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What can neuroimaging findings tell us about sleep disorders?

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Abstract

Models of the pathophysiology of human sleep disorders have only recently been tested using nuclear medicine assessments, which have greatly increased our understanding of the brain mechanisms involved in the human sleep–wake cycle. Dramatic changes in function have been observed in large-scale neuronal networks during sleep. Broad declines in heteromodal-association-cortical function, and relative increases in limbic and paralimbic function have been observed. These cortical areas are responsible for essential aspects of human behavior, allowing us to interact with the world around us and to evaluate the significance of important events in our lives. Preliminary findings suggest that fundamental alterations in the function of these neural systems occur in sleep disorders. In depression, alterations in rapid-eye-movement and slow-wave sleep appear linked to a sleep-related dysfunctional arousal in primary limbic and paralimbic structures (amygdala), and hypofunction in frontal cortical areas. Pharmacologic interventions partially reverse these alterations. Preliminary studies in insomnia indicate a subcortical hyperarousal and a failure of sleep to provide normal restoration of function in the prefrontal cortex, leading to chronic sleep deprivation. This review discusses functional neuroimaging data on normal sleep, and on the pathophysiology of insomnia related to depression and primary insomnia.

Keywords: [^{15}O]H_2O-PET; [^{18}F]FDG-PET; fMRI; HMPAO-SPECT; REM; NREM; Insomnia; Depression

1. Introduction

Our understanding of the basic mechanisms of sleep/wake regulation has advanced considerably since the discovery of rapid-eye-movement (REM) sleep nearly 50 years ago. Research methods subsequently developed to study the living brain in preclinical animal models across the sleep/wake cycle, led to the formulation of theoretical models of the pathophysiology of human sleep disorders. However, prior to the introduction of nuclear medicine assessments to sleep research, our understanding of sleep/brain relationships in humans was limited to surface electrophysiology, as assessed by polysomnography, and it was not possible to test these theoretical models. The recent introduction of nuclear medicine assessments has allowed scientists to study brain function in discrete neural areas not accessible to the surface EEG, resulting in an explosion of new information regarding human brain function. However, despite considerable advances, the union of the fields of nuclear medicine and sleep medicine remains in its infancy, with the majority of studies to date focusing on increasing our understanding of healthy sleep/brain relationships, with only occasional studies on specific sleep disorders.

Nuclear imaging (neuroimaging) techniques have been used to observe dramatic changes in function in large-scale neuronal networks across the sleep/wake cycle. For example, non-rapid-eye-movement (NREM) sleep appears to be related to broad declines in function in the heteromodal association cortex in the frontal, parietal, and temporal lobes, as well as in the thalamus [1–11], whereas REM sleep is characterized by relative increases in limbic and paralimbic function [12–18]. These cortical areas are thought to be responsible for essential aspects of human behavior, allowing us to interact with the world around us and to evaluate the significance of important events in our lives.

Early findings in sleep disorders using neuroimaging techniques suggest that there may be fundamental alterations in the function of these neural systems across the sleep/wake cycle. In depression, alterations in both REM and slow-wave sleep appear to be linked to a sleep-related dysfunctional arousal in primary limbic and paralimbic structures such as the amygdala, as well as hypofunction in frontal cortical areas [19–21], which can be partially reversed by pharmacological interventions [20]. According to preliminary neuroimaging studies, primary insomnia is associated with abnormal physiological arousal to increased function during sleep in the ascending reticular activating system, basal forebrain and hypothalamus, thalamus, and the ventromedial prefrontal cortex [16]. Furthermore, the thalamocortical system involving the prefrontal cortex appears to function at an abnormally low level during both sleep and wakefulness. This pattern suggests that insomniac patients have subcortical hyperarousal and a failure of sleep to provide for the normal restoration of function in the prefrontal cortex, leading to chronic sleep deprivation.

This review will introduce the process of normal sleep, using this as a background to review nuclear medicine (neuroimaging) methods and their application in the study of sleep/brain relationships, in healthy subjects and in patients with depression or primary insomnia.

2. Neuroanatomy of sleep

Three interacting neuronal systems (an arousal system, a sleep system, and a REM system) have been identified that are involved in the regulation of the sleep/wake cycle.

