THEORETICAL REVIEW

Neuroimaging and sleep medicine

Eric A. Nofzinger*

Sleep Neuroimaging Research Program, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O’Hara Street, Pittsburgh, PA 15213, USA

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Summary
In sleep medicine, patients with sleep disorders are evaluated and treated. The primary assessment tool of the field has traditionally been polysomnography. While polysomnography has been helpful in the evaluation of some sleep disorders, such as sleep apnea syndrome and periodic limb movement disorder, it has been less helpful in others, such as the insomnias, or sleep disorders secondary to mental disorders. These disorders are presumed to stem from some alteration in brain function that disrupts sleep. The development of functional neuroimaging methods provides a means to understand brain function in patients with sleep disorders in a manner not accessible to polysomnography. This paper summarizes functional neuroimaging findings during healthy sleep, then, reviews available studies in sleep disorders patients, and studies addressing the pharmacology of sleep and sleep disorders. Areas in which functional neuroimaging methods may be helpful in sleep medicine, and in which future development is advised, include: (1) clarification of pathophysiology; (2) aid in differential diagnosis; (3) assessment of treatment response; (4) guiding new drug development; and (5) monitoring treatment response.

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Introduction
The field of sleep medicine has evolved around the diagnostic tools of the sleep lab, where a patient’s sleep is defined in terms of a collection of electrophysiological measures that assess various aspects of physiology. Over the early years of sleep medicine, there was a hope that the sleep lab assessment could provide some objective and specific understanding of an alteration in sleep that relates to the clinical disturbances in sleep experienced subjectively. This hope has been realized for some, but not all sleep disorders. In obstructive sleep apnea (OSA), for example, the assessment of respiratory patterns in conjunction with some assessment of sleep is paramount to the diagnosis as well as assessment of treatment response. In other disorders, such as insomnia or sleep disorders secondary to psychiatric disorders, the utility of electrophysiological assessment of sleep is less clear in terms of assessment or management. Still, there remains a sense that some aspect of sleep is altered in a pathological manner in these disorders, perhaps in a way that is not captured effectively in a standard sleep lab assessment.

In the past few decades, functional neuroimaging has emerged as a new way to assess brain function in health and in pathology. These methods allow for the quantification of a variety of aspects of brain function including metabolism, blood flow, metabolic, blood flow, and blood flow.
and receptor binding. Given that sleep is regulated by the brain and may ultimately serve brain function, these tools may provide important information regarding abnormal brain function in sleep disorders patients in a manner not accessible to traditional polysomnographic assessment. If so, such assessments may serve an important function in the evaluation and management of sleep disorders patients and in the development of new pharmacologic agents to treat sleep disorder patients.

This chapter will briefly review the functional neuroanatomy of healthy sleep, then turn its attention to the use of functional neuroimaging in the assessment and management of sleep disorders. Up to this point, most studies have addressed normative processes, while early efforts in sleep disorders have focused on pathological mechanisms. In reviewing this work, effort will be applied to potential applications in the evaluation and management of sleep disorders patients in a manner to guide the field in future research development in this area.

Healthy sleep neurophysiology

Prior to conducting functional neuroimaging studies of sleep, it is important to ground the development of hypotheses and the interpretation of results on the basic neuronal mechanisms regulating the sleep/wake cycle. This is important as the spatial and temporal resolution of current imaging modalities provide limited information on function in small structures that are known to be important in the regulation of sleep/wake rhythms. The basic mechanisms of sleep/wake regulation in preclinical models have been described elsewhere.1–29

Functional neuroimaging studies of healthy human sleep

Functional neuroimaging studies have revealed reliable broad changes in cerebral activity across the sleep/wake cycle. Globally, brain activity decreases from waking to NREM sleep, then increases to waking levels again during REM sleep.30–46 Preclinical studies support a deafferentation of the cortex at the level of the thalamus and the occurrence of intrinsic thalamocortical electrical oscillations in NREM sleep. Studies across several laboratories and using various imaging methods have demonstrated that between waking and NREM sleep there are relative regional reductions in activity in heteromodal association cortex in the frontal, parietal and temporal lobes as well as in the thalamus (Fig. 1). This suggests that the thalamocortical circuits that play an important role in NREM sleep function are those involving regions that support waking, conscious, goal directed behavior. Preclinical work shows that REM sleep is associated with an electrophysiologically active cortex, with selective activation of cholinergic networks that originate in the brainstem and basal forebrain and that densely innervate limbic and paralimbic cortex. Consistent with this, in relation to waking and NREM sleep, REM sleep is associated with increased relative activity in the pontine reticular formation, as well as limbic (e.g. amygdala and hypothalamus) and paralimbic cortex (e.g. ventral striatum, anterior cingulate and medial prefrontal cortex) (Fig. 2). This suggests that REM sleep may play an important role in emotional behavior, given the important involvement of these structures in the regulation of affect and in motivated behavior.

