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Opinion

System Consolidation During Sleep – A Common Principle Underlying Psychological and Immunological Memory Formation

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Sleep benefits the consolidation of psychological memory, and there are hints that sleep likewise supports immunological memory formation. Comparing psychological and immunological domains, we make the case for active system consolidation that is similarly established in both domains and partly conveyed by the same sleep-associated processes. In the psychological domain, neuronal reactivation of declarative memory during slow-wave sleep (SWS) promotes the redistribution of representations initially stored in hippocampal circuitry to extra-hippocampal circuitry for long-term storage. In the immunological domain, SWS seems to favor the redistribution of antigenic memories initially held by antigen-presenting cells, to persisting T cells serving as a long-term store. Because storage capacities are limited in both systems, system consolidation presumably reduces information by abstracting ‘gist’ for long-term storage.

Introduction

Why do we form memory? – because innate response patterns do not suffice to warrant survival of a species if the environment of the organism changes at a rate much faster than its reproductive cycle. Thus, memory, in biological systems, refers to a process in which the organism extracts and maintains relevant environmental information to enable sustainable adaptive responses. It is assumed that despite the ever-changing nature of environmental stimulation, the organism can learn and accumulate memories by extracting and storing invariant features from the stimulation, and this eventually enables stable and effective responding.

Memory can be subdivided into three distinct processes (Figure 1): (i) ‘encoding’, which refers to the uptake of information to be stored into a cellular representation; (ii) ‘consolidation’, which refers to a post-encoding process in which the newly encoded representation, which is initially fragile and prone to decay, is transformed into a more stable and longer-lasting cellular representation; and (iii) ‘recall’, which refers to the reactivation of the stored memory to enable the execution of an adaptive response in appropriate environmental contexts. The central nervous system (CNS) mediates adaptive behavioral and accompanying autonomic nervous and endocrine responses to psychological events, and for this purpose it forms lasting neuronal

Trends

Although responding to different environmental events, the central nervous system and the immune system share basic functions of memory.

Sleep benefits the consolidation of psychological and immunological memory.

In the psychological domain, neuronal reactivation of declarative memory during sleep promotes the redistribution of representations initially stored in hippocampal circuitry towards the neocortex and striatum for long-term storage.

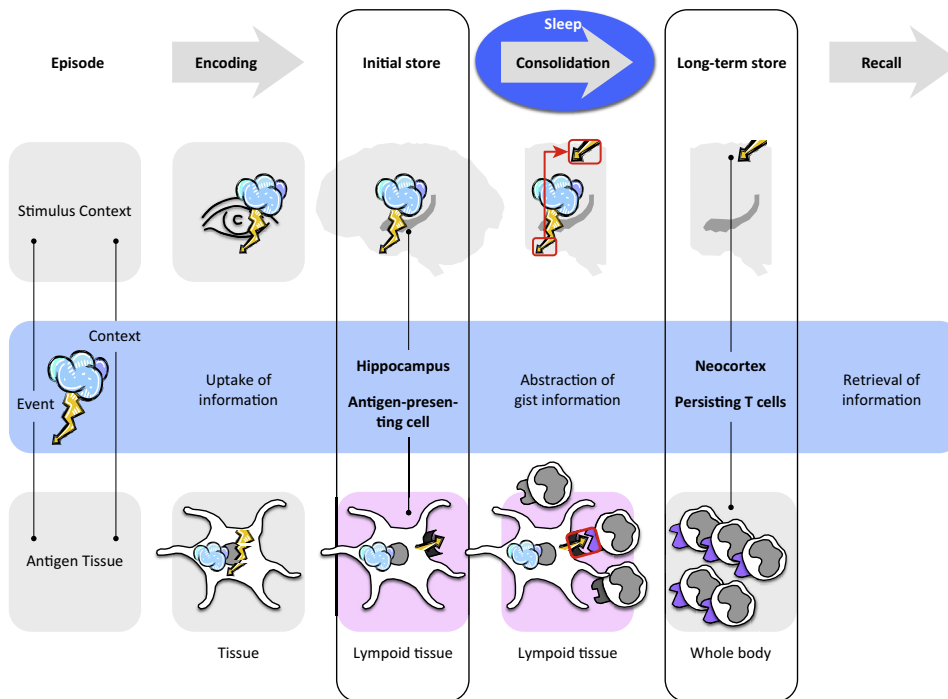
In the immunological domain, sleep promotes the redistribution of antigenic memories initially held by antigen-presenting cells, to persisting T cells serving as a long-term store.

In both systems, the consolidation of memory is mediated by slow-wave sleep that suppresses cholinergic and cortisol activity, and enhances proinflammatory signals.

Long-term memory formation in both systems is associated with information reduction by abstracting gist memory.

