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A sleep to remember: The effects of sleep on memory

Deep P Sarode[1], Iain D Mathie[1], Neng P Gao[1], Lewis I Gray[1], Ian J Monaghan[1], Andrew P Preston[1], Matthew J Twomey[1], Marianne Watters[1]

[1] Year 3 MBChB, University of Edinburgh
Correspondence email: deepsarode@hotmail.co.uk

Abstract

For centuries, the functions of sleep have been researched. Multiple theories have been developed, but even now, scientists are unable to produce a conclusive explanation as to why we sleep. It is evident that sleep is vital, as even in animals, it has been argued that sleep deprivation leads to serious consequences. More recently, research has suggested that sleep plays a role in memory consolidation. This review aims to bring together the evidence concerning the link between sleep and different memory sub-classifications (episodic memory, semantic memory, procedural memory and conditioning) and its potential clinical application will be discussed.

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Introduction

An increasing area of interest in the field of neuroscience is the potential link between sleep and memory. Recent years have seen growing evidence supporting the idea that specific stages of sleep have a beneficial effect on memory, with promising conclusions being drawn.[1] The relevance of this research is its potential to be translated into clinical practice. This review aims to discuss the current evidence regarding the effect of sleep on different memory sub-classifications and the possible practical implications, to elucidate whether it strengthens or refutes our hypothesis that sleep plays a pivotal role in memory consolidation. The scope of this review is to provide a condensed yet relevant summation of this rapidly developing field of research for the curious medical student or doctor.

Memory is defined as the ability to encode, consolidate and retrieve information that has been learnt.[2] It is categorized based on whether the retrieval of information is conscious or subconscious, the former termed declarative (or explicit) memory and the latter termed non-declarative (or implicit) memory.[1,3]

Declarative memory is further divided into episodic memory, described as being the 'diary', and semantic memory, described as being the 'dictionary'[4]; episodic memory comprises autobiographical events whereas semantic memory comprises facts.[5]

Non-declarative memory can be split into procedural memory, conditioning, non-associative memory and priming. This review will focus on procedural memory and conditioning as little research exists regarding the latter two. Procedural memory involves learning a motor skill, such as learning to swim. Conditioning memory is the learnt response to a once neutral stimulus. The classical example is Pavlov's dogs, who associated the ringing of a bell with food and would salivate in response.[6]

Memory consists of three interdependent processes: encoding, consolidation and retrieval. In the process of encoding, new information inputs into neural circuits. This information is unstable and must be strengthened and transferred to long-term storage in the process of consolidation, which this project will focus on. Finally, this information is retrieved from the areas of storage.[2]

Sleep can be divided into two phases: non-rapid eye movement (NREM) and rapid eye movement (REM). NREM consists of four stages: stages 1, 2, 3 and 4. Stages 3 and 4 are referred to collectively as slow wave sleep (SWS) as both exhibit a slow wave EEG pattern.[7]

On average, one night of sleep involves four or five sleep cycles. Sleep cycles are the progression through various stages of NREM sleep and REM sleep, each lasting close to 90 minutes.[8] The stages of NREM do not necessarily occur in order and vary throughout sleep as illustrated in Figure 1.

Methods

Research regarding the effect of sleep on the different memory sub-classifications was identified by searching for both primary research and systematic reviews up until March 17, 2013.

A literature search was carried out using the Medline database and Google Scholar with the following keywords:

"Memory" AND "Sleep"
"Memory" AND "Sleep" limited to meta-analysis or review or systematic review
"Episodic memory" AND "Sleep"
"Semantic memory" AND "Sleep"
"Declarative memory AND "Sleep"
"Procedural memory" AND "Sleep"
"Conditioning" AND "Sleep"
"Non-declarative memory" AND "Sleep"

MeSH terms were used when available. Search terms were kept as broad as possible to ensure that important literature was not missed. No language restrictions were put in place. Articles were selected based on the relevance to our subject topic and aims. An article was deemed relevant according to the title abstract and subsequent critical appraisal of the text.

Episodic Memory

Episodic memory involves the recall of events occurring in a particular place and time.[9] The effects of sleep on episodic memory consolidation can be explored through sleep deprivation and are objectively quantified by using various episodic memory tests.

How does sleep affect episodic memory?