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Table 1
Functional neuroimaging methods for assessing brain function during sleep

Method	Measure	Resolution		Sleep in scanner?	Other characteristics
		Spatial	Temporal		
MEG tomography	Electrical events	10 mm	Milliseconds	Yes	Difficult in sleep; Availability; expense
fMRI	Blood flow	<cm	Seconds	Yes	Noise; technically difficult in sleep
[^{15}O]H_2O-PET	Blood flow	cm	Minute	Yes	Repeated measures possible
[^{18}F]FDG-PET	Glucose metabolism	cm	10–20 minutes	No	Long half-life limits repeated measures
99m-Tc-ECD-SPECT	Blood flow & metabolism	cm	Minutes	No	Repeatable in single night
Receptor imaging	5-HT, ACh, GABA	cm	20–90 minutes	Waking	Expensive, labor intensive

Abbreviations: MEG: Magnetoencephalographic. fMRI: functional magnetic resonance imaging. [^{15}O]H_2O-PET: [^{15}O]H_2O-positron emission tomography. [^{18}F]FDG-PET: [fluorine-18]2-fluoro-2-deoxy-D-glucose positron emission tomography. 99m-Tc-ECD-SPECT: Technetium-99m-ethyl cysteinate dimer single photon emission computed tomography. 5-HT: 5-hydroxy tryptamine or serotonin. ACh: acetylcholine. GABA: gamma-aminobutyric acid.

2.1. Arousal system

The wake-promoting or arousal system is located in the ascending reticular activating system (ARAS) originating in the brainstem. The ARAS projects into a series of specific brainstem systems (pontine cholinergic nuclei, midbrain raphe nuclei and the locus coeruleus) and forebrain structures (midline and medial thalamus with widespread cortical projections, amygdala) involved in arousal [22–24]. The amygdala also has interconnections with the isocortex and other areas involved in arousal such as the hypothalamus and ventral striatum.

The hypothalamus has an important role in arousal via the suprachiasmatic nucleus, which regulates the circadian control of arousal, and the posterior hypothalamus, which contains a group of neurons that produce hypocretin [24–35]. This projection is of particular interest because the hypocretin neurons project not only over the entire isocortex but to additional arousal systems including dense projections to locus coeruleus, raphe nuclei, pontine cholinergics, midline thalamus, nucleus basalis, and amygdala. The absence of the novel hypothalamic peptide, hypocretin (also known as orexin), results in narcolepsy/cataplexy, a neurological disorder characterized by an inability to maintain wakefulness and intrusion of REM into wakefulness [36]. Histaminergic neurons of the posterior hypothalamus are also involved in arousal [37].

2.2. Sleep system

Recent evidence suggests that a sleep system exists in the hypothalamus since the ventrolateral preoptic nucleus (VLPO) contains gamma-aminobutyric-acidergic (GABAergic) and galaninergic neurons that are active during sleep and necessary for normal sleep. The VLPO may represent a "sleep switch" as it sends inhibitory projections to arousal systems in the posterior hypothalamus [38], and receives inputs from multiple brain systems that regulate arousal, autonomic, limbic and circadian functions [39]. Furthermore, the VLPO may also be important in the regulation of REM sleep [40].

2.3. REM system

The REM sleep system comprises the laterodorsal and pedunculopontine tegmental cholinergic nuclei (LDT and PPT) in the pontine reticular formation, which are under the inhibitory influence of wake-active monoaminergic systems [41–46]. The LDT and PPT are disinhibited as the activity of these monoaminergic systems declines during sleep, allowing for the generation of REM sleep [47–55]. The LDT and PPT within the brainstem mediate widespread cortical arousal indicative of the REM sleep state via a dorsal pathway innervating the thalamus, and a ventral pathway innervating the basal forebrain [42,56,57].

It is becoming increasingly apparent that the sleep, arousal, and REM systems do not function in isolation but are modulated by other forebrain structures that maintain functional connections [22,58–62]. For instance, the REM-generating centers in the brainstem are modulated by the amygdala [62–68].