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Trends in Neurosciences

Figure 1. Model of Memory Formation in the Central Nervous System and the Immune System. In both domains long-term memory formation is established as a system consolidation process (top row and middle blue-shaded area), in which an episode consisting of an event (lightening) together with context information (cloud) is encoded into an initial store. During subsequent consolidation, which is supported by sleep, memory representations are reactivated. This involves an enhanced flow of reactivated information from the initial to the long-term store wherein parts of the memory representations become gradually redistributed such that they preferentially reside in long-term storage sites. Some representations also remain in the initial storage system (not depicted). During the redistribution process the representation is transformed such that gist (tip of the lightning bolt, framed in red) is abstracted and contextual details are for the most part forgotten. In the psychological domain (upper row) the initial store is represented by the hippocampus (in the case of declarative memory) and the long-term store by extra-hippocampal, mainly neocortical networks. In the immune system (lower row), the initial store is mainly represented by antigen-presenting cells (APCs) that take up antigens (event) in specific tissues (context), and then migrate to lymphoid tissues to present on their surface antigen-derived peptides in the groove of major histocompatibility complex (MHC) molecules (i.e., epitopes). During consolidation antigenic and context information (in form of co-stimulatory molecules) is reactivated to activate T cells expressing T cell receptors (TCRs) structurally fitting the epitopes. Activated T cells proliferate to form persisting T cells which represent the immunological long-term store. Because their TCRs selectively bind to immunodominant epitopes, and because of their considerable crossreactivity with other epitopes, persisting T cells can be considered to hold a generalized gist representation of the antigen, with little or no contextual information.

memory representations of relevant features of the physical and social environment of the organism. Long-lasting memories are likewise formed in the immune system, which stores key features of antigens in the T and B cell systems to be able to respond faster and more effectively when re-encountering the antigen. Although referring to different domains of environmental events, both the CNS and immune system appear to share basic functions of memory [1]. If so, then could there even be common rules and mechanisms of memory that apply to the two systems?

While the idea of shared rules that control memory processing in different systems is not novel [2,3], the comparison of memory processing in the CNS and immune system is particularly fostered by accumulating evidence indicating that sleep promotes the consolidation of memory in both systems [4–6]. Sleep following the encoding phase appears to favor the extraction and maintenance of psychological as well as antigenic information. In light of these findings, we

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examine whether sleep-dependent consolidation in the two domains is governed by common rules. Going beyond analogy, we also ask whether, and to what extent, sleep-dependent memory consolidation in the CNS and immune system involves the same physiological mechanisms.

Memory in the CNS and its Consolidation by Sleep

Although other mechanisms have been proposed, the currently dominant concept about how memories are formed in the brain derives from Hebb's theory of associative learning and the ensuing concepts of spike time-dependent plasticity and auto-association, which are all based on the assumption that neighboring neurons and neuronal assemblies which, because of concurrent inputs are repeatedly active at the same time, tend to become associated, such that synaptic connections between these assemblies are changed and activity in one facilitates activity in the other [7,8]. Activity patterns formed as a consequence of such synaptic modification in neuronal assemblies are considered to be memory representations. However, the capacity of the brain to form synapses is limited, and Hebbian learning does not suffice to explain memory formation over time in complex learning conditions in which memories formed at one point in time can be easily overwritten by later learning of similar but incongruent materials [9]. For example, in such systems later learning of 'penguins are birds' would simply overwrite former learning of 'birds fly'. To allow the abstraction of more general and **schema**-like memory representations and the later integration of partly-incongruent information into pre-existing schemas, a two-stage model of memory has been proposed, that is, the 'standard consolidation theory' (SCT) [9–11]. SCT assumes a **system consolidation** (see [Glossary](#)) process in which, at the first stage, episodes are encoded in a specialized neuronal network (the hippocampus in the case of **declarative memory**) that rapidly encodes new information but serves only as an initial store. At a second stage, repeated reactivations of the representations in the initial store promote their gradual redistribution to extra-hippocampal, mainly neocortical, networks, which learn at a slower rate and serve as a long-term store [9,12].

More recent accounts on episodic memory, such as the multiple-trace theory and the trace-transformation theory, pose that initially the hippocampus mainly carries out the rapid binding of episodic events into spatiotemporal context [13–15]. The reactivation of the event representation in other contexts generates new, overlapping representations, thereby fostering a transformation process such that the '**gist**' from multiple episodes is abstracted to form a context-independent schema-like representation that resides preferentially in extra-hippocampal networks. These extra-hippocampal representations can be accessed independently from the hippocampal system, and allow fast stimulus recognition and responses at an automatic level.

Central to these concepts of long-term memory formation in complex learning situations is that different neuron networks are used for the initial storage and for the longer-term storage of some of the experienced information. The gradual redistribution of representations from networks primarily serving as initial storage to long-term storage networks implies a gradual strengthening of respective synaptic connections in the long-term storage networks [12]. The redistribution process is assumed to be caused by the repeated reactivation of newly encoded episodic representations, and to involve the abstraction of a gist memory. The neuronal reactivations originate from hippocampal networks serving the initial storage, and occur offline, particularly during sleep [16].

Experimental Evidence for Sleep-Dependent Consolidation of Psychological Memory

A century ago first experiments in humans demonstrated that sleep supports the retention of declarative types of memories, such as lists of syllables learnt before sleep [17], a finding which was supported by numerous subsequent studies (summarized in [4]). More-recent studies have

Glossary

Antigen-presenting cells: highly specialized cells that can process antigens and activate antigen-specific T cells by displaying parts of the antigen on their cell surface.

Declarative memory: memories that are accessible to explicit recollection, comprising memories for episodes and facts. Encoding and retrieval of declarative memory crucially relies on the hippocampus and associated medial temporal lobe structures

Epitope: a short peptide sequence of the antigen that is recognized by the T cell receptor.