Sleep deprivation and daytime alertness

Sleep deprivation is a common consequence of a variety of sleep disorders. In the insomnias, including those related to other mental and
physical disorders, inefficient sleep results in sleep deprivation. Sleep deprivation is also a consequence of sleep apnea syndrome and periodic limb movement disorder (PLMD). Across these disorders, sleep is not providing a restorative function. The impact of sleep deprivation on brain function during waking may be common across multiple sleep disorders. It is important, therefore, to understand the effects of experimentally produced sleep deprivation on waking brain function. Wu et al. assessed regional cerebral metabolism using the $^{[18F]}$ fluorodeoxyglucose ($^{[18F]}$FDG) method in healthy subjects before and after 32 h of sleep deprivation. They noted prominent decreases in metabolism in the thalamus, basal ganglia, temporal lobes, and cerebellum with increases in visual cortex. Whole brain absolute metabolic rate was not different. Thomas et al. described the effects of 24, 48 and 72 h of sleep deprivation on waking regional cerebral metabolism assessed via $^{[18F]}$FDG positron emission tomography (PET), as well as alertness and cognitive performance (Fig. 3). Sleep deprivation was associated with global declines in absolute cerebral metabolism. Regionally, these declines were most notable in frontoparietal cortex and in the thalamus. This is consistent with studies showing that the effects of sleep deprivation on slow wave sleep are
greatest in frontal EEG leads (Fig. 4). Alertness and cognitive performance on a sleep-deprivation sensitive serial addition/subtraction test declined in association with the sleep-deprivation associated regional deactivations. Paus et al.37,50–52 have demonstrated that blood flow in the thalamus and ponto-mesencephalic tegmentum as assessed by \([^{15}\text{O}]\text{H}_2\text{O PET}\) positively correlates with arousal associated with sleep, 37 with performance on vigilance tasks 50 and with loss of consciousness associated with anesthesia. 52 In some instances, this arousal network also included the basal forebrain and anterior cingulate cortex.50 Anesthesia produces declines in alertness to the point of unconsciousness. Alkire et al. 53 assessed functional brain activity in 11 healthy subjects undergoing general anesthesia. They found specific suppression of regional thalamic and midbrain reticular formation activity across two different commonly used volatile agents. In light of other findings in sleep, they suggest that the essential common neurophysiologic mechanism underlying anesthetic-induced unconsciousness is, as with sleep-induced unconsciousness, a hyperpolarization block of thalamocortical neurons. These findings support the role for sleep in restoration of brain function in thalamocortical networks associated with higher order cognition. In terms of sleep disorders, the severity of a sleep disorder on waking brain function may be measured by the degree to which there is a reduction in activity in the thalamus and frontoparietal cortex. Treatment response in sleep disorders may be measured by the ability of an intervention to reverse these alterations in thalamocortical function.

Sleep disorders: pathophysiology

A core principle in medicine is the identification of the causes of illness. In sleep medicine, many of the presumed causes of sleep disorders, such as narcolepsy or insomnia, are thought to reside in the central nervous system. In other sleep disorders, such as sleep apnea syndrome, many of the effects of the disorder, such as sleep disruption leading to sleep deprivation, occur in the central nervous system. The pathophysiology and effects, therefore, of sleep disorders may be clarified by an increased understanding of the brain mechanisms of the disorders. Functional neuroimaging studies may aid in this pursuit. To date, most functional neuroimaging studies in sleep disorder patients have served this overall goal. In general, very limited information is available for most sleep disorders. This represents a major area for future research in sleep disorders medicine.54

Obstructive sleep apnea syndrome

OSA syndrome is characterized by repetitive cessations or reductions in air movement during sleep. OSA has received increased recognition in the past decade owing to its high prevalence and to its recognized adverse health outcomes. 55–62 Early concerns regarding the impact of OSA on health were related to its impact on cardiovascular and cerebrovascular health. There is increasing recognition, however, that its impact on brain function accounts for considerable mortality and morbidity, including motor vehicle accidents, psychosocial dysfunction, and lost productivity.63–69 Despite this increased awareness, comparatively little effort has been devoted to understanding the effects of OSA on brain function or its potential reversibility with therapy. OSA leads to sleep fragmentation and episodic systemic arterial oxyhemoglobin desaturations. Recent integrative models suggest that these disturbances preferentially lead to dysfunction in the prefrontal cortex, a region of the brain that controls various executive functions.70 This may account for problems with behavioral inhibition, 71 set-shifting, 63,71,72 self-regulation of affect and arousal, 73 working memory, 71,72,74 analysis/synthesis, 53,71,74 and contextual memory. 75 These OSA-induced executive function deficits cannot be accounted for by sleepiness itself, 63 do not all reverse following treatment, 71,76–78 and may represent neuronal damage.

