



Behavioral States Modulate Sensory Processing in Early Development

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Abstract

Purpose of Review Sleep-wake states modulate cortical activity in adults. In infants, however, such modulation is less clear; indeed, early cortical activity comprises bursts of neural activity driven predominantly by peripheral sensory input. Consequently, in many studies of sensory development in rodents, sensory processing has been carefully investigated, but the modulatory role of behavioral state has typically been ignored.

Recent Findings In the developing visual and somatosensory systems, it is now known that sleep and wake states modulate sensory processing. Further, in both systems, the nature of this modulation shifts rapidly during the second postnatal week, with subcortical nuclei changing how they gate sensory inputs.

Summary The interactions among sleep and wake movements, sensory processing, and development are dynamic and complex. Now that established methods exist to record neural activity in unanesthetized infant animals, we can provide a more comprehensive understanding of how infant sleep-wake states interact with sensory-driven responses to promote developmental plasticity.

Keywords Cortical development · REM sleep · Activity-dependent development · Movement · Visual system · Somatosensory system

Introduction

For over 50 years, we have known that active (or REM) sleep is most prevalent early in mammalian development, with time spent in quiet sleep and wake increasing with age [1, 2]. For example, human newborns sleep approximately 16 h each day, 8 h of which are spent in active sleep. In the infants of highly altricial species, such as rats, active sleep is even more prevalent. Further, in early development and regardless of sleep-wake state, cortical activity is characterized as

discontinuous, comprising periods of relative silence punctuated by brief bursts of activity [3]. It is not until 2 months after birth in humans [4] and almost 2 weeks after birth in rats [5–7] that cortical activity assumes the continuous pattern of activity that characterizes its patterning in adults.

During the early period of discontinuous cortical activity, bursts of action potentials are triggered by sensory inputs conveyed from peripheral receptors [8]. At one time, sensory inputs were thought to trigger cortical activity independent of behavioral state, but we now know this is not the case. The precise ways that sensory processing is modulated by behavioral state depend on sensory modality and stage of development. Here, we begin by reviewing recent advances in our understanding of state-dependent modulation of cortical activity in the developing visual and somatosensory systems. We then discuss how the interactions among sleep-wake states, behavior, and sensory-driven responses provide a framework for understanding sensory development.

The Pattern and Function of Early Cortical Activity

Consistent with the characterization of early cortical activity as discontinuous, research using infant rats shows that neurons

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in primary somatosensory and visual cortex typically exhibit seconds-long periods of silence interspersed with bursts of neural activity across all behavioral states. This activity includes oscillations in the local field potential, most notably spindle bursts, which are often referred to as delta-brushes in human infants [3, 8, 9]. Spindle bursts are 5- to 30-Hz oscillations with peak power generally occurring at 10–15 Hz. Not to be confused with sleep spindles, which occur exclusively during quiet sleep in adults [10], spindle bursts can occur in any behavioral state; we will see, however, that they occur most frequently during active sleep. Originally detected in the primary somatosensory cortex (S1) of infant rats [8], spindle bursts have since been described in primary visual cortex (V1; [11, 12•]), primary auditory cortex (A1; [13]), and primary motor cortex (M1; [14, 15]), as well as prefrontal cortex [16]. Although spindle bursts are triggered by sensory input, a minority of spindle bursts can arise spontaneously in thalamocortical circuits [8, 17, 18].

The available evidence suggests that spindle bursts are a transient developmental phenomenon, with their disappearance coincident with the emergence of continuous neural activity [12•]. As understood in the visual system, spindle bursts are produced via corticothalamic feedback circuitry that prolongs and amplifies an initial sensory signal within a precise cortical topographic location [8, 12•, 17, 19]. Although not yet demonstrated experimentally, spindle burst production likely relies upon similar thalamocortical circuitry across sensory modalities.

The rhythmic pattern of activity driven by spindle bursts is hypothesized to strengthen thalamocortical connectivity [20]. However, spindle bursts are binary responses; longer or stronger stimuli do not trigger spindle bursts of greater duration or amplitude [5] and even a very brief stimulus can produce a spindle burst lasting up to 1 s in duration. This lack of correspondence between stimulus and cortical response has several important implications for how spindle bursts can promote thalamocortical connections. First, the binary nature of spindle bursts means that only the occurrence of a sensory event—and not information about its amplitude or duration—is coded. Second, because of the long duration of each spindle burst, a series of sensory events over a short period of time would produce overlapping cortical activity, strengthening inappropriate thalamocortical projections and thus weakening topographic divisions. Consequently, for developing, refining, and maintaining cortical topography, it would be best if sensory events were brief and discrete so as to sequentially activate precise locations within a topographic representation. Because the sensory periphery for each modality has its own unique features, we expect each system to develop its own solution for producing topographic organization. However, modulation by behavioral state appears to be a common feature that unites different sensory systems.

