

Section 1

Basic Mechanisms: Cognitive Performance and Sleep

Chapter

1

The true nature of sleep loss-induced “neurocognitive performance deficits”: a critical appraisal

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Introduction

Over the past 100-plus years, a plethora of studies have been performed to determine the effects of sleep loss on cognitive and psychomotor performance [1]. From an “applied science” standpoint, many of these efforts have proven useful, yielding results with clear, readily generalizable implications for real-world application. For example, simulator studies over the past several decades have produced data useful for quantifying the relationship between sleep, the circadian rhythms of alertness, and driving performance – providing the basis for informed decision-making in operational environments (e.g., with respect to work/rest scheduling) and for crafting legislation to generally improve highway safety [2]. Similarly, results from studies of medical personnel have revealed the extent to which extended work hours and resulting sleep loss contribute to medical errors and accidents [3] – findings that (a) have prompted the Accreditation Council for Graduate Medical Education (ACGME) to limit resident duty hours to 80 hours per week, and (b) may ultimately result in increased government (e.g., Occupational Health and Safety Administration (United States) – OSHA) oversight [4].

For those of us who conduct such studies, it is gratifying to see these findings applied to improve human health, performance, productivity, safety, and well-being. However, as scientists, our motivation for conducting such studies also has included a desire to address soul-satisfying basic research questions – i.e., to make discoveries that meaningfully contribute to the store of scientific knowledge. Accordingly, perhaps our fondest collective daydream has been that results of these sleep deprivation studies would ultimately reveal some profound scientific truth about the nature of

sleep.¹ Thus far, despite 100-plus years of assiduous sleep deprivation/performance research, this epiphany remains elusive. Why is this?

Sleep is a unique process

The logic behind sleep deprivation studies is basically sound. Biologists long ago determined that an excellent way to discover the function of an organ is to ablate that organ and see what subsequently goes wrong. However, there are several reasons why ablation strategies have not proven particularly useful for unlocking sleep’s greatest mysteries.

The first (and perhaps most obvious) problem is that sleep is a process that not only occurs in, and is mediated by, the brain, but is also a process that undoubtedly confers unique benefits to the brain itself. This makes sleep far less accessible and less amenable to ablation techniques than actual organs such as the kidney. The kidneys are, of course, the site of glomerular filtration, a process by which waste products are removed from the blood. Glomerular filtration serves to maintain the health and functioning of virtually every living cell in the body. It does not provide any unique benefits to the kidney, *per se*. This makes it possible to ablate the kidneys (and thereby ablate the process of glomerular filtration) in a manner that allows meaningful observation and measurement of

¹ Typically, in this daydream, we are poring over the data from our most recent sleep deprivation study when, suddenly, the “scales fall from our eyes” and, by dint of viewing the world through the new perspective afforded by the fresh findings, we realize how all of the pieces of the puzzle fit together to solve sleep’s most perplexing mysteries (“Eureka!”).

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consequences for the organism – consequences that allow definitive inferences regarding kidney function.

Clearly, it would make no sense to ablate the brain in an attempt to discover the functions of sleep. So instead of eliminating sleep by ablating the brain, the strategy has been to eliminate (ablate) sleep while (presumably) leaving the brain intact – and to then look for deficits in brain function, as manifested behaviorally on neurocognitive performance tests.²

The grand idea (or perhaps it is more accurately described as a “fond hope”) behind this endeavor has been that the accrual of information gleaned from such studies would eventually coalesce into a gestalt in which sleep’s most elusive secrets are revealed. That is, the hope has been that findings from each sleep loss study would serve as “puzzle pieces” that incrementally add to our knowledge regarding sleep function, and achievement of the ultimate goal – a coherent “big picture” revealing the process(es) by which sleep subserves waking brain function – would be achieved when a sufficient number of such puzzle pieces had been added.

Serious doubts about the ultimate utility of this approach date back to at least 1976, when Dr. Paul Naitoh commented that sleep deprivation studies had served only “to confirm a truism: (sleep deprivation) makes animals and humans sleepy” [5]. Nevertheless, a perfunctory search of the recent scientific literature suggests that hope persists. Recent examples include papers describing the effects of sleep loss on neurocognitive functions such as impulsivity [6–7], risk-taking [8], moral reasoning [9], humor appreciation [10], working memory [11], and the ability to recognize human emotions [12–13], to name but a few.

