Status Dissociatus and Its Relation to RBD

28

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Abbreviations

ADCA-DN	Dominant cerebellar ataxia, deafness, and narcolepsy
caspr2	Contactin-associated protein 2
CSF	Cerebrospinal fluid
EEG	Electroencephalography
EMG	Electromyography
GBS	Guillain-Barré syndrome
Hcrt	Hypocretin
Lgi1	Leucine-rich glioma-inactivated 1
MSA	Multiple system atrophy
NT1	Type 1 narcolepsy
NMDA	Anti-*N*-methyl-D-aspartate
PD	Parkinson's disease
PLMs	Periodic leg movements
PSG	Polysomnography
RBD	REM sleep behavior disorder
REM	Rapid eyes movement
RSWA	REM sleep without atonia
SD	Status dissociatus
SOREMP	REM sleep onset periods
VGKC-Ab	Voltage-gated potassium channel complex antibodies
W	Wake

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28.1 Introduction

Status dissociatus is an umbrella term aimed to label different disorders that share as a main feature the vulnerability of "state boundaries." Each state of being is conventionally defined as a recognizable cluster of behavioral, neurophysiological, and autonomic descriptors, occurring over a designated period. Indeed, it is the combination of different parameters, both behavioral and neurophysiological (i.e., EEG, EOG, EMG, ECG, etc.), which empirically identifies clusters defining the different states of being, i.e., wakefulness, rapid eye movement (REM) sleep, and NREM sleep. Each descriptor taken by itself is deceptive in defining a state, as, for example, changes in EEG do not always reflect changes in state (e.g., as seen with the fast rhythms in benzodiazepine-induced sleep or the postictal slow rhythms), and the same applies for the behavioral counterpart (e.g., as seen with enacted dreams).

Status dissociatus represents the result of the breakdown within the association of the different descriptors defining each cluster, resulting in the asynchronous occurrence of the various components of the different states of being, and therefore preventing the recognition of conventionally defined states of being over an established time span.

The term "status dissociatus" was first coined by Raynal [1] to indicate a polysomnographic trait in tricyclic-medicated narcoleptic patients. However, the concept of status dissociatus emerged and was more extensively elaborated with the first case series reported in 1991 by Mahowald and Schenck [2]. At that time, the authors described six patients affected with a severe state dissociation, i.e., quoting the authors, "ambiguous, multiple or rapid oscillation of state-determining variables with simultaneous appearance of elements of all three states, and with the only full-declared state being wakefulness," due to different underlying conditions [2].

28.2 Dissociation of States and Status Dissociatus

The chapter encompasses both "dissociation of states" and "status dissociatus—SD."

With the term "dissociation of states," we refer to paraphysiological or pathological conditions, characterized by the occurrence of episodes due to the transient and usually brief intrusion of features of a state into an ongoing main state. The term "status dissociatus" will instead be used for pathological conditions where recognizable cluster descriptors are lost or with subcontinuous state transitions.

For the first category, we will adopt the original classification proposed by Mahowald and Schenck [2]. Indeed, in their original description and seminal introduction to this novel concept, the authors (1991) classified three types of dissociation of states based on the parent (or main) state: i.e., dissociation from prevailing wakefulness, dissociation from NREM sleep, and dissociation from REM sleep. For SD, we will refer to the classification recently proposed [3], distinguishing two main subtypes of SD, i.e., the classically defined-severe SD and the

intermittent-intermediate one. Of course, both classifications carry the birthmark of all the classifications trying to fit the complexity of human physiological and pathological conditions in conventional boxes.

28.2.1 Dissociation from Wakefulness

These conditions are the result of the intrusion of other states of being into wakefulness.

They include conditions characterized by admixture of mentation of wake and sleep, like hypnagogic or hypnopompic hallucinations, nocturnal hallucinations, and automatic behaviors.

Hallucinations at the wake-sleep transition are typically seen in narcolepsy (ICSD, 3 ed.; [4]) but can occur also as the consequence of alcohol/drug intoxication or withdrawal, brainstem or thalamic lesions, severe visual loss (Charles Bonnet syndrome), and of other neurological conditions, such as neurodegenerative conditions [5] or autoimmune encephalitis [4].

Transient admixtures of states of being might occur also in the normal population at wake-sleep transitions, especially during childhood or in the setting of sleep deprivation or stressful events, resulting in somatosensory illusions or hallucinations [6].

