

## Chapter

## 51

# Functional neuroimaging: sedating medication effects

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## Introduction

Healthy human sleep is characterized by the cyclic occurrence of non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep, as well as a progressive decline of electroencephalographic (EEG) slow-wave activity (SWA, power within 0.75–4.5 Hz) in the course of a sleep episode. These characteristics reflect the influence of three basic processes that are assumed to underlie sleep/wake regulation [1]: [1] A sleep/wake-dependent, homeostatic process keeping track of "sleep need" accumulating during wakefulness and dissipating during sleep; [2] a sleep/wake-independent, circadian process determining the daily phases of high and low propensity for sleep, REM sleep, and wakefulness; and [3] an ultradian process reflecting the cyclic occurrence of NREM and REM sleep. According to the two-process model of sleep regulation (recently reviewed by [1]), the interaction between the homeostatic *Process S* and the circadian *Process C* regulates the variation of sleep propensity in waking, the alternation between wakefulness and sleep, NREM sleep intensity, and the timing of REM sleep. A high sleep efficiency reflecting a consolidated sleep episode without frequent arousals and state changes – but not necessarily a high proportion of deep slow-wave sleep – ensures the subjective perception of "good quality" sleep [2].

## High prevalence of insomnia

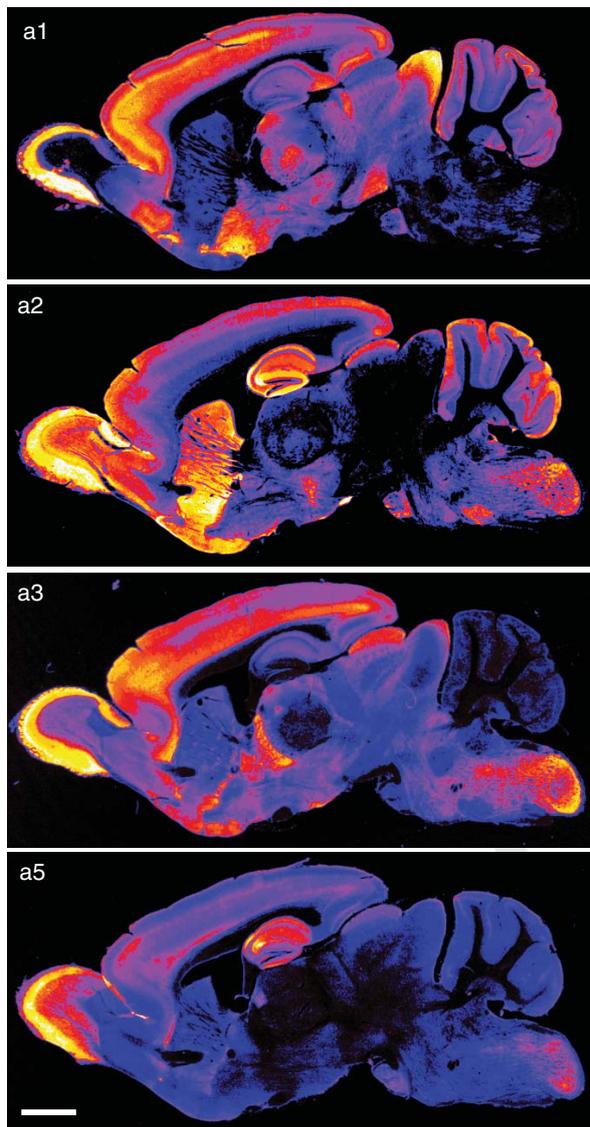
Disturbed sleep as a consequence of acute and chronic insomnia is highly prevalent in society [3, 4]. Insomnia symptoms consist of difficulties of initiating or maintaining sleep, non-restorative or poor sleep quality, and reduced daytime functioning including emotional and cognitive impairments associated with the sleep problem. Non-pharmacological therapies (e.g., cognitive behavioral therapy) and/or sedative-hypnotic medications acting as allosteric agonistic modulators of gamma-amino butyric acid type A (GABA<sub>A</sub>) receptors currently provide the most often used treatment options. These GABA<sub>A</sub> receptor modulators include the traditional benzodiazepines (BDZ) such as diazepam, midazolam, and triazolam, and the non-BDZ zolpidem, zaleplon, zopiclone, and eszopiclone, which are also known as "z-drugs." Because of concerns about unwanted effects of these GABAergic

agents (see below), recent research aimed to develop novel hypnotics targeting serotonin (5-HT), melatonin, hypocretin, or histamine receptors. These efforts have not yet led to major breakthroughs [5]. Thus, we will place the main focus of our review on neuroimaging studies investigating the effects of BDZ and z-drugs on regional glucose metabolism and brain perfusion as measured with <sup>15</sup>O-water (H<sub>2</sub><sup>15</sup>O)-PET and blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) in wakefulness and NREM sleep. We will address the question whether the available studies can help us to better understand neurochemical and neuroanatomical mechanisms underlying physiological sleep and the neurobiological basis of insomnia. Selected findings from pharmacological studies in genetically modified mice, as well as neuroimaging results of the sedating antidepressant, mirtazapine, and of melatonin will also be included.