This is not meant to imply that such papers are devoid of scientific value. Clearly, such studies can be of considerable scientific interest in and of themselves, and can produce results with clear implications for predicting performance in military and civilian operational environments. But it is the thesis of the present chapter that findings from such studies will always be of limited value in the larger quest to unlock the mysteries surrounding the nature of sleep. Here’s why:

² Sleep loss effects have also been measured on many other aspects of performance and physiology. But for the purposes of the present paper, discussion will be limited to the effects of sleep loss on neurocognitive performance.

Measuring of the effects of sleep loss on specific neurocognitive abilities requires some “leaps of faith”

In the parlance familiar to those who (like the present author) are afflicted with a degree in experimental psychology and have thus, at some point in their training, been subjected to a course in “The Philosophy of Science,” the scientific paradigm under which sleep deprivation research is conducted contains some conceptual gaps.

The difficulty is as follows: extended (e.g., 24 hours of) continuous wakefulness is an antecedent condition (i.e., the “cause” in a cause/effect relationship) that leads to a predictable, observable outcome: decremented performance (e.g., slowed reaction time on the Psychomotor Vigilance Test, PVT).

From a strict operationalist³ viewpoint, this empirical relationship is clear and (at least potentially) utilitarian. One does not necessarily need to explain how or why a cause/effect relationship works in order to apply it (e.g., as the basis of a mathematical performance prediction model to inform development of work/rest schedules in an industrial setting). And the logic behind operationalism is irrefutable – if one never “goes beyond the data” by offering conjecture about the unseen mechanisms by which observed variables relate to each other, one can never be “wrong.”

However, strict application of operationalism is also clearly antithetical to the advancement of science, since it eliminates the opportunity to posit possible explanatory mechanisms – i.e., to generate hypotheses regarding the nature of the unseen processes that underlie observed relationships between variables [14]. Therefore, science affords its practitioners some reasonable leeway – hypotheses involving unseen forces and mechanisms are generated, but with the requirement that such hypotheses be parsimonious and plausible (i.e., in a sense, that such hypotheses be produced while maintaining some mindfulness of the logic of operationalism). As described by Marx and Hillix [15],

³ To a strict operationalist, it is not logical to make inferences regarding *how* or *why* the antecedent condition (e.g., extended wakefulness) results in the observed outcome (e.g., decremented neurocognitive performance) – because the *how* and *why* are not directly observable. Logic only permits one to describe the empirically demonstrated relationship, without engaging in conjecture regarding unobserved forces or variables.

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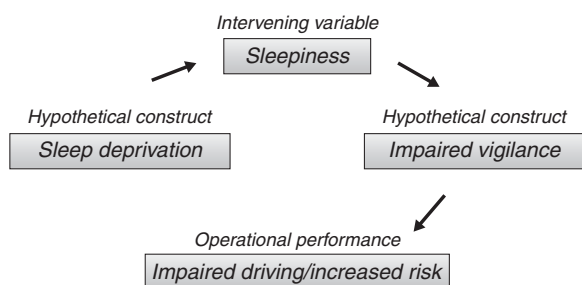


Figure 1.1. In a typical sleep deprivation/neurocognitive performance study the relationship between operationally defined hypothetical constructs such as “sleep deprivation” and “vigilance” is determined, and the intervening variable of “sleepiness” is invoked to help explain the cause-effect relationship. Results from such studies are applied by generalizing to real-world situations such as “highway driving performance.”

“... operationalism, as a loosely interpreted methodological prescription is still viable, and needed ... to prune away ... scientifically meaningless speculation. ...”

Accordingly, as sleep researchers, we are afforded the opportunity to engage in a modicum of such speculation, but with the implied caveat that this speculation must be both minimal and reasonable.⁴ In that spirit we have, as a research and clinical community, adopted a scientific paradigm that includes some practical hypothetical constructs.⁵ As indicated in Figure 1.1, “sleep deprivation” is one. In this example, sleep deprivation is a hypothesized (not directly observable) physiological state reflecting the extent to which unspecified sleep-dependent homeostatic processes mediate neurocognitive performance capacity (more specifically in this example, “vigilance”).