The role of nuclear medicine in further clarifying the mechanisms of sleep/wake regulation and its disturbance in sleep disorders may lie primarily in studying these larger forebrain structures that may modulate sleep, as opposed to the nuclei that generate sleep states, given the spatial resolution constraints of human neuroimaging methods. Additionally, evidence exists for a use-dependent feature of sleep that may be localized in smaller neuronal groups in the central nervous system, which may underlie the actual function of sleep once it is generated. Nuclear medicine is ideally placed to offer insights into these more local processes that occur within sleep.

3. Functional neuroimaging tools for sleep research

The first practical demonstration that nuclear magnetic resonance (NMR) spectroscopy could be applied to the study of the metabolic effects of brain activation *in vivo* came in 1980, with studies of rat brain using a surface coil (reviewed in Kauppinen *et al.* [69]). Nuclear medicine has since created a number of functional neuroimaging tools for assessing varying aspects of brain function, which are versatile and non-invasive (Table 1).

Early neuroimaging techniques such as computer tomography (CT) scanning combined with xenon inhalation [70], were followed by positron emission tomography (PET), which was used to detect positron-emitting isotopes in labeled compounds such as [fluorine-18]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG-PET) [1]. The signal used by PET is based on the fact that changes in brain metabolism in healthy humans or laboratory animals are almost invariably accompanied by changes in local blood flow. PET provided a level of precision in the measurement of cerebral blood flow, which opened up the modern era of functional human brain mapping [71]. Subsequently, technetium-labeled perfusion tracers were introduced (e.g., technetium-99m-hexamethylpropylene amine oxime or HMPAO), which could pass the blood–brain barrier and be detected by single photon emission computed tomography (SPECT) [72], to monitor brain metabolism and/or blood flow during sleep. However, the [^{15}O]H_2O-PET method subsequently took prominence in functional neuroimaging research because it

offered the opportunity to take multiple scans with a higher temporal resolution than the [^{18}F]FDG-PET or SPECT techniques [12].

The availability of improved statistical imaging software also allowed for a greater ease of assessing regional changes throughout the entire brain without *a priori* hypotheses, while correcting for problems of multiple comparisons. Unfortunately, this also came with increasing subject burden since subjects now had to sleep within the scanner during the injection and uptake of the radiolabel.

Assessment of brain function during sleep presents certain challenges. Since sleep is a biological rhythm, it introduces a time domain into a neuroimaging study. Rather than being constant across a 24-hour period, brain function has reliable shifts in patterns of function across not only different types of sleep, but also across the day when alertness can vary widely. It is, therefore, important to choose imaging methods that have the temporal resolution to assess the brain process in question and also that the scan be taken at a specific time across the biological rhythm of sleep.

Some of the available neuroimaging tools can be applied directly to the study of the sleeping brain, although for others this would be somewhat impractical but not impossible (Table 1). It is important, when assessing sleep directly, to choose a method that maintains, as closely as possible, the integrity of sleep. For example, neuroimaging techniques such as functional magnetic resonance imaging (fMRI), [^{15}O]H_2O-PET, and neuroreceptor imaging require that the head be immobilized in the scanner at the time that brain function is being assessed. These techniques, therefore, often require a select group of subjects able to sleep in this type of environment. Furthermore, in order to maximize the chance that the subject will be able to sleep in this restricted environment, investigators often sleep-deprive subjects prior to studying them. However, restricting sleep will result in important changes in brain function, thereby disrupting the object of study.

4. Neuroimaging studies of the functional neuroanatomy of sleep

Although this field is still in its infancy, there have been considerable advances in the functional neuroanatomy of healthy sleep in the past decade.

4.1. REM sleep

A variety of imaging studies have shown that, in contrast to waking, there is activation of the limbic and paralimbic cortex during REM sleep. In addition, their consensus was that the brain as a whole is functionally active during REM sleep. In a [^{18}F]FDG-PET trial, the anterior cingulate cortex was identified as the only cortical region to have greater metabolism during REM in relation to waking [1]. Another [^{18}F]FDG-PET trial observed heterogeneous activation during REM sleep with global metabolism similar to that observed in the waking state [7]. Blood flow assessed by HMPAO-SPECT was shown to increase within the visual association cortex, but decrease in the inferior frontal cortex during REM sleep [72]. Positive correlations between REM sleep and blood flow in the pontine tegmentum, left thalamus, bilateral amygdalas, anterior cingulate cortex, and right parietal operculum have also been observed using [^{15}O]H_2O-PET along with negative correlations between REM sleep and frontoparietal cortex, posterior cingulate and precuneus activity [12].

