5

Possible Relationships of Anesthetic Coma and Pathological Disorders of Consciousness

Nicholas D. Schiff and Fred Plum

INTRODUCTION

This chapter reviews pathological causes of coma and related global disorders of consciousness. We discuss these neurological disorders in the context of how contributions of subcortical arousal and gating systems relate to normal conscious states. We then briefly explore the possible overlap of mechanisms of different forms of anesthesia as compared to the reviewed pathological states.

Definition of Consciousness

We offer a definition of the psychological dimension of consciousness that closely follows that of James *(1)*:

At its least, normal human consciousness consists of a serially time-ordered, organized, restricted and reflective awareness of self and the environment. Moreover, the experience is one of graded complexity and quantity.

Arousal, attention, intention, memory, awareness, and mood-emotion are primary neuropsychologic components of consciousness. Although it is self-evident that these components are interdependent, neuroimaging studies have increasingly confirmed classical neurological observations that particular brain systems develop to process or generate specific functions *(2,3)*. Young, in Chapter 2, discusses these specific cortical contributions to neuropsychological components in greater detail.

Global disorders of human consciousness result from impairment of several neuropsychologic components and result in diffuse, severe, or total loss of meaningful behavior. We briefly review the anatomical substrates of these disorders placing special emphasis on the role of particular subcortical structures that contribute to consciousness. We also develop a distinction between arousal systems and "gating" systems. Arousal is identified with the different functional states that characterize forebrain activation on the basis of brainstem modulation of corticothalamic systems *(4)*. We formulate gating as a set of selective processes that may facilitate transient long-range interactions of large-scale brain networks.

Global disorders of consciousness include stupor and coma, the vegetative state, akinetic mutism, absence and partial complex seizures, delirium, dementia, and a more recently defined state of hyperkinetic mutism (for broader review *see* ref. *5*). However, we focus this chapter on coma, persistent vegetative state, akinetic mutism, and absence seizures (*see* Table 1) because all of these states bear close relationships to forms of pharmacologic anesthesia. We emphasize focal injuries that produce

From: *Contemporary Clinical Neuroscience: Neural Mechanisms of Anesthesia*
Edited by: Joseph F. Antognini et al. © Humana Press Inc., Totowa, NJ

Table 1
Global Disorders of Consciousness

	*Coma**	*PVS*	*ASZ*	*AKM*
Arousal	–	+	+	+
Attention	–	–	–	+
Intention	–	–	–	–
Memory	–	–	–	–
Awareness	–	–	–	–/?

In addition to coma, generalized tonic-clonic seizures, post-ictal unconsciousness, concussion, and asystolic syncope may be included in the first column (*). PVS, persistent vegetative state, ASZ, absence seizure, AKM, akinetic mutism. –, absent; +, present, –/+; incompletely expressed, –/? Apparently absent.

global disorders for two reasons. One of these is that nonselective large cortical injuries or metabolic etiologies of coma usually shed little light on selective mechanisms of anesthesia. The other, as section IV will discuss, is an identifiable overlap between focal etiologies of global disorders and regional effects of several different anesthetic types.

PATHOLOGICAL STATES OF UNCONSCIOUSNESS

Coma

Coma reflects a totally unconscious and unarousable brain state that results from acute pharmacologic anesthesia, physical injuries, and a variety of serious medical disorders. All interfere with the brain's arousal mechanisms (*see* Plum and Posner *[6]* for a comprehensive review of causes). The most prominent behavioral state of coma may clinically resemble deep, sleep-like unconsciousness. Functionally, coma is characterized by unarousable unresponsiveness to internal or external stimuli. In pathologic coma, eyes are closed and even the most vigorous exogenous stimulation cannot evoke awakening. Comatose subjects express neither understandable words nor sounds, nor do they correctly localize specific noxious stimuli applied to any part of the body. While several components of the arousal system are identified (*see* section on Arousal and Gating Systems), only relatively large rostral dorsal-medial pontine, mesencephalic and paramedian thalamic lesions, or global damage to the cerebral hemispheres can produce sustained coma *(7)*. In the comatose state, no evidence exists of awareness of self or environment nor do cyclical state changes appear (*see* Fig. 1, column 1).

Most pathological coma derives from a relatively few causes. Following in order of incidence are: (1) Brain trauma; (2) Cerebral vascular damage, including: a. large cerebral and brain stem ischemic strokes; b. acute ruptured cerebral aneurisms; and c. large, critical cerebral or subtentorial hemorrhages (3). Severe anoxemia or asphyxia owing to cardiac asystole, drowning, immediate absence of atmospheric oxygen, carbon monoxide exposure, or abrupt, severe pulmonary dysfunction; (4) Acute intracranial inflammatory of infectious disease; (5) Intentional or accidentally inhaled or ingested sedative or street drugs, and (6) Several systemic or cerebral metabolic disorders.

Table 1 indicates a concomitant loss of all neuropsychologic components incurred with a coma. Stupor, is an imprecise term applied to patients with marked impairment of arousal who nevertheless, can be sufficiently stimulated from their sleep-like condition to express purposeful, but often inconsistent, responses to their environment. Forms of brief unconsciousness such as syncope, concussion, and brief generalized tonic-clonic seizures or post-ictal unconsciouness may also be included in the first column of Table 1.

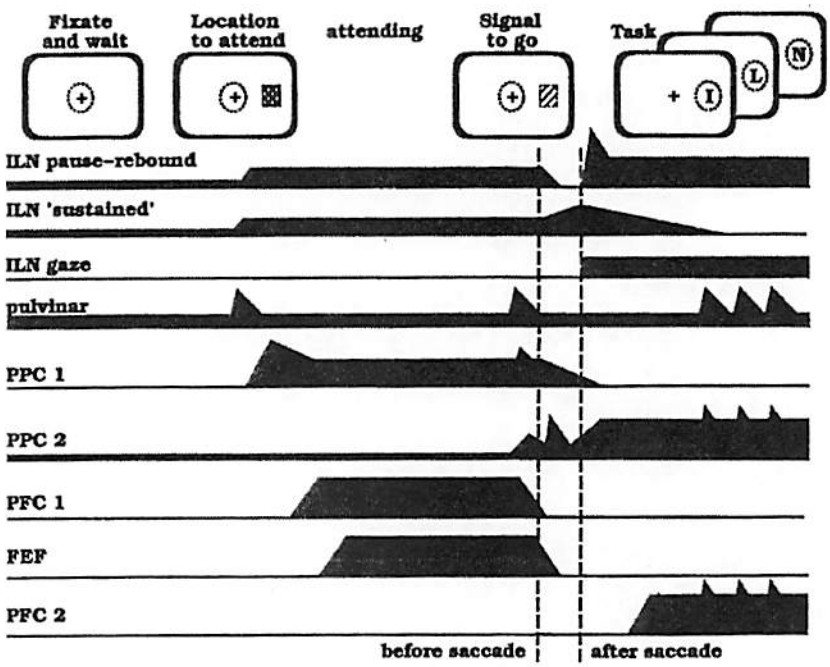

Fig. 1. Timing chart for cortical and subcortical activations during a visual attention task *(97)*. The figure schematizes extracellular unit activity in a hypothetical experiment in which a subject is asked to covertly attend to a target just lateral to a fixation cue and saccade to the target after a cue signal. The shaded regions represent absolute firing rates of neurons in several cortical and thalamic regions; PFC, pre-frontal cortex *(98)*; FEF, frontal eye field *(99)*; PPC; posterior parietal cortex *(118,119)*; pulvinar; and ILN, intralaminar nuclei (cells modeled from central lateral and paracentralis nucleus, Schlag and Schlag-Rey *[111,112]*). The gating role for the ILN is hypothesized to support and modulate such sustained activity across specific long-range corticocortical connections (*see* text).

