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## Editorial

# The far side of sleep: Towards a deeper understanding of parasomnias and nocturnal seizures



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This issue of *Sleep Science* contains an article by Yeh and Schenck about behavioral dyscontrol during sleep emerging with sporadic (non-familial) nocturnal frontal lobe epilepsy (NFLE) [1]. A series of eight cases was reported, with video-polysomnography (vPSG) and sleep EEG documentation, and successful treatment outcome [1]. The sporadic form of NFLE is not as frequently reported and not as well understood compared to familial, autosomal dominant NFLE. Two notable findings in this case series are that (i) the spectrum of clinical features of sporadic NFLE, including its therapy, closely match the well-known clinical features and therapy of familial NFLE; and that (ii) the spectrum of clinical features of sporadic NFLE, including its therapy, in this first published series in Asian patients (from Taiwan), closely match the extensive published findings in Caucasian patients with NFLE, as cited in the article. The challenging issue of distinguishing NFLE from nocturnal temporal lobe epilepsy (NTLE), and from NREM sleep parasomnias is also addressed in this article, with the pertinent literature cited. There are overlapping features of behavioral dyscontrol in sleep with these three conditions, which very likely reflect overlapping activations of central (motor) pattern generators (CPGs) in the brainstem [2]. Sleep related nocturnal dissociative disorder (Noc DD) also shares behavioral features with these conditions, and activation of CPGs was strongly suggested in one reported case in which a 19 y.o. male engaged in prolonged

(for several minutes) constant leg pedaling, both at home and in the sleep laboratory, with both episodes captured on video [3].

It is now known that abnormal ambulation during sleep can be a manifestation of sleepwalking (SW), NFLE, NTLE, REM sleep behavior disorder (RBD), or Noc DD [3–5]. Likewise, screaming during sleep can be a manifestation of these same conditions [6]. So in regards to similar abnormal complex sleep behaviors, there is a broad range of causes and usually separate therapies, which places a premium on establishing the proper diagnosis, which can then direct appropriate therapy. To this end, the validated Frontal Lobe Epilepsy Parasomnias (FLEP) scale, developed by Derry et al. [7], has been particularly useful in distinguishing NFLE from NREM sleep parasomnias, as utilized in the Yeh and Schenck report [1]. Nevertheless, controversial points are still being debated, as the recognized difficulties “in distinguishing nocturnal epileptic seizures from parasomnias reflect just one aspect of the intriguing issue of the pathophysiological relationships between all types of paroxysmal motor behaviors during sleep” [8]. The complexity of these pathophysiological relationships is highlighted by a study finding a greatly increased rate of NREM sleep arousal parasomnias in families of patients with NFLE [9]. Research on the cyclic alternating pattern (CAP), an EEG marker of arousal fluctuations during sleep, calls attention to the unifying role of pathological

arousals, originating in thalamocortical circuits, across epileptic, parasomnia and other abnormal motor events during sleep [10]. A recent study found different CAP characteristics in patients with NREM sleep arousal parasomnias compared to patients with frontal and temporal lobe epilepsies [11], which encourages further research on identifying different CAP profiles across patient populations with behavioral disturbances during sleep.

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### Update on sleepwalking and other NREM sleep parasomnias