It is generally accepted that sleep enhances episodic memory consolidation. For example, van der Helm demonstrated significant memory improvement in subjects who were allowed a two-hour nap 45 minutes after encoding, compared to subjects who were not allowed a nap.[10] This result is in line with many studies that suggest a possible role for sleep in episodic memory consolidation.

Although sleep as a whole has been shown to aid episodic memory consolidation,[11] it is thought that certain sleep stages are more beneficial than others. However, exclusively depriving specific sleep stages is impractical in humans, as this could either lead to disruptions in other sleep stages or affect potentially important sleep stage transitions.[12] Plihal and colleagues discovered that the first half of one night's sleep involves almost five times more SWS than REM sleep, while the second half is associated with twice as much REM sleep as SWS (Figure 2).[13] This concept allows investigation of the effects of certain sleep stages by separating test groups into 'early sleep' and 'late sleep' groups, depending on whether the post-learning sleep occurs in early stages of the night or the late stages, respectively. Therefore, by either preventing early or late sleep, the effects of SWS or REM sleep individually can theoretically be determined.[13]

Using this methodology, and a sample size of 20, Plihal and Born documented improved performance in an episodic memory task in subjects assigned to the 'early sleep' group compared to those assigned to the 'late sleep' group, concluding that SWS was more important in the consolidation of episodic memories than REM sleep.[13] These results, and those of other studies, support the dual-process hypothesis, which suggests SWS is necessary for declarative memory whereas REM sleep is essential for procedural memory.[14-1]

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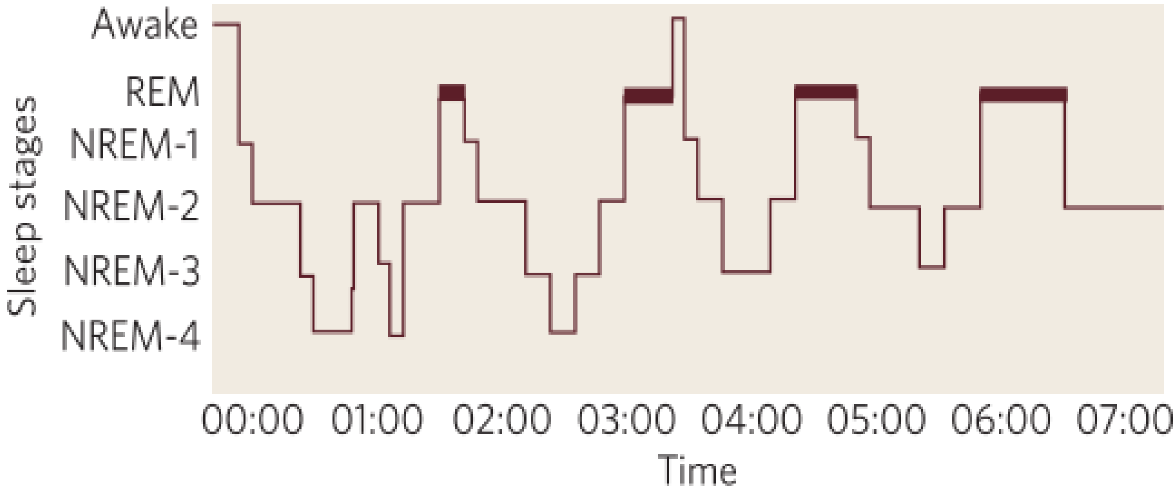

Figure 1: Categorization of sleep stages. (Stickgold et al, 2005)[1]

