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New Perspectives

Status Dissociatus—A Perspective on States of Being

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Summary: During the course of routine clinical study, it has become apparent that the all-or-none concept of state determination (wakefulness, nonrapid eye movement sleep, rapid eye movement sleep) does not always exist, and that ambiguous, multiple, or rapid oscillation of state-determining variables appear in a wide variety of experimental and clinical situations. Six cases of extreme state dissociation are presented, with a review of the human and animal clinical and experimental literature. This multiple component concept of state determination must be kept in mind when pharmacologic or lesion studies are employed to suppress one or another state. Such manipulation may suppress some of the commonly used markers for that state (i.e., polygraphic) without affecting other variables of that state. The existence of mixed states will be a challenge to the development of automated computerized polysomnogram scoring. **Key Words:** Status dissociatus—Sleep disorders—Narcolepsy—Parasomnias—Night terrors—Sleepwalking—REM behavior disorders—Lucid dreaming—Mixed states of sleep/wakefulness.

"The state of a system at a given instant is the set of numerical values which its variables have at that instant" (1).

During the past two decades, the proliferation of clinical sleep disorders centers has permitted the objective study of human sleep. In the course of such studies, the sleep clinician has been witness to a wide variety of peculiar and difficult-to-explain behavioral phenomena, which challenge the three states of being concept [wakefulness (W), nonrapid eye movement sleep (NREM), and rapid eye movement sleep (REM)]. Examination of the voluminous basic science neurophysiologic sleep data available from animal experimentation provides insight into the explanation of these peculiar observed human behaviors. The purposes of this article are to 1) report a new clinical syndrome (status dissociatus), which represents the extreme form of wakefulness/sleep state dissociation, 2) review experimental animal data supporting state dissociation, 3) integrate these experimental data with observed human behaviors, and, 4) make predictions about as yet unrecognized state-dissociated human behaviors.

CASE REPORTS

The theoretical extreme of the concept of state dissociation would be the complete breakdown of state boundaries, resulting in the simultaneous appearance of elements of all three states. Six such cases have been studied in our laboratory.

METHODS

The six patients were identified during routine clinical evaluations at our sleep center. Sleep laboratory data were obtained by protocol. Behaviors were continuously videotaped during standardized monitoring of the electrooculogram (EOG), electroencephalogram (EEG), electromyogram (EMG) (chin and four limbs), electrocardiogram (ECG), and nasal air flow (2). A certified polysomnographic (PSG) technician made written observations of sleep behaviors. Bilateral limb EMG leads recorded extensor digitorum and anterior tibialis activity. Further details of our procedures have been described previously (3).

RESULTS

Case 1

A 39-year-old man with a 20-year history of intractable alcohol abuse and with blood alcohol levels as high as 0.5 mg/ml was observed to have unusual sleep behavior. After 3 weeks of complete abstinence while hospitalized for pancreatitis, his waking behavior was normal, but he displayed nearly continuous limb movements and nonsensical vocalizations during what appeared to be behavioral sleep (eyes closed, reduced

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environmental responsiveness, startle upon stimulation). His perception of his sleep was: "I feel like I'm just about awake." He estimated that mental imagery occurred during 90% of his sleep time. If awakened from behavioral sleep, he reported having been sleeping, with very close correspondence between his observed behavior and reported dream mentation. The neurological examination was unremarkable. A computerized tomographic (CT) scan of the brain revealed cerebral and cerebellar atrophy. Multiple PSG recordings showed no identifiable conventional sleep patterns. Generalized low-voltage fast EEG activity, continuous rapid and slow eye movements, and frequent body and limb twitches and jerks were present during behavioral (and clinically restorative) sleep (Figs. 1A and B). Clonazepam administered at bedtime was associated with the appearance of conventional sleep patterns and nearly complete elimination of the motor/verbal activity during sleep.

