in the cat is only in its early stages (Datta 1995; Hobson et al. 1993; Sakai & Koyama 1996). Moreover, the hyperpolarization by ACh of cholinergic cells cited in these studies might be explained by recent findings suggesting the presence of ACh autoreceptors that contribute to homeostatic control of cholinergic activity (Baghdoyan et al. 1997; El Manseri et al. 1990; Kodama & Honda 1996; Leonard & Llinas 1990; 1994; Roth et al. 1996; Sakai & Koyama 1996; Sakai et al. 1990). 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) to be depolarized by carbachol (e.g., Greene & McCarley 1990). This suggests that the exponential self-stimulatory activation which can be triggered by cholinergic stimulation in diverse meso- and medial pontine sites (Hobson et al. 1986; 1993; Hobson & Steriade 1986; McCarley et al. 1995; 1997; Steriade & McCarley 1990a) may involve noncholinergic excitatory intermediary neurons. Such cholinergic self-regulation combined with cholinergic-noncholinergic mutual excitation is illustrated in Figures 3B and 4.

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 mechanisms; and (2) cholinergic mechanisms are essential to REM sleep and come into full play only when the serotonergic and noradrenergic systems are inhibited. Because many different synaptic mechanisms could mediate these effects, we now turn our attention to some intriguing possibilities.

3.2.3. Other neurotransmitter systems. Beyond the originally proposed cholinergic and aminergic neuronal populations, many additional neurotransmitter systems may participate in the control of REM sleep (see below). Since 1975, much progress has been made in the identification of other chemically specific neuromodulatory systems showing differential activation with particular behavioral states or with specific physiological signs within a behavioral state. We now discuss these new findings in terms of the way that they modify and extend the reciprocal interaction model.

In the brain stem and diencephalon, other neuromodulatory systems may interact with aminergic and cholinergic systems in the generation of REM sleep and its signs (for recent reviews see Jones 2000; Lydic & Baghdoyan 1999; Mallick & Singh 1999; Pace-Schott & Hobson, in press). In brief summary, these systems include:

1. GABAergic systems (Datta 1995; 1997b; Datta et al. 1991; Holmes & Jones 1994; Holmes et al. 1994; Jones 1991; 1993; Jones & Muhlethaler 1999; Luppi et al. 1999a; Nitz & Siegel 1997; Porkka-Heiskanen et al. 1997a; Sanford et al. 1998a; Steriade et al. 1990; Xi et al. 1997; for a recent review see Mallick et al. 1999);

2. Nitroxergic systems (Burlet et al. 1999; Datta et al. 1997; Leonard & Lydic 1997; Sippel et al. 1999; Williams et al. 1997; for recent reviews see Burlet et al. 1999 and Leonard & Lydic 1999);

3. Glutamatergic systems (Bartha et al. 1999; Datta 1997a; Datta & Siwek 1997; Holmes et al. 1994; Inglis & Semba 1996; Jones 1994; Lai & Siegel 1992; Onoe & Sakai 1995; Rye 1997; Sakai & Koyama 1996; Sanchez & Leonard 1996);

4. Glycinergic systems (Chase et al. 1989; Datta 1997b; Luppi et al. 1999a; Stevens et al. 1996; Yamuy et al. 1999);

5. Histaminergic systems (e.g., Lin et al. 1996; Saper et al. 1997; Shiromani et al. 1999);

6. Adenosinergic systems (Mackiewicz et al. 1997; Marks & Birabil 1998; McCarley et al. 1997; Porkka-Heiskanen et al. 1997a; 1997b; Portas et al. 1997; Rannie et al. 1994; 1997; Strecker et al. 1997a; 1997b);

7. A wide variety of neuropeptides such as: galanin

(Saper et al 1997; Sherin et al. 1998); orexin (Chemelli et al. 1999; Lin et al. 1999; Piper et al. 1999); vasoactive intestinal polypeptide (Bourgin et al. 1997; El Kafi et al. 1994; Murck et al. 1996; Obal et al. 1989; Prospero-Garcia et al. 1993; for a review see Steiger & Holsboer 1997) and nerve growth factor (Yamuy et al. 1995) (for a review of such substances see Inoue et al. 1999a); as well as numerous hormones including growth hormone releasing hormone (Zhang et al. 1999), prolactin (Morrison et al. 1999), and corticotropin releasing factor (Lai & Siegel 1999). (For a review of hormonal influences see Krueger et al. 1999; Obal & Krueger 1999.)

8. Dopaminergic systems (de Saint Hilaire et al. 1995; Gaillard et al. 1994; Gillin et al. 1973; 1978; 1994; Nicholson et al. 1989; Nishino & Mignot 1997; Olive et al. 1998; Post et al. 1974; 1978; Seidel et al.1997).

Numerous roles have been proposed for these neuromodulatory systems in the regulation of REM sleep and its physiological signs. Among the better known findings and hypotheses are the following:

1. In the initial stages of PGO wave generation, GABAergic and glycinergic cells may inhibit aminergic cells and thus release the cholinergic PGO-triggering or transmitting cells (Datta 1995; 1997b; 1999; Jones 1991; Nitz & Siegel 1997; for recent reviews see Mallick et al. 1999 and Luppi et al. 1999a; 1999b).

2. GABAergic afferents to the PPT and LDT originating in the substantia nigra pars reticulata (SNr) may exert direct inhibitory influences on PGO-related cells of these nuclei (Datta 1999; Datta et al. 1991; Kang & Kitai 1990; Leonard & Llinas 1990; Maloney & Jones 1997; Rye 1997) and the spike-bursting pattern in pontine PGO-burst cells may be the result of excitatory signals impinging on cells that are tonically inhibited by GABA (Datta et al. 1991; Sanford et al. 1998a; Steriade et al. 1990). Such excitatory signals may include corollary discharge from ocular premotor neurons commanding REMs (Steriade et al. 1990). In addition, GABAergic mechanisms may be involved in the medullary control of muscle atonia during REM (Holmes & Jones 1994).

3. Pontine glutamatergic cells may transmit REM sleep atonia-related signals to medullary sites (Lai & Siegel 1992; 1999; Rye 1997).

4. Medullary glycinergic cells may then affect the postsynaptic inhibition of somatic motoneurons during REM atonia (Chase et al. 1989). Glycinergic neurotransmission is also involved in the pre-motor functions of the pons (Gottesmann 1997; Stevens et al. 1996).

5. Adenosine may exert tonic inhibition over the glutamatergic excitatory inputs to the cholinergic cells of the LDT and PPT (McCarley et al. 1997; Rannie et al. 1994) and may contribute to the REM-related suppression of serotonergic raphe neurons (McCarley et al. 1997; Strecker et al. 1997a). Additionally, extracellular buildup of adenosine may constitute the sleep-promoting factor associated with prolonged wakefulness (McCarley et al. 1997; Portas et al. 1996).

6. Two very recent findings highlight the importance of neuropeptides in the regulation of sleep. The first is that inhibitory neurons in the ventrolateral preoptic area (VLPO) of the hypothalamus, a specifically sleep-active area (Sherin et al. 1996), utilize galanin as well as GABA to inhibit ascending arousal systems such as the the locus coeruleus (Saper et al. 1997). The second finding has come from studies on the genetic basis of narcolepsy using animal models. The neuropeptide orexin (or hypocretin), produced only by neurons in the lateral hypothalamus, may play a key role in sleep regulation via its modulation of ascending cholinergic and monoaminergic arousal systems (Chemelli et al. 1999; Lin et al. 1999).

7. Because dopamine (DA) release does not vary dramatically in phase with the natural sleep cycle as do 5-HT, NE and acetylcholine (ACh) (Mamelak 1991; Miller et al. 1983; Trulson et al. 1981), dopaminergic agents have not been as extensively studied. It is often found, however, that REM sleep deprivation appears to enhance DA levels and DA receptor sensitivities (e.g., Brock et al. 1995; Nunes et al. 1994; Tufik et al. 1978). The effects of DA on sleep appear to be variable and are in need of further study. Studies on the administration of dopaminergic drugs have suggested that dopamine may play a role in dreaming, especially the induction and intensification of nightmares (Hartmann 1978; Hartmann et al. 1981; for recent reviews see Hobson & Pace-Schott 1999, and Thompson & Pierce 1999).

Two recent theories have proposed specific roles for DA in dreaming. First, Solms (1997a; 1999c) suggests that dreams are instigated by dopaminergically mediated appetitive drives from the ventral tegmental area (VTA) component of the mesolimbic reward system. Second, Gottesmann (1999) proposes that, during REM sleep, sustained dopaminergic modulation of the cortex in the absence of serotonergic and noradrenergic inhibitory influences but the renewed presence of cholinergic excitation contributes to the unique features of dream mentation such as its psychotomimetic quality. In keeping with the cholinergic hypothesis of REM and dreaming, mechanisms for dopaminergic enhancement of dreaming may involve mutual excitation by dopaminergic and cholinergic nuclei such as dopaminergic enhancement of cortical acetylcholine release (Moore et al. 1999; Smiley et al. 1999) and/or enhancement of mesolimbic dopamine release by cholinergic mesopontine neurons (Oakman et al. 1999).

Finally, as in much of neuroscience, research on behavioral state control is now beginning to extend its inquiry beyond the neurotransmitter and its receptors to the roles of intracellular second messengers (Capece et al. 1999) as well as intranuclear events (Bentivoglio & Grassi-Zucconi 1999; Prospero-Garcia et al. 1999; Schibler & Tafti 1999). Recent exciting results of a molecular genetic approach to sleep research includes the discovery of the role of orexin in sleep regulation (see above). In addition, molecular bases for consciousness are also now being proposed (e.g., Woolf 1996). Undoubtedly such inquiry, though beyond the scope of the present review, will increasingly enrich our understanding of sleep and dreaming.

3.2.4. REM sleep and other brain stem structures. In addition to this neurochemical diversity, a wide variety of brainstem structures other than the LDT, PPT, locus coeruleus, and raphe are crucially involved in the modulation of REM sleep and its distinctive physiological signs. These include diverse areas in the pontine reticular system such as noncholinergic areas within the pedunculopontine region (Rye 1997), the nucleus pontis oralis (Bourgin et al. 1995; Chase & Morales 1990), the locus coeruleus alpha and adjacent structures (Cespuglio et al. 1982; Sakai 1988; Shouse & Siegel 1992), peribrachial areas caudal to the LDT and PPT (Datta 1995; 1997b), as well as the midbrain central gray area (Maloney & Jones 1997; Sastre et al. 1996) and the medulla (Chase & Morales 1990; Gottesmann 1997). Figure 5 schematizes the generation of the various

physiological signs of REM at different levels of the CNS. Adding to the functional complexity of mesopontine cholinergic areas are their roles in other brain mechanisms such as motor control (Garcia-Rill et al. 1987; Inglis & Winn 1995; Rye 1997) as well as the cytoarchitectonic, cytochemical, and functional diversity within the PPT complex itself (Rye 1997). (For recent reviews on this functional neuroanatomy, see Datta 1995; 1997b; 1999; Gottesmann 1997; Hobson & Steriade 1986; Hobson et al. 1993; Jones 1991; Koyama et al. 1999; Pace-Schott & Hobson, in press; Rye 1997; Sakai 1988; Semba 1999; Siegel 1994; Steriade & McCarley 1990a; Vertes 1984.)

Therefore, even within the brainstem itself (i.e., pons, medulla, and midbrain) a diversity of structures and their neurochemical products modulate control of the REM sleep cycle by the aminergic and cholinergic nuclei. Exciting ongoing research in many laboratories now builds upon early findings summarized in the reciprocal interaction model and pursues the important goal of a more complete description of the complex brainstem mechanisms underlying REM sleep.

3.2.5. REM sleep and forebrain-brain stem interactions. Other important contemporary research now extends the study of sleep-wake and REM sleep control mechanisms rostrally from the pontine brain stem to diencephalic structures in a manner consistent with connectivity studies (Morrison & Reiner 1985; Wainer & Mesulam 1990). In addition to the well described brainstem-thalamus-cortex axis, subcortical sleep control mechanisms intercommunicate with each other and with the cortex via an interconnected network of structures extending rostrally from the brainstem RAS to the hypothalamus, basal forebrain, and limbic system. Saper et al. (1997) classify three ascending arousal systems: the brainstem cortical projection system, the basal forebrain projection system, and the hypothalamic cortical projection system with the basal forebrain system projecting to topographically specific cortical areas and the other two systems projecting diffusely. Woolf (1996) has advanced an intriguing model of how these networks may interact in modulating memory and cognition. We now briefly summarize recent findings on this extended subcortical system that are pertinent to sleep-wake and REM sleep control. We will focus here on findings in the hypothalamus, basal forebrain nuclei, and amygdala.

3.2.5.1. The hypothalamus. Histaminergic neurons originating in the posterior hypothalamus innervate virtually the entire brain (Panula et al. 1989) including brain stem structures such as the mesopontine tegmentum (Lin et al. 1996) and the vestibular nuclei (Tighilet & Lacour 1996). These brainstem regions, in turn, innervate both anterior and posterior hypothalamus (Abrahamson et al. 1997; Kumar et al. 1989; Steriade et al. 1980).

Anterior portions of the hypothalamus (preoptic area and adjacent basal forebrain) are known to be essential to sleep. Lesions here cause insomnia (Sallanon et al. 1989) while stimulation of this area promotes sleep (McGinty et al. 1994). In addition, stimulation of the locus coeruleus inhibits sleep-active neurons in this area (Osaka & Matsumura 1993).

Tonic firing of histaminergic neurons in the posterior hypothalamus play an important role in cortical arousal and the maintenance of wakefulness (Khateb et al. 1995; Lin et al. 1986; 1988; 1993; 1994; McCormick & Williamson 1991;

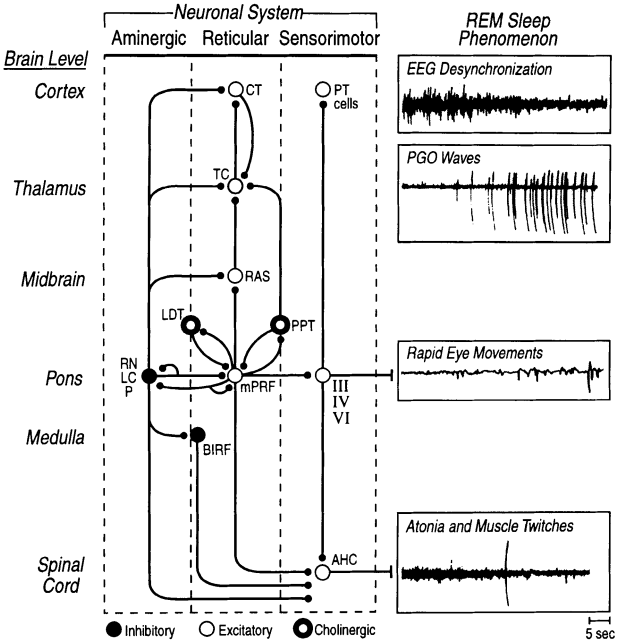


Figure 5. Schematic representation of the REM sleep generation process. A distributed network involves cells at many brain levels (left). The network is represented as comprising three neuronal systems (center) that mediate REM sleep electrographic phenomena (right). Postulated inhibitory connections are shown as solid circles; postulated excitatory connections as open circles; and cholinergic pontine nuclei are shown as open circles with darkened boundaries. It should be noted that the actual synaptic signs of many of the aminergic and reticular pathways remain to be demonstrated, and, in many cases, the neuronal architecture is known to be far more complex than indicated here (e.g., contributions of hypothalamic and basal forebrain systems). During REM, additive facilitatory effects on pontine REM-on cells are postulated to occur via disinhibition (resulting from the marked reduction in firing rate by aminergic neurons at REM sleep onset) and through excitation (resulting from mutually excitatory cholinergic-noncholinergic cell interactions within the pontine tegmentum).

The net result is strong tonic and phasic activation of reticular and sensorimotor neurons in REM sleep. REM sleep phenomena are postulated to be mediated as follows: EEG desynchronization results from a net tonic increase in reticular, basal forebrain, thalamocortical, and cortical neuronal firing rates. PGO waves are the result of tonic disinhibition and phasic excitation of burst cells in the lateral pontomesencephalic tegmentum. Rapid eye movements are the consequence of phasic firing by reticular and vestibular cells; the latter (not shown) directly excite oculomotor neurons. Muscular atonia is the consequence of tonic postsynaptic inhibition of spinal anterior horn cells by the pontomedullary reticular formation. Muscle twitches occur when excitation by reticular and pyramidal tract motorneurons phasically overcomes the tonic inhibition of the anterior horn cells. *Abbreviations:* RN, raphe nuclei; LC, locus coeruleus; P, peribrachial region; PPT, pedunculopontine tegmental nucleus; LDT, laterodorsal tegmental nucleus; mPRF, medial pontine reticular formation (e.g., gigantocellular tegmental field, parvocellular tegmental field); RAS, midbrain reticular activating system; BIRF, bulbospinal inhibitory reticular formation (e.g., gigantocellular tegmental field, parvocellular tegmental field, magnocellular tegmental field); TC, thalamocortical; CT, cortical; PT cell, pyramidal cell; III, oculomotor; IV, trochlear; V, trigmenial motor nuclei; AHC, anterior horn cell. (Modified from Hobson et al. 1986.)

Monti 1993; Saper et al. 1997; Shiromani et al. 1999; Szymusiak 1995) and neurons in this area may directly influence REM sleep (Reiner & McGeer 1987; Sallanon et al. 1989; Vanni-Mercier et al. 1984).

The tuberomammillary nucleus (TMN) plays a particularly important role in the posterior hypothalamic histaminergic arousal system (Saper et al. 1997; Sherin et al. 1996; Shiromani et al. 1999; Steininger et al. 1996; Vanni-Mercier et al. 1984). For example, Sherin et al. (1996) have proposed that a monosynaptic pathway in the hypothalamus may constitute a "switch" for the alternation of sleep and wakefulness. These workers have identified a group of GABAergic and galaninergic neurons in the ventrolateral preoptic anterior hypothalamus (VLPO) which are specifically activated during sleep and constitute the main source of innervation for the histaminergic neurons of the TMN. VLPO neurons may, therefore, specifically inhibit histaminergic neurons of the TMN in order to preserve sleep (Saper et al. 1997; Sherin et al. 1996; 1998).

A recent study has demonstrated extensive histaminergic innervation of the mesopontine tegmentum including the LDT (Lin et al. 1996). Suppression of slow wave activity and an increase in waking follows microinjection of histamine and histamine agonist into these areas (Lin et al. 1996). Recently, histaminergic projections from the TMN to the dorsal raphe as well as to areas of the basal forebrain involved in sleep-wake control have also been demonstrated in the cat (Lin et al. 1997). VLPO neurons have also been shown to innervate other components of ascending arousal systems such as the monoaminergic nuclei of the brainstem and there they may also exert a sleep-promoting inhibitory influence (Sherin et al. 1998). Moreover, also innervating most of the brainstem and diencephalic ascending arousal systems are the orexinergic cells of the lateral hypothalamus and these too may play a modulatory role in the sleep-wake cycle (Chemelli et al. 1999). Tying the hypothalamus to the pons in this dynamic manner may provide a critical link between the circadian clock and the NREM-REM sleep cycle oscillator (see also Liu et al. 1997; O'Hara et al. 1997). In this regard, it is notable that retinal input to the VLPO itself has recently been demonstrated (Lu et al. 1999).

3.2.5.2. The basal forebrain. Basal forebrain (BF) nuclei have close anatomical connections with the locus coeruleus, raphe, and pontine nuclei (Butcher 1995; Jones & Cuello 1989; Szymusiak 1995) and, in turn, project to more rostral structures such as the cortex, thalamus, and limbic systems (Butcher 1995; McCormick 1990; Metherate et al. 1992; Steriade & Buzsazki 1990; Szymusiak 1995; Woolf 1996). In addition to its brain stem and cortical connectivity, the basal forebrain also has close anatomical connections with the anterior and posterior hypothalamus (Gritti et al. 1993; 1994; Szymusiak 1995), the amygdala, and the thalamus (Szymusiak 1995). (For a recent review of BF connectivity see Jones & Muhlethaler 1999.)

