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Konsolidace mentálních schémat ve spánku.

Memory Consolidation of Mental Schemata During Sleep.

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Podpis:

## **Poděkování**

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# Abstract

A core feature of the human mind is the ability of abstraction. Relying on this ability, a mental or cognitive schema is a memory framework which underlies alike memory representations. In order for newly acquired memory representations to be preserved for long-term storage, they have to undergo memory consolidation and sleep is a major factor in this process. In a rat model, learning in the context of an existing schema is faster and it is characterised by IEG up-regulation. It is presumable that consolidation during sleep enables the extraction of commonalities from alike memory representations, resulting in schema formation. On a mechanistic level, schemata might be formed by a process which (a) employs synaptic potentiation induced by neuronal replay, (b) requires synaptic downscaling and (c) affects overlapping memory representations. This overlapping character of schema creation might be reflected by the nature of neuronal replay in the hippocampus. It appears that individual sleep stages influence schemata consolidation differently. In human experiments on schemata consolidation, the amount of knowledge a participant is given prior to training is critical.

**Key words:** memory consolidation, mental schemata, cognitive schemata, hippocampus, sleep, neocortex

## Abstrakt

Abstrakce je základní vlastností lidské mysli. Mentální nebo kognitivní schema je systémem, který sdružuje více paměťových stop na základě jejich podobnosti a jako takový je důsledkem výše zmíněné vlastnosti. V konsolidaci paměti, tedy procesu, který je nezbytný pro dlouhodobé uchovávání paměťových stop, hraje klíčovou roli spánek. V myším modelu je učení v kontextu existujících schemat rychlejší a je spojeno s expresí IEG. Je pravděpodobné, že paměťová konsolidace ve spánku umožňuje tvorbu schemat na základě překryvu jednotlivých paměťových stop. Neurální mechanismus tvorby schemat je zřejmě založen na (a) potenciaci specifických synapsí zapříčiněné neuronálním přehráváním, (b) globální synaptické depotenciací na úrovni neurálních sítí a (c) překryvu paměťových stop. Tento překryv je patrně odrazem specifické povahy neuronálního přehrávání v hipokampu. Je pravděpodobné, že jednotlivá spánková stadia ovlivňují konsolidaci schemat různě. Pro studium spánkové konsolidace schemat u lidí je klíčové, jak moc jsou účastníci seznámeni s experimentem.

**klíčová slova:** konsolidace paměti, mentální schemata, kognitivní schemata, hipokampus, spánek, neokortex

# Abbreviations

ACC	Anterior cingulate cortex
fMRI	Functional magnetic resonance imaging
GABA	Gamma-Aminobutyric acid
iOtA	Information overlay to abstraction
IEG	Immediate early gene
LFP	Local field potential
LTD	Long term depression
LTP	Long term potentiation
mAChR	Muscarinic acetylcholine receptor
NRT	Number reduction task
PA	Paired-associate
REM	Rapid eye movement
RSC	Retrosplenial cortex
SPW	Sharp wave
SPW-R	Sharp wave-ripple
SRTT	Serial reaction time task
Ssp	Barrel cortex
SWS	Slow wave sleep
tDCS	Transcranial direct current stimulation

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# 1. INTRODUCTION

A core feature of the human mind is the ability of abstraction. A mental or cognitive “schema” is the consequence of this ability. The experimental focus on schemata is fairly recent, yet the research of this topic has begun earlier. Indeed, it might be said that the competence of the human mind to take pieces of knowledge obtained by sensory input and merge or assemble them together into knowledge that has never been perceived by the means of one’s senses has been researched, albeit indirectly, from the very beginning of cognitive sciences.

A schema is a memory framework which unites alike memories<sup>1</sup>. Through the process of abstraction, it is created when alike information is extracted from two or more memories and stored into a brand new memory, a schema. Let us consider, for instance, cats. There are many different kinds of cats. However, all of them share some common traits: for example, all of them have whiskers, a tail, all of them purr. These are the traits which make cats recognisable as cats, after all. It is presumable that when a person sees a cat, their mind does not start comparing the visual input with all the memory representations of all the cats they have encountered before. Instead, having extracted commonalities from all of these representations, a schema of a cat is already present in the persons mind. By comparing the visual input with this schema, which encompasses all of the aforementioned traits, a person will be able to recognise a cat when he or she sees one.

Memory consolidation is defined as a process which transforms the newly-encoded, labile memory traces into stable ones. Such definition might suggest that this process simply entails quantitative change; nevertheless, it will be demonstrated further that memory consolidation includes qualitative change of the memory trace. According to the *two-stage model of memory consolidation*, the consolidation process happens in two phases: while the memory representation initially resides in a kind of temporary memory storage, it is eventually transferred into a permanent one for long-term preservation. Nowadays, the beneficial effect of sleep on memory consolidation is unchallenged (for example<sup>2</sup>). The concept of schemata has been around for some time<sup>3</sup>, yet, due to the neurobiologists interest in this topic being fairly recent, relation of sleep consolidation and schemata still remains rather unexplored.

This text aims to resume current knowledge of the issue at hand and to discuss the possible implications of this knowledge. In the first three sections, the fundamentals are laid out: molecular, electrophysiological and theoretical basis which is essential for thorough understanding of the topic. Next, recent and important research of schemata in rat models is presented. Finally, the last and most elaborate section deals with the consolidation of schemata during sleep.

## 2. ELECTROPHYSIOLOGICAL CORRELATES OF MEMORY CONSOLIDATION

According to current classifications sleep comprises several distinct stages<sup>2</sup>. Rapid-Eye Movement (REM) sleep, with its neuronal activity resembling wake state, is traditionally a standalone stage on its own. Non-REM stages (stage 1 to 3) are jointly called non-REM sleep. Stage 4, or Slow-Wave Sleep (SWS) is the deepest of them all. These sleep stages differ in neuronal ensemble activity, which manifests as more or less synchronous LFP oscillations and can be measured experimentally. The most important synchronous brain oscillations are hippocampal Sharp Wave-Ripples (SPW-R), cortical slow waves and sleep spindles. Sleep stages and their characteristic oscillatory patterns with respect to memory consolidation will be the content of this section.

### 2.1. Sharp Waves and Ripples

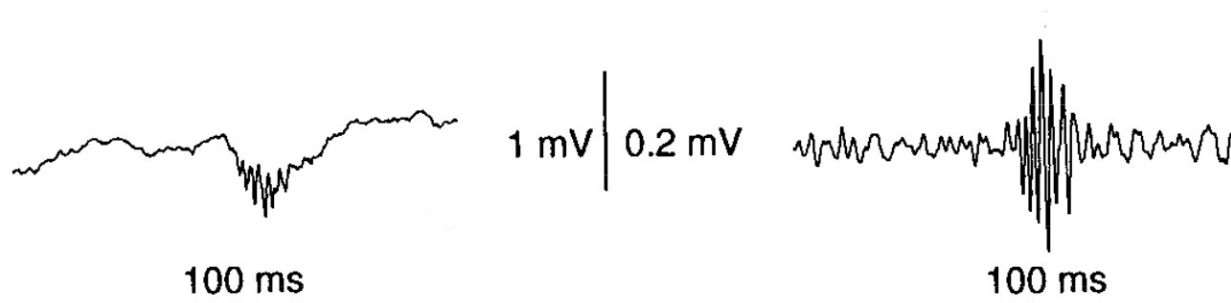


Fig. 1: A SPW-R event recorded from pyramidal cell layers in the CA1 hippocampal region. **Left**, a sharp wave. **Right**, filtered frequencies of 50 to 250 Hz, revealing sharp wave-associated ripple. From Ylinen et al., 1995.

Apart from theta activity, major hippocampal LFP oscillatory patterns are sharp waves (SPW) and ripples, detectable irregularly during quite wakefulness and in deep stages of sleep in the CA3 and CA1 region<sup>4</sup> (fig. 1). SPW are large-amplitude events (40-100 ms long) which appear in conjunction with much faster ripples (50-250 Hz) in the CA1 region; in the CA3 region only SPWs are apparent. These patterns were first observed by C. Vanderwolf in 1969<sup>5</sup>, although he had attributed little importance to them.

Ylinen and his colleagues have done extensive research on the origin of SPWs and ripples in 1995<sup>6</sup>. They have postulated that the EPSPs of CA1 pyramidal cells, which give rise to SPWs, are a direct consequence of those pyramidal neurons being excited by CA3 pyramidal neurons via the Schaffer collaterals. Furthermore, through a series of elegant experiments they have proven that GABA receptor-mediated inhibition is responsible for the existence of fast ripple oscillations. As CA1 pyramidal cells discharge in reaction to EPSPs arriving via Schaffer collaterals, they excite interneurons which in turn exert inhibition on the very same CA1 pyramidal cells. This negative feedback keeps the pyramidal neurons from discharging again until the membrane potential returns to its resting value and the inhibitory effect has

disappeared, wherefore the neurons can accept EPSP coming via Schaffer collaterals once again. The synchronized discharging of inhibitory interneurons manifests as fast ripple oscillations. Due to the joint nature of SPWs and ripples, the term “Sharp Wave-Ripples (SPW-Rs)” has been introduced to describe both of the oscillatory patterns.

The molecular mechanisms responsible for LTP are brought upon *in vivo* by high-frequency oscillations<sup>7</sup>. Simultaneously, it had been shown that the deep layer parahippocampal neurons exhibit increase in activity when SPW-Rs are detectable in the CA1 region<sup>8</sup>. Knowing that the axons of CA1 pyramidal neurons project into the subiculum and entorhinal cortex, Ylinen and his colleagues were one of the first to have hypothesized that ripple oscillations may be a first step in processes leading to potentiation of specific synapses in the neocortex.