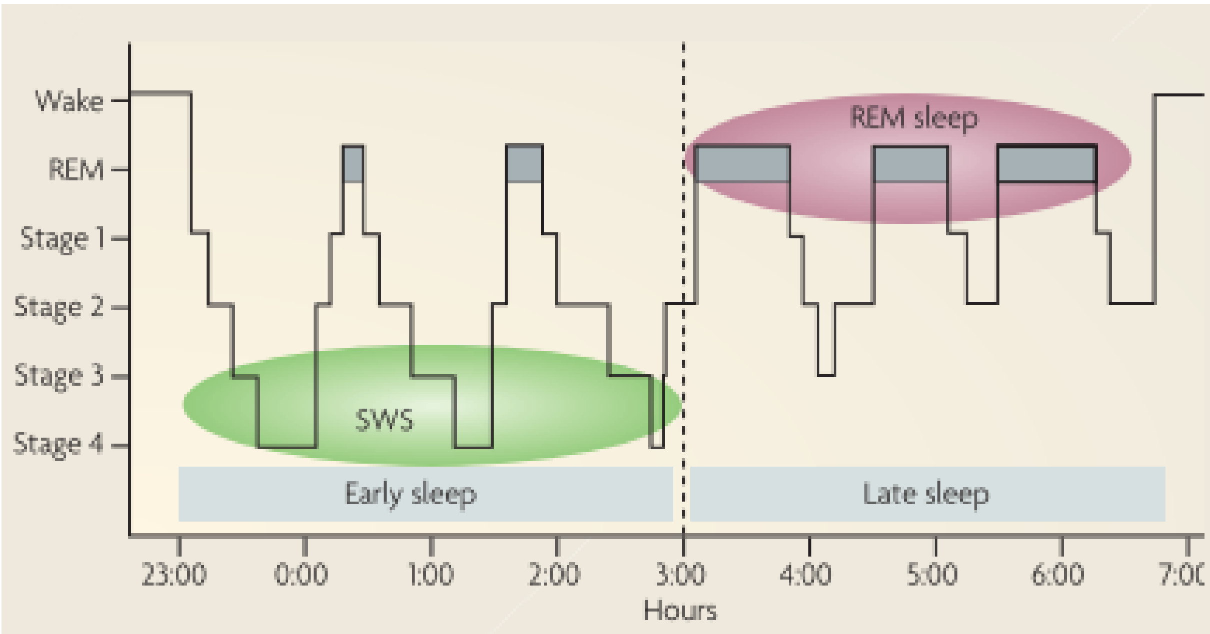

Figure 2: Early sleep contains a high proportion of SWS compared to late sleep which contains a high proportion of REM sleep (Diekelmann S, et al. 2010)[37]

Conversely, there have also been studies demonstrating a correlation between REM sleep and episodic memory performance. Rauchs showed that 'late sleep', associated with mainly REM sleep, correlated with improved episodic memory performance compared to subjects in the 'early sleep' and 'no sleep' groups.[17] Despite these results being 'preliminary' with further research being required in humans, these findings are incongruent with the dual-process hypothesis, and suggest that REM sleep may indeed play a role in episodic memory consolidation.

A possible explanation for the above conflict in evidence (solely SWS or solely REM sleep is essential) is the sequential hypothesis. This hypothesis, suggesting alternation of sleep stages in cycles facilitates memory consolidation,[18] was investigated and it was proposed that SWS promotes integration of new memories into pre-existing memory stores while REM sleep acts to stabilize these memories. However, evidence is lacking and further research is required for a greater understanding of the mechanisms involved.[19]

What flaws and limitations are present in these studies?

Some studies utilize the early/late sleep model which is not entirely reliable. Early and late sleep contain every sleep stage, just in different proportions. This is a possible explanation for the conflicting results seen above. In addition, early and late sleep differ not only in their sleep stage composition but also in the levels of certain hormones, as discussed below, and thus more than one variable exists.

Acetylcholine is an important neurotransmitter in neural circuits and plays a part both in memory and sleep systems. During sleep, acetylcholine is at low levels during SWS and at high levels during REM sleep.

It was shown that increasing synaptic acetylcholine concentration during SWS led to poorer episodic memory consolidation.[20] Therefore, the effects of fluctuating chemicals during sleep, such as acetylcholine and cortisol, could be potential confounding factors to the above evidence.[21]

Semantic Memory

Semantic memory encompasses stored ideas and concepts without the context of where and when the information was formed.[22] Specifically testing the individual aspects of declarative memory can prove challenging due to the episodic factors involved in development of semantic memory.

How does sleep affect semantic memory?