Neurochemically, acetylcholine plays a major role in BF control of behavioral state (Jones 1993; Jones & Muhlethaler 1999). For example, magnocellular cholinergic cells of the BF nuclei promote the activation of those cortical and limbic structures to which they project (Cape & Jones 1998; McCormick 1990; Metherate et al. 1992; Szymusiak 1995; Wainer & Mesulam 1990). For example, those of the Nucleus Basalis of Meynert activate topographically distinct areas of the cortex (Metherate et al. 1992; Szymusiak 1995; Woolf 1996). Recent work in rats has also implicated BF magnocellular cholinergic neurons in the control of high voltage cortical slow waves such as are observed in NREM (Kleiner & Bringmann 1996; Nunez 1996). GABAergic BF cells may also interact with BF cholinergic cells in the regulation of oscillatory rhythms which accompany cortical activation (Jones & Muhlethaler 1999). Other BF cells, anatomically and neurochemically distinct from the cholinergic magnocellular neurons, function as sleep promoting elements (Szymusiak 1995), possibly by GABAergic inhibition of hypothalamic and brain stem arousal systems (Szymusiak 1995), the hippocampus (Mallick et al. 1997), or the cortex (Jones & Muhlethaler 1999).

There are extensive interactions between the brain stem structures (locus coeruleus, raphe nuclei, as well as the LDT and PPT) and the BF in sleep-wake control (Jones & Cuello 1989; Jones & Muhlethaler 1999; Semba 1999; Semba et al. 1988; Szymusiak 1995). Bidirectional interactions between the BF and sleep-related areas of the brainstem modulate behavioral state utilizing a variety of transmitter substances as illustrated by the following findings:

1. The cholinergic system of the mesopontine tegmentum communicates with the BF cholinergic system in a manner functionally relevant to sleep (Baghdoyan et al. 1993; Consolo et al. 1990). For example, simultaneous microinjection of carbachol into cholinoceptive regions of the BF suppresses the ability of carbachol to induce a REM-like state when injected into the pons (Baghdoyan et al. 1993).
2. Cholinergic BF structures, which activate the cortex, can be activated by brain stem glutamatergic cells (Rasmussen et al. 1994).
3. Glutamatergic systems of the BF can, in turn, affect behavioral state via projections to the mesopontine tegmentum (Manfridi & Mancia 1996).
4. Aminergic inputs to the BF nuclei from brainstem nuclei can influence behavioral state in a manner similar to their action in the pons. For example, the noradrenergic agonist isoproterenol increases wakefulness and suppresses REM when infused into the BF (Berridge & Foote 1996).

As in the brainstem, neuromodulatory systems interact within the BF itself. For example, BF cholinergic neurons may be under tonic inhibition by adenosine (Porkka-Heiskanen 1997b; Strecker et al. 1997b) while 5-HT can hyperpolarize cholinergic nucleus basalis neurons and decrease wake-associated gamma frequency oscillations in the cortical areas to which they project (Cape & Jones 1998). The BF nuclei, therefore, both directly participate in behavioral state-related functions and modify the activity of other areas involved in sleep such as the pontine REM generator.

3.2.5.3. The amygdala. Of particular interest in view of the human neurobiology reviewed above (e.g., Maquet et al. 1996; Nofzinger et al. 1997), the amygdala has reciprocal connections with pontine regions involved in the control of REM sleep (Bernard et al. 1993; Calvo & Simon-Arceo 1999; Morrison et al. 1999; Sanford et al. 1995b; Saper & Loewy 1980; Semba & Fibiger 1992; Wainer & Mesulam 1990) and receives serotonergic innervation from the dorsal and medial raphe (Fallon & Ciofi 1992). For a recent thorough review of the amygdala in sleep regulation see Morrison et al. (1999).

Physiological signs of REM have been shown both to occur spontaneously and to be modifiable in the amygdala (see Calvo & Simon-Arceo 1999 for a review; see also Maquet 2000; Maquet & Phillips 1998; 1999 regarding

recent human findings). For example, in the cat, PGO-like EEG activity has been detected in the basolateral amygdala (Calvo & Fernandez-Guardiola 1984). Moreover electrical stimulation of the cat amygdala significantly increased PGO number, spike density, and burst density (Calvo et al. 1987) as well as the amplitude and rate of acoustically elicited pontine PGO waves in the waking rat (Deboer et al. 1997; 1998), and burst firing of pontine cells in the rabbit (Morrison et al. 1999).

Aminergic and cholinergic stimulation of the amygdala has been shown to modify sleep in the directions predicted by reciprocal interaction for the action of these neurotransmitters in the pons. For example, cholinergic stimulation of amygdaloid sites in the cat enhanced REM sleep for several days, an effect akin to the long-term REM enhancement by cholinergic stimulation of the peribrachial pons (Calvo & Simon-Arceo 1995; 1999; Calvo et al. 1996). Furthermore, serotonergic stimulation of the amygdala in the cat caused short latency changes of state from either NREM or REM (Sanford et al. 1995b), while serotonergic antagonism during NREM increased PGO activity (Sanford et al. 1995a) and the relative amount of sleep (Sanford et al. 1995b). Similarly, noradrenergic stimulation of the amygdala suppressed sleep relative to wakefulness (Fuchino et al. 1996). Interestingly, the role of the amygdala in REM sleep control may differ between species (Deboer et al. 1997; Sanford et al. 1997a).

It has been suggested that serotonergic mechanisms in the amygdala constitute a mechanism whereby emotionally significant stimuli can influence the state of arousal (Sanford et al. 1995b). Such a role corresponds well with the proposed role of amygdala in the processing of emotional memory during REM (Maquet & Franck 1997).

3.2.5.4. Other subcortical structures. Other diencephalic structures such as centralis lateralis nucleus of the thalamus possibly participate in the modulation of REM sleep (Mancia & Marini 1997; Marini et al. 1992). In addition, there are extensive striatal projections to the pedunculopontine region (Inglis & Winn 1995; Rye 1997) especially to glutamatergic cells of the midbrain extrapyramidal area (MEA) (Rye 1997). Interaction between the MEA and the basal ganglia may serve to modulate movement to accord with behavioral state (Rye 1997).

In addition to forebrain structures, brain stem structures rostral to the pons such as the ventrolateral periaqueductal gray (Sastre et al. 1996) may also be important in the modulation of REM sleep. Such rostral brainstem connections could facilitate ponto-limbic interactions in REM sleep generation and loss of this mechanism could account for loss of dreaming when such connections are severed by clinical lesions (Solms 1997a).

3.2.6. Neurophysiological evidence which supports the REM-NREM-waking distinction. While the REM-NREM-waking distinction was first defined in standardized terms by the neurophysiological criteria of polysomnography (Rechtschaffen & Kales 1968), abundant additional physiological evidence has since accumulated which supports the biological differentiation of these three states. Although direct measurement of human CNS neuromodulators is still in its infancy, preliminary evidence points to a similar pattern of fluctuation across the sleep-wake cycle as is seen in animal models (Wilson et al. 1997). In addition, the following indirect evidence strongly supports the physiological distinction between REM, NREM, and waking: (1) Autonomic activation is higher during NREM night terrors than during REM nightmares (Fisher et al. 1973). (2) While the locus coeruleus is active during waking and its noradrenergic output is associated with wake state anxiety responses (Bremner et al. 1996; Salzman et al. 1993), this region is quiescent in REM sleep (Hobson & Steriade 1986) despite the predominance of anxiety in the emotions of dreaming (Merritt et al. 1994). (3) Cholinergic activation of limbic structures probably underlies REM dream anxiety (Braun et al. 1997) whereas ACh is not prominently involved in waking anxiety (Salzman et al. 1993). (4) Nielsen (1999; and target article) notes additional physiological differences between REM and NREM sleep such as differing ERP patterns and external stimulus responses, which suggest differing cognitive processes taking place during these two sleep states.

3.2.7. Conclusions. All of these findings indicate that the reciprocal interaction of cholinergic and aminergic systems may operate in areas other than the brain stem in ways that significantly amplify REM sleep generation or suppression. As has been hypothesized for learning and cognition (Woolf 1996), a subcortical medial ascending system of multiple nuclei, extensive reciprocal interconnections between nuclei, and system-wide sensitivity to neuromodulation controls behavioral state at a hierarchical level above that of specific subcomponent oscillators (e.g., the pontine REM generator). Furthermore, in view of the recent evidence of selective activation of the limbic lobe in human REM sleep (Braun et al. 1997; 1998; Maquet et al. 1996; Nofzinger et al. 1997), these new basic neurobiological findings have a particularly strong impact on the neurocognitive theory of dreaming.

We conclude that the essential tenets of the reciprocal interaction model have been strongly confirmed and that the interaction of the pontine structures with other brain structures can now begin to be studied in ways that will enrich our understanding of how the distinctive features of each conscious state are mediated and how their stereotyped sequencing is controlled.

3.3. Contemporary theories of conscious states

We now turn our attention to a review of theories on how conscious states are mediated. As the inadequacies of the Freudian model of dreaming have become more evident, many researchers have increasingly turned toward the establishment of a cognitive neuroscience of brain-mind states. Four major cognitive models of dreaming are discussed below. All four of these have been inspired by modern laboratory research but the degree to which they are deeply brain-based varies dramatically as we hope to make clear. In section 3.3.5, we address the ongoing debate on the relationship of REM eye movements to dream imagery. We do so because this controversy exemplifies both the basic differences between "top-down" (cortically driven) and "bottom-up" (subcortically driven) views on the origin of dreaming as well as the added complexity and realism offered by an approach to the biology of dreaming which takes into account the wide range of perspectives offered by contemporary neuroscience.

3.3.1. Activation models. In 1970, Zimmerman advanced a theory in which dreaming (versus thinking or no mentation) occurred during sleep when "cortical arousal" exceeded a

certain threshold, regardless of sleep stage. We will later describe various ways to measure cortical activation which we call factor "A" and take to be one of three critical factors in determining the probability of dreaming.

Antrobus and his colleagues have proposed an elaborated cortical activation-based model of mentation operating across all mental states (Antrobus 1986; 1990; 1991; Fookson & Antrobus 1992; Reinsel et al. 1992). According to Antrobus, the qualities of mentation in any state result from an interaction between the activation level of cortex and the current level of environmental stimulation as gated by current sensory thresholds. Interaction between cortical modules subserving various sensory, motor, and associative modalities create the dream narrative and integrate any cortical, subcortical or peripheral inputs via a "top-down" cortically controlled process (Antrobus & Bertini 1992). Antrobus and his colleagues describe the dynamics of this process in terms of parallel distributed process neural network models (Antrobus 1991; Fookson & Antrobus 1992). In our terms, the greater the value of "A," the greater the production and retrieval of associative trains of thought.

The Antrobus team theorizes that the high sensory thresholds of REM prevent interruption of ongoing mentation. In our terms, this process is measured as factor "I" which we see as shifted away from external sensory input, and correspondingly favoring internal, fictive sensory input. For Antrobus, the result is a more ongoing, story-like quality of REM mentation compared with wake mentation which, though similarly activated, is continually interrupted by external stimuli (Reinsel et al. 1986; 1992; Wollman & Antrobus 1986). In his model, dream bizarreness results when cortical networks, which are attempting to accurately reconstruct reality based on probabilities learned during waking, fail to fully integrate all of the various constructions being generated (Antrobus & Bertini 1992; Fookson & Antrobus 1992).

Antrobus implicitly rejects the role of aminergic-cholinergic neuromodulation (our model's factor M) in controlling the nature of dream mentation. Instead, he argues that since waking mentation can be dreamlike, this neuromodulatory shift is not necessary for dream mentation to occur and factor M of our three dimensional model is discarded. We invite Antrobus to explain the paradoxical memory defect and loss of self-reflective awareness and volition during dreaming on the basis of activation and sensory gating alone.

3.3.2. The cognitive psychological model of Foulkes. Foulkes has advanced a cognitive, information processing model of dream production which questions the brain basis of conscious states and dream mentation (e.g., Foulkes 1982a; 1985; 1990; 1993b; 1997; Foulkes & Cavallero 1993). Instead, Foulkes describes dreams as resulting from the activation of mnemonic "systems" or "units." In his model, "activation" is conceived as the combination of both excitatory processes and the disinhibition of mnemonic systems previously inhibited by voluntary self-control (Foulkes 1985).

With the exception of general excitatory processes such as the cerebral activation of REM, Foulkes's model is explicitly a psychological, mentalistic construct which does not attempt to link psychological to physiological phenomena (Foulkes 1985; 1990). A similar position has been taken by Bosinelli (1995) and by Mancia (1995). Each of them asserts that mentalistic and physiological sleep phenomena cannot be explained from the same epistemological referents. As such, these models share with Freud's model a decision not to attempt to explain these mental functions in terms of brain actions.

Instead, Foulkes's earlier cognitive models emphasized similarity between the intermediate steps of a psycholinguistic model of language production and a "psychoneiric" model of dream production with the differences between the two processes occurring mainly at input and output stages of production (Foulkes 1982a). In more recent writings, Foulkes (1990) specifically equates the high level cognitive constructive processes which organize waking experience with those processes which organize dreaming. For example, he explains the consonance of dream emotion with dream plot as resulting from the primary narrative demands of the dream (Foulkes 1997; Foulkes et al. 1988b). Further, he specifically eschews any possible information-bearing role for subcortical stimuli in dream form or narrative. In his own words, "subcortical structures . . . simply turn on the light switch upstairs. They don't tell any of the creatures upstairs what to do or how to do it; they simply arouse them, enabling them to do whatever it is they characteristically do" (Foulkes 1997, p. 3).

Foulkes goes on to assert that if such higher level (and implicitly cortically based) cognitive processes cannot *consciously* construct an organized, episodically integrated, self-reflective account of waking (as in the case of an animal or a pre-operational child), they also cannot *unconsciously* construct a coherent dream narrative (Foulkes 1990). As previously noted, this model constrains the dream to adult human sleep mentation and does not account for conscious experiences during sleep which may be possible at a much lower level of integration. For example, given Foulkes's (1990) position, one might argue that severely cognitively regressed adults (e.g., with severe dementia or delirium) should lose much of *their* capacity to dream. However, this prediction is not supported by clinical findings (e.g., Cipolli et al. 1992; Doricchi & Violani 1992; Kramer et al. 1975). Instead, we see loss of dreaming associated with lesions to specific brain areas (for reviews see Doricchi & Violani 1992 and Solms 1997a), a finding which would be expected if specific circuits with a great degree of localization form the neural substrate of dreaming.

Although Foulkes's model cannot be specifically viewed in the context of our physiological AIM model, some hints of these concepts can be found in his work. For example, he does make a generalized claim that cortical activation by the brain stem (the "A" dimension of the AIM model) must be relatively high in dreaming (Foulkes 1997). In addition, he argues that the origin of dream scenarios comes from the quasi-random activation of a "mnemonic focus" (Foulkes 1985, p. 151), and specifically not from external stimuli. This corresponds to a value of low sensory input and high value of internal input on the "I" dimension. No position on the "M" dimension of our AIM model, however, can be inferred from his studies. We invite Foulkes to explain the several robust deficiencies of dream cognition, and especially the amnesia, in terms of his model.

3.3.3. The neuropsychological-psychoanalytic model of Solms. Combining the clinical lesion studies described above in section 3.1.6 and the classical psychoanalytic theory of dreaming, Solms (1997a; 1999c) builds a neuropsychological model of normal dreaming, which is illustrated in Figure 6. Frontal dopaminergic mesolimbic reward cir-

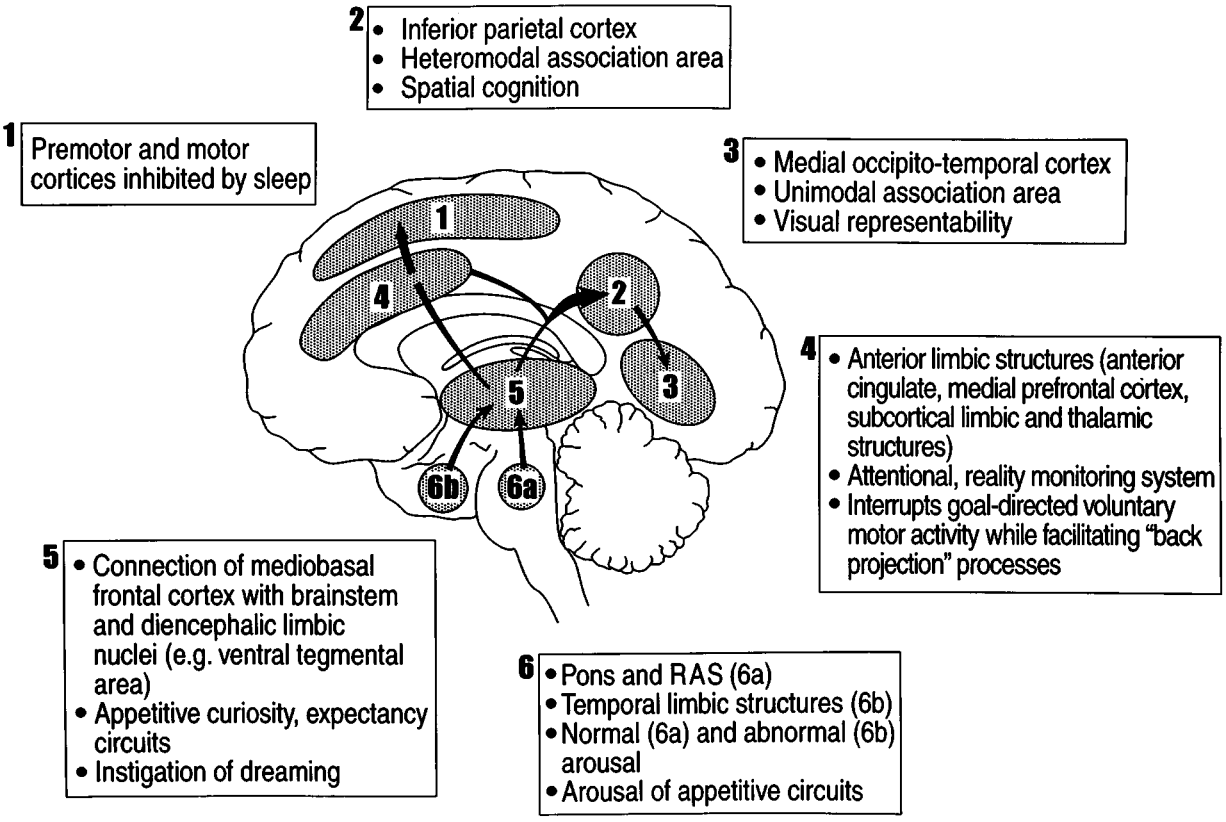


Figure 6. Forebrain processes in dreaming based upon a model proposed by Solms (1997a). Solms proposes that the dopaminergic mesolimbic reward circuits (region 5 in Fig. 6) produce an instigating impetus for dreaming when activated by arousing stimuli such as environmental input, ascending brainstem arousal in REM (region 6a in Fig. 6) or epileptiform discharge (region 6b in Fig. 6). He further hypothesizes that the posterior passage of this subcortical stimulus is gated by a reality monitoring process in anterior limbic areas (region 4 in Fig. 6) which both interrupt voluntary motor activity and facilitate back projection processes from the inferior parietal cortex (region 2 in Fig. 6) to medial temporal-occipital visual association areas (region 3 in Fig. 6). During this process, premotor and motor cortices (region 1 in Fig. 6) remain quiescent due to the combined effects of limbic blockage (region 4 in Fig. 6) of ascending impulses as well a sleep-related inhibition.

cuits produce an instigating impetus for dreaming when activated by arousing stimuli (e.g., ascending brainstem arousal in REM). The passage of this subcortical stimulus to posterior heteromodal association areas in the inferior parietal lobe is gated by a reality monitoring process mediated by anterior limbic areas. These anterior limbic areas also prevent this subcortical stimulus from activating the motor cortex as well as facilitating back projection of this stimulus to the posterior cortex. Back projection continues from the inferior parietal lobe (which contributes the capacity for spatial cognition) to visual association areas in medial occipito-temporal cortex (which contribute visual imagery) but not as far back as primary visual cortex. Solms speculatively assigns to the resultant network the sleep-protective function of Freud's classical dream work: appetitive subcortical impulses are "censored" by the anterior limbic system and then safely back-projected to posterior cortical representational mechanisms.