Case 2

A 60-year-old man had a 2-year history of olivopontocerebellar degeneration and an 8-year history of sleep-related shouting and laughing with prominent, nearly continuous extremity motor activity, occasionally resulting in violent, injurious behaviors corresponding to dream mentation. Neurologic examination revealed static and intentional tremor of the hands, bradykinesia, bilaterally present Babinski signs, and mild impairment of proprioception at the feet. A CT scan of the brain revealed cerebellar atrophy. The sleep recorded during two consecutive PSGs contained a small amount of identifiable stages 3/4 NREM sleep (11%); the remainder was identical to that seen in Case 1. The administration of clonazepam at bedtime increased the percentage of identifiable stages 3/4 NREM sleep (19%), reduced the twitches and jerks, and has resulted in significant clinical reduction of sleep-related motor/verbal activity.

Case 3

A 61-year-old man with no prior sleep complaints developed nearly continuous motor activity during sleep associated with profound excessive daytime sleepiness immediately following open heart surgery at age 59. He also reported that his dreams were "more vivid and of greater length" following surgery. CT and magnetic resonance imaging scans of the brain and waking EEG were normal. The neurologic examination was unremarkable with the exception of a variably present upward deviation of the left eye on left lateral gaze and of the right eye on right lateral gaze. Formal neuropsychometric evaluation revealed "average to bright normal range intellectual and memory skills" with "evidence of selective deficits in the areas of spatial construction and planning ability on a visuospatial task." Two consecutive nightly PSGs consisted of little scorable NREM sleep, no identifiable REM sleep, and nearly continuous desynchronized EEG with muscular twitching, prominent slow and rapid eye movements, and vocalization. When queried during these periods, he reported having been both asleep and dreaming. He has been refractory to treatment with multiple medications (stimulants, benzodiazepines, narcotics, tricyclic antidepressants, carbamazepine, L-dopa/carbidopa, and L-tryptophan).

Other cases

The other three cases included: one 65-year-old man with both obstructive sleep apnea (apnea index = 95) and a history of classic narcolepsy with cataplexy treated with methylphenidate (80 mg/day) and imipramine (25 mg/day); and two women (ages 54 and 43) with long-standing classic narcolepsy with cataplexy by history treated with methylphenidate (80, 100 mg/day) and imipramine (250, 225 mg/day). All complained of sleep-related motor/verbal activity, displayed severe sleep stage disaggregation [the simultaneous occurrence or rapid oscillations of features of W/REM/NREM] by PSG study, and each clinically improved with clonazepam. Complex verbal and/or motor behavior was documented by continuous audiovisual monitoring during the PSG in all cases.

The bizarre clinical and electrographic data displayed by these patients represent examples of extreme state dissociation emerging in diverse clinical settings, with behavioral and self-perceived sleep actually comprised of simultaneously occurring elements of W/REM/NREM states. The self-perceived sleep was behaviorally different from wakefulness. The EEG of this sleep was characterized by a predominately wake-

