diminished levels of dopamine in the striatum leads to hyperactivity of indirect-D2 containing MSNs and hypoactivity of direct-D1 containing MSNs, inducing an imbalance. Thus, reduced level of dopamine could be sufficient to increase FS-MSNs network actions within the indirect pathway generating an increase of the inhibition of D2 MSNs. However, the authors raised two important considerations. First, it is likely that DA depletion leads to a change in firing rate and firing pattern in basal ganglia structures. However, little is known about the long-term effect of DA depletion on the basal ganglia microcircuits. Although Gittis and colleagues show that FS microcircuits switch their functional connectivity from D1 MSNs, which predominate under normal conditions (Gittis et al., 2010), to D2 MSNs after DA depletion, how this reorganization of the striatum affects the function of target structures remains to be elucidated. The authors present a reasonable and simple model whereby the enhanced FS-D2 MSN connectivity and D2 MSN synchrony subsequently increases synchrony in downstream structures such as the STN and the GPe. Although in vitro preparations as used here present some limitations, as afferent processes may be partially severed, this study by Gittis and colleagues is nonetheless particularly provocative, and will probably open new doors for in vivo studies of target-specific reorganization of FS connectivity in intact animals.

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Life and Death Decision in Adult Neurogenesis: In Praise of Napping

Gabriel Lepousez[1,2] and Pierre-Marie Lledo[1,2,*]
[1]Laboratory for Perception and Memory Unit, Institut Pasteur, F-75724 Paris, France
[2]Centre National de la Recherche Scientifique, URA 2182, F-75724 Paris, France
*Correspondence: pmlledo@pasteur.fr
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Among the thousands of new neurons that integrate into the adult olfactory bulb each day, 50% are eliminated through apoptosis. In this issue of *Neuron*, Yokoyama et al. take steps toward deciphering the behavioral contexts that regulate newborn cell elimination.

Everybody has experienced the joy of digging with relish into their preferred meal. You enjoy every crumb and then, with a satisfied smile, you stretch and yawn. Before you know it, you feel drowsy and decide to take a quiet nap. Drowsiness is a subjective state that is commonly experienced following eating. After food consumption, a combination of blood-transported endocrine/metabolite factors and gastrointestinal feedback innervation to the brain contributes to postprandial drowsiness. However, the adaptive value of a postprandial sleep, if any, remains elusive and has been a focus of intense research in recent decades. While we all crave a good night's sleep (as testified by the lucrative market of sleeping pills), the reason why we spend about one-third of our life still and almost immobile is still a mystery. To provide some clues for this apparent conundrum, neuroscientists have studied the function of sleep in many animals from flies to humans. Many of these studies have pointed to potential link between sleep need and neural plasticity (Cirelli and Tononi, 2008). In particular, a common target across species, and across brain regions, seems to be the synaptic strength which increases

during wakefulness and returns to a baseline level during sleep (Cirelli and Tononi, 2008; Diekelmann and Born, 2010).

Since the pioneering work in 1925 by Hans Berger, we know that precise patterns of neural activity in the brain characterize the distinct states across the sleep-wake cycle (Tononi, 2009). These temporal dynamics can be monitored measuring electric field potentials and can be described as slow-wave activity during light sleep, rapid eye movement activity during profound sleep, and waking rhythms. According to the synaptic plasticity hypothesis, sleep serves an essential function by promoting dampening of potentiated synapses during awake state to minimize their energy consumption, reduce their physical volume, and prevent their strength from saturating. Thus, synaptic depression or downscaling during sleep may recalibrate synaptic weights down to a more responsive range (Cirelli and Tononi, 2008). In parallel to this homeostatic process, sleep has been shown to contribute to memory consolidation. Notably, repeated reactivation of activity patterns evoked during learning has been observed during slow-wave sleep both in rats and humans. This reactivation of memory traces ("replay"), which correlate with memory consolidation, may redistribute the neural representations of memory into cortical regions for long-term storage (Diekelmann and Born, 2010). With all these important functions, sleep is no longer considered a passive resting state, but rather an active brain state essential for neuronal plasticity.

In this issue of *Neuron*, Yokoyama et al. (2011) report exciting data extending this concept from synapses to neural circuits, illustrating an unexpected function of sleep in rescaling the number of neurons in the olfactory bulb (OB). In the OB, the first central relay of the olfactory system, adult neurogenesis provides a continuous source of new neurons that mature and integrate into the preexisting OB network to become mainly mature GABAergic granule cells. Alongside this integration is a selection process in which 50% of the new neurons undergo apoptosis during a specific critical window (Yamaguchi and Mori, 2005). How this selection process is regulated is the focus of intense study.

