Review Article

Functional Neuroimaging of Sleep Deprived Healthy Volunteers and Persons with Sleep Disorders: A Brief Review

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Abstract

Sleep loss can severely impact on the integrity of cognitive functions. This review highlights the recent functional neuroimaging studies on the brain's response while performing cognitive tasks when deprived of sleep. Among sleep-deprived healthy volunteers, reduced attention, accompanied by lowered parieto-occipital activation, may underlie performance decrements seen in other "higher cognitive domains". Functional neuroimaging in this setting has increased our understanding of how the brain responds to, and compensates for, sleep loss. Functional neuroimaging may also provide a safe, reproducible and non-invasive means to evaluate the cognitive and neural impact of therapeutic interventions designed to treat sleep disorders and/or to reduce the negative cognitive impact of sleep loss.

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Introduction

Most adults have experienced sleep deprivation at some stage of their lives, be it in the context of work, illness or play. Sleep deprivation can be both total, taking place over 1 to 2 nights, or chronic partial, as characterised by insufficient restorative sleep over days, months and even years. There is little contention that sleep loss can result in significant neurocognitive decline, particularly in the domains of executive control, working memory and attention. Even 1 night of sleep loss can result in increased self-reported sleepiness, involuntary microsleeps, an inability to maintain attention in a sustained fashion, cognitive slowing, and perseveration of responses.[1] Lack of sleep in medical interns have been associated with increased resentment towards patients and the medical system and increased errors at work.[2] Sleepiness may be the largest identifiable and preventable cause of road accidents, surpassing alcohol and drugs.[3,4] Insufficient sleep is linked to excessive daytime sleepiness (EDS); the local prevalence of which has been estimated to be 10.8%.[5]

Here, we review the recent functional magnetic resonance (fMRI) neuroimaging studies on how a sleep-deprived brain responds during cognitive task performance. These studies mainly sought to characterise the neural counterparts of cognitive decline and compensation. Most of this work has been conducted on normal, healthy individuals in the context of total sleep deprivation. Much of the work in this area has been comprehensively reviewed.[6] As such, the primary intention of this review is to highlight the more recent contributions made by functional neuroimaging studies to our understanding of how the brain responds to cognitive challenges under conditions of sleep loss, in both healthy and sleep-disordered individuals (primary insomnia, obstructive sleep apnoea), and to discuss some of their implications. Attention was also paid to studies which have used neuroimaging as a platform to investigate the role of interventions to improve cognitive functioning.

Another popular context in which functional neuroimaging has been applied to investigate the effects of sleep deprivation on cognition is in the area of learning and memory consolidation.[7-9] For such studies, participants typically learnt a task prior to either a good night sleep or a night of sleep deprivation. All participants are tested in-scanner following 2 nights of recovery sleep to minimise any residual effects of acute sleep loss. Research in this area has been extremely fruitful and has improved our understanding of how even 1 night of sleep loss can affect memory consolidation processes. However, as it is outside

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the purview of this review, interested readers are referred to a number of excellent reviews that are available on this topic.[10-12]

Total Sleep Deprivation in Normal Individuals

Several cognitive domains have been studied in this context; the best characterised being working memory.[13-21] Other facets of cognition that have also been studied include verbal learning,[22-25] sustained attention,[26-28] divided attention,[29] inhibitory efficiency,[30] decision making,[31] and emotional responses to pictures.[32]

Working memory involves the temporary storage and manipulation of information in the brain and tasks tapping working memory consistently recruit lateral prefrontal[33] and parietal cortices.[34] Within, this domain, one is struck by the heterogeneity of findings across studies.[16] For instance, 'compensatory' increases in prefrontal activity following sleep deprivation were elicited in 1 study but not in others.[13,16,18] Factors that may account for various inconsistencies include (1) task difficulty,[15,23] (2) the cognitive domain tested,[35] (3) duration of sleep deprivation,[16] (4) the analytical method used and (5) variability across different individuals in their response to sleep deprivation.[36-38] For a more in-depth discussion, please see Chee and Chuah (2008).[39]

Across various studies, it has been found that activity in the parietal and/or occipital cortical regions may be the most reliable neural marker of an individual's response to sleep deprivation.[13,16,18-21,23,24] This observation occurs across several cognitive domains, including working memory, vigilance, verbal learning, mental arithmetic, and divided attention, suggesting that decline of a common cognitive resource, for example, visual attention, may underlie state-related decrements.