This research of SPW-Rs laid the foundations of further inquiries about these characteristic oscillatory patterns and their relationship to memory consolidation. Since then, a considerable body of evidence has emerged proving the importance of SPW-Rs in consolidation of various types of memory. It has been shown that the disruption of SPW-Rs by electrical stimulation during rats post-training sleep results in reduced performance in the learned spatial task<sup>9,10</sup>. As SPW-Rs dominate the hippocampus during SWS, the importance of this sleep stage for memory consolidation is also significant. Experiment with paired-associate learning in humans found a connection between SWS and declarative memory<sup>11</sup>; subjects who slept only the first half of night (when SWS dominates over other sleep stages) improved retention of word pairs over subjects who slept only the second half of night. Last but not least, the existence of hippocampal replay advocates the importance of SWS in memory consolidation.

## 2.2. Hippocampal Replay

Some hippocampal populations are activated in a similar manner during wake state as in subsequent SWS. This phenomenon was named ‘neuronal replay’ (reviewed<sup>12</sup>). Majority of the work done on replay concerns SWS, although there are reports of replay during REM sleep, too<sup>13</sup>. It had been shown that hippocampal place cells whose place fields were overlapping during awake exploration (and which therefore fired at the same time during wake state) discharged together during subsequent SWS as well<sup>14</sup>. It had also been demonstrated that the same principle applies to memory of sequential experience<sup>15,16</sup>: if certain neurons fired in a fixed order during rat’s awake exploration, similar order was preserved during subsequent SWS, only on a tighter time scale (as if the successive firing had been compressed in time). While there were voices in favour of hippocampal replay being a passive result of ‘hard-wiring’, the majority inclined towards the opinion that it reflects previous learning. It is not, however, a result of a cognitive map being simply replayed. The more a pair of CA3-CA1 cells co-fires during awake exploration, the more likely it is to co-fire during subsequent SPW-R episodes, implying that hippocampal replay is also a function of behaviour<sup>17</sup>.

The link between replay and memory consolidation is nowadays an established opinion and, as such, it is not the primary focus of this text. What is rather important, however, for the topic of cognitive schemata, is a recent study which attributes a whole new purpose to replay<sup>18</sup>. In this work, Gupta and his colleagues utilised a training paradigm which allowed the experimenter to abruptly change a rats pathway. There were three different pathways altogether. Let us now focus on only two of them, *route A* and *route B*. During training session, the maze was baited in such a way that the rat took only one route. Then, approximately halfway through the recording session, the bait was relocated, encouraging the rat to take the alternative path (see fig. 7). When the rat stopped to rest at a feeder, replay sequences from hippocampal place cells were recorded. Now, the acquired replay sequences were sorted into two groups: (a) sequences that represented the route which the rat was currently going thorough (e.g. sequence replaying *route A* while the rat was taking *route A*), and (b) sequences that represented a different route than the one the rat was currently taking (e.g. sequence representing *route B* while the rat was going through *route A*). Naturally, the authors have previously obtained recordings from each rat to know the characteristic replay sequence for a specific path. Note that at the time of recording, the rat had far less experience with the route it has had taken most recently as the routes had been switched halfway throughout the recording session. Subsequently gathered data (fig. 2) reveal that a rat did not preferentially replay the route which it had the most experience with nor the most recently taken one; instead, both pathways were replayed equally. This finding is crucial as it could mean that the hippocampus does not passively replay any input which was given to it, instead it ‘reevaluates’ the importance of each input and replays it accordingly. Besides, the work of Gupta and his colleagues has further impact on the topic of schemata consolidation, which will be discussed in section 6.5.

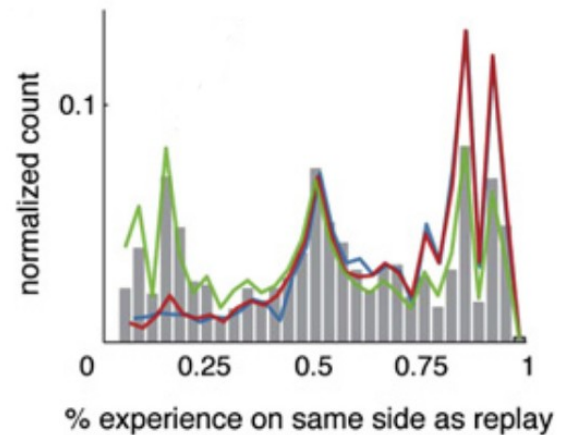


Fig. 2: A histogram showing the percentage of replay sequences representing the same route as the one a rat was currently taking, relative to all replay sequences recorded from the rat. **Grey bars**, actual data from the experiment. **Blue line**, the authors' prediction of sequences representing most recently experienced route being replayed preferentially. **Red line**, prediction of sequences being replayed preferentially based on which path did the rat have the most experience with. **Green line**, prediction of replay not depending on any of those factors. Note that the green line models the actual data well. From Gupta et al., 2010.

### 2.3. Slow Oscillations and Spindles

Apart from SPW-Rs, the major oscillatory patterns characterising sleep are slow oscillations (slow waves) and sleep spindles. Slow waves are prolonged oscillatory events of periodic depolarisation (coined “UP states”) and subsequent hyperpolarisation (“DOWN states”) occurring with a frequency of 0.5 to 4 Hz in almost all cortical neurons, with approx. 10-20 mV difference between UP and DOWN states<sup>19</sup>. Another

brain oscillation traditionally mentioned in the context of sleep are delta waves. However, the discovery of slow waves<sup>20</sup> allowed for an alternative view on delta waves as their negative part is formally equivalent to the DOWN state of slow wave and therefore they may be considered an extended form of a slow wave<sup>19</sup>. Another characteristic oscillatory pattern are sleep spindles<sup>19</sup> - sequestered, in-and-out fading oscillations of 10-15 Hz occurring in deeper stages of sleep (stage 2 and SWS). Originating in the thalamus, each spindle event last about 0.5 s. One can think of slow oscillations as the omnipresent rhythm governing the cortex which other (faster) oscillatory patterns, such as delta waves and sleep spindles, are built upon.

Recent research has linked slow waves and spindles to memory consolidation<sup>21-24</sup>. One study<sup>21</sup> examined EEG of humans, after learning a word-pair task and also of rats, after learning an odour-cued spatial task. The power of slow oscillations remained unaffected, but amplitude of the UP state increased slightly after previous learning. Another publication reported a decrease in slow wave amplitude in sleep following a period of learning deprivation<sup>23</sup>. Transcranial direct current stimulation (tDCS), using the amplitude and frequency of physiologically occurring slow waves, resulted in better performance in rats trained on a radial maze task<sup>21</sup>. However, only working memory (i.e. rat knowing which arm it has already visited) was positively influenced while reference memory (i.e. rat knowing which arms to go to as those were baited during training session) remained unaffected. An increase of power in the sleep spindle frequency was observed in humans after learning of a paired-associate task employing both declarative and visual memory<sup>24</sup>. The same study reported no increase after learning a task relying on purely visual memory.

Sirota and Buzsáki have presented evidence of neocortical and hippocampal oscillations being correlated on both large and fine timescales during SWS<sup>25</sup>. Constructed cross-correlograms showed the discharge of recorded neocortical and CA1 units being phase-locked to the negative and positive peak of spindle oscillations, respectively. Simultaneously, a fine timescale analysis revealed that the recorded neocortical neurons fired approx. 50-100 ms before the neurons in CA1. Hence the neocortical slow oscillations and related sleep spindles exert some degree of influence over hippocampal SPW-Rs. It had been proposed that the two-stage model of memory consolidation needs a mechanism which would provide for temporal organisation of the information being transferred from the temporary to the permanent memory storage and that slow oscillation and associated spindles could be this sought-for mechanism<sup>19</sup>.

## **2.4. REM Sleep**

The trends in research of sleep and memory have shifted: albeit REM sleep used to be the main culprit for memory consolidation during sleep, recent decade have brought other sleep stages to prominence, with the emphasis on SWS. However, REM sleep still bears great importance to memory consolidation. A somewhat basic theorem states that declarative memory benefits from SWS while procedural memory relies more on REM sleep<sup>11</sup>. But the matter at hand is far more complicated.

A recent study<sup>26</sup> measured the rCBF (regional cerebral blood flow) in REM sleep after the participants have learned two different types of serial reaction time tasks<sup>27</sup> (SRTT). One was a classic form of SRTT based on a probabilistic rule while the other SRTT was completely random (and, therefore, not really a SRTT *per se*). The group which has learned the classic SRTT *implicitly* during wake-state showed an increase in rCBF in subsequent REM sleep and this increase was significantly greater than in the other two groups (the explicitly-learning group and the group trained on the random SRTT). As the increase in rCBF indicates functional changes, the authors have interpreted it as an active restructuralisation of the implicit memory traces taking place in REM sleep.

A significant body of research on REM sleep was also done with respect to memory interference. It has been shown that performance in the weather prediction task (a procedural learning paradigm in which the outcome of each trial is based on a hidden probabilistic rule) benefits from naps containing only REM sleep, but the performance can be reduced again by learning an interference task<sup>28</sup>. However, if the interference task is learned prior to sleep, REM sleep (but not SWS on its own) can protect the original task from this interference<sup>29</sup>. The latter study used a perceptual learning paradigm which is prone to retroactive interference (i.e. an interfering task is learned shortly after the original one) by a competing task. The participants who took naps of 1,5 h containing both non-REM and REM sleep performed significantly better at the original task than the participants who napped only in non-REM sleep. Apart from that, rats after exploration of novel objects manifested an up-regulation of several plasticity-related IEGs (such as *Arc*, *Fos* and *Egr1*) immediately after exploring as well as during subsequent REM sleep; yet no such up-regulation was detected in SWS<sup>30</sup>. Finally, research on frequency coupling demonstrates that synchronicity between hippocampal theta and neocortical theta during REM sleep is very low<sup>31,32</sup>.