Generally, studies use sleep deprivation to test the effect on semantic memory of either sleep as a whole or of certain sleep stages. Fischer used total sleep deprivation to compare the semantic memory consolidation in sleep and wake states. 20 subjects with steady sleep patterns were taught material and were allocated to either a 'sleep' group or a 'wake' group. Using a reaction time test, subjects were tested after a nine hour period of either sleep or wakefulness on the previously learnt material. It was found that subjects of the 'sleep' group performed significantly better in the reaction test, indicating a possible link between sleep and semantic memory consolidation.[23]

A similar study also examined the effects of deprivation of different stages of sleep on the ability to recall semantically stored information. 20 subjects were given two short stories to recall the following morning after a night's sleep. However, the sleep was disrupted either during stage 4 or REM sleep to deprive the respective stages. The next day, subjects were given a full night's undisturbed recovery sleep and were tested the following day. Subjects deprived of REM sleep performed worse than subjects deprived of stage 4 sleep.[24]

Interestingly, another study measured semantic processing in all stages of sleep individually avoiding sleep disruption. Pairs of semantically associated words were played to 13 subjects and brain-wave activity was measured using an EEG to determine the pattern of brain waves displayed when two semantically associated words were processed. This was carried out during wakefulness and during sleep and the results were compared. These instances of matched brain waves corresponded to active semantic memory processing and occurred most often in REM and stage 2 of sleep, suggesting that these stages may play an important role in the processing of semantic memory.[25]

What flaws and limitations are present in these studies?

The major limitation of studies regarding semantic memory is the large overlap with episodic memory. This makes it difficult to determine whether beneficial effects of sleep on learnt material are due to a better consolidation of semantic or episodic memory, with the latter being the case in most instances. It is probably because of this reason that evidence in this area of memory is very much lacking.

Procedural Memory

Procedural memory refers to the acquisition of a motor skill, for example, learning to ride a bike or play a musical instrument. This type of learning is implicit (i.e. a subject is not necessarily conscious of their learning) and is recalled subconsciously.[5]

How does sleep affect procedural memory?

There is substantial evidence supporting the role of REM sleep in the consolidation of procedural memory, shown in animal and human models. One method used to demonstrate this is through post-learning sleep deprivation. This involves the animal being trained in a task, then having sleep following the training disrupted at particular sleep stages. These studies often demonstrate that REM sleep deprivation disrupts consolidation of the memory and, when retested, the animals do not perform as well as the control group who receive no sleep disruption.[26] Datta and colleagues highlighted the role of REM sleep by training 22 rats in an avoidance task involving the learning of a particular route in a course, monitoring their sleep and then testing their performance on the task after sleep.[27] After sleeping six hours, a significantly higher performance in the avoidance task than in their previous attempt was observed. However, it could be argued that the improvement in performance may be due to having performed the task previously, and the lack of a control group further reduces the reliability of the results. Furthermore, a major flaw in these types of studies is that waking the animals at certain points during sleep may lead to stress, a factor which may influence performance in the retested task.

The important link between REM sleep and procedural memory can also be observed in human models. Similarly to animal models, various methods demonstrate this association. In general, there are two different approaches to testing the connection between procedural memory and REM sleep.

The first method involves depriving subjects of total sleep or of some specific sleep stage following learning, with memory being retested at a later stage. One study involving six subjects demonstrated that REM sleep deprivation prevented the improvement in the task after a night of normal sleep, while NREM deprivation did not.[28] This latter conclusion is echoed by slightly larger study of 29 subjects.[29]

The second approach is used less frequently. It involves cueing subjects at certain points during sleep to enhance memory formation. The cueing is normally achieved using an auditory stimulus, such as pulses of white noise. In one study, subjects were trained to decipher Morse signals. During subsequent sleep, five subjects were presented with 40 ms pulses of white noise during periods of sleep where little or no rapid eye movement was recorded. The other group received an auditory stimulus during REM sleep episodes. Comparison of the groups showed that there was better performance in the group who received white noise pulses during REM sleep episodes.[30]

What flaws and limitations are present in these studies?

Many tasks involve both a declarative and procedural component. This causes difficulty in distinguishing which specific components of sleep are involved in each process and to what degree these processes overlap. Carefully designed studies may alleviate this problem.

Another area for improvement is the understanding of distinct memory systems. Future research should aim to further clarify the categorization of memory types. 'Procedural memory' may become too broad a category, and conclusions drawn from a range of studies involving formerly unknown subdivisions of procedural memory may be too general. For example, separating studies involving cognitive procedural tasks and motor procedural tasks may produce more accurate and specific conclusions.