Rapid eye-movement (REM)

sleep: the second of the two core sleep stages of sleep. REM sleep is characterized by wake-like low-amplitude fast-frequency activity in the electroencephalogram, and is hence sometimes termed 'paradoxical sleep'. REM sleep always follows periods of NonREM sleep or SWS.

Schema, gist: general, higher-level constructs that encompass representations of salient communalities across experienced events, rather than the specificity that make those events unique.

Slow-wave sleep (SWS): one of the two core sleep stages of sleep. SWS is the deepest form of non-rapid eye movement (NonREM) sleep and is hallmarked by slow waves (0.5–4 Hz) in the electroencephalogram.

System consolidation: a process of memory consolidation that entails the redistribution of the representation towards cellular networks different from those used for encoding; the process leads to qualitative changes in the memory content.

T cells: thymus-derived lymphocytes that can react to a specific antigen and thereby serve to eliminate the antigen or to regulate activation of antibody-producing B cells. Persisting T cells and B cells represent immunological memory.

explored the mechanisms of this function. Sleep consists of the cyclic occurrence of **rapid eye movement** (REM) and non-rapid eye movement (NonREM) sleep periods, with the deepest type of NonREM sleep being termed **slow-wave sleep** (SWS). The EEG during SWS is hallmarked by cortically generated slow oscillations with a dominant spectral frequency <1 Hz in humans. Comparisons of retention periods rich in SWS or REM sleep, as well as experimental stimulation of slow oscillations during retention sleep, have revealed that SWS is crucial for memory consolidation, particularly of hippocampus-dependent declarative material [4,18]. Hippocampus-dependent memory consolidation during sleep can be also enhanced by experimentally reactivating memory representations during SWS by means of contextual cues [19,20]. Together with studies in rats indicating that neural firing patterns present during spatial task performance are repeatedly reactivated during SWS after task performance [16,21], these findings demonstrate a causal role of hippocampal reactivations for memory consolidation during sleep. Hippocampal reactivation is likely driven by neocortical slow oscillations such that they occur in synchrony with the excitable slow oscillation up-state [22]. This favors the spreading of reactivation to extra-hippocampal, mainly neocortical and striatal, networks (i.e., system consolidation) and the induction of plastic synaptic changes in these networks that mediate the longer-term storage of the representation (i.e., synaptic consolidation) [6,23–25].

The emerging picture from this research is that, during wakefulness, distributed episodic memory representations are encoded. With respect to their genuinely episodic features binding the experienced event into a spatiotemporal context, these representations are anchored in hippocampal networks. Reactivations during subsequent SWS, aside from transiently strengthening the hippocampal representation [26], comprise an enhanced passage of reactivated information from hippocampal to extra-hippocampal networks, thereby presumably promoting the redistribution of the representation towards extra-hippocampal networks. The redistribution proceeds alongside a qualitative transformation of the representation and the abstraction of invariants, regularities, and gist. Thus, sleep was found to enhance false but generalized, abstract memories in the Deese–Roediger–McDermott paradigm [27] to facilitate insight into hidden rules underlying stimulus sequences [28–31], to improve distant inferential judgment [32], to favor the abstraction of categories from similar objects [33], and to de-contextualize memories from the original context in which they were learned [34–36].

Processes of reactivation-based system consolidation might likewise support the formation of non-declarative memories of sensory and motor skills. There are hints both for reactivation-induced benefits in motor skill during sleep [37] and for sleep-induced transformation of skill representations towards preferential striatal circuitry and decreased striatal-hippocampal competition [38,39]. Moreover, skill representations after sleep appear to be more generalized [40]. However, overall the picture of a sleep-dependent reactivation-induced system consolidation process is less clear for non-declarative memory.

Memory Formation in the Immune System – A Trans-System Perspective

For the purpose of comparison, we propose a subdivision of immunological memory formation – paralleling psychological memory formation – into the processes of encoding, consolidation, and recall (Figure 1).

Encoding

The immune system perceives environmental stimuli in form of antigens. They enter the body via boundary surfaces, mainly the skin, lung and gut, where they are first recognized by cells of the innate immune system. Innate immune cells initiate defense mechanisms such as phagocytosis and inflammation. If they fail to clear the antigen in a short time, professional **antigen-presenting cells** (APCs) are activated. Based on genetically determined pattern recognition receptors, APCs recognize the antigen as foreign or dangerous and, based upon this recognition, initiate a

Box 1. Information Processing in the Immune System

Similarly to the brain, the immune system can be viewed as a system that senses, processes, stores, and responds to information, specifically to antigenic information and contextual information.

Antigenic Information. Can be structural and genetic. Structural information refers to the 3D form of proteins, lipids, sugars, and other molecules that constitute the antigen, whereas genetic information refers to the amino acid sequences in their original 1D (linear) form defined by DNA and RNA of cellular or viral origin. Whereas cells of the innate immune system and B cells of the adaptive immune system directly recognize structural antigenic information, T cells see antigenic information indirectly via APCs that present complexes of short antigen-derived peptides (epitopes) together with MHC molecules on their surface. There are two classes of MHC molecules. MHC class I presents shorter (8–11 amino acids) peptides derived from intracellular proteins to CD8 T cells (CD, 'cluster of differentiation') which in this way can examine the genome of cells for signs of virus infection and cancer development. MHC class I molecules are expressed by all nucleated cells of the host organism. By contrast, MHC class II molecules present protein fragments (15–24 amino acids) derived from endocytosed extracellular proteins to CD4 T cells.