The neurobehavioral consequences of OSA may be related to a disruption in the usual NREM sleep-related restoration of prefrontal cortex function. Sleep in general, and slow wave sleep, in particular, have been hypothesized to play a role in brain
Several observations suggest that the NREM sleep-related brain restoration preferentially involves the prefrontal cortex. Topographic EEG sleep studies show that slow wave sleep is greatest in frontal EEG leads. Sleep deprivation results in an increase in slow wave sleep that is greatest in frontal EEG leads. Cognitive deficits resulting from sleep deprivation are in domains thought to involve the prefrontal cortex. Studies of the metabolic and cognitive consequences of sleep deprivation support a role for sleep in restoration of function in the prefrontal cortex. OSA is associated with a loss of slow wave sleep in addition to the behavioral deficits reflecting altered prefrontal cortex function.

Given this context, functional neuroimaging studies of sleep apnea lag far behind other studies of the pathophysiology of this disorder. Ficker et al. assessed cerebral blood flow in OSA patients using HMPAO single photon emission computerised tomography (SPET). They reported frontal hyperperfusion by visual inspection. Statistically, they showed parietal hypoperfusion. Both these changes reversed following effective nasal continuous positive airway pressure (nCPAP) therapy. These findings require replication and extension using larger sample sizes and more advanced methods.

Narcolepsy

Recent advances have linked narcolepsy with altered function in the hypocretin system, a peptide produced in the posterior lateral hypothalamus that has activating properties and is functionally related to all known arousal systems in the central nervous system. The role of functional neuroimaging studies in human narcoleptic patients is in further clarifying the mechanisms of the extra-hypothalamic manifestations of the illness, such as cataplexy, sleep attacks, and hypnagogic hallucinations. Few studies have been conducted to date. Hublin et al. performed 123I-iodobenzamide SPECT studies in narcoleptic patients and Parkinsonian controls. They found no differences in striatal/frontal D2 occupancy ratios between these two groups. Asenbaum et al. assessed blood flow during waking and sleep onset REM periods in six narcoleptic patients using the HMPAO SPECT method. They found evidence for right hemispheric increased flow and thalamic decreased flow in REM sleep. Given the small sample sizes, they suggested that a replication of the findings was needed. Sudo et al. assessed muscarinic cholinergic receptors in narcoleptic subjects using [11C]N-methyl-4-piperidylbenzilate ([11C]NMPB) both before and after pharmacotherapy. No differences were observed between patients and healthy subjects at baseline and minimal treatment effects were observed. This complex of findings using a variety of different nuclear medicine techniques do not yet provide any consistent model of alterations in regional cerebral function in this sleep disorder. Additional studies are needed.

Recurrent hypersomnia

Nose et al. report the results of SPECT scans obtained on a single patient with recurrent hypersomnia both during a period of hypersomnia and during insomnia which followed. They report that the hypersomnolent period was associated with decreased blood flow in the thalamus. They propose that this alteration in thalamic function may be pathophysiologically linked with hypersomnia. This single case report requires replication in larger sample sizes and with a control comparison.

Primary insomnia

Three neuroimaging studies have been reported that help to clarify the functional neuroanatomy of insomnia. Smith et al. assessed cerebral blood flow during NREM sleep using Tc-99m-HMPAO SPECT in five insomniacs and four healthy controls. The primary finding of their study was that insomniacs had lower overall blood flow in NREM sleep in relation to healthy controls. Regionally, this was noted to be greater in the basal ganglia. Nofzinger et al. used [18F]-FDG PET to define regional cerebral correlates of arousal in NREM sleep in nine healthy and 12 depressed patients. They assessed EEG power in the beta high frequency spectrum as a measure of cortical arousal. They then correlated beta power with metabolism in NREM sleep. They found that beta power negatively correlated with sleep quality. Further, beta power positively correlated with ventromedial prefrontal cortex metabolism in both a group of depressed and healthy groups. They concluded that elevated function in the ventromedial prefrontal cortex, an area associated with obsessive behavior and anatomically linked with brainstem and hypothalamic arousal centers, may contribute to dysfunctional arousal.
Nofzinger et al. investigated the neurobiological basis of poor sleep and daytime fatigue in insomnia (Fig. 5). Insomnia patients and healthy subjects completed regional cerebral glucose metabolic assessments during both waking and NREM sleep using $[^{18}F]$fluoro-2-deoxy-D-glucose positron emission tomography (PET). Healthy subjects reported better sleep quality than did insomnia subjects. Insomnia subjects scored worse on measures of daytime concentration and fatigue. The two groups did not differ on any measure of visually scored or automated measure of sleep. Insomnia patients showed increased global cerebral glucose metabolism during sleep and wakefulness. A group × state interaction analysis confirmed that insomnia subjects showed a smaller decrease than did healthy subjects in relative metabolism from waking to NREM sleep in the ascending reticular activating system, hypothalamus, thalamus, insular cortex, amygdala and hippocampus and in the anterior cingulate and medial prefrontal cortices. While awake, in relation to healthy subjects, insomnia subjects showed relative hypometabolism in a broad region of the frontal cortex bilaterally, left hemispheric superior temporal, parietal and occipital cortices, the thalamus, hypothalamus and brainstem reticular formation (Fig. 6).