Persistent Vegetative State

Among the most important contributions to our understanding of mechanisms generating arousal and sustained wakefulness in the past half century, have been the discovery of the physiology of arousal by Moruzzi and Magoun (1949 and others, see below) *(8)*, and Jennett and Plum's (1972) *(9)* clinical identification of the automatic and isolated sleep-wake function of the persistent vegetative state. The vegetative state presents the fundamental clinical dissociation of arousal from all other components of consciousness (Table 1). Patients in the vegetative state express irregular cyclic arousal which separate them from chronic coma. Nevertheless, they express no awareness of self or the environment. The structural anatomical damage that can precipitate a persistent vegetative state (PVS) varies widely *(10)*. Autopsy examinations in a large series of patients in a post-traumatic PVS *(10,11)* demonstrate varying degrees of destruction-degeneration that bilaterally affect the cerebral cortex, the cerebral white matter and, sometimes the mesencephalic tegmental structures, either independently or all together. The mesencephalic lesions mostly reflect damage secondary to early compression of the brainstem following swelling due to brain injury (tentorial herniation). Post-mortem studies of nontraumatically-induced PVS have been fewer but also disclose multifocal bilateral cerebral lesions with or without severe destruction of basal ganglia or thalamus *(12)*. In addition to cases of widespread damage owing to anoxic or traumatic brain injury, vegetative states may also result from focal injuries confined to the paramedian rostral brainstem and thalamus *(13–17)*.

The clinical judgment of unconsciousness in PVS has been supported by the results of positron emission tomography (PET) scan studies that reveal overall cerebral metabolism to be reduced by 50% or more below the normal rate *(18–21)*. The observed metabolic levels are equivalent to those found in persons undergoing deep surgical anesthesia) *(22)*. Recently, we have documented behavioral and physiological variations in a few patients in the vegetative state *(23–25)*. One of these patients randomly expressed occasional single, understandable words *(25)*. Her PET studies identified isolated islands of left frontotemporal cerebral structures that operated at an abnormally low metabolic rate but at nearly twice the rates of remaining brain. Similar isolated expressions have been encountered in several other vegetative patients. Typically, the patients express easily identifiable, stereotypical, emotional-limbic responses. These emotional expressions likely reflect distinct and isolated limbic mechanisms; their preservation likely depends on integrative brainstem structures that lie outside of the thalamocortical systems that typically undergo overwhelming injury in PVS patients.

Akinetic Mutism

The term akinetic mutism encompasses an uncommon unique behavior consisting of the appearance of constant wakeful hypervigilance, the making of only rare body movements, and, usually, a preservation of visual tracking in the form of smooth, slow pursuit movements. Classically, akinetic mutism as listed in Table 1 reflects the recovery of a crude wakeful attentiveness without the apparent recovery of any other neuropsychologic function.

Cairns, an English neurosurgeon, coined the term in 1941, to describe a young woman who, although appearing wakeful, became mute, rigidly motionless, not spastic and apparently unconscious, when a craniopharyngiomatous cyst expanded to compress the anterior walls of her third ventricle, plus the posterior medial-ventral surface of the frontal lobe *(26)*. When the cyst was drained, she recovered full awareness of the immediate present but possessed no memory of the previous event. Eye movements were not described in this girl, but almost all recent classic cases have been said to display rare, slow but seemingly attentive conjugate eye movements. Oculocephalic reflex stimulation may slowly evoke limited fractions of lateral gaze in akinetic mute patients.

Additional observers have somewhat widened the abnormal functional anatomy that relates to the syndrome, based on similar behavior. These include selective or associated injuries to the medial-basal prefrontal area including Cairn's zone, the medial forebrain bundle, the anterior cingulum; the general medial-prefrontal region supplied by the anterior cerebral arteries, and, the pallidum and caudate nuclei. The hyperattentive form of classic akinetic mutism typically occurs in patients with bilateral lesions affecting the anterior cingulate and mesial frontal cortices. Frequently, the state reflects medial frontal damage caused by rupture of an anterior communicating artery aneurysm *(27)*. The associated injury may sometimes be accompanied by injury to the hypothalamus and anterior pallidum. A similar picture, but not including absence of eye movements, can rarely be a feature of untreated, severely rigid Parkinson's disease. Recently, a few investigators reported finding strong clinical resemblances to the above syndrome in the terminal state of prion disease *(28)*.

A slightly different clinical expression of the disorder is seen with subcortical or upper brainstem damage. Patients with this form of akinetic mutism appear apathetic and hypersomnolent *(29)* but may speak with understandable words. Castainge et al. *(30)* emphasized that patients suffering structural injuries affecting the medial-dorsal thalamus extending into the mesencephalic tegmentum suffered severe memory loss and apathetic behavior. Segarra *(31)* described 7 more examples of combined damage to the medial caudal thalamus extending into the medial dorsal mesencephalon that appeared to him to cause the same signs and symptoms as having "akinetic mutism". Because of this unfortunate confusion in both behavior and structure, we have termed the behavior of Segarra's patients's as having "slow syndrome". Most of them, after they regain awareness, are able to move and speak, and despite their apathy and amnesia, they are not semi-rigid as are akinetic mute patients. They also slowly communicate, although usually at the edge of severe dementia and their motor system reflects classic corticospinal tract abnormalities. They also lack the appearance of vigilance.A

persistent dementia characterizes the recovery phase of this disorder *(32)*. Subcortical lesions that may produce this state include bilateral lesions of the paramedian anterior or posterior thalamus and basal forebrain *(26,30)* the mesencephalic reticular formation including periaqueductal gray matter *(31)*, and caudate nuclei (or left caudate in isolation, *see* refs. *33–36*).

The common denominator of all akinetic mute states appears to be related to the disabling of several parallel, segregated cortico-straitopallidal-thalamocortical loops that involve the frontal lobes either directly or indirectly *(34)*. The most devastating injury is a bilateral loss of basal-mesial frontal cortical tissue, after which little further recovery develops. Bilateral lesions of the globus pallidus interna are unusual in that this structure contains each of the identified cortico-striato-pallidal-thalamocortical (CSPTC) circuits involving the frontal lobe, striatum, globus pallidus, substantia nigra, and thalamus *(34)*. Thus, a bilateral pallidal injury can disable all of the parallel networks. At least partial cognitive function can recover following some bilateral injuries to the paramedian thalamus and mesencephalon (*see* refs. *31,15,35,* and *36*), discussion in *(38)*. The akinetic mutism resulting from injury to these structures is likely to reflect their unique role along with the nucleus reticularis of the thalamus in gating both these parallel CSPTC loops *(39,40)* and specific long-range cortico-cortical interactions (*see* below). Isolated injury to the periaqueductal grey region has also been described in experimental models of akinetic mutism *(41,42)*. This structure may modulate regions of the paramedian mesodiencephalon. Selective injury to the medial forebrain bundle removes a strong dopaminergic modulation of medial frontal lobe structures functionally down-regulating these regions *(43)*. This loss of modulation is reversible, and can sometimes be corrected by giving patients dopaminergic agonists *(44)*.

Absence Seizures

Absence seizures reflect a unique global alteration of consciousness. These events exhibit attentional and intentional failure, loss of working memory and intra-ictal perceptual dissociation. In their classic form, absence seizures represent momentary vegetative states (c.f. Table 1). Although debate surrounds the underlying mechanism of absence seizures, thalamocortical generation is indicated by both clinical and experimental studies of absence seizures *(45–47)*. The key role of cortico-thalamic projections in organizing large scale coherent EEG patterns has been well demonstrated in recent studies *(48)*. Most current animal models include the nucleus reticularis of the thalamus (NRT) in conjunction with thalamocortical relay cells, and the cortex as the essential substrate for the cortical initiation of the seizure *(46,49)*. In addition, the passage from the thalamus to the cortex must rely on specific and nonspecific relay nuclei that project to the cortex (the NRT does not project to the cortex, [*see* ref. *50*]. Among these thalamic nuclei, the intralaminar nuclei play an important role in the genesis of these seizures. Experimental studies in guinea pig, cat, monkey, and man all demonstrate that generalized 3/s spike-waves and an associated behavioral absence may be elicited by electrical stimulation of the intralaminar nuclei and related nonspecific thalamic nuclei, primarily, the median dorsalis and ventral anterior nuclei, *(51–57)*. These studies show a robust reproducibility of the 3/s spike and wave phenomenon across species and behavioral state. In addition, an important role for brainstem reticular contributions to this seizure has also been argued *(58,59)*.

Taken together, an overlap exists between the anatomical structures involved in absence seizures and those that when injured, induce coma, vegetative states, and akinetic mutism. Absence seizures represent one of few conditions that may produce brief unconsciousness without any evidence of lasting structural injury. Unlike concussions, syncope, or pharmacologic anesthesia, arousal is preserved during the absence seizure demonstrating the selective loss of integrative functions with these events (*see* Section on Early Centrencephalic Theories).

