How Does NREM Sleep Affect the Consolidation of Declarative Memories?

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ABSTRACT. Non-Rapid eye movement [NREM] sleep has been shown to be an influential process in the consolidation of declarative memories. This hypothesis is derived from a variety of experiments that involve manipulation of sleep cycles around word-pair learning tasks. There are two popular theories that attempt to explain the underlying mechanisms: the synaptic homeostasis hypothesis suggests that slow oscillations seen in sleep EEG indicate the global downscaling of synaptic strengths, leading to an improved signal-to-noise ratio for relevant synaptic connections; the active system consolidation hypothesis suggests that memory traces are actively replayed in order to be reorganised and consolidated, involving a continual interchange of information between the hippocampus and the cortex. There is a considerable amount of data from different study paradigms to support both theories. However, they are not mutually exclusive and attempts have been made to combine the theoretical frameworks together to form an overall model. I also consider the overall modulation of memory consolidation during sleep by the activity acetylcholine, which in turn may be controlled by cortisol at an endocrine level. I give an evaluation of various experimental techniques that are shared across many studies in this subject. I highlight a number of issues with the current methodology, including the implications of correlational data provided by EEG activity and the effect of semantic representations in the brain. An overall analysis of the data suggests that theories in this subject are mostly congruent with each other. There are also implications for other areas: REM sleep may also be involved in declarative memory consolidation, contrary to the classical dual-process model; reconsolidation for declarative memories may turn out to be the same process as consolidation. I give suggestions for further experiments that could be conducted to address some of the current uncertainties.

1. Introduction

Studies have shown throughout history that sleep can affect the process of memory formation. Indeed, many theories postulate that one of the functions of sleep is to facilitate or improve memory formation. Recent experiments have shown that non-REM [NREM] sleep in particular can enhance declarative memory formation. It is suggested that specific neural activity present during the various stages of NREM sleep may contribute to the consolidation of declarative memories (Rasch & Born, 2013).

Memory Consolidation

A classical model of memory involves two different types of memories – short-term and long-term. Short-term memory is very dynamic, but is also very labile and susceptible to degradation either over time (tens of seconds) or though interference. Long-term memory, on the other hand, is difficult to establish, often requires a long learning process, but is stable over months or years and is not usually affected by interference (Atkinson and Shiffrin, 1968). Consolidation is often defined as the process through which short-term memory is stabilised into long-term memory after its initial acquisition from sensory inputs (McGaugh, 2000).

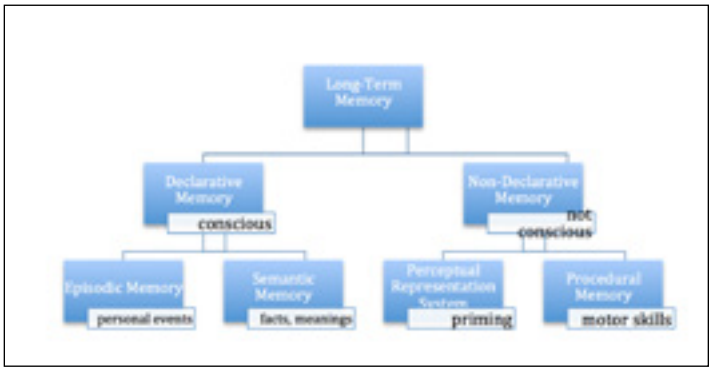
Figure 1. Classical model of the stages of memory formation

Declarative and Non-Declarative Memory

Within the domain of long-term memory, there

are subdivisions containing different types of memory. This is relevant because these have been shown to involve different neurological structures. The most important division is between declarative and non-declarative memory. Declarative memories are memories that a subject can explicitly describe, such as a past event, or the meaning of a word or concept; non-declarative memories are memories that cannot be expressed, and includes things like motor skills, primed responses, habituation etc. Declarative memories have been shown involve the cortex and hippocampus, whereas non-declarative memories involve the cerebellum and amygdala (Squire & Zola-Morgan, 1991).

