E. J. W. Van Someren et al. (Eds.)
Progress in Brain Research, Vol. 193
ISSN: 0079-6123

CHAPTER 14

Sleep and developmental plasticity: not just for kids

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Abstract: In a variety of mammalian species, sleep amounts are highest during developmental periods of rapid brain development and synaptic plasticity than at any other time in life [Frank, M. G. & Heller, H. C. (1997a). Development of REM and slow wave sleep in the rat. *American Journal of Physiology, 272*, R1792–R1799; Jouvet-Mounier, D., Astic, L., & Lacote, D. (1970). Ontogenesis of the states of sleep in rat, cat and guinea pig during the first postnatal month. *Developmental Psychobiology, 2*, 216–239; Roffwarg, H. P., Muzio, J. N., & Dement, W. C. (1966). Ontogenetic development of the human sleep-dream cycle. *Science*, 604–619]. Many of the mechanisms governing developmental plasticity also mediate plasticity in the adult brain. Therefore, studying the role of sleep in developmental plasticity may provide insights more generally into sleep function across the lifespan. In this chapter, I review the evidence that supports a critical role for sleep in developmental brain plasticity. I begin with an overview of past studies that support a role for sleep in general brain maturation. This is followed by more recent findings in the developing visual cortex that more specifically address a possible role for sleep in cortical plasticity.

Keywords: ontogeny; development; plasticity; endogenous; function; synaptic.

Historical approaches to neonatal sleep function

Scientific views about sleep in early life have been greatly influenced by the seminal work of Howard Roffwarg and colleagues. In their present classic study in human infants, Roffwarg et al. (1966) proposed that the large amounts of rapid-eye-movement (REM) sleep in early infancy provide an important source of endogenous neural activity necessary for brain maturation. In the more recent formulations of the "Ontogenetic Hypothesis," it is suggested that REM sleep not only promotes normal brain development but also regulates experience-dependent plasticity (Oksenberg et al., 1996; Roffwarg and Shaffery, 1999). Not surprisingly, many experiments have been designed to test predictions of the Ontogenetic Hypothesis.

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DOI: 10.1016/B978-0-444-53839-0.00014-4

Correlation-based studies

The first are those which have shown associations or correlations between the amount of sleep or sleep phasic activity (e.g., REMs) and certain indices of brain development. For example, placing juvenile rats in enriched environments increased brain weight and REM sleep amounts (Mirmiran et al., 1982). This correlation is intriguing because increases in REM sleep are also reported in adult animals during learning tasks and may be necessary for the consolidation of the learned material (reviewed in Benington and Frank, 2003). Associations were also reported between the frequency of REMs and subsequent eye-opening in the rat, suggesting that endogenous activation of visual motor circuits might prepare the brain for visual experience (Van Someren et al., 1990). In agreement with findings in adult animals (Nakanishi et al., 1997; Ramm and Smith, 1990), Czikk et al. (2003) found that cerebral protein synthesis (as measured by [(14)C] Leucine uptake) was elevated during fetal non-REM sleep, suggesting that sleep may promote morphological or structural changes in the developing brain.

Pharmacological sleep deprivation

A second class of experiment employs REM sleep deprivation (RSD) in the postnatal period followed by behavioral/neurological/biochemical assessments. The majority of these experiments use systemic treatments with REM sleep-inhibiting drugs (e.g., antidepressant medications) in the perinatal period. These treatments induce a number of neurochemical and behavioral abnormalities in adult rats, including changes in REM sleep architecture (Mirmiran et al., 1981, 1983b) circadian rhythms (Dwyer and Rosenwasser, 1998; Klemfuss and Gillin, 1997; Yannielli et al., 1998), anxiety and sexual behavior (Hilakivi and Hilakivi, 1987; Hilakivi and Sinclair, 1986; Hilakivi et al., 1987; Vogel et al., 1990), and alterations in neurotransmission (Henderson et al., 1991; Hilakivi et al., 1987; Prathiba et al., 1998, 2000). However, the behavioral effects are often not uniform across studies and vary depending on the drug (File and Tucker, 1983; Frank and Heller, 1997b).

