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Neuroimaging findings in primary insomnia

Étude de l'insomnie primaire par imagerie cérébrale

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ABSTRACT

State-of-the-art neuroimaging techniques have accelerated progress in the study and understanding of sleep in humans. Neuroimaging studies in primary insomnia remain relatively few, considering the important prevalence of this disorder in the general population. This review examines the contribution of functional and structural neuroimaging to our current understanding of primary insomnia. Functional studies during sleep provided support for the hyperarousal theory of insomnia. Functional neuroimaging also revealed abnormalities in cognitive and emotional processing in primary insomnia. Results from structural studies suggest neuroanatomical alterations in primary insomnia, mostly in the hippocampus, anterior cingulate cortex and orbitofrontal cortex. However, these results are not well replicated across studies. A few magnetic resonance spectroscopy studies revealed abnormalities in neurotransmitter concentrations and bioenergetics in primary insomnia. The inconsistencies among neuroimaging findings on insomnia are likely due to clinical heterogeneity, differences in imaging and overall diversity of techniques and designs employed. Larger samples, replication, as well as innovative methodologies are necessary for the progression of this perplexing, yet promising area of research.

RÉSUMÉ

Les techniques d'imagerie cérébrale ont permis des avancées considérables dans l'étude du sommeil chez l'humain. Cependant, les études par imagerie cérébrale dans l'insomnie primaire demeurent peu nombreuses, particulièrement en regard de la prévalence importante de ce trouble du sommeil dans la population générale. Cette revue examine la contribution des études d'imagerie cérébrale fonctionnelle et structurelle à la compréhension de l'insomnie primaire. Les études d'imagerie fonctionnelle au cours du sommeil appuient la théorie de l'hyperactivation dans l'insomnie. D'autres études fonctionnelles ont révélé des altérations dans le traitement cérébral des processus cognitifs et émotionnels dans l'insomnie primaire. Les résultats des études structurelles suggèrent des modifications neuroanatomiques, particulièrement dans l'hippocampe, le cortex cingulaire antérieur et le cortex orbitofrontal. Cependant, ces résultats ne sont pas concordants d'une étude à l'autre. Quelques études spectroscopiques ont révélé des altérations dans les niveaux de neurotransmetteurs, ainsi que des changements bioénergétiques dans l'insomnie primaire. Le manque de concordance entre les résultats d'imagerie cérébrale en insomnie pourrait être lié à l'hétérogénéité des différentes populations cliniques étudiées, ainsi qu'à la diversité des techniques d'imagerie et d'analyse employées. La neuroimagerie constitue une voie d'exploration prometteuse de l'insomnie, mais la poursuite des avancées dans ce domaine nécessite de réunir de plus grands échantillons, de reproduire et confirmer les résultats existants, tout en développant l'utilisation de nouvelles modalités.

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1. Introduction

Insomnia is a remarkably prevalent disorder. Depending on the definition used, it affects 6–20% of the general population [1–5]. As a result, sleep dissatisfaction counts among the most common health complaints in primary care [6] and the associated healthcare expenditures, in addition to the costs of sleep aids and absenteeism at work, contribute to a considerable economic burden [7,8]. Symptoms of insomnia include difficulties falling asleep and staying asleep, and feelings of non-restorative sleep [4]. Daytime fatigue, mood disruption and cognitive impairments associated with insomnia negatively affect productivity and quality of life [9–11]. While insomnia symptoms can be a transient response to stress or changes in sleep-wake schedule, 70% of individuals with insomnia display persistent symptoms for more than three months (i.e., chronic insomnia) [12].

Relatively few neuroimaging studies have examined the physiology of this common sleep disorder [13]. Neuroimaging techniques can be useful in identifying the cerebral mechanisms of insomnia pathogenesis, and the neural correlates of insomnia symptoms. In this paper, we review the findings of these pioneering studies, which examined insomnia through the lenses of single-photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI), functional MRI (fMRI) and magnetic resonance spectroscopy (MRS). PET, SPECT and fMRI, are functional modalities that examine changes in brain metabolism, blood flow or blood oxygenation. Structural modalities, such as MRI and MRS, map out subtle changes in brain anatomy and content. In synthesizing the strengths and limitations of these studies, we propose future directions in this expanding area of research. The scope of this review will be limited to primary insomnia (PI), which is defined by sleep disturbances occurring in the absence of comorbid medical or psychological conditions [14].