Contextual Information. Refers to signals which are released during the interaction between the immune cells and the antigen in the tissue. Examples are so-called 'danger signals', for example nucleotides such as ATP released by damaged cells, signals of the complement system, and many types of inflammatory signals. Contextual information profoundly influences the handling of antigens. For instance, dendritic cells, which are the most important APCs, base their decision (to leave peripheral tissue and to migrate to lymphoid tissues) largely on contextual information. Moreover, tissue-educated APCs determine the type of effector response by T cells.

Distributed Information Storage. In contrast to the brain, the cells of the immune system are scattered across the entire organism and thereby form a distributed storage system. Following their release from the thymus, T cells continuously migrate through lymphoid (lymph nodes, spleen, etc.) and non-lymphoid organs (skin, lung, gut, etc.). An estimated ~200 million T cells per day enter and leave a human lymph node in healthy conditions. Each T cell spends ~15 h randomly migrating in a given lymph node [106], making contact with more than 200 APCs per transit [43]. During infections the influx of APCs and T cells into a lymphoid organ can increase dramatically. If specific epitopes are presented somewhere in the lymphoid system, the rare antigen-specific T cells (~1:100 000) are able to find them within a few days by stochastic migration [107]. Following activation by APCs, effector and persisting T cells enter the blood and thus can reach all organs.

memory-forming adaptive immune response. Thus, the activation of APCs marks the beginning of an encoding process that ultimately leads to the formation of a specific antigenic memory. The APCs take up the antigen and degrade it to peptides with a length of ~10 amino acids (Box 1), which are loaded into the groove of major histocompatibility complex (MHC) molecules. At this stage the APCs leave the peripheral tissue, migrate into lymphoid tissues such as lymph nodes that drain the tissue under attack, and mature, thus switching from an antigen-capturing to an antigen-presenting mode [41]. In the T cell zone of lymphoid tissues, APCs express complexes of MHC and peptide on their membrane. In this way, encoding in the immune system ultimately generates initial representations of antigen-derived information, termed **epitopes** (Box 1), which survive for at least several hours [42].

Consolidation

APCs in lymphoid organs are continuously scanned by a huge number of **T cells** [43]. Each T cell expresses many thousands of copies of a unique T cell receptor (TCR) on its surface, and these bind to epitopes that are structurally complementary. If the TCR–epitope binding strength exceeds a threshold, and the APC secretes appropriate co-stimulatory molecules, T cells are activated and proliferate – resulting in the generation of two types of antigen-specific T cells: 'effector T cells' and 'persisting T cells' (also termed memory T cells) [44]. What actually determines fate decisions and subsequent differentiation into effector and persisting T cells is presently unclear [45,46]. Effector T cells have a lifespan in the range of days to weeks, and perform a variety of functions that are partly determined by the cytokines released by the APC during T cell activation [41,47], and eventually serve to directly eliminate the antigen. By contrast, persisting T cells are found months to years after the acute infection has ceased, and represent the long-term store of antigenic memory [44,47]. The T cell dependent B cell memory is stored by persisting B cells and by the antigen-specific antibodies they produce [48].

Recall

When antigens invade the body a second time, they face an increased number of antigen-specific persisting T cell, B cells, and antibodies, which enable a faster and stronger memory response. For some infections (e.g., measles), a single exposure in early childhood induces life-long immune protection that prevents recurrence of the disease.

System Consolidation in the CNS and Immune System

The process of memory formation in both domains shares similarities, bearing essential features of a 'system consolidation' process that involves the redistribution of memory representations from a cell system serving as initial store towards another cell system serving as long-term store [49] (Figure 1). In addition, we propose that the redistribution goes alongside a process of gist abstraction.

Redistribution From an Initial to a Long-Term Store

In the CNS, the hippocampus together with neighboring medial temporal lobe structures represents the main building block of an initial store [12,50]. In the adult brain, the hippocampus mainly interacts with prefrontal cortical structures to encode and initially store episodes, that is, psychological events, together with their unique spatiotemporal context in which they are experienced [51]. As long as the memory for the episode is upheld in the initial store, this system is also used to generate acute responses to similar events encountered in similar contexts, implicating that response generation shows context-dependence [52,53]. Neural reactivations promote the redistribution of hippocampal representations towards extra-hippocampal long-term storage sites.

In the immune system, APCs can be considered as the main building block of the initial store. APCs take up antigens in peripheral tissues and thus encode a preliminary version of antigenic information. Moreover, APCs sense contextual information in peripheral tissue (Box 1) which in turn regulates their co-stimulatory molecule signaling once the cells have reached lymphoid tissues [41]. Epitope presentation by such 'tissue-educated' APCs in lymphoid organs can be considered as a reactivation of the newly encoded antigenic information. By stimulating proliferation and differentiation of short-lived effector T cells, APCs generate an acute adaptive response to the infection that is context specific to the tissue in which the antigen was originally encountered (including the expression of adhesion molecules, and the release of cytokines that guide effector T cells to the antigen-containing site and enable tissue-tailored immunity) [41,44]. In parallel, epitope presentation stimulates the proliferation of persisting T cells. This process reflects the redistribution of antigenic memory to the cell system that represents the major building block of the long-term store in the immune system [47].