Indeed, it appears that a theoretical role for REM sleep in memory consolidation exists. There are voices<sup>2</sup> which advocate that the neocortical regions “disentangle” themselves from the hippocampus during REM sleep: in accordance with the two-stage model, SWS would provide for the transfer of memory traces from the hippocampus to the neocortex and subsequent REM sleep would then act independently in further consolidating the transferred traces on a cellular level. Clearly, the aforementioned research regarding interference<sup>28,29</sup> as well as the IEG<sup>30</sup> and phase-coupling<sup>31,32</sup> studies corroborate this opinion. Also the dependency of declarative and procedural memory on non-REM and REM sleep, respectively, fits this hypothesis as the basis for declarative memory is the integration of partial memory traces across different cortical regions<sup>2</sup>. This, though, might be a gross oversimplification as the very same integration is fundamental for the consolidation of cognitive schemata, yet those have been reported to be connected with REM sleep<sup>33</sup> (also see section 6.4.).

### 3. MOLECULAR BASIS OF MEMORY CONSOLIDATION

The hippocampus can exist in two functionally distinct states and the neuromodulator Ach mediates the shift between those states (reviewed<sup>34</sup>). In REM sleep and in wake-state, the hippocampal circuitry is primed to acquire and encode new information whereas in SWS and during quiet wake, it is tuned for memory consolidation. The change in concentration of Ach facilitates the transition between the two states by adjusting the communication between pyramidal cells and inhibitory interneurons in the hippocampus. High cholinergic tone in wake-state and REM sleep leads to the interneurons being depolarised more easily<sup>35</sup>. Simultaneously, high cholinergic tone also leads to decreased IPSPs inflicted on pyramidal cells by the interneurons<sup>35,36</sup>. Overall, the interneurons inflict IPSP on the pyramidal cells more often (even a weak input depolarises the interneurons), but this IPSP is weak in general. Computational analysis have shown that this way, the hippocampus is less prone to interference in the form of a weak input and therefore is primed to receive new, strong input<sup>37</sup>. Weak input will be abolished via the feedback inhibitory activity of the interneurons, but this feedback inhibition will not be strong enough to cancel strong input with informational value. On the other hand, cholinergic tone is low during quiet wake and SWS<sup>37</sup>. Hence, the interneurons can exert full inhibition on the pyramidal cells and this inhibition will be proportional to the input received by the pyramidal cells. Such mechanism is crucial as it provides for the formation of specific hippocampal LFP oscillations, which are indispensable to memory consolidation<sup>6</sup>. This will be later considered in section 3.1.

Another key attribute of acetylcholine is its ability to control the expression of IEGs<sup>38,39</sup>. Immediate-early genes (IEGs) are the direct and transient genetic response to increased neuronal activity (reviewed<sup>40</sup>). In the hippocampus, the increase of IEG counts after novel object exploration as well as after many different learning paradigms is imminent (for instance<sup>41</sup>). The most researched IEGs include *Arc* (which codes for the Activity-regulated Cytoskeleton-associated protein), *Egr* (gene for the Early Growth Response protein, also known as *Zif268*) and *c-Fos*. While the product of *Arc* is an “effector” protein (i.e. a protein which directly modulates specific cell functions) the latter two give rise to zinc-finger transcription factors<sup>41</sup>. Thanks to their rapid responsiveness to neural activation, IEGs have long been thought to be the molecular foundation of LTP and LTD and of synaptic plasticity in general.

As was mentioned, Ach plays a role in controlling IEGs. There is evidence linking signalisation via mAChRs to the up-regulation of *Egr*<sup>38</sup>. Also, activation of m1AChRs and m3AChRs by ACh agonists (such as pilocarpine and carbachol) resulted in increase of *Arc* counts<sup>39</sup>. These pieces of evidence are significant for justifying the dissimilar roles of different sleep stages in memory consolidation and their implications will be discussed further in section 3.4.

## 4. MODELS OF MEMORY CONSOLIDATION

Nowadays, the concept of cognitive processes employing two distinct kinds of memory storage is regarded as a commonplace. In this section, some substantial models of memory processing and memory consolidation will be considered in more detail as their thorough understanding is, in the long run, essential for the concept of mental schemata.

### 4.1. Encoding vs Consolidation

One of the fundamental concepts is the *two-stage model of memory trace formation*<sup>42</sup>. According to this model, memory representations are encoded immediately after exploration in the form of transient, weak potentiation of specific CA3-CA1 synapses. This transient potentiation is driven by the discharge of granule cells in the dentate gyrus during theta waves associated with exploratory behaviour. After that, during subsequent SPW-R activity, reverberation is present and this reverberation further enhances the synaptic strengths of the specific CA3-CA1 synapses which were weakly potentiated before. In summary, the memory is *encoded* during theta activity and, later on, *consolidated* during subsequent SPW-R activity.

The aforementioned reverberation is an important phenomenon and, as such, it deserves further explanation. Buzsáki and his colleagues<sup>42</sup> stimulated the perforant pathway and indeed, single pulses occasionally resulted in doubled responses. Interestingly enough, the amplitude of the second, reverberative response was almost identical to the first, directly evoked one. The authors did not presume, however, that this is a result of the hippocampal circuitry simply being “hard-wired” in such manner. On the contrary, they suggest that the wiring responsible for the reverberation may well be situated outside of hippocampus. Nevertheless, these findings are compatible with the opinion that the neurons whose discharge activates the hippocampal trisynaptic pathway can in turn be activated by the very same pathway’s output.

Apart from reverberation, other observations were recapitulated and reviewed by Buzsáki<sup>42</sup>. As SPWs meet the physiological requirements for induction of LTP, Buzsáki stated that these are solid candidates for induction of LTP in hippocampal pyramidal cells. He had already proven earlier that high-frequency stimulation of the Schaffer collaterals leads to an increase in quantity of SPWs as well as their amplitude<sup>43</sup>. Later findings on SPW-associated ripples also complement this statement<sup>6</sup>. Apart from that, LTP induction in the dentate gyrus’ granule cells by stimulation of the perforant pathway was more successful during theta activity than during SWS and quiet wake<sup>44</sup>, indicating that information processing in the dentate gyrus abides by different rules than processing in CA3 and CA1 regions. All of the observations mentioned above support the model.

Note that the *two-stage model of memory trace formation* is not the same thing as *two-stage model of memory consolidation* (reviewed<sup>2</sup>). While the former describes the process discussed above, the latter refers to the transfer of newly *consolidated*

information from a temporary memory storage to a permanent one. Also, the phrase “two-stage model” nowadays usually refers to the latter. All in all, the fate of a newly acquired memory could be recapitulated as follows: (a) the memory is encoded in the form of transient memory representations, (b) these transient representations are consolidated, thereafter residing in the temporary memory storage, and (c) the memory representations are finally transferred from the temporary to the permanent memory storage.

## 4.2. Complementary Learning Systems

Although the *two-stage model of memory trace formation*, as introduced by Buzsáki in 1989, did not address the issue of hippocampal-neocortical dialogue directly, it did inspire others to do so. Soon enough such possibility was theorized and the concept of *complementary learning systems* has seen the light of day<sup>45</sup> (reviewed<sup>46</sup>). Essentially, this concept came to existence as a result of connectionist neural models not being able to deal with catastrophic interference<sup>47</sup>: confronted with a paired-associates task (in accordance with the *AB-AC paradigm*), human subject manifested only small levels of interference while connectionist neural networks have failed at this task completely<sup>46</sup>.

The *AB-AC* paradigm has subjects learn word paired-associates A and B (e.g. table - chair). Afterwards the subjects learn paired-associates A and C (the first word of the previous group of words is preserved but new word is associated with it, e.g. table - plate). A degree of interference can be extrapolated by testing the knowledge of AB paired-associates during and after the learning of AC paired-associates. This is where classic neural networks based on a purely connectionist approach have failed when compared human subjects.

A solution to such problem, one which does not cope with interference at the expense of undermining other key features of the neural network, would be *interleaved* learning. McClelland and his colleagues<sup>45</sup> have proven that if a neural network is trained in such a way that the incorporation of new information happens gradually, the effect of interference is decreased. If the training for new information (the demand for new output) is interleaved with repeated training for the original information (demand for original output) the effect of interference can be significantly abolished. They have also shown that interleaved learning, albeit a solution for interference, gives rise to another problem: the amount of time needed for such process. An elegant way to deal with this problem would be a presence of two stand-alone networks, one ‘temporary’ and one ‘permanent’. The temporary network would rapidly learn a new piece of information. Then, during an offline period when no input is received by it, the temporary network would pass the information to the permanent network by the process of interleaved learning. One could easily assume that the temporary storage is the hippocampus, the permanent storage are the remote neocortical regions and that the offline period is sleep. This assumption is essential as it has served as a cornerstone of *the two-stage model of memory consolidation*, a concept crucial for the future direction of memory research.

## 5. COGNITIVE SCHEMATA

As was already mentioned, a schema is a memory framework which encompasses alike memories. One can think of it as a memory representation which is superordinate to other partial memory representations because it stores the information mutual to those partial memories. Ever since its introduction, albeit clearly an essential concept, it has received surprisingly little attention from neurobiologists.

The recent work of Tse et al.<sup>48</sup> brought this topic of research back into the light as they were one of the first to emphasize its significance by experimental procedures. They trained rats according to the *spatial-flavour* paradigm, a spatial paired-associate learning procedure which had been proven to be (at least initially) dependent on the hippocampus<sup>49</sup>. In this paradigm, rats were trained to dig in correct “sand-wells” in order to find reward when a specific odour cue was presented to them. The reward, in the form of a food pellet, was scented by the same flavour as the one that was presented in the beginning of the trial (Fig. 3). The authors have verified that the improvement of rat’s performance was not on the account of the flavoured food pellets giving off scent by including a trial session in which the food pellets were not flavoured. There were six training sessions separated by a 48-hour period, each session containing one learning trial for every paired-associate.

