Functional neuroimaging insights into how sleep and sleep deprivation affect memory and cognition

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Purpose of review

The review summarizes current knowledge about what fMRI has revealed regarding the neurobehavioral correlates of sleep deprivation and sleep-dependent memory consolidation.

Recent findings

Functional imaging studies of sleep deprivation have characterized its effects on a number of cognitive domains, the best studied of these being working memory. There is a growing appreciation that it is important to consider interindividual differences in vulnerability to sleep deprivation, task and task difficulty when interpreting imaging results. Our understanding of the role of sleep and the dynamic evolution of offline memory consolidation has benefited greatly from human imaging studies. Both hippocampal-dependent and hippocampal-independent memory systems have been studied.

Summary

Functional imaging studies contrasting sleep-deprived and well-rested brains provide substantial evidence that sleep is highly important for optimal cognitive function and learning. The experimental paradigms developed to date merit evaluation in clinical settings to determine the impact of sleep disruption in sleep disorders.

Keywords

consolidation, fMRI, memory, sleep deprivation

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Introduction

There is mounting evidence attesting to the importance of sleep in health [1,2] and cognition [3]. Deficits in vigilant attention following sleep deprivation can result in fatal transport accidents [4]. Changes in attention, memory and decision contribute to increased physician errors while on shift duty [5,6]. Despite enactment of legislation limiting work hours, epidemiologic data suggest that we are sleeping less than before [7], and part of the strategy to reduce untoward outcomes involves highlighting the evidence supporting the cognitive benefits of sleep as well as the losses associated with sleep deprivation [8]. As there are already a number of recent reviews [9–13] and monographs [14,15] relevant to these themes, this survey will focus on the contribution made by recent human functional imaging studies to our growing knowledge concerning how sleep and sleep deprivation affect memory and cognition.

Imaging the sleep-deprived brain during cognitive performance

A number of functional imaging studies have examined the neuroanatomical correlates of impaired performance during sleep deprivation, as well as possible underlying mechanisms of performance decline and their compensation. The best-characterized cognitive domain in this context is working memory [16–23,24•]. Other facets of cognition studied include verbal learning [25–27], sustained attention [28–30], divided attention [31], inhibitory function [32], decision making [33•] and emotional responses to pictures [34] (Table 1).

Working memory involves temporary storage and manipulation of information in the brain, and tasks tapping working memory consistently recruit lateral prefrontal [37] and parietal cortices [38]. However, the manner in which sleep deprivation affects this task-related activation has differed across studies, possibly as a result of cognitive subtask differences, task difficulty, duration of sleep deprivation, analytical methods used and interindividual variation. For instance, increasing task difficulty elicited 'compensatory' prefrontal activation in one working memory study [17] but in not others [16,18,20]. The importance of task difficulty in eliciting 'compensatory activation' as evidenced by less impaired performance may be task dependent. For example, in contrast to the mixed evidence for 'compensatory

Table 1 Recent functional neuroimaging studies involving sleep deprivation

Cognitive domain	Reference
Working memory	Bell-McGinty *et al.* [16]
	Habeck *et al.* [20]
	Chee and Choo [17]
	Choo *et al.* [19]
	Caldwell *et al.* [21]
	Mu *et al.* [22]
	Mu *et al.* [23]
	Chee *et al.* [18]
	Lim *et al.* [24•]
Attention (sustained and divided)	Thomas *et al.* [28]
	Drummond *et al.* [31]
	Drummond *et al.* [30]
Short-term memory	Chee and Chuah [35•]
Logical reasoning	Drummond *et al.* [26]
Inhibition (go/no-go)	Chuah *et al.* [32]
Risky decision making	Venkatraman *et al.* [33•]
Emotional processing	Yoo *et al.* [34]
Verbal learning	Drummond *et al.* [25]
	Drummond *et al.* [27]
	Yoo *et al.* [36]

activation' in experiments evaluating working memory, this pattern has been consistently found in experiments involving verbal learning [25,27] and logical reasoning [26]. On the contrary, it may be that sleep deprivation amplifies individual differences in task-related brain activation, and that the mixed results from working memory experiments are a consequence of studying small samples picked from a larger, heterogeneous population.

One approach to drawing generalizable conclusions when activation varies across individuals is to look for patterns of covariation across several task-activated brain regions instead of contrasting activation across state in a region-by-region manner [16,20]. An alternative strategy is to characterize differences in activation that are driven by interindividual responses to sleep deprivation [39] akin to the approach taken in behavioral studies [40,41].