From these observations, it was concluded that REM sleep may be involved in the processing of certain types of emotional memories. In another trial, increased blood flow to the thalamus, brainstem, and basal forebrain, as well as in limbic and paralimbic structures was identified during REM sleep compared with NREM sleep or waking [13]. The first trial with [^{18}F]FDG-PET and advanced statistics enabling whole brain analyses [15], found a general pattern of activation of anterior limbic and paralimbic structures during REM sleep relative to waking, strikingly similar to those identified previously in PET studies [12,13]. The same pattern of activation was obtained at two timepoints, separated by 12 weeks in a later trial by the same group, when waking and REM sleep were monitored in healthy subjects [16].

Visual processing within REM sleep may be a closed loop of extrastriate and paralimbic cortex in the absence of either primary visual processing or higher-order processing in frontal areas [14]. In a [^{15}O]H_2O-PET trial, the extrastriate but not primary visual cortex was activated during REM sleep [14]. There was an inverse relationship in blood flow between these visual processing regions and a direct relationship between flow in extrastriate cortex and paralimbic structures. A re-analysis of previous [^{18}F]FDG-PET data [1], obtained during waking and REM sleep in healthy subjects, found increases in anterior cingulate, frontal thalamus and extrastriate cortex during REM relative to NREM [17]. In an assessment of blood flow using [^{15}O]H_2O-PET in 12 healthy men during waking and REM sleep, correlations between flow and eye movements in occipital cortex, anterior cingulate cortex, mesencephalon, thalamus, parahippocampal gyrus, striate cortex and supplementary motor area were noted in REM but not in waking [18]. These correlations with occipital cortex and lateral geniculate were suggested to be functional correlates of the pontine geniculo-occipital wave in humans [18].

4.2. NREM sleep

NREM sleep is a functionally less active state with reduced blood flow and metabolism relative to REM sleep or waking [1,70,73]. Regional reductions in brain function from waking to NREM sleep have been observed in the heteromodal association cortex in the frontal, parietal, and temporal lobes, and in the thalamus in several studies. Reductions in frontal, thalamus, and basal ganglia have also been observed in stages 2 and 3 [1], and bilaterally in the thalamus during stage 2 of NREM sleep [6,7].

Regional cerebral blood flow during NREM sleep has been assessed in several trials utilizing [^{15}O]H_2O-PET [2–5,13,74]. In these trials, reduced flow occurred in "centrencephalic" regions (thalamus, brainstem, and basal forebrain), limbic (prefrontal cortex, basal forebrain, hypothalamus) and paralimbic (basal ganglia, anterior cingulate cortex) structures, precuneus, and mesial aspect of the temporal lobe during NREM sleep. Although blood flow in the cerebellum during NREM sleep was found to be reduced in most studies [2–5], it increased in one study [74]. Reduced blood flow has also been demonstrated in the higher-order association cortex (frontoparietal cortices), but not in the primary sensorimotor cortex during NREM sleep [13,74]. Principal components analysis showed two distinct networks, one in the thalamus and the second involving frontoparietal cortex and cerebellum.

Brain metabolism during waking and NREM sleep has been evaluated in 14 healthy subjects by [^{18}F]FDG-PET scans [9,10]. Whole-brain glucose metabolism declined significantly from waking to NREM sleep. Relative decreases in regional metabolism from waking to NREM sleep occurred in wide areas of frontal, parietal, temporal and occipital association cortex, primary visual cortex, and in anterior/dorsomedial thalamus. After controlling for the whole-brain declines in absolute metabolism, relative increases in regional metabolism from waking to NREM were found bilaterally in the dorsal pontine tegmentum, hypothalamus, basal forebrain, ventral striatum, anterior cingulate cortex and

extensive regions of the mesial temporal lobe, including the amygdala and hippocampus, and in the right dorsal parietal association cortex and primary somatosensory and motor cortices. The reductions in relative metabolism in NREM sleep compared with waking are consistent with prior findings from blood-flow studies. Furthermore, the finding that there were relatively greater decreases in heteromodal association cortex and in the thalamus is consistent with thalamocortical networks associated with conscious awareness, attention, and executive function showing the largest functional declines from waking to NREM sleep. The relative increases in glucose utilization in the basal forebrain, hypothalamus, ventral striatum, amygdala, hippocampus and pontine reticular formation are new observations that are in accordance with the view that NREM sleep is important to brain plasticity in homeostatic regulation and mnemonic processing [9,10].