Figure 2. Divisions of long-term memory, based on (Squire & Zola-Morgan, 1991)



Most of the experiments cited in this paper use methods which test semantic memory as a representation of declarative memory in general. This is also due to the fact that learning tasks such as word-pair association are much easier to be implemented in a controlled fashion compared to episodic events (which would be personal). These experiments usually involve a word-pair learning task followed by a recall test. Non-declarative memory, on the other hand, is usually represented by procedural memory tasks such as a mirror-tracing or finger-sequence tapping. This is sometimes used as a control to highlight the effects of declarative memory alone.

Sleep

Sleep is a process that is characterised by specific patterns of neural activity, usually identified with EEG. There are several stages of sleep, but these can generally be divided into REM sleep – characterised by rapid eye movements – and non-REM [NREM] sleep. NREM sleep has four separate stages, each of which have their own characteristic activity as measured on an EEG. Stages 3 and 4 are classed together as slow-wave sleep.

2. Sleep and Learning Task Performance

Dual-Process Theory. The dual-process theory is the generalisation that declarative memory is enhanced by NREM sleep while non-declarative memory is enhanced by REM sleep (Plihal & Born, 1997). Several different study paradigms have been used to study the differential effects of NREM and REM sleep. The focus here will be on NREM sleep and declarative memory.

Night-half paradigm. This is a classical experimental design that involves splitting the night into two halves. Word-pair learning tasks and procedural mirror-tracing tasks (for declarative memory and non-declarative memory respectively) are introduced before either early sleep or late sleep. The protocols for word-pair association tasks, which are used to analyse declarative memory performance, are usually very similar. For example, this might involve 48 word pairs presented to the subject for learning, with eight pairs discarded (four at beginning, four at end) to account for primacy/recency effects. The subjects are then allowed to rest for a period of time, which may include sleep. Finally, there is recall task where the first (cue) word is presented to test for the associated pair. Mirror-tracing tasks, used to analyse non-declarative memory, may involve the subject being asked to trace around a shape using a pen while only using the reflection of their hands as a guide. This causes a reversal in visual feedback that would improve over time and practice (Gais & Born, 2004a).

Since REM sleep occurs more in the latter stages of the night, and vice versa for NREM sleep, it is hypothesised that a difference in performance in the recall would be due to the effects of the two types of sleep. In one study, a double dissociation was shown: NREM sleep in early sleep improved declarative memory performance, while REM sleep in late sleep improved non-declarative memory performance (Plihal & Born, 1997).

Day-time nap. More recent methods showed that a one-hour daytime nap consisting of only NREM sleep improved subjects' performance in declarative memory tasks but not procedural (non-declarative) memory tasks (Tucker et al., 2006). The control group here simply stayed awake for an hour. This result is important as it shows a causative relationship; it heavily suggests that the underlying mechanisms of NREM might be involved in the consolidation of declarative memories.

Sleep deprivation. Another way to study NREM sleep is through sleep deprivation, though this can be difficult to achieve methodologically. In one study, subjects

were kept awake for 24 hours before a learning task. The result was both reductions in recall in the short term and long term (Gais et al., 2007).

The problem with these results is that they do not tell us anything about the underlying mechanisms NREM sleep on declarative memory. As such, further studies have been conducted to explore this using different experimental techniques.

Theories. Various experiment have given rise to two popular theories that attempt to give an overall model of the mechanisms behind the effects of sleep on declarative memory consolidation: the synaptic homeostasis hypothesis and the active system consolidation hypothesis. Both theories incorporate a wide range of data form different studies. In summary, the synaptic homeostasis hypothesis suggests that the positive effect on consolidation is due to a global downscaling of synaptic strengths (Tononi & Cirelli, 2006), whilst the active system consolidation hypothesis suggests that memory reactivations between the hippocampus and the cortex are actively induced to promote consolidation (Born & Wilhelm, 2012).