Traditional knowledge regarding NREM sleep parasomnias as being exclusively disorders of slow-wave sleep (SWS) and disorders of arousal (DOA) from SWS, without either associated dreaming, any recall of NREM parasomnia events, or any daytime clinical concomitants, is giving way to an updated, data-based perspective and new pathophysiological hypotheses that are considered to represent a “paradigm shift” in understanding SW and other DOA [12]. For example, there is growing evidence suggesting that excessive daytime sleepiness is part of the SW phenotype that is linked to its underlying pathophysiology, and which cannot be explained by any comorbid sleep disorder or PSG evidence of nocturnal sleep disruption [13–15]. Also, in adult SW there can be substantial recall of specific elements of SW episodes and also recall of associated dream mentation, in striking contrast to childhood SW [13]. These findings also highlight current knowledge that SW is an expression of simultaneously activated states of (partial) sleep and (partial) wakefulness, a complex dissociated state, with clinical consequences [13]. These partially activated states of sleep and wakefulness reflect regional brain activity of “local sleep” or of local wakefulness. The concept of sleep as a whole-brain phenomenon has thus been radically reconsidered. In the new framework, parasomnias, as clinical dissociated states, result from coactivations of sleep and wakefulness across different brain regions [16]. As stated by Zadra et al. in regards to the pathophysiology of SW, “a broad and unifying view might implicate the simultaneous activation of localized cortical and subcortical networks that have roles in sleep and wakefulness [13]”.

A study on intracerebral EEG recording during sleep documented a dissociation of regional EEG activities during a parasomnia episode, illustrating how the brain phenomenon of “local sleep” can be the substrate for clinical dissociated states [17]. In this study, a young adult male with refractory focal epilepsy had a CA recorded by vPSG and intracerebral EEG. The dissociated state underlying the CA episode consisted of local arousal of the motor and cingulate cortices that contrasted with simultaneous increased slow waves in the frontoparietal associative cortices. These findings were present before the onset of the CA episode and throughout the CA. Therefore, this carefully documented CA episode was not a global sleep phenomenon, but rather a phenomenon of coexisting and contrasting local states of sleep and wakefulness.

A new clinical frontier for achieving a deeper understanding of NREM sleep parasomnias and other sleep disorders has

been opened up by the use of high-density (256 electrode channels) sleep EEG monitoring during vPSG studies, developed by the Tononi group. In a recent study utilizing high-density sleep EEG in six healthy subjects [18], a total of 141 falling-asleep periods were analyzed to assess changes in slow-wave and spindle activity during this transitional state. The major finding was that the number and amplitude of slow waves followed two dissociated, intersecting courses during the wake-sleep transition: slow wave number increased slowly at the beginning and rapidly at the end of the falling-asleep period, whereas amplitude at first increased rapidly and then decreased linearly. Most slow waves occurring early in the transition to sleep had a large amplitude, a steep slope, and involved broad regions of the cortex. Most slow waves occurring later had a smaller amplitude and slope, and involved more circumscribed parts of the cortex. Spindles were initially sparse, fast, and involved few cortical regions, then became more numerous and slower, and involved more areas. The two types of slow waves identified in the wake-sleep transition had distinct cortical origins and distributions. The authors hypothesized that these two types of slow waves result from two distinct synchronization processes: (1) a subcortico-cortical, arousal system-dependent, process that predominates in the early phase and leads to “type I slow waves”, and (2) a “horizontal”, cortico-cortical synchronization process that predominates in the late phase and leads to “type II slow waves”. The authors concluded that the dissociation between these two slow-wave synchronization processes in time and (brain) space suggests that they could become pathologically disturbed with sleep disorders – including NREM sleep parasomnias that emerge from slow-wave sleep.

Other promising future research areas that could lead to a deeper understanding of NREM sleep parasomnias include various brain imaging techniques (including SPECT, PET, transcranial magnetic stimulation), and familial, genetic, and molecular studies that should provide additional critical information on the neurobiological substrate of NREM sleep parasomnias [13].

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### Update on RBD

The “RBD odyssey” [19] continues at an accelerated pace while covering ever-expanding territories of research. The literature on RBD has continued to grow exponentially, both in breadth and depth since the exponential growth of RBD publications was first quantified [20]. The most compelling research, conducted by numerous international investigators, concerns the strong associations of RBD with neurodegenerative disorders, especially the alpha-synucleinopathies, viz. Parkinson disease (PD) dementia with Lewy bodies (DLB), and Multiple System Atrophy (MSA) [21,22]. There are two perspectives for considering this strong association. First, RBD can be the first clinical manifestation of future alpha-synucleinopathy neurodegeneration. Data from our center and from the Barcelona group have recently documented 81% and 82% “conversion rates”, respectively, from idiopathic RBD (iRBD) to a parkinsonian disorder, with a mean interval of approximately 12–14 years from onset of iRBD to the clinical

