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Visions & Reflections

Issues surrounding sleep-dependent memory consolidation and plasticity

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Abstract. There is a growing body of evidence in support of sleep-dependent memory consolidation and plasticity. However, there are also examples of memory development and plasticity in the absence of sleep, casting doubt on an exclusive sleep-dependent memory hypothesis. As a result, polarized stances have arisen within the field. Here we reflect on these findings, and explore how they maybe reconcilable in a unified approach to understanding the roles of wake, sleep and specific sleep stages in successful memory processing and brain plasticity.

Key words. Sleep; memory; consolidation; plasticity.

An exciting renaissance is currently underway within the biological sciences, centered on the question of why we sleep, and focusing specifically on the consolidation of memory during sleep. Despite this burgeoning growth, there remains some resistance to the idea that sleep contributes meaningfully to the evolution of stable and enhanced memories [1, 2]. Certain aspects of this conflict have focused on methodological issues and inconsistencies, but skepticism has also arisen due to a confusion of exactly what stage of memory development the sleeping brain is claimed to assist. In this article, we discuss issues of when and how sleep-dependent memory processing and plasticity transpire, and contemplate on the exciting future directions within the field.

Appreciating the question

To consider the question of whether sleep plays a role in memory, we must first understand what these terms represent. Sleep has been broadly classified into two distinct types in mammalians; non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, which cycle across the night. NREM sleep has been further divided in primates and cats into four substages (1–4) corresponding, in that order, to increasing depth of sleep [3] (fig. 1). The deepest stages of NREM, stages 3 and 4, are often grouped together under the term 'slow wave sleep' (SWS), reflecting the occurrence of low frequency waves throughout the cortex. Dramatic changes in brain electrophysiology, neurochemistry and functional anatomy accompany these different sleep stages, making them biologically distinct from the waking brain, and dissociable from one another [4]. This contrasting range of biological profiles clearly demonstrates that sleep itself cannot be treated homogeneously, but instead, possesses a range of physiological and a neurochemical means that may contribute to memory consolidation and plasticity [5].

Although often used as a unitary term, 'memory', like sleep, is not a single entity. For example, human memory has been subject to several different classification schemes, the most popular being the distinction of declarative versus non-declarative memory [6]. Declarative memory can be considered as the consciously accessible memories of fact-

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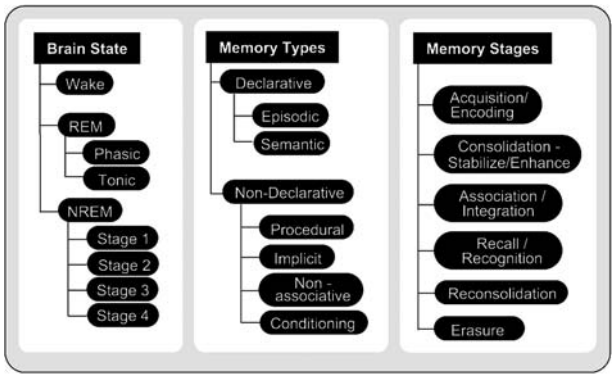

Figure 1. The question: brain-states, memory types, memory stages.

based information (i.e. knowing 'what'), and contains several subcategories, including episodic memory (memory for events of one's past) and semantic memory (memory for general knowledge, not tied to a specific event) [6]. In contrast, non-declarative memory can be regarded as non-conscious, and includes subcategories such as conditioning, implicit memory and procedural memory (i.e. knowing 'how'), which includes the learning of actions and skills (fig. 1).

Just as memory is not monolithic, similarly, there is not one sole event that creates or develops it. Instead, memory appears to evolve in several unique stages over time (fig. 1). Memories are initially formed, or 'acquired', by engaging with an object or performing an action, leading to the rapid formation (seconds-minutes) of a memory representation within the brain. Following acquisition, the most commonly recognized next stage of memory is 'consolidation'. Classically, consolidation refers to a stabilizing process whereby a memory becomes increasingly resistant to interference from competing or disrupting factors over time (hours-days) [7]. Recent findings, however, have begun to extend this definition. For example, consolidation can be thought of as not only stabilizing memories, but enhancing them as well, so that the memory representation is even more efficient, producing subsequently improved behavioural performance on the memory task [5]. Thus, consolidation can be expanded to include more than one phase of post-acquisition memory processing.

Following consolidation, the memory representation can be retrieved, a process termed memory 'recall'. Yet the actual act of memory recall is itself thought to destabilize the memory representation, making it once again labile. An additional step termed 'reconsolidation' may then be required to restabilize and possibly reenhance the memory [8], a process that could offer the ability to reshape and remodel memories in the context of ongoing life experience. Some ancillary memory stages have also been considered, and include the integration of consolidated information with existing knowledge ('memory association') and even the removal of memory strengths ('memory erasure'), but are less well established.