Changes in brain function associated with awakening from NREM sleep have also been examined by the [^{15}O]H_2O-PET method [75]. Blood flow was monitored during sleep for 5 minutes post-awakening and after 20 minutes post-awakening. Early awakening was associated with increased flow in brainstem and thalamus, while increased flow in anterior cortical areas was associated with later awakening [75]. Additional differences in relative flow in various brain structures suggested that the awakening process is associated with reactivation of centrencephalic regions, while the full recovery of consciousness (e.g., loss of sleep inertia) is due to anterior cortical reactivation [75].

4.3. Sleep deprivation

Sleep deprivation of healthy subjects over 24 hours results in global declines in absolute cerebral waking metabolism, as assessed via [^{18}F]FDG-PET, particularly in the frontoparietal cortex and in the thalamus, which correlate with decreased alertness and cognitive performance [76]. This finding supported a role for sleep in the restoration of brain function in thalamocortical networks associated with higher-order cognition, and the idea that these networks are important in regulating arousal [76]. Similarly, blood flow in the thalamus and ponto-mesencephalic tegmentum, as assessed by [^{15}O]H_2O-PET, also positively correlated with arousal associated with sleep, performance on vigilance tasks, and loss of consciousness associated with anesthesia [8,77–79]. In some instances, this arousal network also included the basal forebrain and anterior cingulate cortex [77].

5. Neuroimaging studies of sleep disorders

Since it is now known that brain function changes in reliable ways across the sleep/wake cycle, it is possible to build models for alterations in these patterns in discrete human sleep disorders such as insomnia related to depression or primary insomnia.

5.1. Dysfunctional arousal in depression

Patients with insomnia related to depression can describe difficulty falling asleep, difficulty staying asleep, and/or difficulty returning to sleep after early morning awakenings. Clinically, they often report a paradoxical state of physical daytime fatigue, yet with persistent mental activity that makes it difficult for them to fall asleep at night. Such patients have reduced stage 3 and 4 NREM sleep, an increased amount of REM sleep, a shortening of time to onset of the first REM period of the night, and an increase in the frequency of eye movements during REM periods.

The hypothesis that the alterations in REM sleep in depressed patients reflect a functional dysregulation within limbic and paralimbic forebrain structures during the sleep state has been tested and confirmed by several [^{18}F]FDG-PET studies [19,20,80]. Furthermore, a number of findings suggest a generalized hyperarousal in depressed patients. In an early study, depressed patients, in contrast to healthy subjects, showed greater elevations in glucose metabolism from waking to REM sleep in the tectal area and in left hemispheric areas (sensorimotor cortex, inferior temporal cortex, uncal gyrus-amygdala, and subicular complex) [19]. Treatment with the anti-depressant, bupropion SR, reduced the previously observed deficit in activation of medial prefrontal cortex, right anterior insula, and in particular, the anterior cingulate from waking to REM sleep in depressed patients [20]. These findings suggested that increased anterior cingulate metabolism, in particular, characterized depressed patients and that antidepressant therapy may work in part by providing an inhibitory influence on abnormally elevated function in the anterior cingulate. A larger study demonstrated a supersensitive pattern of activation from waking to REM in depressed subjects along with increased whole-brain metabolism in REM [80].

Increased whole-brain metabolism has also been demonstrated using [^{18}F]FDG-PET during the first period of NREM sleep in depressed patients relative to healthy subjects [21]. These increases were most noticeable in the posterior cingulate, the amygdala, hippocampus, occipital and temporal cortex and the pons. Hypofrontality was also noted in depressed subjects, who also had reduced relative metabolism in the anterior cingulate, caudate, and medial thalamus in relation to healthy subjects.