In this paper, the authors discovered that a food restriction paradigm exerts a peculiar effect on apoptosis of newborn cells. They first observed that while the degree of apoptosis is constant over time in mice allowed unlimited access to food, the number of apoptotic neurons increases strongly after eating when food is formerly and briefly restricted (for 4 hr). Interestingly, most of the apoptotic neurons were newly formed granule cells, confirming that the newborn neuron population is in constant turnover. More puzzling was the time course of this phenomenon: apoptosis approximately doubled two hours after animals begin eating. But food was not the only factor regulating cell death. Apoptosis was potentiated only when animals underwent a postprandial nap, and this correlated with postprandial sleep duration. When animals were selectively sleep deprived after eating, apoptosis was prevented. This phenomenon was also seen to a lesser extent in ad libitum feeding mice when the authors carefully monitored feeding and postprandial behaviors for each individual. By showing that the degree of apoptosis enhancement remains constant at different circadian times, the authors also ruled out potential circadian influences in this phenomenon.

What is the importance of sensory experience to this process? The OB is a great model to test experience-dependent phenomena since the sensory inputs can be easily manipulated and this manipulation can be restricted to one region of the OB, leaving other inputs intact. The authors used two strategies to reduce olfactory activity. They globally deprived the OB of sensory input by closing one nostril, and used a genetic model in which olfactory sensory neurons that innervate specifically the dorsal part of the OB are ablated by targeted expression of the diphtheria toxin gene. With these manipulations, the authors demonstrated that apoptosis is further potentiated during the postprandial period if the OB does not receive olfactory inputs, and is blocked by selective sleep deprivation after feeding. To balance this massive cell death, the authors also observed that local sensory deprivation promotes local recruitment of neuroblasts. They concluded that olfactory experience protects cells from death induced by postprandial sleep. Moreover, to disambiguate the role of food intake in this sensory input-dependent cell elimination, the authors showed that apoptosis still increases in mice entrained to the restricted food paradigm when no food is given but still experience subsequent sleeping behavior. Therefore, a combination of olfactory experience and subsequent sleeping behavior mediates profound reorganization of OB networks within an hour after feeding.

Adult-generated OB neurons are continually turned over, rather than simply added, and the precise balance between new and mature neurons is set through active elimination processes during a critical window. Previous studies have clearly demonstrated that odor learning in an associative task, but not simple exposure to an odor, can efficiently promote newborn cell survival within a critical period (14 to 35 days) after cell birth, while immature (7- to 13-day-old) and older cells are not affected (Mouret et al., 2008). Yokoyama and colleagues (2011) now describe a similar critical window for newborn neuron apoptosis in the context of postprandial sleep. This critical period corresponds to a maturation state when newborn cells first receive direct sensory inputs from principal cells of the OB and also top-down inputs from cortical regions such as olfactory cortex. These similar observations may encourage further studies to establish whether olfactory learning-induced cell survival is related to the postprandial cell elimination reported by Yokoyama et al. (2011). Bearing in mind the relationship between sleep and learning (Maquet, 2001), finding a correlation between the two phenomena should not come as a surprise. Interestingly, the comparison between both behavioral contexts highlights the fact that isolated sensory input alone has no effect. It is only when sensory experience is associated with learning or with postprandrial sleep, two processes that involve top-down inputs to the OB, that it can affect apoptosis. Thus, by detecting the coincidence of sensory and top-down inputs, newborn neurons are ideally positioned to support long-term of memory processes (Lazarini and Lledo, 2011).

One recent work has addressed the question of the biological significance of apoptosis in adult OB circuits (Mouret et al., 2009). Using local diffusion of a broad-spectrum caspase inhibitor, new neurons were significantly rescued from

apoptosis. In this condition, psychophysical tests indicated that a normal rate of new neuron elimination was essential for optimal olfactory exploration and for correct odor discrimination (Mouret et al., 2009). The data provided by Yokoyama and colleagues (2011) brings us one step closer to understanding the selection process that chooses newborn neurons for apoptosis. To explain sensory experience-dependent apoptosis associated with sleep, the authors suggest a two-step mechanism of "tagging" followed by a "selection" process. During the awake state, olfactory experience tags a subpopulation of newborn neurons which will be then selected to survive during subsequent sleep thanks to a "reorganizing signal" (Figure 1).

This model raises a number of important questions. To what extent can odor presentation protect newborn cells from apoptosis and what exactly is the nature of the olfactory signal? Is familiarity relevant? At the cellular level, the molecular mechanism of sensory-dependent cellular tagging is not known. Would a survival tag use a different molecular pathway from a death tag? Since older neurons are not affected by apoptosis, how does this process identify the age of the neuron? Once selected, is the newborn cell conserved for life or could it be tagged later for a subsequent elimination?

