Alteration of sleep microstructure in psychiatric disorders

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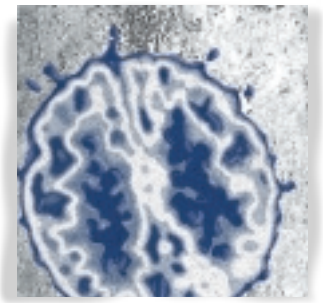

Macrostructure describes the temporal organization of sleep based on successive epochs of conventional length, while microstructure, which is analyzed on the basis of the scoring of phasic events, provides additional important dynamic characteristics in the evaluation of both normal and pathological sleep processes. Relationships between sleep, sleep disorders, and psychiatric disorders are quite complex, and it clearly appears that both the macrostructure and the microstructure of sleep are valuable physiologically and clinically. Psychiatric patients often complain about their sleep, and they may show sleep abnormalities that increase with the severity of their illness. Changes in the occurrence and frequency of phasic events during sleep may be associated with specific psychiatric disorders, and may provide valuable information for both diagnosis and prognosis of these disorders.

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Sleep terminology, recording techniques, and sleep stage scoring are defined by a set of rules discussed and accepted by experienced sleep specialists in 1968.[1] Such standardized assessment of normal sleep in adults allows the description of the temporal organization of sleep—its *macrostructure*—based on successive epochs of conventional length. This approach, however, pays less attention to the electroencephalographic (EEG) features and phasic phenomena occurring in the course of sleep, which do not belong to the time dimension of the conventional 20- to 30-s scoring epoch. These phenomena, which occur during well-defined sleep stages, constitute the *microstructure* of sleep, and provide important additional data in the evaluation of both normal and pathological sleep processes. In fact, phasic events appear to regulate the alternation between stationary sleep stages. For instance, sleep is very rich in arousals of different degrees, and these arousals lead to sleep stage transitions, which, in turn, determine the organization of sleep cycles and the balance between the various stages of sleep. Thus, sleep microstructure provides evidence of some important dynamic characteristics of the sleep process, which are not reflected by macrostructural evaluation.

Therefore, it clearly appears that both the macrostructure and the microstructure of sleep are valuable physiologically and clinically. Traditional stage scoring of polysomnographic records provides necessary descriptions of sleep macroarchitectural abnormalities in a variety of psychiatric disorders. However, the relationships between sleep, sleep disorders, and psychiatric disorders are quite complex. Psychiatric patients often complain about their sleep, and they may show sleep abnormalities that increase with the severity of their illness. Also, psychiatric disorders can be associated with sleep disorders, and most often with insomnia. Therefore, the purpose of this paper is to consider whether analysis of sleep

microstructure can provide an additional significant contribution to the understanding of the relationships between sleep and psychiatric disorders.

Sleep and psychiatric disorders

One of the most fundamental aspects of sleep research is to clarifying what normal sleep is and determining how to quantify sleep disturbance. Existing standards for macrostructure indices, such as amount of sleep, sleep efficiency, sleep latency, time spent in each sleep stage, and so on, must take into account large interindividual variability and large age differences. For microstructure descriptors, the uncertainty is even larger and normative data are still lacking, especially for the appreciation of normal interindividual variability.

Changes in sleep and sleep patterns are often seen with any type of physical or mental impairment. However, classical quantitative measures of sleep, derived from polysomnographic recording, are sometimes insufficient to detect sleep abnormalities in patients suffering from psychiatric disorders. Between 50% and 80% of psychiatric patients complain of sleep disturbances during the acute phase of their illness.[2] Even when macrostructure of sleep appears to be normal, there still can be significant modifications in sleep microstructure as expressed by the arousal-related phasic events.[3]

Epidemiological study results show that, in people complaining of insomnia, almost two thirds can exhibit psychiatric symptoms or develop them within 1 year.[4] Insomnia is a diagnostic criterion or a clinical feature of several psychiatric disorders.[5] A large analysis of studies of sleep pattern characteristics of psychiatric disorders documented the ubiquity of insomnia among patients with mood disorders, alcoholism, anxiety disorders, borderline personality disorder, schizophrenia, and dementia.[6] Among the effects, sleep continuity disturbances were the most prevalent.