The relationship between beta EEG power, an electrophysiological marker of arousal, and regional cerebral glucose metabolism has been observed using [^{18}F]FDG-PET in nine healthy subjects and 12 depressed patients during their first NREM period of sleep [16]. Beta power negatively correlated with subjective sleep quality in healthy and depressed subjects. There was a significant correlation between beta power and relative cerebral glucose metabolism in the right lateral inferior occipital complex, and particularly in the ventromedial prefrontal cortex in healthy and depressed subjects. In addition, there was a trend toward greater beta power in depressed subjects in relation to age- and gender-matched healthy subjects during a baseline night of sleep. Given its functional links with brain structures involved in arousal, it is suggested that the ventromedial prefrontal cortex may have abnormally elevated function in severely aroused depressed subjects, and that this elevation may influence general cortical arousal in this disorder.

5.2. Primary insomnia

Primary insomnia is characterized by inadequate sleep or poor quality of sleep unrelated to other concomitant medical conditions. Patients experience one or more of the following: difficulty falling asleep, difficulty maintaining sleep, and/or early awakenings. Insomnia patients experience daytime dysfunction that may include fatigue, mood symptoms, and cognitive impairment (e.g. reduced attention and concentration). Approximately 10% of the adult population will suffer from chronic insomnia, while 30 to 50% will experience transient insomnia at some point in their life. Consequences of insomnia may include poor daytime performance, an increased likelihood of subsequent development of a mental disorder such as depression or anxiety, and increased medical morbidity and mortality.

In a preliminary HMPAO-SPECT study, overall cerebral blood flow was reduced in five patients with primary insomnia relative to four healthy subjects during NREM sleep [81]. However, this study was limited since blood flow is known to decline with increasing duration of NREM sleep, and the insomnia

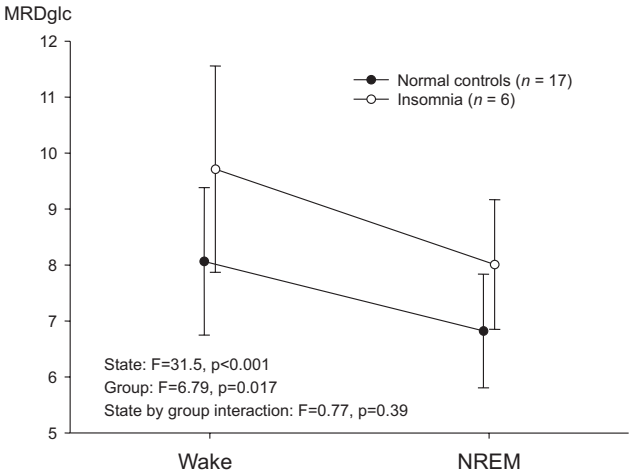

Fig. 1. Increased whole brain metabolism in insomniacs relative to healthy subjects during waking and NREM sleep. Cerebral hypermetabolism in insomniacs. A repeated measures analysis of variance tested group (insomniac *versus* control) × time (wake *versus* NREM sleep) interactions, and group and time effects of the indirect measure of whole brain glucose metabolism (MRDglc). No interaction was noted. Significant effects of group (insomniacs > controls), and time (waking > NREM sleep) were found.

patients received blood-flow assessments after a greater duration of NREM sleep than the healthy subjects. The small sample size investigated in this study also limits the generalizability of these findings to the condition of insomnia as a whole. It is possible that the sleep disruption experienced by insomnia patients may be due to abnormally elevated function in the ventromedial prefrontal cortex during NREM sleep, consistent with observations in severely aroused depressed subjects [16].

A recent neuroimaging trial in primary insomnia patients tested several hypotheses [80]. Firstly, that the hyperarousal of insomnia may be reflected by an overall increase in whole-brain metabolism during both waking and sleeping in relation to healthy subjects. Secondly, that the inability of insomniacs to sleep may be the result of a failure of wake-promoting brain structures to turn off, or decline in function from waking to sleep. Thirdly, that the daytime fatigue of insomniacs may be explained by declines in function during waking in the thalamus and in the frontal and parietal cortex relative to healthy subjects. As already discussed, these structures are known to decline in function following sleep deprivation, something that may occur in insomniacs following prolonged periods of difficulty sleeping at night. In this trial, seven insomniacs and 20 healthy age- and gender-matched subjects underwent [^{18}F]FDG-PET scans during waking and NREM sleep [80]. Consistent with the first hypothesis, whole-brain metabolism was significantly increased in insomniacs compared with healthy subjects during both waking and NREM sleep (Fig. 1). In line with the second hypothesis, the ascending reticular activating system (ARAS), an important arousal system within the brain, was consistently more active in insomnia patients relative to healthy subjects, from waking to NREM sleep (Fig. 2).