Also, in this paradigm “sleepiness” is the manifestation of “sleep deprivation” – it is the “intervening variable”⁶ invoked to explain the causal relationship between sleep deprivation (i.e., extended wakefulness) and deficits in vigilance (e.g., performance on the PVT). In addition, it is important to note that

⁴ In this case, “minimal and reasonable” speculation should generally be considered that which is parsimonious – the minimum (in both amount and complexity) required to fill logical gaps in observed cause-effect relationships.

⁵ A hypothetical construct is an explanatory variable that cannot be observed directly, but is nevertheless invoked broadly to explain phenomena that are observable.

⁶ As used here, an intervening variable is a hypothetical internal state that is invoked specifically to help “explain” the causal relationship between antecedent conditions and outcomes.

“neurocognitive performance” and “vigilance” are themselves hypothetical constructs – in this case, hypothetical constructs that are operationally defined in terms of PVT performance.

So it can be seen that in a typical sleep deprivation/neurocognitive performance study, some period of extended continuous wakefulness is applied to produce “sleep deprivation” (a hypothetical construct that is operationally defined by the intervention) that is, in turn, manifested as reduced vigilance (itself a hypothetical construct that is operationally defined as decremented performance on an objective neurocognitive test, such as the PVT), with “sleepiness” as the underlying, not-directly-observable intervening variable that is invoked to “explain” the causal relationship. Thus, a typical study to determine the effects of sleep loss on neurocognitive performance can be conceptualized as an effort to determine how one operationally defined hypothetical construct impacts another operationally defined hypothetical construct, via a not-directly-observable intervening variable.

Within the realm of sleep research, it is generally considered reasonable to operationally define “sleep deprivation” as a brain state induced by 24 hours of continuous wakefulness – based, for example, on what is known about how much sleep is typically obtained by humans, the effect that this duration of continuous wakefulness has on subjective measures of alertness, etc. Likewise, it is reasonable to operationally define “vigilance” as mean response time on the PVT, since most would agree that “ability to attend to a task and respond to the appearance of intermittently presented stimuli” is central to the concept of vigilance. Thus, the “leaps of faith” between the hypothetical construct of “sleep deprivation” and its operational definition of “24 hours of continuous wakefulness” – and between the hypothetical construct of “vigilance” and its operational definition as “performance of the PVT” – are reasonably small. This is important because the extent to which studies reveal “scientific truth” depends, in part, on the extent to which such operational definitions faithfully reflect the “essence” of the hypothetical constructs they have been assigned to represent.

Accordingly, it is reasonable and appropriate to conduct an experiment in which the duration of continuous EEG-defined wakefulness is extended (i.e., duration of wakefulness is the “independent variable”), and the effect of this manipulation is measured on an instrument such as the PVT (the “dependent variable”). Then, based on the outcome, it may be reasonable to

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conclude from such a study that “sleep deprivation” results in “impaired vigilance” – with implications for real-world outcomes such as “increased risk of highway accidents.”

However, it is quite another matter to look at the results of such a study and draw conclusions about the nature (e.g., physiology, adaptive significance, etc.) of sleep itself. In part, this is because such conclusions require greater distention of the principles of operationalism, with the meaning of “sleep deprivation” expanded from its original, relatively straightforward operational definition (e.g., 24 hours of EEG-defined wakefulness) to something that is at least one step further removed from the “operation” of maintaining EEG-defined wakefulness for 24 hours – i.e., changes in brain physiology that *result from* 24 hours of continuous EEG-defined wakefulness. And the dependent variable, PVT performance, not only represents the hypothetical construct of vigilance, it must likewise be considered a direct reflection of the *brain processes* that *underlie* vigilance.

The price paid for widening the gap (lengthening the “leap of faith”) between hypothetical constructs and their operational definitions is steep: to the extent that independent and dependent variables represent increasingly nebulous hypothetical constructs (that are less directly and firmly tied to the operational definitions), conclusions from such studies likewise become more tenuous and nebulous, with the ability to uncover scientific truths accordingly diminished.

Neurocognitive performance deficits are non-specific

Even if, for the sake of argument, the logical problems associated with bridging the gaps between hypothetical constructs and operational definitions are solved, it would still be impossible to work backward from the results of sleep deprivation/neurocognitive studies to make significant discoveries regarding the nature of sleep. This is because although neurocognitive performance varies as a function of sleep debt, it does not vary *only* as a function of sleep debt.