This study demonstrated that subjectively disturbed sleep in insomnia patients is associated with increased brain metabolism. Their inability to fall asleep may be related to a failure of arousal mechanisms to decline in activity from waking to sleep. Further, their daytime fatigue may reflect decreased activity in prefrontal cortex that results from inefficient sleep. These findings suggest interacting neural networks in the neurobiology of insomnia. These include a general arousal system (ascending reticular formation and hypothalamus), an emotion regulating system (hippocampus, amygdala and anterior cingulate cortex), and a cognitive system (prefrontal cortex). Future studies are needed to determine how these neural systems can be differentially affected by the diverse causes of insomnia. Future work is also needed to determine the impact of interventions on altering function in these networks in order to (1) alleviate the sleep complaints of insomnia sufferers; (2) alter the clinical course of insomnia; and (3) potentially reduce future adverse consequences of insomnia.

**Figure 5** This figure shows brain structures where the decline in relative metabolism from waking to NREM sleep is less in insomnia patients than in healthy subjects. The general pattern includes structures involved in promoting arousal (Reprinted from reference 99).

**Figure 6** This figure shows brain structures where relative metabolism during waking is less in insomnia patients than in healthy subjects. The general pattern includes bilateral prefrontal cortex (Reprinted from reference 99).
Fatal familial insomnia

Perani et al.\textsuperscript{100} assessed cerebral metabolism in four patients with fatal familial insomnia, a prion disease with a mutation at codon 178 of the prion protein gene. Thalamic hypometabolism was found in all cases and more widespread non-specific cortical hypometabolism was noted in others. They suggest that the thalamic dysfunction is consistent with the neuropathologic findings in the disorder and is a hallmark of the disease. Kloppel et al.\textsuperscript{101} report the results of a $[^{123}I]$ beta-CIT SPECT study in two cases of fatal familial insomnia. They showed a 57 and 73% reduced availability of serotonin transporters in a thalamus/hypothalamus region in the two patients in relation to age-expected control values. While the interpretation is not entirely clear, they suggest that this may reflect altered serotonergic function in regions of the brain thought to be important in sleep/wake regulation in this patient group.

Depression

The majority of patients with mood disorders describe difficulty in falling asleep, difficulty in staying asleep, and difficulty in returning to sleep after early morning awakenings. Clinically, they report a paradoxical state of physical daytime fatigue, yet with persistent mental activity that makes it difficult for them to fall asleep at night. EEG sleep changes include increases in sleep latency and decreases in sleep continuity. Depressed patients often show reduced stages 3 and 4 NREM sleep. They also show an increase in the amount of REM sleep, a shortening of the time to onset of the first REM period of the night, a shortened REM latency, and an increase in the frequency of eye movements within a rapid eye movement period.

REM sleep in depression

Given that REM sleep activates limbic and anterior paralimbic cortex in healthy subjects, the increased REM sleep in depressed patients may reflect a greater re-activation of these structures in REM sleep. Three reports to date have addressed this question. A preliminary analysis of $[^{18}F]$FDG PET studies in six depressed patients\textsuperscript{102} showed that depressed subjects showed greater increases from waking to REM sleep in relative metabolism in the tectal area and a series of left hemispheric areas including sensorimotor cortex, inferior temporal cortex, uncal gyrus-amygdala, and subicular complex. Many of these structures are primary brainstem and limbic regions that are important in modulating emotional arousal. This pattern of wake-REM increases suggested that the increases in REM sleep in depressed patients may signal an increase in affective responsivity in depressed patients. In this preliminary report, in contrast to hypotheses, depressed patients did not show increases in relative metabolism in anterior paralimbic structures during REM sleep compared to waking. Subsequent analyses, however,\textsuperscript{103} suggested that the lack of increase from waking to REM sleep in depressed patients may have been related to a ceiling effect, i.e. hypermetabolism in these structures during waking that could not be further increased in REM sleep.

Nofzinger et al.\textsuperscript{104} completed a larger confirmatory analysis that included 24 depressed patients and 14 healthy subjects (Fig. 7). They received EEG sleep studies and regional cerebral glucose metabolism (rCMRglu) assessments during both waking and REM sleep using $[^{18}F]$-FDG. Depressed patients showed greater REM sleep percent. Consistent with the hypothesis that depressed patients would show increased activation in limbic and anterior limbic structures from waking to REM, depressed patients showed greater increases in relative metabolism from waking to REM sleep than healthy subjects in the midbrain reticular formation including the pre-tectal area and in a larger region of anterior paralimbic cortex. Additionally, depressed patients showed greater increases in relative metabolism from waking to REM sleep than healthy subjects in a broadly distributed region of predominantly left hemispheric dorsolateral prefrontal, parietal and temporal cortex. This area included the dorsolateral prefrontal cortex, and the frontal and parietal eye fields (FEF, PEF).

Figure 7 This figure shows brain structures where the increase in relative metabolism from waking to REM sleep is greater in depressed patients than in healthy subjects. Note that this includes a region of the brainstem implicated in the generation of REM sleep (Reprinted from reference 104).
The first primary finding in this study was the increased activation of the brainstem reticular formation from waking to REM sleep in depressed patients. This is consistent with the model of an altered balance in brainstem monoaminergic (norepinephrine and serotonin) systems and brainstem acetylcholine neuronal systems in depressed patients as proposed by McCarley.  