Abstraction of Gist

In the psychological domain, the vast majority of episodes experienced during daily life are not held as long-term memory; however, with their redistribution they undergo transformation such that gist information is abstracted that is stored for the long term. What gist information is in psychological terms can currently be defined only approximately, because the rules underlying this abstraction process are obscure (see Outstanding Questions). There is overlap with the term 'schema' [54] that is commonly used in cognitive neuroscience to refer to long-term knowledge structures. Schemas are general, higher-level constructs that encompass representations of the similarities or communalities across events, rather than the specificity that makes those events unique [55,56]. Because no two episodes are identical, schemas lack detail information as to the specific context in which an event was originally experienced, and this also allows their flexible retrieval in very different conditions. Schemas are thought to have an associative network structure, comprising units (or nodes) and specific inter-relationships among them, with the inter-relationships being often considered more crucial for characterizing the schema. Thus, in

perception, schema can refer to the abstraction of gestalt from complex sensory input and, in the area of procedural motor skills, a schema can refer to the representation of a particular finger motor sequence, whereas in the declarative memory system it may refer to the topographical relationships among spatial landmarks in the physical environment or to the relationships among persons of a social network (e.g., [57,58])

Thus, gist abstraction in the psychological domain refers to the formation of schema-like generalized representations in different memory systems. This does not mean that every detail of information is generally lost during consolidation. Schemas are highly adaptive and, owing to their associative network structure, schemas are capable of organizing new information such that additional meaning and particular details of new episodes are easily assimilated [56,58,59]. For example, while we forget the context in which we learned particular word meanings, we can develop a detailed memory about the word meaning. Hence, gist abstraction does not only comprise the formation of schema-like representations from overlapping episodic representations containing invariant and repetitive features across episodes. Gist also refers to the new information that is assimilated to an existing schema without necessarily leading to changes (accommodation) of this existing schema. From this it follows that a pre-existing schema-like representation is expected to essentially determine what is abstracted as gist from an experienced event during consolidation. Finally, whereas the term schema is most often used in the context of cognitive memory processing, we consider gist abstraction to include also emotional and motivational abstraction processes in the way they underlie, for example, the formation of long-lasting attitudes and plans [60,61].

As in the CNS, in the immune system the redistribution of antigenic memory to persisting T cells appears to be associated with a process of gist abstraction which involves the selection of epitopes to be stored by T cell clones with matching TCR specificities. In fact, the largest part of an immune response is carried out by only a few different T cell clones, and is directed against only a few epitopes, a phenomenon known as 'immunodominance' [62]. For instance, T cells can recognize at least ~500 peptides of vaccinia virus, but T cell responses typically seem to focus on <10 dominant epitopes. In herpes simplex virus infection, the gist even appears to contain only a single epitope [63]. Hence, the few dominant epitopes can be considered the 'immunological gist', the abstraction of which is fairly stable across individuals [64]. Epitope selection can also be viewed as a mechanism favoring generalization at the antigen level because, for a novel antigen to be detected by persisting T cells, this antigen does not need to be identical to any previously encountered one, provided that it shares an epitope of the gist.

Focusing an immune response against a few epitopes bears the risk that an antigen escapes the immune response by mutating a dominant epitope. This risk is partly countered by crossreactivity [65], that is, the ability of T cells to recognize multiple related epitopes. Crossreactivity can be viewed as another mechanism of generalization at the epitope level that is distinct from immunodominance. Although the underlying factors are unclear, there is some evidence that T cells displaying greater crossreactivity preferentially become part of the gist [66]. Finally, patterns of mRNA expression and protein synthesis reveal that, compared with effector T cells, persisting T cells lose information about the specific tissue context in which the infectious agent was encountered [47,67,68]. Overall, persisting T cells can be considered as carrying a more parsimonious and generalized representation of the initially encoded antigen, allowing responses to a wider category of antigens, independently of the context.

Sleep Supports Consolidation of Immunological Memory

More than three decades of research have substantiated the notion of distinct bidirectional interactions between CNS sleep and the immune system. The overall picture from these studies is that immune activation, mainly via proinflammatory signals [e.g., interleukin-1 (IL-1) and tumor