In support of the neuroanatomical details of this network Solms cites his findings on lesion-induced changes in dreaming. Loss of dream imagery (visual anoneria) is accompanied by an analogous waking deficit, visual irreminiscence, which involves the highly processed visual memory functions of unimodal association cortex and not the perceptual functions of the primary visual cortex. Since cortical area V1 lesions do not cause visual anoneria, Solms hypothesizes that any back projection processes involved in dreaming do not extend all the way to primary visual cortex. On the basis of the findings that lesions in Brodmann areas 39 and 40 in either hemisphere appear to be the most restricted damage causing the posterior variant of global anoneria, he proposes that these heteromodal areas are the source of back projection to visual association areas. In support of this network's sleep-protective function, he notes that global anoneric patients report poorer sleep quality than non-cerebrally injured controls (Solms 1997a).

3.3.4. The activation-synthesis model

3.3.4.1. The original-activation synthesis model. Abundant studies in the 1960s and 1970s on the cellular neurophysiology of the sleep cycle as well as the functional reorganization of the visual system during sleep suggested a new conceptual approach to brain-mind states. First expressed as the activation-synthesis hypothesis of dreaming (Hobson & McCarley 1977), this model proposed the global mapping of brain states to mind states. This was the position taken by Freud in his famous *Project for a scientific psychology* (1895) but ostensibly abandoned in the *Interpretation of dreams* (1900). For a detailed discussion of this subject, see McCarley and Hobson (1977).

Enunciating the general principle of brain-mind isomorphism, the activation-synthesis model placed emphasis

on such aspects of the form of dreams which might be expected to have their roots traced to isomorphic forms of brain activity. In so doing, the new theory proposed some of the cellular and molecular mechanisms by which changes in activation, in stimulus origin and in neuromodulation could explain the state-dependent changes in perception, thinking and memory seen in shifts from waking to NREM and REM sleep (Flicker et al. 1981). The activation-synthesis hypothesis proposed that formal aspects of dream mentation reflected the outcome of attempts by sensorimotor and limbic regions of the forebrain to produce a coherent experience from the incomplete and chaotic inputs received from the brain stem. The specific formal features of dream mentation, it was proposed, could best be explained by examining the unique configuration of brain activity that occurs during REM sleep.

To illustrate how this global brain-to-mind mapping concept is articulated, we considered the probable consequences of a shift in visual system input source from the formed visual images on the retina in waking to the chaotic brain stem stimulation of REM sleep (Bizzi 1966a; 1966b; Callaway et al. 1987; Nelson et al. 1983; Pivik et al. 1977). This shift in input source occurs in the context of a concurrent cessation of activity in brain stem noradrenergic and serotonergic neurons (Hobson & Steriade 1986; Steriade & McCarley 1990a). The quiescence seen in these aminergic modulatory neurons results in the demodulation and disinhibition of the visual cortex (Evarts 1962), the lateral geniculate bodies (Bizzi 1966b) and brain stem oculomotor networks (Mouret et al. 1963).

As a result of the aminergic disinhibition, cholinoceptive peribrachial neurons become hyperexcitable and fire in bursts, causing phasic activation of the lateral geniculate bodies and visual cortex. This phasic activation is recordable in the REM sleep of cats as the PGO waves which, in turn, correlate with the direction of the rapid eye movements (Monaco et al. 1984; Nelson et al. 1983). We have speculated that this cholinergically mediated stimulation conveys information to the visual system about the direction of the eye movements which have become, in REM sleep, uncoupled from external sensory stimuli (Callaway et al. 1987).

The net result of these shifts is an activated brain stem and visual system which are (1) deafferentated, (2) aminergically demodulated, and (3) cholinergically auto-stimulated. But the brain stem signals still convey information about the direction of rapid eye movements to the deafferentated, demodulated forebrain. According to the activation-synthesis hypothesis, these changes in sensory input source and neuromodulation could contribute to such cognitive features of dreaming as (1) the hallucinatory visual imagery, (2) the frequent shifts and reorientations of attention, (3) the loss of voluntary control of both motor action and internal attention, (4) the emotional intensification especially of anxiety, elation, and anger, and (5) the memory loss within and after dreaming (Mamelak & Hobson 1989a).

3.3.4.2. Evolution of the activation-synthesis model. The original formulation of the activation-synthesis model of dream construction (Hobson & McCarley 1977) proposed that the phasic signals arising in the pontine brain stem during REM sleep and impinging upon the cortex and limbic forebrain led directly to the visual and motor hallucinations, emotion, and distinctively bizarre cognition that characterize dream mentation. In doing so, these chaotically generated signals arising from the brain stem acted as a physiological Rorschach test, initiating a process of image and narrative synthesis involving associative and language regions of the brain and resulting in the construction of the dream scenarios. Thus, it was the combination of this chaotic, bottom-up activation process and its resultant semi-coherent, top-down synthetic process which made up the overall process of dream construction.

Anticipating activation-synthesis by almost a decade, Molinari and Foulkes's (1969) application of Moruzzi's physiological tonic-phasic model to dream psychology first introduced the concept that the phasic events of sleep contribute hallucinatory raw material that was then secondarily elaborated during dream production. Using neurobiological data to support these concepts, the activation-synthesis model hypothesized that dreaming resulted from the interpretation by the cortex of information concerning eye movements and activated brain stem motor pattern generators. Seligman and Yellen (1987) added the consideration of emotional evaluation to the concepts of primary visual activation and secondary cognitive elaboration to generate a cognitive model of dream production, a suggestion strongly supported by recent PET studies showing preferential activation of limbic structures and adjacent cortices (Braun et al. 1997; Maquet et al. 1996; Nofzinger et al. 1997).

We have recently proposed that both cortical and limbic regions, when cholinergically activated by REM sleep events such as PGO waves, may synthesize their own information (Hobson 1988b; 1990; 1992a; 1997a; Hobson & Stickgold 1994a; 1994b; Mamelak & Hobson 1989a). For example, dream hallucinosis, while probably incorporating eye-movement information coded in PGO bursts, must also incorporate visual material from a variety of memory sources in an otherwise activated cortex. This aspect of the theory is very similar to Solms's suggestion of a "back projection" toward the visual cortex from the limbic forebrain (Solms 1997a) as the brain synthetically fits image to affect. Informing recent presentations of the activation-synthesis hypothesis are concepts from neural net modeling (Mamelak & Hobson 1989a; Sutton & Hobson 1994), self-organization theory (Kahn & Hobson 1993; Kahn et al. 1997), graph theory (Sutton et al. 1994a; 1994b), cognitive neuroscience (Hobson & Stickgold 1994a; 1994b) and, most recently and influentially, the new findings described above in section 3.3 on the functional neuroimaging of sleep and the clinical neuropsychology of dreaming (Hobson et al. 1998a; 1998b; 2000).

3.3.4.3. Activation synthesis updated: An integrated model of REM sleep dreaming. Integration of the original activation-synthesis model with new neuroimaging (Braun et al. 1997; 1998; Maquet et al. 1996; Nofzinger et al. 1997) and lesion (Solms 1997a) data allows the development of a more detailed activation-synthesis model of REM sleep dreaming (Hobson et al. 2000). Although the original activation synthesis model was necessarily weighted toward activation processes (e.g., PGO activation of thalamocortical circuits), these new findings allow us to begin to speculate on the neuroanatomical bases of the synthesis aspect of the model. In doing so, we present a neuropsychological model of dreaming differing substantially from that of Solms (presented above), which was based on lesion studies alone. This model is presented in Figure 7 and its components are described in more detail below.

In this model, dreaming consciousness results from pro-

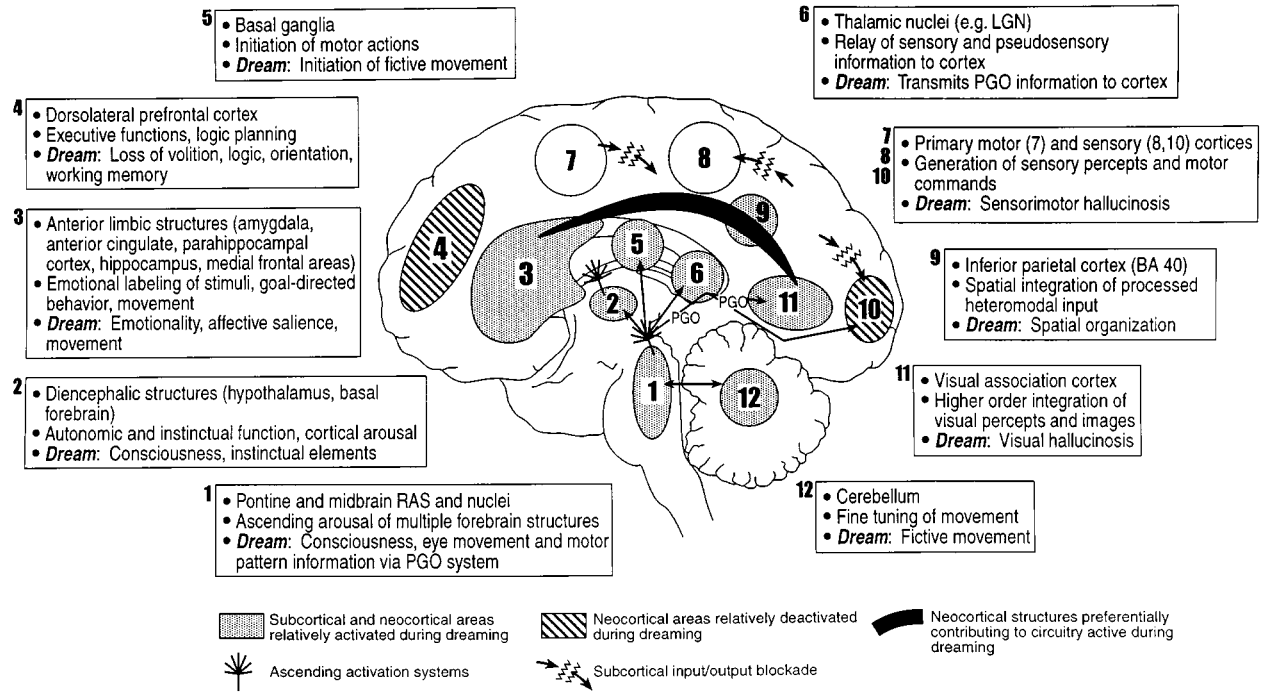


Figure 7. Forebrain processes in normal dreaming: an integration of neurophysiological, neuropsychological and neuroimaging data. Regions 1 and 2: ascending arousal systems; 3: subcortical and cortical limbic and paralimbic structures; 4: dorsolateral prefrontal executive association cortex; 5: motor initiation and control centers; 6: thalamocortical relay centers and thalamic subcortical circuitry; 7: primary motor cortex; 8: primary somatosensory cortex; 9: inferior parietal lobe; 10: primary visual cortex; 11: visual association cortex; 12: cerebellum. This figure serves as a visual model for section 3.3.4.3 ("Activation-synthesis updated: An integrated model of REM sleep dreaming") and each element of the figure is explained in detail in that section. Abbreviations: RAS, reticular activating system; PGO, ponto-geniculo-occipital waves; LGN, lateral geniculate nucleus; BA, Brodmann area. (From Hobson et al. 2000).

cesses of arousal impinging upon selectively facilitated, dysfacilitated or input/output-blockaded forebrain structures. The various elements of normal dreams are contributed by brain networks that include structures known to contribute to analogous processes in waking although, as the model suggests, dreaming is characterized by a deletion of certain circuits active in waking and, perhaps, the accentuation of others. The following text uses the enumerated brain areas in Figure 7 to present a model of the neuropsychological bases of dream phenomena.

Ascending arousal systems (zones 1 and 2 in Fig. 7): As in waking, activation of the forebrain occurs through ascending arousal systems located in the brainstem reticular activating system (Steriade 1996), the basal forebrain (Szymusiak 1995) and possibly the hypothalamus (Saper et al. 1997). Together these structures form an integrated ascending midline network (Woolf 1996) which includes ascending cholinergic systems. Braun et al. (1997) suggest that the ascending reticular activation of REM sleep may proceed relatively more via a ventral cholinergic route from the brainstem to the basal forebrain rather than via the dorsal route through the thalamus which is preferred in waking. This suggestion and the related idea of Solms (1997a), recall the early speculation of Jouvet (1962) that forebrain activation might proceed via the limbic midbrain circuit of Nauta.

The forebrain stimulation arising from such intrinsic arousal systems allows "consciousness" (as opposed to unconsciousness) to exist in dreaming. Such consciousness may be detected by the desynchronization of the traditionally measured cortical EEG frequencies (Hobson 1988b) as well as by the appearance of gamma frequency oscillatory rhythms (Llinas & Ribary 1993; for reviews, see Hobson et al. 1998a; 2000; Kahn et al. 1997). Brainstem and diencephalic structures also contribute information in specific modalities via specific circuitries (such as the PGO network) resulting in distinctive dream features such as directionality of eye movement, distinctive motor pattern automata, and instinctive behavior and feelings such as rage, terror, or sexual arousal (Hobson & McCarley 1977).

Thalamocortical relay centers and thalamic subcortical circuitry (zone 6 in Fig. 7): The release of corticothalamic intrinsic oscillatory rhythms suppresses the experience of perception and mentation during NREM sleep (see above). During REM sleep, this process is reversed and the activated thalamic nuclei, which occupy key sites in sensorimotor relay as well as other brain circuits, contribute to the pseudosensory perceptual aspects of dream consciousness. For example, the lateral geniculate nucleus transmits PGO waves from the brainstem to the visual cortex. As an internal stimulus, PGO waves bear such information as the directionality of gaze shifts encoded in the form of corollary discharge from brainstem oculomotor nuclei (Hobson & McCarley 1977). Recent dipole tracing techniques in humans have shown PGO wave-like activity involving the pons, midbrain, thalamus, hippocampus, and visual cortex (Inoue et al. 1999b). Moreover, it has recently been shown that information encoded in the pattern of activation of geniculate neurons in the cat is sufficient to represent basic elements of natural scenes (Stanley et al. 1999).

As in waking, corollary discharge information from pro-

grammed instinctual motion commanded by brainstem motor pattern generators is transmitted rostrally via the thalamus (Hobson & McCarley 1977). In addition, nuclei within the thalamus participate in the subcortical circuitry of various motor pathways (Braun et al. 1997). Moreover, thalamic nuclei participate in the control of the sleep cycle itself (Mancia & Marini 1997) and recent findings have shown the ventrolateral thalamus may mediate the interaction of arousal and attention in humans (Portas et al. 1999).

Subcortical and cortical limbic and paralimbic structures (zone 3 in Fig. 7): As suggested by PET studies, medial forebrain structures, both cortical and subcortical, are selectively activated during REM sleep dreaming (Braun et al. 1997; 1998; Hobson et al. 1998b; 2000; Maquet et al. 1996; Nofzinger et al. 1997). Among these, limbic and paralimbic structures are consistently found to be active in REM and these contribute distinctive emotion-related dream features as follows.

As in waking (LeDoux 1996), amygdalar activation contributes emotional features, especially anxiety, to dreaming. Maquet emphasizes that 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 1997; Maquet et al. 1996).

As in waking (Devinsky et al. 1995), anterior cingulate activation contributes additional emotional features to dreaming such as valence biases, the assessment of motivational salience, and the integration of dream emotion with fictive actions. Interestingly, in some PET studies, other elements of the rostral limbic and perilimbic circuits such as the ventral striatum and the orbitofrontal, insular, and medial prefrontal cortices have also been found to be activated during REM (Braun et al. 1997; Nofzinger et al. 1997). Such medial areas have the most abundant limbic connections in the prefrontal cortex (Barbas 1995; Braun et al. 1997) and their disruption is often associated with confabulatory or dream-wake confusional syndromes (Braun et al. 1997; Solms 1997a). Several recent findings also suggest the importance of medio-frontal, limbic-associated cortical areas to dreaming. First, during sleep, a scalp-recorded decrease in frontal alpha power and the persistence of waking frontal alpha asymmetry between hemispheres has been suggested to be linked to activation of underlying limbic structures during REM (Benca et al. 1999). Second, magnetic resonance spectroscopy has shown a sleep-related elevation of medial prefrontal glutamine (a glutamate precursor) to the unusually high levels seen in awake schizophrenics (Bartha et al. 1999). These authors go on to suggest that this elevation is linked to brain activity during dreaming.

Activated limbic circuits underlie the phenomenology of recalled dream emotion with its predominance of anxiety over other emotions (Domhoff 1996; Merritt et al. 1994; Nielsen et al. 1991). The finding that dream emotion is usually consistent with the dream narrative (Foulkes et al. 1988b) and that bizarre incongruities between emotion and narrative are rarer than incongruities among other dream elements (Merritt et al. 1994) can now be explained by viewing dream emotion as a primary shaper of plots rather than as a reaction to them (Seligman & Yellen 1987). 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 another in a category that we call "incomplete arrangements."

Two concerns arise when predicting that REM sleep dreaming is hyperemotional in comparison to other behavioral states. The first involves early findings of maximal galvanic skin response (GSR), an indicator of peripheral autonomic activity, in Stage 4 NREM rather than REM (Johnson & Lubin 1966) as well as the complementary findings of an "autonomic storm" accompanying Stage 4 night terrors (Fisher et al. 1973). It must be noted, however, that peripheral autonomic activity may be uncoupled from central autonomic activity in deep sleep. Thus we would not expect GSR to correlate with felt emotion in deep sleep. Moreover, if GSR did so correlate, it would constitute the sleep equivalent of the James-Lange hypothesis that emotion is the perception of peripheral autonomic changes, a hypothesis now felt to be inaccurate even in waking when the peripheral measures may themselves more faithfully reflect central autonomic activation. A second concern is the often reported lack of emotion-related physiological arousal accompanying dream events (e.g., violence) which would easily elicit such arousal in waking (Perlis & Nielsen 1993). Such emotional "numbing" in dreams could result both from a sleep-related dissociation of peripheral and central autonomic activity (as with peripheral arousal in Stage 4) combined with REM-related blockade of central readout to the periphery and peripheral sensory feedback to the CNS.

The amygdala is known to influence memory storage processes in the hippocampus (Cahill & McGaugh 1998). Such circuits could thus underlie the role of REM sleep and dreams in the processing of emotional memories that is often hypothesized by dream psychology theorists and by neuroimaging groups (Braun et al. 1997; Cartwright et al. 1998a; Hobson et al. 1998b; Kramer 1993; Maquet et al. 1996; Maquet & Franck 1997; Nofzinger et al. 1997; Perlis & Nielson 1993). For example, Nofzinger et al. (1997) suggest that an important function of REM sleep is the integration of neocortical function with basal forebrain hypothalamic motivational and reward mechanisms.

Motor initiation and control centers (zone 5 in Fig. 7): As in waking movement (Kolb & Whishaw 1996), the basal ganglia play a role in initiating fictive dream movement and their strong activation in REM relative to both waking and NREM (Braun et al. 1997) contribute to the ubiquity of hallucinated motion in dreams (Hobson 1988b; Porte & Hobson 1996). The cerebellum (zone 12 in Fig. 7) modulates these fictive movements and adds specific features such as vestibular sensations (Hobson et al. 1998c; Leslie & Ogilvie 1996; Sauvageau et al. 1998) via cerebellar connectivity with brainstem vestibular nuclei. It is interesting that pontine cholinergic neurons have recently been shown to project to the cerebellar vermis (Cirelli et al. 1998), a region of the cerebellum which has been found to be activated in REM (Braun et al. 1997). Moreover, the pons serves as a key intermediary structure in cortico-cerebellar and cerebello-cortical pathways (Schwartz & Thier 1999).