A second primary finding in this study was the increased activation of limbic and anterior paralimbic (hippocampus, basal forebrain/ventral pallidum, anterior cingulate and medial prefrontal) cortex from waking to REM sleep in depressed patients. The highest density of cholinergic axons is in core limbic structures such as the hippocampus and amygdala. Limbic and anterior paralimbic cortices also have high densities of inhibitory 5-HT1A post-synaptic receptors in relation to other areas of cortex. Behaviorally, increased activation of limbic and paralimbic cortex in depressed patients may reflect a susceptibility of depressed patients to experience stimuli in a more affectively intense, negative context, given the increased activation of these structures in response to negatively valenced stimuli or increased affective states. A third primary finding in this study is the relatively greater activation of executive cortex from waking to REM sleep in depressed patients. This may reflect a change in modulation of cortical function from monoaminergic during waking to cholinergic in REM sleep, coupled with a monoaminergic/cholinergic imbalance in depressed patients. Behaviorally, this may also reflect a greater involvement of executive function during REM sleep in depressed patients, perhaps in response to the increased affective state produced by the abnormal re-activation of limbic and paralimbic cortex during REM sleep in depressed patients.

NREM sleep in depression

As reviewed above, depressed patients tend to have increased sleep continuity disturbances and reductions in deeper, more restorative aspects of NREM sleep. Several reports to date have assessed regional brain function during NREM sleep in depressed patients to further clarify the neurobiology of these changes in NREM sleep. Ho et al. assessed cerebral metabolism using the [¹⁸F]-FDG PET method in depressed and healthy men during the first NREM period and found increased whole brain metabolism during NREM sleep in the depressed subjects. Regionally, these increases were most noticeable in the posterior cingulate, the amygdala, hippocampus, occipital and temporal cortex and thepons. Relative hypofrontality was noted in the patients as well as reduced relative metabolism in the anterior cingulate, caudate, and medial thalamus in relation to the controls. On the basis of the increased overall brain metabolism, they interpreted these findings to suggest that depressed patients have 'hyperarousal' during NREM sleep.

Several lines of evidence suggest that the restorative aspect of sleep is related to slow wave NREM sleep and that this aspect of sleep has some regional preference for more frontal regions of cortex. NREM sleep is associated with decreases in frontal, parietal, and temporal cortex metabolic activity compared to wakefulness. Depressed patients demonstrate 'lighter' NREM sleep and waking hypofrontality. Therefore, Germain et al. tested the hypothesis that depressed patients would show less of a decrease in frontal metabolism between waking and NREM sleep. They assessed 12 medication-free depressed patients and 13 healthy subjects using [¹⁸F]-fluoro-2-deoxy-D-glucose ([¹⁸F]-FDG) positron emission tomography (PET) scans during presleep wakefulness and during NREM sleep. Compared to healthy subjects, depressed patients showed less of a decrease in relative metabolism from presleep wakefulness to NREM bilaterally in the laterodorsal frontal gyri, right medial prefrontal cortex, right superior and middle temporal gyri and insula, as well as right posterior cingulate cortex, lingual gyrus, striate cortex, cerebellar vermis, and left thalamus. These findings suggest that abnormal thalamocortical network function may underlie non-restorative sleep in depressed patients.

Sleep deprivation in depression

The notion of hyperarousal in paralimbic structures in depressed patients has received further support from an extensive literature describing the functional neuroanatomical correlates of the antidepressant response to sleep deprivation in depressed patients. These studies identify the anterior cingulate cortex as playing an important role in the response to sleep deprivation. Across studies, there is a general tendency for patients who have elevated baseline metabolism in the anterior cingulate cortex to have more favorable responses to sleep deprivation, and normalization
of this increased function following sleep deprivation.\textsuperscript{97,108-113}

**Schizophrenia**

Patients with schizophrenia are known to have severely disturbed subjective sleep. EEG sleep studies have largely supported alterations in NREM slow wave sleep in schizophrenic patients. Slow wave sleep is of particular interest to schizophrenia because of the implication of the prefrontal cortex in this disorder\textsuperscript{114} and in generation of slow wave sleep (SWS).\textsuperscript{115} Only one functional neuroimaging study has explored the relationship between some aspect of sleep and the pathophysiology of schizophrenia. Weller et al.\textsuperscript{116} compared cerebral metabolism between 49 awake schizophrenic patients, 30 awake controls and 12 controls in REM sleep. The aim of the study was to determine if regional metabolism while awake in a psychotic disorder resembled healthy REM sleep, given some phenomenological similarities between the cognitions reported in dreaming and those in psychosis. No similarities were observed discounting the notion that schizophrenia represents an intrusion of REM sleep cognition into wakefulness. More functional neuroimaging studies of sleep in schizophrenia are needed.