AROUSAL AND GATING SYSTEMS

In all cases of selective injuries producing global disorders, unconsciousness appears to arise from either large bilateral damage to frontal or posterior association cortices or selective subcortical

injuries. As noted in the Section on Absence Seizures, the expressed pattern of subcortical injuries suggests that the paramedian mesodiencephalic structures of the "classical" arousal system (the intralaminar nuclei of the thalamus and the mesencephalic reticular formation) may play a primary role in this loss of integration observed in the different pathological states described in Pathological States of Unconsciousness above. The following Section (Arousal Systems) discusses the current concepts of arousal mechanisms and their possible distinction from structures that may be more appropriately considered "gating" systems.

Arousal Systems

The concept of brainstem arousal systems was introduced by the pioneering work of Moruzzi, Magoun, Morrison, and Dempsey (*see* refs. *60–62* and *68*). Initially the role of the mesencephalic reticular formation (MRF) and the thalamic intralaminar nuclei (ILN) were emphasized as mediating arousal and setting the stage for sensory processing in higher integrative brain functions *(8,52) see* recent review *(63)*. Electrical stimulation of these mesodiencephalic structures demonstrated their role in both electroencephalographic desynchronization and behavioral arousal.

The classic interpretations of the arousal system have been incorporated into a present conception that identifies arousal as interdependent on the output of cholinergic, serotoninergic, adrenergic and histaminergic nuclei located predominantly in the brainstem, basal forebrain, and posterior hypothalamus *(64–66)*. Arousal is now viewed in terms of global modulations of the thalamocortical system that define specific functional states *(64)*. Several studies have sought to determine how necessary or sufficient other neuronal groups are for arousal without providing compelling evidence that any single group is indispensable *(65–67)*. Even within global modulatory states increasing evidence identifies the fine structure contributed by selective activation of interdependent arousal systems *(65,68,69)*. For example, varying effects of noradrenergic, dopaminergic, and cholinergic neuromodulators have been identified in visuospatial attention paradigms *(69)*. The nucleus basalis of the basal forebrain has also been partitioned into regions that can become selectively active in different behaviors *(71)*. The increasingly high degrees of interconnection identified in anatomical studies of these neuronal populations provide a substrate for complex interactions among these brainstem nuclei *(72)*.

Cholinergic pathways that originate in the laterodorsal tegmental and pedunculopontine nuclei project rostrally to various targets and play a prominent role in most discussions of arousal mechanisms (*see* ref. *66*) Their selective output is probably insufficient to generate normal arousal (which must require additional glutamatergic and other brainstem populations, *(73)*, although much evidence indicates that they play a role in sharpening attention and modulating conscious activity *(74,69)*. Well documented clinical reports indicate that selective damage to these pontine cholinergic nuclei, can prevent or greatly reduce REM and normal sleep patterns, thereby resulting in chronic hyposomnia, but not necessarily even a transient coma *(75,76)* for further discussion and related findings in olivopontocerebellar atrophy patients). Cognitive ability reportedly remains intact in such persons so long as they do not incur more rostral brainstem damage *(77)* Cholinergic nuclei located more rostrally in the basal forebrain influence cortical cognitive and memory functions as well as EEG desynchronization. Nevertheless, they seem to make no firmly established contribution to arousal per se. The selective contributions of dopaminergic (ventral tegmental area) and histaminergic (tubomammilary nucleus) agents have also been studied *(65)* and may strongly influence the expression of sleep and wake states.

Centrencephalic Integration and Early Models of Forebrain "Gating" Systems

Half a century ago, Penfield and Jasper, refs. *(79,80)* proposed a clinically engendered hypothesis involving brainstem arousal mechanisms and termed the process 'centrencephalic integration', (*see*

refs. *59* and *63* for historical reviews). Penfield drew his speculation from observing the temporary loss of consciousness accompanying absence seizures and linked this unique paroxysmal event to interfering with a "highest level" brain mechanism that underlay conscious awareness. Importantly, he suggested that the observed loss of consciousness was the result of a specific failure of a generalized integrating mechanism. Penfield never precisely detailed the model in physiological terms or anatomical specificity, but he strongly emphasized the role of the thalamic intralaminar nuclei and the adjacent mesencephalic reticular formation in wakeful behavior. The theory was extensively, but nonscientifically, criticized by conflating the hypothetical system with a locus (a "centrencephalon") that would achieve such an integration underlying consciousness *(80–82)*. A close reading of Penfield's writings, however, clearly indicate his concept that these mesodiencephalic structures organized a process that enabled a

> "synchronous central and cortical activity, activity in the brainstem and in those areas of the cortex of either hemisphere whose function is suited to the changing requirements of the moment"*(84)*.

Further extensions of centrencephalic models have been developed. Working with both alert and anaesthetized cats *(83)*, pioneered a series of experiments that examined the integrative physiology of the MRF, the NRT and the medial thalamic-mesial frontal cortical systems (these included the ILN and related nonspecific thalamic nuclei). These investigators proposed that gating of attention was achieved by medial thalamo-frontal cortical and MRF control of NRT inhibition of specific thalamic relay nuclei (*see* Fig. 1B). The model proposed that intentionally directed action emanated from the frontal cortical-thalamocortical projections together with reflex orienting responses able to interrupt via the MRF pathway to NRT, that otherwise remained under cortical direction. Schiebel *(84)* enlarged on this model with a more anatomically detailed treatment of the MRF and Crick *(85)* further proposed that the NRT focused the conscious "searchlight" of attention. Crick's proposal emphasized a role for the low threshold spike burst that results from NRT mediated hyperpolarization. This conductance inactivates, however, during the depolarized states associated with wakefulness and attentive behaviors, a factor that rules out this "searchlight" mechanism *(86)*. Recent anatomical studies have detailed specific sectors within the NRT that could partition thalamocortical activation along the lines envisioned by Crick and others *(87)*. A physiological study in rats recently demonstrated such a selective NRT role in attentional processing using a covert-attention paradigm (Posner task) *(88)*.

Physiological Studies of the Role of "Gating" Systems in Forebrain Integration

The concept of forebrain gating has been enlarged by several physiological investigations that provide evidence of interaction of functional states with selective integrative mechanisms. Recent human PET studies demonstrate that the MRF and ILN coactivate during attentional processing providing further support for the 'gating' concept of selective attention *(90)*. In Kinomura et al.'s studies, PET scans showed increased regional blood flow in the mesencephalic reticular formation, in ILN and, in prefrontal, frontal, parietal, and primary sensory cortices when quiet wakefulness was compared to simple reaction time tasks in a visual or somatosensory attentional paradigm. Along the same lines, Portas et al. *(93)* identified a specific role for the thalamus in mediating interactions of attention and arousal during careful, state-controlled studies using fMRI paradigms.

Recent studies have detailed the physiological connections between the ILN and MRF and further elucidated their essential role in both arousal *(91,92)* and attentive states *(93)*. Both the centromedian-parafascularis complex, Cm-Pf, (posterior intralaminar group) and the central lateral nucleus (CL, anterior intralaminar group), may desynchronize the EEG during arousal *(94,91)* and may play a role similar to the activation observed in Kinomura et al.'s studies. Tonic rapid firing in CL correlates with desynchronization of the EEG and responds to inputs from the MRF *(91)*. These studies

demonstrate specific changes in the spectral content of background brain activity within different behavioral states, including natural awake attentive states that have been found to exhibit increased high frequency activity *(93)*.

Additional anatomical and physiological evidence suggests that the ILN may also contribute to the formation of specific "event-holding" functions that support attention and working memory (*95–97* and *see* below). Such event-holding functions may represent focal, sustained activations or amplifications of cortical activity *(98)* and also, may be associated with neuronal transient responses *(99,100)*, oscillatory activity *(94,101,102)*, or possibly other physiological signatures *(99,103,104)*, identified the possible role of these patterns of sustained cortical firing, supported by the ILN, in working memory. Several experimental results from Mair and colleagues, *(105,107)* have provided evidence that marked deficits in delayed match to sample performance are attributable to lesions specifically, of the intralaminar nuclei (paracentral, central lateral, and central medial, but not the median dorsalis nucleus). The investigators interpret the observed memory deficits primarily as a disabling of mnemonic functions of CSPTC loops by ILN injury.