Braun et al. (1997) suggest a role for the basal ganglia in ascending thalamocortical activation (via their connectivity with the brainstem through the intralaminar thalamic nuclei) as well as a role for the basal ganglia in the rostral transmission of PGO waves (via their back-projections to the pedunculopontine tegmentum). Notably, the basal ganglia show extensive connectivity with regions of the pontine

brainstem also known to regulate REM sleep phenomena (Inglis & Winn 1995; Rye 1997).

Motor input from cerebral levels rostral and caudal to the basal ganglia also contribute to the experience of movement in dreaming. Brainstem motor pattern generators (in zone 1 of Fig. 7) are stimulated along with the widespread pontine reticular activation of REM sleep and they could contribute to the frequent experience of programmed movement such as running in dreams (Hobson & McCarley 1977). The motor cortex (zone 10 in Fig. 7) also commands movement in dreaming as evidenced by the pathological expression of dreamed action in REM sleep behavior disorder (Schenck et al. 1993), although its output is normally blocked by the motor atonia of REM sleep (Chase & Morales 1990; Pompeiano 1967a). The premotor function of the anterior cingulate cortex (Devinsky et al. 1995) may also contribute to the experience of fictive movement in dreaming particularly in regard to emotionally motivated actions.

Visual association cortex (zone 11 in Fig. 7): Areas of the medial occipital and temporal cortices involved in higher order visual processing, as opposed to primary visual cortex, generate the visual imagery of dreams (Braun et al. 1998; Solms 1997a). Specific visual features of dreaming are generated by the same areas of the visual association cortex involved in their higher order processing during waking. For example, areas of the fusiform gyrus are both selectively activated in REM (Braun et al. 1997; 1998; Nofzinger et al. 1997) and are the portion of the ventral object recognition stream involved in face recognition (Kanwisher et al. 1997; McCarthy et al. 1997) which is a common, although often bizarrely uncertain and altered dream feature. Furthermore, in a very important recent finding, the same extrastriate ventral occipital areas are activated during waking hallucinations in patients with Charles Bonnet syndrome (Ffytche et al. 1998).

REM sleep combines the *activation* of visual association (e.g., Brodmann areas 37 and 19) and paralimbic cortices with the *deactivation* of primary visual and dorsolateral prefrontal cortices (Braun et al. 1997; 1998). The far lesser role of primary visual cortex (zone 10 in Fig. 7) in REM activation (Braun et al. 1997; 1998) and dream generation (Solms 1997) combines with the known sensory input and motor output blockade of REM sleep (Hobson 1988b; see zones 7, 8, and 10 in Fig. 7) to reinforce the concept that sensory information processing in dreaming may begin at levels downstream from primary sensory cortices (Braun et al. 1998).

Inferior parietal lobe (zone 9 in Fig. 7): The inferior parietal lobe, especially Brodmann's area 40, may generate the perception of a fictive dream space necessary for the global experience of dreaming (Solms 1997a). This is a brain region thought to be important for spatial imagery construction. Even with visual systems intact, destruction of this area in either hemisphere causes global cessation of dreaming (Solms 1997a). Other neuropsychological studies have suggested a vital role for this area in dreaming (Doricchi & Violani 1992). Turning to PET data, Maquet et al. (1996) note activation of the right parietal operculum despite general deactivation in much of the parietal cortex. Interesting to note, both lesion (Solms 1997a) and PET studies (Maquet et al. 1996) suggest a greater importance to dreaming of this area in the right versus the left hemisphere.

Dorsolateral prefrontal executive association cortex (zone 4 in Fig. 7): Neuronal modeling (Mamelak & Hobson 1989a) as well as neuroimaging (Braun et al. 1997; Maquet & Franck 1997) have suggested a possible origin of dream-associated executive deficiencies in the REM-associated changes in frontal lobe functioning. The REM-associated activation of medial paralimbic frontal cortex contrasts with the prominent deactivation in the executive portions of the frontal cortex. The deactivation of the dorsolateral prefrontal cortices during sleep and their failure to then reactivate along with medial and parietal cortical structures in REM sleep underlies the prominent executive deficiencies of dream mentation.

The left dorsolateral prefrontal cortex has been shown to be selectively activated during human reasoning tasks (Goel et al. 1998). Its deactivation could account for the illogical ad hoc explanations offered for bizarre occurrences (Williams et al. 1992). Similarly, the dorsolateral prefrontal cortices have been consistently shown to activate during episodic and working memory tasks (Brewer et al. 1998; Cohen et al. 1997; Courtney et al. 1997; Fletcher et al. 1997; Tulving et al. 1996; Wagner et al. 1998); their deactivation in REM may contribute to the prominent mnemonic deficits in dreaming noted above in section 2.3.4. The other area found by PET to deactivate in REM compared to waking was the posterior cingulate cortex (Braun et al. 1997; Maquet et al. 1996; Nofzinger et al. 1997). This cortical area, especially its posterior-most retrosplenial portion, has been consistently implicated in episodic memory function with lesions to it resulting in episodic memory deficits (Maddock 1999).

Similarly, the dorsolateral prefrontal cortex is a structure specialized for the central executive function of working memory (Baddely 1998; Goldman-Rakic 1996); its deactivation in REM would thus result in the disorientation and bizarre uncertainties (Hobson et al. 1987) characteristic of dream mentation. Failures of working memory are prominent in dreaming. For example, scene shifts are experienced without reflection (Hobson et al. 1998b). In this sense, the dreamer could be seen as experiencing a frontal lobe dysfunction similar to "goal neglect" (see Baddely 1998; Duncan et al. 1996). Notable also is a recent PET study showing reduced working memory (WM) task-related activity in the right midfrontal gyrus in response to cholinergic enhancement with physostigmine (Furey et al. 1997). However, in this study, improved WM performance also resulted from cholinergic enhancement (Furey et al. 1997). Finally, Doricchi et al. (1993) present a convincing argument for an attenuation of frontal eye field inhibition of reflexive saccades during REM.

Interesting to note, hypoperfusion of the frontal cortex has been associated with pathological temporal limbic activation in epilepsy (Rabinowicz et al. 1997) and reciprocal inhibition between frontal and limbic areas has been hypothesized in theories on the etiology of schizophrenia (Weinberger 1995). REM sleep dreaming could thus be seen to involve a normal physiological state of the brain analogous to psychopathological conditions (Hobson 1994; 1997b; 1999b) in which limbic hyperactivation is combined with frontal hypoactivation.

Hypothetical dynamic interactions of brain regions during normal dreaming: In the view of modern cognitive neuroscience, component subsystems of global states of consciousness like dreaming are physically instantiated in networks or circuits each consisting of several to many discrete brain regions (e.g., Cummings 1993; Mesulam 1998; Nadel 1994).

Mesulam (1998) hypothesizes five global circuits each subserving a broad cognitive domain: spatial awareness;

language; explicit memory and emotion; face and object recognition; and working memory-executive function. In Mesulam's "selectively distributed processing" model of these networks, numerous brain regions participate in each cognitive function as opposed to there being functional brain "centers" for different aspects of cognition. The same individual brain region might participate in several functional networks which are differentiated by their component nodes (Mesulam 1998).

In a particular network, Mesulam suggests that certain multimodal nodes or "epicentres" serve to coordinate the functioning of (or to "bind") subsidiary nodes and are, therefore, key to determining this network's unique cognitive function. For example, epicenters in the transmodal posterior parietal cortex (e.g., Brodmann area 40) and the prefrontal cortex (e.g., Brodmann area 46) may coordinate nodes of a working memory-executive function network (Mesulam 1998). The same network can affect subcomponents of a more global cognitive function (e.g., explicit memory) by varying the relative levels of activation in the component nodes (Mesulam 1998).

We propose that during dreaming relative to waking, there is a relative dysfacilitation of the working memory-executive function network combined with relative facilitation of networks subserving emotional and memory consolidation processes. This echoes Braun et al.'s (1997) suggestion that "the 'limbic' loop connecting ventral striatum, anterior thalamus and paralimbic cortices, appears 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" (p. 1191). Given the sensory phenomenology of dreaming relative to waking (sect. 2), it might also be hypothesized that, during dreaming, the efficient functioning of spatial awareness and object recognition may be better preserved than the language networks resulting in predominance of visual versus auditory hallucinosis.

Flow of information between the regions localized by neuroimaging or lesion studies as crucial to dreaming is undoubtedly multidirectional with abundant re-entrant feedback and feedforward loops. At present, we propose three generalizations regarding this information flow: (1) Ascending arousal systems activate the forebrain regions involved in dream construction and do so in a manner chemically and anatomically different from that subserving waking arousal processes. (2) Cortical circuits activated in dreaming favor more medial circuits linking posterior association and anterior and posterior paralimbic areas (represented by central crescent in Fig. 7) versus circuits including the primary sensory cortex and/or frontal executive regions (see Braun et al. 1998). Such a predominance of medial circuitry in REM may underlie findings from lesion studies that features of dreaming are only weakly lateralized (Antrobus 1987; Doricchi & Violani 1992; Solms 1997a). (3) Subcortical circuits involving the limbic structures, basal ganglia, diencephalon, and the brainstem contribute strongly to regional brain activation in REM and, therefore, probably to the physiological substrate of dreaming.

Very promising new technologies, such as functional magnetic resonance imaging (e.g., Huang-Hellinger et al. 1995; Portas et al. 1999), transcranial magnetic stimulation (e.g., Cohrs et al. 1998), magnetic resonance spectroscopy (e.g., Bartha et al. 1999), receptor radio ligand PET (e.g., Sudo et al. 1998), near infrared spectroscopy (e.g., Tagaya et al. 1999) and dipole tracing (e.g., Inoue et al. 1999b) are just now being applied to sleep science. Further research with such tools will undoubtedly further specify the key brain circuits and systems involved in the global experience and component elements of dreaming.

Accommodation of NREM dreaming in an updated activation synthesis model: As explained in detail in section 4, the AIM model of conscious state control predicts numerous gradations between states as well as possible dissociations of state characteristics during such transitions. This occurs because activation, input source, and modulation can, to some extent, vary independently.

Increased vividness of Stage 2 NREM dreaming near the end of the normal sleep period has been attributed to circadian increases in brain activation occurring at this time (Antrobus et al. 1995; Cicogna et al. 1998). Toward morning, activation (and perhaps also input source and modulation) may *differ the least* between Stage 2 periods and their adjacent REM periods compared to the other times of the night. Therefore, admixture of REM-like phenomena within Stage 2 NREM (including the brain activation accompanying REM) may be *maximal* late in the sleep bout and may sustain much longer and more vivid NREM dreaming. In other words, late night Stage 2 NREM dreaming may occur during a time when cortical and subcortical areas linked to dreaming (see Figs. 6 and 7) are becoming reactivated in anticipation of the next REM period. Alternatively, the activation of these areas may not as greatly diminish with the transition from late REM to late Stage 2 as it does earlier in the night during the descent from waking into slow wave sleep. (For a complete discussion of these possibilities see Nielsen's target article.)

Such transitional states might include the human equivalent of the well documented sleep stage termed SP (slow wave sleep with PGO waves) which heralds REM periods in the cat (Callaway et al. 1987; Datta 1995) and which has recently been hypothesized to occur in humans (Gottesmann 1999). In humans, recent experimental evidence has shown enhancement of visual imagery in Stage 2 NREM by acoustic stimuli below the threshold of awakening but of an intensity comparable to those triggering PGO waves in animals (Conduit et al. 1997; Drucker-Colin et al. 1983; Morrison et al. 1999). Therefore REM-like tonic (enhanced activation) as well as phasic (SP PGO waves) features may accompany late NREM and enhance dreaming at this time without in any way contradicting the assumption that REM sleep phenomena reflect the fullest expression of the physiological substrate of dreaming.

Nielsen (1999; and this volume) has recently proposed a very similar mechanism for the ubiquity of NREM dreaming which he terms "phantom" or "covert" REM sleep. According to this concept, elements of REM-like activation may commonly occur during NREM without, however, producing the full complement of signs necessary to score REM by Rechtschaffen and Kales's (1968) criteria. Nielsen suggests several examples of such partial expressions of REM physiology such as "missing" first REM periods with EEG desynchrony but lacking REMs or atonia, or NREM erections occurring with ultradian periodicity. Indeed, recent evidence has shown that the transition from NREM to REM sleep shows a typical order of appearance of the cardinal physiological signs of REM sleep as follows: atonia, saw-tooth waves, REMs (Sato et al. 1997).

Further candidate markers of "phantom REM sleep" in-

clude the numerous NREM events which investigators have correlated with mental phenomena ever since the lack of an exclusive sleep stage correlate to dreaming led them to seek physiological correlates of dreaming among the discrete phasic physiological events of sleep (Foulkes & Pope 1973; Molinari & Foulkes 1969; Ogilvie et al. 1980; Pivik 1991). For example, within NREM, phasic spinal reflex inhibition was associated with greater recall, auditory imagery, and hostility (Pivik 1991); PIPs (phasic integrated potentials) with enhanced recall (Rechtschaffen et al. 1972); and sleep onset theta bursts with discontinuity (Foulkes & Pope 1973). Such potential correlates continue to be identified and include the very rapid eye movements (VREMs) associated with K-complexes (Serafetinides 1991) as well as NREM imagery envoked by external stimuli (Conduit et al. 1997). As psychophysiological techniques in sleep research become increasingly sophisticated, it is likely that additional tonic and phasic correlates of sleep mentation will emerge in studies of both REM and NREM (e.g., Germain et al. 1999; Miro et al. 1999; Paiva & Guimaraes 1999; Rochlen et al. 1998; Takeuchi et al. 1999a; 1999b).

3.3.5. Comparison of activation-only to activation-synthesis models' explanations for the origin of dream imagery in relation to REM saccades and attentional processes. Perhaps the greatest disagreement between "activation-only" models (sect. 3.3.1 above) and the activation-synthesis model (sect. 3.3.4 above) regards the origin of dream imagery in relation to REM sleep saccades and the dreamer's attentional processes. While the original activation-synthesis model argues that visual imagery and eye movements are largely initiated by chaotic brain stem activity transmitted to the cortex via ascending signals such as PGO waves (Hobson & McCarley 1977), Antrobus has argued for a primarily cortical origin for the visual imagery, REMs and even the PGO waves during dreaming (Antrobus 1990; Antrobus et al. 1995). A similar model for a cortical attentionally driven origin of REM saccades is presented as a revised scanning hypothesis (see below) by Herman (1992). We will address this controversy by integrating data from studies of neuroimaging, the neurophysiology of saccadic eye movement control and attentional processes. We will show that the relationship of dream imagery to REM saccades must involve the integrated activity of heterogenous brain mechanisms only some of which are initiated by exclusively top-down or bottom-up processes.

Before launching into this discussion it is important to situate its significance in a historical context. When REM sleep was first discovered and assumed to be a unique neurophysiological substrate of dreaming, it was logical to postulate a one-to-one correlation between the eye movements and the direction of hallucinated gaze in dreams. This "scanning hypothesis" (Roffwarg et al. 1962) was the strongest and most specific of the many theories of brain-mind isomorphism. In detailing the many difficulties that this theory has encountered, our goal is twofold: first, we want to emphasize that the field of dream research foundered because of its overinvestment in still unresolved arguments about scanning, and second, that promising alternative approaches to the psychophysiology of dreaming were overlooked because of this overinvestment. We will conclude our discussion by an appeal to keep the question of eye movement and dream imagery open until methods more adequate to its investigation are developed.

3.3.5.1. Activation-only theories of a cortical origin for REMs and PGO waves. Antrobus (1990) and Herman (1992) interpret the work of Herman et al. (1981; 1983; 1984) which shows partial confirmation of the scanning hypothesis (Roffwarg et al. 1962) as supportive of a largely cortical origin for the neural signals which initiate processes leading to dream imagery. Antrobus (1990) suggests that when cortical activation reaches a certain level due to the RAS-mediated arousal of REM sleep, the frontal eye fields are activated and begin to attempt to direct the eyes toward the virtual images being generated in a similarly activated posterior cortex.

In this model, REM saccades are the frontal eye fields' attempt to foveate on such fictive images and these cortical signals are transmitted to brainstem oculomotor nuclei via the same cortico-cerebellar pathways used in the fine-tuning of waking saccades (Antrobus 1990; Antrobus et al. 1995). PGO waves, in this model, are conceived as being similarly cortically evoked via cortico-cerebellar pathways connecting with the brachium conjunctivum, which, in turn, connects the cerebellum to pontine PGO elements (Antrobus 1990). In the Antrobus model, PGO waves may then provide secondary feedback to the frontal eye fields which remain the original instigator of both REMs and PGO waves (Antrobus 1990; Antrobus et al. 1995).

The failure of others (e.g., Jacobs et al. 1972; Moskowitz & Berger 1969) to replicate Roffwarg's original finding as well as the dissimilarities between waking and REM saccades are explained in various ways by current proponents of the scanning hypothesis. Herman (1992) emphasizes that early studies failed to take into account the dreamer's fictive head movements which, in dreaming, may coincide with cortically directed saccades and modify such saccades via the vestibuloocular reflex. Others suggest that visually guided, cortically initiated REM eye movements, in contrast to waking REMs, are saccadic movements toward stationary hallucinatory versus moving real targets (Hong et al. 1997). Although such explanations are plausible and are supported by some data (Herman 1992; Hong et al. 1997), much more work will be required to fully resolve the conflicting findings and daunting methodological challenges imposed by the various versions of the scanning hypothesis.

3.3.5.2. Contributions from neuroimaging studies of REM sleep. Recently, some investigators have suggested that neuroimaging technologies can shed new light on the scanning hypothesis. In particular, Antrobus et al. (1995) and Hong et al. (1997) cite a recent ^{18}fluorodeoxyglucose (FDG) PET study (Hong et al. 1995) as supporting their revised scanning hypothesis. Hong et al. (1995) showed that REM period eye movement number was positively correlated with glucose uptake in frontal cortical areas associated with saccadic eye movement control, the midline executive attentional system, and the visuospatial attentional system. Other authors have since interpreted these results as generally supporting visual scanning of the hallucinatory dream scene (e.g., Gottesmann 1997).

The major drawback of the Hong et al. (1995) study is that the measured variable was not REM activation relative to waking or NREM but rather the *within* REM and within waking correlations between eye movements and glucose uptake. Therefore, the only state-dependent comparison here involves comparing the *degree of covariation* between REM counts and cerebral metabolism in regions of interest during waking as compared to during REM. In an ear-

lier analysis of the same data set, this group had compared actual regional glucose metabolic rate between REM and waking reporting relatively fewer differences than did later PET studies (see below) although they did observe relatively greater activation of the anterior cingulate in REM (Buchsbaum et al. 1989).

Unlike the Hong study, later ^{15}O PET studies found state-specific *negative* correlations between REM and cerebral blood flow in the dorsolateral prefrontal cortex with the positive correlations found instead in pontine tegmental, thalamic, and subcortical and cortical limbic structures (Braun et al. 1997; Maquet et al. 1996). Using the ^{18}FDG PET method, Nofzinger et al. (1997) also found this thalamic, amygdala, and cingulate activation. Significantly for the scanning hypothesis, the ^{15}O PET studies (Braun et al. 1997, 1998; Maquet et al. 1996) did not find relative activation during REM, as compared to waking or to NREM, in many of the saccade and attention-related cortical areas where Hong et al. (1995) found their positive correlations between eye movement number and glucose uptake (e.g., frontal eye fields, dorsolateral prefrontal cortex, left parietal operculum, precuneus).