emergence of parkinsonism and/or dementia [23,24]. Second, RBD has a strong presence in established neurodegenerative disorders: 90–100% in MSA, approximately 75% in DLB, and up to nearly 50% in PD [21]. The pathogenesis for how RBD can emerge before, during or after the emergence of an alpha-synucleinopathy has been proposed [22].

The presence of RBD in PD is associated with more widespread disease across multiple dimensions of PD (e.g. motor and cognition dysfunction, visual hallucinations, deteriorated quality of life, etc.), compared to PD without RBD, as documented in numerous studies. Furthermore, a recent study has extended this ominous association by reporting a very high predictive value of RBD in PD for future PD-related dementia (PDD) [25]. In this study, 80 PD patients without dementia had assessments of autonomic nervous system, sleep, visual, olfactory, and motor functioning at baseline. After 4.4 year follow-up, patients were evaluated for dementia. Of these 80 patients, 27 (34%) developed dementia. The presence of RBD at baseline dramatically increased dementia risk (Odds Ratio=49.7,  $p=0.001$ ). In contrast, neither daytime sleepiness nor insomnia predicted dementia.

The intersection of the fields of psychiatry, psychopharmacology, RBD and neurodegeneration has been the focus of attention in two recent publications [26,27]. Postuma et al. tested for neurodegeneration markers in 73 unmedicated iRBD patients, 27 iRBD patients taking antidepressants, and 45 controls [26]. The iRBD patients taking antidepressants, compared to controls, had significant abnormalities in 12/14 neurodegenerative markers – olfaction, color vision, UPDRS II/III, alternate tap test, systolic BP drop, constipation, mild cognitive impairment, etc. All these abnormalities were indistinguishable in severity from iRBD patients not taking antidepressants. However, on prospective follow-up, iRBD patients taking antidepressants had a significantly lower risk of developing neurodegenerative disease compared to iRBD patients not taking antidepressants: 22% vs. 59% 5-year risk. The most reasonable explanation for this unpredicted finding is that development of RBD with antidepressants can be an early signal of an underlying neurodegenerative disorder. In other words, in patients already at risk for alpha-neurodegeneration, antidepressant use accelerates the emergence of RBD (which is very common in alpha-neurodegeneration) without accelerating the clinical emergence of alpha-neurodegeneration. The presence of RBD, irrespective of antidepressant use, was strongly linked to the presence of neurodegeneration markers. Presumably, the antidepressant-induced RBD patients already had REM sleep-without-tonia as a risk factor for RBD, but they were also presumably less advanced in their progression to neurodegeneration than iRBD patients not taking antidepressants. The five year neurodegenerative disease conversion risk supports this conclusion.

Wing et al. [27] address an important question raised by the Postuma et al. study [26], viz. to what extent is RBD and major depressive disorder (MDD), or the antidepressant medication therapy of MDD, related to the prodromal phase of future alpha-synuclein neurodegeneration? The case-control study of adults <50 years old included 11 medicated patient with combined RBD-MDD, 8 medicated patients with MDD alone, and 10 healthy