Finally, and in accordance with the third hypothesis, insomniacs exhibited a relative hypometabolism in the thalamus and frontoparietal cortex while awake, a pattern also seen in healthy subjects following sleep deprivation (Fig. 3). These findings suggest that, across the sleep/wake cycle, the brains of patients with insomnia exhibit signs of both hyperarousal and sleep deprivation.

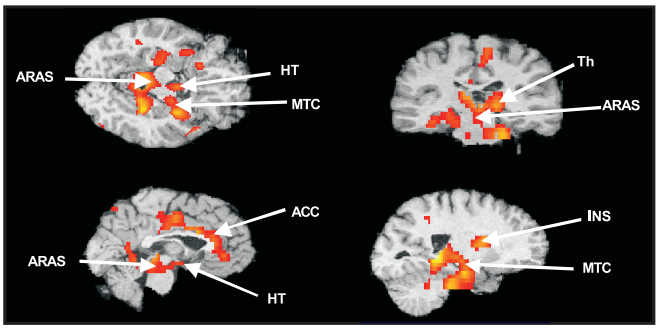

Fig. 2. Arousal systems do not deactivate from waking to NREM sleep in insomnia patients, and brain structures that do not show decreased metabolic rate from waking to sleep in insomniacs. ACC = anterior cingulate cortex; ARAS = ascending reticular activating system; Hy = Hypothalamus; INS = insula; MTC = mesial temporal cortex; Th = thalamus.

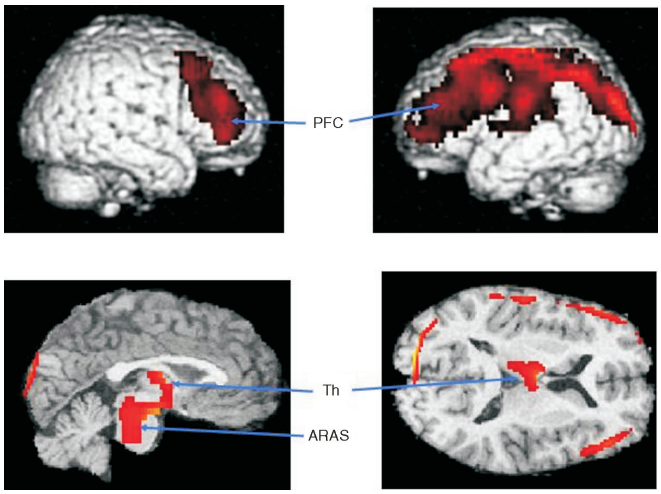

Fig. 3. Daytime fatigue in insomnia patients is related to frontal relative hypometabolism in waking. Panels show brain structures where relative metabolism during waking is higher in healthy subjects than it is in insomniacs. All regions shown reach statistical significance at the $p < 0.05$, corrected, level of significance. ARAS = ascending reticular activating system; Th = thalamus; PFC = prefrontal cortex.

6. Summary and areas for future research

Neuroimaging techniques have already led to very important advances in our understanding of the sleep/wake cycle in healthy subjects. Early studies demonstrate promise that these nuclear medicine techniques can add significantly to our understanding of clinical sleep disorders medicine. However, despite these advances, the use of neuroimaging techniques in sleep research remains in its infancy and additional studies are needed in several areas. Further studies are required to clarify the basic mechanisms of sleep processes, including the circadian and homeostatic functions of sleep. In addition, neuroimaging techniques should be applied to clarify the role of sleep in cognitive processes that may occur within sleep, as well as changes in very primitive limbic and paralimbic brain systems activated in REM sleep, which may also be dysfunctional in neuropsychiatric disorders such as depression, schizophrenia, Parkinson's disease and the dementias. The unique effects of sleep deprivation on brain function could be further investigated using neuroimaging techniques as well as the effects of interventions to reverse these changes. Neuroimaging studies will ultimately further our knowledge of the pathophysiological

mechanisms underlying a wide assortment of clinical sleep disorders.

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