For example, even vigilance performance – a neurocognitive capability that is widely known to vary as a function of alertness/sleepiness – is recognized to be a function of multiple factors. This is illustrated in the equation below (adapted from [18]):

$$P_v = \frac{f(M, S, U, B, C)E}{BS}$$

in which P_v is performance on a vigilance test. P_v is a function of several factors including “signal modality” (M , the sensory modality of the signal being tested); salience (S , the meaningfulness of the signal being presented, e.g., the subject’s name vs. a neutral tone); the uncertainty of the signal (U , which depends on the mathematical likelihood of a signal presentation; the “background events density” (B , for example the density of “competing signals” that are presented and must be distinguished from the target signal); and “signal complexity” (C , reflecting, for example, the amount of mental processing required to identify the signal).

To make matters more complicated, in addition to interacting with each other, each of these factors can interact with a potentially infinite variety of environmental factors (E , e.g., environmental noise, ambient temperature, vibration) – at least as potential distracters, if not as factors that more directly influence vigilance performance.

And finally, the influence of each of these factors is potentially mediated by “brain state” (BS) – i.e., the variable readiness and capacity of the brain to perceive, process, and react to all of the factors that reside in the numerator of the depicted equation. For the purpose of the present discussion, BS could refer specifically to the brain’s level of “sleep debt” (although it could also refer to severity of intoxication, hypoxia, neuronal pathology, etc.).

Obviously, because there are numerous unknowns in this equation, and because there are numerous potential interactions among these unknowns, it would be absurd to actually try to solve this equation for “brain state” (BS), as follows:

$$BS = \frac{f(M, S, U, B, C)E}{P_v}$$

The hope that findings from studies of sleep deprivation loss effects on neurocognitive performance (P_v in the present equation in which “ v ” is replaced by the neurocognitive performance task at hand) can be utilized to reveal the nature of sleep/sleep deprivation (BS in the present equation) is essentially to hope that this unsolvable equation can be solved.

And to hope that the accretion of findings from additional sleep deprivation studies [e.g., on “moral reasoning” (Pmr), “emotional intelligence” (Pei), “arithmetic problem solving” ($Paps$) etc.] will somehow result in an improved understanding of the nature of sleep is to compound the error. Such optimism amounts to

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hoping that the scientific truths that remain hidden in the current store of unsolvable equations will somehow emerge with the accrual of additional unsolvable equations, i.e., that the basic problem is not that the equations are unsolvable *but that the number of unsolvable equations is inadequate*.

A given task’s sensitivity to sleep deprivation varies as a function of that task’s parameters

Finally, even if bridging the gaps between hypothetical constructs and operational definitions presented no difficulty, and even if there was some aspect of neurocognitive performance that varied *only* as a function of sleep deprivation (i.e., non-specificity was not a problem), attempting to discern the nature of sleep based on findings from sleep deprivation/neurocognitive performance studies would *still* be a fool’s errand.

This is because the sensitivity (to sleep loss) of neurocognitive tests depends not only on the *content* of the tests (i.e., the neurocognitive abilities that these tests purportedly reflect) but also on the *parameters* of the tests. In a classic series of studies in the 1960s, Wilkinson [16] showed that the sensitivity of behavioral measures to sleep deprivation varies as a function of (a) test duration/time-on-task (with longer tests being more sensitive); (b) the extent to which the task is inherently interesting (with more interesting/

rewarding tasks generally less affected by sleep loss); (c) the amount of feedback provided (tests for which no feedback is provided are generally more sensitive to the effects of sleep loss); and (d) “task complexity” (with those tasks that are more “complex” and thus require more effort being relatively more sensitive to the effects of sleep loss). In addition, “task sequence” can affect a given task’s sensitivity: tasks administered toward the end of a block of tests appear to be more sensitive to sleep loss when in reality decrements on these tasks reflect residual fatigue, boredom, cognitive resource depletion, etc.