**Restless legs syndrome (RLS)/periodic limb movement disorders (PLMD) of sleep**

RLS and PLMD are effectively treated with dopaminergic agents. This suggests a central dopaminergic dysfunction contributes to the pathophysiology of these disorders. In a series of studies,\textsuperscript{117-119} measured central dopamine D2-receptor occupancy with $^{[123]}$I-labeled (S1)-2-hydroxy-3-iodo-6-methoxy-(1-ethyl-2-pyrollidinyl)methyl benzamide (IBZM) and single photon emission tomography in patients with PLMD. They found lower striatal $^{[123]}$IBZM binding in patients with PLMD and higher binding following dopaminergic therapy. Michaud et al.\textsuperscript{120} report the results of pre- and post-synaptic dopaminergic status using $^{[123]}$I-beta-CIT and $^{[123]}$IBZM SPECT, respectively, in five patients with RLS, 7 age, sex-matched controls, 14 Parkinson’s patients. They found decreased DA transporter binding in RBD in relation to controls, although not as severe as in Parkinson’s patients, and no change in striatal D2-receptor binding in RBD. They suggest that this supports a central striatal dopamine transporter abnormality in the pathophysiology of RBD. Albin et al.\textsuperscript{124} assessed $^{[11]}$C-dihydrotetrabenzazene (DTBZ) PET in six patients with RBD and in 19 age, sex-matched controls. They found decreased DTBZ binding in RBD in relation to controls. This study supports a loss of dopaminergic midbrain neurons in chronic RBD, however it remains unclear whether this is primary or a secondary effect of the pontine abnormality in RBD.

**Sleepwalking**

Only one nuclear medicine study has studied regional brain function associated with sleepwalking. Bassetti et al.\textsuperscript{121} performed 99mTc ECD SPECT studies during stages 3 and 4 sleep one night before, and one night during a sleepwalking episode. They reported increased blood flow in the cerebellar vermis and the posterior cingulate cortex during sleepwalking. In relation to healthy wakefulness, the sleepwalking episode was associated with a decline in frontoparietal association cortices as would be typical of NREM sleep, albeit in the absence of declines in thalamic blood flow. They interpret the results to reflect both unconsciousness, as reflected by a loss of frontoparietal function, and a persistence of motor generators, as reflected by preserved thalamocingulate circuits, in sleepwalking behavior.

**REM sleep behavior disorder**

Shirakawa et al.\textsuperscript{122} reported the results of a $^{[123]}$I IMP SPECT study of 20 patients with REM sleep behavior disorder in comparison with seven healthy controls. They reported decreased blood flow in the upper frontal lobe and pons. They suggest that these findings may be associated with the pathogenesis of RBD, especially the decreased blood flow in the pons as this has theoretically thought to play a role in RBD. Eisensehr et al.\textsuperscript{123} studied pre- and post-synaptic dopaminergic status using $^{[123]}$I-IPT and $^{[123]}$IBZM SPECT, respectively, in five patients with RBD, 7 age, sex-matched controls, 14 Parkinson’s patients. They found decreased DA transporter binding in RBD in relation to controls, although not as severe as in Parkinson’s patients, and no change in striatal D2-receptor binding in RBD. They suggest that this supports a central striatal dopamine transporter abnormality in the pathophysiology of RBD. Albin et al.\textsuperscript{124} assessed $^{[11]}$C-dihydrotetrabenzazene (DTBZ) PET in six patients with RBD and in 19 age, sex-matched controls. They found decreased DTBZ binding in RBD in relation to controls. This study supports a loss of dopaminergic midbrain neurons in chronic RBD, however it remains unclear whether this is primary or a secondary effect of the pontine abnormality in RBD.

**Sleep disorders: differential diagnosis**

Functional neuroimaging studies are showing great promise in helping to diagnose and manage a variety
of disorders that affect the central nervous system including Alzheimer’s Disease, movement disorders, cerebrovascular disease, brain tumors, and epilepsy. The above studies in sleep disorders begin to support alterations in functional neuroimaging studies in a variety of sleep disorders. At this point, they suggest that these methods show promise in helping to clarify the pathophysiology of distinct sleep disorders. Considerably more research needs to be conducted in these areas.

Beyond pathophysiology, the next question is whether functional neuroimaging studies can be used in the clinical assessment or management of sleep disorders patients. Even more work remains to be done before any conclusions can be made in this area, although several sleep disorders appear worthwhile pursuing in this context. The insomnias would appear to be one area where functional neuroimaging studies may aid in differential diagnosis. At this point, models of insomnia rely heavily on behavioral theories of insomnia (e.g. Drummond et al.; Nofzinger) with very unclear models of the neurobiological basis of this sleep disorder. Defining the pathophysiology of insomnia is currently troubled by the inclusion of a variety of pathologies that may result in insomnia as a final common complaint. These include the primary insomnias, acute, transient and chronic insomnias, and insomnias secondary to various mental and physical disorders. The pathophysiology of the various mental and physical disorders, themselves, can clearly be distinguished. The pathways leading from the pathology of the disorders to the pathology of the sleep disruptions that occur as part of the disorders are not known. Functional neuroimaging studies may help to distinguish one type of insomnia vs. another based on the underlying causes of the insomnia complaints in affected individuals.