After 48 hours, when the animals have learned the paired-associates (PAs), a single training session was conducted, only two of the original paired-associates were replaced by completely new ones. 24 hours later, during non-rewarded probe trials, the animals were able to locate the correct sand well, be it the original or the new paired-associates. Finally, hippocampal lesion induced in some of the rats another 24 hours later (48 hours in total after the acquisition of new paired-associates) did not impair memory for the new paired-associates (fig. 4). These results are most notable for two reasons. First, only one learning trial was necessary for the acquisition of new PAs, in comparison with the original PAs. Second, contradictory to opinions that system-wide memory consolidation is normally a gradual and slow process<sup>50</sup>, the memory for the new PAs was safely residing outside of the hippocampus only 48 hours after acquisition. This suggests that a framework consisting of memory representations of original PAs, a *schema*, had been present during the acquisition of the new PAs and this schema facilitated and sped up the subsequent consolidation process.

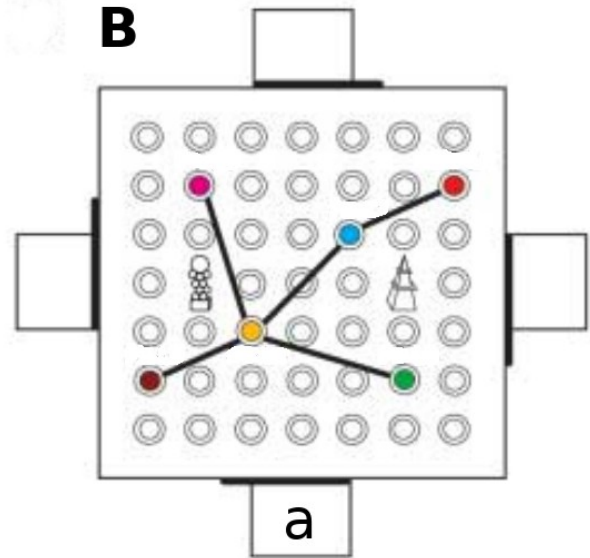
**A****B**

Fig. 3: Experimental setup. **A**, locations of the "sand-wells" relative to intramaze cues. **B**, diagram of the experimental maze. Six out of 49 sand-wells were selected for a set of PAs. After being given an olfactory cue in one of the start boxes (lowercase a), the rats were to locate a corresponding sand-well and dig in order to find reward. From Tse et al., 2007.

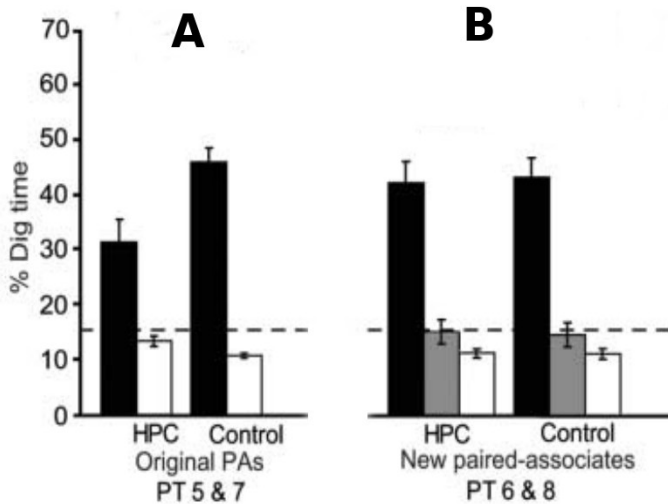


Fig. 4: Both hippocampal-lesioned and sham-lesioned animals remembered original as well as new PAs. The memory retention of a PA was quantified by the amount of time a rat spent digging in the corresponding sand-well relative to other sand-wells ("% Dig Time"). Hippocampal-lesioned (HPC) animals are compared with sham-lesioned (Control) animals. **A**, retention of the original PAs when cue was (black columns) or was not (white columns) given in the start box. **B**, retention of the new PAs, cued (black columns) or non-cued (gray columns), compared with the retention of non-cued original PAs (white columns). From Tse et al., 2007.

## 5.1. Cellular or Systems Consolidation

The year it was published, the work of Tse and her colleagues led to a discussion which should not escape the readers attention. The main reasons for discord were the two distinct processes responsible for memory consolidation: *cellular consolidation* and *systems consolidation* (reviewed<sup>51</sup>). Cellular consolidation is understood to be all the molecular machinery responsible for changes at a synaptic level; at the same time, cellular consolidation is defined as a process which results in the memories being ultimately independent of such machinery and, therefore, the memory being consolidated. Systems consolidation, on the other hand, is simply defined as a process which a memory goes through to become independent of the hippocampus. Naturally, systems consolidation is a matter of completely different time scale than cellular consolidation, which happens as soon as hours after memory acquisition<sup>52</sup>.

In the ensuing discussion<sup>53</sup>, Rudy and Sutherland pointed out that what Tse et al. had attributed to systems consolidation might as well be the result of cellular consolidation. The critical piece of information here is the fact that in the hippocampal-lesioned animals, the memories of new PAs were preserved 48 hours after acquisition but not 3 hours after acquisition. Tse et al. concluded that 48 hours after the acquisition, the memory representations of the new PAs had been securely located outside of hippocampus and, therefore, were save from hippocampal lesion. Rudy and Sutherland, however, offered a different interpretation. They argued that cellular consolidation might have been responsible, as it would have employed this exact time frame (i.e. 3 to 48 hours). Furthermore, they emphasized that the specific method of lesion induction also validates their interpretation. Due to the injections of ibotenic acid causing excitotoxic death in the neurons, the not yet complete cellular consolidation would too be disrupted 3 hours after acquisition: the excitatory barrage associated with excitotoxic death of neurons projecting into the neocortex would lead to destruction of the incomplete memories stored in there.

The authors of the original paper reacted briefly<sup>54</sup>, disproving this alternative interpretation yet appreciating some of its details. Nevertheless, when inspecting the correspondence, one might begin to question the significance of such strict terminological separation. Clearly, there was a mental framework which has facilitated the consolidation of new, but alike memories, no matter the exact mechanism. One can imagine memory consolidation as a gradual process, in which molecular changes, acting on a synaptic level, slowly verge into network-wide modifications. Those molecular processes were in the end responsible for the network-level changes. To conclude, it might be said that in the context of schemata, the borderline between *cellular* and *systems* consolidation slowly fades away.

## 5.2. IEGs in Schema Formation

Among different methods of studying cognitive schemata, molecular approaches do not fall behind. Recent analysis of IEG expression in selected cortical regions yielded interesting results<sup>55</sup>. In this study, the expression of *Arc* and *Zif268*

(synonymous to *Egr*) in certain cortical as well as hippocampal areas in rats was examined. The cortical regions in question were the prelimbic cortex, ACC (anterior cingulate cortex) and RSC (retrosplenial cortex). The rats were trained in accordance with a similar training paradigm as was previously mentioned<sup>48</sup> as the experiment was done by the same authors. After training them for six PAs, the rats were assigned into three groups: OPA (original paired-associates), NPA (new paired-associates) and NM (new map). Two groups differed in treatment during subsequent training sessions: the NPA group was trained once for two new PAs (which were supposed to be rapidly assimilated into an existing schema) while the OPA group had only to retrieve two of the original PAs. NM group was trained for six different PAs altogether in a manner which was supposed not to allow schema formation and assimilation.

Subsequent testing of the animals confirmed that the original PAs (OPA group) as well as new PAs (NPA group) were learned successfully while the NM group failed to recall any of the PAs. 80 minutes after that, cross-sections of the rat's brains were prepared for histochemical analysis. Interestingly enough, the NPA group showed much higher *Arc* and *Zif268* counts than the NM and OPA group (fig. 5A), albeit the NM group was, arguably, exposed to at least the same amount of novelty. On the other hand, the *Arc* counts in the hippocampal CA1 region were high in both NM and NPA rats (fig 5B). Apparently, both the NM group and the OPA group successfully processed the information in the hippocampus, but only the OPA group was able to deposit the information in cortical areas on such a short notice. These findings further corroborate the theory that the OPA group indeed possessed a cognitive schema which would facilitate the assimilation of new PAs while the NM group had no such thing. If this theory is true, the results would also suggest that the creation of schema took place outside the hippocampus; a simple, yet important notion.

However, even more can be extrapolated from those results. According to one concept of memory retrieval, the memory is reactivated actively, in a top-down manner<sup>56</sup>, i.e. based on a stimulus coming from some "upstream" network. As the authors point out, the fact that the NM group showed high amount of *Arc* in CA1 but lower counts of *Arc* in the prelimbic cortex would imply that the urge to down-regulate *Arc* originated somewhere "upstream" of prelimbic cortex and not within the hippocampus, therefore the IEG activation was regulated in a top-down fashion.

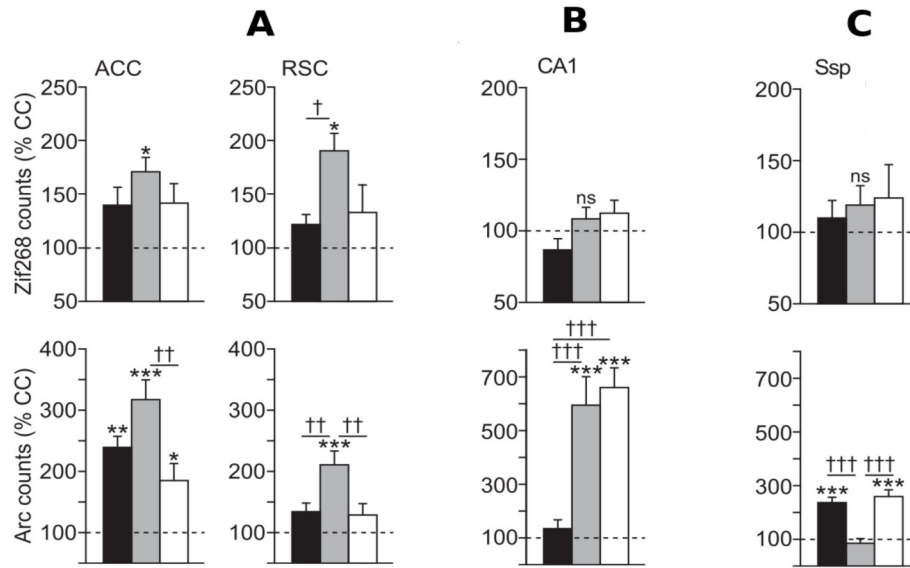


Fig. 5: IEG counts in different cortical regions. **Black columns**, OPA group; **gray columns**, NPA group; **white columns**, NM group. IEG counts in trial animals were expressed relatively to a group of control animals, whose IEG counts were arbitrarily set to 100%. **A**, Arc and Zif counts in the ACC and RSC. Note that both IEGs were up-regulated in the NPA group even more than in the NM group. **B**, Arc and Zif counts in the CA1 region. Note the elevated Arc, but not Zif counts in both the OPA and NM groups. **C**, Arc and Zif counts in the barrel cortex (Ssp), which was picked as a control region for the experiment. From Tse et al. 2011.