3. Synaptic Homeostasis Hypothesis

The synaptic homeostasis hypothesis [SHY] suggests that SWS downscales synaptic strength globally (Tononi & Cirelli, 2006). This indirectly promotes consolidation by depressing weak synaptic connections and thus improving the signal-to-noise ratio of stronger connections that were encoded in wakefulness. The main claims are that: (1) Synapses are globally potentiated during waking, (2) Synapses are globally depressed during SWS, and (3) Synaptic potentiation influences the homeostatic control of SWS.

Downscaling may be necessary because the brain cannot be in a constant state of acquiring new memories and laying down new connections. Since it takes energy to establish a synaptic connection as well as to maintain it, the brain will need a way to prune old or unnecessary connections. The SHY identifies slow oscillations as the key indication of this global downscaling.

Slow Oscillations

Slow oscillations are a characteristic EEG pattern that is seen during SWS (stages 3 and 4 of NREM sleep). They indicate global synchronous transitions between periods of sustained firing and periods of diminished activity, at around 1-4Hz. These patterns are generated in the cortex (Rasch & Born, 2013).

One study showed that the negative phase of slow wave oscillations, as recorded on an EEG, correlate with reduced activity in individual neurones (Vyazovskiy et al., 2009). Another computational study showed that a decrease in the strength of excitatory cortico-cortical connections could account for the decrease global activity seen in SWS, including various aspects of the waveform of slow oscillations (amplitude, slop, incidence of multiple-wave peaks etc.) (Esser et al., 2007). These studies support the SHY as they suggest that the low frequency oscillations are a manifestation of reduced global synaptic activity.

Further experiments highlight the link to memory consolidation. Anodal transcranial direct current stimulation [tDCS] has been used as a non-invasive technique to depolarise neurones in human brains. This was carried out in one study in SWS as a way of inducing slow oscillations in subjects during the retention interval (Gais & Born, 2004a). The result was that retention was increased compared to placebo group. It is interesting that this effect was only seen when tDCS was applied during SWS, and not in waking, nor for a procedural task (non-declarative memory).

In another study, a slow oscillatory potential was applied transcranially at 0.75 Hz during SWS, imitating the normal slow wave activity. The result was that learning performance was significantly improved (Marshall et al., 2006). The opposite effect was seen for tDCS applying theta frequency oscillations at 5Hz, which suppresses normal slow wave activity (Marshall et al., 2011).

LTP

Long-term potentiation [LTP] is presented as a synaptic-level mechanism for the changes in synaptic potential (even though SHY is more vague on the precise mechanism, referring to it as 'LTP-like') (Tononi & Cirelli, 2012). LTP has been widely shown to be a reliable mechanism that explains permanent changes in the strength of synapses. It is essentially a process through which synaptic connections become stronger through repeated and synchronous activation. It occurs when a presynaptic neurone is activated weakly at the same time as a strong postsynaptic depolarization, leading to the strengthening of this synapse and a lowered threshold for activation in future. LTP can be non-associative (for a single input) or associative between multiple inputs, where it is also co-operative and input-specific. The timescale of

LTP is also appropriate as synaptic consolidation occurs over hours.

4. Active System Consolidation

The active consolidation hypothesis is another theory that attempts to explain memory consolidation. This is a more integrative theory that is focussed on the idea of systems level consolidation (Born & Wilhelm, 2012).

Essentially, it involves a bidirectional transfer of information between the cortex and hippocampus over time, which provides the basis for memory consolidation at a systems level. Neural activity, including hippocampal ripples and thalamo-cortical spindles – as measured by EEG – underlie this process. Since there is a finite amount of space in the cortex, old memories are reorganised so that they can be re-integrated with new memories, thus improving efficiency and preventing them from being overwritten. Similar to the SHY, this theory identifies LTP as a potential candidate for changes in synaptic activity at a local scale (Born & Wilhelm, 2012).

