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Chapter XVI

Neuroimaging Insights into Insomnia

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Abstract

Insomnia is a frequent symptom or syndrome defined by complaints of trouble in initiating or maintaining sleep or of nonrestorative sleep. This causes significant impairments in several areas of daytime functioning including mood, motivation, attention and vigilance.

Significant advances in our neurobiological knowledge of insomnia have been brought by electrophysiological data (e.g. electroencephalography (EEG) and by functional neuroimaging data (e.g. single photon emission computed tomography (SPECT), positron emission tomography (PET) acquired during wakefulness, transition from waking to non rapid-eye-movement (NREM) sleep and REM sleep itself.

Indeed it has been shown that idiopathic insomnia is characterized by a specific pattern of regional brain activity: (i) during the transition from waking to NREM sleep: failure to decrease brain activity in the ascending reticular activating system, medial prefrontal cortex, limbic/paralimbic areas (including insular cortex, amygdala,

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hippocampus, anterior cingulate), thalamus and hypothalamus, (ii) during NREM sleep: deactivation of the parietal and occipital cortices, and basal ganglia, and (iii) during wakefulness: deactivation in brainstem reticular formation, thalamus, hypothalamus, prefrontal, left superior temporal, parietal and occipital cortices.

This specific distribution of brain activity might relate to (i) specific impairments in daytime functioning (e.g. hypoactivity in prefrontal cortex during wakefulness is consistent with reduced attentional abilities), (ii) hyperarousal hypothesis as a common pathway in the pathophysiology of insomnia (e.g. overall cortical hyperarousal characterized by an increase in EEG beta/gamma activity (14-35 / 35-45 Hz) at sleep onset and during NREM sleep) and (iii) the potentially overlapping pathophysiology with major depressive disorder as this illness has shown similarly altered cortical patterns (e.g. both illnesses have impairments in limbic/paralimbic areas as well as in basal ganglia).

The goal of this chapter is to show that combining recent neurophysiological and neuroimaging data on human sleep offers new insights into the pathophysiological mechanisms of insomnia and potentially opens new therapeutic perspectives.

Keywords: insomnia, sleep, REM, NREM, functional neuroimaging, cognitive neuroscience, hyperarousal, major depressive disorder, brain.

1. Introduction

In healthy humans, functional and structural neuroimaging has been successfully used to characterize normal stage and pathological conditions of sleep, as reviewed elsewere (Dang-Vu, Desseilles et al. 2007; Desseilles, Dang-Vu et al. 2008). Here we focus on the brain imaging studies devoted to insomnia.

Insomnia is characterized by complaints of repeated difficulty in initiating or maintaining sleep or of nonrestorative sleep, which cause clinically significant distress or impairment in cognitive, social, and occupational, or other important areas of functioning (Cortoos, Verstraeten et al. 2006). Insomnia therefore presents with subjective symptoms. Insomnia can arise directly from sleep/wake regulatory dysfunction or indirectly from comorbid behavioral, psychiatric, neurological, immune, or endocrine disorders, including disturbances secondary to the use of drugs. In this respect, insomnia appears to be a 24-h disorder because it is not restricted to sleep complaints alone but can affect several aspects of daytime functioning as well. Importantly, insomnia is a common disorder in our society, with 10% to 20% of the general population reporting insomnia complaints and related impairment of daytime functioning (Ohayon 2002). We should note that prevalence of insomnia increases with several factors such as: age (increase in older), gender (more frequent in women), occupational status (increase in people undergoing particular private or professional pressure), and medical condition (substance users, neurological or psychiatric comorbid condition). Insomnia can be either acute or chronic and either idiopathic or secondary to several conditions including physical disease or mental illnesses. Several manuals (American Psychiatric Association 1994; American Academy of Sleep Medicine 2005) propose a classification of different subtypes of insomnia but full description of these subtypes goes beyond the aim of our chapter.

The hyperarousal hypothesis of insomnia has gained growing attention as an integrative approach to the mechanism of insomnia (Perlis, Giles et al. 1997). This hypothesis presupposes interplay between psychological and physiological factors in the onset and maintenance of insomnia. It postulates that subjects who tend to focus cognitively on the insomnia and start to ruminate about their sleep complaint are prone to perpetuate the disorder, especially when it is associated to maladaptive behaviors such as prolongation of bedtime or daytime napping.

We will first review the structural and functional imaging findings in insomnia. Then we will describe successively the functional imaging of drug response, daytime functioning impairment and the hyperarousal hypothesis. Because depression is often associated with insomnia (Tsuno, Besset et al. 2005) we review hereafter the data pointing to some common underlying neurophysiological mechanisms for both sleep and mood regulation.

2. Structural and Functional Imaging in Insomnia

Structural imaging make possible to detect small differences in brain morphology associated with a particular condition. In particular, voxel-based morphometry (VBM) is based on high-resolution magnetic resonance imaging (MRI) scans and allows comparisons of grey and white matter across the brain and between groups. Proton magnetic resonance spectroscopy (1H-MRS) allows to assess the regional brain content in different compounds such as gamma-aminobutyric acid (GABA).