Conditioning

Conditioning is a process by which a non-specific stimulus can be used to elicit a physical and emotional response through an association between the stimulus and response.[2] This section will concentrate on fear conditioning, as much of the research conducted into conditioning memory focuses on this.

How does sleep affect fear conditioning?

There is evidence suggesting that full night sleep deprivation (FNSD) could prevent memory formation. Subjects were shown videos of road traffic accidents to investigate post-traumatic stress disorder (PTSD) often associated with accidents, and their reaction was rated based on skin conductance rates. Skin conductance rates were raised when an emotional response, such as fear, was experienced. After subjects were split into FNSD and non-FNSD groups, they were shown different clips and responses were rated; the sleep deprived group showed significantly lower emotional responses. As

PTSD is associated with a high emotional response, it was suggested that the sleep-deprived group had not formed the stressful memory that would be present in PTSD.[31]

A study by Menz also found that sleep, particularly REM sleep, enhanced the consolidation of fear conditioning memories. Subjects were shown a series of pictures associated with either an electric shock or no electric shock and then split into two even groups (Figure 3), a sleep group and a wake group, with the latter being deprived of sleep for the first night. On day 3, subjects were shown the pictures again and were required to predict whether they expected to receive a shock for each picture. The results found that knowledge of the conditioned stimulus was greater in the sleep group than in the wake group, reflected by the enhanced shock expectancy ratings and skin conductance responses. Furthermore, the consolidation of fear memory correlated with the time spent in REM sleep during the first night. This study design, which allowed a recovery sleep on night 2, attempted to eliminate potential confounding factors associated with lack of sleep, such as reduced concentration .[32]

In another study, arachnophobic subjects were shown short video clips of spiders and were instructed to imagine the spiders being with them in the room, the theory being that nothing untoward would happen and they would form an extinction memory. The videos consisted of one session showing one species and a second showing a series of different species. To investigate the generalization of fear extinction, subjects were asked to rate their fear. After one night of either sleep or sleep deprivation, the video clips were shown to them again. The FNSD group showed only very slight fear reduction to the first spider and were still sensitive to the other species of spider. The non-FNSD group showed significantly reduced reaction to both, again suggesting sleep aided this group in forming a generalized fear extinction memory.[33]

What flaws and limitations are present in these studies?

A significant source of confound is that the human studies required their subjects to adhere to strict guidelines and rules; it would be unsurprising to learn of some non-compliance. For example, subjects would not be allowed to drink caffeine the week before; it is possible people did not comply with these restrictions. In the study with arachnophobic subjects, fears were rated using a questionnaire; this method depends on subjective judgement so is not a completely reliable means of measurement.

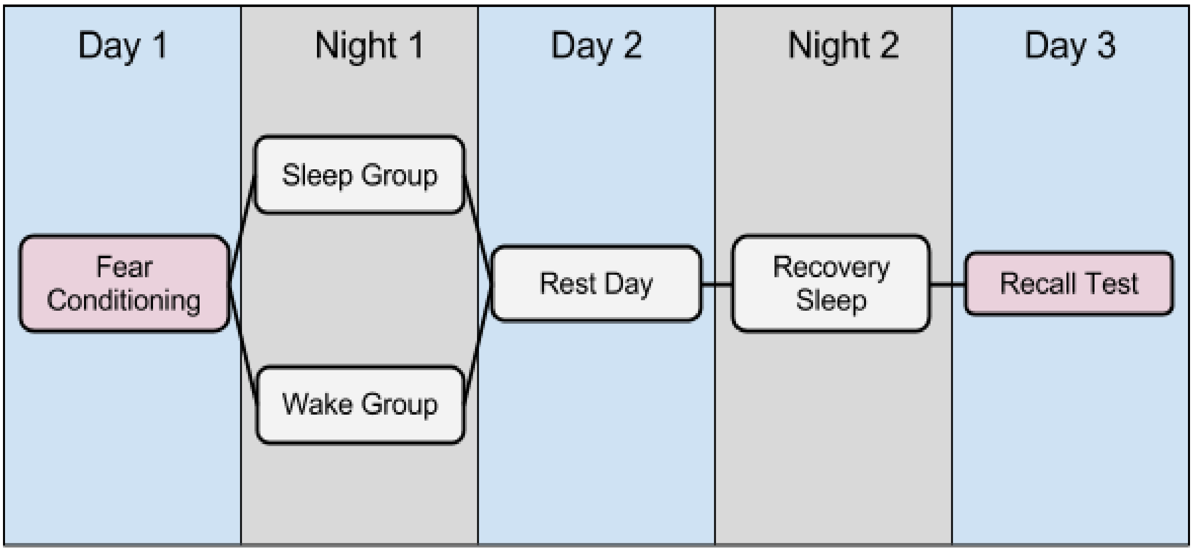

Figure 3: Adapted from (Menz et al. 2013)[32]