Using the latter approach, it has been suggested that the magnitude of task-related activation following a normal night's sleep can predict an individual's resistance to decline in working memory performance following sleep deprivation [21,22], harking to a form of 'cognitive reserve' in sleep deprivation resistant individuals. Taking into account interindividual differences in vulnerability to sleep deprivation may also serve to identify meaningful state effects in activation which may otherwise be obscured, as documented in the evaluation of inhibitory function [32].

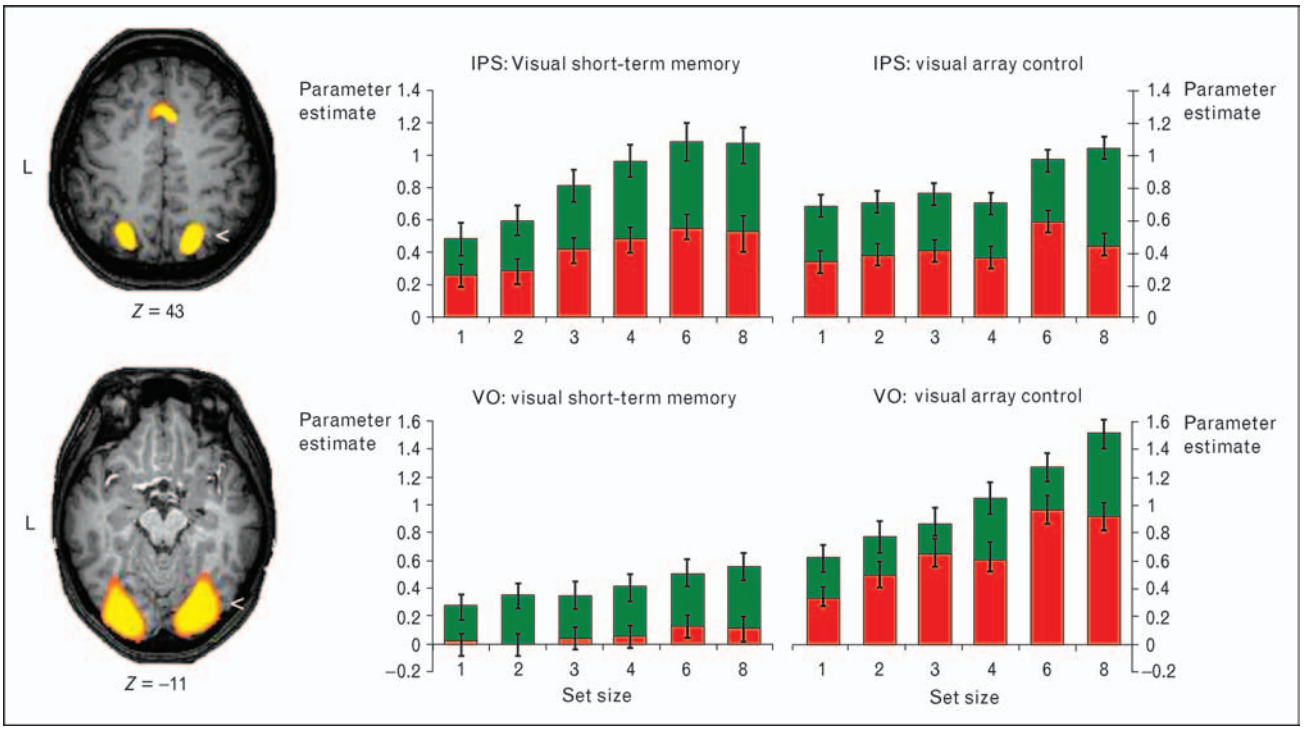
Given the differences in reported findings across some studies, one might ask if fMRI is capable of yielding reproducible results when studying sleep deprivation. This concern was addressed in a study in which 19 volunteers underwent a total of four scans: two with sleep deprivation and two without. Across these two pairs of normal sleep–sleep deprivation scans, the extent to which parietal activation declined following sleep deprivation reproducibly correlated with behavioral decline across state [24•]. Interestingly, the behavioral metric most reproducibly affected by state was intraindividual variation in response time, suggesting that deficits in attention might in fact explain much of the decline in working memory following sleep deprivation.