Only one study has assessed the structural anatomy of idiopathic (or primary) insomnia by using VBM (Riemann, Voderholzer et al. 2007). Riemann and collaborators used MRI (1.5 Tesla) in 8 unmedicated patients suffering from chronic idiopathic insomnia (3 males; mean age (standard deviation) of 48.4 (16.3) years) and 8 good sleepers matched for age, sex, body mass index, and education level. They found that patients have a significant reduction of hippocampal volumes bilaterally (see Figure 1), as compared to the good sleepers (Riemann, Voderholzer et al. 2007). Because of the size of the study sample, the results should be interpretated with caution. However, findings are congruent with the empirical data on (i) sleep-dependent encoding capacity of the hippocampus (Walker 2009) and (ii) impaired sleep-related memory consolidation in idiopathic insomnia (Nissen, Kloepfer et al. 2006).

The first study on neurochemical differences in patients with insomnia was recently conducted using 1H-MRS in 16 non-medicated individuals (8 women) with idiopathic insomnia (mean age (SD) = 37.3 (8.1) years) and 16 (7 women) normal sleepers (37.6 (4.5) years) (Winkelman, Buxton et al. 2008). Average brain GABA levels were nearly 30% lower in patients as compared to controls and were negatively correlated with wake after sleep onset (WASO). Since GABA is a major inhibitory neurotransmitter, this result may be consistent with the increase of brain glucose metabolism in several areas covered by this 1H-MRS study, such as the thalamus (Nofzinger, Buysse et al. 2004). Nevertheless an important methodological limitation of this study is the lack of anatomical specificity that limits further interpretations.

Several functional imaging techniques make possible to assess regional brain activity at rest, between two distinct conditions during a task or in association with any physiological

process. While single photon emission computed tomography (SPECT) and positron emission tomography (PET) show the distribution of radioisotope emitting single gamma photons or compounds labeled with positron-emitting isotopes, functional magnetic resonance imaging (fMRI) measures the variation in brain perfusion related to neural activity by using a method based on the assessment of the blood-oxygen-level-dependent (BOLD) signal. The latter reflects the relative decrease in deoxyhemoglobin concentration that follows the local increase in cerebral blood flow in an activated brain region.

To our knowledge, only a few studies have assessed the functional neuroanatomy of idiopathic insomnia disorder by recording brain activity during NREM sleep. Nofzinger et al. used 18fluorodeoxyglucose (18FDG) PET to measure regional brain metabolism (indexed by cerebral metabolic regional glucose consumption, CMRglu) in 7 patients with idiopathic insomnia and 20 healthy age-matched and gender-matched subjects during waking and NREM sleep (Nofzinger, Buysse et al. 2004). Insomnia patients showed a global CMRglu increase during the transition from waking to sleep onset as compared to healthy subjects, suggesting that there is an overall cortical hyperarousal in insomnia. Moreover, insomniac patients exhibited less reduction of relative CMRglu from waking to NREM sleep in the ascending reticular activating system, hypothalamus, insular cortex, amygdala, hippocampus, anterior cingulate, and medial prefrontal cortices, as illustrated in Figure 1. An increased metabolism was also observed in the thalamus, which might reflect persistent sensory processing and information processing as well as subsequent shallower sleep. In contrast, during wakefulness, decreased metabolism was found in subcortical (thalamus, hypothalamus, and brainstem reticular formation) as well as in cortical regions (prefrontal cortex bilaterally, left superior temporal, parietal, and occipital cortices). These findings suggest that insomnia might involve abnormally high regional brain activity during sleep, associated with reduced brain metabolism during waking. The observed reduction in prefrontal cortex activity during wakefulness is consistent with reduced attentional abilities and impaired cognitive flexibility resulting from inefficient sleep and is consistent with a chronic state of sleep deprivation (Thomas, Sing et al. 2000; Drummond and Brown 2001; Durmer and Dinges 2005).

Another early study by Smith et al. (Smith, Perlis et al. 2002), which compared 5 insomniacs with 4 normal sleepers using SPECT, found no significant regional increase during NREM sleep but reduced regional cerebral blood flow (rCBF) in frontal medial, occipital, and parietal cortices, as well as in the basal ganglia during this period (see Figure 1). Interestingly, in Nofzinger's study, decreases in activity in these same regions were also found in insomniacs, but during wakefulness. However, some methodological limitations in the Smith's study need to be considered. Firstly, the blood flow was only sampled during the first NREM cycle. Therefore, the observed decreased metabolism in insomniacs might reflect cortical hypoarousal during the initial phases of NREM sleep following sleep onset, while it remains possible that the patients were more aroused over later NREM sleep cycles, which would be more consistent with higher beta activity later at night (Perlis, Merica et al. 2001). Secondly, the blood flow was measured after a longer duration of NREM sleep in insomnia patients than in healthy subjects, leading to a possible underestimation of activity in the patients because blood flow decreases over long NREM periods. Because of such

methodological limitations, these preliminary results cannot rule out the hyperarousal hypothesis of idiopathic insomnia.

Four of the insomnia patients from the Smith's study were rescanned after they had been treated by cognitive behavioral therapy (which included sleep restriction and stimulus control (Smith, Perlis et al. 2005). After treatment, sleep latency was reduced by at least 43%, and there was a global 24% increase in CBF with significant increases in the basal ganglia. The authors proposed that such increase in brain activity might reflect the normalization of sleep homeostatic processes.

