COMMENTARY

The Sleep-Like Nature of Early Mammalian Behavioral Rhythms: Theoretical Comment on Todd et al. (2010)

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Early sleep patterns lack several of the major defining physiological criteria used to identify sleep states in adult animals, but many typical aspects of mature sleep can nevertheless be demonstrated at surprisingly early stages of development. In Todd, Gibson, Shaw, & Blumberg (2010), the ability to compensate for enforced sleep deprivation is found to be present already shortly after birth in laboratory rats, an altricial mammalian species. Whereas the brainstem is capable of resisting enforced wakefulness by an increasing “pressure” to fall asleep, “catch-up” replacement of the lost sleep by means of longer subsequent sleep durations requires forebrain participation. This investigation represents an initial foray into the theoretically important area of the ontogeny of homeostatic regulatory mechanisms for behaviorally crucial neurophysiological processes.

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“Sleep” as a concept must have begun with recognition, since no cognizant organism, let alone ourselves, could have failed to be struck with the qualitative difference between its fellow beings—or itself for that matter—while awake and when sleeping. The behavioral difference between being alert and upright as opposed to recumbent and scarcely responsive is so great as to create an unmistakable perceptual core of two completely different states of being. So great, in fact, that there could have been no danger of confusion in subsuming many species-specific instinctive variants of body position, type of sensory response, or degree of movement under one or the other of these categories, to which some sort of gestural or guttural designation must have been assigned very early in human evolution . . . “Call it sleep” (as opposed to wakefulness): for example, Moruzzi, 1969.

The need for an explicit verbal definition must have arisen only when confronted with behaviors that closely resemble one another but which have some strikingly deviant aspects, in other words when boundaries between recognizably distinct clusters of behavioral states turn out to be not so sharp as they seemed at first. Even then, however, certain deviations are readily allocated to one or other of the existing classes: talking, walking, fighting or otherwise acting out in vacuo (Tinbergen, 1951) when obviously not in a waking state are unproblematically acceptable as aberrant sleep conditions, whereas hysteric, berserk, dazed, or paralyzed conditions can still be recognized as forms of “wakefulness.”

Many such parasomnias and other borderline behavioral states have been discovered and investigated in recent years (see Schenck, 2005), some of which are so hybrid (Voss, Holzmann, Tuin, & Hobson, 2009) as to make classification as either sleep or wakefulness a semantically dubious venture. At the other extreme, even such a distinctive behavioral state as “rapid-eye-movement” sleep (Jouvet, 1967) fails to engender any serious discussion about its classification as a sleep state. Short bouts of global body movements occur repeatedly during “quiet” sleep, moreover, and these are generally regarded simply as being an intermittent component of that state despite the fact that they have all the hallmarks of brief brainstem arousals (Corner, 1985).

Quantitative physiological criteria have been employed in recent years to unequivocally establish the presence of what must reasonably be called “sleep,” as opposed to merely “resting,” in a wide variety of poikilothermic vertebrates and invertebrates (e.g., Tononi & Cirelli, 2006). Even parasomnic phenomena such as migrating birds sleeping on the wing or cetaceans swimming while half asleep could only have been revealed by appropriate brain activity measurements (Siegel, 2009). The problem of accurate classification becomes still more acute when the question arises of the extent to which the spontaneous motility that characterizes early ontogeny throughout the animal kingdom (Corner, 1977, 1987) might be analogous to, or even homologous with, rapid-eye-movement (REM) sleep in mature homeothermic organisms. Application of modern recording methods carries with it the danger, however, of redefining sleep and wake states on the basis of what are merely newly discovered aspects of these states as originally considered.

The last-mentioned problem is especially acute in developmental studies: I still recall vividly some discussions in which my (apparently premature!) vision of an ontogenetic continuum ranging from spontaneous fetal motility cycles to mature sleep patterns (Corner, 1977, 1987) was countered with such arguments as: “by definition (sic) there’s no such thing as quiet (= ’slow-wave’) sleep prior to the appearance of a delta wave EEG in the neocortex,
whereas ‘paradoxical’ (= REM) sleep is a contradiction in terms prior to the appearance of EEG desynchronization. Given the fact that, in addition, very early sleep is often characterized by a variety of atypical phenomena (from an adult sleep perspective) such as exaggerated, diffusely generated movements, absence of total muscular atonia, and loosely coordinated multiple motility cycles, arguments have been advanced for calling this state, at best, ‘PRE-sleep’ (Frank & Heller, 2003).”

