

Sleep on it: cortical reorganization after-the-fact

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Sleep can facilitate memory formation, but its role in cortical plasticity is poorly understood. A recent study found that sleep, following monocular deprivation (MD), facilitated cortical changes in ocular dominance. The magnitude of plasticity was similar to that observed after continued MD, and larger than that seen after sleep deprivation in darkness, suggesting that sleep *per se* enables mechanisms of cortical plasticity. Experience-dependent plasticity during sleep could be part of a more global process of memory consolidation.

The establishment of long-term memory involves a complex series of molecular, cellular and network-level events that take place on timescales from milliseconds to months. Many types of memory undergo an initial period of susceptibility after which they become resistant to disruptive events, such as damage to the hippocampal formation. This stabilization process is known as memory consolidation. One possible reason why events are not immediately and permanently encoded is that the number of neurons in the mammalian cortex exceeds, by many orders of magnitude, the number of connections that can be supported by a given neuron. This means that the formation of arbitrary associations 'on-the-fly' is theoretically impossible. The brain might overcome this problem through a hierarchical, pyramid-like, organization that permits the formation of indirect associations between neurons receiving common 'top-down' information.

According to this view, dense local interconnections within higher-level populations initially encode arbitrarily associated patterns that are unique to a given experience. Later, retrieval of the high-level patterns can be used to reactivate the corresponding patterns across sparsely connected lower-level regions. Repeated retrieval in the low-level regions by this indirect means might enable the gradual establishment of connections necessary to encode the information directly. Marr [1] was perhaps

the first to suggest that such 'virtual' training should occur while the brain was not engaged in processing and encoding incoming data (e.g. during sleep).

This model provides one account of the time-limited role for the hippocampus in memory consolidation [2], but it is not necessarily limited to hippocampus-dependent memory. Latent consolidation has been demonstrated in the hours following learning of a variety of perceptual, tactile and motor tasks [3–5] in which learning does not depend on a functional hippocampus. Typically, effects are seen six–eight hours after training, and there is evidence that latent consolidation is facilitated by sleep [6].

The theory that long-term memory formation in the neocortex either depends on or is facilitated by such 'top-down'-mediated reorganization requires the following kinds of support: (1) evidence of experience-specific, coherent reactivation of recent neural activity patterns within both the higher-level and lower-level areas (e.g. between hippocampus and neocortex, or between higher-level and lower-level neocortical areas); (2) evidence that plasticity occurs during periods of reactivation; and (3) evidence that plasticity is the result of reactivation.

Reinstantiation of neural activity patterns recorded during earlier behavior ('memory trace reactivation') has been observed in the hippocampus of rats during sleep and quiet wakefulness [7–9] and in the neocortex of monkeys [10]. Moreover, simultaneous recordings of hippocampal and parietal neural ensembles in rats, and of neocortical ensembles in monkeys, show coherent reactivation between and within structures [10,11]. Thus, there is a growing body of evidence that some form of reactivation of patterns corresponding to recent experience occurs during sleep. Frank *et al.* [12] provide the first strong evidence that this period is accompanied by reorganization of neural circuits in the lower levels of the neocortex.

Frank *et al.* studied a crucial period of visual cortex development in cats that had experienced six hours of monocular

deprivation (MD) followed by one of four conditions: immediate anesthetization (MD6), six hours of sleep (MDS), six hours of sleep deprivation in complete darkness (MDSd), or an additional six hours of monocular deprivation (MD12).

Afterwards, ocular dominance was measured using intrinsic optical imaging and extracellular single-unit recordings from primary visual cortex.

In MD6 cats, there was a small reduction in the response to the deprived eye, whether measured with optical or with unit recordings. By contrast, the response to the deprived eye for the MDS group was greatly reduced (i.e. cortical plasticity was enhanced by sleep). The enhancement resulting from six hours of sleep was almost as great as that which occurred following an additional six hours of MD, both of which were greater than that of the MDSd group. This dramatic result indicates that sleep itself, not merely the passage of time, might play an important role in the experience-dependent cortical reorganization of ocular dominance columns.