Results obtained in epidemiological, cross-sectional, and longitudinal studies suggest a high rate of comorbidity between sleep disturbance and psychopathology, and most specifically with insomnia, anxiety, and depression. Although there is a positive relationship between severity of sleep disturbances and concurrent psychopathology, unequivocal evidence of a cause-and-effect relationship is still lacking.[7] However, longitudinal data suggest that anxiety and stressful life events often precede acute sleep difficulties, whereas persistent insomnia may be a risk factor for subsequent development of depression. Complaints of 2 weeks or more of insomnia nearly every day might be a useful marker of subsequent onset of major depression.[8] Although more than 40% of subjects with sleep complaints had diagnosable psychiatric disorders,[4,9] it is unclear whether abnormal polysomnographic findings could be prevalent in subjects with sleep complaints and underlying psychiatric disorders.[10]

Phasic events: arousals

The criteria given for arousal in sleep refer to a rapid shift towards more rapid frequencies preceded by at least 10 s of continuous sleep.[11] In the American Sleep Disorders Association (ASDA) definition, arousals are basically considered as markers of sleep disorders.[11] However, arousals are usual EEG features in normal sleep,[12] even though they are also clearly influenced by the environment of the sleeper.[13] The term "arousal" is often related to the concept of awakening, but in multiple cases, arousal is limited in length and amplitude, and it does not lead to the state of wakefulness (desynchronized, low amplitude, and fast EEG activities seen on all recording sites).

Arousals, for instance, are important in the determination of the possible impact of sleep disturbance on daytime sleepiness. However, arousals vary in intensity and frequency during sleep. Bonnet[14] investigated three levels of arousal responses: full awakening requiring a verbal response; body movement; and transient EEG arousal. Daytime effects of recurrent pathological arousals could be related not only to the sleep stage transition from deep sleep to shallower sleep stages, but also to the difficulty in returning rapidly to these initial states.[15]

Minor arousals are almost always associated with autonomic changes that reflect the underlying sympathetic activation, such as heart rate, blood pressure, peripheral vasoconstriction, or skin responses. Transient activation phases are associated with EEG desynchronization, increased muscle activity, and autonomic changes.[16] These autonomic changes vary in amplitude depending on the intensity of the arousal, but they may occur in response to minor stimuli producing no visible cortical effect, and they are resistant to habituation.[17,18]

Kupfer et al[19] showed that depressed patients had significantly lower EEG power than control subjects in the delta band (0.5 to 2 Hz) and in a 4- to 10-Hz band (including theta and part of alpha activities) during the

first 100 min of the sleep period. Over the whole night, a significantly lower EEG power was found in the depressed patient group compared with the control group, but only in the delta activity. Previously, Borbely et al[20] suggested that it was intermittent wakefulness and microarousals in depressed patients that resulted in decreased delta amplitude.

Increased phasic activity during rapid eye movement (REM) sleep, such as microarousals and body movements, has been also found in posttraumatic stress disorder.[21,22]

Awakenings

Among arousals, a specific place should be reserved for those large arousals that lead to awakenings. While awakenings in normal subjects are relatively rare during the first sleep cycle, they appear to be more frequent in patients suffering from mental disorders.[23] However, in contrast to healthy subjects and patients suffering from chronic schizophrenia, episodes of wakefulness in the first sleep cycle do not increase the REM sleep latency in patients with major depression.[24]

Arousals constitute the basis for sleep fragmentation leading to daytime impairment.[25] Sleep continuity problems are also quite a common complaint among patients with psychiatric disorders.[26-29] Objective laboratory findings indicate that sleep is shortened and fragmented (due to increased awakenings/arousals) in patients with mania,[27] generalized anxiety disorder,[28,30] panic disorder,[26] obsessive-compulsive disorder,[31] schizophrenia,[29,31] posttraumatic stress disorder,[31] and borderline personality disorder.[31]

Many studies have reported increased number of awakenings to be characteristic of posttraumatic stress disorder. However, experimental studies have found reduced thresholds for awakening, and particularly arousal thresholds using neutral tones from stages 3 and 4.[32] Nightmares (stereotyped anxiety dreams) are generally associated with psychopathology[33] and they are common in patients suffering from posttraumatic stress disorder.[34,35] These anxious awakenings are related to REM sleep,[21] but they can also be found in non-REM (NREM) sleep.[36] The sleep of schizophrenic patients is profoundly disturbed in the acute phase of the illness, and nightmares often precede this phase.[37]

Depressed patients show prevalent sleep continuity disturbances (eg, frequent and prolonged awakenings together with longer sleep latency and diminished total sleep time), although not specific to affective disorders.[38,39] In fact, depression in patients with complaints of sleep disturbance is more persistent or less likely to resolve.[40]

Sleep fragmentation, characterized by an increase in the number of nocturnal awakenings and time awake after sleep onset, is also a common sleep disturbance in patients with dementia of the type associated with Alzheimer's disease.[41] In Alzheimer dementia patients living in a residential care unit, it has been found that every hour of the night sleep was disturbed by wakefulness episodes and that every hour of daytime wakefulness was characterized by microsleeps.[42] Also, sleep maintenance problems, secondary to psychiatric or medical disorders, may be more pronounced in elderly patients. This is mainly due to more fragmented sleep related to decreases in arousal threshold and sleep maintenance drive.