Below, we review evidence that sleep and wake states differentially modulate activity in the developing visual and somatosensory systems. We focus on how these two systems take advantage of behavioral states to produce structured patterns of early cortical activity. We then discuss how state-dependent modulation of sensory responses in these two systems appears to achieve the same goal, namely to control the flow of sensory input from the periphery so as to strengthen and sharpen cortical topographic representations.

Modulation of Early Visual System Activity by Behavioral State

In the visual system, the early patterning of activity arising from the retina is well understood. In rats, before the onset of patterned vision at P14 (when the eyes open), retinal waves provide structured activation of visual circuits independent of behavioral state. Retinal waves occur before the onset of light sensitivity in rods and cones at P8 [5] and persist through at least P20 [21]. Although retinal waves largely arise from spontaneous activation of retinal interneurons, there is now evidence that, during the second postnatal week, they can be triggered by light passing through closed eyelids [22]. Retinal waves travel across the retina through sequential activation of adjacent ganglion cells, producing patterns of coactivation in adjacent retinotopic regions [23]. This retinal activity drives activity in the dorsolateral geniculate nucleus (dLGN) that, in turn, triggers spindle bursts in V1 [11]. The structured activity in the developing visual system contributes to the building and strengthening of retinotopic maps [23].

Until recently, the V1 activity that is driven by retinal waves was thought to be unaffected by behavioral state [5]. However, through P12 in both V1 [24•] and the dLGN [25••], visually driven activity is inhibited during active wake, that is, when the pup is awake and moves its limbs. This inhibition is specific to active wake, as movements during active sleep have no such effect [24•]. It follows from these observations that sleep deprivation, by increasing the number of wake movements, would likely decrease activity in the dLGN and V1 at these early ages. If so, then early sleep deprivation would constitute a form of sensory deprivation for the developing visual system.

The inhibition of dLGN and V1 activity during active wake reverses at P13 [25••]. At that age, activity in those structures is increased throughout active wake, a feature of this system that persists into adulthood [26–28]. The switch at P13 results from a change in the modulation of dLGN inputs [25••], but the precise cause of the switch has not yet been identified. It is also not known how the switch affects sleep-related activity in V1.

Modulation of Early Sensorimotor System Activity by Behavioral State

Sensory responses in the developing visual system are modulated only during active wake. The same, however, cannot be said of the developing sensorimotor system, for which behavioral state modulation is a central feature. The difference between these two sensory modalities may arise from a fundamental functional difference between them: Whereas much of visual system development occurs before the onset of patterned vision, the sensorimotor system must develop even as it is being used to guide such critical infant behaviors as suckling, huddling, and locomotion [28–32]. Accordingly, it may be that the modulation of somatosensory processing by behavioral state, as described below, is a necessary outcome of a need to temporally segregate sensorimotor activity into wake- and sleep-related functions.

The cerebral cortex does not contribute to the production of movement during either wake or sleep states [33, 34]. In fact, the contributions of M1—the archetype of cortical motor areas—to behavior emerge relatively late in development in humans and other mammals [35, 36]. In rats, for example, M1's role in the production of movement is not clearly established until as late as P35 [34]. Consequently, infant behavior arises from activity in brainstem motor structures [37]. Moreover, at those early ages when M1 does not participate in the production of movement, it responds like a prototypical somatosensory area, similar to S1 [38••].

As in V1, neural activity in developing S1 and M1 predominantly consists of spindle bursts, but triggered by somatosensory stimuli [8, 15]. Somatosensory stimuli can be broadly divided into two classes: those arising from other-generated movements (i.e., exafference) and sensory feedback arising from self-generated movements (i.e., reafference). In turn, reafference can arise from wake movements or from the myoclonic twitches that occur exclusively during active sleep. As we will see, these two categories of self-generated movement produce very different patterns of brain activity.

Myoclonic twitches are discrete, jerky movements of the limbs that occur against a background of muscle atonia. Although they may appear to the naked eye as disorganized flailing of the limbs, they provide—like retinal waves for the visual system—spatiotemporally organized input to the developing somatosensory system [39]. Myoclonic twitches are particularly abundant early in development when active sleep is the predominant behavioral state [1, 2]. In contrast, during wake, limb movements typically occur simultaneously, are high in amplitude, are of variable duration, and occur against a background of high muscle tone.

Reafference from twitches produces somatotopically restricted activation of neural structures throughout the sensorimotor system [14, 38••, 40•]. However, and somewhat paradoxically, these same structures fail to respond to reafference

from wake movements [38••, 40•]. Focusing on the forelimbs, reafference from wake movements is inhibited via sensory gating in the medullary external cuneate nucleus (ECN; [40•]), a dorsal column nucleus that receives proprioceptive afferents from the forelimbs and projects to the thalamus and the sensorimotor cortex [41, 42]. In rats, this state-dependent gating persists through P10. As a consequence, twitches are primarily responsible for triggering spindle bursts in S1 and M1 across the early postnatal period [15, 40•].