This idea that sleep deprivation may affect "lower-level" processes which in turn impact on "higher-level" functions was investigated in a study which tested sleep-deprived healthy adults with a pair of tasks that parametrically varied visual item load and visual short-term memory load.[40] Twenty-four hours of sleep deprivation resulted in pronounced decline of visual short-term memory, accompanied by decreases in parietal and extrastriate activity. Notably, declines in performance and decreases in parietal and extrastriate activity were also present for the visual attention task. Further, reduced parietal and extrastriate cortical activity occurred even under conditions of minimal short-term memory demands. These findings suggest that while short-term memory is affected by sleep deprivation, its decline is accompanied, and may be accounted for, by declines in visual perception and/or attention.

Sleep deprivation can influence decision making[41] in a manner that resembles deficits arising from an orbitofrontal lesion in that persons sleep deprived for 49 hours continue to make risky, disadvantageous choices despite sustaining losses.[42] Even 1 night of sleep deprivation resulted in a selective increase in activation towards risky decisions in the nucleus accumbens (a region involved in reward anticipation), as well as decreases in activity towards losses in the insula and orbitofrontal cortex, regions known to be involved in emotional processing and associative learning, respectively.[31] These results suggest that sleep deprivation may pose a dual threat to competent decision making by increasing an individual's expectation of a reward following a risky decision and reducing the emotional impact of a loss. However, these neural changes were not accompanied by changes in decision preferences and suggest the possibility that these neural changes may precede behavioural effects.

Emotional processing following sleep deprivation was studied recently by fMRI.[32] The study reported higher activity in bilateral amygdala for sleep-deprived individuals selectively for emotionally-aversive stimuli. There were also differences between the sleep-deprived and well-rested individuals in terms of the functional connectivity of the amygdala. Greater functional connectivity was present between the amygdala and medial prefrontal regions for well-rested individuals relative to the sleep-deprived individuals. In contrast, for the sleep-deprived individuals, a greater connectivity was present between the amygdala and the autonomic-activating centers of brainstem. Taken together, these results suggest that sleep deprivation may result in an amplified, hyper-limbic response from the amygdala towards negative emotional stimuli as well as a reduction in top-down control with possible implications for understanding the relationship between sleep and mood disturbances.

Presently, few neuroimaging studies have examined the effects of cognitive enhancing drugs in the context of total sleep deprivation. Modafinil, a wake-promoting drug that is FDA approved for the treatment of narcolepsy, is increasingly used off-label to promote alertness and enhance performance in the setting of sleep deprivation. While its mechanism of action is not established, there is much evidence to support its use as a cognitive enhancer in sleep-deprived individuals.[43] The n-back is a commonly used working memory task that involves online maintenance and updating of memory items. A typical 1-back task involves matching a currently presented item with an item presented just one previously. With a 2-back task, subjects have to keep in mind the item presented 2 trials previously. Modafinil-related improvement in n-back performance, following 28 hours of sleep deprivation, was accompanied by increases in activity in the prefrontal and parietal,

"executive-network" regions.[44] No appreciable effects were present in the well-rested state for both behaviour and neural activation. However, the limited sample size (n = 8), restricted analysis (fixed effects) and non-uniformity of findings (clear behavioural effects of drug only for accuracy on the 3-back task while drug-related increases in activation was present mainly for the 2-back component) make these findings preliminary.

Based on observations that decrements of neural activity in the parieto-occipital cortex may underlie sleep-deprivation-related decline in visual short-term memory,[40] we investigated the potential role of an acetylcholinesterase inhibitor in improving visual short-term memory following sleep deprivation in 28 young, healthy adults.[45] Behavioural benefits for both visual short-term memory and visual attention were present only following sleep deprivation and the extent of this benefit correlated with the extent to which an individual declined following sleep deprivation when untreated. The correlates of this behavioural benefit were also primarily present in parieto-occipital regions.

