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Review

Sleep and cognitive (memory) function: research and clinical perspectives

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Abstract

The field of memory and sleep is controversial and extremely interesting, and the relationships between thought processes, i.e. cognition and sleep, have recently been examined in a variety of clinical and basic research settings, as well as being the object of intense interest by the general public. For example, there are data which demonstrate that insomnia, as well as specific sleep disorders, can have a negative impact on sleep cognition as well as affect daytime patterns of cognitive functioning. Thus, sleep, disturbed sleep and the lack of sleep appear to affect cognitive and memory functions. An International Workshop dealing with Sleep and Cognitive Function: Research and Clinical Perspectives was convened in Cancún, Mexico, 1–4 March 1999 under the auspices of the World Health Organization Worldwide Project on Sleep and Health and the World Federation of Sleep Research Societies. A great number of areas of intersection between sleep and cognitive function were examined during the course of the Workshop, such as aging, cognition and sleep and the dream process and sleep. The results of these discussions are included in a WHO publication (WHO Doc.: MSD/MBD/00.8). In the present report we concentrate on presenting a summary of a coherent set of data which examine memory consolidation during sleep and the impact of insomnia on cognitive functions. Based upon these data, a review of memory and drug effects that are sleep-related, and an examination of the relationship between hypnotics and cognitive function are included. Finally, a summary of recommendations of the Workshop participants is presented.

Keywords: Cognition; Sleep; Sleep disorders; Public health; Mental disorders; Treatment

1. Introduction

Although it is generally accepted that variations in sleepiness/alertness affect memory processes, the memory and sleep literature is complex and somewhat contradictory. As with many inter-disciplinary fields, in many cases sleep scientists have not adequately assessed different memory systems and processes, while cognitive scientists have not paid sufficient attention to sleep variables and methods, nor have they objectively documented the level of sleepiness or the extent of arousal from sleep.

Nevertheless, it is clear that biological states such as sleep and wakefulness, as well as levels of sleepiness/alertness, can affect different memory systems differentially. The concept or process of memory arises when successive stimuli are compared and a response

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can be made that is contingent on that comparison. The underlying mechanistic assumption is that the original event leaves a trace, or engrains, in the brain that allows the present event to be related to it.

To the extent that one studies memory from a behavioral perspective dealing with the retention and retrieval of past experiences, the distinction between the process of recall vs. recognition should be taken into account. Recognition is a form of remembering characterized by a feeling of familiarity when something previously experienced is again encountered; in such situations a correct response can be identified when presented but may not be reproduced in the absence of such a stimulus. Recognizing a familiar face without being able to recall the person's name is a common example. Recognition seems to indicate selective retention and forgetting of certain elements of experience. On the other hand, recall occurs when, for example, subjects are asked to reproduce (recall) previously learned data in any order or in the original order in which they were learned. The subject's task is simpler in tests of recognition, since reproduction or retrieval (as in recall) is not required. The subject simply is asked to remember previously presented information when it is offered to him again.

To begin this discussion, it is important to note that memory consists of several phases or processes: a stimulus registration or acquisition phase of short duration, a consolidation from short-term to long-term memory phase, and the retrieval from long-term memory.

There are a number of different memory systems such as perceptual, procedural, episodic, and semantic memory. Perceptual memory, also referred to as implicit, is an unconscious form of memory in that the individual does not intend to learn anything. Procedural memory refers to any skilled performance. Historically, this type of memory was referred to as motor skills and involved study of how motor performance is learned. Semantic memory refers to the use and accumulation of factual knowledge. This type of memory is typically associated with formal education and learning. Finally, episodic memory is the recall of personal life experiences such as recalling having done a performance test. Declarative memory can be subdivided into semantic and episodic components, whereas procedural memory consists of simple conditioning, perceptual and skills memory.

Whether the sleep/wake state and level of sleepiness/alertness differentially affect the various memory processes and systems described above is not clear; however, the following provide a basis for evaluating the state of knowledge regarding certain aspects of sleep and cognitive (memory) function.