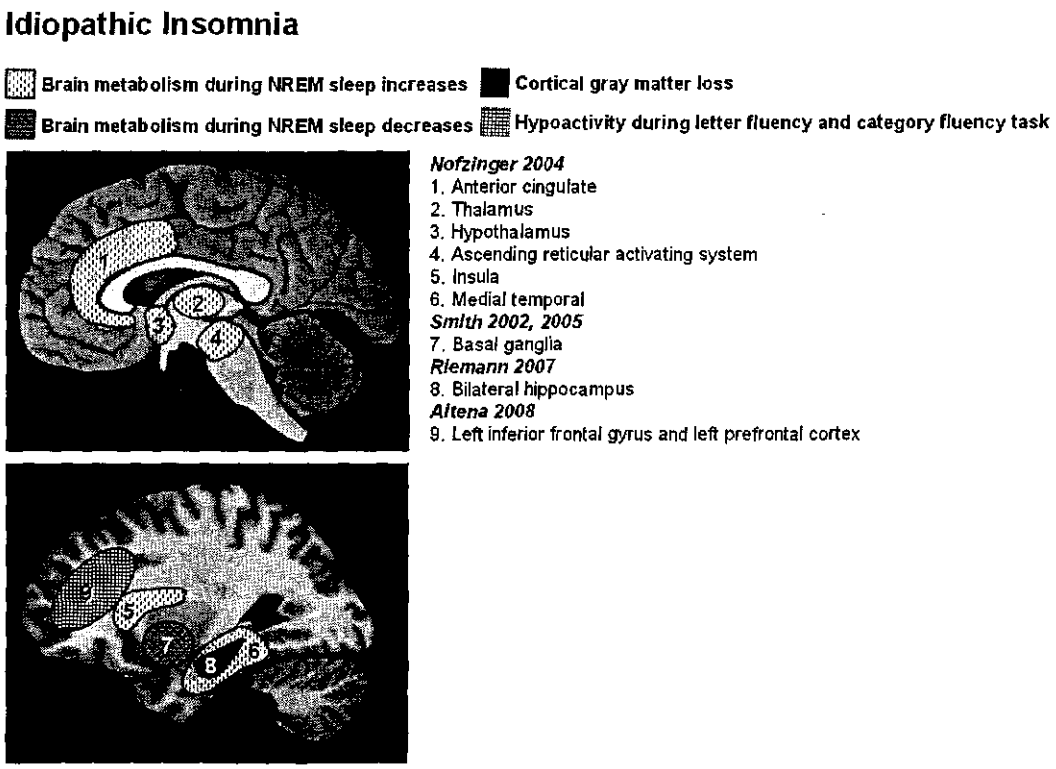

Figure 1. Structural and functional abnormalities in insomnia. Regional cerebral metabolism during NREM sleep in idiopathic insomnia. Nofzinger et al. found increased regional metabolism (18FDG PET) from waking to NREM sleep in patients with idiopathic insomnia (Nofzinger, Buysse et al. 2004). Smith et al. found reduced regional cerebral blood flow (SPECT) in the basal ganglia in insomniacs (Smith, Perlis et al. 2002; Smith, Perlis et al. 2005). Altena et al. found a hypoactivity duringletter fluency and category fluency task in frontal areas (Altena, Van Der Werf et al. 2008). Riemann et al. found a cortical grey matter loss in both hippocampus (Riemann, Voderholzer et al. 2007). Adapted from Desseilles et al., SLEEP, 2008.

Similarly, a recent fMRI study showed that 21 old patients suffering from chronic insomnia, compared to 12 matched controls, displayed a hypoactivation of the medial and inferior prefrontal cortical areas (BA9, 44-45) (Altena, Van Der Werf et al. 2008). The prefrontal abnormalities were revealed by using a category and a letter fluency task during a waking fMRI acquisition before and after a 6 weeks period of nonpharmacological sleep therapy. This therapy included cognitive behavioral therapy, body temperature and bright light interventions, sleep hygiene and physical activity counseling. There were no significant

behavioral differences between groups, allowing thus the interpretation in term of differential recruitment of brain areas. Interestingly, abnormalities recovered after a nonpharmacological sleep therapy (n = 10) but not after a wait list period (n = 10).

Theses results should be refined by using larger samples of well diagnosed patients and matched controls in protocols combining structural, neuropsychological, neuroendocrine, neurochemical, functional imaging and polysomnographic studies. Hopefully, these interesting initial results will inspire further investigation on the effects of psychotherapy on brain functioning in insomnia.

3. Functional Imaging of Hypnotic Drugs Response in Healthy Individuals

To our knowledge, there is no neuroimaging study of hyponotic drugs response in insomniacs but only in healthy subjects. In addition, most of the studies studied the effect of acute and not chronic administration.