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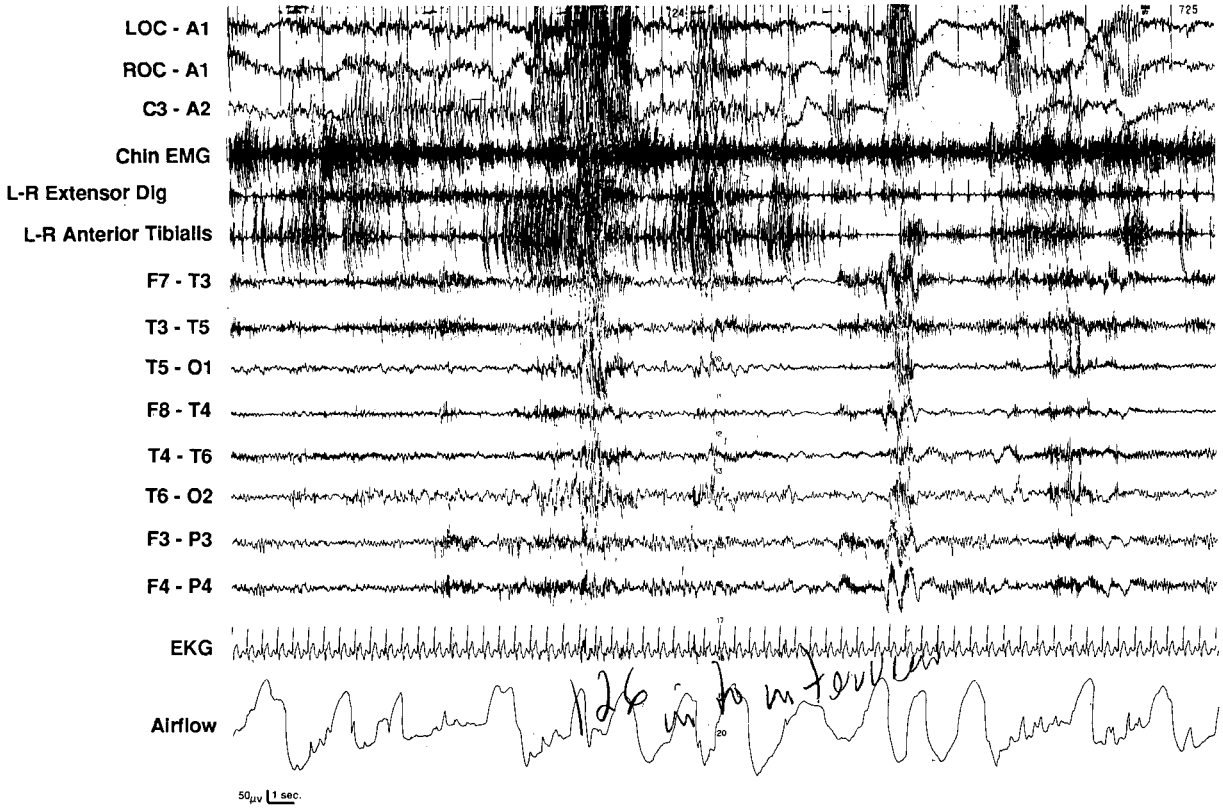
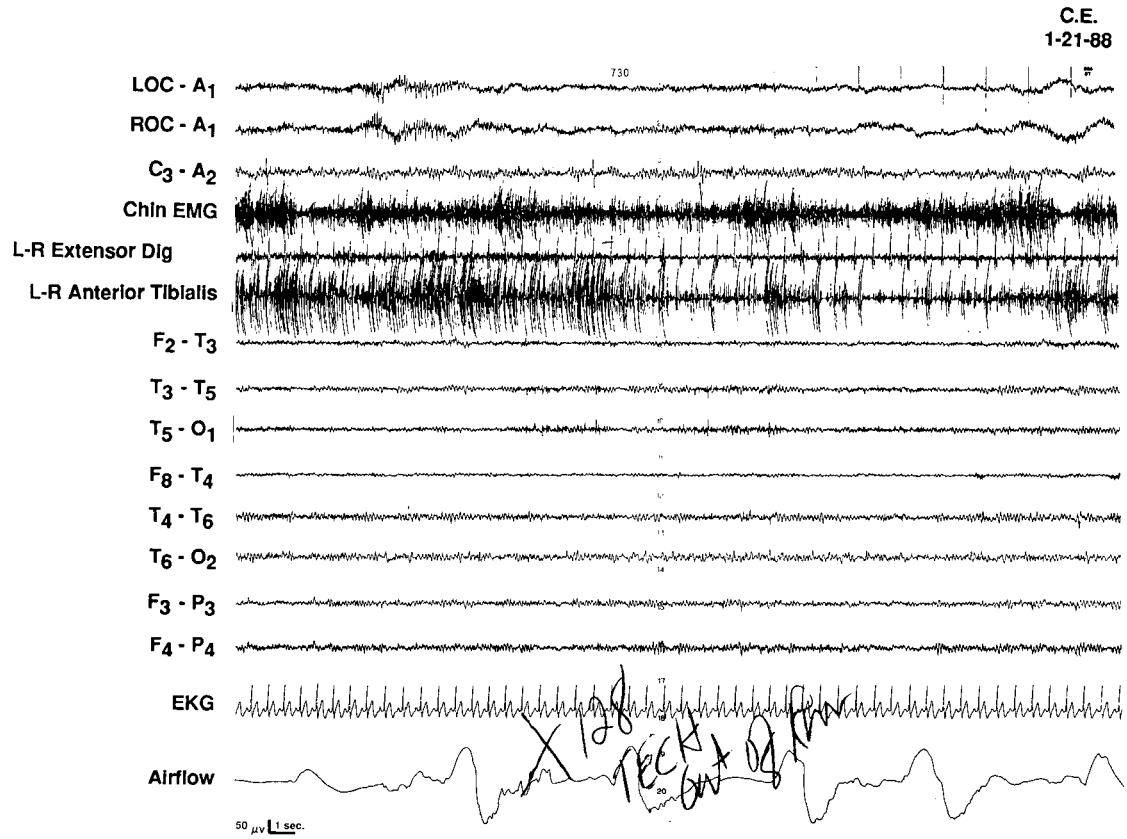
FIG. 1A. Polygraphic correlate of behavioral and subjectively reported sleep during which dream-mentation occurred. Note absence of conventionally identifiable features of either REM or NREM such as atonia for REM or EEG synchronization for NREM. The twitching is reminiscent of REM. Simply speaking to the patient from this state resulted in immediate attention to the environment, the report of having been "asleep and dreaming," and the appearance of a normal, waking EEG (Fig. 1B). **B.** Polygraphic correlate of behavioral and subjectively reported wakefulness. Note the striking polygraphic similarity to Figure 1A, despite the difference in perceived and behavioral state. LOC-A1, ROC-A1—left, right eye movements; electroencephalographic leads: F—frontal, C—central, T—temporal, O—occipital, and A—ear.