Experimental studies also support a selective integrative role for the ILN. Integrative problems in visuospatial awareness associate with both anterior and posterior thalamic lesions involving the ILN. Circumscribed thalamic lesions thought to be restricted to the Cm-Pf complex result in specific impairments in trying to use extraretinal eye position signals to produce accurate memory-guided saccades (an example consists of following a truncal rotation or caloric stimulus, [*see* ref. *108*]). Studies of CL also demonstrate a role in visual awareness. In cats, contraversive head turning and conjugate and contraversive saccadic eye movements are elicited by stimulation of CL *(109)*. Similarly, unilateral lesions of CL in cats lead to contralateral visual neglect *(110)*.

Schlag-Rey and Schlag *(111,112)*, first described a role for the ILN in primate visuo-spatial awareness. They characterized visuomotor functions in the rostral intralaminar nuclei (primarily CL) of alert monkeys using single-unit recordings in animals performing behavioral tasks. One population of neurons ceased firing during a saccade and then rebounded with a burst of action potentials at the start of the next intersaccadic interval ("pause-rebound", *see* Fig. 2). Most of these neurons demonstrated this behavior for any saccade, with the direction or amplitude of the saccade having no effect on the dynamics of the response. Other neighboring visuomotor units in the ILN (eye position and saccadic burst cells) were highly sensitive to the parameters (amplitude, latency, direction) of the saccade ("gaze" and "sustained", *see* Fig. 2). Schlag and Schlag-Rey *(112)* interpreted their findings as antithetical to the concept of "mass action" in the ILN but rather hinting at "control signals" or a "clocking device synchronized on saccades used to pace operations at the next stage of (cortical processing)".

Based on Schlag and Schlag-Rey's pioneering studies, Purpura and Schiff *(97)* proposed that the CL firing responses, which are sensitive to levels of arousal, also have a multifunctional purpose in both setting up large areas of cortical activation and in facilitating more local activations related to visual awareness. ILN neurons are presumed to share intrinsic membrane properties that are common to all thalamic neurons *(113)*. This means that these neurons should be capable of two modes of firing behavior, i.e., when hyperpolarized they should fire a short high frequency burst superimposed on slower lower amplitude Ca^{2+} spikes; or, if depolarized, they should fire spikes at a regular rate determined by the level of depolarization. The temporal structure of firing patterns of CL neurons may be controlled both by levels of arousal and visuomotor behavior. Such local activations may be excited by the saccade related bursts identified by Schlag and Schlag-Rey *(111)* thereby facilitating processing, in separated cortical regions that receive input during the intersaccadic interval. One requirement of this proposal is that fast bursting neurons must be able to burst in the active depolarized states associated with wakefulness *(65)*. New evidence from in vivo intracellular recordings during natural sleep-wake cycles shows that such a mechanism may be available *(11)*.

Figure 2 illustrates a hypothesis by Purpura and Schiff *(97)* for how ILN populations may play a role in selectively gating forebrain activity in addition to facilitating tonic changes in arousal states.

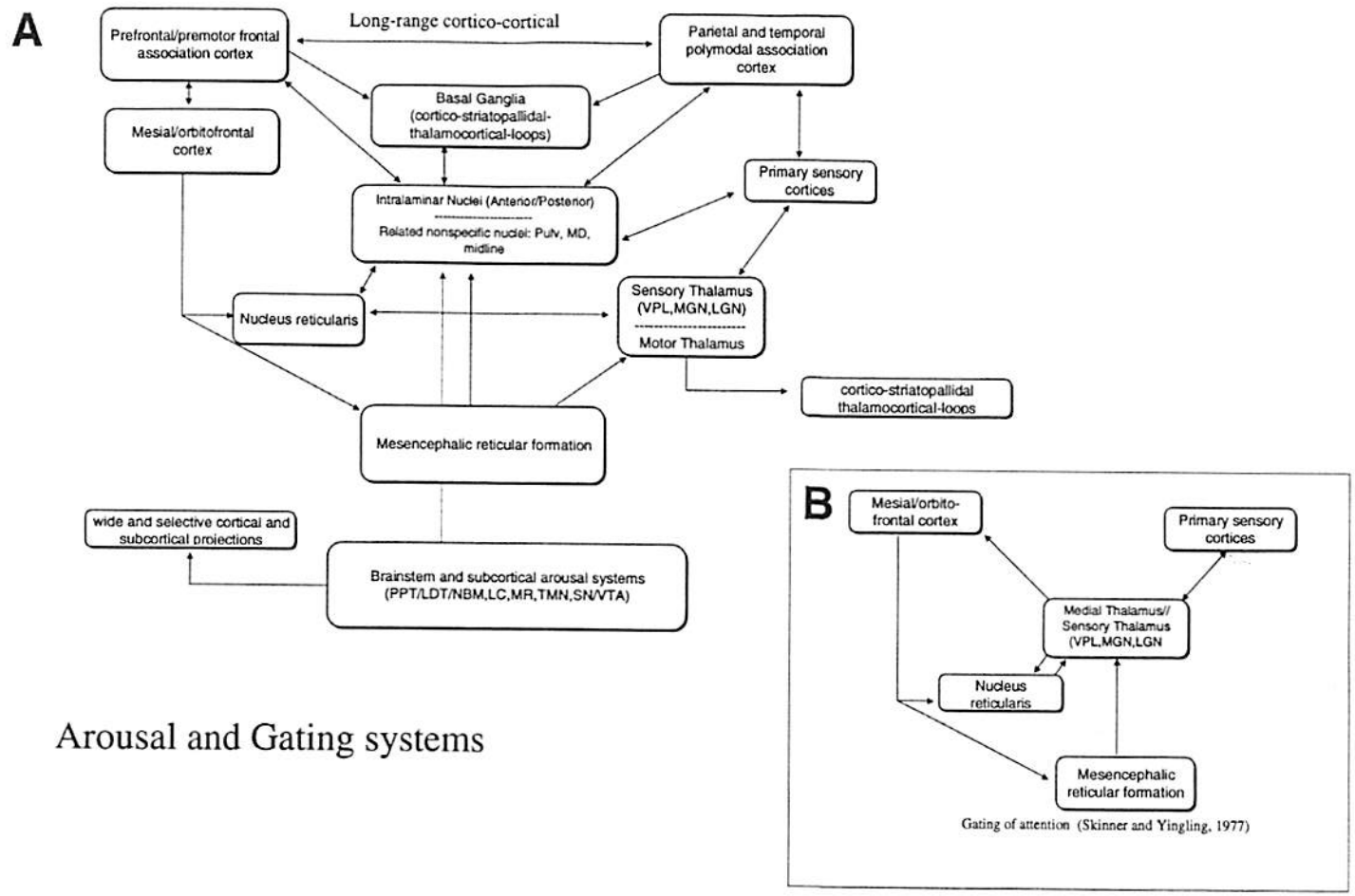

Fig. 2. **(A)** A schematic overview of brainstem arousal and mesodiencephalic gating systems. **(B)** Early model of gating of attention by Skinner and Yingling ca. 1977 *(83)*.

In this hypothetical experiment, recordings from several cortical and thalamic (ILN and pulvinar) sites are illustrated. The responses are modeled from recordings in the alert primate as reviewed above and below. Unlike neurons of the specific thalamic relay nuclei, neurons of the ILN make their synapse in layer I onto the apical dendrites of pyramidal cells in layers II–III, and layers V and VI *(114)*. Following this input pattern, ILN stimulation activates both the supragranular and infragranular layers of the cortical microcircuit *(115)*. During the tonic firing mode of ILN cells, activation of NMDA channels in the supragranular layers may support sustained activity in local populations of cortical pyramidal cells *(96,97,116)*. In primates that have learned selective attention paradigms, neuronal activity with these characteristics can be recorded from the prefrontal cortex (PFC) *(98)*, the frontal eye fields (FEF) *(117)*, and posterior parietal cortex (PPC) *(118,119)*. In such paradigms, a period of sustained activation in cortical neurons is observed between presentation of a peripheral target and a subsequent saccade to the target's location (*see* Fig. 2). Such shifts of attention relate closely to saccadic eye-movements and may reflect similar transient activation patterns in the forebrain. ILN subdivisions selectively project to PFC (Pf, CL and paralaminar MD), FEF (CL and paralaminar MD), and PPC (Cm-Pf, CL). Through these specific projections, they may facilitate, and possibly trigger such sustained activations or "event-holding functions" utilized in visuospatial attention. These sustained neuronal responses may act as "activity envelopes" that gate many different carriers generated by relatively independent local network processes *(120)*. The transient activation of such activity envelopes may be the basis for episodic cortical processing linking attention and working memory to oculomotor behavior and the intersaccadic interval *(97)*.