There was a strong positive correlation between the amount of non-REM sleep and enhancement of ocular dominance using data from MDS and MDSd groups. Moreover, in the MDS group, there was a negative correlation between amount of REM sleep and changes in ocular dominance. This suggests that non-REM rather than REM sleep is important for ocular dominance plasticity, at least during the first six hours after MD. This result is consistent with studies in rodents that indicate that the strongest reactivation in the immediate post-experience period occurs in non-REM sleep [9], thus providing the foundation for a link between these two phenomena.

Future directions

A key remaining issue is whether the enhancement of cortical plasticity observed by Frank *et al.* is a consequence of reactivation of the neural activity patterns expressed during the earlier monocular experience or merely reflects a facilitation of ongoing molecular cascades

induced by the original experience. At present it is unknown whether reactivation even occurs in the cat visual cortex under the experimental conditions of Frank *et al.* By recording from neocortical ensembles before, during and after an experience that induces neocortical plasticity (e.g. MD), it might be possible to connect the phenomenon of reactivation to the degree of plasticity observed. In rodent studies, the strength of reactivation declines over about one hour. The reactivation–plasticity hypothesis predicts that the benefit of further sleep beyond the reactivation period would be minimal. This is readily testable and might close the current gap between studies of cortical plasticity and memory trace reactivation.

Frank *et al.* show an example of plasticity induced during non-REM sleep that immediately followed a novel experience of MD. Other future studies, exploring the interactions of vigilance state and the time elapsed since an experience could shed further light on the mechanisms of cortical plasticity. Whereas non-REM sleep appears important immediately after experience, there is growing evidence that REM sleep facilitates reactivation and consolidation after some delay following experience [13–16]. It is thus possible that REM sleep

occurring at longer intervals after MD might provide even further enhancement or stabilization of the ocular dominance shift. In our opinion, the successful combination of the developmental plasticity paradigm with that of memory trace reactivation by ensemble neural recording has the potential to provide a crucial link in our understanding of how long-term memories are encoded in the brain.

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Nodes of Ranvier come of age

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Sodium channel subtypes are frequently coexpressed within neurons. Recent studies demonstrate that targeting of specific channel subtypes to distinct membrane domains of axons is regulated by local signals from myelinating glia; they also show that channel subtypes are sequentially expressed at nodes of Ranvier, indicating an unexpected regulation in the composition of these domains.

Na⁺ channels are nonhomogeneously distributed on neurons, notably in myelinated axons, where they are strikingly enriched at nodes of Ranvier. The high density of Na⁺ channels at the node is critical for normal saltatory conduction and develops as the result of extrinsic signals from myelinating glial cells (i.e. Schwann cells in the peripheral

nervous system and oligodendrocytes in the central nervous system). Na⁺ channels are believed to be part of a complex of proteins at the node. In addition to the large, pore-forming α -subunit, one or more accessory β -subunits might also be present [1]. The precise stoichiometry of the channel complex at the node, including which β -subunits are present, is not well defined. Nodal Na⁺ channels are linked to the multivalent cytoskeletal protein ankyrin G [2] which, in turn, is likely to interact with the cytoskeletal protein β IV spectrin [3] and the neural cell adhesion molecules, neurofascin and NrCAM, all of which are also enriched at this site [2]. Whether this complex of proteins is assembled locally or transported as a larger complex is not known, although earlier studies of node

formation in the PNS suggest that at least some components of the node assemble sequentially [4]. In addition, the glial signals involved, and the mechanisms by which Na⁺ channels and associated proteins concentrate at the node, have not been elucidated.

The α -subunits comprise a multigene family with ten known members [5]. Na_v1.1, 1.2, 1.3 and 1.6 are the predominant subtypes expressed in the CNS. In general, these subtypes have different subcellular distributions: Na_v1.1 and 1.3 are principally expressed on neuronal cell bodies, 1.2 is expressed on axons and 1.6 is present on both dendrites and axons [6,7]. These distinct localization patterns presumably reflect vesicular transport mechanisms that selectively target proteins to the axonal or