This notion that visual cortex dysfunction may contribute to cognitive deficits in sleep deprivation was also supported by a recent finding of improvement in working memory in sleep-deprived adults following the application of transcranial magnetic stimulation (TMS) to the left lateral occipital lobe.[46] Interestingly, mirroring the above study to some extent, this benefit was present only during sleep deprivation, and the extent of TMS-related improvement correlated positively with the extent to which there was a decline in the neural network associated with sleep-deprivation-related performance decrements.

Functional Neuroimaging in Patients With Sleep Disorders

Primary insomnia. Insomnia is typically defined as complaints of difficulties in falling asleep, staying asleep, and/or non-restorative sleep, with daytime consequences. This most common form of sleep disturbance has several significant associations, including increased daytime sleepiness,[47] impaired function and alienation,[48] reduced quality of life,[49] increased risk for psychiatry disorders[50] and increased healthcare and other societal costs.[51,52] The incidence of insomnia in the UK adult population has been recently estimated to be around 37%,[53] of which 69% reported persistent symptoms at the 12-month follow-up. The incidence of insomnia in the Singaporean Chinese and Malay communities was estimated to be around 15% in the mid 90s.[54]

The notion of hyperarousal, one of the most compelling explanations for insomnia,[55] has received support from SPECT and PET studies of insomnia patients during sleep and wakefulness.[6,56-59] Blunted attenuation of the cerebral rate of glucose consumption during non-REM sleep has been reported in the subcortical, limbic/arousal systems and in the anterior cingulate and medial prefrontal areas of patients compared to normal controls.[60] In addition, during wakefulness, patients had relatively decreased glucose metabolic rates in widespread cortical areas as well as in the thalamus, hypothalamus, and brainstem reticular formation.[6]

Surprisingly, at this point in time, there are almost no task-related activation studies of patients with insomnia. This gap is important to fill because, in spite of the number of studies that have shown clear negative consequences of total and chronic partial sleep deprivation on cognition,[1,61] there is no consistent evidence of objective cognitive impairment in individuals with primary insomnia.[62] Specifically, while some studies which have reported mild impairments in selected domains, for example, long-term semantic memory,[63] procedural learning,[64] vigilance and working memory,[65] and declarative memory consolidation,[66] others have shown null findings.[67-70]

Currently, there is only 1 study that has investigated cognitive task performance and associated brain activity in patients with chronic insomnia.[71] While patients and well-sleeping controls performed similarly on tasks of verbal fluency, there was reduced activity in prefrontal task-related areas in patients relative to controls. Insomnia patients who underwent cognitive behavioural therapy, sleep restriction, sleep hygiene measures, bright light, physical activity and temperature interventions, showed behavioural improvement accompanied by a reversal of the frontal hypoactivity. In contrast, patients who were assigned to a waiting list condition for the same period showed neither changes in behaviour nor imaging. These findings suggest that there may be subtle neurocognitive changes in patients with insomnia that cannot be fully captured using only behavioural measures.

Obstructive sleep apnoea. Patients with obstructive sleep apnoea (OSA) experience repetitive pharyngeal collapse during sleep, leading to nocturnal hypoxia and sleep fragmentation, with resultant neurocognitive and cardiovascular sequelae.[72] It has been estimated that 1 out of 5 adults has mild OSA and 1 out of every 15 has at least moderate OSA.[73] The prevalence of OSA in Singapore has also been estimated at around 15%,[74] and the majority of these patients suffer from associated excessive daytime sleepiness.[75]

Cognitive deficits are commonly linked with sleep apnoea[76,77] and broadly worsen with disease severity.[78] However, these deficits are not consistent across all cognitive domains, being most marked in the domains of sustained attention, vigilance and executive functions, while general intelligence and verbal abilities may be spared.[77] These deficits could potentially stem from 2 sources: reversible

deficits associated with sleep fragmentation as well as deficits associated with neuronal loss, arising from irreversible hypoxic damage.[80-82] Imaging studies have reported evidence for brain morphological changes in OSA including loss of gray matter in cortical and subcortical structures[79,80] and reduced cerebral metabolism.[81-83]