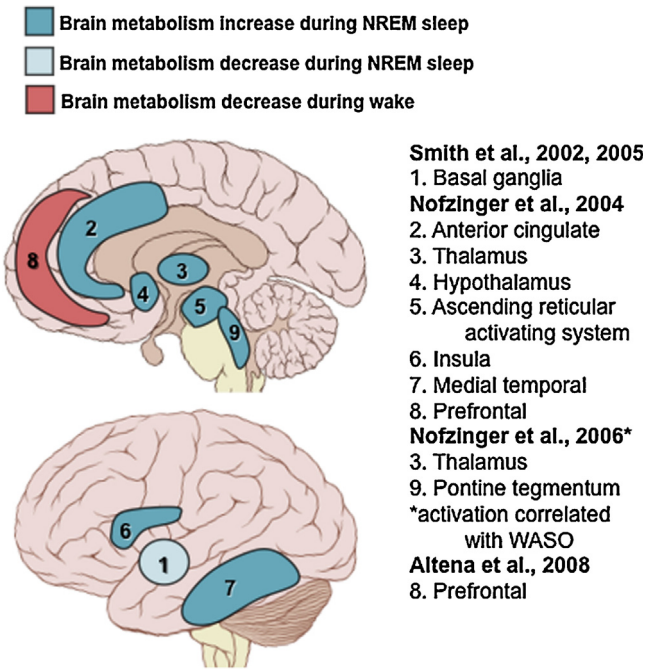

Fig. 1. Primary insomia: functional studies. Regional cerebral metabolism during wake and NREM sleep in PI. Smith et al. [15,16] found reduced regional cerebral blood flow (SPECT) in the basal ganglia in insomniacs. Nofzinger et al. [17] found smaller reductions in regional metabolism (^{18}F-FDG PET) during the transition to from wake to NREM sleep in patients with PI. Nofzinger et al. [18] found a correlation between WASO and metabolism in thalamocortical pathways and the pontine tegmentum. Altena et al. [19] and Nofzinger et al. [17] found evidence for prefrontal deactivation during wake. Adapted from Desseilles et al. [13], and from illustrations by Patrick J. Lynch and C. Carl Jaffe. http://creativecommons.org/licenses/by/2.5/.

2. Functional neuroimaging

2.1. PET and SPECT

The first neuroimaging studies to examine PI used PET and SPECT functional imaging techniques. PET and SPECT both involve the injection of a radiolabeled isotope (the tracer) into the bloodstream. Depending on the tracer employed, the scans can offer indices of cerebral blood flow, cerebral metabolic rate of glucose (CMRglu) or neurotransmission. Smith et al. [15] employed SPECT with technetium-99m-hexamethylpropylenamine oxime (^{99m}Tc-HMPAO), a gamma-emitting radionuclide imaging agent, in order to observe regional cerebral blood flow during non-rapid-eye-movement (NREM) sleep in 5 PI patients and 4 good sleepers, all 9 of them female. Compared to controls, PI patients displayed cerebral hypoperfusion during NREM sleep in eight pre-selected regions of interest. The most pronounced hypoperfusions were observed in the basal ganglia (Fig. 1), and to a lesser extent in the frontal medial, occipital and parietal cortices. In a later study, the same group re-scanned 4 of the 5 PI patients after 8 weeks of behavioral therapy for insomnia. They found that a 43% reduction in sleep onset latency after treatment was accompanied by a 24% restoration of regional cerebral blood flow, especially in the basal ganglia [16]. These changes were thought to represent normalization of sleep processes. The authors further speculated that increased sleep debt from partial sleep deprivation in PI may accentuate the normal cerebral deactivation during sleep, as a homeostatic compensatory mechanism.

In contrast, the next functional study by Nofzinger et al. provided support for the hyperarousal theory of insomnia [17]. The hyperarousal theory explains PI as a fundamental imbalance in the sleep-promoting and arousal systems, resulting in a state of global cortical and physiological arousal across the sleep-wake cycle [20,21]. In the study by Nofzinger et al., 7 men and women with PI were compared to 20 age- and gender-matched healthy controls during wakefulness and NREM sleep, using ^{18}F-fludeoxyglucose (^{18}F-FDG) PET in order to measure regional cerebral metabolism, indexed by CMRglu. In line with hyperarousal theory, PI patients relative to controls were found to have a smaller reduction in relative metabolism from wakefulness to NREM sleep in the ascending reticular activating system, hypothalamus, thalamus, hippocampus, anterior cingulate cortex (ACC), medial prefrontal and insular cortices (Fig. 1). In addition, PI patients had lower waking metabolism than healthy controls in cortical (bilateral frontal, left superior temporal, parietal and occipital cortices) and subcortical regions (thalamus, hypothalamus and brainstem reticular formation).

Nofzinger et al.'s results lend support to Espie's integrated psychobiological inhibition model [22], according to which heightened arousal in PI is attributable to the inhibition of normal cortical deactivation during the transition from waking to NREM sleep. This model at once explains two major symptoms of insomnia:

- difficulty falling asleep because of restricted sleep onset-related cortical inhibition and;
- difficulty staying asleep because of the same disinhibition occurring following arousals over the course of the night. These arousals would otherwise go unnoticed because of rapid cortical deactivation in normal sleep [22].