Cyclic alternating pattern

Another sleep microstructure phenomenon is the cyclic alternating pattern (CAP).[3] CAP is a periodic EEG activity of NREM sleep, characterized by sequences of transient electrocortical events that are distinct from background EEG activity and recur at quite regular intervals. CAP is mainly composed of phase A (activation) and phase B (the quiet interval until the next phase A), and it is a sign of sleep instability often accompanied by sleep stage changes or awakenings.[3] The appearance of CAP sequences reflects arousal instability in a higher duration range than individual microarousals. In normal sleepers, CAP rate (percentage of CAP time in NREM sleep time) varies according to a U-shaped, age-related curve; the lower values are found in young adults, while the highest values are seen in elderly sleepers.[43]

CAP appears spontaneously, but also in association with identifiable sleep pathologies; its rate significantly increases in patients suffering from insomnia. In a study comparing a large number of untreated depressed patients with an age-matched, gender-balanced, controlled group,[44] no major difference was found in terms of sleep efficiency (above 95% in both groups) or any other sleep macrostructure index. However, a significant increase in unstable sleep was found in depressed patients, as reflected by the rate of CAP (60% in patients and 35% in normal subjects). This case underlines the value of microstructural scoring performed in addition to the usual sleep evaluation via macrostructural analysis.

EEG patterns

It is often discussed whether slow phasic EEG activities, such as K-complexes and delta bursts, can be considered as arousals, since they often are associated with clear activation signs: heart rate acceleration, vasoconstriction, change in ventilation, and motor activation.[45,46] The same question may apply to another phasic EEG activity, which is not necessarily clearly associated with activation signs, called sleep spindles.

Sleep spindles and K-complexes constitute EEG markers of NREM sleep and particularly stage 2 sleep. Sleep spindles were first described by Hans Berger in 1933,[47] but named by Loomis et al in 1935.[48] They are rhythmic 12- to 14-Hz oscillations lasting from 0.5 to 3 s, while the K-complex is a phasic EEG waveform of approximately 0.5 s, characterized by a well-delineated negative component followed by a positive deflection. K-complexes may be spontaneous or elicited by stimulation.

While sleep spindles are often viewed as playing a sleep-protective role and contributing to sleep maintenance, the functional significance of K-complexes remains a matter of debate. In fact, K-complexes are considered to be elementary forms of arousal during slow-wave sleep (SWS). They carry characteristics of evoked potentials, which provide subattentive information processing. There has been a debate as to whether the appearance of a K-complex in response to a stimulus is indicative of a partial arousal process that leaves the central nervous system more likely to arouse if further stimulation occurs,[12,49] or whether it reflects a sleep maintenance process involving a response to stimulation that would inhibit arousal and prevent the fragmentation of sleep.[50,51] The interrelationship between sleep spindles and K-complexes is not entirely clear, although they are often associated.[52]

There are reports of spindles and K-complexes varying together, for example, in the case of dementia where both spindles and K-complexes are reduced.[53] Spindle density has been reported to be drastically decreased in Alzheimer's disease.[54] Dysthymic patients have fewer K-complexes and arousals than controls, though they do exhibit a higher rate of nocturnal awakenings.[55]

Rapid eye movements

REMs are controlled by a cholinergic–aminergic balance.[56] They constitute a major event in the scoring of REM sleep, but their frequency or density can also be used to quantify the intensity of REM sleep process.