Functional neuroimaging allows some insights into the mechanisms of several sedative drugs, although the neuroimaging data are still sparse. Most of the studies concern the class of benzodiazepines (see Table 1). For instance, lorazepam administration markedly decreases regional brain glucose metabolism in thalamus and occipital cortex during wakefulness (Volkow, Wang et al. 1995; Schreckenberger, Lange-Asschenfeldt et al. 2004). In the former study, changes in metabolic activity in thalamus were significantly related to lorazepam-induced sleepiness and were partially reversed by flumazenil, a benzodiazepine antagonist (Volkow, Wang et al. 1995). It was suggested that benzodiazepine-induced changes in thalamic activity may account for their sedative properties. This is reinforced by a study in normal subjects that finds a close relationship between bilateral thalamic activity and alpha rhythm, generally considered to be the marker of restful wakefulness. Both glucose metabolism and alpha rhythms are reduced under lorazepam in bilateral thalamus (Schreckenberger, Lange-Asschenfeldt et al. 2004).

Another type of short-acting benzodiazepine, triazolam, is correlated with a decrease in blood flow in the basal forebrain and amygdaloid complexes during NREM sleep (Kajimura, Nishikawa et al. 2004). These results suggest that hypnotic effect of the benzodiazepines may be mediated mainly by deactivation of the forebrain control system for wakefulness and also by the anxiolytic effect induced by deactivation of the amygdaloid complexes (Kajimura, Nishikawa et al. 2004). The impairment of episodic memory encoding by this drug, on the other hand, is associated with dose-related deactivation in prefrontal cortex, medial temporal lobe and left anterior cingulate cortex (Mintzer, Kuwabara et al. 2006).

Midazolam, another drug of this class with short half-life and known to cause anterograde amnesia in healthy subjects, diminishes functional connectivity in posterior cingulate cortex (Greicius, Kiviniemi et al. 2008) in resting state analysis of fMRI data. PET studies found decrease of cerebral blood flow in prefrontal cortex, insula, temporal lobe, and associative areas comparing before and after infusion of midazolam (Veselis, Reinsel et al. 1997; Bagary, Fluck et al. 2000; Reinsel, Veselis et al. 2000).

Table 1. Functional imaging of hypnotic drugs response in healthy individuals.

Study	Imaging	State	Treatment	Number of subjects	Placebo	Paradigm /Task	Results
Volkow et al. (1995)	PET ^{18}F-FDG	Wakefulness, sedation	Lorazepam Flumazenil	21 9	Yes No	No task After lorazepam	Decrease in thalamus, occipital cortex Partial reverse of the decrease
Schreckenberger et al. (2004)	PET ^{18}F-FDG /EEG	Wakefulness, sedation	Lorazepam	10	Yes	No task	Decrease in thalamus, occipital cortex, temporo-insular areas Decrease of alpha power
Kajimura et al. (2004)	PET ^{15}O-H_2O /EEG	Wakefulness, NREM (stage 2, 3 and 4)	Triazolam	15	Yes	No task	Decrease in basal forebrain and amygdaloid complexes
Mintzer et al. (2006)	PET ^{15}O-H_2O	Wakefulness, sedation	Triazolam	12	Yes	Episodic memory encoding	Decrease in right PFC, left parahippocampus, left ACC
Veselis et al. (1997)	PET ^{15}O-H_2O / EEG	Wakefulness, sedation	Midazolam, one or two infusions	14	No	Low vs high midazolam EEG effect No task	Decrease in insula, cingulate gyrus, PFC, thalamus, parietal and temporal
Bagary et al. (2000)	PET ^{15}O-H_2O	Wakefulness, sedation	Midazolam	15	Yes	7 with drug, 8 with placebo explicit memory encoding	Decrease in PFC, superior temporal, parieto-occipital at baseline Increase in left PFC during task in both groups
Reinsel et al. (2000)	PET ^{15}O-H_2O / EEG	Wakefulness, sedation, stage 2 sleep	Midazolam	14	No	Low vs high midazolam EEG effect No task	Decrease in left DLPFC, bilateral OFC, left middle temporal, right hippocampus
Greicius et al. (2008)	fMRI (1.5 T)	Resting state, sedation	Midazolam	9	No	No task	Decreased functional connectivity in posterior Cingulate Cortex
Gillin et al. (1996)	PET ^{18}F-FDG /EEG	NREM	Zolpidem	12	Yes	No task	Decrease in cingulate gyrus, medial frontal cortex, putamen, thalamus, hippocampus
Finelli et al. (2000)	PET ^{15}O-H_2O /EEG	Wakefulness, stage 2, stage 4 and REM sleep	Zolpidem	8	Yes	Prior sleep deprivation No task	During sleep (all stage): decrease in basal ganglia and insula; increase in parietal cortex During REM sleep: decrease in anterior cingulate; increase in occipital, parietal, parahippocampal cortex and cerebellum
Schlaepfer et al. (1998)	SPECT ^{99}mTc-HMPAO	Wakefulness	Opiates : hydromorphone butorphanol	9	Yes	No task	Hydromorphone: increase in ACC, both amygdala, thalamus. Butorphanol: increase in both temporal lobes.

From top to bottom: sorted by treatment and then by date of publiscation. From left to right: reference of the study, modality of brain imaging, state in which the study is conductied and task paradigm used, number of studied subjects, placebo-controlled study, and main result of the study (PFC = prefrontal cortex; ACC = Anterior cingulated cortex; OFC = orbitofrontal cortex; DLPFC = dorsolateral prefrontal cortex).