Adapted from Balkin et al. [17], Figure 1.2 depicts the relative sensitivity of various measures to sleep loss during a sleep restriction study. In this study, mean sleep latency was found to be most sensitive, followed by PVT speed, standard deviation of lane position on a simulated driving task, mean speed on a 4-choice reaction time test, etc. Based on such findings, one might be tempted to conclude that the primary function of sleep is to maintain wakefulness (i.e., prevent frank sleep onset during waking hours), followed by facilitation of brain processes that mediate vigilance, reaction time, etc. However, considering the fact that the relative sensitivity of the various measures depends not only on the aspect of neurocognitive performance being measured but also on content-independent test parameters (such as test duration), it becomes clear that such interpretations are not possible. This is because, for

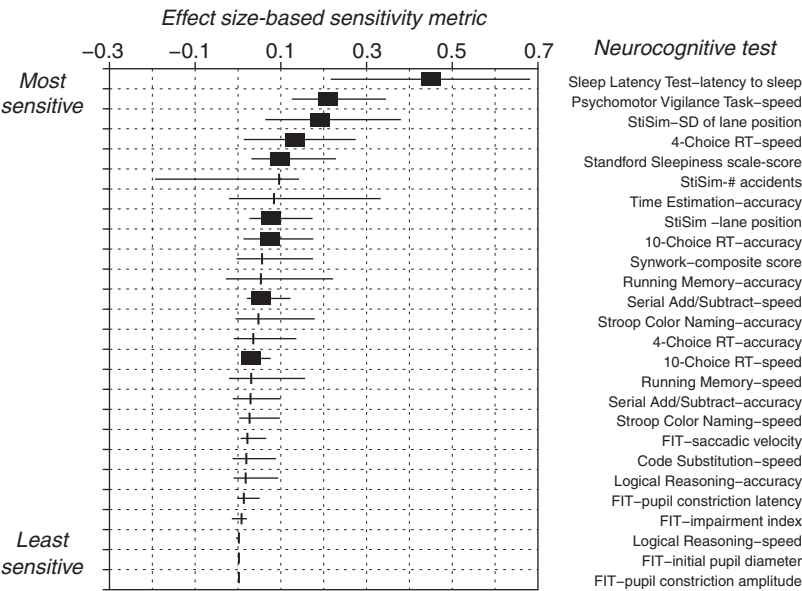


Figure 1.2. Relative sensitivity of various neurocognitive, behavioral, and physiological measures to chronic (7 nights) sleep restriction. From [17], with permission.

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example, it is plausible to hypothesize that extending the duration of the PVT to 15 minutes would increase the sensitivity of the PVT to such an extent that the PVT would displace mean sleep latency as “the most sensitive measure” in this study.

In short, while it is appropriate to conclude that sleep loss impacts “ability to maintain wakefulness,” vigilance, reaction time, etc., it is not possible, based on such studies, to conclude that sleep loss impacts one neurocognitive ability to a greater extent than it impacts another – a logical limitation that substantially delimits the extent to which such studies can be used to reveal the nature or function of sleep.

Summary and conclusions

Results from studies conducted to determine the effects of sleep loss on various neurocognitive abilities have proven useful for informing policy- and decision-making in a variety of operational and regulatory environments – and the utilitarian value of such studies for testing work/rest schedules, drug effects, etc. remains high. However, the value of such studies for addressing basic questions regarding the nature and function of sleep is severely limited because (a) logical “leaps of faith” are required to bridge gaps between operational definitions and hypothetical constructs; (b) the specificity of neurocognitive performance is low (i.e., neurocognitive performance is affected by a potentially infinite number of factors); and (c) the sensitivity of a neurocognitive test to sleep loss depends as much upon test parameters as it does on the specific neurocognitive ability reflected by that test.

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Chapter

2

Using fMRI to study cognitive function and its modulation in sleep-deprived persons: a selective overview

Michael W. L. Chee and Su Mei Lee

Introduction

The behavioral consequences of sleep deprivation (SD) are multifaceted and have been described in some detail in Chapter 1 (this volume). In this chapter, we discuss how the effects of sleep deprivation on the brain can be studied using functional magnetic resonance imaging (fMRI). We then proceed to discuss: (1) how attention and decision-making are affected in sleep deprivation, (2) how interindividual differences in vulnerability to sleep deprivation can alter task-driven brain activation and what factors may contribute to this variation, and (3) the prospects and challenges involved when using functional brain imaging as a probe to evaluate countermeasures for SD.

