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From REM sleep behaviour disorder to status dissociatus: Insights into the maze of states of being

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ABSTRACT

Sleep is a coordinated process involving more or less simultaneous changes in sensory, motor, autonomic, hormonal, and cerebral processes. On the other hand, none of the changes occurring with sleep are invariably coupled to sleep. EEG synchrony, heat loss, sleep-related hormone secretion, and even REM-related motoneuron paralysis may occur independent of the parent state. In REM sleep behaviour disorder (RBD) the muscle tone of wakefulness intrudes into REM sleep, allowing the release of dream-enacting behaviours. Status dissociatus (SD) is a condition in which brain and mind are in disarray along the boundaries of sleep and wakefulness. The existence of such dissociated behaviours shows that they have separate neuronal control systems and indicates that the whole organization of sleep is an emergent property of the collective neuronal systems to synchronize. Insults to the brain can drastically alter the circuitries responsible for maintaining the integrity of wakefulness, NREM sleep, and REM sleep. As a consequence, the basic states of existence can become admixed and interchanged with striking disturbances of consciousness, brain electrophysiology, and the behavioural and polygraphic expression of sleep and wakefulness. The evolution of RBD into SD may result from a disarray of (brainstem) structures that orchestrate the whole brain wake–sleep conditions, but with preserved discrete systems and dissociable strategies to still place navigation in wake and sleep. Advances in the fields of genetics, neuroimaging, and behavioural neurology will expand the understanding of the mechanisms underlying the organization of the states of being along with their somatic/behavioural manifestations.

1. Introduction

Sleep is a coordinated process involving more or less simultaneous changes in sensory, motor, autonomic, hormonal and cerebral processes [1,2]. On the other hand, none of the changes occurring with sleep are invariably coupled to sleep. Examples of such dissociated behaviours do exist in nature. For example, EEG synchrony, heat loss, sleep-related hormone secretion, and even REM-related motoneuron paralysis may occur independent of the parent state [3]. In naturally occurring patterns of normal sleep, parts of the brain can be awake while other parts are asleep, as happens in dolphins, who do not exhibit high-amplitude electroencephalogram (EEG) delta waves simultaneously in both cerebral hemispheres [4]. In monotremes (i.e., the echidna) the brainstem may show an REM sleep-like activity pattern at the same time in which the forebrain shows NREM sleep-like activity pattern [5,6]. In humans, as NREM epochs unfold, the EEG delta-wave power increases in the frontal cortex earlier than in more posterior cortical areas, suggesting differential sleep intensities in different brain regions [7]. Similarly, measurements of cerebral blood flow show regional differences during NREM and REM sleep [8]. Mahowald and Schenck have long recognized that, in human parasomnias, the brain can be awake and asleep simultaneously [9]. Studies of strokes and other brain lesions indicate that if a human or animal survives acute brain damage for more than a few days, sleep reemerges [10]. The existence of such dissociated behaviours shows that they have separate neural control systems and indicates that sleep must be regulated by a network that integrates and orchestrates a variety of neural systems. All together, these findings suggest that sleep is a robust fundamental self-organizing property of any group of neurons.

1.1. Dissociation of states of being: from REM sleep behaviour disorder to status dissociatus

REM sleep behaviour disorder (RBD) is a fascinating experiment in nature, predicted by animal experiments nearly 55 years ago [11] and presenting in humans as complex behaviours arising from REM sleep as the persistence of muscle tone during REM sleep per-

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mits the "acting out of dreams," often with violent or injurious consequences to the patient or bed partner [12,13].

Status dissociatus (SD) is a condition in which brain and mind are in disarray along the boundaries of sleep and wakefulness [14]. Insults to the brain can drastically alter the circuitries responsible for maintaining the integrity of wakefulness, NREM sleep, and REM sleep. As a consequence, the basic states of existence can become admixed and interchanged, or rapidly oscillate, with striking disturbances of consciousness, brain electrophysiology, and the behavioural and polygraphic expression of sleep and wakefulness [14,15].

We recently described two patients with multiple system atrophy (MSA) and RBD who later developed abnormal patterns during sleep consistent with SD, with nearly continuous motor and verbal behaviours in the absence of polygraphically defined conventional REM and NREM sleep stages [16]. In particular, both patients progressed from RBD, conceptualized as a kind of paroxysmal motor behaviour arising during REM sleep in the context of a substantially normal sleep structure, to an even odder state, a kind of twilight zone in which the boundaries between sleep and wakefulness, according to conventional criteria, were completely abolished, i.e., SD (Figs. 1 and 2). Interestingly, when subjected to a battery of neuropsychological tests the patients showed no intellectual decline (i.e., dementia). Our cases of MSA document that RBD may represent a phenomenon in some stages of the neurodegenerative disease, only later evolving into SD. This pattern may also explain the fact that some patients report disappearance of the paroxysmal sleep-related events in later stages of the disease (personal communication), since SD is generally quieter than RBD. It was remarkable that our patients were cognitively intact even when SD was present, raising the question of how the disappearance of a normal pattern of nocturnal sleep impacts cognitive functions.