A



B

ful-like pattern with superimposed slowing and poorly developed sleep spindles and vertex-like activity (see Fig. 1A). The reported dreamlike mentation and complex motor activity and vocalization (both appropriate to the remembered mentation) are suggestive of REM sleep, clinically resembling the motor activity/vocalization seen during REM sleep without atonia in patients with documented REM sleep behavior disorder (RBD). The EEG slowing seen during sleep was most likely a NREM phenomenon, as its complete disappearance in these patients during clinical W indicated that the slowing did not represent an underlying pathologic pattern. The only fully declared clinical or polygraphic state demonstrated by these subjects was W. Clonazepam was administered because of its striking effectiveness in controlling the complex and vigorous behaviors of RBD (4). Its mechanism of action in these conditions is unknown.

DISCUSSION AND IMPLICATIONS FOR IDENTIFICATION OF THEORETICALLY PREDICTABLE STATE DISSOCIATIONS

Evolution of concept of state

The clinical concept of states of being has changed dramatically over the past few decades. It was formerly thought that human existence encompassed only two states: wakefulness and sleep, with sleep being considered as simply the passive absence of wakefulness. With the discovery of REM sleep in 1953, it became apparent that sleep is not a unitary phenomenon, but rather consists of two completely different states, and each state is an active, rather than quiescent, process (5). Each state consists of a number of physiologic variables, which tend to occur in concert, resulting in the appearance of one of the three conventional states of being: W, REM, and NREM (6,7). Animal experiments and evaluation of humans in the sleep laboratory indicate that the three states of being concept must be further expanded to include the observations that the physiologic event markers of one state may intrude into other states, and that the states may oscillate rapidly, resulting in the appearance of bizarre, previously difficult-to-explain, and occasionally extraordinary animal and human behaviors, which can occur in diverse natural and clinical settings, with important treatment implications.

Normal state determination

State determination may be made using various criteria: behavioral (eyes open/closed, body position, movements, reactivity to the environment); electrographic (EEG, EOG, EMG); and neuronal state (brain neuronal activity) as outlined in Table 1. The state-determining properties of each state usually cycle in a predictable and uniform manner, resulting in the behavioral appearance of a single prevailing state. However, even in normal subjects, the electrographic and neuronal activity transition among states is gradual and variable, with the simultaneous occurrence or rapid oscillation of multiple state-determining markers. Within each state, there is ongoing variability and fluctuation of central nervous system (CNS) activity (6,8).