Two-Stage Model

The active consolidation hypothesis is based on the two-stage model of memory consolidation (Diekelmann & Born, 2010). This model hypothesises that the hippocampus and the cortex serve distinct roles in memory consolidation. The hippocampus is presented as a short-term store, which is capable of learning very quickly and is highly plastic and volatile. The cortex is presented as a long-term store, which has high stability but is slow to learn. A period of time (days) is needed for the short-term store to teach newly acquired information traces to the long-term store (Buzsaki, 1989).

This theory can also account for how the brain might acquire new memory traces without disrupting existing traces; this is called the stability-plasticity dilemma. The two-stage model offers a solution as it hypothesises that old information is brought out of the long-term store (cortex) into the short-term store (hippocampus), where it is reorganised and integrated with new information. This is then put back into the long-term store (Diekelmann & Born, 2010).

Reactivation of Memories

Reactivation of memories is central to the active system consolidation hypothesis, which suggests that it is the active replay of newly acquired traces during sleep that drives memory consolidation.

Experiments in rats have shown that spatial memory is replayed during SWS (Ji & Wilson, 2007). In this study, rats were exposed to a spatial learning task; neuronal spikes were recorded in SWS following the exposure using a tetrode implanted in the rats' skulls.

The raw recordings from cells show a clear correlation between start time and end time of frames, which are patterns of firing across several neurones in the same recording area. Meanwhile, the distribution of the time differences, with the median to the right of zero, indicates that the cortex fires immediately before the hippocampus.

This could imply that during sleep, the cortex initiates a transfer of information to the hippocampus. The purpose of this could be that select 'packets' of information are extracted from the cortex in order to be reorganised within the hippocampus. This means that when the information is transferred back to the cortex, it is in a much more compact and efficient form, both in terms of storage and later retrieval.

Firing of individual cells was also recorded. The same patterns of firing were seen in both waking and sleeping across multiple cells, again suggesting that there is a replay in the memory that had been formed; the temporal order in particular was preserved. This was seen in both the cortex and the hippocampus.

Studies in humans have also supported the idea of memory reactivations. PET imaging showed that the activity was increased in the right hippocampal and parahippocampal areas in SWS following a daytime navigation task (Peigneux et al., 2004). There was also a positive correlation between cerebral blood flow to these areas and overnight improvement in performance in the spatial navigation.

Memories can also be activated through cueing during sleep (Rasch et al. 2007). In this study odours were presented to waking subjects in conjunction with a visuospatial object-location learning task. The same odour was subsequently reintroduced during SWS, REM sleep or waking. Results showed that there was a significant improvement in recall for the SWS group alone, even though they were not even consciously aware that they had been presented with a cue. Also, fMRI data indicate that there was activation of the left anterior and left posterior hippocampus during odour presentation.

The extraction of old memories from the cortex could manifest as the reactivation of memories seen in some studies. This would explain why cueing reactivations e.g. by odours might improve memory consolidation – as it enhances this interplay between the hippocampus and the cortex.

Long-Term Activity of Cortex and Hippocampus

In a sleep deprivation study, subjects were put into two groups following a learning task; one group was allowed to have a full night's sleep, while the other group was sleep-deprived for 24 hours. The subjects were then imaged using fMRI 48 hours later whilst recalling word-pairs (Gais et al., 2007).

In the sleep group, there was functionally related activity between hippocampal activity and frontal activity, which included the precuneus and the medial prefrontal cortex (mPFC). But in the sleep-deprived group there was no related activity. There was also a significant effect, over a time frame of months, in the overall activation of the hippocampus and the mPFC.

Results indicate that in the sleep group, the hippocampus is more active immediately following learning, but the mPFC is more active over the long term. However, this is opposite in the sleep-deprived group.

A possible explanation here is that the hippocampus could be acting as a teacher for the cortex, which accounts for the higher activity in the normal group. In the sleep-deprived group, on the other hand, the hippocampus is not given an opportunity to carry out this teaching, which accounts for the lower level of activation. Eventually this information is degraded over a few days. Six months later, however, when the normal group is asked to recall word-pairs, they can rely on a well-constructed array of information that is stored in the cortex. But in the sleep-deprived group, since this information was never processed efficiently, the hippocampus is recruited at this stage either as a buffer in the retrieval of old information, or to recommence the proper consolidation of the old memory.