The model in Fig. 2 focuses on projections of the ILN to networks related to attention and oculomotor activity. Each cortical region in the example is identified with functions that are selectively vulnerable to anesthetics (*see* Young Chapter 2). In the PFC, neuronal activations would reflect working memory processing, whereas in the PPC these cortical activations would determine the dynamics of the attentional gate with the ILN facilitating the well-documented interdependence of these psychophysical variables *(121,122)*. In FEF, these activations would prepare saccadic eye-movements to attended targets. Though not illustrated, important projections to the basal ganglia and modulation of the cortico-striato-pallidal-thalamocortical components of the frontal cortices involved would significantly contribute to the performance of the hypothetical task. Thus, through the activation of widely separated local patches of cortex and subcortical structures, particular subdivisions of the ILN may facilitate specific long-range cortico-cortical interactions *(93,123,124)*. Thus, forebrain gating per se, would reflect the ongoing formation of episodic activity within these circuits organized around behaviorally significant events.

Other subdivisions of the ILN and related gating system components may engage in different behavioral states. Of note, some evidence exists for similarly selective single-unit behavior in the MRF *(125)*. Knowledge of the specific functional contributions of the thalamic reticular nucleus in alert humans or primates is very limited outside of interesting attentional and memory failures associated with somewhat selective injury to the NRT, following poisoning with domoic acid *(126,127)*, or anoxic injury *(128)*.

Taken together, the main role of the ILN, MRF, and NRT, following on the earlier models of Penfield and Jasper, Skinner and Yingling, and others as reviewed above, is to facilitate the gating of cortico-cortical information processing and not arousal, per se (*see* Fig. 1A and 1B). Several lines of evidence support a selective role for subcortical gating systems in the mechanism of global disorders, interdependent upon contributions from the arousal systems. The clinical expression of global disorders produced by subcortical injuries may thus depend on whether such selective gating processes are completely or only partially disabled. The specific gating processes may be identified with activity envelopes organized around important endogenous transient events. Examples include eye-movements or shifts of attention, that are used to facilitate long-range communication in the forebrain. The episodic dynamics of these activity envelopes, operating within the background arousal state, may be primarily facilitated by the gating systems and themselves may organize many different ongoing neuronal assembly processes.

POSSIBLE RELATIONSHIPS OF ANESTHETIC MECHANISMS AND PATHOLOGIC STATES OF UNCONSCIOUSNESS

Both subcortical arousal and gating systems play key roles in global disorders of consciousness. Whether or not these structures play such a role in selective mechanisms underlying anesthesia is unknown. A few recent studies have examined the regionally selective effects of pharmacologic anesthesia. While preliminary, these data do show some overlap between the areas of significant reduction in cerebral metabolic activity or blood flow that are associated with anesthesia and those selective areas that produce global disorders of consciousness following structural injury.

Veselis and colleagues *(129)* examined alterations in regional cerebral blood flow (rCBF) in normal subjects undergoing midzolam infusions of different concentrations. In their studies, that evaluated blood flow using 15-O positron emission tomography (PET) techniques (*see* Chapter 3), several cortical association areas and the thalamus demonstrated significant reductions of rCBF compared to the generalized decrease observed throughout the brain in each subject. The findings are consistent with similar observations of marked reduction of thalamic metabolism with other benzodiazepine agents *(130)*. These investigators interpret their findings in the context of coinactivation of both cortical and subcortical regions important for attention, working memory (*see* Chapters 2 and 3) and arousal.

Alkire and colleagues *(131)* have postulated a unified mechanism for anesthetics that involves a hyperpolarization block of thalamocortical transmission, they emphasize the role of both the thalamus and the MRF in activating specific populations of cortical neurons. In a recent FDG-PET study examining regional cerebral metabolic rates (rCMR), the investigators compared two inhalational anesthetics (halothane and isoflurane) for overlapping regions affected by both agents. A strong overlap was identified in rCMR reductions in the thalamus and MRF. These findings were noted to be consistent with rCMR studies and 15-O rCBF studies of benzodiazepine agents discussed in Veselis and colleagues' results. Their opinion closely follows that of Angel *(132)* who, in a comprehensive review of neuronal responses to anesthetic agents, identified suppression of thalamic activity (particularly the NRT and ILN), and a relatively stronger effect on cortical pyramidal cells in both layer III and layer V. These selective effects within the cortical microcircuit, particularly upon layer V cells, may be important and relate to several present theories of cellular underpinnings of the conscious state (*122,134,135*, and Chapter 8).

Other investigators have examined variations in depth of anesthesia and preservation of selected systems. Logothetis and colleagues recently demonstrated the partial preservation of perceptual sensorimotor integration in monkeys undergoing ketamine anesthesia *(136)*. They systematically varied anesthetic levels and tracked the optokinetic nystagmus (OKN) response; the results demonstrate that this elemental aspect of sensorimotor integration can remain despite low doses of ketamine anesthesia. The response; however, is changed to reflect an asymmetric activation pattern consistent with functional loss of top-down influences. This elegant model demonstrates that integrated circuits may remain functional even with substantial reductions of other modulatory forebrain activity. The OKN response is often preserved in akinetic mutism, and along with occasional isolated behavioral fragments seen in some PVS patients, may simply reflect very limited preservation of forebrain circuits.

These functional studies hint at an intersection of common action of anesthetics in MRF and thalamus. It is possible that, in general, anesthetics act first to disable selective integrative cerebral functions, followed by more global impairment of the cortico-thalamic system, as neuronal firing is suppressed. The patterns of behavior in the clinical syndromes reviewed above and the considerations of selective cellular effects of anesthetics on the basic corticothalamic microcircuit and brainstem (*see* Chapters 6–10) support such a view. A strict structure-function correlation, however, is difficult to identify between the loss of consciousness seen with anesthetic agents that produce widespread hemodynamic and metabolic changes, and regional physiological suppression of cerebral function. As Cariani *(137)* has argued, it is not clear whether anesthesia primarily overwhelms and