Automatic behaviors are another example of such dissociation, characterized by the occurrence of inappropriate action or pronunciation of "out-of-context" sentences while awake and reputedly related to a brief dream mentation. They are mainly observed in the context of pathological conditions, such as idiopathic hypersomnia and narcolepsy, but rarely they may be experienced also by healthy individuals [4] and mainly in subjects who are severely sleep deprived.

It may also happen that the body is "asleep" (paralyzed) while the mind is awake, as in cataplexy and sleep paralysis. Cataplexy is the typical motor feature of type 1 narcolepsy (ICSD, 3rd ed.). Sleep paralysis is instead a conscious state of involuntary immobility typically arising on awakening from REM sleep or at the beginning of a REM sleep onset period and due to persistence/anticipation of REM sleep atonia (ICSD, 3rd ed.). It can occur rarely in healthy subjects, but it is more frequent in conditions of central hypersomnia (e.g., type 1 narcolepsy—NT1).

28.2.2 Dissociation from NREM Sleep

Admixture of wakefulness and NREM sleep results in a NREM parasomnia, which may present with different degrees of behavioral and autonomic features and include a spectrum of overlapping conditions, such as confusional arousals, somnambulism and sleep terrors, or the peculiar behaviors described in "sleep-related eating disorder" and "sleep-related sexual activity" ([7]; ICSD, 3rd ed.).

NREM parasomnias are generally more frequent during childhood but may persist or even arise during adulthood [8]. Hereditary factors have been strongly implicated in sleepwalking and sleep terrors, and specific DQB1 genes were implicated

in a study of 60 Caucasian subjects with different types of NREM parasomnia and their families [9], as well as the first genetic locus for sleepwalking being found at chromosome 20q12-q13.12 in an extended family pedigree with sleepwalking. Episodes may be precipitated by external triggers (sleep deprivation, sleeping in novel or other particular settings, noise, etc.) or by internal triggers (anxiety, stress, fever).

Subjects typically present with eyes open and preserved ability to move or (limited) to interact with the environment while performing inappropriate behaviors. Scalp EEG shows admixed features of NREM sleep. The intracerebral EEG recording capturing an episode of confusional arousal in an epileptic patient showed EEG features of W over the motor and cingulate cortices, concurrent with delta activity over the frontoparietal associative cortices [10], while a study with single-photon emission computed tomography during an episode of sleepwalking showed activation of thalamo-cingulate pathways and persistent deactivation of other thalamocortical arousal systems [11]. Recently, a gray matter volume decline in the dorsal posterior and posterior midcingulate cortex at the brain MRI has been found while comparing 14 patients with NREM parasomnia versus healthy controls [12], as a possible anatomical substrate explaining simultaneous coexistence of different states of being, i.e., wakefulness originating from the motor and cingulate cortices and sleep in associative cortical regions.

28.2.3 Dissociation from REM Sleep

RBD, due to incomplete declaration of REM sleep because of the intermittent lack of REM sleep muscle atonia (RSWA), is the most well-known example of this subtype of dissociation of states. Put into simple words to explain the concept, in RBD, the mind is asleep (REM dream mentation) while the body is awake (spinal motor neurons are still excitable).

RBD may present as an acute phenomenon or as a chronic disorder. We will not report on RBD here, but we want just to remark that similarly to status dissociatus, transient RBD has been described in the context of autoimmune diseases ([13–18]; see also Chap. 8 of the current textbook).

A further condition fitting in this box is lucid dreaming, which consists of the experience of being aware of dreaming (and often directing the dream) while being asleep (REM sleep) [19, 20].

The experience of lucid dreaming is quite frequent in the younger population, as pioneering studied by La Berge in the early 1980s [20], and it has been reported to be even more frequent in narcoleptic patients [19].

28.3 Status Dissociatus

SD labels the extreme degree of severity of dissociation states, which can be either continuous with the complete breakdown of state-determining boundaries and aberration of state descriptors or may occur intermittently and still preserve recognizable, although at times ambiguous, state descriptors.

In 1991, thanks to Mahowald and Schenck, status dissociatus was theorized as a condition characterized by ambiguous oscillations of state-determining variables with the simultaneous appearance of elements of all three states of beings. In their original report, the authors reported this status to occur in six patients affected with different underlying neurological conditions (i.e., chronic alcohol abuse and acute withdrawal, olivopontocerebellar atrophy, cardiac surgery-related central nervous system anoxic injury, OSA/narcolepsy-cataplexy with methylphenidate/imipramine therapy, and narcolepsy-cataplexy with methylphenidate/imipramine therapy).