The fact that twitches are abundant during early development and that they trigger sensorimotor activity suggests that they are well suited to contribute to activity-dependent development in this system. Similar to how subtle differences in the patterning of retinal waves can have downstream consequences for retinotopic organization [43, 44], there may be specific features of twitch-related reafference that are particularly important for shaping somatotopic organization.

One consequence of sensory gating in the developing sensorimotor system is that it is selectively “blind” to wake movements. But this blindness is transient: By P11, the ECN no longer gates wake-related reafference, permitting neurons in S1 and M1 to respond to the sensory consequences of wake movements [38••]. As with the similar switch within the dLGN [25••], the mechanisms responsible for the ECN switch are currently unknown.

Why Are Early Sensory Responses Inhibited During Active Wake?

In contrast with adults, in which activity in visual and sensorimotor cortex is enhanced during active wake [27, 45, 46], cortical activity in early infancy is inhibited during active wake [25••, 38••]. In both modalities, this inhibition occurs at the earliest stages of sensory processing (dLGN, ECN) and exhibits a transition to more adult-like responding at similar ages (P11–13). The mechanisms underlying active-wake inhibition and the sudden transformation to adult-like responses are not yet understood.

In the sensorimotor system, the spatiotemporal features of twitches may make them better suited than wake movements for developing somatotopy [47]. In contrast, in the visual system, there is no evidence that the spatiotemporal features of retinal waves differ across behavioral states, thus making it more difficult to explain the inhibition of V1 activity during active wake. Indeed, it may be that wake-related V1 inhibition serves no function in early development; if so, then disinhibiting retinal input during active wake should not affect the development of retinotopy. No such experiment has yet been performed.

It is also possible that cortical inhibition during active wake serves a similar function across sensory modalities. In adults, active wake is associated with distinct patterns of

neuromodulatory activity [48–50], and many of these neuromodulators (e.g., acetylcholine, norepinephrine) are present in rat cortex in the first postnatal week [51–53]. Thus, increases in neuromodulatory activity during active wake may interfere with cortical plasticity in a way that disrupts cortical topographic development, regardless of sensory modality.

Discovering the neural mechanisms that produce wake-related cortical inhibition of sensory input will permit precise experimental manipulations of these systems. Determining whether these manipulations alter topographic development will be important for understanding the contributions of behavioral state to the development of sensory systems.

Conclusions

In contrast with what we know about development in the visual and somatosensory systems, our knowledge of other modalities is still quite limited. But some parallels are apparent. For example, in the auditory system before the opening of the ear canal, the cochlea produces localized patterns of activity similar to those produced by twitches and retinal waves [54, 55]. Further, in ferrets, auditory stimuli can drive A1 activity at very early stages of cortical development [56] and trigger spindle bursts in premature human infants [13]. Given that cochlear projections are well developed in rats a week before the ear canals open [57], the spontaneous, structured activity in the cochlea may help produce tonotopic maps in auditory cortex before the onset of hearing. It is not known whether activity in A1, as in V1, S1, and M1, is modulated by behavioral state.

It is hard to imagine a study today of sensory processing in adult animals in which the investigators fail to mention whether their subjects were asleep or awake. As we now know, for studies of sensory processing in infant animals, similar attention must be provided to behavioral state. Moreover, because rat pups cycle so rapidly between sleep and wake—with individual bouts typically much shorter than a minute [58]—the functional status of sensory systems is changing rapidly. Keeping track of behavioral state requires some effort, but doing so is critical for accurately assessing sensory processing in early development.

If behavioral state is important for accurate assessments of early sensory processing, it follows that the use of anesthesia should be avoided whenever possible. This includes experiments that employ “light anesthesia” such that subjects are pacified still exhibiting some spontaneous behavior [14]. In infant rats, even light anesthesia interferes with the expression of behavioral states and alters the patterning of spontaneous neural activity and sensory responses [5]. In adults, anesthetics reduce or even eliminate sensory responses in higher-

order cortical areas and thalamic nuclei by inhibiting thalamocortical loops [59].

Research into the development of sensory-driven cortical activity has typically ignored behavioral state. Today, with the emergence and refinement of methods for conducting neurophysiological experiments in unanesthetized infant animals [60], we are now able to provide a more comprehensive understanding of the mechanisms and functions of state-dependent sensory processing within and across modalities. As described here, recent work in rats demonstrates that it is the state of active sleep, not active wake, that is best positioned to promote developmental plasticity in the somatosensory system. Further, given the many similarities between developing rats and humans with respect to the prevalence of active sleep, the occurrence of twitch-triggered spindle bursts against a background of discontinuous cortical activity, and the late onset of motor control by M1, it seems likely that additional similarities will emerge and translational opportunities will present themselves. Ultimately, increased attention to the role of sleep-wake states in modulating the functional properties of the developing nervous system will be critical to achieving a comprehensive understanding of intramodal and intermodal sensory development and plasticity.

Compliance with Ethical Standards

Conflict of Interest James C. Dooley, Greta Sokoloff, and Mark S. Blumberg each declare no conflict of interest.

Human and Animal Rights Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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