The chief weakness of these studies is that it is impossible to separate the effects of RSD *per se* from nonspecific teratogenetic effects induced by these drugs. For example, most of the deficits are probably caused by persistent alterations in monaminergic function. Changes in adult sleep architecture ascribed to pharmacological RSD are only observed following neonatal treatments with agents that alter serotonergic neurotransmission. Other REM sleep-inhibiting compounds administered neonatally have no effect on subsequent adult sleep patterns (Frank and Heller, 1997b). Likewise, the changes in anxiety and sexual behavior reported after neonatal RSD are more likely due to abnormalities in serotonergic neurotransmission than RSD. Agents (e.g., PCPA) that reduce serotonin and REM sleep in neonatal rats decrease anxiety and increase sexual behavior in adulthood; effects that are precisely opposite to those reported after neonatal clomipramine administration (Adlard and Smart, 1974; Farabollini et al., 1988; Wilson et al., 1986). Since both compounds decrease REM sleep but have opposite effects on serotonin levels, it is unlikely that pharmacological RSD contributes to the behavioral changes noted in later life. Interestingly, gentle forms of mechanical RSD do not produce the suite of deficits reported after neonatal clomipramine exposure (Mirmiran et al., 1983a). More vigorous, chronic mechanical RSD produces some effects similar to pharmacological RSD (Feng, 2001), but the interpretation of this study is complicated by the chronic stress likely imposed on the animal.

Sleep and subcortical development in central visual pathways

A series of studies in the 1980s demonstrated a potential role for REM sleep in the early development of the LGN. Davenne and Adrien examined

changes in neuronal morphology in the LGN in kittens after lesioning PGO generating centers in the brainstem (Davenne and Adrien, 1984). Bilateral electrolytic lesions in the rostral pontine tegmentum abolished PGO waves in the neonatal cat, resulting in smaller LGN volumes and reduced LGN soma sizes. A second study showed that PGO wave elimination resulted in much slower LGN responses to stimulation of the optic chiasm (compared to control cats), and also more LGN cells with "mixed" ON–OFF responses (as opposed to pure "ON" or "OFF" responses to an annulus of light centered in the receptive field), and fewer X cell responses (relative to ON–OFF responses; Davenne et al., 1989). These morphological and functional changes in LGN cells are consistent with delayed development in the LGN (Daniels et al., 1978; Williams and Jeffery, 2001) and suggest that REM sleep neuronal activity may be necessary for normal LGN development.

Sleep and developmentally regulated cortical plasticity in vitro

REM sleep has also been reported to play an important role in a developmentally regulated form of long-term potentiation (LTP; Shaffery et al., 2002). In this type of LTP, high-frequency white-matter stimulation in cortical slices prepared from (postnatal (P) day 28–30 rats produces synaptic potentiation in cortical layers II/III. This form of LTP decreases with age (P35+) and is not observed in cortical slices from adult rats (Kirkwood et al., 1995). Using a less stressful version of the pedestal technique of RSD (multiple small-platform), Shaffery et al. (2002) measured the effects of 1 week of RSD on this form of LTP in rat visual cortex.

The authors reported that 1 week of RSD prolonged the critical period for the developmentally regulated form of LTP (LTP was evoked from slices of visual cortex from RSD rats at ages when this type of LTP is not normally observed; P34–P40). A similar extension of the critical period was not seen in cortical slices from control rats that were left in their nests or from rats placed on larger platforms (large-platform control) that presumably permitted REM sleep. Conversely, RSD had no effect on a non-developmentally regulated form of LTP evoked by layer IV stimulation. The extension of the critical period by RSD was similar to effects produced by dark rearing, which also prolongs the period of induction of this form of LTP (Shaffery et al., 2002). These findings suggest a maturational delay in visual cortex and are in general agreement with previous findings from the same group suggesting that RSD impairs normal brain maturation.

Sleep and morphological plasticity in the LGN

Blocking vision in one eye (monocular deprivation, MD) during a critical period of development alters responsiveness and morphology in LGN neurons (reviewed in Sengpiel et al., 1998; Singer, 1979). Several studies indicate that total sleep deprivation or selective RSD augments the effects of MD on LGN cells (Oksenberg et al., 1996; Pompeiano et al., 1995). Oksenberg et al. (1996) found that LGN cells innervated by the occluded eye were smaller in kittens deprived of REM sleep, resulting in a greater difference in the size-ratio of LGN cells activated by both eyes. A similar increase in LGN cell size disparity was found when MD was combined with brainstem lesions that remove PGO waves. In this case, LGN cells receiving input from the open eye appeared to increase in size (Shaffery et al., 1999). An additional, somewhat unusual finding is that RSD combined with MD also reduces cell sizes in the monocular segment of the LGN, which does not depend upon competitive interactions between the two eyes (Shaffery et al., 1998). Work from this laboratory has also shown that RSD for 1 week reduces immunoreactivity for the parvalbumin in GABAergic

interneurons in the developing LGN (Hogan et al., 2001). These latter findings are interesting since parvalbumin may play a role in certain forms of synaptic plasticity (Caillard et al., 2000). In sum, these results suggest that RSD or RSDP may influence morphological plasticity in the LGN.