It is important to note the significant methodological differences between the two PET imaging techniques (see Braun et al. 1997 and Nofzinger et al. 1997 for discussions). For example, ^{18}FDG techniques integrate cortical activity over a much longer time than ^{15}O PET (30 minutes versus 5 minutes) and thus ^{15}O may better characterize shorter, more discrete PSG-defined sleep conditions (Braun et al. 1997). Therefore, although conclusions from both PET methods must acknowledge the limitations described above (sect. 3.1.1), activation of broader areas may be inherent to ^{18}FDG compared to ^{15}O PET. This difference is evidenced here by the greater area activated in ^{18}FDG studies (Nofzinger et al. 1997) compared to ^{15}O PET studies (Braun et al. 1997; Maquet et al. 1996) (see Table 2).

The utility of both methods for testing the scanning hypothesis is, therefore, limited because: (1) neither method can distinguish between tonic and phasic changes associated with REM sleep, and (2) neither can provide information on whether cortical activation precedes or follows REMs. Moreover, human PET studies could support either frontal eye fields and attentional systems being activated in response to brain stem activity or *vice versa.*

It seems quite likely to us that both possibilities will prove to be true. In other words, we suggest that some REM sleep eye movements are initiated in the brain stem, some in the frontal eye fields and, possibly, some in other nodes in the saccade-generation network (e.g., superior colliculus). Moreover, being elements of a network, these loci will robustly interact. Therefore, in the Hong et al. study, the similar patterns of correlation between metabolic activation and eye movement counts in both REM sleep and waking is not surprising given the approximately 30 minutes of ^{18}FDG uptake during REM and waking saccade generation. Over this extended period, many nodes in saccade-generation networks may become activated in rough proportion to total eye movement counts.

3.3.5.3. Contributions from the neurophysiology of saccadic eye movement control. A heterogeneity among the brain mechanisms controlling waking saccades in primates is a widely documented finding (Brooks 1999; Tehovnik et al. 1994) and certain of these circuits are independent of the frontal eye fields (Tehovnik et al. 1994). Heterogeneity of REM saccadic eye movement control mechanisms was first suggested by an extensive series of lesion experiments in Jouvet's laboratory which showed that various forebrain structures add complexity to eye movements arising in the pons of cats (Jeannerod et al. 1965). Even the pontine cat, which lacked all the forebrain structures involved in eye movement control, still had some eye movements in REM (Jeannerod et al. 1965; Jouvet 1962). (For a thorough review and interpretation of these lesion studies see Doricchi et al. 1993.) Although citing those studies showing persistence of REMs and PGOs in decerebrate animals, Herman (1992) and Antrobus (1990) suggested that the decreased number, loss of bursting patterns, and stereotyped repetitiveness of REMs in such preparations indicates that the cortex controls the phasic components of REMs (presumably directing them toward internal hallucinatory stimuli). In their opinion, such purely pontine-generated REMs reflect only a tonic, repetitious baseline activation of the oculomotor nuclei while the cortex controls all potentially information-bearing REMs.

But additional findings must also be explained. For example, in the decerebrate cat, Pompeiano has been able to increase the frequency and clustering of REMs simply by increasing the cholinergic drive on the brain stem with physostigmine (Pompeiano 1980). Recent work in the cat has further demonstrated a diversity in neural mechanisms generating the saccades of REM and waking (Vanni-Mercier & Debilly 1998; Vanni-Mercier et al. 1994) with a specific region of the pons being implicated in the synchronization of REMs and PGO waves (Vanni-Mercier & Debilly 1998; Vanni-Mercier et al. 1996). This proves that the pons is not only necessary for all REM sleep eye movements but sufficient to generate many of them on its own. Under normal conditions, however, REM saccades, like those of waking, are very likely controlled by the final common pathway pontine generator whose output is modified by interactions with forebrain structures (Goldberg et al. 1991; Hepp et al. 1989; Ito 1987; Pierrot-Deseilligny et al. 1995), especially interactions between reflexively orienting attentional systems in the parietal cortex and superior colliculus as has been recently discovered and elucidated by Doricchi et al (1993).

3.3.5.4. The heterogeneity of attentional mechanisms. The diversity of attentional mechanisms (see Posner 1994a and Kinchla 1992) further argues for a heterogeneity of attentional-oculomotor interaction among behavioral states. A widely distributed network of interconnected structures is known to participate in both attentional processes and the oculomotor control of saccades in waking (see, for example, Corbetta et al. 1993; Paus et al. 1993; Petit et al. 1996; Pierrot-Deseilligny et al. 1995; Sweeny et al. 1996; Wurtz & Munoz 1994). Such structures include those found by neuroimaging (e.g., Maquet et al. 1996) to be activated in REM such as the anterior cingulate cortex (Paus et al. 1993) as well as those shown to be deactivated in REM such as the prefrontal cortex (Boch & Goldberg 1989). An important dissociation between the frontally based attentional modulation of waking saccades and the lack of such frontal modulation in REM has been described by Doricchi et al. (1993; 1996) via the study of hemineglect patients.

3.3.5.5. Systems producing REM saccades with and without participation of cortical attentional structures. Given the above-documented diversity and connectivity within

functional brain networks, it is likely that complex, reentrant interplay between cortical and subcortical structures will determine the relationships between REM saccades, dream imagery, and attentional processes (see Doricchi et al. 1993). In contrast, Antrobus's theory of an autogenous cortical origin of REM saccades predicts that phasic activity of the pontine generator, which must occur to produce any saccade (Goldberg et al. 1991), should always *follow* an initiating event in the cortex (the hallucinated, attended-to and then "saccaded-to" dream image). This can be termed a "top-down-only" mechanism. Contrary to this prediction, we now show that there are data indicating that pontine brain stem cells fire *prior* to REM saccades (a "bottom-up-only" mechanism) as well as *simultaneously* with REM saccades (a "mixed bottom-up and top-down" mechanism) in addition to *after* a saccade (as predicted by Antrobus's "top-down-only" mechanism).

Evidence for bottom-up only mechanisms: In the cat, pontine gigantocellular tegmental field (FTG) cells increase their firing rate 150 to 100 msec before eye movement (EM) onset in REM sleep (Pivik et al. 1977). Additional evidence for subcortical potentials anticipating REMs has recently been reviewed in Gottesmann (1997). Therefore, pontine PGO-triggering or transmitting cells may directly excite paramedian pontine reticular saccade burst cells within the pons and thereby initiate horizontal saccades whose directionality is conveyed to the occipital cortex by PGO waves to elicit visual imagery *following* the saccade (Hobson & McCarley 1977). The fact that the primary PGO wave is consistently ipsilateral to the directionality of a REM suggests that PGO waves can convey eye movement directional information to the posterior cortex (Datta & Hobson 1994; Monaco et al. 1984; Nelson et al. 1983). In this regard, it is also notable that, at the level of the pontine generation system, burst cells trigger saccades which are ipsiversive while at the level of the superior colliculus and above, control is contralateral (Goldberg et al. 1991). The impingement of ocular premotor excitatory corollary discharge on PGO bursting cells in the pons provides a mechanism whereby such directional information can be transferred from oculomotor neurons to rostral structures (Callaway et al. 1987; Nelson et al. 1983; Steriade et al. 1990).

A collicular intermediary allows mixed bottom-up and top-down control of REMs: The hypothesis that the superior colliculus can generate REM saccades independently of the frontal eye fields was first proposed and elaborated by Doricchi et al. (1993; 1996). Efferents from the PPT project to the superior colliculus (Beninato & Spencer 1986; Krauthamer et al. 1995; Rye 1997) and most cortical saccade-generating commands communicate with the brain stem saccade-generating system via the superior colliculus (Goldberg et al. 1991; Sparks & Hartwich-Young 1989). Moreover, the superior colliculus is able to initiate saccades even when frontal eye fields are damaged (Henik et al. 1994; Rafal et al. 1990; Tehovnik et al. 1994).

The potential importance of collicular mechanisms to the generation of REM sleep saccades is further suggested by the following three findings: (1) In REM sleep of the cat, superior colliculus damage decreases amplitude of saccades (Jeannerod et al. 1965). (2) In the albino rat, the superior colliculus is essential to the initiation of REM by the "lights-off" stimulus (Miller et al. 1997). (3) In humans, an extrageniculate or retinotectal orienting system centered in the superior colliculus has recently been extensively documented (Henik et al. 1994; Rafal & Robertson 1994; Rafal et al. 1990; 1991; Sparks & Groh 1994; Wurtz & Munoz 1994). The failure of leftward hemineglect (i.e., right hemisphere parietal damage) patients to generate leftward REM-sleep saccades despite preserved (and rehabilitatively improvable) waking leftward saccades has led Doricchi et al. (1993; 1996) to propose the predominant involvement of reflexively orienting parieto-collicular circuits in the generation of REM saccades. Doricchi et al. (1993) go on to suggest that subcortically generated impulses (such as PGO waves) may constitute the endogenous stimuli to which the parieto-collicular system reflexively responds in REM.

If pontine PGO-triggering or transmitting cells directly excited collicular cells, then paramedian pontine reticular saccade burst cells could be excited and produce saccades without the involvement of cortical saccade-related centers. Under such conditions, PGO activation of the occipital cortex via the LGB and PGO-related initiation of saccades could occur *simultaneously.*

Evidence for top-down only mechanisms: At least some of the saccades of REM may be commanded by preceding activity of cortical structures (e.g., frontal eye fields), although even this possibility does not require that the dreamer is specifically orienting to hallucinated imagery from the posterior cortex. For example, although the Hong et al. (1995) PET data suggests that activation of certain cortical areas is temporally coincident with REM periods containing a high eye movement density, this correlation could either indicate causality or simply be secondary to intense PGO-associated activation of multiple cortical foci (see Amzica & Steriade 1996).

Additional evidence, however, suggests that cortical initiation of REM sleep saccades is in fact possible. For example: (1) REM density is reduced in patients with parietal damage (Greenberg 1966). (2) Hemi-inattention patients lose most REM-sleep saccades that are directed toward the visual field contralateral to their lesion (Doricchi et al. 1991; 1993; 1996) indicating the importance of parietal but not frontal cortices. (3) Directional eye movements can be voluntarily made during lucid REM dreaming (LaBerge et al. 1981). Again, however, none of these findings argue for an exclusively cortical initiation of REM saccades.

The robust heterogeneity of mechanisms for REM sleep saccade generation suggests that REM sleep saccades might differ from waking saccades: Behavioral state-related differences in saccade generation could arise either from an actual differential activation of brain regions or from differential contributions among the multiple cerebral saccade mechanisms (networks) in different behavioral states. And in fact such differences have frequently been described in both humans and in animal models (see Doricchi et al. 1993 and Gottesmann 1997 for recent reviews). For example, in humans, REM sleep saccades have been shown to be slower than those occurring during waking (Aserinsky et al. 1985; Fukuda et al. 1981; Jeannerod & Mouret 1963; Porte 1996). Moreover, saccades in the two states have been shown to possess a different velocity/amplitude relationship (Aserinsky et al. 1985; Fukuda et al. 1981). Studies of human eye movements in sleep predating the discovery of REM (reviewed by Gottesmann 1997) also revealed eye movements atypical in comparison to waking eye movements. In humans, another suggestion of neural control differences between REM and waking saccades in addition to their dissociation in hemi-inattention patients (Doricchi et al. 1991; 1993; 1996) are the amplitude-related constraints in a re-

ported complementary relationship between experimentally controlled waking saccades and subsequent saccades in REM (DeGennaro et al. 1995). One final argument that REM-sleep saccades do not require the scanning of hallucinated dream imagery is the fact that such saccades are ubiquitous in the REM sleep of the congenitally blind who generally lack all visual dream imagery (Amadeo & Gomez 1966; Gross et al. 1965; see Weinstein et al. 1991 for a review).

In cats, REM saccades show a differing maximum velocity/amplitude (main sequence) relationship from that observed in waking (Vanni-Mercier et al. 1994). Moreover, in monkeys, REM saccades are disjunctive between the two eyes (Zhou & King 1997) and otherwise unlike those of waking (Fuchs & Ron 1968) while, unlike wake saccades, the REM saccades of cats are directionally asymmetrical (Vanni-Mercier et al. 1994). These results have led the authors of these three animal studies to argue against the scanning hypothesis. Studies such as these lead Vanni-Mercier et al. (1994) to conclude that REM and wake saccades do not share the same neural control circuits and that "eye movements of paradoxical sleep rather represent a stereotyped repeated pattern which is independent of dream content" (p. 1301). Authors of one cat study have, however, suggested that the REM saccades they observed are suggestive of scanning hallucinated imagery (Soh et al. 1992).

3.3.5.6. Conclusion. In conclusion, although some authors have interpreted the findings of Hong et al. (1995) as evidence for the scanning hypothesis (Antrobus et al. 1995; Hong et al. 1995; 1997), considerable improvement in temporal and deep structural resolution will be necessary before such evidence can be considered to be definitive. Such agnosticism is shared by the originator of the scanning hypothesis, Roffwarg (Roffwarg & Belenky 1996), who also emphasizes the need to visualize both cortical and subcortical structures simultaneously before assigning the initiation of REM sleep eye movements to either region. We therefore regard the question of exactly how the specific visual imagery of dreams is generated and attended to as being still entirely open at this time. One way to close this gap would be to compare cerebral blood flow patterns in subjects making directed visual images in waking with directed visual image-making in lucid REM sleep dreaming. In addition, it may soon be possible to temporarily deactivate specific cortical areas with transcranial magnetic stimulation during REM.

4. A new state space model: AIM

As the activation-synthesis model has evolved, it has metamorphosed into the three-dimensional framework of the AIM model. We now update the activation-synthesis concept as follows: (1) high levels of cortical activation (high values of "A") are a correlate of the mind's ability to access and manipulate significant amounts of stored information from the brain during dream synthesis; (2) the blockade of external sensory input and its functional replacement by internally generated REM sleep events such as PGO waves (internal sources of "I") provide the specific activation of sensory and affective centers that prime the cortex for dream construction; and (3) the shift of the brain from aminergic to cholinergic neuromodulation (low ratios of aminergic to cholinergic neuromodulation, "M") alters the mnemonic capacity of the brain-mind and reduces the reliability of cortical circuits, increasing the likelihood of bizarre temporal sequences and associations which are uncritically accepted as waking reality when we are dreaming.

As the brain shifts from alert waking through drowsiness to NREM and REM sleep, a concerted set of physiological and chemical changes occur in the brain and periphery. Global changes are seen in all major physiological systems, including the nervous, respiratory, cardiac, renal, immunological, endocrine, and motor systems (Gottesmann 1997; Hobson 1989; Orem 1980; 2000). The changes in central neurophysiology include changes in gating of sensory input, inhibition of motor output and neuromodulation of widespread regions of the cortex (Gottesmann 1997; Hobson 1988b; Hobson & Steriade 1986; Steriade & McCarley 1990a). More specific neurophysiological changes involve both tonic and phasic activation of numerous brain regions, including, but not limited to, the medullary bulbar reticular formation, the pontine reticular formation, the hypothalamus, the lateral geniculate nucleus, the amygdala, the hippocampus, and the limbic and unimodal visual associative cortex, as well as regional *de*activation of the dorsal raphe, locus coeruleus, and multimodal association cortices (Amzica & Steriade 1996; Braun et al. 1997; Hobson & Steriade 1986; Maquet et al. 1996; Nofzinger et al. 1997; Steriade & McCarley 1990a). (See Table 2 and Fig. 7.) Not surprisingly, these changes are accompanied by dramatic shifts in the activity of the mind.

In the past, there has been a tendency to describe these shifting brain-mind states along a single axis, from wide awake to deeply asleep. The changes in mental state were perceived as dependent on variations in a single underlying parameter such as activity of the reticular activation system or overall brain activity as reflected in the EEG (e.g., Moruzzi & Magoun 1949). While conceptually useful at the time, it was clear from the outset that this activation concept was inadequate. And nowhere was this inadequacy more evident than in REM sleep, otherwise known as "paradoxical" sleep specifically because of the dissociation between level of behavioral arousal (low) and level of brain activation (high) (e.g., Jouvet & Michel 1959).

In response to this problem, researchers have recently suggested that the source of inputs for the brain-mind be considered a second dimension of brain-mind state (e.g., Antrobus 1991; Hobson 1990; 1992a). In their analysis of waking and dreaming, the neurophysiologists Llinas and Pare (1991) have ascribed all of the differences in subjective experience to the off-line status of the brain in REM. Likewise, the psychologist Antrobus has argued that sensory deprivation in the wake state produces dreamlike mentation because: (1) the brain is highly activated as it is in REM sleep (indicated by high frequency, low amplitude EEG patterns); and (2) the brain-mind has lost external sensory inputs and, again as in REM sleep, must turn to internal sources of input (Antrobus 1991; Reinsel et al. 1992). Although these two parameters tend to shift in concert, with brain activation and external input sources both decreasing as one moves from alert waking to deep sleep, such states as REM sleep (high brain activation and low external inputs) and sleep walking (low brain activation with some degree of preserved external inputs as evidenced by sleep walkers' ability to navigate) point out the potential independence of these two axes.

To this two-dimensional model we have added a critical third dimension which reflects the "mode" of information processing carried out by the brain-mind, a mode determined by the action of cortical neuromodulators (Hobson

1990; 1992a; 1997a). Within the brain, widespread cortical neuromodulation is effected by at least five specific neurotransmitters – acetylcholine, serotonin, norepinephrine, dopamine, and histamine (Cooper et al. 1996; Hobson & Steriade 1986; Saper et al. 1997; Steriade & McCarley 1990a) and probably others such as adenosine (McCarley et al. 1997) and orexin (Chimelli et al. 1999; Lin et al. 1999). With the exception of adenosine, each of the above neuromodulatory substances is produced by a highly localized group of subcortical neurons which project directly to widespread areas of the forebrain and are known to have powerful effects on mental state. Three of these – acetylcholine, serotonin, and norepinephrine – are known to play critical roles in the transitions from waking to NREM and then to REM sleep (Hobson & Steriade 1986; Steriade & McCarley 1990a).

Histamine and orexin also appear to be involved in sleep-wake transitions (Saper et al. 1997; Shiromani et al. 1999; Chimelli et al. 1999). Although dopamine does not appear to be a prime mover of normal conscious state regulation (Miller et al. 1983; Steinfels et al. 1983), it probably plays a major if perhaps secondary role in sleep regulation as evidenced by its interactions with other neuromodulatory systems (e.g., Kapur & Remington 1996; Mamelak 1991), its effects on normal sleep (Gillin et al. 1973; Olive et al. 1998; Post et al. 1974; Python et al. 1996; Trampus et al. 1993), and the effects of REM sleep deprivation on dopaminergic neurotransmission (Brock et al. 1995; Nunes et al. 1994; Tufik et al. 1978). It is thus not surprising that most of the psychopharmacological drugs used today which directly affect this neuromodulatory mode (Function M), often alter sleep and dreaming as well (e.g., Armitage et al. 1995; Lepkifker et al. 1995; Markowitz 1991; Pace-Schott et al. 1998; 1999; 2001; Sharf et al. 1978; Silvestri et al. 1998; in press; Vogel 1975; Vogel et al. 1990).

We have described this three-dimensional model of brain-mind state in our "AIM Model" (Hobson 1990; 1992a; 1997a; Hobson & Stickgold 1994b; Kahn et al. 1997). AIM makes three major claims:

1. AIM proposes that conscious states are in large part determined by three interdependent processes, namely the level of brain activation ("A"), the origin of inputs ("I") to the activated areas, and the relative levels of activation of aminergic (noradrenergic and serotonergic) and cholinergic neuromodulators ("M"). While these variables tend to vary in concert with one another, many paradoxical and dissociated mental states, both normal and abnormal, arise from the sometimes strikingly independent variation of these parameters as we will shortly illustrate.

2. The AIM Model proposes that the universe of possible brain-mind states can be construed as a three-dimensional state space, with axes A, I, and M (activation, input, and mode), and that the state of the brain-mind at any given instant of time can be described as a point in this space. Since the AIM model represents brain-mind state as a sequence of points, time is a fourth dimension of the model.