During sleep induced by zolpidem (an imidazopyridine hypnotic relatively selective for alpha-1 subunit of the omega-1 (BZ1) receptor of the gamma-aminobutyric acid type A) in healthy subjects, rCBF decreases compared to pacebo in the anterior cingulate cortex during REM sleep while it decreases in the prefrontal cortex and the insula during NREM sleep (Finelli, Landolt et al. 2000). Another study finds metabolic decreases in the metbolism in the cingulate, the thalamus and the putamen during NREM sleep (Gillin, Buchsbaum et al. 1996). Data on the sedative effect of opiates are rare. One study aimed at comparing the general effect of hydromorphone (μ-receptor agonist) and butorphanol (agonist/antagonist with κ component of activity) found different pattern of activation in a SPECT study: hydromorphone compared to plabebo elicited activation of the anterior cingulate cortex, thalamus and amygdala bilaterally, while butorphanol produced a more diffuse pattern (Schlaepfer, Strain et al. 1998).

Despite these interesting results, none of these reports has studied the placebo-controlled effects of sedative agents in a large sample of well diagnosed insomniac patients compared to healthy subjects matched. It is also remarquable that while antidepressant are widely used for the treatement of insomnia, outside of depression context, at our knowledge no brain imaging studies of antidepressants use in idiopathic insomnia patients exists. The same observation applies for over the counter drugs such as melatonine or diphenhydramine. Additionaly, another striking feature is the absence, for a large part of the studies, of EEG control for the state of vigilance that could inform us if the subjects were actually sleeping or not.

4. Daytime Functioning Impairments

Poor sleep may have detrimental consequences on daytime functioning such as altered mood and motivation, decreased attention and vigilance, low levels of energy and concentration, and increased daytime fatigue (Bonnet and Arand 1997).

Several studies have suggested cognitive abnormalities in patients with idiopathic insomnia such as sleep-related attentional bias (Spiegelhalder, Espie et al. 2008) or impaired sleep-related memory consolidation (Nissen, Kloepfer et al. 2006). Nevertheless, few behavioral studies have found abnormal performances and, even, several studies found similar performances, e.g. using category and letter fluency task (Altena, Van Der Werf et al. 2008). Putatively, an hyperarousal and a high level of perfectionism in these patients could mask performance decreases due to poor sleep (Vincent and Walker 2000; Drummond, Smith et al. 2004).

The specific distribution of brain activity or structure shown in patients with insomnia might relate to specific impairments in daytime functioning, e.g. hypoactivity in prefrontal cortex during wakefulness is consistent with reduced attentional abilities or reduced hippocampal volume is consistent with impaired sleep-related memory consolidation.

The extensive review of the impact of sleep deprivation is beyond the scope of this chapter. Nevertheless, insomnia could be considered as a chronic sleep deprivation and the growing body of evidence indicating the involvement of sleep in several functions suggests that sleep deprivation is an interesting domain to investigate in order to better understand the pathophysiology of insomnia (Ellenbogen 2005). For instance, sleep deprivation has several

effects on neural functioning (Boonstra, Stins et al. 2007) and is considered as a neurobiological and physiological stressor (McEwen 2006) having an impact on cognition (Durmer and Dinges 2005), memory (Walker and Stickgold 2004; Walker and Stickgold 2005) as well as emotion (Sterpenich, Albouy et al. 2009; Walker 2009) and metabolism (Copinschi 2005).

Interestingly, several sources of evidence show that (i) sleep difficulties are common among persons with suicidal ideations, suicide attempts and suicide completion (Sabo, Reynolds et al. 1991; Roberts, Roberts et al. 2001; Smith, Perlis et al. 2004); (ii) sleep disturbances are strongly linked to aggressive and impulsive behavior, as well as mood lability (Pakyurek, Gutkovich et al. 2002); (iii) sleep deprivation is associated with panic and anxiety, which is independently linked with suicidal ideations and suicide attempts in humans (Friedman, Smith et al. 1999). Recently short sleep (less than 5 hours of sleep) was associated with suicidal ideation and attempts among adults in the general population (Goodwin and Marusic 2008).

Overall, these results are of first importance since insomnia, a chronic deprivation of sleep, has been linked to depression (Riemann and Voderholzer 2003; Tsuno, Besset et al. 2005) (see below).

5. Hyperarousal Hypothesis in Insomnia

5.1. Insomnia and Hyperarousal

According to the *International Classification of Sleep Disorders* (ICSD-2), idiopathic insomnia "is a lifelong inability to obtain adequate sleep that is presumably due to an abnormality of the neurological control of the sleep-wake system."(American Academy of Sleep Medicine 2005). Idiopathic insomnia is thought to reflect an imbalance between arousal and sleep promoting systems, which results in a global cortical hyperactivity as evidenced by EEG studies (see below). In line with the elevated arousal levels, several studies have reported increased alertness using the multiple sleep latency test as well as increased tension and anxiety during wakefulness, associated with a reduction of total sleep duration (Bonnet and Arand 1997). In addition, quantitative EEG recordings in idiopathic insomnia patients are characterized by an increase in EEG beta/gamma activity (14-35 / 35-45 Hz) at sleep onset and during NREM sleep (Perlis, Merica et al. 2001) and are thus congruent with an overall cortical hyperarousal in idiopathic insomnia. Insomnia would therefore result from a conditioned state of central nervous system (CNS) arousal, which enhances a variety of sensory and cognitive phenomena that are normally suppressed or at least diminished at sleep onset. Uncommon high-frequency activity associated with sleep onset might thus contribute to the frequent misperception of insomniacs of not being asleep while objective EEG parameters indicate otherwise (Perlis, Merica et al. 2001). In addition, specific distribution of brain activity shown in patients with insomnia might relate to hyperarousal hypothesis as a common pathway in the pathophysiology of insomnia (e.g. overall cortical hyperarousal characterized by an increase in beta/gamma activity at sleep onset and during NREM sleep) (see above).