Discussion

It is important to acknowledge several factors problematic to sleep and memory testing. Studies generally used small sample sizes, ranging from 5 to 66 subjects (s.d.=15.8; mean=26.1; median=22), with lack of evidence of a statistical power test to justify this. This reduces the confidence in the conclusions drawn in specific studies, as there is an increased element of chance. Another significant flaw was that many tasks did not solely test one specific memory sub-classification but instead also contained small elements of other memory sub-classifications, further complicating result interpretations. Deprivation of sleep, a common study design, is distressing for the subject with evidence showing raised stress hormones which may suppress memory consolidation.[34] Furthermore, lack of sleep negatively impacts on the subjects' concentration ability and, although some studies took this into account by separately testing concentration ability (such as Backhaus[35]), it was overlooked in many studies.

To make the conclusions drawn from these studies more accurate, future research in this field should focus on addressing possible confounding factors and flaws. A key step would be to increase sample sizes used in these studies. It may be that memory consolidation is highly variable between individuals and increasing sample sizes would increase confidence in the results. Increasing sample size may also allow for comparison across different populations, potentially showing whether there is genetic variability between how sleep affects memory. One way of reducing confounding factors such as stress influencing results would be for studies to use methods which do not disturb sleep, for example PET scans, to detect changes in the brain during sleep.[36]

Conclusion

This review investigated the relationship between sleep and four types of memory (Box 1). Most studies indicated that sleep and memory were indeed linked: sleep deprivation impairs the capacity to

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consolidate the memory types studied. In each section we concluded the following:

Box 1. Different types of memory and their relationship with sleep.

Episodic memory. There is no clear consensus which sleep stages are predominantly important as some studies outline the importance of SWS whereas others show evidence supporting solely REM sleep. On the other hand, sleep stages may work synergistically and be dependant of each other.

Semantic memory. Stage 2 of NREM sleep and REM sleep may have a role in semantic memory consolidation. However, the evidence available is limited so drawing firm conclusions is difficult.

Procedural memory. There is significant evidence that REM sleep increases procedural memory consolidation in humans whereas NREM sleep does not have an effect.

Conditioning. Total sleep deprivation impairs the ability to consolidate fear memory and the ability to form fear extinction memories. There is a lack of evidence investigating the interaction between individual sleep stages and conditioning memory consolidation.

In a clinical setting, this research has many potential practical applications. As sleep deprivation is such a common occurrence in modern medicine, it would be beneficial for both medical students and doctors to know about the implications of sleep deprivation. For example, there are some occasions when it may be beneficial to forget an event, such as following a traumatic experience. Intentional sleep deprivation could potentially prevent development of PTSD and this is a possible area for research.[37,38] Furthermore, some antidepressant drugs result in REM sleep deprivation.[39] Therefore, since it has been found that there is a link between REM sleep and procedural memory, further research should be carried out investigating the effects of these drugs on procedural memory consolidation.

Thus, to learn more about how sleep influences memory, studies are needed to investigate mechanisms of memory consolidation during sleep. It is hoped that a greater understanding of memory systems and sleep may contribute to a more comprehensive description of the effect of sleep on memory and possible therapeutic options.

Key Learning Points

- Substantial evidence shows that sleep deprivation is detrimental to the consolidation of the 4 memory types studied: episodic, semantic, procedural and conditioning.
- Different stages of sleep have been shown to be important for different memory sub-classifications.
- The implications of this link could potentially be used in the medical field to treat disorders such as PTSD.
- This link may complicate treatment strategies such as the use of antidepressants.
- A better understanding of this link could lead to the development of more effective study programs for individuals throughout their education to maximise learning.

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