102. Singer, W. and Gray, C. (1995) Visual feature integration and the temporal correlation hypothesis. *Ann. Rev. Physiol.* **55,** 349–374.
103. Vaadia, E. et al. (1995) Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. *Nature* **373,** 515–518.
104. Schiff, N. D., Purpura, K. P., and Victor, J. D. (1999c) Gating of local network signals appear as stimulus-dependent activity envelopes in striate cortex. *J. Neurophysiol.* **82,** 2182–2196.
105. Mair, R. G., Burk, J. A., and Porter, M. C. (1998) Lesions of the frontal cortex, hippocampus, and intralaminar thalamic nuclei have distinct effects on remembering in rats. *Behav. Neurosci.* **112,** 772–791.
106. Burk, J. A. and Mair, R. G. (1998) Thalamic amnesia reconsidered: excitotoxic lesions of the intralaminar nuclei, but not the mediodorsal nucleus, distrupt place delayed matching-to-sample performance in rats (Rattus norvegicus). *Behav. Neurosci.* **112,** 54–67.
107. Zhang, Y., Burk, J. A., Glode, B. M., and Mair, R. G. (1998) Effects of thalamic and olfactory cortical lesions on contiuous olafactory delayed non-matching-to-sample and olfactory discriminationin rats (Rattus norvegicus). *Behav. Neurosci.* **112,** 39–53.
108. Gaymard, B., Rivaud, and S., Pierrot-Deseilligny (1994) Impairment of extraretinal eye position signals after central thalamic lesions in humans. *Exp. Brain Res.* **102,** 1–9.
109. Schlag, J. and Schlag-Rey, M. (1971) Induction of oculomotor responses from thalamic internal medullary lamina in the cat. *Exp. Neurol.* **33,** 498–508.
110. Orem, J., Schlag-Rey, M., and Schlag, J. (1973) Unilateral visual neglect and thalamic intralaminar lesions in the cat. *Exp. Neurol.* **40,** 784–797.
111. Schlag-Rey, M. and Schlag, J. (1984) Visuomotor functions of central thalamus in monkey. II unit activity related to visual events, targeting and fixation. *J. Neurophysiol.* **40,** 1175–1195.
112. Schlag-Rey, M. and Schlag, J. (1984b) Visuomotor functions of central thalamus in monkey. II. Unit activity related to visual events, targeting and fixation. *J. Neurophysiol.* **40,** 1175–1195.
113. Jahnsen, H. and Llinas, R. (1984) Electrophysiological properties of guinea-pig thalamic neurones: an in vitro study. *J. Physiol.* **349,** 205–226.
114. Macchi, G. and Bentivoglio, M. (1985) The thalamic intralaminar nuclei and the cerebral cortex. In: Jones, E. G. and Peters, A, (eds.), Cerebral Cortex. Vol. 5. New York, Plenum Press, pp. 355–389.
115. Sukov, W. and Barth, D. S. (1998) Three-dimensional analysis of spontaneous and thalamically evoked gamma oscillations in the auditory cortex. *J. Neurophysiol.* **79(6),** 2875–2884.
116. Larkum, M. E., Zhu, J. J., and Sakmann, B. (1999) A new cellular mechanism for coupling inputs arriving at different cortical layers. *Nature,* **398,** 338–341.
117. Schall, J. D. (1991) Neuronal activity related to visually guided saccades in the frontal eye fields of rhesus monkeys: comparison with supplementary eye fields. *J. Neurophysiol.* **66,** 559–579.
118. Andersen, R. (1989) Visual and eye movement functions of the posterior parietal cortex. *Ann. Rev. Neurosci.* **12,** 377–403.
119. Colby, C. L. (1991) The neuroanatomy and neurophysiology of attention. *J. Child Neurol.* **6,** S90–S118.
120. Schiff, N. D., Ribary, U. Plum, F., et al. (1999c) Words without mind. *J. Cogn. Neurosci.* **11,** 650–656.
121. Reeves, A. and Sperling, G. (1986) Attention gating in short-term visual memory. *Psychol. Rev.* **93(2),** 180–206.
122. Sperling, G. and Weichselgartner, E. (1995) Episodic theory of the dynamics of spatial attention. *Psychol. Rev.* **102(3),** 503–532.
123. Barth, D. S. and MacDonald, K. D. (1996) Thalamic modulation of high-frequency oscillating potentials in auditory cortex. *Nature* **383,** 78–81.
124. Amzica, F., Neckelmann, D., and Steriade, M. (1997) Instrumental conditioning of fast (20–50 Hz) oscillation in corticothalamic networks. *Proc. Natl. Acad. Sci. USA* **94,** 1985–1989.
125. Waitzman, D. M., Silakov, V. L., and Cohen, B. (1996) Central mesencephalic reticular formation (cMRF) neurons discharging before and during eye movements. *J. Neurophysiol.* **75(4),** 1546–1572.
126. Newman, J. (1997) Putting the puzzle together Part II. *J. Conscious. Stud.* **4(2),** 100–122.
127. Teitelbaum, J. S. et al. (1990) Neurologic sequelae of domoic acid intoxication due to the ingestion of contaminated mussels. *N. Engl. J. Med.* **322(25),** 1781–1787.
128. Ross, D. T. and Graham, D. I. (1993) Selective loss and selective sparing of neurons in the thalamic reticular nucleus following human cardiac arrest. *J. Cereb. Blood Flow Metab.* **13(4),** 558–567.
129. Veselis, R. A., Reinsel, R. A., Beattie, B. J., et al. (1997)Midazolam changes cerebral blood flow in discrete brain regions: an H2(15)O positron emission tomography study. *Anesthesiology* **87(5),** 1106–1117.
130. Volkow, N. D., Wang, G. J., Hitzemann, R., Fowler, J. S., Pappas, N., Lowrimore, P., Burr, G., Pascani, K., Overall, J., Wolf, A. P. (1995) Depression of thalamic metabolism by lorazepam is associated with sleepiness. *Neuropsychopharmacology* **12(2),** 123–132.
131. Alkire, M. T., Haier, R., and Fallon, J. H. (2000) Toward a unified theory of narcosis. *Conscious. Cogn.* **9,** 370–386.
132. Crick, F. and Koch, C. (1990) Foward a neurobiological theory of consciousness. *Sem. Neurosci.* **2,** 263–275.
133. Llinas, R., Ribary, U., Contreras, D., and Pedroarena, C. (1998) The neuronal basis for consciousness. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* **353(1377),** 1841–1849.
134. Steriade, M. (2000) Corticothalamic netwarks, oscillations, and plactiaty. *Adv. Neurol.* **77,** 105–134.
135. Plettenberg, H. K. W., Leopold, D. A., Smirnakis, S. M., and Logothetis, N. K. (2000) Perception—related optokinetic responses in the semi-conscious monkey. Society for Nuroscience abstract 2000 #250.11.
136. Angel, A. (1993) Central neuronal pathways and the process of anaesthesia. *Br. J. Anaesth.* **71(1),** 148–163.
137. Cariani, P. (2000) Anesthesia, neural information processing, and conscious awareness. *Conscious. Cogn.* **9,** 387–395.