3. The AIM model proposes that while stable and reproducible mental states reflect the tendency of the brain-mind to occupy a small number of fixed locations in this state space, corresponding to such identified brain-mind states as alert wake or vivid REM sleep dreaming (see Kahn et al. 1997), all three parameters defining the state space are continuous variables, and any point in the state space can in theory be occupied. In the remainder of this section, we will discuss each of these three claims in detail.

4.1. The three dimensions of the state space

Experimental testing of the AIM Model requires that each of the three parametric axes of the brain-mind state space be directly measured and, ideally, manipulated. Toward this end, we have attempted to define the underlying parameters as well as to indicate how they can best be measured (see again Fig. 1). As we shall show below, reasonable measures of A and I can be readily obtained in both humans and animals. At the present time, M can only be measured directly in animals, but because its value can be manipulated experimentally in humans with pharmacological agents, its role in human conscious state determination can be indirectly assessed.

4.1.1. Activation. Conscious states show a clear-cut dependence on brain activation level. The production of conscious experience, as reflected in the length, intensity, and complexity of subjective reports of mental activity, as well as in levels of arousal and alertness, is generally greater in waking and in REM sleep than it is in deep NREM sleep and greater in alert waking than in quiet resting. The AIM model predicts that this physiological measure, "A," reflects the rate at which the brain-mind can process information regardless of its source (measured as "I") or its mode of processing ("M"). This activation parameter is based upon Moruzzi and Magoun's concept of a reticular activating system (Moruzzi & Magoun 1949; Steriade et al. 1980). Broad consensus already exists for the importance of this first dimension of the AIM Model.

In its simplest form, brain activation is defined as the mean firing frequency of brain stem neurons. It can be approximated in both humans and animals from the EEG spectrum, with increasing activation reflected by relatively high power in the high frequency range and relatively low power at low frequencies. In animals, the activity of the reticular activating system can be precisely quantified from the frequency of firing of neurons in the midbrain reticular formation (Hutenlocher 1961; Kasamatsu 1970; Steriade et al. 1980).

In humans, an alternative measure of overall brain activation might be the level of gamma frequency (30–70 Hz) oscillation in the brain (Llinas & Ribary 1993; Llinas et al. 1994). Although some recent work questions the association of gamma oscillation with REM sleep (Germain & Nielsen 1996), other work appears to confirm it (Uchida et al. 1997). Such gamma activity in humans has been shown to correlate with discrete cognitive events (Lutzenberger et al. 1995; Muller et al. 1996; Tallon-Baudry & Bertrand 1999; Tallon-Baudry et al. 1996; 1997; 1998) and to be measurable with depth electrodes in the human medial temporal lobe (Hirai et al. 1999).

4.1.2. Input source. Waking, NREM sleep and REM sleep represent states in which the sources of information processed by the brain differ dramatically. The second parameter of our AIM Model, input source (I), is a measure of the extent to which the brain-mind is processing external sensory data impinging upon receptors (as it is in waking) or from internal data sources (as in day dreaming or REM sleep). Because one component of sensory input is proprioceptive feedback reflecting the extent of motor activity, we also include the efficacy of such feedback in parameter I. Internally generated pseudosensory data can be produced by brain stem mechanisms (e.g., via PGO stimulation of visual cortex in REM sleep), it can be recalled from memory, or it can be intentionally created by directed mental imagery.

In alert waking, the contents of our conscious experience (e.g., our thoughts and our feelings) tend to be driven by external stimuli and are predictive of subsequent motor behavior. During sleep, in contrast, conscious experience is normally driven by internally generated stimuli and has no apparent behavioral consequence. In the AIM Model, waking is characterized as both more exteroceptive and exteroeffective than either NREM or REM sleep, while REM sleep is markedly more interoceptive than NREM sleep but less exteroeffective than either waking or NREM sleep.

This second dimension of our AIM Model, though robust, has not been specified by many cognitive theorists who tend to regard internally generated signals as simply the phasic intensification of activation level. Such a view ignores what to us are very significant differences in such mental functions as vision, visual imagery, and visual hallucination. But while some seem to consider it an irrelevant factor, Llinas and Pare (1991) have suggested that this dimension by itself could be an adequate explanation of the phenomenological differences between such high activation states as waking and REM sleep (Llinas & Pare 1991). We agree with Llinas and Pare that both in waking and in sleeping, input source represents a major determinant of the nature of conscious experience. However, we do not regard the differences in input source to be an adequate explanation of the phenomenological distinction between waking and dreaming. How, for example, could it account for dream forgetting or the relatively low visual intensity and bizarreness of daydreams?

Physiologically, the input source axis of the AIM Model reflects both input-output gating and nonsensory activation of sensorimotor cortices. The activation of these cortical regions by external sensory stimuli can be directly measured in humans using evoked potential (ERP) techniques (e.g., Niiyama et al. 1997; Sallinen et al. 1996) or using stimulus threshold studies (see Arkin & Antrobus 1978 and Price & Kremen 1980 for reviews). In this regard, it is notable that Price and Kremen (1980) measured a rise in auditory stimulus threshold and Sallinen et al. (1996) observed a decreased ERP response in human phasic compared to tonic REM sleep. Similarly, the H-reflex can be used to measure motor blockade (Hodes & Dement 1964). In animals the same measures can be obtained and complemented by more refined assessments. For example, the amount of presynaptic inhibition of 1A afferent terminals (Bizzi & Brooks 1963; Pompeiano 1967b) specifically measures the sensory gate function while the amount of motoneuronal hyperpolarization (Chase & Morales 1990; Pompeiano 1967a) measures gating of motor activity. (For a recent review of such measurements see Gottesmann 1997.)

In humans and animals, eye movement density in REM sleep provides an estimate of the amount of internally generated pseudosensory data because eye movement density reflects brain stem PGO and motor pattern generator activity. In addition, the frequency of PGO waves (or the burst intensity of PGO waves) can be measured in animals to determine this parameter more directly. Currently, PGO waves cannot be easily or confidently recorded from humans although numerous suggestive EEG findings have been reported (McCarley et al. 1983; Miyauchi et al. 1987; 1990; Niiyama et al. 1988; Salzarulo et al. 1975) and new dipole tracing techniques show promise in identifying human PGO waves (Inoue et al. 1999b).

4.1.3. Modulation. The third major and clear-cut physiological difference among waking, REM, and NREM is in the neuromodulation of the brain. In the AIM Model, we focus on the marked shift in modulatory balance seen from aminergic (noradrenergic and serotonergic) predominance in waking to cholinergic predominance in the REM sleep of animals. We call this modulatory factor M and define it as the ratio of aminergic to cholinergic chemical influence upon the brain.

It is our contention that this shift of neuromodulatory balance underlies the similar modal shifts in information processing (data processing, storage, and retrieval) seen as the brain shifts from one wake-sleep state to another. We propose that this modulatory factor M is involved in the regulation of such conscious state functions as directed attention, deliberate thought, self reflective awareness, orientation, emotion, memory, and insight. All of these functions are altered in the transition from waking to NREM sleep as a function of the diminished activation and sensory input level. But their even more marked dramatic alteration in dreaming, when the activation level is as high as in waking, must have another brain basis, which we think the changes in input-output gating alone are inadequate to explain. This element of our model has found little support among sleep psychologists who, we believe, either have failed to fully appreciate the extent of the alteration of cognitive features (such as the defective memory of REM sleep) or have simply rejected the concept of a neurophysiological description of psychological phenomenology (for one exception see Hartmann 1982).

Measurement of "M" is based on comparing the rates of firing or amounts of transmitter released by norepinephrine-containing locus coeruleus neurons and serotonin-containing raphe neurons to that of putatively cholinergic, PGO burst cells in the peribrachial region. State-dependent shifts in this parameter have been extensively documented in animal models (Datta 1995; 1997b; Foote et al. 1983; Hobson 1992b; Hobson & Steriade 1986; Hobson et al. 1986; Jacobs & Azmita 1992; Lin et al. 1994; Sanford et al. 1995b; Sherin et al. 1996; Steriade & Biesold 1990; Steriade & Hobson 1976; Steriade & McCarley 1990a; Szymusiak 1995). A more accurate measure of this parameter may be obtained by the simultaneous measure of release of the two classes of modulator using microdialysis techniques (e.g., Kodama & Honda 1996; Lydic et al. 1991b; Portas et al. 1998; Williams et al. 1994). Unfortunately, methodological constraints have so far largely prevented the measurement of this parameter in humans (although see Bartha et al. 1999; Sudo et al. 1998; Wilson et al. 1997). Evidence that such changes occur, and are significant, in humans is indirect but consistently confirmatory.

The role of this parameter in human conscious experience has been extensively studied in waking experiments using drugs known to alter neuromodulatory balance (see Perry & Perry 1995; Perry et al. 1999). In addition, cholinergic stimulation has been found to potentiate REM sleep (Berger et al. 1989; Gillin et al. 1991; Sitaram et al. 1976; 1978b) and dreaming (Sitaram et al. 1978a) while many aminergic agents are known to have REM suppressive and alerting effects (Gaillard et al. 1994; Nicholson et al. 1989) as well as effects on dreaming (Hobson & Pace-Schott 1999; Thompson & Pierce 1999). Reviews of psychopharmacological evidence suggests that the role of modulation in humans is homologous to that in experimental animals

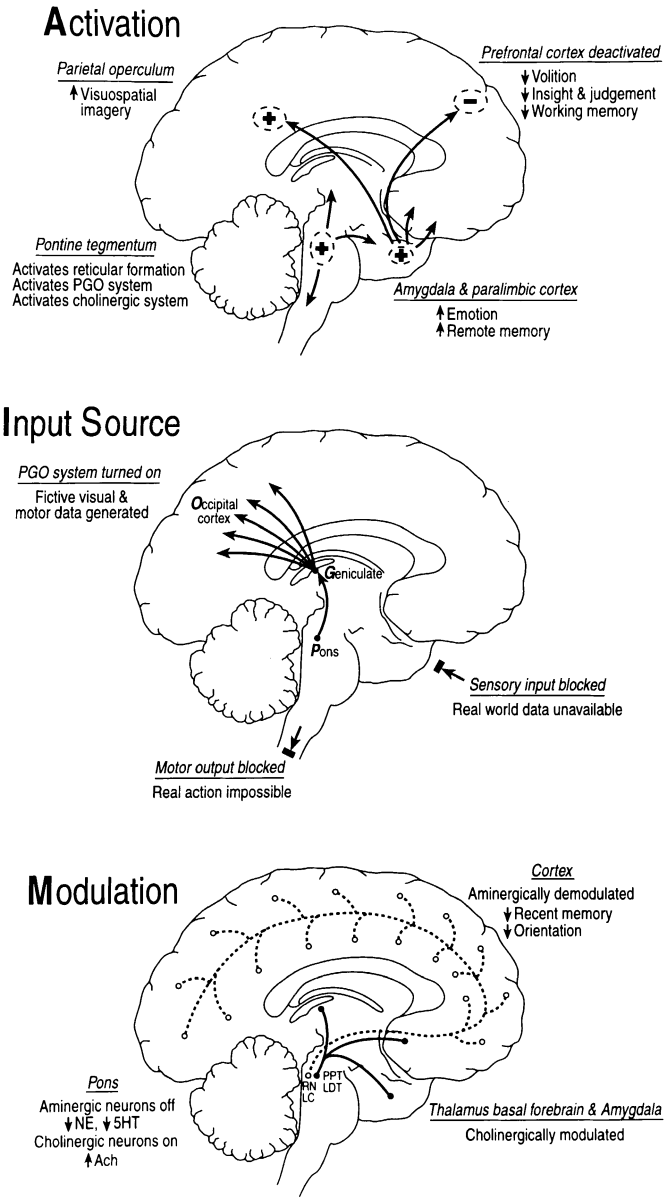


Figure 8. Physiological signs and regional brain mechanisms of REM sleep dreaming separated into the activation (A), input source (I) and modulation (M) functional components of the AIM model. Dynamic changes in A, I, and M during REM sleep dreaming are noted adjacent to each figure. Note that these 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 Table 2 for additional anatomic details).

(e.g., Everitt & Robbins 1997; Hasselmo 1999; Perry & Perry 1995; Robbins & Everitt 1995).

An important aspect of the AIM model is its effort to mirror cognition's psychological features in its three physiological dimensions. Thus, "Activation" has a specific meaning at both the neurobiological and cognitive levels (see Anderson's ACT* model; Anderson 1983). Cognitivists also speak of information processing and thus share the concept of "input source" with neurobiologists, who express this dimension in terms of sensory thresholds, the excitability of motor pattern and efferent copy circuits, and the threshold for motor output. Finally, the mode concept is important to cognitivists as a memory/amnesia dimension (as well as, possibly, an attention/inattention axis) while neurobiologists represent mode as the ratio of aminergic to cholinergic neuromodulator release. It is by these formal homologies between neurobiology and the cognitive sciences that the AIM model attempts to produce an integrated picture of the brain-mind.

An initial attempt to model the neuroanatomical structures participating in REM-state-dependent changes in activation, input source and neuromodulation is illustrated in Figure 8.

4.2. The AIM state space

The AIM model proposes that conscious states can be defined and distinguished from one another by the values of three parameters. These parameters can be considered as the axes of a three-dimensional state space. This state space can be represented visually as a cube where normal values for the parameters range along the three axes (Figs. 1 and 9). The model is not only useful in representing normal states but is also helpful as a heuristic tool to illustrate several critical issues in sleep research.

In quantitative renditions of the model (Hobson 1990; 1992a) the activation parameter (A) was derived from either the mean rate of firing of reticular formation neuronal populations that varies in animals from a low of 25/second in NREM sleep to 50/second in REM or from the inverse of the voltage amplitude of the EEG which varies from 25–50 μV in waking to 150–200 mV in Stage IV NREM sleep in humans. A four-fold range of values is assumed in visual representations of the model. The input source parameter can be derived from arousal threshold or H-reflex amplitude in humans or PGO wave frequency in animals. The range of these values is roughly the same order of magnitude as factor A. The modulatory parameter, M, is derived from the mean rate of neuronal population discharge of the aminergic populations (2–4 cycles/second in waking, 1–2 cycles/second in NREM, 0.01–0.1 cycles/second in REM) or from the concentration of norepinephrine, serotonin or acetylcholine in microdialysis studies which vary over a range of about 10-fold (Hobson & Steriade 1986; McCarley & Steriade 1990; Steriade & Hobson 1976).

All the parameters of the model are known to vary over the sleep cycle in a nonlinear manner. For example, factor M has a clearly exponential deceleration in the NREM-REM transition. Some aspects of this nonlinearity are embodied in earlier mathematical modeling of the reciprocal interaction model using the Volterra-Lotka equations (McCarley & Hobson 1975; McCarley & Massaquoi 1986) which yield ellipses as the graphical representation of the sleep cycle.

We acknowledge the tentative and necessarily speculative nature of our assumption of homology across mammalian sleep mechanisms, but point out that it is supported by abundant indirect evidence. And we recognize one important exception to this homology assumption: the relative complexity of the human forebrain gives rise to a greater complexity of EEG patterns in human NREM sleep compared to animals. We believe that this complexity is underestimated by currently available measures and that activation models of cognition likewise underestimate the differences between NREM states.

We do not pretend to have solved the problem of modeling conscious states, only to have proposed more realistic and

heuristically valuable approaches to this problem. AIM constitutes only a simplified framework for modeling the physiology underlying changes of behavioral state and we in no way claim that it can fully account for the wide variety of human subjective experience, which includes thought, imagery, fantasy, and altered or pathological states as well as dreaming. Moreover, we recognize that the axes of the AIM state space are not independent. For example, at sleep onset a decline in general activation is likely to parallel a decline in aminergic modulation and a decline in the strength of external stimulus drive. Likewise at REM sleep onset the steep rise in cholinergic activity is likely to parallel the rise in internal stimulus drive and a rise in general activation level. But the axes of the model are uniquely capable of accounting for just the kinds of paradoxes that arise from an interactive system that changes its states paradoxically: that is, has high levels of activation in *both* waking and REM sleep; shifts from external to internal stimulus processing; and processes information differently in two equally activated states.

Current developments in basic and clinical neurobiology suggest the exciting possibility that the M dimension may become measurable in behaving (i.e., waking, thinking, performing, sleeping, dreaming) human beings. Already, microdialysis techniques with depth electrodes implanted to localize epileptic foci have shown fluctuations in serotonin across the wake-NREM-REM cycle paralleling those seen in animals (Wilson et al. 1997). Moreover, the newest PET techniques for radiolabeling receptor ligands as well as magnetic resonance spectroscopy (Rauch & Renshaw 1995) may yield further possibilities for the localization and quantitation of neuromodulatory dynamics in the human CNS.

One use of the AIM model is to depict the highly dynamic and variable nature of human consciousness, and thus to visually plot specific "states" of consciousness within the state space. As an example, normal consciousness, at the coarsest level, can be divided into the states of waking, REM, and NREM sleep. Each of these states can be characterized both by distinct physiologies and by distinct differences in mentation. To help the reader orient to the AIM state space, the positions of these three states in the AIM state space, as well as the trajectory from waking through NREM into REM sleep, are shown in Figure 9.

In this figure, the fully alert, wake state is depicted in the upper-right corner of the back plane of the cube. This corresponds to maximal levels of brain activation (right surface of cube), maximal external input sources with minimal internal sources (back surface), and maximal aminergic and minimal cholinergic neuromodulation (top surface). Cognitively, this corresponds to alertness with attention focused on the outside world.

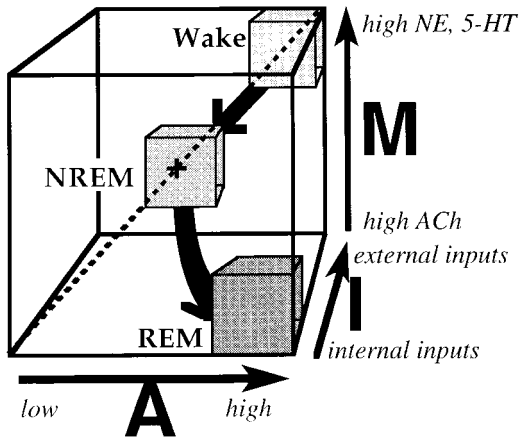


Figure 9. Normal transitioning within the AIM state space from wake to NREM and then to REM.

In the center of the cube lies deep NREM sleep, with low levels of brain activation, intermediate levels of both aminergic and cholinergic neuromodulation, and minimal levels of both external and internal input. In this state, the mind tends towards perseverative, non-progressive thinking with minimal hallucinatory activity, and this is reflected in the brevity and poverty of NREM sleep reports.

As cholinergic modulation increases and aminergic modulation decreases, the modulatory function falls to its low point. The brain-mind, however, regains waking levels of activation and moves from NREM into REM sleep. AIM (now referring to the brain's location in the AIM state space) moves to the bottom front edge of the cube, with input now internally driven (front surface) and neuromodulation predominantly cholinergic (bottom surface). We emphasize the paradox that instead of moving to the left surface of the cube – to a position diametrically opposed to waking (dotted line) – brain activation returns to waking level. This forces AIM to the right surface of the cube. As a result the mind is alert, but because it is demodulated and driven by powerful internal stimuli, it becomes both hallucinatory and unfocused. REM sleep's deviation from the main diagonal axis provides a visual representation of the distinctively unique phenomenology of REM sleep and shows why that state favors dreaming.

A second function of the AIM state space model is as a tool to clarify the concept of substates. While consciousness can be coarsely divided into waking, REM, and NREM sleep, these are only a few of many possible brain-mind states. For example, NREM sleep can be subdivided on physiological bases into substates: sleep onset, Stage II of NREM sleep, and deep Stages III and IV NREM sleep. Presumably, sleep mentation changes in concert with these physiological changes. Similarly, REM sleep can be subdivided physiologically into phasic and tonic REM or psychologically into lucid and nonlucid dreaming substates. Finally, the waking state can be subdivided into a vast multiplicity of substates, defined by attentive parameters (alert, attentive, vigilant vs. drowsy, inattentive, day dreaming), emotional parameters (calm, angry, sad, afraid), or even by information processing strategies (focused and goal directed vs. creative and freely associating). Other substates of waking can be produced by specific induction procedures, such as trance, hypnosis, sleep deprivation, and by the ingestion of psychoactive drugs.