A breakthrough on this matter was made by Elio Lugaresi in 1986 with the description of fatal familial insomnia and, years later [21–23], by coining the term "agrypnia excitata," to describe the extreme dissociation state that they observed in fatal familial insomnia and to some extent also in alcohol withdrawal syndrome and Morvan's syndrome. All these three different conditions indeed are examples of an extremely severe dissociation, sharing the presence of the inability to generate and sustain sleep, accompanied by severe mental confusion and motor and autonomic hyperactivity [23].

Nowadays, we might say that while Mahowald and Schenck [2, 24] described conditions mainly ascribed to the intermittent/intermediate form of SD, Lugaresi et al. [25] reported the first case of a severe and continuous SD.

In the current ICSD3, SD is classified among the subtypes of RBD (ICSD, 3rd ed.).

According to a recently proposed classification [3], it is possible to recognize two main subtypes of SD, i.e., the classically defined-severe subtype and the intermediate-intermittent subtype.

28.3.1 Classically Defined/Severe Status Dissociatus

This subtype of SD was firstly spotted by the Bologna Group [21–23] under the name of "agrypnia excitata," from ancient Greek (*agreo*, to chase, and *hypnos*, sleep), which meant to indicate loss of sleep [26].

The term aimed at synthesizing the common discrete features of three different conditions, i.e., fatal familial insomnia, alcohol withdrawal syndrome, and Morvan's syndrome. All these conditions shared a similar phenotypic features and clinical markers, even if the etiologies and the neurophysiological backgrounds may be different among each other (see later).

Fatal familial insomnia is an autosomal dominant prion disease with selective thalamic and inferior olivary degeneration [25], due to a missense mutation at codon 178 of the prion protein gene co-segregating with methionine (met) at methionine-valine (Val) polymorphic codon 129 in the mutated allele [27]. Patients may have a short (from 8 months) or a prolonged (up to 72 months) clinical course according to whether they are homozygote met/met or heterozygote met/val at codon 129.

Morvan's syndrome is a rare autoimmune disease, due to contactin-associated protein-like 2 (caspr2) antibodies subtypes of antibodies to the VGKC. The main clinical features are acute or subacute onset of insomnia, nearly continuous muscle activities (myokimias and cramps), autonomic imbalance, and pain in the

extremities [21, 28, 29]. Plasma exchange or intravenous immunoglobulins are usually efficacious within a few months, except for few non-responder cases, where a progressive worsening until death has been reported [21, 29].

Finally, alcohol withdrawal syndrome (delirium tremens) brought about by sudden alcohol withdrawal in alcohol abusers [2, 30] is characterized by the acute-subacute onset of a nearly continuous status during which the patients present with tremors, nausea, anxiety, insomnia, motor, and autonomic activation with agitation and hallucinations. In this condition, the dream enactment is mainly violent, but an eventual pattern with calmer gestures has been reported [30]. A similar condition may occur after withdrawal from meprobamate, barbiturates, and benzodiazepines (ICSD, 3rd ed.).

All these three conditions combine organic insomnia (i.e., the inability to initiate and sustain sleep) with a confusional-oneiric state, together with motor hyperactivity, autonomic hyperactivity (with tachycardia, tachypnea, hypertension, fever, hyperhidrosis, etc.), and persistently (through the 24-h) increased blood cortisol and plasma catecholamine when compared to normative values [23, 31]. Both the cyclic structure of sleep and the circadian rhythmicity are lost [31]. The disease usually starts with reduced sleep time, hypnagogic hallucinations, and RBD, until reaching the full-blown state during which patients spend most of the time in a state of sub-wakefulness with the EEG showing features of stage 1 of NREM sleep, while spindles and delta activity were lost. Neurophysiological features of REM sleep persist but occur mainly in the form of "covert" EEG REM sleep or REM sleep without atonia and in short recurrent episodes, isolated, or mixed with stage 1 NREM potentials (Fig. 28.1). Clustered REM sleep episodes frequently coincide with gestures mimicking task-oriented daily life activities, such as dressing, combing the hair, washing, or manipulating an imaginary object. These episodes may also occur with open eyes. If questioned at the end of these behaviors, patients often do not admit that they were asleep, although they link these gestures to an oneiric/hallucinatory scene, and the motor activity appears to be clearly related to the oneiric/hallucinatory content. This peculiar behavior, named "oneiric stupor," represents in fact the motor and behavioral marker of *agrypnia excitata* [23] (Fig. 28.2).