Neural Basis of Reactivations – Ripples and Spindles

EEG recordings have shown that changes in certain patterns (hippocampal sharp wave-ripples and spindles) correlate with the performance in learning tasks. This has lead to the idea that these patterns indicate neural activity that is involved in memory consolidation, or indeed the reactivation of memory traces. Studies have shown phase synchronisation between slow oscillations and the activity of ripples and spindles, which could indicate that the up-phases in slow oscillations initiate information transfer between the hippocampus and the cortex (Contreras & Steriade, 1995).

Hippocampal Sharp Wave-Ripples

Hippocampal sharp wave-ripples [ripples] are high frequency oscillations seen in EEG recordings during sleep. Specifically, they appear to be originating from the hippocampus (Diekelmann & Born, 2010).

One study that investigated ripple activity constructed a spatial discrimination task in which rats were provided reward at the end of a correct selection of route (Ramadan et al., 2009) .The rats were split into three groups: control, trained and pseudo-trained (where they were given a reward regardless of whether they made the right choice). The amount of ripple activity was recorded after each training session, which mostly involved SWS.

The results show a correlation between ripple activity and the training process, which would have instigated memory consolidation. The behavioural aspect was also investigated by comparing ripple activity in day 6 to mean errors in day 7. The rationale was that if ripple activity was correlated with memory consolidation then the peak performance would be the day following the night with the highest mean ripple activity (day 6). The result show a negative relationship, indicating that ripple activity corresponds with better learning task performance.

Spindles

Spindles are found mostly in stage 2 NREM sleep, but can also be present in SWS. These are patterns of oscillatory activity at 10-15Hz that appear for periods up to 3 seconds. Sleep spindles are thought to be generated in the GABAergic neurones of the nucleus reticularis and propagated globally via cortico-thalamic circuits (Rasch & Born, 2013).

Increases in spindle activity have been associated with declarative memory learning (Schabus et al., 2004). This is another observational study involving word-pair learning tasks. The results show that the subjects who had a positive change in the spindle activity between the experimental and control nights achieved better results in the test.

Another study looked at the association of spindle activity with the integration of new memories with old memories. The experiment involved introducing novel words in a learning task that are similar to existing words in the subject's vocabulary (e.g. cathedruke-cathedral) (Tamminen et al. 2010). The sub-experiment of interest was an auditory lexical decision task, where the subject had to decide whether a presented spoken word was a real word or not; real-control words were mixed with real-cue words (cathedral) and nonsense-associated words (cathedruke). The results show a clear positive correlation in the spindle activity in the night's sleep that immediately followed. This supports the hypothesis that memories are indeed reorganised after their initial acquisition, as this task specifically tests the ability of the subject to combine new information with old information (marked by increased lexical competition).

5. Combining the Synaptic Homeostasis Hypothesis and the Active System Consolidation Hypothesis

Though they contend to be independent theories in themselves, the synaptic homeostasis hypothesis and the active system consolidation hypothesis are not mutually exclusive (Diekelmann & Born, 2010).

Genzel et al. attempt to bring the two theories together by focusing on the exact sleep stages at which these various EEG recordings are observed (Genzel et al., 2014). They suggest that the whilst reactivations of memories can occur in all stages of NREM sleep, exchange of information at a global level is likely to be more significant in light sleep (stages 1 and 2 of NREM sleep). Synaptic downscaling, on the other hand, would occur more during the deeper stages of NREM sleep (SWS).

Genzel's theory suggests that synaptic downscaling itself is insufficient as a way of consolidating memories, as it does nothing to integrate or reorganise new and old memories at a systems level. This is especially considering that the SHY is not specific about which neurological structures drive learning. Instead, it focuses on the specific neural environment that sleep produces and its relevance to memory consolidation, at a much more synaptic level.