For each of these substates, a subregion of AIM state space could, in theory, be defined which would characterize its physiological and psychological nature. However, as the distinctions between states become more subtle, these regions necessarily begin to overlap and blur. At the same time, the three dimensions of the AIM model quickly become inadequate. For example, the model is strained to account for differences between various emotional substates of waking. This could be partially resolved by adding a regional activation dimension to our model, such as the ratio of limbic to neocortical activation as suggested by neuroimaging studies (e.g., Maquet et al. 1996; Nofzinger et al. 1997).

Could the changes in regional activation of the brain be related to the shift in neuromodulatory balance that we have

described? It seems likely to us that the changes in regional activation (A_R) are a combined function of changes in I and M so that, for example, it is the cholinergic pathway from pons to amygdala that is responsible for the selective activation of the limbic brain in REM sleep. Similarly, it could be that the deactivation of the frontal lobe is caused by the withdrawal of aminergic inputs to that region in REM sleep. These suggestions are not simply ways of saving the model's relative simplicity. Rather they demonstrate the capacity of the model to generate new, testable hypotheses about the cellular and molecular basis of regional brain activations.

4.2.1. Dissociated states. Given the multiplicity of parameters contributing to conscious states and the complex dynamics of their interaction, it is to the credit of evolutionary tinkering that the cardinal states of wake, NREM, and REM sleep appear so discrete and that their temporal sequence is normally so canonical. But this discreteness and canonical sequencing is only approximate. As the AIM state-space model attempts to make clear, any point within the state space can be occupied, and the parametric values which define the canonical states of waking, NREM, and REM sleep can be dissociated from one another. As a result, the appearance of dissociated states – states in which, for example, some parameters match their canonical NREM values while others match canonical REM or wake values – should be considered both natural and inevitable. Acknowledging this propensity of the conscious state system to dissociate enriches our view of both normal and abnormal neurological and psychiatric conditions.

These dissociations occur most commonly during the transition from one stable state to another as exemplified by state carry-over phenomena tapped by neurocognitive and psychological testing following the awakening of human subjects from NREM and REM sleep (Bonnet 1983; Doricchi et al. 1991; 1993; Fiss et al. 1966; Gordon et al. 1982; Lavie 1974b; Lavie & Giora 1975; Lavie & Sutter 1975; Rittenhouse et al. 1993; Rosenblatt et al. 1992; Stickgold et al. 1999b; Stones 1977), with perhaps the best known of these being the persistent lethargy termed as "sleep inertia" (Achermann et al. 1995; Dinges 1990). In such cases, the transitions of some parameters lag behind those of others and the dissociations are usually quite transient. But in other cases, they are more stable, as in sleep walking (Broughton 1968; Guilleminault 1987), where waking values of locomotor output are reached in NREM sleep. Interesting to note, recent PET data have shown persistence of selective deactivation, especially in the prefrontal and posterior inferior cortices, for more than 5 minutes post awakening from Stage 2 sleep (Balkin et al. 1999). Many of these dissociated states can be represented using the AIM state space model.

Thus, another function of the model is to organize and visually represent some of the conscious state dissociations seen in normal subjects, in patients with neurological and psychiatric symptoms, and in both groups when treated with drugs that affect brain neuromodulatory systems. The basic concept that we wish to convey is that while the three dimensions of AIM state space usually change synchronously as the brain-mind shifts between the three stable canonical states, genetic bias, life events, and pharmaceutical intervention can all conspire either to desynchronize the shifts occurring along the three axes or to create new stable states in which one or another dimension takes on an unexpected value.

The net result is a departure from the usual trajectory (shown in Fig. 9) or the creation of normal-hybrid states with mixtures of wake, NREM, and REM features as suggested in Figures 10–18. In these examples, dissociations along each of the three axes of the state space are examined. It should be emphasized that the discussion that follows is speculative and is intended to be heuristic rather than definitive. Although we have chosen examples that we believe to be realistic and have made assumptions that we hold to be reasonable, empirical tests of these hypotheses remain to be conducted.

4.2.2. Activation. To illustrate the vicissitudes of the activation function, we consider two normal phenomena, quiet waking and sleep onset, which are related to each other in ways that have a critical bearing on the issues discussed earlier in our target article. We will show how both quiet waking and the transition from wake to sleep may vary significantly depending upon the current level and the rate of change of the activation function. The transitional state of sleep onset has been extensively studied because of the unique mentation reports that can be obtained on arousal from this state. Yet the exact position of sleep onset in AIM state space is critically dependent on the precise temporal pattern of sleep onset.

Quiet waking: We first consider the period of quiet waking preceding sleep onset. Before lying down and closing his eyes, a subject is usually in an alert state (see again Fig. 9, "Wake"). Normally, on lying down and closing his eyes, he will shift into an alpha wave EEG pattern, reflecting a decrease in "A" and, because visual stimulation has been shut off, a decrease in "I" as well. At the same time, neuromodulatory shifts may begin to decrease aminergic output. Thus, he will begin to move along the main axis from Wake toward NREM, as indicated in Figure 9.

But when examined in detail, each individual will take a unique path through the state space from waking to NREM, depending on both the relative and absolute rates of decline of each of the three state space parameters. For example, if an individual is drowsy before retiring (Fig. 10, "Drowsy"),

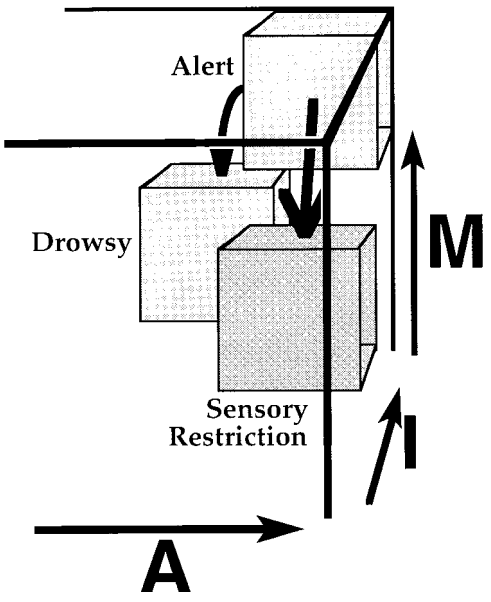


Figure 10. Quiet rest: Movement within the AIM state space prior to sleep onset depends on how sleepy the subject is as well as the extent of external sensory input.

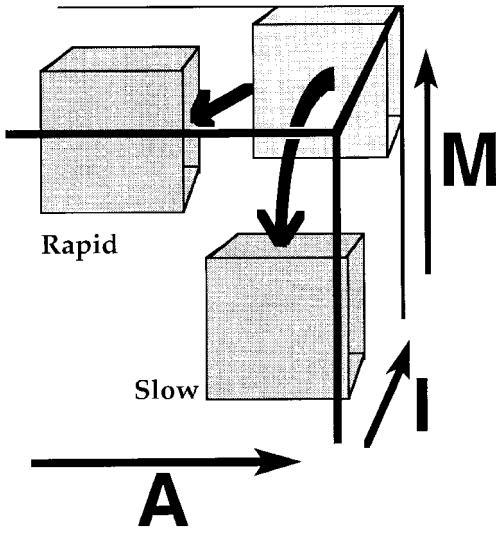


Figure 11. Sleep onset: With more rapid sleep onset, lowered activation precedes aminergic demodulation; with slow onset, the order is reversed.

values for "A" and perhaps also "M" will begin to drop well before the subject even goes to bed, while "I" remains high, placing one in the center of the back surface of the cube. In contrast, if an individual is quite alert when going to bed, "I" might drop before either "A" or "M" (not shown), followed by a small drop in "A" as alpha patterns appear in the EEG.

Under other conditions of quiet waking, such as when subjects were placed in a darkened, sound attenuated room by Antrobus in his "waking controls" for dream mentation (Reinsel et al. 1992), "I" would immediately shift because of the elimination of external sensory stimulation, and we expect that "M" would then slowly shift to relatively low values while "A" stayed high, placing one in the center of the right-hand surface of the cube (Fig. 10, "Sensory Restriction"). Under these conditions, the brain-mind state moves to a position midway between waking and REM sleep (cf. Fig. 9), rather than between waking and NREM. It is therefore not surprising to us that Reinsel et al. (1992) found that mentation became more dreamlike under these waking conditions.

We can use the AIM state space model to investigate the implications of Antrobus's paradigm. Since "I" falls virtually instantaneously upon being placed in the dark, AIM should initially occupy a position in the state space just in front of normal waking, with only "I" decreased. Then, over time, neuromodulatory shifts would move AIM lower in the state space, to the position shown in Figure 10 ("Sensory Restriction"). Because the AIM model hypothesized that "M" plays an important role in modulating cognitive processes, we would expect reports to become more and more dreamlike over the first 5 to 10 minutes in this condition. In contrast, Antrobus's activation-only model would seem to predict that reports should become *less* dreamlike with time, since activation would be expected to drop during quiet wake as EEG alpha increases. In fact, hallucinosis has been shown to increase over time as arousal diminishes during sensory deprivation protocols (Rossi et al. 1964). Indeed, it would be quite surprising to find mentation becoming more wakelike and less dreamlike with an increased period of waking sensory deprivation.

Sleep onset: As the subject moves from wake to sleep onset, further movement occurs within the state space (Fig. 11). The box labeled "Rapid" in Figure 11 represents a possible initial sleep onset state when the transition from waking to sleep is precipitous following sleep deprivation. In this case, the transition occurs before there is time for aminergic neuromodulatory levels to decrease. As a result, the "M" function remains on the top surface of the cube (modulation highly aminergic) while brain activation and external inputs diminish. In contrast, the box labeled "Slow" (Fig. 11) represents a gradual transition from waking to sleep as might be seen in situational insomnia. In this case, decreases in aminergic neuromodulation and external inputs might occur prior to the decrease in brain activation. In both cases, AIM would then move into the standard Stage NREM position (Fig. 9).

Lucid dreaming: Another dissociation along the "A" axis of the AIM cube may arise during lucid dreaming. Under normal circumstances, dreamers believe themselves to be awake – but occasionally individuals become aware that they are dreaming. In this state of "lucid dreaming" (Laberge 1990; 1992) waking insight combines with dream hallucinosis in an intriguing and informative dissociation. We assume that for lucidity to occur, the normally deactivated dorsolateral prefrontal cortex (DLPFC) must be reactivated but not so strongly as to suppress the pontolimbic systems signals to it. This dissociation is represented in the AIM model by splitting AIM so the portion representing the DLPFC can take a position dissociated from that of the rest of the brain (Fig. 12). When this partial reactivation of the DLPFC occurs, internally generated images are seen for what they are and are not misinterpreted as coming from the outside world.

The fact that lucidity can arise when the DLPFC is deactivated can also be explained using AIM. Lucid dreaming occurs spontaneously or can be cultivated by pre-sleep autosuggestion. Spontaneous lucidity indicates that the reduced amount of reflective self-awareness during dreaming is sometimes enhanced enough for the subject to recognize the dream state for what it is. Autosuggestion probably increases this probability by priming the brain circuitry – presumably in prefrontal areas – that subserves self-reflective awareness. In both cases, the phenomenon of lucidity clearly illustrates the always statistical and always dissociable quality of brain-mind states. AIM accommodates

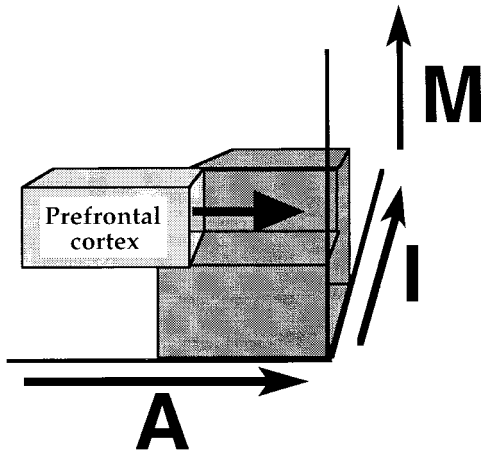


Figure 12. Lucid dreaming: Prefrontal cortical systems, which are normally inactive in REM sleep, shift toward higher, wake-like levels of activation, permitting conscious awareness of the dream state.

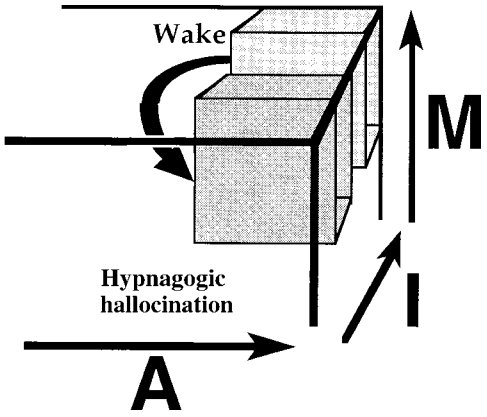


Figure 13. Hallucinosis: Internal stimuli shift the brain/mind forward along the "I" axis in AIM state space, with both internal and external inputs high. This condition may prevail during hypnagogic hallucinosis.

these features very well by proposing that lucid dreaming is a hybrid state lying across the wake-REM interface.

4.2.3. Input source. During waking, internal inputs are used mainly in the service of the ongoing sensorimotor integration of external signals. If, for any reason, internal signals became unusually strong, they could come to dominate the system with resulting hallucinosis. In this case, mentation would be driven by a combination of undifferentiated internally and externally driven imagery (see Mahowald et al. 1998).

Hypnagogic and hypnopompic hallucination: From the perspective of the AIM model, hypnagogic and hypnopompic hallucinations, associated with transitions into and out of sleep respectively, result from the REM-like enhancement of internal stimuli coupled with an activated, aminergically modulated waking brain (Figs. 13 and 14).

With internal and external inputs in an unstable balance (as occur during the hypnagogic period), AIM moves to a position half-way between the front and back surfaces of the cube (Fig. 13). But unlike NREM sleep, which is also at this midpoint of input source (with minimal internal and external inputs), both sources are being powerfully driven in hallucinosis. It is this unexpected combination of high internal and high external inputs that defines the functional dissociation of these hallucinoid states. The frequency of this combination may be elevated by the abnormal physiology of narcolepsy, a condition in which the frequency of hypnagogic hallucinations is likewise elevated (Broughton et al. 1982; Mignot & Nishino 1999; also see Fasse 2000).

We can approximate a representation of the hypnopompic hallucinoid state by hypothesizing that while the brainstem signals continue to evoke internal representations in the cortex in the hypnopompic period, the blockade of external stimuli has broken down. As a result, the dissociated state results from a dissociation of the forebrain from the brainstem. This dissociation is represented in the AIM model by splitting the cube representing the brain-mind into forebrain (F) and brainstem (B) sections and showing their relative positions in AIM space (Fig. 14).

A more extreme example of this kind of dissociation is temporal lobe epilepsy in which abnormal phasic activation signals of limbic origin commandeer the cortex and force it to process external world data on limbic terms (e.g., Rabinowicz et al. 1997). Given the new findings on selective limbic activation in REM sleep (Braun et al. 1997; 1998; Maquet et al. 1996; Nofzinger et al. 1997), it seems reasonable to suppose that a similar, though normal, process may also drive the dreaming brain. By this we mean that the cortex of the dreaming brain is compelled to process internal signals arising from the pons and amygdala, as was originally suggested by the activation synthesis hypothesis. This epilepsy analogy is also cogent because the internal signals of REM sleep are spike and wave complexes arising in the pons and amygdala (Elazar & Hobson 1985). The limbic lobe may then direct the forebrain to construct dreams in a manner similar to that by which it creates the dreamy states of temporal lobe epilepsy (see Epstein 1995). Indeed, a recent study has shown more unpleasant and higher intensity emotions in the dreams of epileptics as compared to normals (Gruen et al. 1997).

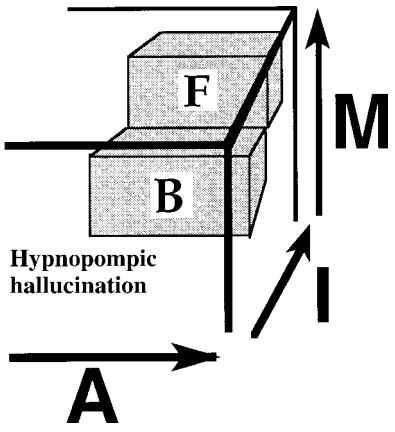


Figure 14. Hypnopompic hallucinosis: Forebrain (F) and brainstem (B) regions occupy different locations in the state space, with the brainstem initiating internal inputs while the forebrain continues to process external stimuli.

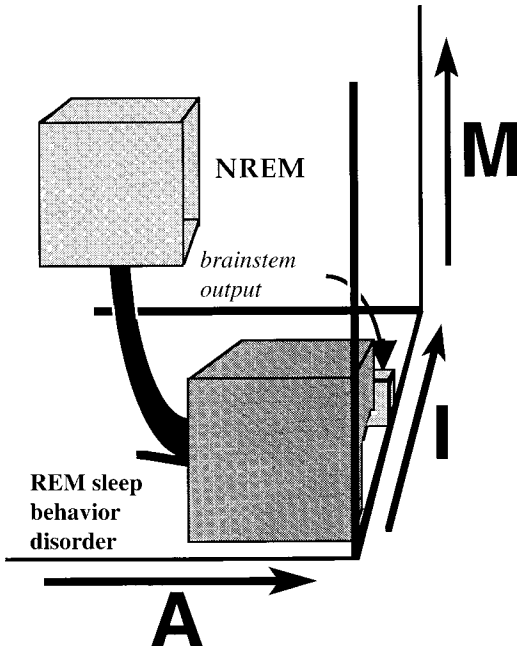


Figure 15. REM sleep behavior disorder: Brainstem inhibition of motor output is dissociated from other brain systems during REM sleep, moving toward waking values of the "I" parameter and leading to disinhibited motor output.

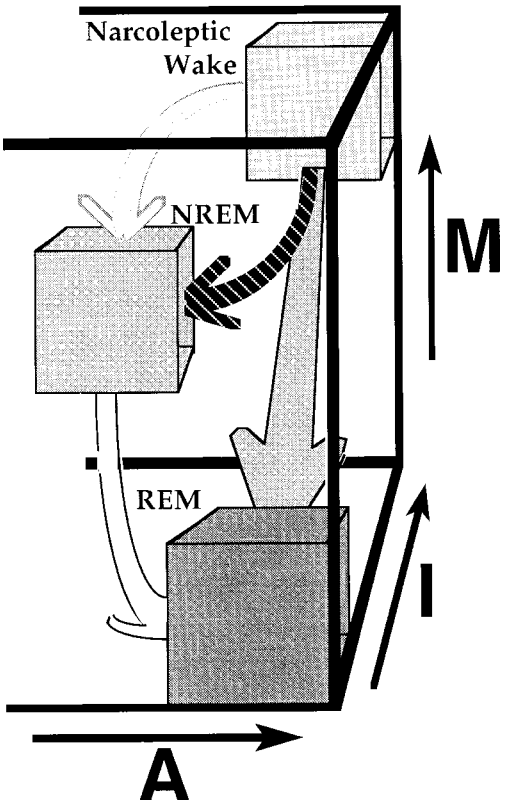


Figure 16A. Sleep onset in narcolepsy: the brain shifts down and forward in the AIM space prior to sleep onset, thereby inducing sleep onset hallucinations and direct entry into REM sleep at sleep onset.