*"*Oneiric stupor*"* with the subcontinuous gesturing that mimics almost purposeful behavior of daily life is different from the typical energetic and vivid quality of RBD episodes. This is mirrored by the different mentation reported in these conditions, i.e., patients usually describe an ordinary scene of daily life in *agrypnia excitata*, in contrast to a bizarre, complex, and vivid scene in RBD.

Agrypnia excitata has also been reported in two unrelated cases affected by Mulvihill-Smith syndrome, which is a rare and complex congenital neurodegenerative disease, characterized by a progeria-like aspect, peculiar multiple pigmented nevi, low stature, and cognitive impairment leading to premature death [32, 33].

Features of *agrypnia excitata* have been observed also in the sporadic and in the variant forms of Creutzfeldt-Jakob disease and as a consequence of CNS lesions, but apart from the cases where a clear and prominent thalamic involvement was reported, they did not reach the full-blown clinical picture.

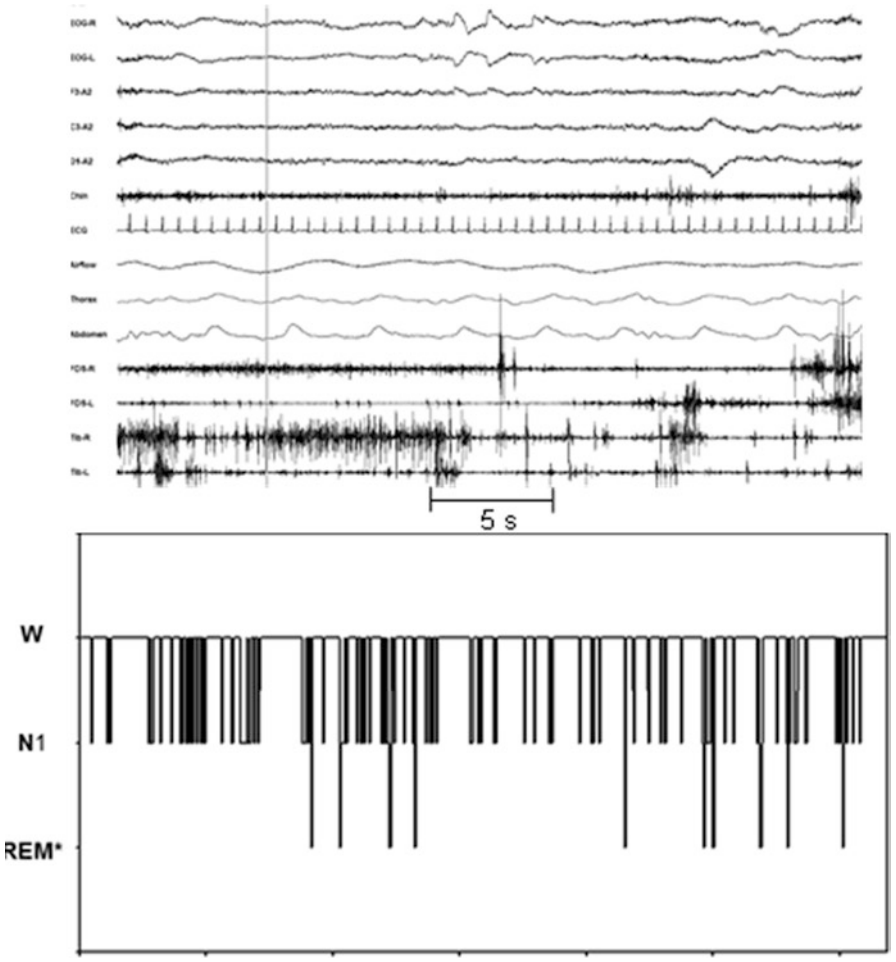

Fig. 28.1 Hypnogram of 24-h duration, in a patient affected with autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN) due to DNMT1 gene mutation. Ordinate (y) reports the time of the day. *W* wakefulness, *R* REM sleep, *1* stage 1 of NREM sleep, *2* stage 2 of NREM sleep, *3* stage 3 of NREM sleep