## 6. THE ROLE OF SLEEP IN SCHEMA CONSOLIDATION

Thanks to the work reviewed in the previous section, a schema is now reliably defined in a rat model. From now on, the focus of this text can move to the effect of sleep on schema consolidation. Not all publications discussed in this section investigate this issue directly; however, relevant theories can be built upon their implications.

### 6.1. Sleep Inspires Insight.

Not only does sleep-dependent consolidation promote quantitative changes in memory representations, there is also a considerable evidence of qualitative changes taking place<sup>57–60</sup>. This topic has been approached in different ways, yet all of the experiments focus on one principal idea: the participants, subjected to a simple task of the experimenters choosing, were to attain insight into the task's hidden rule. Their performance improved abruptly the very moment they would grasp this underlying rule. This is the moment in which insight, i.e. an explicit knowledge of the underlying principle, is gained. In one study<sup>58</sup> the participants were given a modified version of *NRT* (number reduction task), in which the correct result could have been achieved

either slowly, by working through a series of digits, or fast, if they understood a simple principle underlying the task. The participants who have slept before subsequent retesting were more than twice as successful at understanding the principle than both daytime and nighttime wakefulness groups. Naturally, no insight was observed in participants who did not come in contact with the task before sleep.

The transformation of implicit into explicit knowledge may also be considered a kind of insight. SRTT<sup>27</sup> is similar to aforementioned NRT in that there is a covert, underlying principle to it. This task is also a perfect candidate for investigating the issue at hand as it can be learned either implicitly or explicitly, and the moment of gaining explicit knowledge can be precisely defined. Recent work<sup>59</sup> employed a modified version of SRTT to examine the effect of sleep on conversion of implicit into explicit memories. The participants were asked to press a key upon seeing a corresponding visual stimulus as fast as they could; the moment their reaction times significantly decreased was the moment they have gained implicit knowledge of the principle. Naturally, the appearance of the visual stimuli was not random as it followed a hidden rule. After the participants have learned the task on an implicit level, they were subjected to a *generation task* in which they had to predict the appearance of visual stimuli and therefore take advantage of explicit memories (if available). This task decided whether they have also gained explicit knowledge. The participants who slept after SRTT were much more successful at the subsequent generation task in comparison with the daytime wakefulness group. Ergo, sleep positively influences the transformation of implicitly into explicitly coded memories.

## 6.2. The Overlapping Hypothesis

A simple, yet efficient hypothesis on how such a schema comes to existence was proposed by Lewis and Durrant<sup>1</sup>. Let there be two similar memories represented by two similar neural networks. As the memories are similar, the authors suggest that some nodes of the neural networks must be shared by both of said memories. Therefore, when neuronal replay occurs during SWS, the shared nodes are reactivated more often and, in accordance with principles of Hebbian learning, will form stronger synapses among each other. Furthermore, the shared nodes being reactivated more often, the synapses among them are less prone to synaptic downscaling and that is why they are more likely to prevail while synapses among non-shared nodes will most likely be reset. Such processes underlying the creation of cognitive schemata were named “information overlay to abstract” (iOtA)<sup>1</sup>.

## 6.3. Synaptic Homeostasis

To thoroughly grasp the iOtA, one needs to understand the concept of synaptic downscaling. Synaptic weight, a term used as much in neurobiology as in the science of artificial intelligence, can be defined as the amount of impact one specific neuron can exert on another neuron. This weight is mediated by the synapse between the

neurons, hence “synaptic” weight. In the course of rat’s early development the synaptic weights do not stay the same; in this particular model, the increasing number of synaptic input a neuron obtains is reflected by the decrease of those synapses’ weights and vice versa<sup>61</sup>. This indicates that the brain truly is capable of adjusting the weights, capable of scaling them.

To briefly summarize the hypothesis of synaptic homeostasis<sup>62,63</sup>, it states that SWS is associated with decrease of synaptic weights globally. During wake state, the learning of new information is mediated by the process of synaptic potentiation, i.e. an increase of synaptic strengths (synaptic weights). This synaptic potentiation generates the need for a baseline to which those weights could be reset after a while, otherwise the brain’s plasticity would be threatened. The hypothesis suggests that this decrease of synaptic weights, this synaptic downscaling, would take place during sleep as it is the state in which the brain obtains no sensory input. Essentially, one might consider synaptic downscaling one of the possible solutions of the stability-plasticity dilemma<sup>64</sup>, together with aforementioned interleaved learning. Note that those two concepts are not in disagreement. It also appears that the downscaling affects primarily synapses that were more active during preceding wake-state (and therefore have probably encoded new information), thus preventing the loss of previously stored information<sup>65</sup>.

Additionally, the concept of synaptic downscaling differs from standard long-term depression (LTD) mainly because it affects all synapses belonging to a single neuron while LTD is defined for a selected group of neuron’s synapses; however, this does not mean that they both employ different molecular mechanisms. Indeed, later publication from the authors of this hypothesis points towards possible proof of synaptic downscaling being based on the same molecular principles as LTD<sup>66</sup>. Recent work with rats as well as *in vitro* preparations also suggests the relevance of hippocampal ripple activity for synaptic downscaling<sup>67</sup>.

## 6.4. Assimilation into Pre-existing Schema

The mechanism of schema creation has been laid out by Lewis and Durant. Even more interesting, though, might be their account on how a new memory is incorporated into an existing schema<sup>1</sup> (fig. 6). Let us assume a pre-existing cognitive schema represented by a neural network in the neocortex. For better explanation of the following mechanism, memory representations stored in the hippocampus are denoted “traces” while their corresponding representations in the neocortex are denoted “neural networks”. Let there be a fairly new hippocampal memory representation (*trace A*) which projects into the neocortex and forms a corresponding neural network (*network A*) in there. If *network A* were to share some of its nodes with an existing schema, reactivation of *trace A* would trigger simultaneous reactivation of both the schema and *network A*, resulting in strengthening of synapses among the two. However, up until now, it can-not be said that the new memory has incorporated into the schema. As the authors stress out, the newly formed synapses are far too weak to withstand synaptic downscaling. Here, another new memory representation (*trace B*), which, projects to a corresponding cortical network (*network B*), is crucial. If *network*