Viewed together, one becomes aware of the truly staggering number of possible ways that brain states may affect memory systems and memory stages, and by overlooking this complexity, confusions surrounding the role of sleep in memory development have emerged.

When and how is sleep important to memory processing?

The majority of studies, in both animals and humans, have described evidence implicating sleep in the consolidation stage of memory development. Early work in humans focused on declarative learning tasks, with mixed conclusions, some arguing for sleep-dependent memory processing and others against it [for reviews, see 9, 11]. More recently, reports have shown the beneficial effects of sleep on the consolidation of a declarative word paired associates task, which may preferentially develop after early night sleep, rich in SWS [10]. Indeed, it may be that sleep's role in declarative memory consolidation, rather than being absolute, depends on more subtle aspects of the task, such as whether the learned information has any pre-existing memory associations. One interpretation of the beneficial influence on declarative memory is that sleep provides a time of minimal sensory and cognitive processing, thus protecting these memory representations from interference [11]. There is the alternative possibility that the physiological state of sleep itself is more actively involved in the consolidation process, rather than simply being a passive time of minimal interference. For example, in the above report, the effect was selectively expressed only after SWS-rich periods early in the night, rather than across any sleeping period ubiquitously lacking interference, supporting the latter claim. Nevertheless, this remains an evolving area of understanding.

In contrast to the declarative system, the reliance of non-declarative, procedural memory consolidation on sleep has been a robust and consistent finding. Specifically, sleep in humans has been shown to trigger a form of consolidation that results in additional overnight learning, whereby skill performance is selectively improved across sleeping intervals, while equivalent waking periods confer no such performance benefits [5]. This overnight learning reflects a form of consolidation that enhances memory representations, beyond simply stabilizing them. Demonstrations of sleep-dependent memory enhancement have now been reported using a plethora of sensory and motor skill tasks [for review see 12], an example of which is shown in figure 2 [13, 14].

Interestingly, while these overnight enhancements are seen across a range of memory tasks, they appear to rely