Sleep and ocular dominance plasticity

Ocular dominance plasticity (ODP) refers to physiological and anatomical changes in visual cortical circuits triggered by alterations in binocular vision. Although originally described in developing animals (Hubel and Wiesel, 1970; Wiesel and Hubel, 1963), ODP also occurs in the adult brain (Sato and Stryker, 2008; Sawtell et al., 2003) and shares in common numerous mechanisms that mediate plasticity in the hippocampus and nonsensory cortex. For example, like hippocampal-based synaptic plasticity, ODP involves AMPA receptor (AMPAR) trafficking, NMDAR activation, kinases (e.g., PKA, CaMKII, ERK), acetylcholine and monoamines, neurotrophins, protease activity, CREB activity, and protein synthesis (Abel and Lattal, 2001; Bear et al., 1990; Berardi et al., 2003, 2004; Chen and Bear, 2007; Cho et al., 2009; Citri and Malenka, 2007; Gu, 2002; Heynen et al., 2003; Jedlicka et al., 2008; Laurent and Wetbrook, 2008; Liao et al., 2002; Lynch, 2004; Lynch et al., 2007; Mataga et al., 2002, 2004; Taha and Stryker, 2002; Tropea et al., 2009). It is now widely recognized as a canonical model of synaptic plasticity *in vivo* (Spolidoro et al., 2008; Tropea et al., 2009).

ODP has several characteristics that make it especially suited for investigating the role of sleep in brain plasticity. First, it occurs in the intact, unanaesthetized brain and is triggered by natural forms of stimuli (i.e., changes in vision as opposed to artificial trains of action potentials). Second, it is associated with behavioral outputs that have adaptive significance for the animal (stereoscopic vision and acuity) and is well-described on a cellular level (Taha and Stryker, 2005; Tropea et al., 2009). Changes in ocular dominance occur within hours, which allows for minimal manipulations of sleep and wake in the experimental design (Frank et al., 2001). Third, the study of ODP has provided important insights into synaptic plasticity in other sensory systems (Tropea et al., 2009). Therefore, by demonstrating a role for sleep in this system, one may solve the deeper mystery of how sleep interacts with specific plasticity mechanisms across the lifespan and in many parts of the brain.

Early investigations of ODP

We began our investigations by combining MD with periods of sleep or sleep deprivation (Frank et al., 2001; see Fig. 1). Kittens at the height of the critical period were divided into four experimental groups, all of which had one eye closed and were kept awake in a lighted environment for 6 h. This MD period provided a common stimulus for the synaptic remodeling in all groups. The four groups differed in their experience thereafter. Cats in the "MD-only" group (MD6) were then immediately anesthetized for physiological measurement of ocular dominance in primary visual cortex using optical imaging of intrinsic cortical signals and microelectrode unit recording. Cats in a second group (MDS) were allowed to sleep *ad lib.* for 6 h in complete darkness before plasticity was assayed. The third group of kittens (MDSD) were treated identically to those in the MDS group except that they were kept awake, rather than allowed to sleep, during the 6 h in complete darkness. The fourth group (MD12) was also kept awake for six additional hours but remained in a lighted environment, effectively giving them six additional hours of MD before the recordings.

Optical imaging of intrinsic cortical signals and extracellular unit recording showed that sleep approximately doubled the effects of MD, while wakefulness in complete darkness tended to erase