5.2. Locus Coeruleus and Arousal

Much evidence in the regulation of alterness is available for the noradrenergic locus coeruleus. The importance of arousal is patent because of its undeniable link to other phenomena such as sleep, attention, anxiety, stress and motivation (Aston-Jones and Cohen 2005). Contrarily to reduced arousal that leads to sleepiness, increased arousal (e.g. elicited by the sudden appearance of an environmentally salient event or a strongly motivating memory) can facilitate behavior but in the limit can also lead to distractibility and anxiety (Aston-Jones and Cohen 2005). Traditional theories of locus coeruleus (LC) – norepinephrine (NE) function have attached this structure to arousal (Berridge and Waterhouse 2003). Recently, Aston-Jones and Cohen proposed a role for the LC system in optimizing behavioral performance, which in turn may explain effects traditionally interpreted in terms of arousal (Aston-Jones and Cohen 2005). In their theory, they detail the two modes of activity that the LC neurons exhibit: phasic and tonic. Phasic LC activation is driven by the outcome of task-related decision processes (highly salient and arousing stimuli) and is proposed to facilitate ensuing behaviors and to help optimizing task performance (or exploitation). Interestingly, LC neuronal activity has recently been shown to fire synchronously and phasically with the cortical slow oscillation in rats suggesting a role in modulating cortical function even during the deepest stages of sleep (Yeshenko, Moelle et al. 2006). Accordingly a recent fMRI study has shown that slow oscillations were associated with the activation of a brainstem area compatible with the LC during slow wave sleep (SWS) in humans (Dang-Vu, Schabus et al. 2008).

Tonic LC activation, when utility in the task wanes, is associated with disengagement from the current task and a search for alternative behaviors (or exploration). Interestingly, in monkeys, both orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), which are thought to monitor task-related utility, give projections to LC (Aston-Jones and Cohen 2005). In addition, these two areas receive inputs from a wide array of sensorimotor areas (Carmichael and Price 1995), the same areas that have been shown with increased activity in depression (Nofzinger, Buysse et al. 2004). LC was involved in diurnal rhythm (Schmidt, Collette et al. 2009), sleep and wakefulness (Steriade, McCormick et al. 1993). Low levels of LC activity facilitate sleep and disengagement from the environment (Aston-Jones and Cohen 2005).

This recent integrative theory of LC is in good accordance with the relative increase of CMRglu from waking to NREM sleep in the anterior cingulate of patients suffering from insomnia (Nofzinger, Buysse et al. 2004) and with the increased activity during REM sleep in frontal and sensorimotor cortices in patients suffering from depression (Nofzinger, Buysse et al. 2004) (see below). Overall, we hypothesize that the increase of activity in frontal regions subserving the monitoring of task-related utility could be associated with an increase of firing of LC neurons in tonic mode thus increasing arousal. This hypothesis still has to be further documented.

6. Insomnia and Depression

Depression is the most common primary diagnosis in patients suffering from insomnia (Benca 2000). Of all psychiatric conditions associated with insomnia, depression (in particular unipolar depression) is the most frequently diagnosed one (Tsuno, Besset et al. 2005). Depressed patients frequently report increased daytime fatigue and tend to compensate with daytime napping. Patients with bipolar disorder, on the other hand, report insomnia while depressed, but also hypersomnia, with extended nocturnal sleep periods, difficulty in awakening, and excessive daytime sleepiness (Benca 2000). Thus, sleep disturbances appear to vary even across depression subtypes.

Recently short sleep duration (less than 5 hours by 24 hours) was associated with suicidal ideation and attempts among adults in the general population independently of the effects of comorbid mental disorders (Goodwin and Marusic 2008).

In addition, depression is associated with other sleep disorders like obstructive sleep apnea syndrome (Schroder and O'Hara 2005). Here, we only focus on the links between depression and insomnia. Specifically, indications of hyperarousal in both conditions suggest shared neurophysiological mechanisms underlying both sleep and mood regulation (Roth, Roehrs et al. 2007).

6.1. Hyperarousal Hypothesis in Depression

In depressed patients, modifications of the sleep architecture is characterized by reduced slow wave sleep (SWS), early onset of the first episode of REM sleep, and increased phasic REM sleep (Thase 1998). Gillin et al. postulated that depression is closely linked to an abnormal increase in some aspects of physiological arousal (Gillin, Buchsbaum et al. 2001). Consistent with this hypothesis, total scores on the Hamilton Depression Rating Scale (HDRS) as well as sleep disturbance in depression, a distinct symptoms cluster included in the HDRS, have been found to correlate with increased metabolism and regional cerebral blood flow during wakefulness in a large set of cerebral areas including limbic structures, anterior cingulate, thalamus, and basal ganglia (Milak, Parsey et al. 2005).