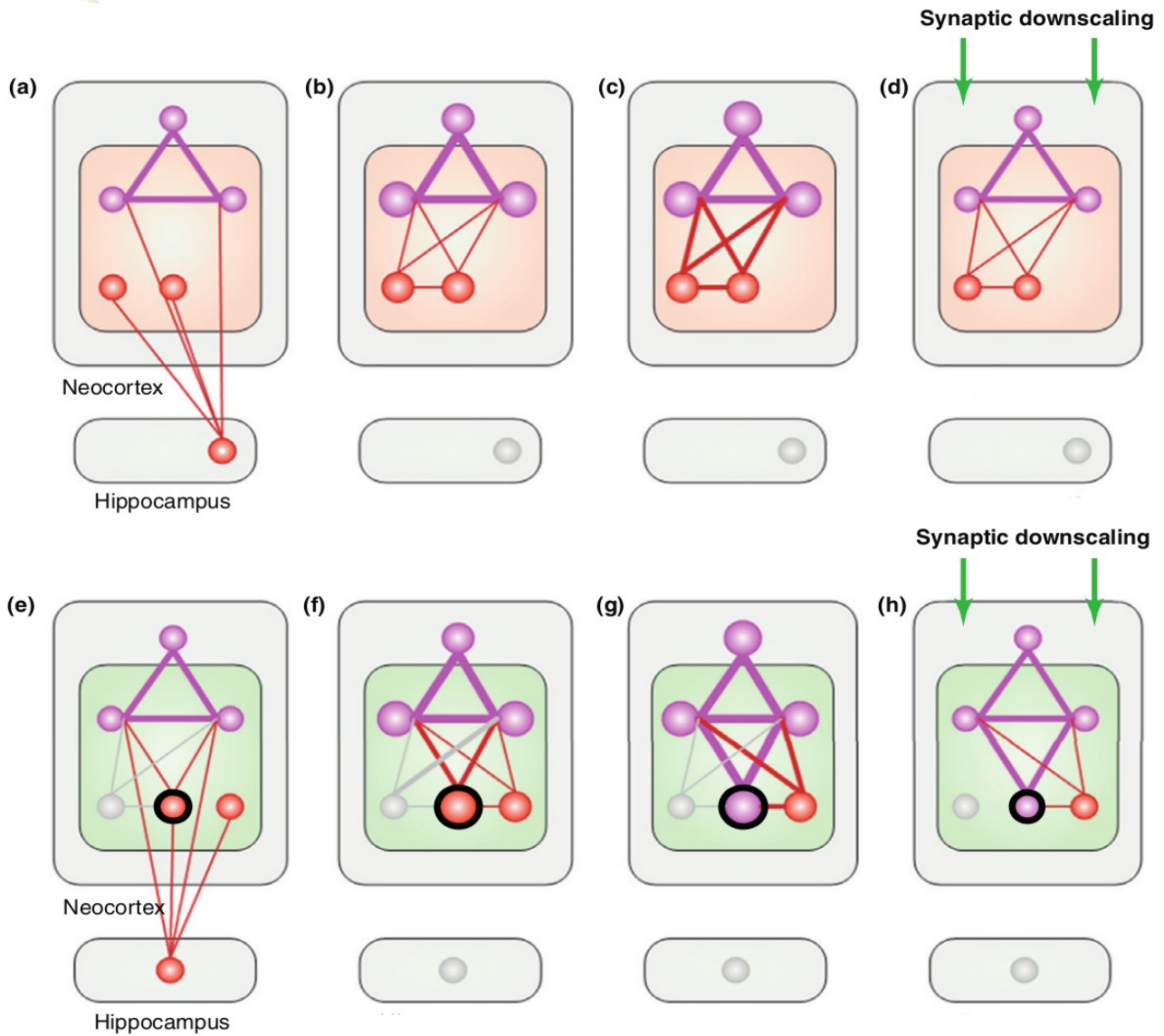


Fig. 6: Incorporation of new memory into a pre-existing schema, according to the i0tA hypothesis. Nodes are denoted by circles, synapses by lines among them, with the thickness of lines indicating the strengths of these synapses. New memory representations are drawn in red, neocortical schema is drawn in purple. **(a)** Reactivation of *trace A* triggers corresponding reactivation of *network A*, which partially overlaps with an existing schema. This leads to **(b)** "creation" of synapses among *network A* and schema. **(c)** During subsequent sleep, the synapses are further strengthened by replay; however, they are also **(d)** weakened by synaptic downscaling and, thus, are too weak to provide for incorporation of *network A* into the schema. **(e)** Reactivation of *trace B* results in reactivation of *network B*, which shares one node (black circle) with both *network A* and schema. The shared node is now strongly connected to the schema **(f)** and subsequent sleep strengthens this connection even further. As the shared node and schema were reactivated concomitantly multiple times, the node is now incorporated **(g)** and the newly-formed schema will withstand synaptic downscaling **(h)**. From Lewis and Durrant, 2011.

*A*, *network B* and the existing schema all show some degree of overlap, the reactivation of *trace B* in the hippocampus results in subsequent neocortical reactivation of all the shared nodes, which produces further strengthening of synapses among them. Note that the synapses connecting nodes shared by *network A* and the schema have now been activated multiple times and thus, the synapses among them are already strong enough to prevail. When synaptic downscaling occurs the following night, these synapses will survive while other will be downscaled “completely” (i.e. their synaptic weights will be decreased so much that they will no longer be relevant for the storage of information). In summary, if new memories are to be incorporated into a pre-existing schema, they need to (a) overlap with the schema and (b) be reactivated multiple times.

This mechanism, albeit elegant, can-not be readily used to explain the findings of Tse and her colleagues<sup>48</sup>. The key point of Lewis’ and Durrant’s theory is the fact that the crucial, shared nodes must be reactivated together multiple times in order for strong enough synapses to form among them. This would be, in practice, accomplished either by acquisition of another overlapping memory or by multiple activation of the original memory. However, Tse et al. state that the new PAs were trained only once. Hence, taken the Lewis’ and Durrant’s theory into consideration, it would appear that the new memory traces were reactivated, either during post-acquisition wakefulness or during subsequent sleep.

Such contemplation inevitably unveils the contradictory nature of two fundamental concepts: SWS-associated neuronal replay and synaptic downscaling, both of which had been discussed above. The concept of hippocampal neuronal replay suggests that the role of sleep in schema consolidation is to allow for hippocampal replay and, therefore, to allow for synaptic potentiation in corresponding neocortical regions. On the other hand, the synaptic downscaling hypothesis infers that the role of sleep is to provide for system-wide diminishing of synaptic weights, a sort of global synaptic depotentiation. What is more, recent work suggests that hippocampal ripples, a pattern widely associated with neuronal replay, is responsible for synaptic downscaling as well<sup>67</sup>. What is the role of sleep, then: potentiation, or depression? Or could it be both? Theoretically, the two distinct processes could co-exist peacefully. Indeed, the probabilities of different CA1 pyramidal cells firing during SPW-R episodes are not equal - some discharge up to 40% of SPW-R episodes while others discharge scarcely<sup>6</sup>. Furthermore, if a CA1 pyramidal cell fires frequently during preceding theta oscillation in REM sleep, there is a slightly higher probability that the same cell will fire during subsequent SPW-R episodes<sup>16</sup>. It could be hypothesized that monotonous repetitive spike-trains would emerge globally within hippocampal pyramidal cell population, but not all neurons would partake. Some neurons would produce isolated bursts of action potential, thus providing for selective potentiation of some synapses amidst the ubiquitous decrease of synaptic weights brought about by the repetitive spike-trains. Most certainly, further research is needed to shed some light on the situation.

## **6.5. REM Sleep Supports Incorporation into Pre-existing Schema.**

An interesting approach towards sleep and mental schemata was taken in a recent study<sup>33</sup>. Human participants were presented with auditory cues - short melodies of two different kinds: tonal melodies (in other words, what the majority of people would imagine under the term “melody”) and atonal melodies. The underlying idea of the experiment claimed that the vast majority of western population, even if musically illiterate, have been in contact with tonal music throughout their lives and therefore have created a mental schema for it. Tonality is the attribute of music which sounds euphonious to most. On the other hand, atonal music was designed artificially to satisfy a man-made set of rules. It is presumable that the majority of population had never encountered it and as such, never have developed a mental schema for it.

Expectedly, after a 24 hour consolidation interval, the participants were able to recognise the schema-conformant melodies better than the non-conformant ones. What was less expected, though, was the impact of REM sleep. In simple terms, the authors calculated a variable describing how efficient the retrieval of a type of melody was, thereafter they correlated this number with the time the subject spent in a specific sleep stage. Interestingly, they have found a strong correlation between retrieval of schema-dependent melodies and REM sleep, yet no correlation for retrieval and SWS. One might consider this unusual at first. However, those results do not necessarily infer that SWS is unimportant for consolidation of these specific, auditory memory traces. Indeed, there is evidence<sup>68</sup> of naps as short as 2 hours providing for successful memory consolidation. One might hypothesize that there is a base amount of SWS, past which this sleep stage can-not influence the consolidation process of some memory trace any further. Naturally, if this base amount were low, no correlation between retrieval of melody and SWS would be found.

## **6.6. Overlapping Is Beneficial for Schema but Harmful to Perceptual Task.**

As was mentioned in section 3.4., a recent study<sup>29</sup> investigated the effect of REM sleep on memory interference. Having learned a perceptual task, the participants were subjected to another, interfering task. The second task was similar to the original one and, since a perceptual task is prone to interference, its learning led to deterioration of memory for the original task. However, participants who took naps containing both non-REM and REM sleep were affected much less by this interference than both participants who napped only in non-REM sleep and those who stayed awake. Ergo, the authors have concluded that REM sleep was able to “rescue” the memory from interference.

The authors have also proposed a neural mechanism for the learning of a perceptual task. According to them, it relies on a “template”, i.e. set of neurons specifically dedicated to processing the particular task. Presumably, stronger synapses

among these neurons should result in better performance of the network, and therefore in qualitative improvement of the participants performance. As the authors presume, interference is due to the interfering task being represented by a neural network which overlaps with the original task's network. Since the original task needs to be represented by the corresponding neural ensemble *as precisely as possible*, any degree of overlapping is unwelcome. Therefore, while the synergy of SWS and REM sleep might be essential for the consolidation of a cognitive schema (in its traditional, declarative sense), it might be harmful to consolidation of a perceptual task.

## 6.7. Hippocampal Replay Predicts Routes Never Taken.

Let us briefly get back to the work of Gupta et al.<sup>18</sup>. Apart from the aforementioned findings, they have also reported some animals surpassing their training paradigm: some rats, trained only on routes A and B, have managed to take a shortcut path right from the feeder in route A to the feeder in route B (fig. 7). Interestingly enough, the replay sequences reflecting this shortcut route had been observed (in a time-compressed form) during awake rest prior to the rats taking the shortcut.

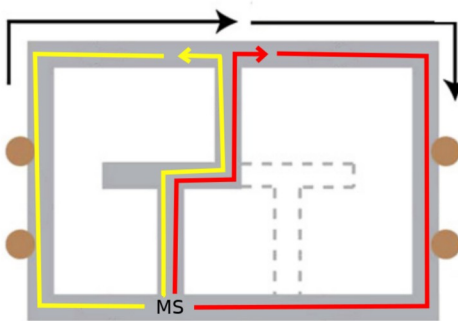


Fig. 7: Maze configuration. MS, maze start. Feeders (where the rats were rewarded) are depicted as brown circles. Rats were trained either on route A (yellow) or route B (red). Grey dashed lines suggest an alternative arrangement of the maze. Black arrows denote a shortcut route from one feeder to another, consisting of *part a* (left black arrow) and *part b* (right black arrow). From Gupta et al., 2010.

However, there are further implications of the findings of Gupta et al. Let us denote the relevant parts of routes A and B by lowercase letters *a* and *b*, respectively (see fig. 7). The shortcut taken by the rats consisted of part *a* and part *b*. Data shows that the sequence representing the shortcut was made up of backwards-played sequence representing part *a* and forward-played sequence representing part *b*. So far the data fit the iOtA hypothesis<sup>1</sup> surprisingly well. If one were to prove that place fields for part *a* and part *b* show some degree of overlap, it could be hypothesized that such behaviour was indeed conditioned by the assembly of a schema in the form of a cognitive map representing the whole maze. Concurrently, the authors have reported that the occurrence of the shortcut sequence during awake SPW-R episodes was relatively rare<sup>18</sup>. One could reckon that SPW-R oscillations during SWS might provide for more frequent replay of the shortcut sequence.