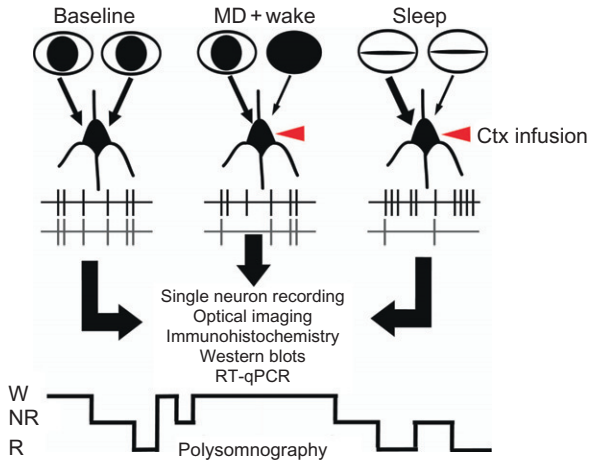

Fig. 1. Investigating sleep-dependent plasticity in the developing cortex *in vivo*. The effects of experience and sleep on plasticity can be separately measured in developing cats. (a) Following a 6-h baseline period, plasticity is induced by 6 h of monocular deprivation (MD) in an awaken animal. This initiates a shift in visual responses in favor of the nondeprived eye that is enhanced by sleep and prevented by sleep deprivation. Changes in plasticity, proteins, and mRNAs are measured in each phase of the experiment in separate groups. The necessity of a signaling pathway during waking MD or post-MD sleep can be determined using intracortical infusion (red arrow "Ctx") of receptor or kinase agonists or antagonists. Polysomnography allows for quantitative measurements of wakefulness (W), non-REM sleep (NR), and REM sleep (R) during all phases of the experiment. The black and gray lines represent idealized unit spike rasters generated by right eye or left eye (deprived) stimulation, respectively. RT-qPCR: real-time quantitative polymerase chain reaction.

the effects of the preceding visual experience. Interestingly, no brain state other than sleep is known have such augmenting effects on ODP since anesthetic states and cortical inactivation suppress ODP (Freeman, 1979; Imamura and Kasamatsu, 1991; Rauschecker and Hahn, 1987; Reiter et al., 1986). Nor could these results be ascribed to indirect effects of the sleep deprivation procedure (e.g., motor activity, stress). Plasticity in the MD12 cats (who were awake as long as the MDSD cats) was normal. In addition, ODP is remarkably resistant to the effects of the principal stress hormone corticosterone (Daw et al., 1991).

Revealing the cellular mechanisms

Subsequent investigations have shown that this form of sleep-dependent plasticity requires cortical neuronal activity (Jha et al., 2005). Using a modified version of the experimental design described above, we found that reversible inactivation of the sleeping visual cortex (after a preceding period of MD) inhibited the enhancement of ODP normally observed after sleep. These results were not due to abnormal sleep or visual processing upon testing—as sleep architecture and basic visual response properties were unchanged in infused animals. Interestingly, additional sleep (with cortical activity restored) did not "rescue" ODP. This indicated that sleep immediately following waking experience was critical for the consolidation of this type of plasticity. Similar results were obtained following cortical infusion of the GABA-A receptor agonist muscimol (Frank et al., 2006). Since muscimol predominantly reduces postsynaptic activity while sparing presynaptic input, these findings indicated that the underlying mechanisms were postsynaptic.

We next explored the nature of this postsynaptic mechanism by examining the role of the NMDA receptor. NMDA receptor(R)s mediate many forms of plasticity both *in vitro* and *in vivo* (Malenka and Bear, 2004) and have been implicated in long-term memory consolidation (Wang et al., 2006), a process that may be specifically enhanced by sleep (Born et al., 2006; Walker and Stickgold, 2004). To determine if NMDAR and downstream kinase activation during sleep governs sleep-dependent ODP consolidation, we performed three experiments. First, using the same basic design described above, we infused the NMDAR antagonist APV, the PKA inhibitor Rp-8-Cl-cAMPS, or as a control vehicle-only into the visual cortex during post-MD sleep. Second, using Western blot analyses, we examined sleep-dependent changes in the activity of kinases activated by the NMDAR and the phosphorylation of GluR1 AMPAR subunits at sites known to mediate NMDAR-dependent LTP. Third, to determine if reactivation of remodeling neuronal circuits occurred during sleep (an event that would lead to NMDAR activation), we chronically recorded multiunit activity from the visual cortex in freely behaving animals before, during and after a period of MD (Aton et al., 2009b).

We found that intracortical inhibition of the NMDAR or the downstream kinase PKA completely blocked the normal enhancement of ODP observed after sleep. As was true for our studies using reversible inactivation, a series of control experiments showed these results could not be ascribed to side-effects of pharmacopeia. Interestingly, Western blot analyses and electrophysiological measurements of single-neurons suggested that sleep specifically strengthened cortical circuits in favor of the nondeprived eye. After sleep, kinases downstream of the NMDAR (CaMKII and ERK) and the AMPA receptor were phosphorylated in a manner consistent with LTP and responses to the nondeprived eye became stronger. Chronic, longitudinal MUA recording in freely behaving animals showed that remodeling cortical circuits transiently increased their activity at times when this kinase activation was maximal. In sum, these findings strongly suggest that synaptic changes in wakefulness are consolidated by cortical reactivation and a secondary series of NMDAR- and kinase-mediated signaling cascades during sleep (see Fig. 2).