2. The view that memory is consolidated during sleep

Over the last 20 years it has become increasingly evident that sleep plays an important role in the efficiency of memory consolidation. Rapid eye movement (REM) sleep has been observed to increase following successful learning in animals and in humans (but not after unsuccessful attempts to learn). These REM sleep increases persist for many days following the end of task acquisition and can take the form of increased duration of REM sleep, increased REM intensity or both. Conversely, the selective deprivation of REM sleep following the end of task acquisition results in memory losses that can be 20–50% lower than the original acquisition scores. The REM sleep times that are vulnerable to memory loss have been called REM sleep windows. The timing of these REM windows depends on the strain/type of organism learning the task, the type of task and the number of training trials per session. These REM windows can be as short as 3–4 h and yet their interruption can still induce marked memory loss. Preliminary experiments in animals indicate that the cholinergic transmitter system is involved. In humans, there is compelling evidence that cognitive procedural learning material is sensitive to REM sleep loss, while motor procedural or 'skills' tasks are sensitive to Stage 2 sleep loss or interruption. Declarative learning material seems unaffected by sleep loss of any kind.

Although there have been a number of arguments that memory processing is not related to the states of sleep, they have been presented because in the animal studies some negative results were observed. It seems clear that the failure to observe memory loss after REM sleep deprivation (REMD) was due to the variable position of the REM window, which can fluctuate from 0 to 56 h after the end of the training task. Most REMD in the early studies was applied in the first 4 h

after the end of training, and many of these windows were undoubtedly missed. In addition, some tasks were probably too simple for any impairment to be observed. It has also been argued that the sleep/memory relationship has never been reliably demonstrated in humans. This is no longer true. What has become clear is that cognitive procedural tasks are vulnerable to REMD, while simple motor skill tasks are vulnerable to Stage 2 loss or interruption. Declarative or explicit material (which comprised the majority of the tasks chosen in the early studies) is immune to sleep loss of any kind. Recent positron emission tomography (PET) scan data strongly support these human behavioral and EEG studies.

3. The view that memories are not consolidated during sleep

The view that memory is not consolidated in REM sleep is derived from: (1) an evaluation of the relevant literature on this subject which provides no firm support for a role for REM sleep in memory consolidation; and (2) knowledge of the workings of memory, which makes it difficult to envision how memories would be processed or consolidated in unconscious states of sleep/REM sleep.

There is a long history of studies in animals and humans examining the role of REM sleep in memory. These studies essentially involve two main types of manipulations: (1) an examination of potential increases in REM following heightened experiences during waking; and (2) an examination of the effects of REMD on previously learned tasks. Horne [1] evaluated studies involving the first set of manipulations and concluded that animals receiving either prior training on specific tasks or exposure to enriched environments showed, at best, minimal increases in the amount of REM sleep. In addition, these procedures produced equivalent increases in percentages of slow-wave sleep (SWS) as REM sleep. In humans, Horne and colleagues [2,3] reported that human subjects exposed to enriched environments exhibited increases in SWS, particularly delta sleep, but no changes in REM sleep. Finally, reviewing this area, McGrath and Cohen [4] concluded that: "non-deprivation studies employing humans seemingly provided little support for a relationship between sleep and learning".

The results of extensive examinations of the effects of REMD on memory in animals are equivocal; some studies have reported effects on memory, but at least equal numbers have not. It appears that many studies reporting deficits in memory with REMD used relatively stressful REMD techniques and/or the loss of REM was accompanied by significant loss of SWS. In reports in which these two factors (stress and total sleep loss) were minimized, the effects of REMD on memory were negligible or absent. A review of this literature led Horne [1] to conclude: "In sum, and in relation to the memory consolidation hypothesis for REM sleep, I find the field of REM sleep deprivation and learning in animals unconvincing." Similar conclusions were reached following an assessment of the human literature on this subject [4].