Sleep disorders: pharmacotherapy

Management of several sleep disorders is improved with pharmacologic interventions. Examples include PLMDs, narcolepsy, and the insomnias. Functional neuroimaging studies may provide important information regarding pharmacotherapy in several realms: drug development, assessment of mechanism of action of therapeutic compounds and assessment of treatment response/non-response to pharmacologic agents.

A variety of compounds have been discovered with mechanisms of actions that may affect sleep/wake regulation. Testing in preclinical models suggest that these compounds may have novel mechanisms of action, however, the degree to which these mechanisms will translate into a clinical application are often unknown. Functional neuroimaging studies may identify the degree to which these compounds have beneficial mechanisms of action on brain structures that are known to regulate behavioral states in humans. One way of achieving this goal is to administer the compound to human subjects, then assess a functional neuroanatomic response to the compound within sleep in humans, such as a blood flow or metabolic response. Further, these studies may help to determine the optimum dose of the compound in humans that maximizes beneficial effects of the compound, yet does not lead to adverse effects. The use of receptor ligands may clarify whether one compound has a unique mechanism of action on a specific receptor subtype that may not be shared by other compounds in its class and may therefore hold a therapeutic advantage over other agents. Finally, once a compound has been identified and shown to have effects in the central nervous system in humans, functional neuroimaging studies can then be used to determine the degree to which the compound reverses distinct alterations in neural function in a clinical population. The review below reveals some of the early studies in these areas.

Receptor ligand studies

Nuclear medicine has developed methods to label central nervous system (CNS) active compounds, then define their presence in the brain via imaging the radiation emitted by the radiopharmaceutical via positron emission tomography or SPECT. Such studies can be used to determine if there are alterations in receptor distributions or densities of receptors in distinct sleep disorders. Such studies can also be used to determine the specific receptor types where pharmacologically active compounds are having their mechanism of action.

Cholinergic and dopamine receptor density and distributions have been studied in narcolepsy and sleep-related movement disorders. Sudo et al. assessed muscarinic cholinergic receptors in narcoleptic subjects using [11C]N-methyl-4-piperidylbenzilate ([11C]NMPB) both before and after pharmacotherapy. No differences were observed between patients and healthy subjects at baseline and minimal treatment effects were observed. While these findings are largely negative in this disorder, future studies could explore cholinergic function in other sleep disorders in
which alterations in REM sleep have been shown, such as depression. Several studies assessed dopaminergic function in PLMD, RLS and REM sleep behavior disorder, given the putative role of dopaminergic dysfunction in these disorders. These have been reviewed above in the sections on sleep disorders.

Several studies have assessed changes in receptor-binding following administration of pharmacologically active agents. Tashiro et al.\textsuperscript{132} report the effects of antihistamine medications on histamine H1 receptor binding in the human brain using \([11C]\)-doxepin PET. They report that fexofenadine, an antihistamine with little sedation, manifested no significant cerebral H1 receptor occupancy, while cetirizine, a second generation antihistamine with moderate sedation, occupied 20–50% of cerebral H1 receptors. They propose that measurement of H1 receptor occupancy is a sensitive tool for assessing the potential CNS sedative side effects of antihistamine agents. Okamura et al.\textsuperscript{133} assessed regional changes in histamine H1 occupancy and blood flow associated with antihistamine associated cognitive decline. They found blockade of H1R in frontal, temporal and anterior cingulate cortices following \(d\)-chlorpheniramine administration. They suggest that attention systems of the brain may be altered by antihistamines.

**Regional cerebral responses to sleep-related pharmacological probes**

Functional neuroimaging studies can assess changes in blood flow and metabolism as correlates of overall cerebral function in response to a variety of medications that affect the sleep/wake cycle. Reinsel et al.\textsuperscript{134} studied the effects of a sedating short acting benzodiazepine, midazolam, on regional cerebral blood flow using \([15O]\) H2O. They found dose-dependent reductions in left dorsolateral prefrontal cortex, bilateral orbital-frontal cortex, the left middle temporal gyrus and the right hippocampus. They suggest that the prefrontal reductions in blood flow may underlie some of the anterograde amnesia effects of midazolam. Two studies have assessed the effects of the sedative-hypnotic zolpidem on NREM and REM sleep-related relative cerebral blood flow \([15O]\) H2O-PET in relation to a placebo. They reported that across all sleep periods, there was decreased flow in the basal ganglia and insula after treatment with zolpidem. Volkow et al.\textsuperscript{137} assessed the effects of the benzodiazepine, lorazepam, on regional cerebral glucose metabolism using \([18F]\)FDG PET. They found marked reductions in thalamic metabolism and these reductions correlated with sleepiness. They suggested that the marked changes in the thalamus may account for the sedative properties of this medication.