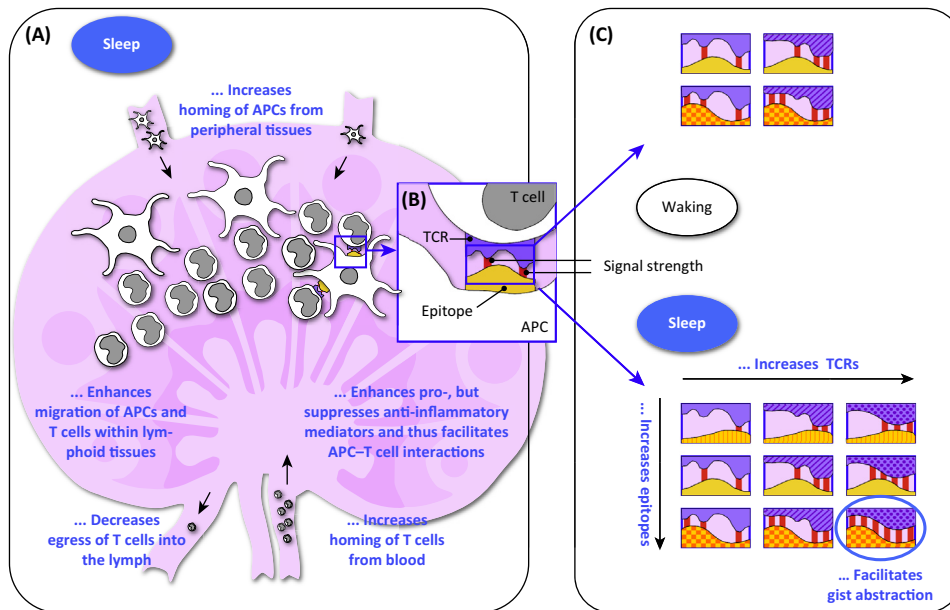
necrosis factor (TNF)], can promote sleep and that sleep, in turn, can acutely enhance immune defense [5,69–71]. Using vaccination as an experimental model of infection, several human studies have shown that sleep particularly supports adaptive immune processes and, thus, the formation of immunological memory, as indicated by increased numbers of antigen-specific persisting T cells as well as by increased levels of antigen-specific antibodies in peripheral blood [72–76]. Notably, these beneficial effects of sleep on adaptive immunity are long-lasting and still detectable after 1 year [74]. Comparable to the CNS domain, the effect of sleep on persisting T cells is accompanied by a transient reinforcing effect on contextual antigenic memory, because sleep after vaccination also increased the number of effector T cells as well as their capacity to produce cytokines such as interferon- γ [74]. The latter change represents a ‘contextual’ information regarding the tissue where the antigen was encountered and which facilitates immune responses uniquely tailored for this tissue [41,44]. By contrast, the sleep-induced increase in numbers of persisting T cells present after 1 year was not associated with such qualitative changes in the cytokine profile [74], consistent with the view that these long-term representations contain less contextual information.

Remarkably, the enhancement of long-term memory in these studies was inducible by sleep occurring within 24 h after vaccination [73,74], with this time-window speaking for a direct effect on APC–T cell interactions before the differentiation of effector and persisting T cells. Sleep probably strengthens antigenic memory formation in two ways: (i) by favoring the accumulation of APCs and T cells in lymphoid tissues, thereby increasing the likelihood of APC–T cell interactions, and (ii) by modifying the signaling strength between these cells through reinforcing inflammatory signals such that the formation of effector and persisting T cell is facilitated (Figure 2). There are first hints from studies of lymph node cell traffic in animals, as well as from blood measures in humans, that sleep facilitates the extravasation of APCs and T cells and their migration to lymphatic tissues [77,78]. In addition, sleep increased the production of proinflammatory cytokines and suppressed the production of anti-inflammatory cytokines by APC-like cells [78,79]. Effects on T cell cytokines in these studies were overall less consistent, suggesting that, rather than on T cells, the primary impact of sleep with respect to cell function is on APCs which, via APC–T cell interactions in lymphoid tissues, ultimately translates into an enhanced number of antigen-specific persisting T cells [5].

Are There Shared Mechanisms of Sleep-Dependent Memory Formation in the Psychological and Immunological Domain?

We are only beginning to understand some of the mechanisms mediating the enhancing effects of sleep on memory formation in the CNS and immune system. There are hints indicating that the function of sleep in both systems does not represent a coincidental parallelism but, indeed, shares some common factors, despite of the obvious differences in the organization of the two systems. Indeed, this might not come as a surprise considering the growing number of signal molecules identified that serve in parallel the regulation of sleep, synaptic plasticity, and adaptive immunity, thereby closely linking memory processing in the two systems of interest [70,80,81].

In both systems the beneficial effect of sleep on memory formation appears to originate primarily from SWS, whereas the contributions of REM sleep are unclear (Box 2). Numerous studies have demonstrated the importance of SWS and associated EEG slow oscillatory activity for the consolidation of hippocampus-dependent psychological memories [4,82]. Immunological studies identified SWS as part of the immune response that facilitates recovery from infections [69,83]. In humans, long-term increases in antigen-specific persisting T cells, as a reflection of an abstracted antigenic memory representation, were strongly associated with deep SWS and EEG slow oscillatory activity on the nights after vaccination [74]. SWS does not only benefit antigenic memory formation but also it is itself induced by proinflammatory cytokine activity [70,71]. Likewise, SWS is deepened after encoding of psychological information [84].



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Figure 2. Effects of Sleep on Consolidation of Immunological Memory. (A) The available evidence suggests that sleep, mainly through the regulation of hormonal release during slow wave sleep (SWS), promotes the accumulation of antigen-presenting cells (APCs) and T cells (and B cells) in lymphoid tissues by increasing their homing and reducing their subsequent egress. This increases the total number and duration of APC-T cell interactions. The SWS-associated regulation of hormones, cytokines, and chemokines probably also affects [enlarged in (B)] signal strength (red) between an epitope (yellow) presented by an APC and the T cell receptor (TCR, purple). (C) Proposed mechanism of gist abstraction. Examples of epitope immunodominance hierarchies based on signal strength (red lines) at the interface between epitope (yellow) and TCR (purple) are illustrated for the awake and sleep states, respectively. Sleep might favor abstraction of antigenic gist simply by increasing numbers of epitopes and TCRs making contact (three different epitopes and TCRs, marked with different graphical patterns), thereby increasing the options and chance for selecting (encircled) immunodominant epitopes showing high signaling strength with TCRs, which leads to subsequent expansion of the respective T cell clones.