6. Homeostatic Modulation

Another factor that should be considered is how the brain controls the overall process of consolidation. Sleep itself is initiated by structures in the thalamus, and propagates globally via different neurotransmitter systems. This includes cholinergic, noradrenergic and serotonergic neurones, whose activity in general is decreased during sleep. Acetylcholine in particular has been studied in relation to memory consolidation.

Ach

The activity of acetylcholine [Ach] systems on memory consolidation has been studied using pharmacological methods to modulate its tonal activity (Gais & Born, 2004b). At sleep onset, subjects were given an infusion of physostigmine, a cholinesterase inhibitor that indirectly increases the activity of pathways involving Ach as a neurotransmitter. The result showed a decrease in memory task performance that was specific to declarative memory.

Activation of Ach has been shown to also increase synaptic LTP in in vitro preparations of hippocampal structures (Hasselmo & McGaughy, 2004). This does seem to support the synaptic homeostasis hypothesis as well, as it is possible that the differential activation of Ach between and waking and sleep could account for changes neural activity in general, and hence in synaptic potentiation.

Equally, this can support the active consolidation hypothesis – cholinergic activity could be directing the brain between a state of encoding new memories and a state of consolidation. Specifically, the pathways inhibited by cholinergic activity are feedback circuits in the CA3 as well as projections to CA1 and the cortex; these are circuits that are involved in active consolidation – where information is transferred between the hippocampus to the cortex.

Endocrine Control

The endocrine system has also been implicated in memory consolidation. Cortisol is a glucocorticoid that has a wide range of effects throughout the body. Its level during sleep is usually low, and when this is raised pharmacologically then the enhancing effect of SWS sleep on declarative memory consolidation is reduced (Plihal & Born, 1999). Pre-encoding levels of cortisol also seem to have a positive correlation with memory recall performance (Bennion et al., 2013).

This is reflective of the waking state as highlighted by high Ach levels. Cortisol could act on the brain to increase alertness (by up regulating Ach). From an evolu-

tionary point of view it is beneficial to maximise the capacity of the brain to acquire new information in a stressful situation (as survival may depend on remembering an escape route, for example). Equally, cortisol levels would decrease at night to allow for the switch into a 'consolidation state' to enable these new memory traces to be retrieved more efficiently at a later time.

7. Evaluation of Experimental Technique

Semantic Representations in the Brain

As with any experiment, the methods used to obtain the data must be carefully scrutinised. As has been mentioned earlier most studies used word-pair association tasks as the parameter for learning, with an associated cued-recall task.

A question should be raised as to whether the semantic meaning of words can affect how they are stored in a memory system. There are two popular models of how semantic information is represented in the brain. The network model involves individual concepts that can be connected in any way, such that 'red' might be linked to either 'fire truck' or 'apples' (Collins & Loftus, 1975). The strength of these connections will depend on the relevance between the two concepts. For example, 'eagle' will be better associated with 'hummingbird' than 'squirrel', because they are both birds and can fly etc., but 'eagle' might be better connected to 'squirrel' than 'table' because they are both animals. The feature model, on the other hand, is based on the idea that any object can be broken down into its constituent features, such as a 'squirrel' into 'tail' and 'head' (Tyler & Moss, 2001). Each object is then identified through a statistical analysis of the most relevant features. 'Head', for example, might be attributed to 'squirrel' or 'eagle', but 'wings' will be specific to 'eagle'.

This is relevant because experiments involving learning tasks have used different designs in the word pairing. In Tucker's experiments (2006), these words were semantically related (e.g. clock-hands). However, other experiments involved word pairs of undetermined semantic relationship e.g. two German nouns (Plihal & Born, 1999) or even words that are specifically not semantically related (Schabus et al., 2004).