Recently, Kajimura et al.\textsuperscript{138} assessed regional cerebral blood flow during NREM sleep in response to triazolam, a short acting benzodiazepine sedative-hypnotic. They found that blood flow in the basal forebrain and amygdaloid complexes was lower during NREM sleep following triazolam administration than following placebo. They suggest that the hypnotic effects of benzodiazepines may be mediated by deactivation of the basal forebrain and amygdaloid arousal systems.

Only one study has reported on the effects of antidepressant medications on regional cerebral function during sleep. Nofzinger et al.\textsuperscript{98} measured regional cerebral glucose metabolism using \([18F]\)FDG PET during waking and REM sleep in nine depressed patients before and after treatment with bupropion SR. Based on prior research showing a blunted waking to REM sleep activation of anterior paralimbic cortex, they predicted that bupropion SR treatment would reverse this alteration given its effects on both noradrenergic and dopaminergic systems. They found a significant reversal of some anterior paralimbic deficits following treatment.

**Practice points**

- Neuroimaging studies have defined reliable changes in brain function across the states of waking, NREM and REM sleep.
- Neuroimaging studies can provide information on regional brain activity and receptor densities in relation to clinical sleep disorders.
- While early studies demonstrate the promise of these methods for clinical sleep medicine, significant work remains before these techniques can be applied in the routine assessment and management of sleep disorders patients.
Appendix A

Fundamentals of functional neuroimaging

Understanding the potential application of neuroimaging assessments to the field of sleep disorders medicine requires a general understanding of the various functional neuroimaging methods available. They differ in terms of the physiological process measured and in the practicalities of obtaining the measurements. While complete descriptions of these methods are beyond the scope of this review, brief descriptions of measures currently available are provided below.

Positron emission tomography (PET)

PET is the non-invasive dynamic measurement of the distribution in the body of compounds labeled with positron-emitting isotopes. Detectors in the PET cameras reveal the regions in the brain where the positrons were emitted and thereby define the area of the labeled compound. Common physiological processes measured with PET include glucose utilization ([18F]fluorodeoxyglucose), perfusion ([15O]H2O), and blood volume ([15O]CO). PET can also be used to determine the distribution of neurotransmitters across the brain by labeling transmitters with unstable positron-emitting isotopes.

Single-photon emission computerized tomography (SPECT)

SPECT produces images based on the detection of single gamma photons derived from the decay of radioactive isotope that has been injected into a subject. The rate of clearance of the probes was initially detected using an array of sodium iodide photon detectors placed around the head. More recent approaches have used a gamma camera that can be rapidly moved around the head to collect photons from many different angles, thus permitting a more accurate three-dimensional image. The spatial resolution of SPECT is inferior to PET especially in deeper brain structures, although it is much less expensive than PET and is more widely available.

Magnetic resonance imaging

BOLD-fMRI

Blood-Oxygen-Level-Dependent fMRI (BOLD-fMRI) is the most commonly used fMRI technique. BOLD-fMRI measures regional differences in oxygenated blood, which is thought to relate to variations in neuronal activity across brain regions. This method is good for measuring relatively rapid changes in brain activity in which there is a stable background of blood flow across the study. It is sensitive to movement artifacts and there are some regions of the brain that are more difficult to study due to artifacts from surrounding tissues. This method only provides information on relative changes in blood flow between conditions. Blood-oxygen-level-dependent fMRI potentially offers imaging with a temporal resolution on the order of 100 ms and a spatial resolution of 1-2 mm. Most fMRI techniques are non-invasive and allow for multiple repeated measures within a subject.

Perfusion fMRI

Perfusion fMRI measures absolute regional cerebral blood flow. Arterial spin-labeling is a T1-weighted non-invasive technique where intrinsic hydrogen atoms in arterial water outside of the slice of interest are magnetically tagged (‘flipped’) as they course through the blood. Then they are imaged as they enter the slice of interest. This method is limited in that it takes several minutes to acquired information on slices of brain such that within subject analyses are difficult.

Diffusion-weighted fMRI

Diffusion-weighted fMRI measures random movement of water molecules. In the while matter of the brain, water diffusion is highly directional along the long axis of fibre tracts. Application of large magnetic field gradients during MR imaging, allows the determination of the diffusion of water, hence the direction of flow of information in these tracts throughout the brain. The importance of this method is to help define functional connectivity between different regions of the brain.

Research agenda

Research needs to be conducted in order to determine if neuroimaging methods can be helpful in sleep disorders medicine in the following areas:

- clarification of pathophysiology;
- aid in differential diagnosis;
- assessment of treatment response;
- guiding new drug development; and
- monitoring treatment response.

E.A. Nofzinger
MRI spectroscopy

MRI spectroscopy measures certain cerebral metabolites. This is complex method of analysis in which a spectrum is based on quantitative spin values, and magnetic coupling of nearby magnetically unpaired nuclei. It can be used to detect differences in the compositions of certain metabolites in different brains.

References


* The most important references are denoted by an asterisk.


Neuroimaging and sleep medicine