In both systems sleep effects on memory appear to be partly mediated by the SWS-induced suppression of cortisol release [5,85]. Administration of corticosteroids has been shown to block consolidation of hippocampus-dependent memory in rats and humans when these substances are administered during SWS-rich periods of sleep, but not when administered during wakefulness [86]. Low cortisol presumably synergizes with minimum levels of acetylcholine during SWS to facilitate both neuronal memory reactivation in hippocampal networks as well as output towards extra-hippocampal sites [85,87–90]. There is likewise evidence that low cortisol concentrations contribute to enhancing T cell homing to lymph nodes, APC-T cell interactions, and the development of persisting T cells during sleep [5,74,78,79,91,92]. Immunological memory consolidation concurrently appears to benefit from growth hormone and prolactin, which are proinflammatory hormones whose release is enhanced by SWS and which are particularly effective within 24 h after inoculation of an antigen [93]. For psychological memory consolidation the role of SWS-associated activation of somatotrophic activity and prolactin release is currently less well characterized [94]. Many other signals, such as extracellular ATP, TNF, IL-1, complement, mammalian target of rapamycin (mTOR), to name but a few, as well as basic cellular processes of energy supply and protein translation, are all regulated by sleep, and might hence exert parallel actions on central nervous and immunological memory formation (e.g., [70,95–97]), although this remains to be scrutinized in systematic studies.

Box 2. Contributions of REM Sleep to Memory Consolidation – A Matter of Controversy

Presently there is no clear picture of the role REM sleep plays in the process of system consolidation, and especially for abstracting gist and generalized memory representations. In the psychological domain, a sequential process has been proposed in which newly encoded representations are transformed during SWS, and the transformed representations are then stabilized during ensuing periods of REM sleep [6,108]. This notion concurs with the neurochemical conditions during REM sleep, such the strong increase in cholinergic activity, that overall favor synaptic consolidation processes. However, challenging this view, experimental reactivation of hippocampus-dependent memory during SWS (without any ensuing periods of REM sleep) can immediately stabilize memories, thus apparently omitting a period of labilization which is typical when memory is reactivated during wakefulness and which is deemed to be necessary for transforming episodic memory into more schema-like memory [109]. Consequently, it was proposed that effects of SWS might be restricted to merely strengthening the original episodic memory, whereas the transformation of representations would occur in REM sleep [110,111]. However, others also found signs of memory labilization after reactivation induced during NonREM sleep [112]. Moreover, sleep-related gains in performance on tasks (such the number-reduction and sequence-generation tasks), that directly assess the formation of schema-like abstracted memory, appeared to be consistently associated with SWS rather than with REM sleep-related EEG activity during the retention period (e.g., [29,113,114]). In addition, the underlying plastic synaptic processes that enable representational transformations at the neuronal level are established during SWS [24,25]. However, other studies have suggested that some aspects of memory abstraction and the underlying synaptic plasticity involve REM sleep (e.g., [115–117]). The issue is complicated by observations indicating that the presumed abstraction process develops more or less slowly, depending on the stimulus material and pre-existing knowledge, and thus may manifests itself at retrieval only with some delay, and not immediately after the experimental sleep period [118,119]. In sum, whereas the crucial role of SWS in sleep-associated system consolidation is well established, the putative process of gist abstraction might additionally depend on ensuing REM sleep. This conclusion might likewise hold for the immune domain where preliminary data indeed point to an involvement of SWS in gist abstraction [74], but research directly addressing the issue of differential contributions of sleep stages to memory is so far completely lacking.

Why is Consolidation Supported by Sleep in the Brain and Immune System?

A basic communality of both systems is their limited storage capacity. In the brain neither networks of the neocortex ($\sim 20 \times 10^9$ neurons) nor of the hippocampus ($\sim 35 \times 10^6$ neurons) are considered sufficient to allow the separate storage of the many episodes experienced during daily life. Likewise, the $\sim 10^{12}$ T cells of the immune system could by no means adequately represent the enormous heterogeneity of antigenic information encountered during life. We assume that, as a solution to this problem, long-term memory formation in both systems is associated with information reduction by the abstraction of gist. Sleep optimizes gist abstraction (i) by facilitating the information flow from initial to long-term storage systems, and (ii) by preventing a biasing of gist abstraction through ongoing encoding of information into the initial storage system.

In the brain, it appears that minimum cholinergic and cortisol activities during nocturnal SWS are the predominant factors that synergize to favor, via disinhibiting CA3 and CA1 principal cells, the reactivation of hippocampal memory traces and their redistribution to preferentially extra-hippocampal sites [85–90]. In the immune system, sleep seems to generally favor APC–T cell transfer of antigenic information by supporting the synchronized migration and accumulation of both types of cells in lymphoid tissues, as well as by enhancing proinflammatory signals and suppressing anti-inflammatory signals [5,74].