Using fMRI to infer brain function and its alteration

Most contemporary functional brain imaging experiments are conducted using functional magnetic resonance imaging (fMRI). This technique measures changes in blood oxygenation level dependent (BOLD) signal in capillaries and venules adjacent to neuronal clusters whose firing rate is modulated by task performance [1]. An increase in MR signal occurs as a result of a relatively disproportionate elevation in blood flow relative to oxygen consumption when neural firing increases. Signal change associated with brief visual stimulation (around 2 seconds) peaks after a delay of 4–6 seconds, declines to baseline about 10 seconds after stimulus onset, and undershoots for a further 4–8 seconds before finally returning to baseline. This temporal response profile, while superior to positron emission tomography (PET), is considerably slower than that obtained using electrophysiological

techniques. However, with appropriate interstimulus spacing, it is possible to selectively remove trials of non-interest: for example, those in which a sleep-deprived person is not responding can be removed, or behaviorally different responses can be separated (such as remembered versus forgotten words in experiments evaluating episodic memory).

Task-related deactivation

In addition to task-related activation [2], some parts of the brain consistently show task-related deactivation (i.e., falling below baseline). Signal alterations of this sort typically occur in the brain's "default mode network" – brain regions active in the absence of overt task performance and whose activity is diminished by engagement of attention and/or controlled processing [3]. The default mode network is thought to be involved in self-referential cognition relating to an awareness of oneself and reflections about personal actions. Activity in these regions is anticorrelated to varying degrees with that of the externally oriented "task-positive" network evaluated in most fMRI studies.

Quantifying changes in blood flow using fMRI

While we can measure the magnitude of task-related signal change with a multitude of tasks and physiological manipulations using BOLD imaging, it is not possible to ascertain absolute blood flow and how it changes. However, the quantification of blood flow in terms of flow rate (ml/100 g/minute) may occasionally be useful, for example, to study any systematic state-related change in cerebral perfusion such as that taking place during sleep [4], time-on-task effects [5], and

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other phenomena that last minutes instead of seconds. Such measurements can be obtained using a variety of Arterial Spin Labeling (ASL) techniques, which have different levels of precision [6, 7]. However, a general disadvantage of these methods limiting their wider use is their inferior signal-to-noise ratio. Furthermore, flow rate can only be measured after recording tens of seconds of MR signal, thus precluding the use of event-related designs.

Measuring functional connectivity

Up to this point, we have discussed how the changes in brain activation that reflect altered cognition can be deduced from piecemeal observation of task-related signal changes in particular regions of interest, without considering their interaction. The evaluation of functional connectivity, conducted by assessing signal covariation in pairs of regions or by determining the extent to which signal in a “target” region relates to that of a “seed” region according to state/task context (psycho-physiological interaction, PPI [8]), can also shed light on state-induced modulation of brain function.

Evaluating resting state networks: information from doing nothing

In addition to fMRI studies designed to evaluate signal changes in response to task performance or levels of task performance, it has recently been discovered that it may also be informative to evaluate “resting state” activity [9, 10]. This refers to the observation of low frequency oscillations (<0.01 Hz) in BOLD signal that are *not* time locked to task performance or sensory stimulation. Results of studies of this type in sleeping individuals have shown changes in connectivity within the default mode network described above [11, 12]. Analyses of resting state data hold promise of being informative of alterations in brain function without requiring motivated performance on the part of a participant [13].

From brain mapping to understanding altered cognition and interindividual differences

fMRI was originally used to map particular cognitive operations to specific brain regions or networks of brain regions. Deviations from a canonical spatial distribution of activation in specific groups (e.g., aged persons, persons with mental illness), states (e.g., sleep

deprivation, persistent vegetative state), or following drug administration could then be interpreted as an indicator of altered brain function [14].

However, more frequently, altered magnitude of activation in particular regions of interest, rather than altered spatial distribution of activation, is what distinguishes groups, conditions, or states of interest. In the setting of SD studies, interactions between task difficulty and state are of particular interest as they signify functional alteration in the cognitive domain of interest. In addition to task-related activation, the evaluation of task-related deactivation where signal changes fall below baseline levels during task performance can also inform regarding state-driven changes in brain function [15, 16].

Correlating signal change across state with behavioral change under different levels of task load/difficulty [17–19] can give insights into the mechanisms underlying cognitive decline in SD. Ideally, this would be achieved by having the individual perform several tasks in the same scanning session so that either different facets of the same cognitive domain can be evaluated or several different cognitive domains can be evaluated simultaneously to determine if these are affected together [20, 21]. This is relevant in the evaluation of “countermeasures” against SD. For example, most persons take stimulants to maintain wakefulness [22, 23], but if the cost of maintaining vigilance is an increased tendency to take risks, persons making critical decisions under conditions of sustained wakefulness might want to weigh the trade-offs in an informed manner.