controls. They underwent clinical assessments, vPSG, neuropsychological testing, and neuroimaging studies. Compared to the other two groups, patients with combined RBD-MDD had significantly lower  $^{18}\text{F}$ -DOPA uptake in the putamen and caudate at 60 min, after controlling for age and gender effects.  $^{18}\text{F}$ -DOPA uptake in the putamen had a significant inverse correlation with both the severity of RBD and the extent of loss of REM-atonia. This group also had significantly lower  $K_i$  of the putamen compared to the two other groups. The combined RBD-MDD group had impaired olfaction compared to the other two groups, as the only other clinical sign suggesting neurodegeneration. The authors concluded that patients with combined RBD-MDD had presynaptic dopamine dysfunction and olfactory dysfunction. This suggests that the emergence of RBD in MDD patients (mainly in the 40–50 year age range) may represent a prodromal phase of alpha-synucleinopathy neurodegeneration, rather than RBD being merely an antidepressant side effect in the therapy of MDD. It should be noted that SSRIs and SNRIs were the antidepressants used in all but two cases, which is in line with published findings on antidepressant medication-induced RBD. Large-scale studies are clearly needed to further confirm, refine and expand the provocative findings from this study.

It is evident that RBD is situated at a strategic and busy crossroad of clinical (sleep) medicine and the neurosciences. RBD offers great breadth and depth of research opportunities, including extensive inter-disciplinary and multi-national research opportunities [20]. To this end, the International RBD Study Group (IRBD-SG) was founded and legally incorporated in Marburg, Germany. The IRBD-SG comprises a network of leading basic science and clinical RBD researchers, with the purpose of promoting international scientific research and education on RBD and its related fields, and optimizing medical care for afflicted patients by improving diagnostic and therapeutic measures. The IRBD-SG has so far held eight research symposia, in Marburg (2007, 2008, 2011), Montreal (2010), Otsu City, Japan (2011), and Paris (2012), Valencia (2013) and Helsinki (2015). Given the relatively low number of patients with RBD identified at individual RBD research centers, a major focus of the IRBD-SG is to facilitate multicenter studies.

To date, six IRBD-SG studies have been published in peer-reviewed journals [28–33], the notable findings of which will now be summarized, together with a seventh collaborative group study that involved many members of the IRBD-SG [34]. In an environmental risk factor study [28], patients with iRBD who were free of dementia and parkinsonism were recruited from 13 centers. Controls were matched according to age and sex. Potential environmental and lifestyle risk factors were assessed via standardized questionnaire. A total of 694 participants (347 patients, 347 controls) were recruited. Compared to controls, RBD patients were significantly more likely to have been smokers, and to have had head injury, pesticide exposure, and worked as farmers, and so it was concluded that these comprised risk factors for iRBD.

A second study tested a single screening question for RBD [29]. 242 RBD iRBD patients and 242 controls were given a screening question about dream-enactment, with a yes/no response option. All patients and controls had undergone

vPSG studies that confirmed the RBD diagnosis or excluded a RBD diagnosis (in the controls). There was a 93.8% sensitivity and 87.2% specificity to this single question, which compared favorably to reports on longer RBD screening questionnaires.

A third study devised controlled active treatment studies for symptomatic and neuroprotective therapies, which also represented a consensus statement by the IRBD-SG [30]. This publication serves to anticipate the arrival of promising neuroprotective, or disease-modifying, therapies to be tested in double-blind fashion in newly-diagnosed iRBD patients. However, it is currently not known when such promising agents will be identified for testing. This remains the most pressing and challenging issue in the convergent fields of RBD and PD.

A fourth study investigated the frequency of proxy-reported RBD (viz. dream-enactment) among relatives of patients with vPSG-confirmed iRBD [31]. A total of 316 patients and 316 controls were recruited from 12 IRBD-SG centers. A positive family history of dream enactment was reported in 13.8% of iRBD cases compared to 4.8% of controls (odds ratio [OR]=3.9, 95% confidence interval [CI] 2.0–7.7). ORs were increased for both siblings and parents. These findings suggest a possible genetic contribution to RBD. However, a limitation of this study was the lack of vPSG studies (to confirm or exclude RBD) in the first-degree relatives.

A fifth study addressed the topic of comorbidity and medication use in iRBD patients, in a multi-center case-control study [32]. Patients with iRBD were significantly more likely to report depression and concomitant antidepressant use (predominantly SSRIs). Patients with iRBD also reported significantly more ischemic heart disease, after adjusting for cardiovascular risk factors.