68. Silberstein, R. (1995) Neuromodulation of neocortical dynamics. In: Nunez, P. (ed.), Neocortical Dynamics and Human EEG Rhythms. Oxford University Press.
69. Marracco, R. T. and Davidson, M. C. (1998) Neurochemistry of attention. In: Parasuraman, R. (ed.), The attentive brain. Cambridge, MA: MIT Press, pp. 35–50.
70. Coull, J. T., Frith, C. D., Dolan, R. J., Frackowiak, R. S., and Grasby, P. M. (1997) The neural correlates of the noradrenergic modulation of human attention, arousal and learning. *Eur. J. Neurosci.* **9(3),** 589–598.
71. Sarter, M. and Bruno, J. P. (2000) Cortical cholinergic imputs mediating arousal, attentional processing and dreaming: differential afferent regulation of the basal forebrain by telencephalic and brainstem afferents. *Neuroscience* **95,** 933–952.
72. Smiley, J. F., Subramanian, M., and Mesulam, M. M. (1999) Monaminergic-cholinergic interactions in the primate basal forebrain. *Neuroscience* **93(3),** 817–829.
73. Steriade, M. (1999) Invited commentary. Disorders of Consciousness. Association for Scientific Study of consciousness Electronic Seminar Series. http://athena.englishh.vt.edu/cgi-bin/netforum/nic/a/14-1.2.2.
74. Posner, M. I. and Rothbart, M. K. (1998) Attention, self regulation and consciousness. *Trans. R. Soc. Lond.* **353,** 1915–1929.
75. Autret, A., Laffont, F., de Toffol, B., and Cathala, H. P. (1988) A syndrome of REM and non-REM sleep reduction and lateral gaze paresis after medial tegmental pontine stroke. Computed tomographic scans and anatomical correlations in four patients. *Arch. Neurol.* **45(11),** 1236–1242.
76. Plum, F. (1991) Coma and related global disturbances of the human conscious state. In: Jones, E., Peters, P. (eds.), Cerebral cortex. Vol. 9. New York: Plenum Press.
77. Lavie, P., Pratt, H., Scharf, B., Peled, R., and Brown, J. (1984) Localized pontine lesion: nearly total absence of REM sleep. *Neurology* **34(1),** 118–120.
78. Penfield, W. (1952) Epileptic automatism and the centrencephalic integrating system. *Res. Ass. Nerv. Ment. Disc. Proc.* **30,** 513–528.
79. Penfield, W. G. and Jasper, H. H. (1954) Epilepsy and the functional anatomy of the human brain. Boston: Little Brown.
80. Walshe, F. M. R. (1957) The brainstem conceived as the "highest level" of function in the nervous system; with particular reference to the "automatic apparatus" of Carpenter (1850) and to the "centrencephalic integrating system" of Penfield. *Brain* **80,** 510–539.
81. Penfield, W. (1958) Centrencephalic integrating system. *Brain* **81,** 231–234.
82. Thompson, R. (1993) Centrencephalic theory, generalized learning system and subcortical dementia. In: Crinella, F. and Yu, J., (eds.), Brain Mechanisms. New York Academy of Sciences: **702** pp. 197–224.
83. Skinner, J. E. and Yingling, C. D. (1977) Central gating mechanisms that regulate event-related potentials and behavior. In: Desmedt, J. E. (ed.), Progress in clinical neurophysiology. Vol 1. Attention, voluntary contraction, and event-related cerebral potentials. Basel:Karger, pp. 70–96.
84. Schiebel, A. B. (1980) Anatomical and physiological substrates of arousal: view from the bridge. In: Hobson, J. A. and Brazier, M. A. B. (eds.), The Reticular Formation Revisted, (New York, Raven Press).
85. Crick, F. (1984) Function of the thalamic reticular complex: the searchlight hypothesis. *Proc. Natl. Acad. Sci. USA* **81,** 4586–4590.
86. Steriade, M, Timofeev, I., and Grenier, F. (1999) Intracellular activity of various neocortical cell-clasess during the natural sleep-wake cycle. Society for Neuroscience 29th Annual Meeting Abstract 664.14
87. Guillery, R. W., Feig, S. L., and Lozsadi, D. A. (1981) Paying attention to the thalamic reticular nucleaus. *Trends Neurosci.* **21,** 28–32.
88. Weese, G. D., Phillips, J. M., and Brown, V. J. (1999) Attentional orienting is impaired by unilateral lesions of the thalamic reticular nucleus in the rat. *J. Neurosci.* **19(22),** 10,135–10,139.
89. Kinomura, S., Larssen, J., Gulyas, B., and Roland, P. E. (1996) Activation by attention of the human reticular formation and thalamic intralaminar nuclei. *Science* **271,** 512–515.
90. Portas, C. M., Rees, G., Howseman, A. M., Josephs, O., Turner, R., and Frith, C. D. (1998) A specific role for the thalamus in mediating the interaction of attention and arousal in humans. *J. Neurosci.* **18(21),** 8979–8989.
91. Glenn, L. L. and Steriade, M. (1982) Discharge rate and excitability of cortically projecting intralaminar neurons during waking and sleep states. *J. Neurosci.* **2(10),** 1387–1404.
92. Pare, D., Smith, Y., Parent, A., and Steriade, M. (1988) Projections of brainstem core cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic nuclei. *Neuroscience* **25(1),** 69–86.
93. Steriade, M., Amzica, F., and Contreras, D. (1996) Slynchronization of fast 30–40 Hz spontaneous cortical rhythms during brain activation. *J. Neurosci.* **16,** 392–417.
94. Steriade, M. and Buzsaki, G. (1990) Parallel activation of thalamic and cortical neurons by brainstem and basal forebrain cholinergic systems. In: Steriade, M., Bliesold, D., (eds.), Brain cholinergic system. New York: Oxford University Press.
95. Vogt, B. A. (1990) The role of layer 1 in cortical function. In: Jones, E. G., Peters, A., (eds.), Cerebral Cortex. Vol. 9. New York: Plenum Press, pp. 49–80.
96. Mair, R. (1994) On the role of thalamic pathology in diencephalic amnesia. *Rev. Neurosci.* **5,** 105–140.
97. Purpura, K. P. and Schiff, N. D. (1997) The thalamic intralaminar nuclei: role in visual awareness. *Neuroscientist* **3,** 8–14.
98. Fuster, J. M. (1973) Unit activity in prefrontal cortex during delayed-response performance: neuronal correlates of transient memory. *J. Neurophysiol.* **36,** 61–78.
99. Schall, J. D. (1991) Neuronal activity related to visually guided saccades in the frontal eye fields of rhesus monkeys: comparison with supplementary eye fields. *J. Neurophysiol.* **66,** 559–579.
100. Friston, K. (1995) Neuronal transients. *Proc. R. Soc. Lond. B.* **261,** 401–405.
101. Llinas, R. and Ribary, U. (1993)Coherent 40-Hz oscillation characterizes dream state in humans. *Proc. Natl. Acad. Sci. USA* **90(5),** 2078–2081.

33. Bhatia, K. P. and Marsden, C. D. (1994) The behavioural and motor consequences of focal lesions of the basal ganglia in man. *Brain* **117(4),** 859–876.
34. Mega, M. S. and Cohenour, R. C. (1997) Akinetic mutism: disconnection of frontal-subcortical circuits. *Neuropsychiatry Neuropsychol. Behav. Neurol.* **10(4),** 254–259.
35. Stuss, D. T., Guberman, A., Nelson, R., and Larochelle, S. (1988) The neuropsychology of paramedial thalamic infarction. *Brain Cogn.* **8(3),** 348–378.
36. van Domburg, P. H., ten Donkelaar, H. J., and Notermans, S. L. (1996) Akinetic mutism with bithalamic infarction. Neurophysiological correlates *J. Neurol. Sci.* **139,** 58–65.
38. Schiff, N. D. and Plum, F. (1999) Target article: The neurology of impaired consciousness: global disorders and implied models. Association for Scientific Study of Consciousness Electronic Seminar Series http://athena.english.vt.edu/cgi-bin/netforum/nic/a/1.
39. Groenewegen, H. and Berendse, H. (1994a) The specificity of the "nonspecific" midline and intralaminar thalamic nuclei. *Trends Neurosci.* **17,** 52–66.
40. Groenewegen, H. and Berendse, H. (1994b) Anatomical relationships between prefrontal cortex and basal ganglia in rat. In: Thierry, A.M. et al. (eds.), Motor and cognitive functions of the prefrontal cortex. Springer Verlag Berlin.
41. Panksepp J. (1998) Affective Neuroscience. Oxford UK: Oxford University Press.
42. Watt, D. (1998) Emotions and Consciousness: Implications of affective neuroscience for extended reticular thalamic activating system theories of consciousness. ASSC Eseminar Target article. http://server.phil.vt.edu/assc/watt/default.html.
43. Ross, E. D. and Stewart, R. M. (1981) Akinetic mutism from hypothalamic damage: successful treatment with dopamine agonists. *Neurology*, **31,** 1435–1439.
44. Fleet, W. S., Valenstein, E., and Watson, R. T. (1987) Dopamine agonist therapy for neglect in humans. *Neurology* **37(11)** 1765–1770.
45. Snead, O. C. (1995) Basic mechanisms of generalized absence seizures. *Ann. Neurol.* **37,** 146–157.
46. Steriade, M. and Contreras, D. (1995) Relations between cortical and thalamic cellular events during transition from sleep patterns to paroxysmal activity. *J. Neurosci.* **15(2),** 623–642.
47. McCormick, D. A. and Bal, T. (1997) Sleep and arousal: thalamocortical mechanisms. *Ann. Rev Neurosci.* **20,** 185–215.
48. Contreras, D., Destexhe, A., Sejnowski, T. J., and Steriade, M. (1997) Spatiotemporal patterns of spindle oscillations in cortex and thalamus. *J. Neurosci.* Feb 1; **17(3),** 1179–1196.
49. Huguenard, J. (1999) Neuronal circuitry of thalamocortical epilepsy and mechanisms of antiabsence drug action. In: Delgado-Escueta, A. V. et al. (eds.), Jasper's Basic Mechanisms of the Epilepsies, Third Edition. Advances in Neurology Vol 79.
50. Scheibel, M. E. and Schiebel, A. B. (1966) The organization of the nucleus reticularis: a golgi studu. *Brain Res.* **1,** 43–62.
51. Jasper, H. H. and Droogelever-Fortuyn, J. (1948) Experimental studies on the functional anatomy of petit mal epilepsy. *Rs. Pub. Assist. Nerv. Ment. Disord.* **26,** 272–298.
52. Hunter, J. and Jasper, H. H. (1949) Effects of thalamic stimulation in unanesthetized animals. *Electroencephalogr. Clin. Neurophysiol.* **1,** 305–324
53. Ingvar, D. H. (1955) Reproduction of 3 per second spike and wave EEG pattern by subcortical electrical stimulation in cats. *Acta Physiol. Scan.* **33,** 137–150.
54. Pollen, D. A., Perot, P., and Reid, K. H. (1963) Experimental bilateral wave and spike from thalamic stimulation in relation to level of arousal. *Electroencephalogr. Clin. Neurophysiol.* **15,** 1017–1028.
55. Steriade, M. (1974) Interneuronal epileptic discharges related to spike-and-wave conical seizure in behaving monkeys. *Electroencephalogr Clin. Neurophysiol.* **37,** 247–263.
56. David, J., Marathe, S. B., Patil, S. D., and Grewal, R. S. (1982) Behavioral and electrical correlates of absence seizures induced by thalamic stimulation in juvenile rhesus monkeys with frontal aluminum hydroxide implants: a pharmacologic evaluation. *J. Pharmacol. Meth.* **7,** 219–229.
57. Velasco, F., Velasco, M., Marquez, I., and Velasco, G. (1993) Role of centromedian thalamic nucleus in the genesis, propagation, and arrest of epileptic activity. An electrophysiological study in man. *Acta Neurochir. (Suppl).* **58,** 201–204.
58. Gloor, P., and Fariello, R. G. (1988) Generalized epilepsy: some of its cellular mechanisms differ from those of focal epilepsy. *Trends Neurosci.* **11(2),** 63–68.
59. Jasper, H. H. (1991) Current evaluation of concepts of centrencephalic and corticoreticular seizures. *Electroencephalogr. Clin. Neurophysiol.* **78,** 2–12.
60. Morison, R. S. and Dempsey, E. W. (1942) A study of thalamo-cortical relationships. *Am. J. Physiology* **135,** 281–292.
61. Jasper, H. (1949) Diffuse projection systems. *Electronencephalogr. Clin. Neurophysiol.* **1,** 405–420.
62. Jasper, H. H. and Droogelever-Fortuyn, J. (1947) Experimental studies on the functional anatomy of petit mal epilepsy. *Res. Pub. Assist. Nerv. Ment. Disord.* **26,** 272–298.
63. Jasper, H. (1998) Consciousness and sensory processing. In: Consciouness at the frontiers of neurology. Advances in Neurology Vol. 77 Lippincott Raven Publishers, Philadelphia, PA, pp. 33–48.
64. McCormick (1992)
65. Marracco, R. T., Witte, E., and Davidson, M. C. (1994) Arousal systems. *Curr. Opin. Neurobiol.* **4,** 166–170.
66. Steriade, M. (1997) Thalamic substrates of disturbances in states of vigilance and consciousness in humans. In: Steriade, M., Jones, E. and McCormick, D. (eds.), Thalamus. Elsevier Publishers.
67. Dringenberg, H. C. and Vanderwolf, C. H. (1997) Neocortical activation: modulation by multiple pathways acting on central cholinergic and serotonergic systems. *Exp. Brain* **116(1),** 160–174.