## 6.8. A fine line between schema and potentiation

A recent study used the *transient inference paradigm* to investigate schema formation in relation to the length of retention period<sup>57</sup>. This study also serves to

prove that seemingly trivial details in the experiments configuration can eventually decide whether a schema is still being researched. In the study, the participants were taught pairs of images called ‘premise pairs’ (e.g. *image A* + *image B*; after that *image B* + *image C*), with images in each pair being hierarchically organised (e.g.  $A > B$ ;  $B > C$ ). The participants have not, however, been told that all of the pairs belong to one set of images, a set in which the same hierarchy applies ( $A > B > C$ ). A brief test after training ensured that the premise pairs have indeed been learned correctly. Second testing comprised not only the original premise pairs, but also new “inference pairs”, i.e. pairs of images that have not been taught originally (e.g.  $A > C$ ). Based on how much time has elapsed before the second testing, the participants were separated into three groups: 20-minute, 12-hours or 24-hour group. While all groups demonstrated solid recollection of premise pairs, only the 12-hour and 24-hour groups (in other words, those which have slept before testing) were significantly better at ascertaining the correct hierarchical relationship of inference pairs.

The elegance of this experiment lies in its configuration. The participants were originally unaware that knowledge of something other than premise pairs will be required, ergo their subsequent knowledge of inference pairs was truly a result of partial memories being interconnected into a schema. Had they known about inference pairs from the very beginning, most participants would probably try to actively look for inference relations during training - they would consciously try to categorise the premise pairs into a hierarchical collection. Therefore, the sleep-induced performance gain would simply be a result of a quantitative potentiation of an already formed memory representation. No transformation of memory traces, no qualitative changes would take place. In this case, the exact amount of information the participant is given at the beginning determines the line between the creation of a cognitive schema and mere quantitative potentiation of an already formed memory.

## 6.9. Will Sleep Provide for a Schema of Spatial Experience?

Hypothetically, many different types of memory could be the basis for a schema. There is evidence for sleep supporting qualitative transformations of memory representations: giving rise to knowledge of an underlying principle<sup>58</sup>, allowing for abstraction<sup>57</sup> and even facilitating the conversion of implicit into explicit knowledge<sup>59</sup>. Consolidation of spatial memory has been researched extensively in relation to sleep. Human studies employing a virtual navigation task suggest that sleep improves spatial memory<sup>69,70</sup>, although the scientific community is not in total agreement on that matter<sup>71</sup>. However, with the idea being relatively novel, spatial memory has not yet been studied in the context of a mental schema.

I have recently joined the research group of E. Kelemen, which, in collaboration with K. Vlček, is currently working on an experiment to investigate the sleep consolidation of a schema for spatial experience in humans<sup>72</sup>. For the purpose of this experiment a special spatial task is devised, in which the participants explore a virtual map consisting of different areas. Each area is unique in that it holds different spatial cues and the participants are allowed to explore only two adjacent areas at a

time. Hypothetically, during training the participants will have formed partial cognitive maps for every pair of adjacent areas and, consequently, sleep will facilitate the fusion of these partial maps into a schema in the form of a cognitive map representing the whole task. Despite having explored the task only piece-by-piece, the participants should now be able to navigate between cues located in non-adjacent fields even though they have never taken this exact path. In theory, thanks to the overlapping nature of the partial cognitive maps, sleep will have provided for a schema of the spatial task.

## 7. CONCLUSION

In the preceding text, current knowledge of schemata and their consolidation in sleep has been reviewed. In the rat model, the incorporation of newly acquired memory trace is fast, provided there is a schema which the trace can incorporate into. In the same model, the up-regulation of IEGs in ACC and RSC was associated with learning of new, schema-conformant PAs while the learning of new, unrelated PAs was not. However, in CA1, some IEGs were up-regulated in both cases. This indicates that the newly-acquired memory was treated differently in ACC and RSC, but not in CA1, depending on whether there is or is not a schema which the memory could incorporate into. Indirectly, this also suggests that qualitative changes associated with schema formation did not take place in CA1.

A mechanism, the iOtA, has been proposed to explain the neuronal principles of schemata. This hypothesis relies on two distinct processes occurring during sleep: (a) the potentiation of specific synapses and (b) synaptic downscaling, i.e. a global, network-wide depotentiation which affects all relevant synapses equally. The iOtA postulates that if two memory representations show some degree of overlap, the reactivation of one will result in simultaneous reactivation of the other and, therefore, the strengthening of synapses between them, until the representations are part of a mutual schema. The schema is formed only when the synapses have been strengthened enough to withstand synaptic downscaling. It is possible that neuronal replay during SWS would drive the necessary reactivation.

Using an auditory learning paradigm in humans, it has been demonstrated that the incorporation of memories into an existing schema is correlated with the amount of non-REM sleep, but not SWS. This, might be due to a threshold, past which SWS can-not improve schema consolidation any further.

Place-cell sequences of routes never experienced during training, but taken during subsequent testing were replayed by rats in quite wake. Due to the similar electrophysiological characteristics of SWS and quiet wake, it could be theorised that, in accordance with the iOtA hypothesis, the rats were able to follow a route they have never taken before because they have formed a schema for it.

When investigating sleep consolidation of schemata in humans, the amount of information a participants is given prior to training is critical. A schema, by its

definition, requires restructuralisation of memory representations. If the participants were told too much, this restructuralisation would take place before sleep and, therefore, the effect of sleep would no longer be the main focus of the experiment.

To conclude, the concept of cognitive schemata offers a unique perspective on memory consolidation. As sleep is important for memory consolidation, it is eligible to study schemata in this context. As of this moment, publications addressing the issue exist, but few address it directly and this situation raises more questions than answers. Certainly, further research of schemata and their consolidation during sleep is needed.

## 8. REFERENCES

1. Lewis, P. A. & Durrant, S. J. Overlapping memory replay during sleep builds cognitive schemata. *Trends Cogn. Sci.* **15**, 343–351 (2011).
2. Diekelmann, S. & Born, J. The memory function of sleep. *Nat. Rev. Neurosci.* **11**, 114–126 (2010).
3. Barlett, F. C. Remembering: A Study in Experimental and Social Psychology. (1932).
4. Buzsáki, G., Leung, L. W. & Vanderwolf, C. H. Cellular bases of hippocampal EEG in the behaving rat. *Brain Res.* **287**, 139–171 (1983).
5. Vanderwolf, C. H. Hippocampal electrical activity and voluntary movement in the rat. *Electroencephalogr. Clin. Neurophysiol.* **26**, 407–418 (1969).
6. Ylinen, A. *et al.* Sharp wave-associated high-frequency oscillation (200 Hz) in the intact hippocampus: network and intracellular mechanisms. *J. Neurosci. Off. J. Soc. Neurosci.* **15**, 30–46 (1995).
7. Bliss, T. V. P. & Collingridge, G. L. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* **361**, 31–39 (1993).
8. Chrobak, J. J. & Buzsáki, G. Selective activation of deep layer (V–VI) retrohippocampal cortical neurons during hippocampal sharp waves in the behaving rat. *J. Neurosci. Off. J. Soc. Neurosci.* **14**, 6160–6170 (1994).
9. Girardeau, G., Benchenane, K., Wiener, S. I., Buzsáki, G. & Zugaro, M. B. Selective suppression of hippocampal ripples impairs spatial memory. *Nat. Neurosci.* **12**, 1222–1223 (2009).
10. Ego-Stengel, V. & Wilson, M. A. Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. *Hippocampus* **20**, 1–10 (2010).
11. Plihal, W. & Born, J. Effects of Early and Late Nocturnal Sleep on Declarative and Procedural Memory. *J. Cogn. Neurosci.* **9**, 534–547 (1997).
12. O’Neill, J., Pleydell-Bouverie, B., Dupret, D. & Csicsvari, J. Play it again: reactivation of waking experience and memory. *Trends Neurosci.* **33**, 220–229 (2010).
13. Louie, K. & Wilson, M. A. Temporally Structured Replay of Awake Hippocampal Ensemble Activity during Rapid Eye Movement Sleep. *Neuron* **29**, 145–156 (2001).
14. Wilson, M. & McNaughton, B. Reactivation of hippocampal ensemble memories during sleep. *Science* **265**, 676–679 (1994).
15. Lee, A. K. & Wilson, M. A. Memory of Sequential Experience in the Hippocampus during Slow Wave Sleep. *Neuron* **36**, 1183–1194 (2002).
16. Nádasdy, Z., Hirase, H., Czurkó, A., Csicsvari, J. & Buzsáki, G. Replay and Time Compression of Recurring Spike Sequences in the Hippocampus. *J. Neurosci.* **19**, 9497–9507 (1999).
17. O’Neill, J., Senior, T. J., Allen, K., Huxter, J. R. & Csicsvari, J. Reactivation of experience-dependent cell assembly patterns in the hippocampus. *Nat. Neurosci.* **11**, 209 (2008).
18. Gupta, A. S., van der Meer, M. A. A., Touretzky, D. S. & Redish, A. D. Hippocampal Replay Is Not a Simple Function of Experience. *Neuron* **65**, 695–705 (2010).
19. Sirota, A. & Buzsáki, G. Interaction between neocortical and hippocampal networks via slow oscillations. *Thalamus Relat. Syst.* **3**, 245 (2005).
20. Steriade, M., Nuñez, A. & Amzica, F. A novel slow (< 1 Hz) oscillation of neocortical neurons in vivo: depolarizing and hyperpolarizing components. *J. Neurosci. Off. J. Soc. Neurosci.* **13**, 3252–3265 (1993).
21. Mölle, M., Eschenko, O., Gais, S., Sara, S. J. & Born, J. The influence of learning on sleep slow oscillations and associated spindles and ripples in humans and rats. *Eur. J. Neurosci.* **29**, 1071–1081 (2009).
22. Binder, S., Rawohl, J., Born, J. & Marshall, L. Transcranial slow oscillation stimulation during NREM sleep enhances acquisition of the radial maze task and modulates cortical network activity in rats. *Front. Behav. Neurosci.* **7**, (2014).
23. Huber, R. *et al.* Arm immobilization causes cortical plastic changes and locally decreases sleep slow wave activity. *Nat. Neurosci.* **9**, 1169–1176 (2006).
24. Clemens, Z., Fabó, D. & Halász, P. Overnight verbal memory retention correlates with the number of sleep spindles. *Neuroscience* **132**, 529–535 (2005).
25. Sirota, A., Csicsvari, J., Buhl, D. & Buzsáki, G. Communication between neocortex and hippocampus during sleep in rodents. *Proc. Natl. Acad. Sci.* **100**, 2065–2069 (2003).
26. Peigneux, P. *et al.* Learned material content and acquisition level modulate cerebral reactivation during posttraining rapid-eye-movements sleep. *NeuroImage* **20**, 125–134 (2003).

