Cortical Development, Electroencephalogram Rhythms, and the Sleep/Wake Cycle

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ABSTRACT

During adulthood, electroencephalogram (EEG) recordings are used to distinguish wake, non–rapid eye movement sleep, and rapid eye movement sleep states. The close association between behavioral states and EEG rhythms is reached late during development, after birth in humans and by the end of the second postnatal week in rats and mice. This critical time is also when cortical activity switches from a discontinuous to a continuous pattern. We review the major cellular and network changes that can account for this transition. After this close link is established, new evidence suggests that the slow waves of non–rapid eye movement sleep may function as markers to track cortical development. However, before the EEG can be used to identify behavioral states, two distinct sleep phases —quiet sleep and active sleep—are identified based on behavioral criteria and muscle activity. During this early phase of development, cortical activity is far from being disorganized, despite the presence of long periods of neuronal silence and the poor modulation by behavioral states. Specific EEG patterns, such as spindle bursts and gamma oscillations, have been identified very early on and are believed to play a significant role in the refinement of brain circuits. Because most early EEG patterns do not map to a specific behavioral state, their contribution to the presumptive role of sleep in brain maturation remains to be established and should be a major focus for future research.

Keywords: Active sleep, Gamma activity, NREM sleep, Quiet sleep, REM sleep, Spindle bursts, Theta activity

http://dx.doi.org/10.1016/j.biopsych.2014.12.017

DISSOCIATION BETWEEN CORTICAL RHYTHMS AND SLEEP/WAKE BEHAVIOR IN EARLY DEVELOPMENT

In the adult mammalian brain, specific cortical electroencephalogram (EEG) patterns are used to define behavioral states. In the wake state, the EEG is dominated by low-voltage fast activity in the beta (16–30 Hz) and gamma (>30 Hz) range ("activated" EEG). During non–rapid eye movement (NREM) sleep, the EEG mainly shows waxing and waning oscillations at around 12–15 Hz called sleep spindles and slow (delta) waves of large amplitude. Slow wave activity (SWA) (.5–4.5 Hz) is a convenient way to assess number and amplitude of slow waves and is a marker of NREM sleep intensity (i.e., arousal thresholds during sleep are higher when SWA is higher) (1). Also, SWA is an established marker of sleep pressure because its value reflects the duration of the prior wake state, peaking at sleep onset, further increasing after acute sleep deprivation, and declining in the course of sleep (2). The number and amplitude of slow waves in the adult brain reflect both the need for sleep and its depth. Rapid eye movement (REM) sleep is characterized by a wake-like, tonically activated EEG but can be distinguished from wake state because of the presence of phasic events (e.g., rapid eye movements and twitches of the limbs) and tonic phenomena (e.g., loss of tone in antigravity muscles).

The close association between specific cortical EEG patterns and behavioral states occurs only after the cerebral cortex has completed most of its anatomic development. In rodents, this occurs by the end of the second week after birth, at around postnatal (P) days P11–P12. Between P0 and P10, a period during which the rat cortex shows explosive growth, cortical oscillations are only weakly modulated by behavioral states, and EEG activity is discontinuous, with long periods of neuronal silence interrupted by spindle bursts, evoked gamma oscillations, and other short-lasting EEG patterns (Figure 1). Because rodents are altricial—born in a far less mature condition than humans—the cortical maturity of the rat during the first postnatal week corresponds to that of the young premature human brain (3–5). Rodents are good models to study the development of the sleep/wake cycle and its EEG rhythms because more immature stages of these processes can be studied in postnatal life when they are more experimentally accessible. In this review, we focus on studies in rats and mice because the development of the sleep/wake cycle, the maturation of EEG rhythms, and their underlying cellular mechanisms are best characterized in these species.

DEVELOPMENT OF THE RODENT CORTEX

The development of the rat brain has been subdivided into four stages (6). Briefly, in the fetal period, cell division produces 94%–97% of all brain cells. The first postnatal phase (P0–P10)

ISSN: 0006-3223

Biological Psychiatry June 15, 2015; 77:1071–1078 www.sobp.org/journal

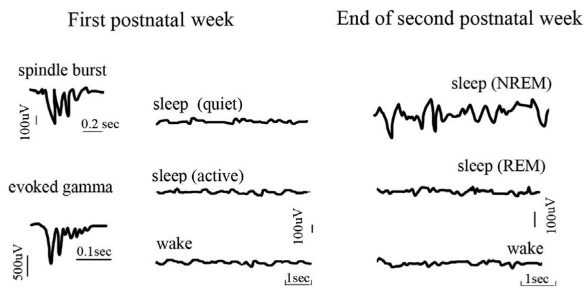

Figure 1. Schematic representations of cortical electroencephalogram recordings in a rat pup. During the first postnatal week, transient events such as spindle bursts and evoked gamma oscillations can be observed, but electroencephalogram activity is mainly independent of behavioral states (see text for details). Behavioral states during the first postnatal week were defined based on behavioral observation (respiration pattern; body, vibrissae, and tail movements; eyes open/closed). NREM, non-rapid eye movement; REM, rapid eye movement.