Recently, a case of SD with cortico-basal degeneration, and with neuroimaging and anatomopathological documentation showing neurodegeneration with neuronal and glial tau deposition within the thalamus, has been described [34]. It has been suggested that neurodegenerative conditions may at time evolve into a condition of severe SD [34, 35]. Indeed, the severe metabolic and structural damage involving the CNS system may progressively render the network orchestrating the states of being powerless. In this regard, we have recently observed a patient affected with dominant cerebellar ataxia, deafness, and narcolepsy (ADCA-DN) due to DNMT1 mutation, who at the very end stage of the disease prior to passing away had

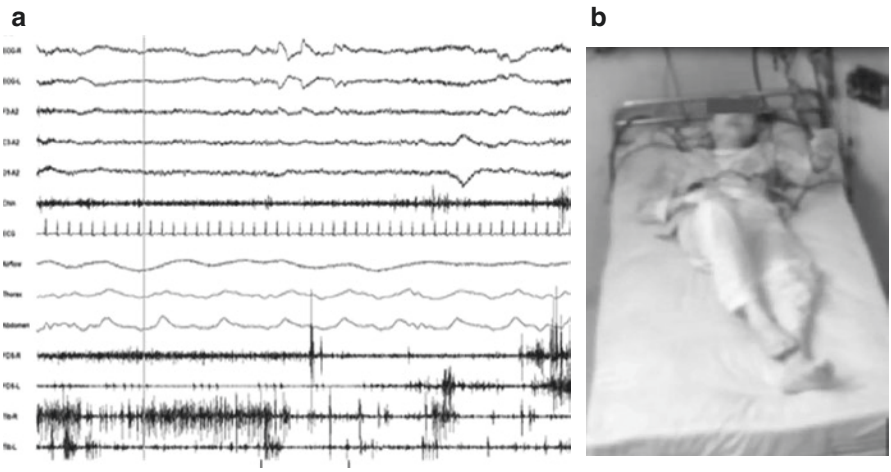

Fig. 28.2 Polygraphic features of status dissociatus in a patient affected with Morvan's syndrome. (**a**) A 30-second epoch showing admixtures of stage 1-REM sleep in the EEG tracing. (**b**) Hypnogram of the same patient

continuous state transitions with poorly recognizable state descriptors (Fig. 28.3), and he was in a nearly continuous hallucinatory state accompanied by subcontinuous gesturing [unpublished findings].

28.3.2 The Intermittent/Intermediate Status Dissociatus

In this subtype, state descriptors and proper states of being are still recognizable, but subcontinuous paroxysmal shifts versus ambiguous states of being occur, with consequent extremely fragmented and abnormal W, NREM, and REM sleep architecture. The circadian pattern might be impaired but never reaching the degree of severity seen in "agrypnia excitata."

The typical example of this subtype is found in NT1 or in conditions described in the context of autoimmune encephalitis.

NT1 is a central hypersomnia due to a deficiency of hypothalamic hypocretin 1 (orexin) signaling, of a likely autoimmune etiology (ICSD, 3rd ed.). Loss of boundaries between sleep and wake, with frequent state transitions and intrusions of REM sleep into the other ongoing states of being [36], is the neurophysiological hallmark of NT1, resulting in a pentad of symptoms, including cataplexy, excessive daytime sleepiness, sleep paralysis, hypnagogic hallucinations, and disturbed nocturnal sleep (ICSD, 3 ed.).

Cataplexy, sleep paralysis, hallucinations, and automatic behaviors are examples of wakefulness dissociation, while lucid dreaming and RBD are examples of REM dissociation.