The circadian cycling of these states is, in part, controlled by a pacemaker (the suprachiasmatic nucleus), which resides in the hypothalamus (9). Other factors involved in appearance of state include a wide variety of humoral (sleep-promoting) substances (10). The ultradian (<24 h) cycling of the W/REM/NREM cycles appears to be generated in the brainstem, and may, in part, be explained by the reciprocal inhibition hypothesis of Hobson and McCarley, which proposes that sleep cycling is generated by the interaction of two opposing, reciprocally discharging, anatomically distributed neuronal populations (9,11).

In the past, there has been much attention directed toward the identification of specific state-determining centers in the CNS. It is now apparent that there is no one locus that is responsible for all components of any given state. The declaration of W/REM/NREM states is a complex phenomenon, involving multiple neuronal networks, many different transmitters, and multiple levels of the neuraxis, which become recruited to produce a recognizable state (9). Some identical neuronal groups are extremely active in more than one state, with differing state-dependent effects, i.e., many REM sleep phenomena are similar to the alerting response seen in wakefulness (noted in Table 2) (12–14); some brainstem regions effect motor suppression in REM sleep but motor facilitation in W (15). This phenomenon of state-dependent motor control has been termed the "reticular response-reversal," indicating that excitation of the same anatomic site may have opposite effects upon reflex motor activity, depending upon the state (W or REM) during stimulation (16,17). The involvement of similar neural structures or networks in multiple states is supported by the similarity of the middle latency auditory evoked potentials and of thalamic activity during W and REM (18,19). Such functional variability of neurons between differing neural networks has recently been well demonstrated (20,21).

REM is the best-studied sleep state. One of the hallmarks of REM sleep is the ponto-geniculo-occipital (PGO) spike, which begins to appear shortly before the onset of fully declared REM sleep, and becomes maximally developed during REM sleep (19). REM sleep is comprised of both tonic (occurring throughout the entire REM cycle) and phasic (occurring intermittently

TABLE 1. *State determinants*[a]

	Wake	NREM	REM
Behavioral/cognitive			
Movement	Frequent, voluntary	Infrequent, episodic, involuntary, gross movements	Inhibited; frequent, small brief twitches
Thought	Logical, progressive, remembered	Logical, progressive, not usually remembered	Illogical, bizarre, not remembered (unless awakened)
Sensation and perception	Vivid, externally generated	Dull or absent	Vivid, internally generated
Position	Variable, erect	Recumbent	Recumbent
Level of consciousness	+	−	−
Eyes	Open, moving	Closed, slow or not moving	Closed, moving
Electrographic			
EEG	Desynchronized	Synchronized	Desynchronized
Eye movements	+	−	+
Muscle tone	++	+	−
Neuronal activity			
REM-on cells[b]	−	+	++
REM-off cells[c]	++	+	−
Integration of sensation/cognition/premotor systems and motor expression	+	−	−

[a] Adapted from refs. 6, 7, 9, and 104.
[b] Gigantotegmental field, central tegmental field, lateral tegmental field, tegmental reticular nucleus.
[c] Raphe nuclei, locus ceruleus, peribrachial region, gigantotegmental field.

during the REM cycle) components (Table 2). Each of these elements is generated, modulated, and executed by different neuronal groups located at multiple levels of the neuraxis—from cerebral cortex to spinal cord—orchestrated by the dorsomedial pontine region (22–24). Although the pons is the source of all the components of REM sleep, descending influences from the cortex and thalamus may influence this activity [e. g., forebrain lesions may alter the temporal distribution of PGO waves recorded from the occipital cortex (25); midbrain transection in cats modulates REM sleep trigeminal reflexes 26)].

Experimental state dissociation (animal)

The recurrent recruitment of state-determining parameters is amazingly consistent. However, multiple experimental examples of state component dissociation exist (27). These fall into three categories:

1) Lesion/stimulation: Hypothalamic, thalamic, and brainstem manipulation/stimulation induces state dissociation (28–34).
2) Pharmacologic: Manipulation of the cholinergic/glutamate neurotransmitter systems results in a variety of state dissociations (35–44).
3) Deprivation: REM sleep deprivation in cats results in the appearance of PGO spikes during NREM sleep (45).