To date, only 2 studies have investigated task-related brain activation in OSA patients using fMRI. Impaired performance on a 2-back working memory paradigm was accompanied by reduced activation in the prefrontal cortex, anterior cingulate and posterior parietal lobule.[84] These findings are in contrast with another study which involved a verbal learning task.[85] In the latter study, patients had similar verbal learning performance (immediate and delayed) relative to controls. Moreover, they also showed increased activation, purportedly of a compensatory nature, in several task-relevant regions. These included bilateral inferior and middle frontal gyri, cingulate gyrus, superior and parietal lobules, bilateral parieto-temporal junction and thalamus.

Possible task-specific nature of impairments present in OSA patients (verbal abilities may be relatively preserved while vigilance and executive functions are usually impaired) and differences in severity of OSA between the 2 studies were suggested as possible explanations for the divergent findings.[86]

Continuous positive airway pressure (CPAP) is an important treatment modality in OSA. Both positive, and null, findings of CPAP treatment have been reported in various cognitive domains.[86,87] In the sole functional imaging study that investigated the effect of CPAP treatment on task-related brain activation,[84] 6 OSA patients were tested following a minimum of 8 weeks, and at least 7 hours per night, of CPAP use. CPAP resulted in reduced self-reported daytime sleepiness. There were trends towards improved working memory performance, but the differences were not considered significant. A significant increase in activation post-treatment was present in the posterior parietal cortex but not the dorsolateral prefrontal cortex.

More studies are clearly needed in patients that suffer from sleep disorders. The paucity of studies is surprising given that daytime functional neuroimaging in sleep disordered patients can be potentially much more interesting for clinical purposes, by offering more strategies to define a diagnosis or to improve the clinical management of individual patients.[88] Work of this type can also improve understanding of the true neuropsychological consequences that these patients may face. Functional neuroimaging can also potentially provide clues as to the neural compensatory mechanisms that such patients may be invoking in order to function cognitively at an acceptable level. The experimental paradigms developed to date in the context of total sleep deprivation merit evaluation in clinical settings to determine the impact of sleep disruption in sleep disorders. Given the lack of consistent behavioural evidence of cognitive impairment, or improvement following treatment in these patients, functional neuroimaging could also potentially provide a more sensitive platform to study the benefit of different therapies on cognition in these individuals.

Summary and Conclusions

Functional neuroimaging has given us additional novel insights into how sleep loss affects an individual's ability to perform cognitive tasks. Some changes in brain activation are not evident by observing behaviour alone.

Most studies, to date, have involved healthy individuals, with some preliminary studies in patients (primary insomnia and OSA). Studies in healthy individuals have suggested a role of the parietal/occipital network in determining an individual's ability to maintain performance on a variety of cognitive tasks, including working/short-term memory, verbal learning and attention. This suggests that decrements in attention may account for much of the decline seen in other "higher-level" faculties. This hypothesis has lead to work aimed at reducing the cognitive impact of sleep deprivation by modulating neurotransmission. Additional insights into the cognitive impact of sleep deprivation have also been gleaned in the area of decision making and emotional processing.

Much more remains to be uncovered regarding the neural substrates that may account for why individuals vary in their tolerance to sleep deprivation and also why sleep deprivation may have differential impact across different cognitive domains. This highlights the issue of inter-individual differences, an important factor which should be taken into account when studying cognition in the context of sleep deprivation. Part of the variability of findings across studies may reflect inter-individual differences in the resistance to reduced sleep and, in the case of patients, the extent of neural changes associated with the illness. Given that fMRI is non-invasive and easily repeatable, it has great potential to characterise the regions and networks that are affected by sleep loss both in normal individuals as well as in patients. Functional MRI may also provide a sensitive and powerful platform from which to evaluate the benefit and mechanism underlying therapeutic interventions aimed at alleviating the effects of short-term total sleep loss or longer-term restriction of sleep duration.

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