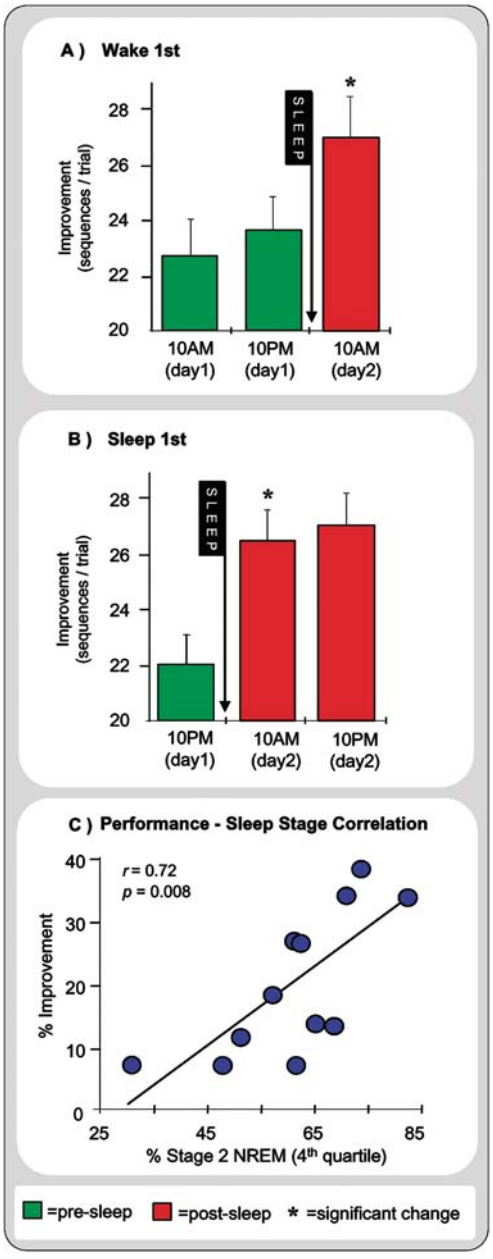

Figure 2. Sleep-dependent motor skill learning in the human brain. Subjects were training and then retested on a motor skill task across a 24 h period, either beginning in the morning (Wake 1st) or evening (Sleep 1st). (*A*) Wake 1st: Following morning training (green bar, 10 AM), subjects (n = 15) showed no significant change in performance when retest after 12 h of wake (green bar, 10 PM). However, when retested following a night of sleep (red bar, 10 AM), performance had improved significantly by 19%. (*B*) Sleep 1st: Following evening training (green bar, 10PM), subjects (n = 15) immediately showed a significant 21% improvement in performance just 12 h after training, following a night of sleep (red bar, 10 AM), but expressed no further significant change in performance following an additional 12 h of wake (red bar, 10 PM). Therefore, significant delayed improvement was only seen across a night of sleep and not over an equivalent period of wake, regardless of whether the time awake or time asleep came first. (*C*) The amount of overnight improvement on the motor skill task correlated with the percentage of stage 2 NREM sleep, particularly in the last (4^{th}) quarter of the night. Error Bars, SEM. Modified from [14].

on different sleep stages or sleep characteristics. For example, stage 2 NREM sleep, and prominent electrophysiological phenomena of NREM, have been related to the consolidation of motor skills [14–18], while NREM SWS and REM sleep have been associated with the consolidation of visual skill memory [19, 20]. This would indicate that subtly different forms of memory require uniquely different sleep stages (or sleep characteristics) for consolidation enhancement.

Animal models have demonstrated that training on both spatial and shock avoidance tasks trigger alterations in sleep-stage characteristics [for review see 12, 21], suggesting, as in humans, a homeostatic response to increased demands on sleep-dependent consolidation. As with humans, sleep deprivation following task acquisition has also been shown to produce learning impairments at subsequent retests, reflecting a potential disruption of intervening consolidation [for review see 12, 21]. While several of these early studies have been legitimately criticized for a failure to control for general effects of sleep deprivation [1, 2], more recent studies have demonstrated that impaired performance is still seen several days after sleep deprivation, when alertness or attention have returned to normal [e. g. 22]. In addition, selective deprivation of specific sleep stages, and even specific sleep-stage time windows, still inhibit memory consolidation [23, 24], making arguments of sleep deprivation-induced stress untenable.

Taken as a whole, behavioural studies across many species offer strong evidence that sleep plays a critical role in consolidation throughout multiple memory systems, specifically related to the form of consolidation which enhances memory representations, resulting in improved skill performance. To date, all stages of sleep, except sleep onset stage 1 NREM sleep, have been implicated in this consolidation process.

Sleep-dependent plasticity

Memory development depends on brain 'plasticity' – a lasting structural and functional change in a neuron's response to a stimulus. If sleep is to be considered a critical mediator of consolidation, then evidence of sleep-dependent plasticity would greatly strengthen this claim.

In humans, Maquet et al. [25] have demonstrated sleep-dependent plasticity using functional magnetic resonance imaging (fMRI). Subjects were trained on a non-declarative procedural skill task and subsequently retested 3 days later, with half the subjects deprived of sleep the first night following training. The remaining half, who slept all 3 nights, showed both enhanced behavioral performance (indicative of successful consolidation) and a selective increase in activation in a region of the superior temporal sulcus at retest. In contrast, subjects deprived of

sleep the first night showed no change in behavior or brain activity, despite the two ensuing recovery nights of sleep.

Throughout the sleep cycle, both REM and NREM sleep stages contain numerous unique electrophysiological events. Several of these electrical phenomena have been implicated in the process of plasticity by potentiating or depressing synaptic connections [26]. For example, it has been proposed that sleep spindles, seen most commonly during stage 2 NREM sleep, can provide brief trains of depolarizing inputs to targets in the neocortex, similar to those used experimentally to induce long-term synaptic potentiation (LTP) [27–29].

Electrophysiological events during REM sleep, specifically a phasic wave form recorded most easily in the pons (P), geniculate nuclei of the thalamus (G) and the occipital cortex (O) (termed 'PGO waves'), have also been associated with learning [30,31]. In addition, Sanford et al. [32] have demonstrated that fear conditioning in rats can increase the amplitude of elicited PGO waves during REM sleep, indicative of a homeostatically regulated component of a sleep-dependent consolidation mechanism [31]. Interestingly, these PGO waves occur in a phase-locked manner with theta wave activity during REM sleep [33]. Furthermore, while experimental stimulation to several regions of the hippocampus at the peaks of theta waves facilitates LTP, the same stimulation applied at the troughs of the theta waves instead leads to long-term depression of synaptic responses [34]. PGO waves may therefore serve as an endogenous sleep-dependent mediator of synaptic plasticity, and based on the phase relationship of the PGO and theta waves, could lead to either potentiation or depotentiation of synaptic strengths.