This idea was tested in a pair of experiments that parametrically varied visual item load and visual short-term memory (VSTM) load in parallel experiments conducted following normal sleep and after sleep deprivation. As expected, already limited VSTM capacity was reduced in sleep-deprived persons. Intriguingly, however, state-related activation decline in the parietal cortex occurred well before memory capacity was saturated [35•] (Fig. 1). This finding, together with the attenuation of extrastriate activation at low levels of perceptual load, lends support to the proposition that deficits in visual attention or visual processing make significant contributions to the reduction of memory capacity observed in sleep deprivation (also see [36]). A parallel can be found in aged adults in whom decline in task-driven visual cortex activation has been correlated with cognitive decline [42]. Another support for the notion that visual cortex dysfunction could contribute to cognitive deficits in sleep deprivation lies in the recent finding that transcranial magnetic stimulation (TMS) applied to the left lateral occipital lobe can improve working memory in sleep-deprived individuals [43].

Sleep deprivation can influence decision making [44] in a manner that resembles deficits arising from an orbitofrontal lesion [45] in that persons sleep deprived for 49 h continue to make risky, disadvantageous choices despite sustaining losses. Risky decision making following even a single night of total sleep deprivation was found to elicit greater activation of the nucleus accumbens when the riskier of two choices was selected. This suggests greater anticipation of reward without any change in actual stakes. Compounding this, right insula and lateral orbitofrontal activation was reduced following loss trials signaling a reduced reaction to loss that could impair aversive learning. Interestingly, these gamble-related brain activation changes were not accompanied by changes in behavior expected with longer periods of sleep deprivation [45]. As such, brain imaging may be a leading indicator of poor decision making in this setting.

Sleep deprivation can also influence emotional responses and emotional memories. The first functional imaging study to evaluate the relationship between sleep loss and emotion found increased amygdala responses to emotionally charged scenes along with increased brainstem limbic connectivity and reduced amygdalo-medial prefrontal

Figure 1 Sleep deprivation results in reduced engagement of the intraparietal sulcus and ventral occipital cortex even at subcapacity memory/perceptual loads



In the visual short-term memory condition, memory load varied from one to eight items. In the visual array control condition, item load was increased without modulating memory load. Increasing memory load elicited a commensurate increase in IPS activation that leveled off when memory capacity (four items) was reached. Increasing item load did not significantly modulate IPS activation. In the extrastriate cortex, increasing both memory and item load raised activation in a monotonic manner. Sleep deprivation had a significant effect on parieto-occipital activation at all levels of memory or item load. IPS, intraparietal sulcus (green = normal sleep; red = sleep deprivation); VO, ventral occipital cortex. Adapted with permission from [35•].

connectivity [34]. These changes portend to less circumspect behavior in the setting of sleep deprivation, but more research with different tasks is encouraged. For example, there are data showing slowed responding to moral choices [46] that could indicate awareness of a need to be less hasty when making decisions when sleep deprived.

Inhibition of inappropriate responses can be compromised following sleep deprivation. While sleep deprivation uniformly depressed task-related activation in the ventral, anterior prefrontal cortex and anterior insula, individuals who were better able to maintain inhibitory efficiency when sleep deprived showed more efficient engagement of a right inferior frontal region known to support response inhibition when well rested [32]. These individuals were able to increase activation when sleep deprived, whereas poorer performers who activated this region to a greater extent while rested were unable to further engage this region when sleep deprived.

Apart from regional changes in brain activation across state that are task specific, there appear to be brain regions whose activities are modulated by factors that are not task specific but, rather, present with any task that engages attention. For example, reduction in task-related deactivation in the brain's 'default network' has been observed in experiments evaluating working memory, short-term visual memory and psychomotor vigilance [17,30,35•]. In addition, attention or arousal-related activation of the thalamus appear to correlate with whether or not performance is relatively intact [17,19,20,47] or impaired [28,29] as a result of sleep deprivation.

Imaging studies on sleep, memory consolidation and learning

In the preceding section, we discussed how sleep deprivation affects short-term and working memory. However, as might be expected, sleep is also important in long-term memory. Total sleep deprivation prior to viewing and classifying pictures reduced encoding-related hippocampal signal relative to when volunteers were allowed to sleep. This correlated with poorer picture recognition scores at test [36]. Sleep deprivation also altered the functional connectivity associated with the hippocampus at encoding in addition to affecting the prefrontal regions that predicted successful encoding.