These clinical observations, if confirmed in larger cohorts, also raise questions about our concepts of both consciousness and sleep: may wakefulness not be as much of an all-or-nothing phenomenon as it is usually conceived? Are the primary states of being (wake, NREM sleep, REM sleep) mutually exclusive? May sleep in the human brain be a "local" process, also, at the subcortical level, as documented to date in individual cortical columns, i.e., the so-called mosaic pattern of sleep [10]? Were our patients experiencing some sort of mosaic sleep? Can sleep occur in the absence of the markers that currently define it?

Sleep is a recurrent, physiologic, but not pathologic, form of reduced consciousness in which the responsiveness of brain systems is globally reduced, so that the brain does not respond readily to inner and outer stimuli. Instead, the pathological impairment of conscious states represents more or less protracted deviation from the normal healthy alternation of sleep and wakefulness [17]. Parasomnias are disorders of behaviour, autonomic nervous system functioning, and experience occurring in relation to sleep [18]. They can emerge during entry into sleep, within sleep, or during arousals from sleep, moreover occurring in all NREM and REM sleep stages. Parasomnias have been described, intuitively, as the result of "state boundary dissociation," the breakdown of the boundaries that normally separate the principal conscious states, allowing elements of these states to comingle [9]. Thus, sleep paralysis, caused by persistence of the atonia of REM sleep into wakefulness, results from a partial breakdown of the normal separation between these two states. In RBD, the muscle tone of wakefulness intrudes into REM sleep, allowing the release of dream-enacting behaviours. Hypnagogic hallucinations, intrusion of dream mentation into wakefulness, are expressions of a similar overlap. Sleepwalking occurs as a result of incomplete arousal from NREM sleep, with motor activity appropriate to wakefulness occurring in conjunction with mentation of a kind that normally occurs during NREM sleep [19]. All together, the above considerations mean that the state-dependent changes in the brain systems regulating our state of beings may not be mutually inhibited [2,20,21]. The possible consequence of this is the appearance of maladaptive behaviours such as walking around half-asleep or spending long portions of the normal sleep cycle half-awake.

Under normal conditions, sleep is modulated by a two-process model, i.e., the homeostatic drive and a near 24-h oscillatory circadian rhythm, and is currently defined in terms of whole animal behavioural state. However, the two-process model provides information on the timing and duration of sleep [22–24] but not on underlying sleep mechanisms or sleep functions. Additionally, aspects of sleep can be observed in something less than the whole brain. Evidence suggests that brain regions that have been disproportionately used during waking will require a greater intensity and/or duration of sleep. In humans, sensory stimulation of one hand increases EEG slow waves in the opposite hemisphere during subsequent sleep [25]. In contrast, if an arm is immobilized during the day and motor performances deteriorate, both somatosensory and motor evoked potentials decrease over the contralateral sensorimotor cortex and slow wave activity over the same cortical areas are markedly reduced [26]. Slow wave activity may be selectively induced during sleep in circumscribed regions of the cerebral cortex when the same cortical regions have been trained during wake by specific tasks [27]. Similarly, slow wave activity during sleep is greater in the somatosensory cortex of rats during the dark period when they use their whiskers more, and greater in the visual cortex during the light period when they use their eyes more [28]. These studies support the local regulation of sleep, up to a cellular level [29–31]. The consequence is that the minimal component of the brain that can exhibit the contrasting states of sleep and wake is a single neuronal assembly, and that the whole organization of sleep is an emergent property of the collective neuronal assemblies to synchronize [32]. This is not in contrast with the fact that subcortical mechanisms can influence sleep in a top–down fashion, timing sleep to periods when the animal is not disadvantaged by being asleep [2]. They may further serve to avoid mixed whole animal states with only portions of the neuronal networks being

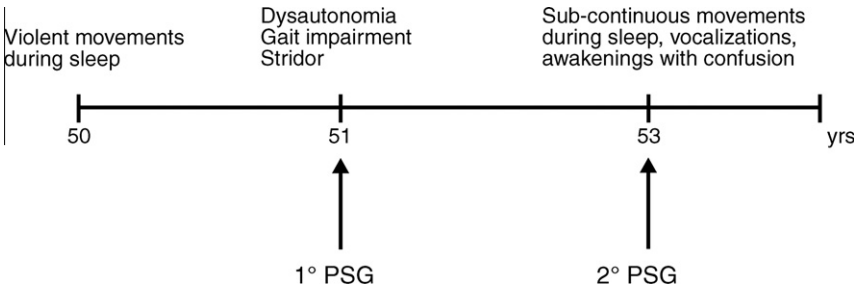

Fig. 1. Histogram illustrating the evolution of sleep disorders in a patient with multiple system atrophy.