It appears that an essential element of the position that REM sleep plays a role in memory is that events of waking are reviewed and evaluated in REM and then, presumably depending on their value to the organism, they are either stored or not stored in memory. In effect, information is suspended in waking for later storage in REM; without REM, information is essentially lost to memory. REM is the ultimate arbiter of events permanently stored in memory. Various reports in animals and humans showing relatively profound deficits in very simple tasks following even short-term REMD would seem to support this basic scheme. For example, in a well-cited study in humans, Karni et al. [5] exposed human subjects to a visual perceptual task involving a set of three lines oriented differently than a background pattern of lines (i.e. three diagonal lines embedded in an array of horizontal lines). The task consisted of a determination of the quadrant in which the diagonal lines appeared and latency to detection was the measure of performance. Subjects were shown diagonal lines in one quadrant and before going to sleep (SWS only, REM only) the lines were switched to a new quadrant and remained there for testing post-sleep. The task was to 'remember' the switch in quadrants. The results showed that the SWS-deprived subjects showed marked improvement in the task (i.e. shorter latency to identify the test stimulus in the new quadrant), whereas REM-deprived subjects showed no improvement in the task. Presumably, the REM-deprived subjects did not learn or 'remember' that the stimulus had been moved to a new quadrant.

The reported improvement in the foregoing task of subjects with REM but not those without it would seem to indicate that REM performs the following functions: (1) a survey of the entire events of the day (an incomplete survey may overlook potentially important data such as the approximate 15 s pre-sleep exposure to the test display); (2) weighing events of waking for significance (a strong case could be made that if information came biased for significance, rather than neutral, it would have already been differentially coded in memory); (3) sorting significant from non-significant information (e.g. diagonal lines in a horizontal array of lines from other presumably inconsequential visual stimuli of the day); and (4) disregarding insignificant data and storing significant information of waking.

As discussed previously [6], although physiological/neurophysiological events of REM mimic those of wakefulness, it is nonetheless the case that REM is a very different state than wakefulness; that is, REM lacks the rich array of sensorimotor, emotional and cognitive processes present during wakefulness. It is therefore unlikely that requisite mechanisms are present in REM to perform the complex manipulations required for memory.

4. The impact of insomnia on cognitive function

Insomnia is the most prevalent sleep problem [7], whereby the frequency strongly depends on factors such as the type and severity of insomnia, and on the age distribution of the population studied. The sleep of patients with insomnia shows characteristic deviations from that of normal subjects: Sleep latency is increased, total sleep time is decreased and the NREM-REM cycle is fragmented by intervening wakefulness. There is an increase of shallow sleep (sleep Stage 1) and a pronounced deficit of SWS [8,9]. The microstructure of sleep of patients with insomnia shows an increase in arousals [10] and an increase of high frequency beta and gamma EEG activity [11].

A key feature in the diagnosis of insomnia is a complaint on impairment of daytime functioning [12,17]. Patients with insomnia typically complain of disturbed mood, increased irritability, and cognitive problems such as a deficit of concentration and memory. While such sequaelae are very typical for insomnia patients, objective data corroborating cognitive deficits in this group of patients are much less convincing [11,13]. This is in sharp contrast to those sleep/wake disorders which are accompanied by excessive daytime sleepiness (e.g. narcolepsy, and sleep apnea syndrome), where deficiencies in the performance of cognitive tests have been shown consistently [14–16,41].

Table 1 summarizes experimental data of patients who have insomnia in cognitive performance tests. The literature on this topic is rather limited and few

Table 1
Laboratory-based cognitive performance studies with insomnia patients

Author(s)	Year	Function	Performance of insomnia patients
Mendelson et al. [13]	1984	Semantic memory	Lower than normals
		Recent memory	Not different from normals
Pedrosi et al. [18]	1995	Choice reaction time	Slower than normals
		Divided attention	Not different from normals
		Recent memory	Not different from normals
Hauri [17]	1997	Simple reaction time	Slower and more variable than normals
		Choice reaction time	Slower than normals
		Digit span	Lower than normals
		Digit symbol substitution	Not different from normals
		Divided attention	Not different from normals
		Auditory verbal learning	Not different from normals
		Auditory vigilance task	Not different from normals

effects were replicated in independent studies. There is much broader literature on cognitive functioning in relation to hypnotics, but the primary aim of the studies was to evaluate for drug-induced impairment of performance. Reaction time was prolonged in insomnia patients in two studies, and this effect was more pronounced for simple compared to complex reaction times in the Hauri study [17]. While memory for newly learned information showed no impairment in the three studies which are shown in the table [13,17,18], semantic memory (reproduction of earlier learned material) was impaired in the Mendelson et al. study [13], and digit span of insomnia patients was reduced in the Hauri study [17]. Insomnia patients did not differ from normal controls in divided attention (two studies) and in a 40 min vigilance task (Hauri study).