A sixth study addressed autonomic symptoms in iRBD [33]. The study was encouraged by knowledge that patients with iRBD are at very high risk of developing neurodegenerative synucleinopathies, which are disorders with prominent autonomic dysfunction. Patients with vPSG-confirmed iRBD (318 cases) and 318 controls were recruited from 13 neurological centers in 10 countries. A validated scale to study the disorders of the autonomic nervous system in Parkinson's disease (PD) patients, the SCOPA-AUT, was administered to all the patients and controls. Patients with iRBD experienced significantly more problems with gastrointestinal, urinary, and cardiovascular functioning. The most prominent differences in severity of autonomic symptoms between our iRBD patients and controls emerged in the gastrointestinal domain. Interestingly, it has been reported that an altered gastrointestinal motility, with clinical complaints of constipation, can predate the motor phase of PD. These findings underscore the importance of collecting data on autonomic symptoms in iRBD patients.

A seventh study sought to determine the pathologic substrates in patients with RBD with or without a coexisting neurologic disorder [34]. Clinical and neuropathologic findings were analyzed on all autopsied RBD cases from collaborating sites in North America and Europe. 172 RBD cases were identified (83% male). The primary clinical diagnoses among those with a coexisting neurologic disorder were DLB ( $n=97$ ), PD with or without mild cognitive impairment or dementia ( $n=32$ ), MSA ( $n=19$ ), Alzheimer's disease (AD) ( $n=9$ ) and

other various disorders ( $n=3$ ). The neuropathologic diagnoses were Lewy body disease (LBD) ( $n=77$ ), combined LBD and AD ( $n=59$ ), MSA ( $n=19$ ), AD ( $n=6$ ), progressive supranuclear palsy (PSP) ( $n=2$ ), and other disorders ( $n=9$ ). The key finding was that among the neurodegenerative disorders associated with RBD ( $n=170$ ), 160 (94%) were synucleinopathies. Furthermore, the RBD-synucleinopathy association was particularly high when RBD preceded the onset of other neurodegenerative syndrome features.

An indication of the currently regarded importance of RBD research is exemplified by a regular issue of the journal "Sleep Medicine [2013; 14(8)]" being devoted exclusively to RBD. In that issue, there were 18 peer-reviewed papers covering basic and clinical science topics related to RBD, including original research and review articles.

Finally, Brazilian investigators have broken new ground with RBD research in at least three directions: (i) Wilson's disease (hepatolenticular degeneration) presenting with RBD as the initial symptom [35], which comprises the first published description of RBD in Wilson's disease in the literature, and adds further evidence to the parallelism of PD and Wilson's disease in phenotype and brainstem topography. (ii) Cannabidiol (CBD) therapy in RBD associated with PD [36]. CBD is the main non-psychotropic component of the Cannabis sativa plant. Four patients with RBD-PD treated with CBD had prompt and substantial reduction in the frequency of RBD-related events, without side effects. (iii) A new category of Parasomnia Overlap Disorder (i.e. RBD combined with a NREM parasomnia [37]) was identified, consisting of Sleep Related Eating Disorder combined with RBD-PD [38].

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## Conclusion

The current, rapidly-evolving knowledge on the NREM sleep parasomnias, nocturnal seizures and RBD reflects the beneficial interplay of the fields of neuroscience and clinical (sleep) medicine, which will continue to deepen as additional neuroscientific tools become available. Parasomnias are clearly embedded within the core of sleep medicine and sleep science. One striking example consists of the many parasomnias that can be associated with sleep-disordered breathing and its therapy [39]. Other major examples consist of the strong association of sleep related eating disorder with RLS [40,41], and with narcolepsy [42]. Consequently, sleep clinicians and clinical investigators are encouraged to increase their interest and knowledge on the parasomnias, and in so doing they can hopefully make useful and important contributions to the field, while enhancing patient care.

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