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Sleep, Development, and Human Health

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WITH THE RECENT CREATION OF A NEW SECTION WITHIN THE SLEEP RESEARCH SOCIETY DEVOTED TO DEVELOPMENT, THE TIME IS RIPE TO RECONSIDER ways in which developmental analysis can inform our understanding of sleep. Although some consider any study to be developmental when the subjects are fetuses or infants, developmental analyses are most informative when they address *processes of change* across the lifespan. Moreover, because our field has traditionally focused on sleep in adults, infant sleep is typically compared against an adult standard. Such comparisons can lead to gross misinterpretations, even distortions, of infant behavior and physiology.[1]

No one doubts the clinical and diagnostic value of the neocortical EEG for assessing sleep in human adults. But overreliance on this measure can be problematic when other ages or species are considered. For example, the fact that delta activity only emerges toward the end of the second postnatal week in rats helped inspire a recent reconceptualization of infant sleep—the so-called *pre-sleep hypothesis*.[2] In contrast, for our studies in infant rats before the emergence of delta activity, we have used measures of muscle tone and myoclonic twitching (including twitching of the extraocular muscles) to describe a basic sleep-wake cycle that progresses from active wakefulness through quiet wakefulness, quiet sleep, and active sleep.[3,4] Then, contrary to the predictions of the pre-sleep hypothesis,[2] we demonstrated brainstem, hypothalamic, and basal forebrain modulation of sleep in early infancy.[5-8] But what has been most striking to us is not the presence or identity of the neural mechanisms involved in infant sleep, but the *temporal* features of infant sleep and how they change with age. Some of these features have recently been revealed through the use of analytical procedures that are relatively new to the field.

In our standard procedure, bouts of sleep and wakefulness are derived from continuous recordings of nuchal EMG. Because infant rats transition between states many times per minute, recordings lasting just 1-2 hours typically generate many dozens of bout durations. From these bout durations, log-survivor distributions can be produced that are then plotted using semi-log or log-log coordinates. Durations that fall along a straight line on a semi-log plot follow an exponential distribution, whereas durations that fall along a straight line on a log-log plot follow a power-law distribution.[9]

In a recent paper on sleep-wake cyclicity in adult humans, cats, rats, and mice, fluctuations in nuchal muscle tone were used to describe the statistical features of sleep and wake bout

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durations.[10] In all 4 species, sleep durations followed exponential distributions, whereas wake durations followed power-law distributions. Because we had found earlier that wake bout durations in infant rats exhibit exponential, not power-law behavior,[11] we decided to fully characterize the early development of sleep and wake bout distributions in rats from postnatal day 2 (P2) to P21.[9] Consistent with the earlier findings in adults, we found that sleep durations always exhibit exponential behavior. In contrast, wake durations gradually transform from exponential to power-law behavior beginning around P15, thus indicating a dramatic restructuring of wakefulness that coincides in this species with eye opening and the initiation of weaning.

Noting that sleep and wake bouts are fragmented in both infants and narcoleptics, we hypothesized that narcolepsy entails a reversion back toward the normally fragmented bouts of infancy. To test this hypothesis, we used the experimental procedures described above to assess sleep and wakefulness in orexin (hypocretin) knockout and wild-type mice at P4, P12, and P21.[12] At P4 and P12, we found little difference between the 2 strains, although both exhibited age-related consolidation of sleep and wake bouts. By P21, further consolidation occurred in both strains, along with the emergence of power-law behavior in the wake bouts. But now, the knockouts were lagging behind their same-age wild-type counterparts, retaining the more fragmented bouts characteristic of earlier ages. We concluded that the orexinergic system is not necessary to consolidate sleep and wake bouts during the first 2 postnatal weeks, nor is it necessary for the developmental emergence of power-law wake behavior. Orexin does appear, however, to further consolidate bouts beyond the values attained in early infancy.

We suggest that these methods might be used effectively to track with greater precision the changes in narcoleptic sleep-wake patterns across the lifespan. In addition, by comparing assessments of narcoleptic sleep and wakefulness with normative developmental data, we might determine whether the sleep-wake patterns of narcoleptics regress toward those typical of younger individuals. With this approach, valuable information may be gained regarding the neural mechanisms and developmental onset of narcolepsy, the progression of the disease, and responses to treatment.

Beyond narcolepsy, this analytical approach may provide useful information concerning normal and pathological human development. Because sleep disturbances are associated with many aspects of disease and psychopathology,[13,14] any method that provides greater sensitivity for tracking developmental milestones, detecting the onset of sleep disturbances, and assessing responses to treatment could be of use to clinicians. Accordingly, we believe that the analyses of sleep and wake bout durations described here are superior to gross measures of total sleep and wake time because they reveal more about the fine structure of sleep-wake organization and they more closely reflect the brainstem processes that govern transitions between states.

We envision a basic and clinical science of sleep that takes development seriously by seeking to describe and explain the processes of developmental change. To that end, detailed assessment of the temporal organization of sleep and wake bouts will provide a more accurate picture of normal development and a more sensitive instrument for identifying pathological development. In addition, because evolutionary transformations arise through modifications of developmental processes,[15] detailed developmental analyses of sleep-wake rhythms across a diversity of species will provide valuable insights into the evolution and function of sleep. Finally, we anticipate that the newly constituted section on development in the Sleep Research Society will provide the impetus for applying these newly acquired insights from developmental research toward a better understanding of the interconnections between sleep and human health.

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