In addition to these experimental dissociations, there is evidence in the animal kingdom for the natural occurrence of clinically wakeful behavior during physiologic sleep. Two examples that dispel the concept of all-or-none state declaration are the concurrence of swimming or flight during sleep in birds (46) and the phenomenon of unihemispheric sleep in some aquatic mammals (bottle-nosed dolphin, common porpoise, and northern fur seal) guaranteeing continued respiration while sleeping (47). Another naturally occurring dissociated state is seen during the arousal from torpor in hibernating ground squirrels, when there is an "uncoupling between thalamic, EMG, and cortical REM correlates" (48). Both experimentally induced and nat-

TABLE 2. *Tonic and phasic compoents of REM sleep*[a]

Tonic
EEG—desynchronization[b]
EMG—atonia[b]
Brain temperature[b]
Hippocampal theta rhythm[b]
Poikilothermia
Olfactory bulb activity
Penile tumescence
(Dreaming?)[c]
Phasic
PGO waves[b]
REM[b]
MEMA[d]
Tongue movements
Muscle twitches
Cardiopulmonary variability
(Dreaming?)[c]

[a] Adapted from refs. 13, 14, 22, 27, 105, 142–144.
[b] Part of generalized alerting response, present during both wakefulness and REM sleep.
[c] It is not known whether dreaming is tonic or phasic during REM sleep.
[d] Middle ear muscle activity.

urally occurring state dissociations in animals serve to predict spontaneously occurring experiments in nature and drug-induced state dissociation in humans, which undoubtedly exist on a broad spectrum of expression.

Clinical state dissociation (human)

There are a number of well-documented state dissociations in humans that occur spontaneously or as the result of neurologic dysfunction or medication administration. It may be more valid and practical to assign each as a variant of the predominant or prevailing parent state (W/NREM/REM), instead of identifying each possible dissociated state as an independent entity.

Wakefulness variations. Narcolepsy is the prototypic dissociated state arising from the background of wakefulness. The symptom of cataplexy (sudden loss of muscle tone, usually in response to an emotionally laden event) is simply the isolated intrusion of REM sleep atonia into wakefulness. The element of surprise in triggering cataplexy supports the described similarity between the alerting response and REM sleep (13). The symptom of sleep paralysis is the persistence of REM atonia into wakefulness. The hypnagogic (occurring at sleep onset) and hypnopompic (occurring upon awakening) hallucinations are dream mentation occurring during wakefulness, which are often more frightening if accompanied by sleep paralysis (49). Although hallucinations (? wakeful dreams) are frequently associated with psychiatric disease, some may represent the release of REM sleep mentation into wakefulness. Narcoleptic patients may experience waking dreams, particularly during drowsiness, and may be misdiagnosed and even treated as schizophrenics (50, 51). The occurrence of ambiguous or dissociated sleep is well documented in the untreated narcoleptic (52). The induction of dissociated states in narcolepsy by tricyclic antidepressant administration indicates that genetically determined and pharmacologically potentiated state-disrupting factors may act in concert (53–55).

Other examples include: drug (56–58) and sleep deprivation-induced hallucinations (59) and a case of simultaneously occurring EEG patterns of W and NREM sleep (60). Another likely example is peduncular hallucinosis, a condition associated with deep midline intracranial lesions (61–69). Interestingly, the lesions (diencephalic, hypothalamic, third ventricular region) reported to result in these hallucinations are virtually identical to those that cause symptomatic narcolepsy (70,71). The fact that these symptoms of narcolepsy were for many years felt to be psychiatric in nature should serve as a caveat for the interpretation of other unusual behavioral symptoms.

REM sleep variations. RBD is the best-studied and perhaps most frequently documented dissociated state arising from the background of REM sleep. In retrospect, RBD was predicted in 1965 by animal experiments (32) but not formally recognized in humans until 1986 (4). During normal REM sleep, there is background atonia involving all somatic musculature (sparing the diaphragm and extraocular muscles). Although this generalized atonia may be briefly interrupted by excitatory inputs resulting in muscle jerks and twitches (72), the prevailing atonia prevents motor activity associated with dream mentation. In RBD, motor behavior attendant with dream imagery may be vigorous, occasionally with injurious results.