The effect of hypnotics, if taken as an evening dose, on cognitive functioning is puzzling. While the great majority of drug treatment studies showed an improvement of sleep duration and sleep quality, measured by self-rating instruments and polygraphic recordings, not much benefit in objectively measured psychomotor or cognitive performance has been demonstrated. Most studies showed either residual daytime impairments as a consequence of prolonged drug action, or a negative rebound effect after abruptly stopping drug treatment [19–21]. There are only a few exceptions from the rule [22]. The general picture suggests that the link between sleep quality and objectively measured cognitive performance is weak in patients with insomnia, and that hypnotics improve subjective and objective sleep but not daytime cognitive functions. Accumulated evidence suggests that imidazopyridines, such as zolpidem, have either nil or only minor residual effects on daytime cognitive performance [23]. The lack of positive effects of hypnotics on performance could be due to the short duration of these trials.[1] Long-term efficacy studies with daytime outcome measures are needed.

The traditional approach of testing cognitive functions in the day after nighttime intake of a hypnotic was rather defensive in the sense that testing was mainly performed to detect or to exclude residual drug effects. Since selective hypnotics like zolpidem seem to be largely void of residual effects, a more offensive research strategy should be applied in the future.

[1] The negative impact of insomnia on cognitive function may develop over time, and similarly, reverse with extended therapy.

5. Memory systems and drugs effects

Cognitive scientists have hypothesized that memory involves different systems and subsystems with differing neurobiologies. One system described by Squire [24] distinguishes declarative and procedural memory. Declarative memory is explicit and is subdivided into semantic and episodic, whereas procedural memory is implicit and it includes perceptual, motor skills, and simple conditioning. Squire hypothesizes that declarative memory is organized in the brain at the hippocampus and procedural is global and non-specific. Another system, that of Tulving [25], distinguishes episodic, semantic, procedural, perceptual, and implicit memory. Episodic memory is the recall of personal life experiences and semantic memory refers to the use and accumulation of factual knowledge. Procedural memory refers to the learning of motor and cognitive skills, those skills used in solving problems and performing motor tasks (i.e. riding a bike). Perceptual memory is visual and auditory recall (i.e. recalling a face or tune). Finally, implicit memory is an unconscious form of memory in that the individual does not intend to learn anything, but by having been exposed to information it can be recalled. Perceptual and procedural memory can also be implicit.

Psychopharmacologists have only recently begun to assess drug effects on specific memory systems and subsystems. In addition to outlining the different memory systems, Table 2 summarizes the effects of the different drug classes on memory systems. The table includes, for comparative purposes, studies in which sleepiness is produced in healthy normals by restricting or depriving sleep, rather than administering drugs. According to Squire's hypothesis, declarative memory, which is specifically hippocampal and cholinergic, should be less affected by drugs with differing mechanisms of action, whereas procedural memory, which is more global, would more likely be affected by a variety of drugs.

By the Squire system, declarative memory includes semantic and episodic memory. All the drug classes

Table 2
Effects of drugs on different memory systems

	Declarative		Procedural			
	Semantic	Episodic	Procedural	Perceptual	Implicit	Condition
Alcohol	Impaired	*[a]	*	*	Not impaired	
Benzodiazepine agonists	Impaired	*	Impaired	Impaired	Equivocal	
Anticholinergics	Equivocal	Impaired				
Antihistamines	Impaired					
Sleepiness	Impaired	Impaired			Equivocal	Impaired

[a] *Learning impaired/retrieval facilitated.

appear to impair semantic memory, that is, the recall of factual information. Importantly, non-drug-induced sleepiness does the same. They also appear to impair the learning of new episodic material. But, interestingly, recall of episodic material learned prior to the administration of both alcohol and benzodiazepine receptor agonists (BzRAs) is facilitated. The facilitation is attributed to reduced interference from new material due to the drug state.