Consolidation refers to processes that render memories less liable to disruption from interference or disrupting

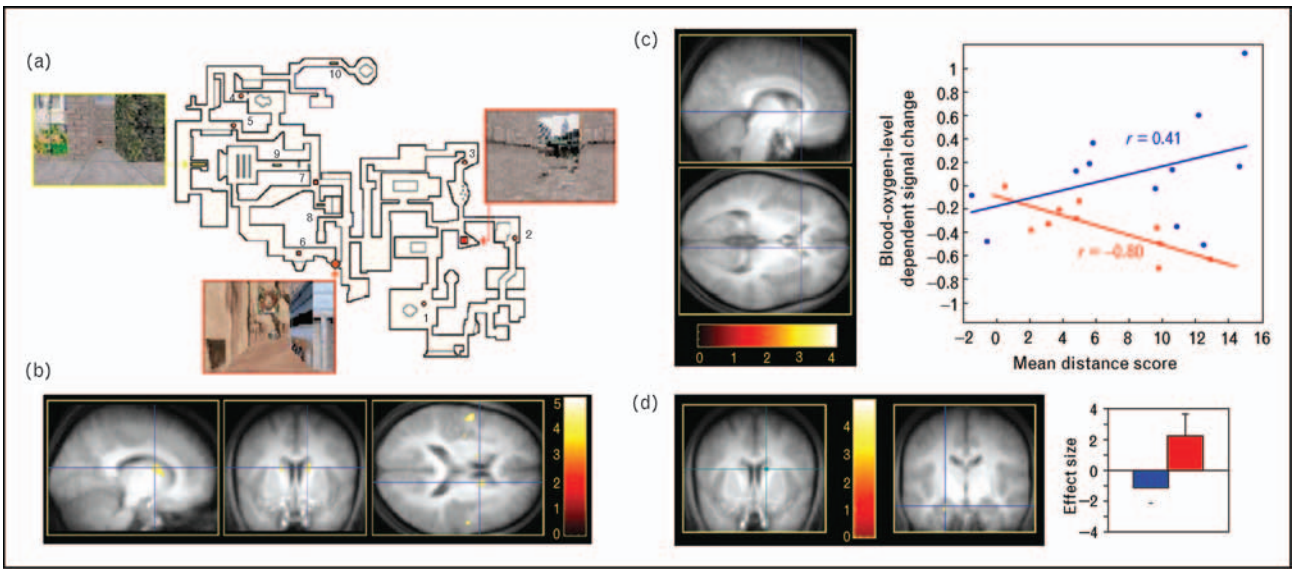
factors [48]. 'Offline' consolidation of memory occurs during sleep, improving performance during later testing even without additional practice [10,11]. Sleep improves nonhippocampal-dependent procedural and hippocampal-dependent declarative and spatial memory consolidation (but see [49]).

Offline, hippocampal-dependent memory consolidation occurs during slow wave sleep (SWS). Improvement in the speed of maze navigation following a night of post-learning sleep correlated positively with increases in right hippocampal blood flow during SWS. This finding was specific to learning and task in that the positive correlation found with maze training was absent if volunteers learned a serial reaction time task or slept without prior maze training [50]. Speeded replay of spatial memories acquired during wakefulness has been reported in the hippocampus of sleeping rats [51•,52] and may explain the increased hippocampal blood flow observed in human studies. The specificity of the link between hippocampal reactivation during SWS and consolidation of spatial memories was further explored in an elegant series of studies that associated an odor cue with either a hippocampal-dependent spatial memory task or a nonhippocampal-dependent procedural task. Re-exposure to the odor during SWS improved hippocampus-dependent but not hippocampus-independent memories. Further, odor re-exposure was ineffective during REM sleep, wakefulness or when the odor was omitted at encoding [53••].

The circuits recruited during successful task performance change following learning. These transitions in neural substrate supporting performance may result in less effortful, more automatic responses over time. Sleep deprivation interferes with this transition, often resulting in poorer learning. This interference seems to generalize across hippocampal-independent as well as hippocampal-dependent learning systems although different anatomical regions are involved in each case. For example, after learning a sequence of finger movements, individuals who slept performed more quickly and showed less activation of prefrontal and premotor areas during retrieval. They also showed greater basal ganglia and parietal activation when compared to those who were sleep deprived [54].

In contrast, the consolidation of hippocampal–neocortical-dependent spatial memory associated with maze navigation involved different brain regions in individuals who were allowed to sleep after learning. Days after initial learning, these persons showed relatively greater activation of striatum-based circuits than similarly trained but sleep-deprived individuals [55] (Fig. 2).