The dependent variable in most of these experiments is the error rate in recall, and difference of this before and after sleep, to highlight its effects. However, the way that two semantically related words are encoded and stored in the brain is likely to be different than for two words which are not semantically related. Related word-pairs might undergo much further integration over time, in either the network or the feature model. This means that sleep might have a great effect in enhancing the association between these words, compared to non-related words where further processing would not be useful.

Most experiments currently do use a protocol that utilise word pairs that are semantically related words, but even then there is an issue of variability between pairs depending on their semantic meaning. According to the feature model, remembering a word pair that consists of an object ('dog') and a feature of that object ('tail'), for example, would involve simple and direct link between object and component. On the other hand, remembering a word pair that consists of two objects that share similar features ('dog') and ('cat') would involve retrieving two sets of different features, which may involve many different links (tail+nose+etc.). The latter would be a much more complicated process in terms of retrieval, and this might have an influence on performance in recall.

Implications of Correlational Data

Generally, the first step towards uncovering the underlying mechanism behind a particular physiological process is to find a correlation between two elements within that process. However, a very basic but important point is that correlation does not imply causation. A correlation between A and B, for example, could mean that A causes B, B causes A, a third element C causing both A and B, or something much more complex.

This is important because many studies involving EEG activity show correlations, but there is seldom much indication of a causative relationship. The reason behind this is mostly to do this limits on experimental technique – sleep is a very complicated process whose mechanisms we do not understand fully, so it is difficult to a) identify a single mechanistic process and b) manipulate this in human subjects. Though slow oscillation, spindle and ripple activity have all been implicated in memory consolidation, only manipulations of slow oscillations have demonstrated a causative effect (Marshall et al., 2006; Marshall et al., 2011).

Limits of EEG Studies

An EEG study involves recording changes in potential across electrodes that are placed around the skull.

It is a good way of detecting global changes in activity. However, this is still examining neural activity at a very basic level. There could be many interactions happening between brain structures during sleep that do not produce any EEG activity, or more than one process which contribute to the overall EEG trace (such as slow oscillation or spindles).

Factors Affected in Sleep Deprivation

Most sleep-deprivation studies simply involve not allowing the subject to sleep at all following a learning task (Gais et al., 2007). This could be a problem as other stages of sleep could also be involved in physiological processes which we are not yet aware of, but have an effect on cognitive and memory functions indirectly.

One study had attempted to specifically deprive SWS to test for effects on the following nights of sleep. They did this by using an auditory stimulus to disturb the subject enough to prevent them from entering SWS, but without waking them completely; this was guided by a polysomnograph (Ferrara et al., 1999). The subjects received two nights of SWS-deprived sleep followed by a normal recovery night. The result was that though the overall length of sleep did not increase following deprivation, the percentage of Stage-4 NREM sleep and also SWS in general was increased. The results show that there is a need for SWS and that its deprivation will incur a 'debt' that must be paid later on, as evidenced by the increase in the recovery night. The same technique might be applied to a declarative memory task, with an experiment set up to test the effects of SWS deprivation on learning.

8. Overall Analysis

Ultimately, these studies aim to provide a full model of the functions of sleep and how it relates to all types of memories, though this is yet to be achieved. Of the two main theories discussed, the active system consolidation hypothesis is probably more complete as a model, as it brings together much more data involving the interactions of the hippocampus with the cortex. It is worth noting that the results from the vast of majority of studies would either concur with this theory, or provide extensions to its parameters.

Its suggestion of the roles that the hippocampus plays in declarative memory consolidation also fits well with neuropsychological evidence that lesions to this structure lead to amnesia. In patient R.B., for example, localised lesions to CA1 of the hippocampus was accompanied by severe anterograde amnesia but limited retrograde amnesia (Zola-Morgan et al., 1986). Data from other patients show that more extensive damage to the hippocampus and its surrounding structures will lead to more severe retrograde amnesia (Rempel-Clower et al., 1996). The reason could be that CA1 is primarily responsible for teaching of new information to the cortex, and lesions to this area will impair only the encoding of new information. Lesions extending to further areas including CA3 and the dentate gyrus [DG], which are involved in the extraction of memory traces from the cortex, will hence impair the retrieval of old information as well, leading to more severe retrograde amnesia.