Numerous groups have investigated the firing patterns of neuronal populations across the wake-sleep cycle. The signature firing patterns of these networks, expressed during waking performance of spatial tasks and novel experiences, appear to be replayed during SWS and REM sleep, albeit at somewhat different temporal speeds [35–41]. Similar findings of neural reactivation have also been reported in humans using brain-imaging techniques [42]. Together, these data indicate that sleep-dependent replay of temporal patterns of network activity consistently occur following learning experiences during wake, and may offer a mechanism for the adaptation and modification of synaptic strengths within specific networks.

Recently, a form of sleep-dependent plasticity at the cellular level was elegantly demonstrated during early postnatal development [43–45]. Under normal circumstances, brief periods of monocular visual deprivation during critical periods of maturation can lead to the remodeling of synaptic connectivity, with the deprived eye's inputs to cortical neurons being diminished [46]. Frank et al. [47] have shown that when 6 h of monocular deprivation are followed by 6 h of sleep, the size of the monocularity shift doubles. In contrast, if the animals were kept awake for these same 6 h (in the dark, without input to either eye), a non-significant reduction in the size of the shift occurs. Thus, sleep can contribute as much to developmental changes in synaptic connectivity as does visual experience, while sleep deprivation results in a loss of previously formed, experience-dependent synaptic changes. Furthermore, it is not simply that a non-waking brain state can achieve such results, since, as the authors point out, the state of anesthesia actually inhibits ocular column plasticity, in stark contrast to the effects of sleep [48].

At the molecular level, Smith et al. [49] have shown that administration of protein synthesis inhibitors to rats during REM sleep time segments thought to be critical for consolidation prevents behavioural improvement following the sleep period, while rats receiving saline injections show normal sleep-dependent learning. Such protein synthesis could reflect a fundamental mechanism regulating sleep-dependent plasticity, namely the activation of genetic cascades important for synaptic remodeling. Indeed, the exploration of gene activity during sleep has only recently begun. While, several of the known 'immediate early genes' (IEGs) are specifically down-regulated during sleep [50, 51], approximately 100 genes have been identified that are preferentially up-regulated during sleep (almost the same number that are up-regulated during wakefulness) [52], some of which may serve to regulate modifications of synaptic function.

This extensive up-regulation of genes during sleep is striking, as was seen in the absence of any specific form of learning prior to sleep (although some incidental learning may have occurred). Ribeiro and colleagues have addressed this question more specifically, and found up-regulation of *zif-268*, a plasticity-associated IEG, during REM sleep following exposure to a rich sensorimotor environment, but its down-regulation during both SWS and REM sleep without such exposure [53] (fig. 3). Thus, in the absence of a particular learning experience prior to sleep, there may be a limited plastic response from the sleeping brain since there is little new information to consolidate. Yet in information-rich environments, when new associations are being learned, there are sleep windows of increased neuronal plasticity, and with each passing REM cycle, gene expression can continue to spread throughout several brain regions [54].

Collectively, these findings build a coherent argument in favor of sleep-dependent plasticity, ranging from whole brain, systems-level plasticity through to plasticity at the cellular and molecular level during sleep, providing a brain basis for the known beneficial influence of sleep on behavioral performance.

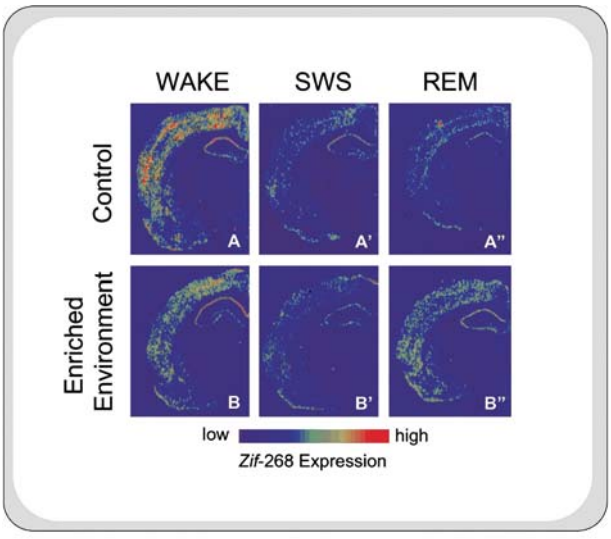

Figure 3. Experience-dependent up-regulation of *zif*-268 gene expression during wake, SWS and REM sleep states in the rat. Autoradiograms of *zif*-268 gene expression in frontal coronal brain sections. In controls, *zif*-268 expression decreased from WAKE (*A*) to SWS (*A′*) and REM (*A″*). In enriched environment animals, *zif*-268 levels decreased from WAKE (*B*) to SWS (*B′*), but increased from the latter to REM (*B″*). This effect was particularly noticeable in the cerebral cortex and the hippocampus. With permission from [53].