Figure 2 Maze learning related brain activity and performance is dependent on whether an individual is allowed to sleep following training



(a) After training on the maze, individuals were either sleep deprived or allowed to sleep on the first posttraining night. They were all retested and scanned on day 4 (delayed retrieval). The map depicts an aerial view of the color 3D virtual town in which individuals navigated at the ground level. Snapshots show the three locations used as targets for testing during the fMRI sessions. The 10 starting points are represented by numbers, with associated symbols indicating the target location to reach. (b) Bilateral caudate regions showed higher activation during maze navigation during delayed retrieval testing for the normal sleep condition than the sleep-deprived condition. (c) The caudate region indicated shows relatively greater activity in individuals (blue line) who were more successful at maze navigation if they slept after learning. Individuals who were sleep deprived showed a negative correlation between caudate activation and navigation proficiency (red line). (d) Psychophysical interaction analysis showing reduced functional connectivity between the caudate region and the hippocampus in those who slept after maze learning (blue bar); individuals who were sleep deprived (red bar). Adapted with permission from [55].

Along similar lines, memory circuits associated with declarative memory evidenced striking reciprocal plastic changes with memory consolidation. Over the course of months, successfully memorized pictures [56] and words [57] elicited progressively lower hippocampal activation together with increasing medial prefrontal neocortical activation. Amazingly, the duration of postlearning SWS in the single night following learning can continue to affect the extent of hippocampal memory reorganization to the neocortex for at least 6 months.

Does sleep benefit all memories to the same extent? Whereas after a normal night of sleep, emotional stimuli of any sort are better remembered than neutral pictures [58], negative emotional pictures appear to be better remembered than positive pictures after sleep deprivation [11]. Specifically, sleep deprivation seems not to affect memory for negative pictures although it impairs memory for positive pictures, highlighting the importance of sleep in the consolidation of positive emotional memories [59•]. The differential effect of emotional valence on memory might relate to the routes available for the encoding of each type of picture. Whereas negative pictures recruited the hippocampus and medial prefrontal region in all persons, positive pictures recruited these regions according to how well a given individual remembered these pictures. Critically, relative to non-sleep-deprived individuals, negative pictures in the sleep-deprived group elicited greater amygdalo-cortical activation suggesting that negative emotional memories have an alternate route of processing that affords their relative preservation despite sleep deprivation [59•].

Sleep affects learning but learning also affects sleep. This has been demonstrated using motor learning tasks that involve learning a new skill such as guiding a tracking device or learning a new sequence of piano key presses. The topographically distinct engagement of neural circuits during motor learning has a local effect that carries over into sleep. For example, parietal cortex engaged during motor learning elicited localized increases in slow wave activity (SWA) during postlearning sleep [60]. This local increase in SWA is postulated to correlate with gains in synaptic strength arising from task learning [61•,62], thus linking plastic changes and local regulation of sleep. In support of this hypothesis, postexperience-related local increase in SWA was reproduced by artificially depolarizing neurons during wakefulness by applying TMS to the motor cortex [63]. Conversely, local SWA was attenuated by locally reducing motor cortex stimulation by limb immobilization [64]. Importantly, correlations between motor learning and changes in local electrical activity during postlearning sleep have also been observed with sleep spindles [65], that is, postlearning differences in electrical activity are not confined to SWA.

While these studies support the importance of offline consolidation or even the development of new insights [66] into daytime experiences during sleep, it is important to recognize that postlearning plastic changes can occur even while we are awake. To demonstrate this, a 'tracking' task was used to evaluate the modulatory effects of spatial and procedural learning on brain activation across multiple scanning sessions. Impressively, the spatial distribution of activation associated with this third, unrelated 'tracking' task was influenced by whether the individual was exposed to the spatial or the procedural task, that is, in a task-specific fashion. Critically, the pattern of brain activation associated with the unrelated task shifted over a 2-h period of repeated scans during which volunteers remained awake and were not practiced on the learned tasks [67••]. In addition, these imaging effects were not reflected in behavioral differences in performance suggesting that, akin to the result with risky decision making in sleep deprivation, fMRI may sometimes provide novel insights not evident by observing behavior alone.

Conclusion

Functional imaging studies of sleep-deprived individuals are at a relatively earlier phase of development than the theoretically more mature studies concerning the benefit of sleep on memory consolidation. Much remains to be uncovered regarding the neural substrates that could account for why individuals vary in their tolerance of sleep deprivation as well as why there appears to be differential impact across cognitive domains. Most studies to date have involved healthy individuals but given that fMRI is noninvasive and frequently repeatable, it has tremendous potential to characterize brain regions or networks affected in patients who experience sleep loss from a variety of conditions including chronic insomnia, sleep apnea or periodic leg movements of sleep. Functional imaging could also provide a functionally meaningful biomarker to evaluate the cognitive effects of psychoactive medications that promote or attenuate sleep or modify its structure.

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