Intriguingly, total sleep deprivation is the only known therapeutic intervention in depression that has proven antidepressant effects within 24 hours. Sleep deprivation can have rapid beneficial effects, but unfortunately only for about half of the depressive population, with depressive symptoms reappearing after 1 night of recovery sleep (Tsuno, Besset et al. 2005). One hypothesis is that sleep deprivation can transiently counteract global hyperarousal in the responder population (Clark, Brown et al. 2006).

Since hyperarousal has also been described in insomnia, this may be a common pathway underpinning the close relationship between sleep and mood disorders. Evidence for reciprocal relationship between sleep and depression is twofold: sleep disturbances often accompany depression whereas chronic insomnia is a risk factor for the development of depression (Lustberg and Reynolds 2000). Subclinical sleep EEG alterations may persist in patients at risk for a depressive episode, thus offering further evidence of a close link between sleep and mood regulation.

In addition to this main hypothesis, several other hypotheses have been made in order to explain the huge frequency of depression in patients suffering from insomnia (Benca and Peterson 2008): including (i) deficits in monoaminergic neurotransmission, (ii) abnormalities in circadian genes, (iii) overactivity of the hypothalamic–pituitary–adrenal (HPA) axis, and (iv) impaired functioning of plasticity-related gene cascades.

i) Deficits in monoaminergic neurotransmission. Classically, during sleep, EEG activity normally shows progressive transitions from "light" sleep to "deep sleep", and the alternation across the night of NREM sleep (including SWS) with episodes of REM sleep. This latter stage is initiated when the monoamines (serotonergic and noradrenergic) activity decreases and cholinergic activity increases, and ceases with the opposite changes (Pace-Schott and Hobson 2002). Depressed patients present several characteristics including increased REM sleep propensity (leading to reduced REM latency), increased proportion of REM sleep, an increase of REM density (i.e. number of eye movements), and a decrease of time spent in SWS (Benca, Obermeyer et al. 1992). Depression symptomatology and sleep characteristics may be exacerbated when levels of monoaminergic neurotransmitters are decreased. Conversely, antidepressant drugs that increase monoaminergic drive seem to reverse these abnormalities (Thase 1998; Argyropoulos and Wilson 2005).

ii) Abnormalities in circadian genes. Circadian genes, involved in the control of biological rhythms, are another link between depression and insomnia. The central pacemaker within the suprachiasmatic nuclei (SCN) of the anterior hypothalamus controls circadian rhythms (Glass, Hauser et al. 1993). Chronotype or circadian type refers to the preference in sleep habits and the level of alertness across the day. There is a continuum between "morningness" with subjects waking up early and being more alert in the first part of the day and "eveningness" with subjects going to bed late and being more alert in the late evening hours. Among the genes supposed to work together with the SCN pacemaker, irregularities in the circadian locomotor output cycles kaput (clock) gene might have a major influence on sleep patterns. Recent studies showed that a polymorphism (C to T nucleotide substitution) in the 3′ flanking region of the human clock gene is associated with diurnal preferences of human healthy subjects, with higher "eveningness" in subjects carrying at least one copy of the C allele (Benedetti, Serretti et al. 2003). Depressed patients who have a C/C variant polymorphism in their clock gene, compared to patients without this variant, experience more frequently lifetime insomnia, present higher recurrence of initial insomnia, and experience worse insomnia during antidepressant treatment (Serretti, Benedetti et al. 2003; Serretti, Cusin et al. 2005; Artioli, Lorenzi et al. 2007). In addition to clock gene, period gene (per) and timeless gene (tim) have been involved in mental disorders (Lamont, Legault-Coutu et al. 2007).

iii) Overactivity of the hypothalamic–pituitary–adrenal (HPA) axis. Hypothalamus is also involved in HPA axis abnormalities that are considered as a final common pathway for many depressive symptoms. HPA overactivation has been involved in the development of mood disorders and sleep disturbance (Nestler, Barrot et al. 2002; Steiger 2007; Bao, Meynen et al. 2008). Corticotrophin-releasing hormone

(CRH) neurons in the paraventricular nucleus of the hypothalamus play a key role in HPA axis activity. Several evidences link insomnia and depression since, in depression, corticotrophin-releasing hormone (CRH) neurons in the paraventricular nucleus (PVN) of the hypothalamus are activated, CRH mRNA is increased in the PVN, antidepressants decrease CRH levels, and CRH antagonists are proposed in the treatment of depression (Steiger 2007; Bao, Meynen et al. 2008) while, on the sleep side, growth hormone inhibits the HPA axis, growth hormone-releasing hormone (GHRH) stimulates NREM sleep, CRH reduces NREM cycles, suppresses SWS and may enhance REM sleep (Holsboer, von Bardeleben et al. 1988; Tsuchiyama, Uchimura et al. 1995; Steiger 2007).

iv) Impaired functioning of plasticity-related gene cascades. The synaptic homeostasis hypothesis proposed by Tononi and Cirelli states that plastic processes occurring during wakefulness result in a net increase in synaptic strength in many brain networks. According to this hypothesis, the role of NREM sleep might be to downscale synaptic strength to a baseline level that (1) is energetically sustainable, (2) makes efficient use of gray matter space, and (3) is beneficial for learning and memory (Massimini, Ferrarelli et al. 2005; Tononi and Cirelli 2006). On the one hand, homeostatic regulation of the total synaptic weight impinging on neurons could be impaired in insomnia and in depression. On the other hand, sleep deprivation might increase plasticity-related gene expression during wakefulness, consequently potentially strengthens synapses in brain networks closely involved in mood regulation, and thus accounting for the acute antidepressant effects of sleep deprivation therapies (Manji, Quiroz et al. 2003; Zarate, Singh et al. 2006).