Claims made by the SHY regarding the need for synaptic downscaling are probably valid. However, the data is less congruent. One study, for example, suggests that SWS in fact promotes the opposite process of synaptic upscaling (Chauvette et al., 2012). Another study recommends REM sleep instead of SWS stage where synaptic downscaling occurs (Grosmark et al. 2012). Further experiments will be needed to clarify this apparent disparity.

Although these experiments have shown that SWS sleep is primarily involved in declarative memory consolidation, it is likely that other stages, including REM sleep will have an effect either directly or indirectly. A potential role of REM sleep is in synaptic consolidation, which could occur separately from SWS-mediated systems consolidation. A reduced interaction between the cortex and hippocampus (systems-level consolidation) could enable consolidation to occur at a synaptic level, with LTP being enhanced. This is the basis of the sequential hypothesis, which suggests that memory consolidation requires a cyclical alternation between both NREM and REM sleep.

Another concern is that it may be too simplistic to separate information into distinct and independent memory systems. Declarative memories (episodic memory in particular, but perhaps also semantic memory) could be associated with emotional responses, which under the dual system hypothesis are based on completely different neural structures. This raises the question of whether a single memory trace can be processed in two different memory subsystems.

Implications for Reconsolidation

The active system consolidation hypothesis also

has an implication for memory reconsolidation, which is a more controversial topic. Memory reconsolidation is the process through which a stable long-term memory that has become labile is re-stabilised. This has been studied mostly for fear conditioning, a type of non-declarative memory that involves the amygdala and the associated limbic system. However, reconsolidation has also been identified for declarative memory (Forcato et al., 2010).

The puzzling feature for reconsolidation is why established memory traces would be made labile again. The active system consolidation hypothesis would explain this as a part of the normal consolidation process between the hippocampus and the cortex. When a memory is retrieved the information it contains is extracted and transferred to areas where it is needed elsewhere in the brain (such as motor cortex). It is possible that this information is also transferred to the hippocampus to enable this to be updated. The hippocampus will always attempt keep memories updated. If there were new information that is relevant to existing memories, then this would be integrated together and transferred back into the cortex. This means that the old memory would be deleted and replaced with an updated 'version'. This has been demonstrated in evidence which suggests that NREM sleep affects the integration of new memories into old memories (Tamminen et al., 2010). Therefore, reconsolidation could be not a separate process, but a manifestation of the long-term continuation of consolidation.

9. Further Experiments and Conclusions

There are still many questions that are yet to be answered; further experiments could be carried out to test some of these considerations:

Experimental designs should reflect on that the nature of semantic associations could have an effect on the way memories are encoded. Control protocols should be introduced to take into account the semantic meaning of word pairs.

Different experiments techniques need to be developed in order to manipulate activities such as spindle and ripple activity, to demonstrate that these processes have a causative effect on consolidation. As an example, Marshall's experiments (2006, 2011) involved modifying slow oscillation activity using tDCS; this technique could perhaps be adapted to give stimulations that replicate spindles or ripples.

Other neuromodulators, such as noradrenaline and serotonin, may also be relevant in controlling global neural activity. Again, manipulative techniques could be used to investigate their importance in the top-down control of memory consolidation.

The role of REM sleep on declarative memory is unclear. Studies should expand their premises to other stages of sleep, as sleep is likely to be a very integrated process.

Possible interactions with emotional memory as well as other types of non-declarative memory should also be explored. A single memory trace could be represented in more than one memory system; alternatively, two memory systems could interact to encode the same memory process.

On the whole, the studies I have discussed collate well to give a general picture of the mechanisms behind how NREM sleep affects the consolidation of declarative memories. However, more experiments are needed to clarify some aspects of an overall theory, as well as to investigate further the mechanistic details.

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