Todd, Gibson, Shaw, & Blumberg (2010) represents, in contrast, a continuation by the Blumberg laboratory to explore early manifestations of the phenomena typically associated with mature sleep, especially of the active or REM variety, and by so doing to emphasize the lifelong presence of an underlying primitive physiological state of being (Blumberg, 2010; Blumberg, Seelke, Löwen, & Karlsson, 2008). Not that there are no semantic problems in defining the onset of such a state—who in their right mind, for instance, would regard a quiescent embryo prior to neuromuscular differentiation as being asleep—but at what point does the similarity between prenatal intermittent spontaneous body twitching (Hamburger, 1973; Corner, 1977), which itself undergoes major progressive as well as abrupt changes as maturation proceeds (Corner, 1985, 1987), and “sleep-with-jerks” (Jouvet, 1967) alternating with quiescent periods become simply too great to be dismissed?

Despite some difficulty at very early stages of development in consistently recognizing sufficiently coherent variables to justify their classification as a repetition of discrete states (de Vries, Visser, & Prechtl, 1982; Dreyfus-Brisac, 1975), quantification of the relative proportion of active to total sleep time as a function of postnatal age results in a smoothly monotonically descending curve whether or not polygraphic criteria are used (Mirmiran, van de Poll, Corner, van Oyen, & Bour, 1981; Seelke, Karlsson, Gall, & Blumberg, 2005; Seelke & Blumberg, 2008). This fact certainly justifies the authors’ claim in their present and previous papers that this is likely to be a reflection of progressive changes taking place within one and the same underlying system, modulated successively by influences from later maturing regions of the brain. At the same time, however, the argument may be skirting the borders of tautology by isolating, for purposes of definition, a restricted aspect of REM sleep (viz., spontaneous movements against a strongly hypotonic muscle tonus level) from a complex of physiological variables whose inconsistent association was one of the reasons for questioning this designation in the first place (see Frank & Heller, 2003).

The Blumberg laboratory has gone on to identify a number of light anesthesia (Golshani et al., 2009) implicates them as being sleep-like in nature.

Todd et al. (2010) pursues this line of enquiry further into the general area of neuroplasticity (Blumberg, Middelmis-Brown, & Johnson, 2004), by examining one of the most striking activity-dependent aspects of mature sleep, namely its proclivity for rebounding following prolonged deprivation (see Borbély, 2001). The authors make the important observation that even a partial reduction in sleep time over a 30-minute period in neonatal rats, using a nonstressful brief cold stimulus, leads to an immediate post-treatment enhancement of sleep bout duration as well as of total sleep time, declining toward baseline values over a period of an hour. In addition, sleep pressure (i.e., the effort required to keep the animal awake) increases steadily throughout the deprivation period. A homeostatic aspect of sleep, well-known from adult studies (Borbély, 2001), could hereby be shown to be operative at extremely immature stages of maturation. Implicitly, sleep must therefore be important enough to be maintained at a certain level although, as in adult animals, the reason(s) why this should be so still need to be elucidated (Siegel, 2009; Tononi & Cirelli, 2006; Vassali & Dijk, 2009).

The adult dissociation between pressure and rebound is also shown in Todd et al. (2010) to be present already in early neonatal rats, and the interesting observation is made that forebrain structures are required for the latter but not the former phenomenon. The pinpointing of hypothalamic nuclei that respond especially strongly to sleep deprivation is in line with the strong involvement of the hypothalamus for “paradoxical” sleep regulation in adult cats (Jouvet, 1988). The absence of sleep rebound in decerebrated rats is nonetheless somewhat surprising in view of the ubiquity of this phenomenon throughout the animal kingdom (see McNamara, Barton, & Nunn, 2009), which might have suggested that it would prove to be a primitive property of neural networks in general. In any case, even isolated forebrain structures developing in vitro typically respond to a reduction in spontaneous burst firing by increasing their activity well above the control level upon return to normal medium (Corner, 2008; Corner, van Pelt, Wolters, Baker, & Nuytinck, 2002).

The authors’ supposition that, because of the predominance of REM sleep during the first few weeks of postnatal life sleep, the rebound effect should be more pronounced in REM than in quiet sleep needs to be empirically verified and quantified. Given the strong enhancement of synchronized delta waves following sleep deprivation, and the fact that these bioelectric potentials originate within the forebrain (see Corner, 1994, 2008) whereas REM sleep is a brainstem generated state (Jouvet, 1967), makes it plausible to expect that the slow-wave as well as the desynchronized phase of the sleep cycle contributes strongly to the reported rebound.