27. Nissen, M. J. & Bullemer, P. Attentional requirements of learning: Evidence from performance measures. *Cognit. Psychol.* **19**, 1–32 (1987).
28. Barsky, M. M., Tucker, M. A. & Stickgold, R. REM sleep enhancement of probabilistic classification learning is sensitive to subsequent interference. *Neurobiol. Learn. Mem.* **122**, 63–68 (2015).
29. McDevitt, E. A., Duggan, K. A. & Mednick, S. C. REM sleep rescues learning from interference. *Neurobiol. Learn. Mem.* **122**, 51–62 (2015).
30. Calais, J. B., Ojopi, E. B., Morya, E., Sameshima, K. & Ribeiro, S. Experience-dependent upregulation of multiple plasticity factors in the hippocampus during early REM sleep. *Neurobiol. Learn. Mem.* **122**, 19–27 (2015).
31. Axmacher, N., Helmstaedter, C., Elger, C. E. & Fell, J. Enhancement of Neocortical-Medial Temporal EEG Correlations during Non-REM Sleep. *Neural Plast.* **2008**, 1–7 (2008).
32. Cantero, J. L. *et al.* Sleep-Dependent  $\theta$  Oscillations in the Human Hippocampus and Neocortex. *J. Neurosci.* **23**, 10897–10903 (2003).
33. Durrant, S. J., Cairney, S. A., McDermott, C. & Lewis, P. A. Schema-conformant memories are preferentially consolidated during REM sleep. *Neurobiol. Learn. Mem.* **122**, 41–50 (2015).
34. Hasselmo, M. E. & McGaughy, J. High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidation. *Prog. Brain Res.* **145**, 207–231 (2004).
35. Behrends, J. C. & ten Bruggencate, G. Cholinergic modulation of synaptic inhibition in the guinea pig hippocampus in vitro: excitation of GABAergic interneurons and inhibition of GABA-release. *J. Neurophysiol.* **69**, 626–629 (1993).
36. Pitler, T. A. & Alger, B. E. Cholinergic excitation of GABAergic interneurons in the rat hippocampal slice. *J. Physiol.* **450**, 127–142 (1992).
37. Hasselmo, M. E. & McGaughy, J. High acetylcholine levels set circuit dynamics for attention and encoding and low acetylcholine levels set dynamics for consolidation. in *Progress in Brain Research* **145**, 207–231 (Elsevier, 2004).
38. Kammer, H. von der *et al.* Muscarinic Acetylcholine Receptors Activate Expression of the Egr Gene Family of Transcription Factors. *J. Biol. Chem.* **273**, 14538–14544 (1998).
39. Teber, I., Köhling, R., Speckmann, E.-J., Barnekow, A. & Kremerskothen, J. Muscarinic acetylcholine receptor stimulation induces expression of the activity-regulated cytoskeleton-associated gene (ARC). *Brain Res. Mol. Brain Res.* **121**, 131–136 (2004).
40. Minatohara, K., Akiyoshi, M. & Okuno, H. Role of Immediate-Early Genes in Synaptic Plasticity and Neuronal Ensembles Underlying the Memory Trace. *Front. Mol. Neurosci.* **8**, (2016).
41. Guzowski, J. F., Setlow, B., Wagner, E. K. & McGaugh, J. L. Experience-dependent gene expression in the rat hippocampus after spatial learning: a comparison of the immediate-early genes Arc, c-fos, and zif268. *J. Neurosci. Off. J. Soc. Neurosci.* **21**, 5089–5098 (2001).
42. Buzsáki, G. Two-stage model of memory trace formation: a role for ‘noisy’ brain states. *Neuroscience* **31**, 551–570 (1989).
43. Buzsáki, G. Long-term changes of hippocampal sharp-waves following high frequency afferent activation. *Brain Res.* **300**, 179–182 (1984).
44. Bramham, C. R. & Srebro, B. Synaptic plasticity in the hippocampus is modulated by behavioral state. *Brain Res.* **493**, 74–86 (1989).
45. McClelland, J. L., McNaughton, B. L. & O’Reilly, R. C. Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* **102**, 419–457 (1995).
46. O’Reilly, R. C., Bhattacharyya, R., Howard, M. D. & Ketz, N. Complementary Learning Systems. *Cogn. Sci.* **38**, 1229–1248 (2014).
47. McCloskey, M. & Cohen, N. J. Catastrophic Interference in Connectionist Networks: The Sequential Learning Problem. in *Psychology of Learning and Motivation* **24**, 109–165 (1989).
48. Tse, D. *et al.* Schemas and Memory Consolidation. *Science* **316**, 76–82 (2007).
49. Kesner, R. P., Hunsaker, M. R. & Gilbert, P. E. The Role of CA1 in the Acquisition of an Object-Trace-Odor Paired Associate Task. *Behav. Neurosci.* **119**, 781–786
50. Frankland, P. W. & Bontempi, B. The organization of recent and remote memories. *Nat. Rev. Neurosci.* **6**, 119–130 (2005).
51. Dash, P. K., Hebert, A. E. & Runyan, J. D. A unified theory for systems and cellular memory consolidation. *Brain Res. Brain Res. Rev.* **45**, 30–37 (2004).
52. Squire, L. R., Genzel, L., Wixted, J. T. & Morris, R. G. Memory Consolidation. *Cold Spring Harb. Perspect. Biol.* **7**, a021766 (2015).

53. Rudy, J. W. & Sutherland, R. J. Is it systems or cellular consolidation? Time will tell. An alternative interpretation of the Morris group's recent science paper. *Neurobiol. Learn. Mem.* **89**, 366–369 (2008).
54. Tse, D. *et al.* Does assimilation into schemas involve systems or cellular consolidation? It's not just time. *Neurobiol. Learn. Mem.* **89**, 361–365 (2008).
55. Tse, D. *et al.* Schema-Dependent Gene Activation and Memory Encoding in Neocortex. *Science* **333**, 891–895 (2011).
56. Osada, T., Adachi, Y., Kimura, H. M. & Miyashita, Y. Towards understanding of the cortical network underlying associative memory. *Philos. Trans. R. Soc. B Biol. Sci.* **363**, 2187–2199 (2008).
57. Ellenbogen, J. M., Hu, P. T., Payne, J. D., Titone, D. & Walker, M. P. Human relational memory requires time and sleep. *Proc. Natl. Acad. Sci. U. S. A.* **104**, 7723–7728 (2007).
58. Wagner, U., Gais, S., Haider, H., Verleger, R. & Born, J. Sleep inspires insight. *Nature* **427**, 352–355 (2004).
59. Fischer, S., Drosopoulos, S., Tsen, J. & Born, J. Implicit Learning–Explicit Knowing: A Role for Sleep in Memory System Interaction. *J. Cogn. Neurosci.* **18**, 311–319 (2006).
60. Verleger, R., Rose, M., Wagner, U., Yordanova, J. & Kolev, V. Insights into sleep's role for insight: Studies with the number reduction task. *Adv. Cogn. Psychol.* **9**, 160 (2013).
61. Desai, N. S., Cudmore, R. H., Nelson, S. B. & Turrigiano, G. G. Critical periods for experience-dependent synaptic scaling in visual cortex. *Nat. Neurosci.* **5**, 783–789 (2002).
62. Tononi, G. & Cirelli, C. Sleep and synaptic homeostasis: a hypothesis. *Brain Res. Bull.* **62**, 143–150 (2003).
63. Tononi, G. & Cirelli, C. Sleep function and synaptic homeostasis. *Sleep Med. Rev.* **10**, 49–62 (2006).
64. Mermillod, M., Bugaiska, A. & Bonin, P. The stability-plasticity dilemma: investigating the continuum from catastrophic forgetting to age-limited learning effects. *Front. Psychol.* **4**, (2013).
65. Niethard, N. & Born, J. Back to baseline: sleep recalibrates synapses. *Nat. Neurosci.* **22**, 149–151 (2019).
66. Tononi, G. & Cirelli, C. Sleep and synaptic down-selection. *Eur. J. Neurosci.* (2019). doi:10.1111/ejn.14335 [Epub ahead of print]
67. Norimoto, H. *et al.* Hippocampal ripples down-regulate synapses. *Science* **359**, 1524–1527 (2018).
68. Mednick, S., Nakayama, K. & Stickgold, R. Sleep-dependent learning: a nap is as good as a night. *Nat. Neurosci.* **6**, 697–698 (2003).
69. Nguyen, N. D., Tucker, M. A., Stickgold, R. & Wamsley, E. J. Overnight Sleep Enhances Hippocampus-Dependent Aspects of Spatial Memory. *Sleep* **36**, 1051–1057 (2013).
70. Ferrara, M. *et al.* Sleep to find your way: the role of sleep in the consolidation of memory for navigation in humans. *Hippocampus* **18**, 844–851 (2008).
71. Orban, P. *et al.* Sleep after spatial learning promotes covert reorganization of brain activity. *Proc. Natl. Acad. Sci. U. S. A.* **103**, 7124–7129 (2006).
72. Vlček, K., Brukhnová, A., Kopřivová, J. & Kelemen, E. Vliv spánku na organizaci prostorové paměti. Poster presented in CSEtS conference. (2018).