Making sensible inferences from fMRI studies

Inference is most straightforward when the activated (or modulated) brain region participates in a circumscribed set of cognitive functions. For example, state-related modulation of amygdala activity in response to affective pictures can be reasonably related to changes in emotional processing [24]. Similarly, alteration in object-selective attention can also be appropriately inferred from alterations in parahippocampal place area (PPA) activation when a subject is instructed to attend to or ignore pictures of scenes [25].

In contrast, the interpretation of structure–function relationships must be judiciously conducted in polymodal areas of the brain, for example, the lateral prefrontal and superior parietal areas. These areas receive converging inputs from multiple brain regions

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and are involved in many different tasks. For example, reduced visual short-term memory capacity in sleep-deprived persons is associated with reduced superior parietal activation. As “memory” and “attention” both engage the parietal region in question, the reduction in parietal activity could either be interpreted as a decline in memory storage capacity or as a deficit in attention, which affects processing at all levels of item load [16]. It was thus informative to evaluate brain activation under varying item load and state. Adopting this strategy led to the inference that SD most likely impairs performance in a short-term memory task through its effects on attention or visual processing (see below for details). Hence “reverse inferences” [26] – inferring altered cognitive function(s) from changes in brain activation – require care.

Because SD generally results in decline in cognitive performance [27, 28] accompanied by decreased activation [15, 18], any elevated activation that is accompanied by preserved performance has been inferred as being compensatory. However, there are those who manifest activation patterns and performance that do not differ significantly from those recorded after a normal night of sleep, and these individuals are said to be less vulnerable to the effects of SD [29]. Such a finding has a parallel in research on cognitive aging. While elderly persons who showed “compensatory” increases in bilateral frontal lobe activation generally performed better than age-matched individuals who showed attenuated task-related activation [30, 31], the best performers were those who manifested behavioral performance and activation that resembled that observed in young individuals [32].

These illustrations and the more detailed examples that follow highlight that interpreting fMRI signal changes is not a simple matter of looking for greater or less activation. Signal increases and decreases can occur in different brain regions within the same participant and may serve to characterize different aspects of that individual’s response to SD.

Using fMRI in neurocognitive studies of sleep deprivation

As there already exist a number of excellent reviews discussing the neurocognitive effects of sleep deprivation that broadly summarize the results of neuroimaging studies [27, 33], this overview focuses on studies relating to attention and decision-making, and we discuss selected experiments in greater detail.

Attention

The taxonomy of attention is varied, motivating a brief introduction to how this term is used in this article. Attention is necessitated by a person’s limited capacity to process information. This limited capacity results in the need to make choices concerning what to direct or focus one’s attention on, hence the notion of selectivity.

For example, in a complex scene, one can choose to attend to a particular location, object, feature, color, state of motion, or some combination of these. Attended items are given priority by a “top-down” system that includes lateral prefrontal/premotor and superior parietal regions – the so-called “dorsal attention network” [34]. Attended items are detected more quickly than non-attended items whose processing tends to be suppressed as a result of “biased competition.” In most of the experiments described subsequently, the effects of SD are evident in the frontoparietal system that mediates this “top-down” biasing of attention [35].

“Top-down” attention notwithstanding, if something very salient emerges, for example if a person were to jump in front of you, that person would suddenly assume the focus of attention. This refers to the “bottom-up” aspect of attention where salience contributes to what is attended to. This re-orienting of attention involves a “ventral attention network” [34].

Although all forms of attention involve selection, the term “selective attention” is often used in reference to studies that involve directing focus to a specific location, object, or visual features. Detection of selected items is facilitated if we are cued or *oriented* in advance to where to look. However, this advantage tends to be short-lived, lasting on the order of seconds.

Vigilance is required for the detection of infrequent and temporally unpredictable targets. Most authors use this term interchangeably with “sustained attention” although the latter term may also be used to refer to being able to perform a task over an extended period, corresponding to the notion of tonic arousal [36]. We use the latter definition in this review. Sustained attention is supported by a right hemisphere lateralized fronto-parietal network [37, 38].