7. Neuroimaging of Sleep in Depression

A pioneering study by Ho et al. examined NREM using PET in 10 patients with depression and 12 controls (Ho, Gillin et al. 1996). The depressed patients showed higher CMRglu during NREM sleep in the pons, posterior cingulate, amygdala, hippocampus, and occipital and temporal cortices. There was a significant reduction of relative CMRglu in medial-orbital frontal and anterior cingulate cortices, caudate nucleus, and medial thalamus. These early findings support the hypothesis that hyperarousal in depression affects a network of limbic and posterior cortical regions, but also that the decreased medial frontal and striatal metabolism may be a hallmark of depression (Drevets, Price et al. 1997). More recent studies have confirmed that depressed patients have relatively persistent "elevated" activity measured by CMRglu across many brain regions during sleep compared to presleep wakefulness (REM: 24 depressed patients compared to 14 controls (Nofzinger, Buysse et al. 2004); NREM: 12 depressed patients compared to 13 controls (Germain, Nofzinger et al. 2004). Regions more activated during REM sleep included frontal, parietal, premotor, and sensorimotor cortices, as well as the insula, the ventral pallidum, and the midbrain reticular formation (Nofzinger, Buysse et al. 2004). Regions more activated during NREM sleep included the temporal and occipital cortices, as well as the insula, posterior cingulate, cerebellum, and thalamus (Germain, Nofzinger et al. 2004). However, increased metabolism was also found in

prefrontal cortex (unlike (Ho, Gillin et al. 1996). These results are again consistent with a general hyperactivation of arousal systems in depression that may underlie both sleep disturbances such as insomnia as well as nonrestorative sleep complaints in depressed patients.

Increased rapid eye movement density (number of REMs per minute of REM sleep) was found to correlate with depression severity and clinical outcomes (Buysse, Tu et al. 1999). In humans, REM bursts are classically thought to reflect ponto-geniculo-occipital (PGO) waves, possibly associated with orienting responses and arousal processes during sleep (Peigneux, Laureys et al. 2001; Wehrle, Czisch et al. 2005). An 18FDG PET study assessed cerebral glucose consumption in a group of 13 medication-free depressed patients during REM sleep (Germain, Buysse et al. 2004). The average REM count (an automated analog of REM density) was found to positively correlate with the metabolism in a network of regions involved in emotional regulation and emotion-induced arousal (medial and ventrolateral prefrontal cortex) as well as in regions linking emotion and attentional systems (striate cortex, precuneus, and posterior parietal cortex) (Vuilleumier and Driver 2007). Whether the increased activity in these regions may drive hyperarousal during REM sleep remains unclear. However, these results might not be specific to depression because no control data were provided in that study and because the observed activation pattern overlapped with results of healthy controls from other studies (Braun, Balkin et al. 1998; Peigneux, Laureys et al. 2001).

Overall, the specific distribution of brain activity shown in patients with insomnia might relate to the potentially overlapping pathophysiology with major depressive disorder as this illness has shown similarly altered cortical patterns (e.g. both illnesses have impairments in limbic/paralimbic areas as well as in basal ganglia).

8. Summary

Because currently available data are limited and not perfectly consistent, any conclusion about the cerebral correlates of insomnia during NREM sleep has to remain tentative. Whilst there is some evidence for decreased activity in cortical areas during early NREM sleep as well as during wakefulness, several subcortical regions involved in sleep/wake regulation, including limbic and paralimbic regions, were found to be more active during the transition from waking to sleep states. Current data generally support the hyperarousal theory of insomnia with increased neuronal activity during NREM sleep being a possible key factor contributing to sleep misperception and disturbances occurring in insomnia. Interestingly, recent integrative theory of the noradrenergic activity, previously linked to arousals, might be a future target for upcoming studies.

Depression is often associated with insomnia, as well as with hyperarousal characterized by persistent "elevated" activity across many brain regions during NREM sleep. Strong evidence for hyperarousal in both idiopathic insomnia and depression, together with persistent alterations in sleep architecture in remitted depression, corroborate common neurophysiological mechanisms underlying sleep and mood regulation.

Changes in brain functions after insomnia treatments have to be assessed more carefully in future neuroimaging studies by using larger samples of well diagnosed patients and

matched controls in protocols combining structural, neuropsychological, neuroendocrine, neurochemical, functional and polysomnographic approach. In addition, early studies suggest that functional imaging could be coupled with pharmacological or psychotherapeutic treatments in order to assess the neurophysiological response to such interventions, and thus allow a better understanding of the neural mechanisms underlying the recovery from idiopathic insomnia.

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