Reactivating memory in the offline condition of sleep might serve to prevent processes of gist abstraction from being distorted by acute information encoding. With ongoing encoding more-recent inputs are expected to dominate and overwrite more-remote inputs which, indeed, happens in the brain when reactivation of hippocampal memory during wakefulness leads to the updating of pre-existing memory to novel context [98–100]. Instead, reactivation in offline conditions appears to allow balanced integration of similar events experienced in different episodic contexts, and thus might allow the abstraction of truly invariant features.

Sleep likewise establishes offline conditions in the immune system by favoring the accumulation of APCs and T cells in lymphoid tissues where APC–T cell interactions occur in a sheltered

location. APCs mature from an antigen-uptaking mode in tissues to an antigen-presenting mode in lymphoid tissues, a process which is conceivably fostered by sleep. Sleep might likewise support an unbiased abstraction of gist in terms of epitope immunodominance and crossreactivity of the T cell clones selected during the APC–T cell interaction (Figure 2). Thus, by synchronizing the accumulation of T cells in lymph nodes to a specific time-window, sleep does not only enhance the range of different TCRs which are recruited into the immune response, thereby increasing the options for gist abstraction, but might also produce a steeper hierarchy of immunodominance.

Concluding Remarks

We have here provided evidence suggesting that, despite obvious differences between the CNS and immune system, the formation of long-term memory in both systems is based on the same principles of a system consolidation process, and even shares common mechanisms linked to the presence of SWS accompanied by reduced levels of glucocorticoid activity. Of course, similarities between the two systems do not imply that the mechanisms for memory formation are all the same. Nevertheless, it is surprising that shared mechanisms exist at all, given how different the systems indeed are. Our observation adds to ontogenetic as well as phylogenetic evidence indicating that sleep-associated active system consolidation in the central nervous domain is established already very early during development [101], and represents an evolutionarily well-conserved function [102]. The emergent picture thus underlines the importance of system consolidation as a basic biological mechanism of memory, whereby sleep represents the preferred organismic state for this process. Eventually, this theorizing also suggests a holistic concept of sleep in which long-term memory formation is an integral function of this state that, beyond serving the brain, captures very different organismic systems.

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Outstanding Questions

Our trans-systems view assuming comparable processes of sleep-dependent long-term memory formation in the CNS and immune system should attract neuroscientists interested in memory to have a look at immunology, which offers a very distinct molecular characterization of the antigenic memory trace – the epitope. Importantly, the approach helps to identify central issues and questions to be tackled in the two systems. The most imminent issue is that of 'gist' abstraction as a proposed ultimate function of system consolidation, and this touches on the fundamental question in neurobiology of how cellular activity translates into memory and thought.

(i) What are the exact mechanisms and rules underlying the abstraction of gist? In the psychological domain, overlap in representations as a reflection of communalities across episodes are discussed as a bottom-up mechanism promoting gist abstraction [36], whereas schema-like representations might bias gist abstraction during consolidation in a top-down manner [58]. However, it might also be promising to consider in this research concepts such as 'representational entropy', 'dissimilarity to the self', and 'epitope structure' which are discussed as factors determining immunological gist abstraction ([103,104], see also [105]).

(ii) Are there mechanisms, such as emotions and danger signals, that tag information during encoding and thereby favor their access to sleep-dependent consolidation, and that share essential similarities between the domains? [26,41]

(iii) Does system consolidation, and especially gist abstraction, require REM sleep in addition to SWS? Does REM sleep do more than merely stabilizing representations transformed during prior SWS (Box 2)?

(iv) Some information, for example autobiographical memories in the psychological domain, appears to remain in the initial storage system [13]. What are the mechanisms preventing the reactivation-induced redistribution of these representations? Related to this: does maintenance of a memory in the long-term store require renewed reactivation, in terms of neuronal assembly replay and epitope presentation by APCs, respectively? [16].

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Future research must translate these open issues into experiments testing specific hypotheses. For example, a straightforward approach to examine effects of sleep on psychological gist abstraction could be based on gestalt perception. Sleep after a training session would be expected to enhance the ability to identify specific complex gestalts placed in a noisy background. During initial training of such tasks the adult brain is expected to involve the prefrontal-hippocampal system for encoding the complex patterns, whereas sleep would be expected to redistribute the respective representations towards neocortical sites, probably including the medial prefrontal cortex and anterior cingulate cortex. For the study of the rules underlying gist abstraction at the neuronal level, assembly recordings could be used to examine how sleep affects overlapping spatial representations in hippocampal circuitry. Sleep might enhance signs of generalization or pattern separation in these assemblies, depending also on the presence of relevant pre-existing spatial schemas. In the immunological domain, for example, APCs of the skin could be labeled to investigate whether during sleep these cells migrate in higher numbers into the draining lymph node. Such sleep-dependent accumulation of APCs in lymph nodes would favor the effective redistribution of antigenic information these cells carry, towards T cells. Similarly, T cells could be labeled to demonstrate their increased accumulation in secondary lymphoid organs during sleep. Central to demonstrating the long-term benefits of immunological system consolidation would be the study of the T cell receptor repertoire of antigen-specific T cells and how it is modified by sleep.

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