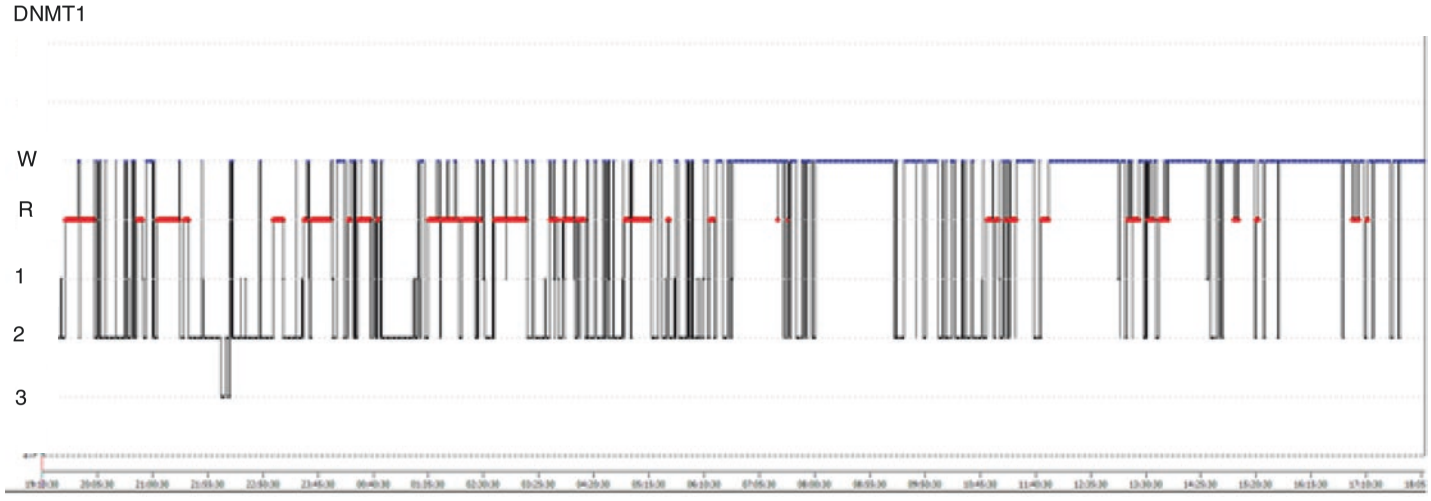

Fig. 28.3 Polygraphic and behavioral features of status dissociatus in a patient affected with Morvan's syndrome. EEG channels (Fp2-F4; F4-C4; C4-P4; P4-O2; Fp2-F8; F8-T4; T4-T6; Fz-Cz; Fp1-F3; F3-C3; C3-P3; P3-O1; Fp1-F7; F7-T3; T3-T5); *R. EOG-A2* right electrooculogram, *L. EOG-A2* left electrooculogram, *mylo* mylohyoid muscle EMG, *R. Tib* right tibialis EMG channel, *L. Tib* left tibialis muscle EMG channel

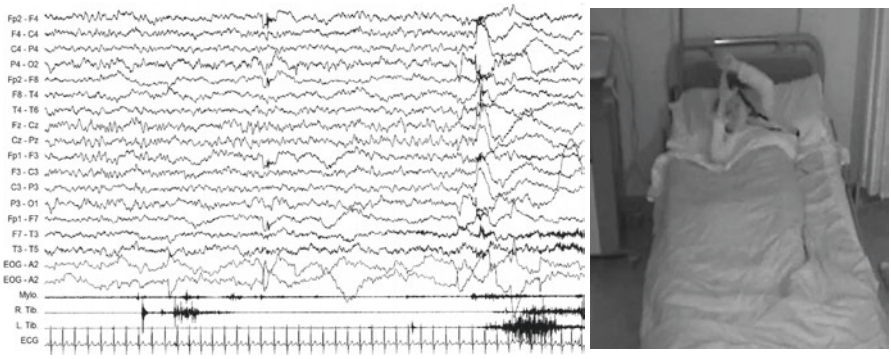

Fig. 28.4 Polygraphic and behavioral features of status dissociatus in a child affected with NT1. EEG channels (Fp2-F4; F4-C4; C4-P4; P4-O2; Fp2-F8; F8-T4; T4-T6; Fz-Cz; Fp1-F3; F3-C3; C3-P3; P3-O1; Fp1-F7; F7-T3; T3-T5). *R. EOG-A2* right electrooculogram, *L. EOG-A2* left electrooculogram, *mylo* mylohyoid muscle EMG, *R. Tib* right tibialis EMG channel, *L. Tib* left tibialis muscle EMG channel

State boundary instability in NT1 has been reported to be even more severe in children, culminating in a nearly subcontinuous state in about 30% of them. This subcontinuous state shift may emerge both from wakefulness, with what has been reported as a "cataplectic face" [37], and also from sleep with subcontinuous complex behaviors emerging from a dissociated REM sleep [38] (Fig. 28.4).

In regard to autoimmune encephalitis, sleep abnormalities have been long recognized in the context of Morvan's syndrome [21, 28, 29] and thought to be discrete of caspr2 antibody-associated encephalitis. However, recently state boundary instability and sleep disorders have also been reported in other types of autoimmune encephalitis.