is characterized by explosive growth: At P0, the brain is only 15% of its final size, but by P10, most growth of cells, and especially of axons and dendrites, has been completed (7–9). In the third phase (P11–P20), the rate of growth is much reduced, the extracellular space decreases significantly, blood vessels grow, mature astrocytes and oligodendrocytes are easily found, and myelinization starts (10,11). After weaning (usually at P21 in mice and rats), growth is very slow (fourth phase). As described in detail in Supplement 1, the second week represents a pivotal point in the transition from immature to mature cortex: Number of synapses and overall connectivity increase, silent synapses almost disappear, gamma-aminobutyric acid A signaling becomes hyperpolarizing, and the rules of synaptic plasticity change.

DEVELOPMENT OF THE SLEEP/WAKE CYCLE IN RODENTS

Several studies in rodent pups described how specific behaviors emerge and evolve during the first postnatal weeks, concurrent with the profound anatomic changes occurring in cortex. In an early study, Bolles and Woods (12) provided a detailed behavioral observation of wake and sleep activities in rat litters and their mothers from birth to P26. They described sleep as "very fitful" in the first few days, constantly interrupted by "convulsion-like spasms," attempts to find the preferred sleeping position, and movements from siblings. At P1, movements during sleep are described as gentle fluttering often involving the whole body, whereas twitching becomes more localized to the limbs and tail starting at P4, increases in frequency and strength until P9, and becomes more "peaceful" in the next 10 days. Pups were estimated to spend >80% of total time "sleeping or resting." However, according to Bolles and Woods (12), this percentage was probably an overestimation owing to two reasons: 1) the inability to see the pups clearly when lying under the mother, and 2) the use of visual observation as the only criterion to define sleep.

More recent studies identified sleep by combining visual observation with measurements of muscle activity and EEG recordings (13–15). Using this approach, some authors suggested that sleep starts as a disorganized mixed state (16,17). However, more recent evidence is more consistent with the presence from birth of two distinct sleep phases, quiet sleep and active sleep, which represent early forms of what later, by the end of the second postnatal week, are recognizable as NREM sleep and REM sleep, respectively (14,18,19). Quiet sleep is a state of behavioral immobility and reduced muscle tone sometimes interrupted by startles. Startles are among the first behavioral events recorded in human fetuses and neonatal rats and consist of sudden, spontaneous, and simultaneous contractions of muscles throughout the body. Although rare (1–2/min), startles occur in all behavioral states and are not a unique feature of quiet sleep (20). Active sleep, by contrast, is uniquely characterized by frequent myoclonic twitches of isolated muscles that occur on a background of muscle atonia. Several pontine and medullary areas that mediate muscle atonia and twitches during REM sleep in adults are also involved in the generation of these REM sleep components in infants, consistent with the view that infant sleep is qualitatively similar to adult sleep (21,22).

During the second postnatal week, EEG activity becomes continuous and strongly modulated by behavioral states. Specifically, the total power in the cortical EEG signal in all behavioral states increases after P9 (13), consistent with P10 being a crucial step in cortical maturation and synaptogenesis (23,24). Neuronal firing in the rat visual cortex also increases sharply in quiet and active sleep at P11–P12 (25). After P12, the total power in the EEG signal during quiet sleep is consistently higher than in wake and active sleep states because slow waves start to be detected from the scalp (13–15). After the appearance of slow waves, which map into quiet sleep exclusively, this state can be unambiguously identified as NREM sleep. Spindles start appearing during NREM sleep at P14, and the EEG resembles an EEG in an adult by P18 (13). At the same time, during the second postnatal week, the frequency of twitches during active sleep declines sharply, the EEG becomes tonically activated, and active sleep can be unambiguously identified with REM sleep (14,18,26). A single discrete event does not occur after P11–P12 that dramatically changes the structure of sleep and wake states. Rather, by the end of the second postnatal week, the distinction among the three behavioral states as defined in adults becomes obvious because of the appearance of slow waves in the scalp EEG and the progressive evolution of EEG activity from discontinuous to continuous.

It was generally assumed that in newborn pups most, if not all, sleep is active sleep. The estimates for time spent in each sleep phase differ widely in early studies, perhaps in part because of differences in the duration of the recordings and their precise timing during the day. According to one report (27), quiet sleep is not present during the first postnatal week, and pups are either awake or, more often, in active sleep (60%–70% of the time). By contrast, two other studies reported that at least 30% of total sleep is quiet sleep (28,29). The discrepancy may be due to the fact that in the study that failed to identify quiet sleep in the first postnatal week, this behavioral state was defined as a period of at least 30 sec of behavioral quiescence (27). This is a very conservative criterion because quiescent periods in rats are often