suppresses neuronal firing rates, or whether it alters specific patterns of neuronal activity such as that engendered by alteration of gating mechanisms, as suggested in the section on Gating Systems. The further elucidation of the relative importance of the alteration of global cerebral activation vs specific patterns of forebrain activity associated with anesthetic agents, will strengthen our understanding of relationships between pathological and pharmacological forms of impaired consciousness.

REFERENCES

1. James, W. (1890) Principles of Psychology. Reprinted Dover Books, 1950.
2. Fracowiak, R. S. J., Friston, K., Frith, C., Dolan, R., and Mazziota, J. C. (1998) Human brain mapping. London: Academic Press.
3. Johnson, M (1997) Developmental Cognitive Neuroscience. Blackwell Press.
4. Steriade, M. and Llinas, R. R. (1988) The functional states of the thalamus and the associated neuronal interplay. *Physiol. Rev.* **68(3),** 649–742.
5. Schiff and Plum, (2000) The Role of Arousal and "Gating" Systems in the Neurology of Impaired Consciousness. *J. Clin. Neurophysiol.* **17(5),** 438–452.
6. Plum, F. and Posner, J. (1982) The Diagnosis of Stupor and Coma. Third Edition F. A. Davis, Philadelphia, PA.
7. Plum, F. (1991) Coma and related global disturbances of the human conscious state. In Jones, E. and Peters, P. (eds.), Cerebral Cortex, Vol. 9, Plenum Press.
8. Moruzzi, G. and Magoun, H. W. (1949) Brainstem reticular formation and activation of the EEG. *Electroencephalog. Clin. Neurophysiol.* **1,** 455–473.
9. Jennett, B. and Plum, F. (1972) Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet* **1,** 734–737.
10. Multisociety Task Force on PVS. (1994) Medical aspects of the persistent vegetative state. Part 1. *N. Engl. J. Med.* **330,** 1499–1508.
11. Danze, F., Brule, J. F., and Haddad, K. (1989) Chronic vegetative state after severe head injury: clinical study; electrophysiological investigations and CT scan in 15 cases. Neurosurg. Rev. **12 Suppl. 1,** 477–499
12. Dougherty, J. H., Jr, Rawlinson, D. G., Levy, D. E., and Plum, F. (1981) Hypoxic-ischemic brain injury and the vegetative state: clinical and neuropathologic correlation. *Neurology* **31(8)** 991–997.
13. Facon, M., Steriade, M., and Wertheim, N. (1958) Hypersomie prolonge engendere par des lesions bilatereles du systeme activateur medial. Le syndrome thrombotique de la bifurcation du tronc basilaire. *Rev. Neurol.* **98,** 117–133.
14. Plum, F. and Posner J. (1966) The diagnosis of stupor and coma. Philadelphia: Davis, F.A.
15. Castaigne, P. et al. (1981) Paramedian thalamic and midbrain infarcts: clinical and neuropathological study. *Ann. Neurol.* **10,** 127–148.
16. Kinney, HC et al. (1994) Neuropathological findings in the brain of Karen Ann Quinlan. *N. Engl. J. Med.* **330,** 1469–1475.
17. Relkin, N. R., Petito, C., and Plum, F. (1990) Coma and vegetative state secondary to severe anoxic-ischemic damage involving the thalamus. *Ann. Neurol.* **28,** 221–222.
18. Levy, D. E., Sidtis, J. J., and Rottenberg, D. A., (1987) Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. *Ann. Neurol.* **22,** 673–682.
19. DeVolder, A. G. et al. (1990) Brain glucose metabolism in postanoxic stroke. *Arch. Neurol.* **47,** 197–204.
20. Tomassino, C., Grana, C., Lucignani, G., Torri, G., and Ferrucio, F. (1995) Regional metabolism of comatose and vegetative state patients. *J. Neurosurg. Anesthesiol.* **7(2),** 109–116.
21. Rudolf, J., Ghaemi, M., Ghaemi, M., Haupt, W. F., Szelies, B., and Heiss, W. D. (1999) Cerebral glucose metabolism in acute and persistent vegetative state.*J. Neurosurg. Anesthesiol.* **11(1),** 17–24.
22. Blacklock, J. B. (1987) Effect of barbituate coma on glucose utilization in normal brain versus gliomas. Positron emission tomography studies. *J. Neurosurg.* **67,** 71–75.
23. Plum, F., Schiff, N., Ribary, U., and Llinas, R. (1998) Coordinated expression in chronically unconscious persons. *Trans. R. Soc. Lond.* **353,** 1929–1933.
24. Ribary, U., Schiff, N., Kronberg, E., Plum, F., and Llinas, R. (1998) Fractured brain function in unconscious humans: Functional brain imaging using MEG. *Neuroimage* **7(4),** S106.
25. Schiff, N., D., Ribary, U., Plum, F., and Llinas, R. (1999a) Words without mind. *J. Cogn. Neurosci.* **11(6),** 650–656.
26. Cairns, H., Olfield, R. C., Pennybacker, J. B., and Whitteridge, D. (1941) Akinetic mutism with an epidermoid cyst of the third ventricle. *Brain* **64,** 273–290.
27. Nemeth, G., Hegedus, K., and Molnar, L. (1988) Akinetic mutism associated with bicingular lesions: clinicopathological and functional anatomical correlates. *Eur. Arch. Psychiatry Neurol. Sci.* **237(4),** 218–222.
28. Otto, A., Zerr, I., Lantsch, M., Weidehaas, K., Riedemann, C., and Poser, S. (1998) Akinetic mutism as a classification criterion for the diagnosis of Creutzfeldt-Jakob disease. *J. Neurol. Neurosurg. Psychiatry* **64(4),** 524–528.
29. Fisher, C. M. (1983) Honored guest presentation: abulia minor vs. agitated behavior. *Clin. Neurosurg.* **31,** 9–31.
30. Castaigne, P. et al. (1966) Demence thalamique d'origine vasculaire par 'ramollissement bilateral limite au territorie du pedicle retro-mamillaire. *Rev. Neurol.* **114,** 89–107.
31. Segarra, J. M. (1970) Cerebral vascular disease and behavior. The syndrome of the mesencephalic artery (basilar artery bifurcation). *Arch. Neurol.* **22,** 408–418.
32. Katz, D. I., Alexander, M. P., and Mandell, A. M. (1987) Dementia following strokes in the mesencephalon and diencephalon. *Arch. Neurol.* **44,** 1127–1133