Anti-leucine-rich glioma-inactivated 1 (LgI1) antibody subtypes of VGCK encephalitis are typically characterized by pathognomonic early faciobrachial dystonic seizures and other focal seizures, followed by memory disturbances [39]. In addition, insomnia along with RBD and partial loss of recognizable sleep and enacted dreams have been reported in this context [40, 41].

Anti-Ma1 and anti-Ma2 antibody-positive encephalitis are instead characterized by memory deficits, vertical supranuclear gaze palsy, excessive daytime sleepiness, diplopia, dysarthria, ataxia, parkinsonism, or hypokinesia. In a small percentage (13%) of cases, patients may have also narcolepsy with cataplexy with low cerebrospinal fluid hypocretin-1 levels (13%) [42], along with the occurrence of enacted dreams [14, 16, 43]. In such cases, PSG demonstrated severe sleep disruption, absent slow wave sleep, and sleep spindles, with subcontinuous intrusion of REM sleep into NREM sleep and complete loss of REM sleep atonia [14, 43].

Features suggestive of dissociation of states have also been reported in up to 20% of patients over a cohort of 139 patients affected with Guillain-Barré syndrome (GBS). Clinical features included hallucinations, mainly hypnagogic, and enacted dreams, while neurophysiological features consisted in fragmented sleep with

frequent state transitions and presence of RSWA [13]. Compared to patients without sleep abnormalities, CSF Hcrt A levels were reported to be reduced. Both clinical features and CSF Hcrt A levels normalize afar treatment, suggesting that GBS autoantibodies may also be causally targeting structures of the CNS [13].

Encephalopathy associated with autoantibodies to IgLON5 is a recently described syndrome characterized by a unique sleep disorder presenting with both NREM and REM parasomnias and sleep breathing dysfunction, brainstem involvement (dysphagia, dysarthria), and different combinations of movement disorders (gait problems, chorea) [44–47]. Patients usually presented with an acute or subacute onset of insomnia sleepiness and abnormal sleep-related behaviors, which can be undifferentiated NREM movements and brief and myoclonic-like RBD events or even behaviors, which share phenomenological similarities with those reported as oneiric stupor. From a neurophysiological point of view, even if NREM sleep stages 2 and 3 may be at times recognizable (though usually very disturbed), sleep architecture is unstable with frequent stage transitions and with features of different states that at times merge. Autoantibodies against IgLON5, a neuronal cell adhesion protein, and positivity to haplotypes DQB1*0501 and DRB1*1001 were detected in most of them. Their pathogenicity however is still questionable, and the disorder does not respond to immunotherapy, apart from exceptional cases [44]. Neuropathology shows a peculiar tauopathy, mainly involving the tegmentum of the brainstem and the hypothalamus [46, 48]. The association with a rare HLA subtype and the presence of specific antibodies suggest an autoimmune cause or trigger, while the chronic clinical course, poor response to immunotherapy, and pathological findings suggested a neurodegenerative process.

Clinical experience and sporadic reports suggest that an admixture of states of being may eventually occur also in critical illness due to infectious or metabolic conditions, but instrumental examinations (including video-PSG recordings) in these conditions are lacking, and this hampers any conclusion.

28.4 Pathophysiology

In this chapter, we have reported conditions characterized by dissociation of states and SD occurring in a wide spectrum of clinical conditions and therefore linked to different underlying causes. Overall, both structural and functional abnormalities involving thalamo-limbic and the brainstem structures may result in conditions characterized by state of boundary instability.

Sleep and wake states indeed are the result of the dynamic interactions within the sleep/wake circuitry [49], with the brainstem, the hypothalamus, and the basal forebrain involved in the promotion of the waking state, while structures of the preoptic area and of the contiguous basal forebrain promoting sleep. However, the ultimate mechanisms of such orchestration are still puzzling.

A great body of evidence recognizes the thalamus as the hallmark anatomical location of *agrypnia excitata*, linked therefore to the thalamo-limbic GABAergic dysfunction and to the consequent release of the hypothalamus and of the brainstem

from cortico-limbic control [23]. GABAergic impairment might be linked to different causes, such as the direct degeneration of the thalamus in FFI, autoantibodies targeting the thalamo-limbic structures in Morvan's syndrome, or acute imbalance of the GABAergic synapses in the limbic system due to a downregulation induced by alcohol or drugs.