There is an acute, transient form of RBD seen most frequently in the setting of drug intoxication or withdrawal states and also a chronic form of RBD, most often affecting older males. One-third of subjects with chronic RBD have identifiable underlying neurologic disorders (4). The fact that over half of cases are idiopathic and tend to occur in the elderly suggests that RBD may be the reverse of sleep ontogeny (see comment section). The absence of identifiable peri-locus ceruleus lesions in the symptomatic subgroup is of interest and confirms animal experimental data, which indicate that suprapontine lesions may also affect REM sleep atonia (73). That hemispheral lesions in monkeys may affect metabolism of the thalamus and brainstem (74) and that stimulation of suprapontine structures in cats may inhibit muscle tone (75) suggest that the peri-locus ceruleus may be the final common pathway in the generation of REM sleep atonia and may not necessarily be directly involved in the clinical appearance of RBD. Chloramphenicol administration can reverse the peri-locus ceruleus lesion-induced REM without atonia, indicating that other structures are capable of inducing REM atonia (76). An analogous situation during W is the fact that cortical, rubral, and pontine neurons all contribute to anterior horn cell phasic excitation, indicating that motor activity may be initiated at several levels of the CNS (9).

Electrographic dissociation of REM sleep (absence of muscle atonia during REM sleep) may be induced in humans by the administration of tricyclic antidepressants (77,78). Spontaneously occurring RBD has been reported in dogs and cats (79).

Another example of a mixed W/REM state is that of lucid dreaming, during which the dreamer is aware of the fact that he/she is dreaming and has the ability to influence the course of the dream. REM sleep is the parent state during lucid dreaming, yet the subject has the facility to physically signal the presence of such a dream by means of voluntary eye and digit movements. Suppression of the H-reflex, a characteristic of REM sleep, is present during such dreaming (80). Some

out-of-body experiences may represent a variation on this theme (81).

NREM dissociations. A frequent wake/sleep dissociation is that of night terrors/sleepwalking (NT/SW), occurring in up to 40% of normal children (82). Contrary to popular opinion, this condition may persist into or develop during adulthood and is associated with psychiatric disease in less than 50% of affected adults (83). NT/SW represents a dissociation of wakefulness and consciousness (84). Such dissociation is exemplified by the absence of reactivity of the waking-like alpha frequency EEG activity recorded during attacks (85). Although usually associated with amnesia or only fragmentary mental imagery, there may be recall of vivid and elaborate dreamlike mentation (83). The usual timing of NT/SW in the sleep cycle at 1–2 h after sleep onset and the attendant mentation have led to the suggestion that NT/SW represents an anomalous REM sleep component occurring in deep NREM sleep (86). The triggering of NT/SW by medications and sleep deprivation (both of which may alter W/NREM/REM cycling) supports a state dissociation etiology (87). NT/SW may be induced in susceptible individuals by standing them up or administering an auditory stimulus during deep NREM sleep, which suggests that these states need not be the culmination of complex, prolonged mentation (88).

Another example of NREM/W dissociation is sleep drunkenness (SD), a disturbance of cognition and attention occurring in the transition between sleep and wakefulness, resulting in the appearance of complex motor behavior without conscious awareness (89–91). Sleep inertia (SI) (the deterioration of waking prenap task performance or the disorientation immediately following a nap) is a mild form of SD, representing incompletely declared W (92). The combination of EEG features of W and light NREM sleep during SI following naps is good evidence for such a mixed W/NREM state (93). Neurophysiological markers of either REM or NREM sleep precede and follow naps containing each respective sleep state, indicating that the transition among states is anticipated and gradual (94). It is likely that SD and SI are milder variants of NT/SW and all are excellent examples of the prolonged simultaneous occurrence or rapid oscillation of sleep (probably NREM) and W.

A common thread running through RBD, NT/SW, and SD/SI is the appearance of motor activity which is dissociated from waking consciousness. In RBD, the motor behavior closely correlates with dream imagery, and in NT/SW/SD/SI it often occurs in the absence of (remembered) mentation. It is well known that decorticate experimental and barnyard animals are capable of performing very complex, integrated motor acts. This is explained by the presence of locomotor centers (LMCs), from the mesencephalon to the medulla, which are capable of generating complex behaviors without cortical input (95–99).