Recent unpublished experiments have made the unexpected observation that prolonged desynchronized tonic firing, induced in developing cortical networks in vitro by the cholinergic agonist carbachol, has (upon return to control medium) an enhancing effect on phasic spontaneous slow-wave generation similar to that caused by tetrodotoxin induced suppression of bioelectric activity (see Figure 1). This finding implicates the neocortex itself as a source of the intensification (rebound) of synchronized neuronal burst firing that is observed during quiet sleep following hypometabolic states such as torpor and hibernation as well as after prolonged wakefulness (Borbély, 2001). Computer simulation
studies have established that simply a global increase in excitatory synaptic connectivity suffices to account for such enhancement (Esser, Hill, & Tononi, 2007).

Extracellular glutamate concentrations in the neocortex increase progressively during desynchronized neuronal activity, in REM sleep as well as waking (Dash, Douglas, Vyzazovskiy, Cirelli, & Tononi, 2009), and cerebral glutamate availability is an important rate-limiting factor in the emergence of synchronized EEG slow-waves during ontogeny (see Corner, 1994). Conversely, cortical glutamate concentrations decline during non-REM sleep, in parallel with a reduction in the intensity of phasic EEG activity (Dash et al., 2009). This demonstration of functionally coupled glutamate homeostasis is thus in accordance with in vitro observations that prolonged suppression of spontaneous bursting leads to greatly enhanced synchronized neuronal activity—that is, a rebound effect—upon return to normal medium (see Figure 1), whereas chronic intensification has the opposite effect (reviewed in Corner, 2008).

The emerging picture from all these studies is that developing cortical networks have an intrinsic tendency to become more and more excitable, but that this tendency is counteracted by phasic (burst) firing during slow-wave sleep (and possibly to some extent also during REM in the form of repetitive widespread PGO waves: see Jouvet, 1967; Shaffery & Roffwarg, 2009). The desynchronized neuronal activity characteristic of normal cortical arousal episodes apparently lacks such a capacity to prevent an increase in network excitability, so that pressure is built up during waking and REM sleep which eventually helps trigger the onset of restorative slow-wave activity. A multiplicity of cellular mechanisms has been found to be involved in such regulation (see Corner, 2008), and the origins of the multiple homeostatic set-points that govern the overall balance between excitation and inhibition constitute one of the major unknowns in developmental physiology. Pioneering work such as in Todd et al. (2010), enquiring into activity-dependent brain and behavior mechanisms operating early in life, thus represents the spearhead of important future research.

The model sketched above further implies that the inordinate amounts of REM sleep seen very early in ontogeny are not necessarily serving only to provide needed excitation for brain development in the absence of adequate sensory stimulation (see Shaffery & Roffwarg, 2009). On the contrary, REM sleep may also be preventing intrinsically generated synchronized burst activity from tempering the initially rapid establishment of diffuse intracortical excitatory interconnections (Corner, 1994, 2008). As maturation progresses, the need for an optimal global balance between neuronal excitation and inhibition would be met by an increasing replacement of dispersed tonic by coherent phasic firing during sleep, thus attenuating intrinsic excitatory developmental processes within the cerebral cortex.

Since, as discussed above, the tendency toward synchronized bursting is enhanced by its own absence, EEG maturation during sleep reflects a higher level homeostatic mechanism, operating within a restricted ontogenetic window and over a longer time scale than daily sleep/wake oscillations. As such, it offers still another golden opportunity for developmental physiologists, such as those at the Blumberg laboratory, who are dealing with such theoretically fundamental research questions.

Figure 1. Representative 20 s stretches (10 s in the lower right-hand panel) of relative total spike counts in consecutive 100 ms bins recorded from a spontaneously active neonatal rodent neocortex network cultured in vitro for two weeks on a 60-electrode matrix. Subsequent assay: (left-hand panels) in normal growth medium; (central panels) after 1 h in carbachol containing medium; and (right-hand panels) 1 h after return to normal medium on the following day. The bottom traces are from a culture treated from the preceding day with tetrodotoxin prior to assay (after 1 h) in control medium. [These experiments are part of a series carried out in April-May, 2009, while the author was a visiting investigator at the Technion Israel Institute of Technology, Haifa: Network Biology Research Laboratory.]

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