Probing the impact of hypnotic sleep in early life

ODP can also be used to probe the effects of commonly prescribed psychotropic medications

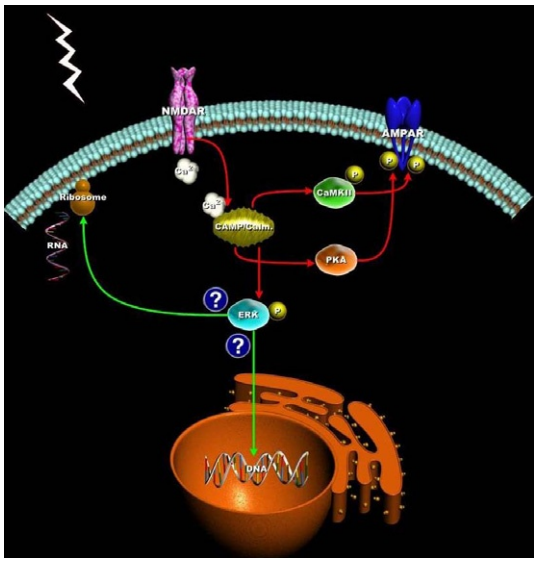

Fig. 2. Mechanisms governing sleep-dependent, developmental plasticity. Cortical activity (indicated by lightning bolt) is required for sleep-dependent plasticity, as this process is prevented when the sleeping cortex is reversibly silenced with cation blockers or GABA-A (R)eceptor agonists. The activity-dependent mechanisms are not entirely known but involve NMDAR receptors and protein kinase A (PKA), as inhibition of NMDAR and PKA during sleep also inhibits sleep-dependent plasticity. Suspected downstream events of NMDAR activation include CAMP/calmodulin activation and phosphorylation of CaMKII, PKA, and ERK. Activation of CaMKII and PKA results in phosphorylation of AMPAR which promotes the trafficking and insertion of AMPAR into the postsynaptic membrane. The significance of ERK signaling in sleep is unknown, but ERK can promote mRNA transcription and translation.

on sleep-mediated functions. Such research is critically important as the use of these medications is on the rise in the general pediatric/adolescent population and within special clinical populations (e.g., autism, bipolar disorder; Mindell et al., 2006; Scharf and Williams, 2006; Vitiello, 2007). For example, the use of antidepressants in children and adolescents in the United States increased by 150% between 2000 and 2005 (representing 2.5% of all patients referred to a pediatrician; Bonati and Clavenna, 2005). The prevalence of childhood/adolescent mental disorders currently treated with psychotropics, as a whole, is also considerable (e.g., major depressive disorder 5–15%; obsessive compulsive disorder 1–3%; ADHD 6.7%; Bonati and Clavenna, 2005), and stimulants and hypnotics have become increasingly common drugs of abuse in children, adolescents, and young adults (Rogers and Copley, 2009). Nevertheless, little is known about the acute and long-term effects of these agents on the developing brain.

We explored the effects of several commonly used hypnotic agents on the sleep-dependent consolidation of ODP (Aton et al., 2009a; Seibt et al., 2008). In two parallel studies, developing cats underwent a period of MD, as described above, followed by *ad lib.* sleep combined with systemic administration of a benzodiazepine (triazolam), one of the following nonbenzodiazepines (zolpidem, eszopiclone, zaleplon), the melatonin agonist ramelteon, or the antidepressant trazodone (all at clinical dose ranges). With the exception of ramelteon, all hypnotics caused abnormal sleep architecture (either a reduction of REM sleep or EEG slow-wave activity, or both), but this was unrelated to changes in cortical plasticity. Of these hypnotic agents, only trazodone and zolpidem significantly reduced the amount of plasticity normally observed after sleep. These findings thus demonstrated that hypnotic agents increasingly used by developing humans may indeed have adverse effects on critical brain processes mediated by sleep.

Summary

The Ontogenetic Hypothesis, at least in broad strokes, appears to have stood the test of time. Although much less work has been done in this area compared to other areas in sleep biology, there is a core set of findings that supports a role for sleep in brain development and plasticity. There are also a number of intriguing, unanswered questions yet to be explored.