Procedural memory, by the Squire system, includes procedural, perceptual, implicit and simple conditioning. Drug effects on procedural memory have not been extensively evaluated. Alcohol, as it does to episodic memory, impairs new procedural and perceptual memories, but it facilitates the recall of previously learned procedural and perceptual material. Both procedural and perceptual memory after experimentally-induced sleepiness have not been specifically studied. The results of studies of drug effects on implicit memory have primarily been inconclusive; in one study alcohol did not affect implicit memory, whereas the studies of BzRAs are equivocal.

6. Hypnotics and cognitive functions

Drugs with quite different mechanisms of action have sedating effects as well as amnestic effects. The extent to which the sedative effect of a given drug, irrespective of its mechanism of action, is responsible for its amnestic effect is a matter of current dispute and investigation. Non-specificity as to drug mechanism and also memory system would be strong evidence to support the view that the amnesia found with these drugs is mediated by their sedating effect.

Traditionally, the sedative effects of drugs have been assessed using performance tests, such as digit symbol substitution or critical flicker fusion, and self-reports of fatigue and energy. Insensitivity and inconsistency of results have been a weakness in the use of these measures. The Multiple Sleep Latency Test (MSLT), a direct physiological measure of sleepiness, is a highly reliable and sensitive method of assessing the sedative effects of drugs and is the method of choice to assess the sedative effects of a drug.

The sedative effects of alcohol have been directly demonstrated using the MSLT. Average daily sleep latency on the MSLT after consumption of alcohol is reduced in a dose-related manner over dose ranges that produce breath ethanol concentrations below legal intoxication [26]. The amnestic effects of alcohol have a long history of extensive study in acute and chronic use [27]. However, to date, studies that have attempted to relate the sedative and amnestic effects of alcohol are equivocal [28].

Sedative effects of BzRAs also have been well-demonstrated after both nocturnal and daytime administration; that is one of their dose-dependent effects and the primary therapeutic indication of some of them [29]. The BzRAs also have amnestic effects that parallel their sedative effects as measured by the MSLT [30]. But, the extent to which the sedative effects mediate the amnestic effects has been disputed extensively and several studies have attempted to dissociate the two effects, with somewhat equivocal results [21,31,32] (see Fig. 1).

Studies of cognitive impairment in normals and patients have been conducted, including specific assessments of memory, in order to assess the safety profile of antidepressants [33]. Those antidepressants

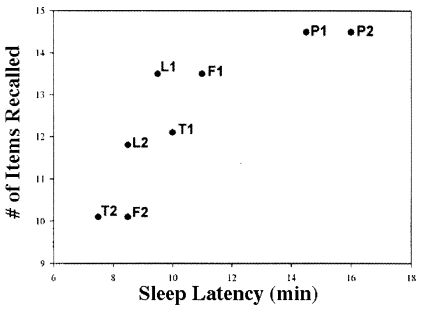

Fig. 1. Relationship of sleep onset latency to morning recall of item presented at peak plasma concentration across drug conditions.

which have memory-impairing effects include drugs that block muscarinic acetylcholine receptors with high affinity, such as amitriptyline. Also those antidepressants with H_1 antihistaminic effects (i.e. doxepin, mianserin) or alpha-1 noradrenergic blocking effects (i.e. trazoadone), produce amnesia. Many of these antidepressants are non-selective in their receptor activity and possess different combinations of anticholinergic, antihistaminic or noradrenergic blocking activity. The sedative effects associated with these antidepressants have not been directly or systematically assessed; the information is inferred from clinical evaluations and a variety of performance tests. Also, studies have not related their sedating and amnestic effects. Furthermore, due to their non-specificity, as noted previously, it is difficult to attribute either their sedating or amnestic effects to a specific neurobiological mechanism. Those selective anticholinergic and antihistaminic drugs discussed below provide better information to address this question.