These areas project to the central pattern generator of the spinal cord, which itself is able to produce complex stepping movements in the absence of supraspinal influence (100).

It is likely that during NREM sleep, the LMCs are not activated. The thesis that LMCs are actively inhibited during REM sleep is supported by the observations that smaller peri-locus ceruleus lesions result in REM sleep without atonia—without any behavioral manifestations—but larger lesions are necessary to produce active motor movements. Clearly, the isolated loss of REM atonia is insufficient to explain complex REM sleep motor activity in the experimental animal (101), suggesting a release of LMCs during the parent state, just as is seen in the loss of REM atonia. Dissociation of the LMCs from the parent state of REM or NREM sleep would explain the presence of complex motor behavior seen in RBD and NT/SW/SD/SI. Dissociation between LMCs and waking consciousness or memory may explain the complex motor activity associated with amnesia, which is characteristic of alcohol-induced black-outs (102) and with unconscious behavior occurring during partial complex seizures (103). This dissociation between behavior and consciousness may be related to inactivation of attentional or memory systems (104).

Miscellaneous dissociations: NPT/REM dissociation. Penile tumescence in males is one of the tonic elements of REM sleep, usually occurring with the other markers of the REM state (105). Administration of tricyclic antidepressants (106) and monoamine oxidase inhibitors (107,108) may selectively suppress the electrographic features of REM with persistence of at least one tonic component—penile tumescence. Similar penile tumescence/REM polygraphic dissociation has been reported in a posttraumatic pontine lesion in a man (109).

Miscellaneous dissociations: status dissociatus. This term is offered to describe the complete state boundary breakdown or rapid state oscillation and is exemplified by the above-mentioned cases. The well-studied case of fatal familial thalamic degeneration described by Lugaresi et al. appears to represent another such case (110,111).

COMMENT

Review of the ontogeny of state appearance facilitates the analysis of observed experimental and clinical state dissociations. During embryogenesis, there are no clearcut states, but rather the simultaneous admixture of all states, which gradually coalesce to form the three recognizable states of W/REM/NREM (112–115). The

mechanisms of complex synchronization/recruitment of the state-specific variables are unknown. Basic science neurophysiologists have long known that state dissociation in animals occurs frequently, under many circumstances (116). The inability of animals to report or indicate mentation and consciousness (i.e., waking hallucinations, mental imagery with NT/SW, dream-mentation-associated motor behavior in RBD) has been a significant limitation upon the evaluation of animal state dissociation and its application to the human clinical experience.

Many endogenous and exogenous factors can affect state cycling/synchronization. These include (10,117, 118):

1) age,
2) sleep deprivation,
3) shift-work/rapid travel across time zones,
4) endogenous humoral factors (hormonal),
5) drugs/medications,
6) affective disorders,
7) environmental stress (posttraumatic stress disorder).

With the multiplicity of state markers, and the relatively rapid normal cycling of states requiring recruitment of these numerous physiologic markers, there are innumerable theoretically possible state combinations. It is likely that major psychic or neural insults can result in an acquired functional restructuring of the CNS, which then may interfere with conventional state determination (119). There is strong evidence that environmentally mediated events can and do affect the structure and function of the CNS (118,120–122), and that the CNS displays learning of new neural behaviors (123–125) [i.e., the development of secondary epileptogenesis (mirror foci) (126) or acquired sensory synesthesia (127,128)]. Such dissociated states may play a role in the appearance of the posttraumatic stress disorder, nocturnal panic attacks, and even in psychogenic dissociative states. Given the genetic variability of CNS development and its plasticity (119,129–131), the relentless cycling, and the ever-present multiplicity of endogenous and environmental influences upon both CNS plasticity and cycling, it is surprising that state-component timing errors have not been identified more frequently. The drive for complete state determination must be very strong, indeed. Striking sleep abnormalities have been reported in a wide variety of degenerative (111,132–137) and acquired (138–141) neurologic conditions. This patient population should serve as a rich source of "high risk for state-dissociation" subjects.

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