The relative roles of REM and non-REM sleep

One interesting question is the relative roles of different sleep states in brain development and plasticity. The Ontogenetic Hypothesis casts REM sleep as the critical brain state, but as has been suggested for adult mammals (Diekelmann and Born, 2010; Tononi and Cirelli, 2006; Walker, 2009), non-REM sleep may also be important. In our own studies, the precise contribution of REM and non-REM sleep to ODP consolidation awaits detailed investigation. However, we do find that the enhancement of cortical plasticity is highly correlated with non-REM sleep time (Frank et al., 2001).

A role for non-REM sleep in developmental cortical plasticity is further suggested by ontogenetic changes in non-REM sleep that coincide with periods of heightened cortical plasticity. In the cat, there is a rapid decline in REM sleep and a corresponding increase in non-REM sleep amounts near the beginning of the critical period for visual development (Jouvet-Mounier et al., 1970). In rats, the beginning of the critical period for visual development coincides with the development of non-REM sleep homeostasis. Sleep deprivation does not increase non-REM sleep EEG activity until the fourth postnatal week, indicating that the regulatory relationship between wake and non-REM sleep develops in parallel with periods of heightened cortical plasticity (Frank et al., 1998). These findings suggest that non-REM sleep may consolidate waking

experience; a process that begins during critical periods of brain development when the animal is most sensitive to waking experience but is retained throughout life.

Sleep and plasticity in developing and adult brains: same or different?

A related question is whether the effects of sleep on brain plasticity change across the lifespan. One possibility is that REM and non-REM sleep exert comparable effects on synapses at all ages, and what matters instead is the relative amount of each state. For example, REM sleep is maximally expressed when endogenous neuronal activity is critical for the establishment of rudimentary neural circuitry. Non-REM sleep seems to be more strongly associated with synaptic changes elicited by experience, since it rapidly matures after eye-opening (Frank and Heller, 1997a; Gramsbergen, 1976; Jouvet-Mounier et al., 1970) and becomes homeostatically regulated by wake in a manner similar to adult non-REM sleep during critical periods of experience-dependent synaptic plasticity (Frank et al., 1998). Thus, it is possible that the need for REM sleep wanes, just as the need for endogenous stimulation wanes, during the course of development. Non-REM sleep, on the other hand, being necessary for the consolidation of experience, retains its importance until senescence. However, this leaves unanswered the question of why REM sleep is still retained in adults, even if at a low level compared to what is observed in early life.

On the other hand, it might be that sleep in early life engages categorically different plasticity mechanisms than those in the adult brain. For certain developmental events, such as neurite outgrowth, neuron path-finding, etc., this seems a reasonable proposition. For experience-dependent plasticity—which occurs much later in development—this seems less likely. As described above, while there are differences between ODP and adult forms of plasticity (Sato and Stryker, 2008), they also share numerous mechanisms in common. Nevertheless, findings in this system at some point must be integrated with existing hypotheses concerning sleep and plasticity in adult brains. There are, for example, findings in adult animal consistent (Destexhe et al., 2007; Diekelmann and Born, 2010; Steriade, 1999) and seemingly at odds (Liu et al., 2010; Vyazovskiy et al., 2008) with our results in the visual cortex.

In conclusion, there are no definitive explanations for why infant animal sleep, just as there is no single, accepted explanation for why adult animals sleep. But over the last 40 years, there has been a steady (if slow) accumulation of findings strongly suggesting that sleep promotes brain development and plasticity. The slow growth of this field is not due to lack of imagination. The Ontogenetic Hypothesis was simply ahead of its time, proposed as it was when our knowledge of neural development and plasticity was … in its infancy. Times have changed and neuroscientists should now revisit this beautiful idea, armed with modern tools and concepts. They might be surprised at what they find.

Abbreviations

AMPAR	2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl)propanoic acid receptor
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
cAMP	cyclic adenosine monophosphate
CREB	cAMP response element-binding protein
ERK	extracellular-signal-regulated kinase
LGN	Lateral geniculate nucleus
LTD	Long-term depression
LTP	Long-term potentiation
MD	Monocular deprivation
NMDAR	*N*-methyl-D-aspartic acid receptor
ODP	ocular dominance plasticity
PCPA	*p*-chlorophenylalanine

PGO	pontine-geniculate-occipital
PKA	protein kinase A
RSD	REM sleep deprivation

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