The sedating effects of H_1 antihistamines have been extensively defined and directly demonstrated using the MSLT [34]. For example, in one study 50 mg diphenhydramine reduced mean sleep latency to a level similar to that of 0.5 g/kg ethanol and slightly less than that of 0.25 mg triazolam [29]. The sedating effects are dose-related and limited to those antihistamines that readily cross the blood-brain barrier [34]. Less well-studied are their amnestic effects. Recall of factual knowledge was reduced with diphenhydramine relative to placebo or loratadine, which is an antihistamine that does not readily cross the blood-brain barrier and does not have sedating effects [34,35]. However, studies have not attempted to relate the sedative and amnestic effects.

Acetylcholine has long been considered important in learning and memory processes and anticholinergic drugs are known to produce amnesia [36]. For example, 0.5 mg scopolamine (i.v.) reduced free recall of a word list [37]. Self-rated levels of alertness and fatigue suggest that scopolamine also has sedative effects, but no studies have directly measured its sedative effects using the MSLT. Several studies have also attempted to dissociate the sedative and amnestic effects that are associated with scopolamine by pharmacologically reversing the amnesia without affecting the sedation and vice-versa, but with limited success [37,38].

7. Conclusions

There is a considerable lack of knowledge on the consequences of short-term and chronic insomnia on cognitive function. More systematic studies on cognitive functioning in well-defined groups of untreated insomnia patients are needed. In addition, the discrepancy between the well-documented subjective complaints and the large absence of objective correlates needs further clarification. The fact that there is only a very weak relationship between chronically disordered sleep and daytime cognitive functioning in insomnia patients is a challenge for the understanding of the function of sleep. A new research strategy would be to reclassify insomnia patients according to polysomnographic criteria and to study which basic

physiological processes are disturbed. The proposed interaction of homeostatic and circadian processes could be a starting point for such an analysis in insomnia patients [39,40]. Based on such a physiologically oriented classification, cognitive deficits in insomnia patients should be studied anew.

A variety of sedating drugs with quite different mechanisms of action can produce amnesia. Efforts to dissociate the sedative and amnestic effects have been limited. Pharmacological and behavioral interventions aimed at differentially reversing the sedative and amnestic effects of drugs are needed to unravel the relation between the two pharmacological effects. These include probes such as sleep deprivation and pharmacological antagonists. Even less clear are the effects of various sedating drugs on specific memory systems and subsystems. One approach to tease these two effects apart would be to test multiple drugs on multiple memory systems. The memory system hypothesized as being more globally organized should not be affected by multiple drugs. On the other hand, the system hypothesized to be specifically organized should be affected by different drugs with different mechanisms.

At this point, there are two conclusions that can be drawn: (1) the fact that all drugs with documented sedative effects, regardless of neurobiological mechanism, have negative effects on memory supports the fact that the amnestic effects of drugs are mediated, at least in part, by sedation; and (2) the fact that the administration of a single drug differentially impairs different memory systems suggests that there are other mediators beyond sedation which can produce memory impairment. The future studies need to focus on evaluating multiple memory systems, while administering drugs from different chemical classes, or a single drug with differing levels of sedative effects.

8. Recommendations

There was a consensus that neither the public nor health professionals know enough about sleep and its disorders and the importance of the associated functional impairment. In addition, the following research recommendations emanated from the Workshop.

It was recognized that cellular and molecular work on neural structures responsible for sleep and cognitive functions is needed, and that computerized imaging techniques such as PET, SPECT, magnetic resonance imaging and functional magnetic resonance imaging could be employed in this regard. Research dealing with the mathematical modeling of sleep control systems and their relation to daytime cognitive functions should be encouraged also.

Large-scale clinical trials in both patient populations and industrial populations will be required to evaluate the relation between cognitive function and disturbed or insufficient sleep. In these trials there is a need to stratify the sample by disease severity and degree of sleep disturbance. There is also a need to build consensus on the standardization of cognitive probes that are used in sleep studies, to use and/or develop outcome measures which have clear ecological validity (e.g. job performance, driving, decision making, risk taking, etc.), and to evaluate the relation of normal and abnormal sleep, in children and the elderly, to cognitive function. Finally, research must not simply examine the physiologic impairments, but it must also focus on cognitive and performance impairments, how to measure them and how to document changes with treatment.

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