The relevance of studying attention in short-term total sleep deprivation

Cognitive failures associated with 24–48 hours of total sleep deprivation have been better characterized than the effects of chronic sleep restriction (what most

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people typically encounter). In behavioral studies conducted before the advent of brain imaging, considerable emphasis was placed on evaluating attentional processes and complex real-world tasks [27]. The decline of “higher” cognitive functions like learning, memory, and executive function observed in SD were of immediate practical concern. As these functions are largely served by the prefrontal cortex, it was anticipated that prefrontal cortex would be particularly vulnerable to the effects of SD [39] and in a manner that could be visualized using functional imaging [40, 41].

Contrary to these expectations, SD has been found to have varied effects on prefrontal activation – it can elevate [15, 42], have no effect [43, 44], or depress [45, 46] task-related prefrontal activation in different experiments. These findings are also at odds with observations that markers of sleep propensity in both waking and sleep EEG are largest over the frontal areas [47, 48]. Variation in task demands, response to task difficulty, and individual differences in ability to compensate for the effects of sleep deprivation have been offered as explanations for differing imaging findings [49], but perhaps functional imaging and EEG evaluate different facets of sleep homeostasis. For example, fMRI is often used to evaluate neural activity in the context of task performance, whereas EEG recordings are conducted at rest.

In contrast to observations concerning prefrontal cortical activation, results of many fMRI experiments conducted on sleep-deprived subjects have consistently shown reduced superior parietal and lateral occipital activation during task performance. These results from studies using tasks that evaluate a variety of cognitive domains, including working memory [49–51], visual short-term memory [16, 17], selective attention for letter features [29, 52], houses/scenes [25, 53], or moving balls [54], suggest a *common mechanism* underlying performance decline.

Failure of attention may underlie decline in memory performance

This notion was clearly illustrated in an experiment designed to evaluate the effect of SD on visual short-term memory (VSTM) [16]. VSTM is capacity-limited to about four visual items, depending on the visual complexity of the items [55, 56]. As test items only need to be stored for a few seconds and retrieved without internal manipulation, varying the size of the storage array and comparing activation in this condition

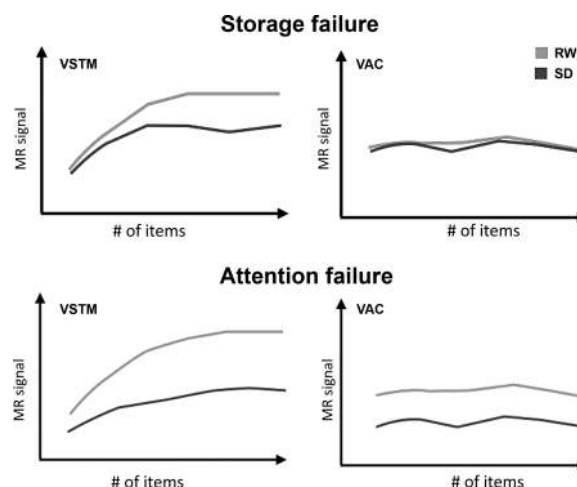


Figure 2.1. Storage failure versus attention failure accounts of the effects of SD on parietal activation. In the storage failure account (top panel), if SD were to affect memory storage alone, we would expect parietal activation to show increasing reduction as larger numbers of items have to be remembered, in the Visual Short-Term Memory (VSTM) condition. Parietal activation should, however, be indifferent to the increasing number of items presented in the Visual Array size Control (VAC) condition, where items need not be remembered. In the attention failure account (bottom panel), we would expect to see parietal activation reduced across all item set sizes, even when mnemonic demands are not required. SD, sleep deprivation; RW, rested wakefulness.

with a control condition where item number was varied without necessity for recall served to evaluate the neural substrate of storage capacity. After a normal night of sleep, the superior parietal region showed an increase in activation with greater storage array size but relative indifference to changing array size without mnemonic demands. If sleep deprivation were to affect storage alone, we would expect activation associated with short-term retention to be reduced with increasing memory set sizes (Figure 2.1). Instead, we observed SD-induced reductions in parietal activation at all set sizes. Additionally, visual extrastriate cortex that was sensitive to set size irrespective of whether recall was required showed attenuated activation even with singleton stimuli. This was striking evidence that a more general factor like attention or reduced visual processing was responsible for performance decline following SD.

This finding was replicated using an event-related version of the same task [17], a design that afforded restriction of analyses to correctly answered trials. Additionally, it was found that donepezil (a cholinesterase inhibitor) altered parietal and occipital activation in a manner that correlated with the extent to which state-related change in performance was modulated by the