Can memory processing and plasticity occur independent of sleep?

We have already discussed evidence that a form of consolidation – the stage of enhancing certain types of memory representations – is largely dependent on sleep for its development, supported by a range of plastic brain changes. However, there is some evidence that another stage of consolidation – that which simply stabilizes memory representations, but does not enhance them – can develop without the need for sleep.

A collection of studies in humans have demonstrated that following initial procedural memory acquisition, a time period ranging from 3–6 h across waking intervals is sufficient to allow memory stabilization, protecting newly formed memory representations from disruption [55–57]. Complimenting these behavioral findings, numerous cellular and molecular studies have indicated that plastic changes can develop within several hours following memory acquisition or experimentally induced LTP [for review, see 58]. Although sleep was not explicitly monitored in these studies, it does indicate that some aspects of plasticity develop within the first few hours post-acquisition, potentially without sleep, in the endeavor of stabilizing a memory. This could represent a logical fail-safe, allowing information that is learned many hours before the occurrence of sleep to be retained and thus still be available for later sleep-dependent enhancement. However, the possibility that sleep and wake stabilize memories at different rates or efficiencies remains unknown. It is thus conceivable that sleep is a preferred time for stabilizing memory representations (rather than a necessity as in memory enhancement), but since memories can be formed several hours prior to the onset of sleep, wake is also endowed with this stabilizing ability.

Yet there are other memory stages that take place both before and after episodes of consolidation – those being acquisition and reconsolidation, respectively. What then is the role of sleep in these memory stages?

There is an enormous constellation of findings describing successful memory acquisition during the wake state. This is not to say information cannot be assimilated in such a way during sleep [for recent review, see 59], simply that wake may be the most preferable time for memory acquisition, with focused perceptual attention to external stimuli and the ability for conscious driven motor output. Rapid learning during acquisition could also be too fast for extensive changes involving the synthesis of new proteins, and may explain why sleep, with its more protracted mechanisms of plasticity, is not a requisite. Instead, acquisition may rely on more short term plastic changes (seconds-minutes), including structural modulations of neuronal cytoskeletal and adhesion molecules [58], and the disinhibition or 'unmasking' of already existing cortical connections, which normally lie dormant in a state of inhibition [e.g. 60]. Both these mechanisms could permit the rapid fine tuning of existing synaptic networks, allowing immediate learning and acquisition of a memory representation during initial practice.

Currently, very little is known about the brain-state dependency of later memory reactivation and reconsolidation stages. Walker et al. have demonstrated that upon reactivation of a once consolidated procedural motor memory, immediate learning of a second competing memory causes interference of the first memory, yet the effects of interference were not evident until after a subsequent night of sleep [56]. Nevertheless, it remains unknown whether reactivation during sleep, or upon awakening from sleep, confers greater or lesser susceptibility to disruption than in waking. Furthermore, following reactivation of a memory, it is also unknown whether sleep and wake are able to reconsolidate memories independently, or at different rates or using different pathways. Considering recent findings which suggest that reconsolidation may rely on somewhat different cerebral machinery than consolidation [61], the exploration of memory reconsolidation as a function of wake and sleep states remains fertile ground for future research.

Conclusions and the future

Memory development is reliant on mechanisms of brain plasticity, and both wake- and sleep-dependent memory

processes must be mediated by such mechanisms. In separating out distinct stages of memory, we become aware that these steps are uniquely accomplished by wake (acquisition and stabilization) and by sleep (consolidation triggering additional learning improvements). It would be a mistake to give more importance to the responsibilities of one brain state relative to another in their contributions to memory. Clearly, if an organism is not awake and immersed in learning experiences, there is little hope of forming a memory. Equally, without successfully consolidating those newly formed representations during sleep, there is little chance of enhancing that information in the endeavor of improving behavioral repertoires. In the end, it seems logical, if not biological, to accept that wake and sleep both contribute meaningfully and necessarily to the formation and development of efficient memories, and without these brain states, our systems of memory are equally compromised.

As we look to the future, a greater appreciation of brain states and their influence in determining memory stage formation and plasticity is required across a range of descriptive levels, from molecules to whole-brain functional analysis. By way of this multidisciplinary approach, and with a measured appreciation that both wake and sleep play their roles in forming, consolidating and reforming memories, we can look forward to new advances in treating disorders of memory, and perhaps even improving the capacity of our own.

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