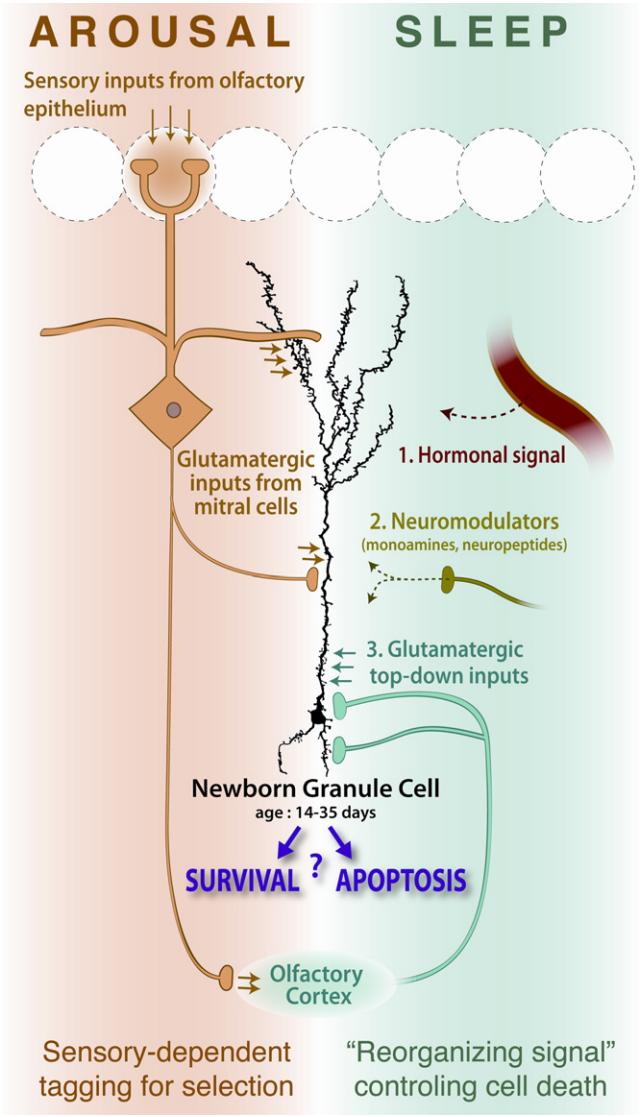

Figure 1. Newborn Granule Cells in the Olfactory Bulb (OB) Function as a Coincidence Detector for Life/Death Decisions

During arousal and feeding (left panel), mitral cells, the principal cells of the OB, activate and "tag" newborn granule cells, via dendritic and axonal release of glutamate (orange arrows). During subsequent sleep, a "reorganizing signal" triggers survival in "tagged" newborn neurons and apoptosis in "untagged" neurons. Three possible candidates for this "reorganizing signal" are here presented: blood-circulating hormones, neuromodulators and glutamatergic top-down inputs from the olfactory cortex. Drawing of granule cell is adapted with permission from Price and Powell (1970).

Regarding postprandrial sleep, the identity of the presumed "reorganizing signal" that prompts apoptosis of only new neurons is also not known. Moreover, some data suggest that this "reorganizing signal" may be also active outside of the sleeping period during specific behavioral contexts. For this signal, the authors suggest three candidates: blood-circulating hormones, neuromodulators such as monoamines or neuropeptides locally released in the OB, or top-down synaptic inputs coming from cortical regions such as olfactory cortex (Figure 1). This third candidate has gained recent interest. Glutamatergic top-down inputs from the olfactory cortex are the first glutamatergic contact to establish onto newborn neurons. These inputs undergo LTP specifically onto newborn neurons and not preexisting cells (Nissant et al., 2009) and they are particularly active during learning and slow-wave sleep (Manabe et al., 2011), two contexts known to modulate newborn cell apoptosis. Even if a causal link between synchronized top-down inputs from the olfactory cortex and newborn cell survival is still missing, this possibility also raises the question of how a precise synaptic activity would be able to trigger cell apoptosis in a very short time period of one or two hours (i.e., Hardingham et al., 2002).

Independent of the answers to these questions, it is clear that such a process is reminiscent of memory formation in the hippocampus. There, memory-related structural changes occur following the combination of learning experience during waking and neuronal activity during subsequent sleep and rest periods (Diekelmann and Born, 2010). Sleep-associated changes described in the OB by Yokoyama et al. (2011) also echo the homeostatic depression and downscaling of synapses that occurs during sleep in the hippocampus, with the significant distinction that selection in the OB occurs at the whole cell level rather than the synaptic level. This extreme form of structural plasticity at the level of cell population might be important for enhancing the storage capacity of the olfactory system, providing flexibility unmatched by synaptic plasticity and spine turnover alone. Moreover, adult neurogenesis offers a unique source of metaplasticity: newborn cells that are selected to survive experience long-term synaptic plasticity at their proximal inputs, a feature that is absent in preexisting neurons and that fades progressively with time.

The work of Yamaguchi and colleagues is the first to provide strong evidence for

the role of sleep on the structural reorganization of the OB. Recent data indicates that self-organized synchronous activity patterns, similar to the one occurring during hippocampal "replays" can be recorded in the olfactory system specifically during slow-wave sleep (Manabe et al., 2011). The field is now mature enough to search for traces of our exquisite olfactory dreams.

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