

Functional Imaging of Primary Insomnia: New Images and Fresh Opportunities

Commentary on Drummond et al. Neural correlates of working memory performance in primary insomnia. *SLEEP* 2013;36:1307-1316.

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An enduring puzzle in sleep medicine concerns the dissociation between subjective complaints and objective measures of functional impairment in persons with primary insomnia.^{1,2} While up to a third of adults may complain of insomnia symptoms,³ considerably fewer—around 5% of persons, fulfill formal diagnostic criteria.⁴ Critical to resolving this discrepancy may be the differentiation of insomnia with objectively short sleep (< 6 h nocturnal sleep a night) from insomnia with normal sleep duration.⁵ Persons suffering from insomnia with objectively shorter sleep duration exhibit greater emotional and cortical arousal,^{6,7} increased activation of the stress system and elevated risk of hypertension, cognitive impairment and mortality.⁵ A clearer understanding of the pathophysiology underlying this more severe insomnia subtype would benefit from obtaining other objective measures of altered physiology such as functional brain imaging.

Perhaps discouraged by the heterogeneity of objective neurobehavioral findings in past studies, there is a dearth of functional imaging investigations into *primary* insomnia. To date only singleton task-related fMRI,⁸ resting state fMRI,⁹ SPECT,¹⁰ and PET studies¹¹ have been reported. In this issue of *SLEEP*, Drummond and colleagues document the largest fMRI investigation of primary insomnia to date, comparing 25 persons with insomnia and 25 control participants with good sleep.¹² Patients with insomnia were carefully characterized, having longer sleep latency, shorter total sleep, time and higher symptom scores unaccompanied by alteration of sleep architecture or continuity. Of note, sleep durations in their primary insomniacs were verified to be shorter than those of control subjects by actigraphy during the week prior to imaging, and by PSG the night before the fMRI session (~6.5 vs. 7 h).

Participants in the investigation by Drummond and colleagues¹² underwent fMRI while performing a well-studied¹³ verbal N-back task that evaluates both maintenance and manipulation of the contents of short-term memory (working memory). Both groups demonstrated comparable performance accuracy and response times at each of three levels of task difficulty. Against this backdrop, the insomnia group showed lower activation in multiple areas engaged during task performance as well as lower deactivation of two regions within the default mode network (DMN). The latter are so called because they deactivate when a person is focused on a specific task, but activate when attention

is not focused on the external world.¹⁴ Such task-related deactivation or “default mode suppression” is typically reduced in aging and disease.¹⁵ Paralleling the behavioral findings, both activated brain regions as well as deactivated brain regions in insomniacs evidenced less increase (or in the case of default mode regions, less decrease) in MR signal with increasing task difficulty.

The results of Drummond et al.¹² are unique as well as enigmatic. The group differences in functional imaging across three levels of difficulty make it improbable that they are spurious. Indeed, reduced orbitofrontal task-related activation in association with intact performance has been previously observed in insomniacs.⁸ The challenge lies in how to explain preservation of behavioral performance without some “compensatory” shift in task related activation or deactivation. Typically, in contexts as varied as cognitive aging¹⁶ and schizophrenia,¹⁷ when performance is equated or almost equated across conditions or groups of interest, decreases in task-related activation are accompanied by “compensatory” increases in activation elsewhere. In recent work cited by the authors, sleep-deprived participants who were able to maintain auditory oddball detection performance, showed increased (“compensatory”) anterior insula activation in the face of reduced task-related deactivation in part of the DMN.¹⁸ Reduced task-related deactivation of the DMN features prominently the psychopathology of schizophrenia and depression, and it may arise from impaired disengagement from self-referential thoughts or rumination.¹⁹ Such reduced deactivation however, tends to correlate with disease severity and is accompanied by overactivation of the dorsolateral prefrontal cortex.²⁰

Drummond et al.¹² posit that the DMN may have been tonically deactivated even in the baseline “0-back” condition restricting further modulation of fMRI response. This in turn was theorized to reflect insomniacs having to engage externally oriented processing to a greater degree at even the lowest level of task difficulty. Although this explanation has superficial appeal, it is problematic for several reasons. The primary insomnia participants did not report exercising greater mental effort. Further, the biggest jump in cognitive load and task-related activation in N-back tasks, particularly in dorsolateral prefrontal cortex, occurs between the 2-back and 1-back conditions.²¹ This is also apparent in the current work (Figure 2C) and applies to deactivation as well (Figure 2B). As such, there was demonstrated capacity to recruit (or suppress) neurovascular responses beyond the baseline “0-back” condition.

As an alternative explanation, and one that is more plausible, Drummond and colleagues hypothesize that reduced task-related MR responses in insomniacs might reflect a fundamental change in brain physiology. They suggest that baseline CBF is increased secondary to the effects of hyperarousal.^{6,7} Perturbation of resting cerebral blood flow involving both default mode and

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“task-positive” regions in the same direction might be expected when neurovascular responses are disrupted by exogenous agents such as caffeine²² but would be unusual in neuropsychiatric disorders.^{15,19} Imaging alterations tend to be more functionally specific. For example, primary insomnia patients undergoing 18FDG-PET evidenced regional decreases in prefrontal glucose metabolism while awake and at rest.¹¹ In contrast, when they fell asleep, compared to control subjects there was less reduction in subcortical and brainstem glucose metabolism, in accord with the hyperarousal expected in primary insomnia.^{6,7}

These concerns aside, Drummond and colleagues¹² may have hit upon an interesting manifestation of altered physiology that is not without precedent. Persons at *high risk* of Alzheimer disease were found to have elevated resting perfusion in the medial temporal lobe compared to low risk participants. As in the report by Drummond et al., the high-risk participants had decreased fractional Blood Oxygen Level Dependent (BOLD) responses when performing a memory task.²³ Notably, in contrast to the baseline differences in perfusion, there was no between-group difference in the *absolute* cerebral blood flow during task performance. As this study focused exclusively on the medial temporal lobe, it is unknown if the more widespread alteration in neurovascular responses alluded to by Drummond et al. were present.

Clearly, more than “activation” should be considered when assessing fMRI alterations by disease. The type of signal obtained (whether baseline or task-activated); physiological parameters such as respiration; locus of the effect of interest, and the MR measure used (BOLD signal or perfusion) are all pertinent factors. The interaction of these reflects the complex relationship between vascular reactivity, cerebral blood flow, oxygen utilization, and the baseline state of neural activity.²⁴ While it may be impractical to account for all factors in a single study, future investigations should at least consider engaging a limited combination of modalities in the same participants, for example combined Arterial Spin Labeled (ASL) perfusion and BOLD imaging.²⁵ Obtaining a “resting state” scan would be another means of increasing useful data from the same measurement session. Intrinsic functional connectivity has been studied in many neuropsychiatric conditions,¹⁵ but there is currently only a single fMRI study involving primary insomnia.⁹ The analysis of temporally synchronized low frequency (0.01-0.1Hz) BOLD signal fluctuations in such data would allow investigators to probe multiple brain networks simultaneously²⁶ without having the participant perform a task.

In sum, while the findings of Drummond et al.¹² are not fully explained, their carefully conducted study is thought provoking, and should inspire a new generation of sophisticated functional imaging studies that shed light on the pathophysiology that accompanies insomnia with objectively short sleep duration.

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