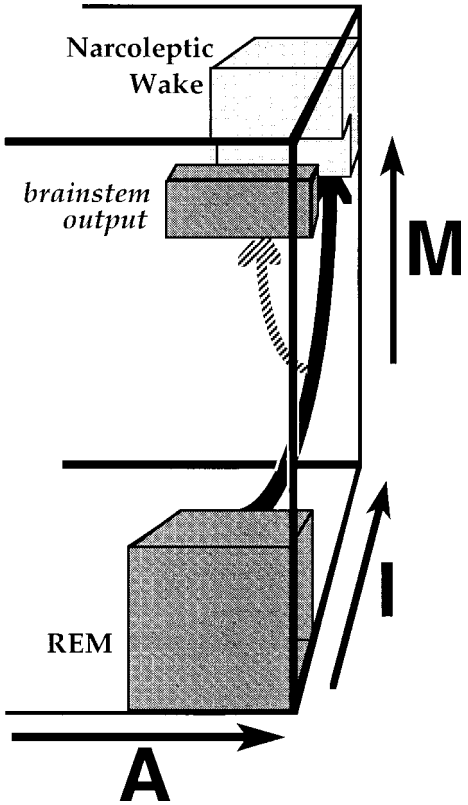


Figure 16B. Sleep paralysis in narcolepsy: Enhanced aminergic demodulation in narcolepsy increases inhibition of motor outputs, leading to dissociation of brainstem functions and continued motor inhibition after waking.

REM sleep behavior disorder: A particularly dramatic example of sensorimotor dissociation is seen in the REM sleep behavior disorder, in which the normal inhibition of motor output during REM fails (Mahowald & Schenck 1999; Schenck & Mahowald 1996; Schenck et al. 1993). Motor behaviors normally seen only in waking now arise completely involuntarily and automatically during REM, and patients physically act out their dreams (Mahowald et al. 1998). The historically oriented reader will recognize the similarity between this disorder and the dissociative phenomena that interested Charcot, Janet, and Freud.

During REM sleep, the motor cortex activation produces outputs similar to those seen in waking, but in response to exclusively internal inputs. Since the inhibition of spinal motorneurons usually occurs in concert with motor cortex activation, our single "I" parameter normally reflects the net inhibition of motor output. But in this case (as in the case of lucid dreaming) we represent this regional dissociation by a fragmenting of the AIM icon. In this case, the lower back quarter of the icon, representing brainstem output systems, has moved back in the state space toward a waking level of output (Fig. 15). It is this dissociation which produces the REM sleep behavior disorder.

4.2.4. Modulation. If aminergic modulatory power is weakened, as it is in narcolepsy (Mamelak 1991) and depression (Berger & Riemann 1993), and if cholinergic modulatory power is enhanced as it also appears to be in these two conditions (Berger & Riemann 1993; Mamelak 1991), then the value of M will decline. As a consequence, the ability of subjects to maintain alertness may be compromised producing excessive daytime sleepiness. This would lead to a minor shift in the normal "alert" position in state space (Fig. 16A, "Narcoleptic Wake"). Moreover, REM sleep may be entered more rapidly or even directly from waking as in narcolepsy (Mitler et al. 1979). This shift in baseline values of M may also produce shortened REM latency (as in some forms of depression) or difficulty awakening fully from REM (as in narcolepsy).

These transitional abnormalities represent some of the clearest demonstrations of conscious state dissociation in sleep disorders medicine but they also instruct us about the normal phenomena, which they exaggerate. For example, narcoleptic subjects (Kayed 1995; Roth 1978) may hallucinate at sleep onset (Fig. 16A, striped arrow from Wake to NREM) as they move down and forward in the state space (more cholinergic modulation and hence more internal inputs) prior to sleep onset and its associated decrease in activation. This can be followed by normal entry into NREM sleep (striped arrow) or immediate entry into REM sleep without passing through NREM (gray arrow from wake to REM).

At the other end of the night, an inability to move, termed sleep paralysis (Mignot & Nishino 1999), which sometimes compounds the terror of hypnopompic hallucinations, represents a carry-over of the inhibition of spinal motorneurons into waking. This dissociation during narcoleptic awakening can be represented as a dissociation of brainstem motor activity along the "I" dimension secondary to a shift in "M" (Fig. 16B) as AIM moves toward the waking corner of the

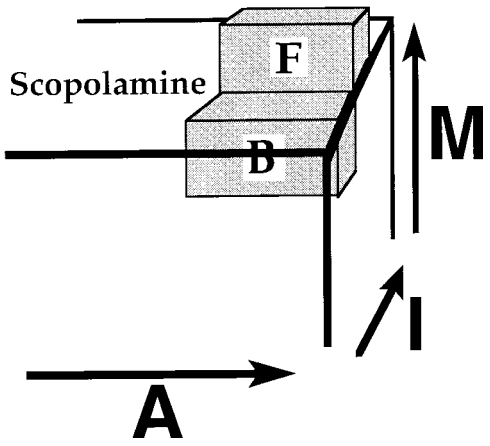


Figure 17. Scopolamine inhibition of REM sleep: Cholinergic inhibitors force the brain-mind to abnormally high ratios of aminergic to cholinergic neuromodulation, preventing entry into REM sleep and leading to simultaneous processing of external and internal inputs by forebrain (F) and brainstem (B) systems.

state space. This is the inverse of the dissociation seen in REM sleep behavior disorder (Fig. 15). The sleep abnormalities of narcolepsy, as well as those of depression, are relieved by drugs (e.g., tricyclic antidepressents and SSRIs) which enhance aminergic efficacy and suppress the cholinergic system (Gaillard et al. 1994; Nishino & Mignot 1997).

Other drugs that influence the M parameter produce "altered states of consciousness." Thus drugs which, like LSD, interfere with serotonergic neuromodulation (Aghajanian 1994), create dreamlike distortions of imagery and inhibit executive prefrontal cortical functions during waking, while anticholinergics (e.g., scopolamine) produce a delirious waking state with dream-like hallucinosis, disorientation, anxiety, and confabulation (Perry & Perry 1995). As seen in Fig. 17, scopolamine pushes AIM above the normal state space, pharmacologically reducing the levels of cholinergic neuromodulation below any normal physiological levels. At the same time, AIM splits as both external and internal inputs are activated.

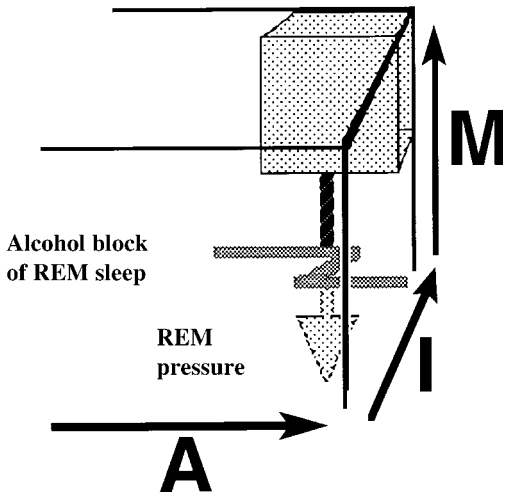


Figure 18A. Ethanol-induced suppression of REM sleep: Blockade of REM sleep leads to an increased biological pressure toward movement down in the state space, towards increased cholinergic modulation, but the blockade prevents movement.

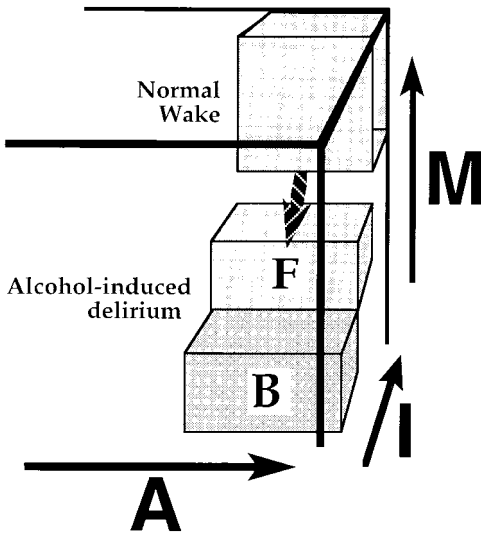


Figure 18B. Ethanol withdrawal: When the ethanol block is removed, the brain/mind shifts to abnormally high levels of cholinergic modulation, activating brainstem mechanisms for internal "sensory" inputs. This dissociates forebrain and brainstem systems and leads to alcohol-induced delirium.

4.2.5. Dissociations. In most of the cases described above, we have hypothesized that dissociation results from a fragmentation of normally unified neuromodulatory states. In short, the forebrain, midbrain, and brainstem fail to occupy a single position in the AIM state space. Instead, there is a split along the Activation or Input axis, with different brain regions occupying different positions in AIM space. Insight into how these dissociations might arise comes from the example of delirium associated with alcohol withdrawal.

Chronic alcohol usage blocks REM and upon withdrawal there is a REM rebound, marked by increased amounts and intensity of REM sleep (Pokorny 1978). It is during this period of REM rebound that delirium occurs. Presumably, the brain reacts dynamically to the alcohol-induced REM deprivation with an increased pressure towards REM sleep. We imagine this as pressure to move the brain lower in the AIM state space, towards lower aminergic and higher cholinergic neuromodulation. But while this pressure is exerted by the brain, the alcohol blocks the actual movement through the state space (Fig. 18).

When alcohol is withdrawn, the REM pressure forces AIM down in the state space causing increased REM sleep, but also causing hallucinations and delirium during waking (Fig. 18B). These symptoms of psychosis are caused by the release of brain systems which are normally inhibited except in REM sleep. In this case, it is an abnormal shift downward along the "M" axis of the state space which produces the splitting of AIM and causes its dissociation along the "I" axis. The net result is to move the brain-mind close to a position of REM sleep in waking.

4.3. Discrete conscious states and the continuous state space model

It is common, when discussing consciousness, to speak of "states" of consciousness. In doing so, it is often assumed that these are discrete brain-mind states with clearly definable boundaries; it is also assumed that at any given mo-

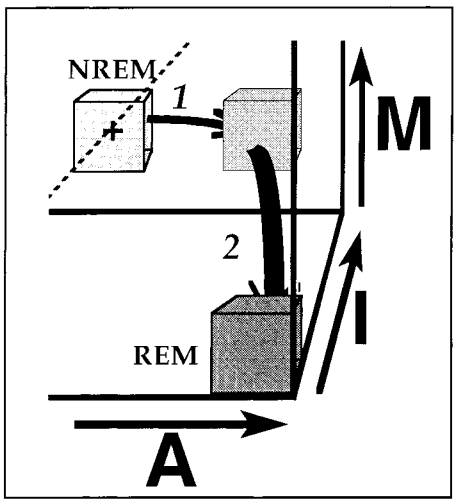


Figure 19. Time course of NREM to REM transition: Movement through AIM state space reflects the nonsynchronous shifts in EEG, neuromodulation, and muscle atonia. In this example, EEG desynchrony (1) occurs before this shift in neuromedulation and inputs (2). (Dashed lines as used in Fig. 9.)

ment the brain-mind is in one or another of these states. If this were true, then the transition between states would be absolute and instantaneous. As suggested by the examples presented above, the AIM state space model specifically rejects this conclusion. Rather, it proposes that although specific states of consciousness can be meaningfully described, shifts in consciousness reflect movements through a continuously varying state space, and not discontinuous jumps between discrete states. It also serves to demonstrate how a continuous state-space is compatible with the notion of discrete conscious states.

Specific states become defined because normal subjects tend to remain in a highly constrained region of the state space for long periods of time and then rapidly move to another similarly constrained region. Thus, after 16 hours of waking, the transition from waking to sleep can occur in less than one minute, and appears virtually instantaneous. Yet most researchers would agree that the transition is a continuous process rather than a sudden jump from one state to another; it is only the speed of the transition relative to the time spent in each "state" that makes it appear as a quantum shift.

Similarly, the transition from NREM to REM sleep, although rapid, shows a clear and finite time course (Fig. 19), with the typical REM signs of EEG desynchronization, muscle atonia, and rapid eye movements appearing in a variety of sequences over the course of 30 to 60 seconds – an observation familiar to all polysomnographers (see Butkov 1996; Rechtschaffen & Kales 1968; Sato et al. 1997). Recordings from single neurons in the cat brainstem further suggest that the shift in neuromodulation (the M axis in AIM state space) may be slower still as the shift from NREM to REM follows a continuous path from one state to the next (Hobson et al. 1975).

We emphasize that the AIM brain-mind state space is not a discontinuous collection of discrete states. Instead, any combination of values for A, I, and M is in theory possible, and although some ranges of these values are much more likely to be observed than others, movement from one stable state to another involves passing continuously along a path through the several state space domains.

A similar distinction is critical when the AIM state space is used to map both physiological states and states of consciousness. In its most specific description, AIM state space is mapped along three dimensions of physiology. When we map consciousness onto the three related dimensions of cognition, we achieve the same continuity and overlap of values that are seen in mapping physiology itself. And both domains thus achieve a realistic range of association-dissociation. Just as there is no absolute boundary between the waking, NREM, and REM domains in the physiological state space, there is no absolute boundary between the cognitive states determined by them. Thus, we do not claim that there can be *no* "NREM-like" mentation in REM sleep and *no* "REM-like" mentation in NREM or even in waking. Rather, we claim that there is a strong probabilistic relationship between positions in the physiological and cognitive state spaces; when a subject is in a given position in the physiological state space, he is most likely to occupy a nearly identical position in the cognitive state space. While we do believe that cognition and consciousness are totally determined by underlying physiological processes, we make no claim that we have more than begun to map the parameters (dimensions) of the state space which ultimately combine to define these psychological states.

4.4. Summary of the AIM model and the nature of conscious states

The AIM model describes a method of mapping conscious states onto an underlying physiological state space. In its strongest form, the AIM model relates not just to wake-sleep states of consciousness, but to all states of consciousness. It is limited by describing only three of what are undoubtedly numerous dimensions that must be specified to completely define this state space, but we have chosen those parameters that we feel are most critical for distinguishing among the basic wake-sleep states of consciousness.

By choosing activation, input source, and mode of neuromodulation as our three dimensions, we have selected *how much* information is being processed by the brain (A), *what* information is being processed (I), and *how* it is being processed (M). It is our belief that these three parameters are both necessary and sufficient to distinguish in a preliminary way among the basic wake-sleep states.

While the brain normally exists in specific regions of the AIM state space, only shifting from one area to another at relatively infrequent intervals, the brain is nonetheless theoretically capable of occupying any position in this state space, displaying any set of values of A, I, and M. As such, intermediate states and dissociated states are recognized as not only eminently possible but highly probable, and specific states of consciousness are seen more as convenient names for frequently occupied regions of the state space than as discrete, tightly bounded areas of the state space. In addition, transition from one stable brain/mind state to another involves moving along a continuous path through the state space, linking the two stable states.

Finally, although we believe that these three dimensions go a long way towards mapping what we know about the physiological processes underlying conscious states today, we believe that many more exist and as a result, our mapping from physiological state space to conscious states is an

approximation that further experimentation can only serve to refine.

5. Conclusions

Our goal, as stated in the Introduction, was to begin to bridge interdisciplinary gaps in the study of sleep and dreaming; we have accordingly reviewed contemporary perspectives primarily from research psychology, neuropsychology, neurobiology, and clinical sleep medicine. Our AIM state-space model and a revised activation-synthesis theory of dreaming, summarized below, constitute our current and necessarily approximate synthesis of these data, which we hope will stimulate many future hypothesis-testing experiments. With regard to the areas not covered here, we refer the reader to published works (and we eagerly await future reviews) on dreaming and consciousness from scientists and scholars with specific expertise in clinical psychology, philosophy, literature, neural networks, artifical intelligence, as well as functional-evolutionary and molecular biology perspectives on sleep and dreaming.

We have shown that phenomenological differences between waking, NREM, and REM sleep are measurable. In our view, these differences are so great that they represent qualitative differences. A better understanding of the physiological processes underlying dream construction may be necessary before this issue can finally be laid to rest. But even when dream features appear to be specifically linked to distinctive REM physiology, interpretations can still be cast toward either camp. Hong et al. (1997) reported an impressive correlation between visual imagery and REM density ($r = 0.8$), which we would argue as evidence for a dependence of dream imagery on a qualitative feature of REM sleep. In contrast, Antrobus et al. (1995) consider this to be another example of the simple dependence of dream content on levels of brain activation, arguing that rapid eye movements are not under strict brainstem cholinergic control, but come increasingly under the control of the frontal eye fields as general cortical activation increases.

In the end, the issue may best be addressed in other forms. In the case of the major stages of sleep, it may be more useful to envisage psychophysiological continua, manifested at the levels of both the brain and the mind, whose various combinations define not only commonly experienced states of the brain-mind but uncommon ones as well. This is the strategy adopted by the AIM model with the dimensions activation (A), input source (I), and neuromodulation (M) representing three such continua.

Rather than fixed conditions, which must always show similar characteristics in order for brain-mind-body isomorphisms to be valid, behavioral states can be seen as relatively stable sets of values for these continua that have evolved as a result of adaptive benefit to the organism. Such multidimensional combinations can be influenced both at the level of the brain (as when we take a sleeping pill) and at that of the mind (as when we count sheep).

Along the dimension of Activation (A), neuroimaging studies strongly support an updated view of brain arousal in REM sleep as resulting from ascending influences from the brainstem and subcortex. The limbic subcortex and related cortex play a major part in the translation of this activation to associative, and perhaps even to sensorimotor areas of the cortex. Along the dimension of Input Source (I), newer research reinforces earlier findings on maximal sensorimotor blockade in REM. Along the dimension of modulation (M), recent research has confirmed the neuromodulation of conscious states by the interplay of cholinergic and aminergic influences arising from brainstem nuclei. This interplay is mediated and modulated by a diversity of cell populations and their neuromodulators in both the brain stem and the subcortical forebrain.

In a revised version of our activation-synthesis theory, the distinctive form of dream cognition may be explained at the level of the brain as follows:

1. The intense and vivid visual hallucinosis is due to autoactivation of the visual brain by pontine activation processes impinging, initially, at the level of unimodal visual association cortex and heteromodal parietal areas subserving spatial cognition.

2. The intense emotions, especially anxiety, elation, and anger are due to activation of the amygdala and more medial limbic structures. The emotional salience of dream imagery is possibly due to the activation of the paralimbic cortices by the amygdala and other subcortical limbic structures.

3. 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 are due to the combined and possibly related effects of aminergic demodulation and the selective inactivation of the dorsolateral prefrontal cortices.

4. The bizarre cognition of dreaming, characterized by incongruities and discontinuities of dream characters, loci, and actions, is due to an orientational instability caused by the chaotic nature of the pontine autoactivation process, its sporadic engagement of association cortices, the absence of frontal cortical monitoring, and episodic memory deficits that are, in part, due to failures of aminergic neuromodulation. We present a schematic explanation for the generation of these cognitive dream features which combines the above findings on state-dependent regional activation with the reciprocal interaction model for the neuromodulation of conscious states.

ACKNOWLEDGMENTS

This project was funded by the MacArthur Foundation Mind Body Network and NIH MH-48,832, MH13923, and MH01287. The authors wish to thank Eric A. Nofzinger, Allen R. Braun, James Quattrochi, David Kahn, Subimal Datta; Roar Fosse; also Jill Gustafson, Dorothea Abbott, Jennifer Holmes, Dawn Opstad, and April Malia.

NOTE

1. "Dreaming" was found to be better than "Total Recall Frequency" (TRF) (Table 3–8, $F[1,71] = 15.89$, $p < 0.01$), than TRF + "Waking Perception" (Table 3–10, $F[1,70] = 15.17$, $p < 0.01$), and than FRF + "Dreamer Participation" (Table 3–15, $F[1,70] = 13.70$, $p < 0.01$). In contrast, TRF + Dreamer Participation and TRF alone explained no significant amount of variance not already explained by Dreaming alone. In addition, judged Dreaming adds significantly to the REM/NREM variance when his "trichotomized' judges' scores versus their log-transformed scores are used in a step-wise analysis (Antrobus 1983).