According to Kupfer and Reynolds,[57] EEG sleep changes in depression include much more than shortened sleep latency. The frequency of REM, or REM density, is dependent on the subject's mood, and is higher in patients suffering from depression.[58,59] REM density is also higher in dreams with strong emotional content[60] and after stressful situations.[61] However, due to its very large variability, it is questionable whether overall REM density can be considered as a biological marker for affective illness.[62]

REM density has been found to be increased in schizophrenia,[63,64] but, in contrast, in other reports, previously treated and drug-naive patients with schizophrenia were reported to show normal REM density.[62,65-67]

In a recent study,[68] borderline personality disorder patients were compared with patients with major depression and matched healthy control subjects. All patients fulfilled the *International Classification of Diseases, 10th revision* (ICD-10) criteria.[69] In both patient groups, REM density for the whole night, as well as REM density for the first REM period, was significantly increased compared with the control group. Szuba et al[27] also found an increased REM density in depressed patients, while other authors found similarly increased REM density during the first REM period in depressed patients.[70,71] Psychotic patients with suicidal behavior tendencies had increased REM density during sleep.[72]

The sleep of posttraumatic stress disorder patients is characterized by increased REM density,[21,22,73,74] and the severity of this disorder is correlated with REM density.[22] Polysomnographic recordings made in patients with Alzheimer's disease showed decreased REM density, and the gradual loss of this phasic activity is parallel to the progression of the illness. Similar findings have also been found with sleep spindles and K-complexes.

Body movements

Polysomnographic studies performed in patients with panic attacks show an increase in movements occurring during sleep,[75,76] and particularly large body movements in stages 1 and 2 sleep and REM sleep.[75-77]

Patients suffering from posttraumatic stress disorders show excessive body movements[78] and sudden awakenings during sleep, often related to dream content.[22] Panic awakenings generally occur from NREM sleep stages, and particularly during the transition between stage 2 to

SWS (stages 3 and 4).[77] Inman et al[79] compared Vietnam veterans with posttraumatic stress disorder and patients with insomnia. While no differences between the two groups were observed in the severity of the insomnia, the posttraumatic stress disorder patients were more likely than the insomniacs to report restless legs in bed and excessive body movement during sleep.

Conclusion

It is obvious that polysomnographic sleep recording and its derived macrostructure evaluation provide valuable information for detecting sleep abnormalities in patients suffering from psychiatric disorders. However, this macrostructural approach might in some cases be insufficient and, therefore, it should be combined with a complementary microstructural analysis. Phasic events occurring during sleep have direct effects on sleep maintenance and sleep organization. Depending on their characteristics, they may lead to sleep disturbance, sleep fragmentation, or sleep interruption, while other phasic events play a more protective role in promoting sleep. Changes in occurrence and frequency of these events during sleep may be associated with specific psychiatric disorders, and they may provide valuable information for both the diagnosis and the prognosis of these disorders. ❑

Alteración de la microestructura del sueño en los trastornos psiquiátricos

La macroestructura del sueño describe la organización temporal de éste basada en las sucesivas etapas de duración convencional, mientras que la microestructura —que es analizada mediante el resultado de acontecimientos fásicos— aporta importantes características dinámicas en la evaluación de los procesos de sueño normal y sueño patológico. Las relaciones entre sueño, trastornos del sueño y trastornos psiquiátricos son bastante complejas y es claro que la macroestructura y la microestructura del sueño son de gran valor tanto a nivel fisiológico como clínico. Los pacientes psiquiátricos a menudo se quejan de su sueño y ellos pueden presentar alteraciones del sueño que aumentan con la gravedad de su enfermedad. Los cambios en la ocurrencia y frecuencia de los acontecimientos fásicos durante el sueño pueden estar asociados con trastornos psiquiátricos específicos y pueden aportar valiosa información tanto para el diagnóstico como para el pronóstico de estos trastornos.

Altérations de la microstructure du sommeil dans les troubles psychiatriques

L'approche macrostructurelle décrit l'organisation temporelle du sommeil sur la base d'époques successives de durée fixée par convention, alors que l'approche microstructurelle est fondée sur la prise en compte des éléments phasiques, qui apportent des caractéristiques dynamiques additionnelles importantes pour l'évaluation des processus de sommeil normaux ou pathologiques. Les relations entre le sommeil, les troubles du sommeil et les troubles psychiatriques sont assez complexes et il apparaît clairement que la macrostructure et la microstructure du sommeil ont une valeur significative, aussi bien sur le plan physiologique que clinique. Les patients présentant des troubles psychiatriques se plaignent souvent de leur sommeil et ils peuvent présenter des anomalies du sommeil qui augmentent avec la sévérité de leur maladie. Des modifications dans la survenue et la fréquence des événements phasiques au cours du sommeil peuvent être associées avec des troubles psychiatriques spécifiques et elles peuvent apporter une information importante aussi bien sur le plan du diagnostic que sur celui du pronostic de ces troubles.

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