Along with the thalamus, impairment of the network orchestrating the states of being may occur at different levels, and abnormalities within the structures that interact with the thalamus (mainly frontal and cingulate cortices) may account for SD in the different spectrum of diseases.

Neuropathological abnormalities have been reported at the level of the dorsolateral midbrain, the amygdala, the hypothalamus, and the mammillary bodies in anti-Ma encephalitis [14, 16], the neocortex, and the limbic area in anti-Lgi1 antibodies encephalitis [39] and the hypothalamus and the limbic area in GBS [13] and in NT1.

In anti-VGKC encephalitis, a direct role of potassium channels has been suggested, given the reported role of those subfamilies of VGKCs in regulating the wake-sleep cycle [41].

In NT1, a great body of literature supports the lack of Hcrt-producing cells, resulting in undetectable Hcrt-1 levels in the CSF in promoting SD.

Indeed, Hcrt-1 has a pivotal role in controlling sleep-wake transitions and REM sleep [50] and in orchestrating motor control during wakefulness and sleep [51]. Similarly, low levels of hypocretin have been also reported in patients affected with anti-Ma encephalitis and presenting with narcolepsy and cataplexy, along with the other spectrum features [14, 16] or in patients with GBS having hallucinations and RBD [13].

States of being instability also result in peculiar motor behaviors, due to the loss of the physiological inhibition of motor activity and of muscle tone that physiologically occurs during sleep.

Excessive muscle twitching and jerks, and RBD, are mainly seen in the context of intermittent/intermediate SD, as well as with autoimmune encephalitis and NT1, while "oneiric stupor" is the motor hallmark of *agrypnia excitata*.

The different motor patterns possibly reflect the different degree of states of being instability.

Indeed, while in the first case dissociated REM mainly comes into the form of RSWA (i.e., absence of muscle atonia, but other ways preserved descriptor of REM stage), in *agrypnia excitata*, EEG is an admixture of stage 1/REM sleep, and therefore the movements/behaviors may reflect this "undefined" status, merging mentation of NREM and REM sleep.

Conclusion

Even if lately it has been emphasized that sleep and wake are properties of small groups of neurons [52], usually they manifest as a whole phenomenon.

However, when central structures orchestrating state of being fail for different reasons and at different levels of the network, deviant pattern of states of being will be seen.

Everybody may experience a dissociation of states, especially at state transition, as, for example, when we experienced an illusion or a hallucination just

prior to falling asleep. What makes this often-normal condition a disorder is the frequency, duration, and degree of severity of such dissociation.

Dissociation of state disorders, such as RBD, cataplexy, hypnagogic hallucinations, etc., is more frequent in particular diseases and therefore may be a clue toward their correct diagnosis, such as for cataplexy, which is the motor hallmark of NT1, or may be a biomarker of other related conditions, such as RBD for alpha-synuclein-mediated diseases.

The extreme expression of state dissociation is SD, characterized by frequent state transitions and asynchronous and aberrant occurrence of features of different states of being as seen in pediatric NT1 or in autoimmune encephalitis, until reaching the maximum degree of severity in *agrypnia excitata*, where the brain is no longer able to produce a full-blown state of being (This topic is also discussed in Chap. 12 on Acute RBD).

Extensive video-polysomnography is mandatory in order to recognize all the above conditions, but currently the scoring can be only descriptive as the conventional scoring system lacks the labels for categorizing the neurophysiological and behavioral features of SD.

The pathological process underlying state dissociation more frequently involves structures located in the forebrain or brainstem, which are known to orchestrate sleep/wake regulation [49]. The network may be interrupted at different levels, giving rise to an imbalance in communication and synchronization between the neuronal structures involved.

Nowadays, the study of these conditions is partly hampered by the lack of a shared classifications of SD and by the absence of labels for state dissociation (as, e.g., we do not have a neurophysiological label in order to indicate conditions where elements of NREM and REM are present at the same time). Additional video-PSG documentations of different conditions associated with dissociation of states along with a consensus on SD classification/subtypes are therefore willing to that regard.

Note Added in Proof An additional case has recently been published: 1) Puligheddu M, Congiu P, Laccu I, et al. Overlap parasomnia disorder in a case of Creutzfeldt-Jakob disease. Sleep Med. 2017;36:75–7.

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