## Most sedative-hypnotics target GABA<sub>A</sub> receptors

The GABA<sub>A</sub> receptors belong to the superfamily of ligand-gated ion channels, and mediate phasic and tonic inhibition in the central nervous system (CNS). These ubiquitous receptors form a chloride (Cl<sup>-</sup>) ion pore, which is opened by GABA and structural analogs and inhibited by bicuculline and picrotoxin. They consist of various combinations of 19 different subunits (α, β, γ, δ, ε, θ, and ρ subunits). To form a Cl<sup>-</sup> ion channel *in vitro* with the full functional properties of native GABA<sub>A</sub> receptors, at least one α, one β, and one γ subunit are required [6]. Most GABA<sub>A</sub> receptors in the CNS are composed of two α subunits (α<sub>1</sub>, α<sub>2</sub>, α<sub>3</sub> or α<sub>5</sub>), two β subunits, and one γ<sub>2</sub> subunit [7]. These receptors are present throughout the rodent brain, but have different regional and cellular distributions *in vivo*; α<sub>1</sub>-, α<sub>2</sub>-, α<sub>3</sub>-, and α<sub>5</sub>-containing receptor subtypes are attributed to largely distinct neuronal circuits [8] (Figure 51.1). In mice, α<sub>1</sub> is expressed in the cortex, thalamus, pallidum, and hippocampus; α<sub>2</sub> is expressed in the hippocampus, cortex, striatum, and nucleus accumbens; α<sub>3</sub> is expressed in the cortex and reticular nucleus of the thalamus; α<sub>5</sub> is expressed in the hippocampus and deep layers of the cortex.

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**Figure 51.1** Immunohistochemical distribution of GABA<sub>A</sub> receptor subtypes in mouse brain. Color coding indicates different levels of α-subunit expression; white (high expression) > yellow > red > purple (low expression) > blue (no expression). (Reproduced, with permission, from 61).

Flumazenil is a specific *antagonist* at the BDZ binding site of GABA<sub>A</sub> receptors containing α<sub>1</sub>, α<sub>2</sub>, α<sub>3</sub>, or α<sub>5</sub> subunits. Position emission tomography (PET) studies with radio labeled flumazenil demonstrate that these receptors are widely expressed also in living human brain, particularly in the primary visual cortex and throughout frontal brain regions, especially in the lateral prefrontal and fronto basal cortices [9–11] (Figure 51.2). Lower receptor densities are found in the thalamus, caudate/putamen, pons, and cerebellum.

### Complex role for GABA<sub>A</sub> receptor subunit(s) in hypnotic action of BDZ and z-drugs

Binding of BDZ and z-drugs at the interface between α and γ<sub>2</sub> subunits of GABA<sub>A</sub> receptors underlies their sedative-hypnotic properties (for reviews, see: [7, 12, 13]). The classical BDZ have similar binding affinities (i.e., probability to form a drug–receptor complex) to all GABA<sub>A</sub> receptors containing α<sub>1</sub>, α<sub>2</sub>, α<sub>3</sub>, and α<sub>5</sub> subunits. By contrast, the z-drugs have different affinities, potencies (i.e., drug dose required to produce an effect of given intensity), and efficacies (i.e., maximum response achievable for a drug) at specific receptor subtypes that may result in specific, functionally discrete pharmacodynamics effects [14] (Table 51.1). For example, the imidazopyridine, zolpidem, has high affinity for α<sub>1</sub>-containing receptors, ~20-fold reduced affinity for α<sub>2</sub>- and α<sub>3</sub>-containing receptors, and negligible affinity for α<sub>5</sub>-containing receptors [15]. The pharmacodynamics of zolpidem suggests that α<sub>1</sub>-containing GABA<sub>A</sub> receptors may be the important target for the sedative-hypnotic actions of BDZ and z-drugs. Studies in genetically modified mice indeed show that the α<sub>1</sub> subtype facilitates the sedative actions of these compounds [16]. Nevertheless, sedative and hypnotic properties appear to be mediated by different neuronal circuits. More specifically, enhancement of sleep continuity – as quantified by the number of brief awakenings in mice – occurs independently of α<sub>1</sub>-containing GABA<sub>A</sub> receptors [17]. In accordance with these findings in transgenic animals, the effects of zolpidem and the physiological promotion of deep NREM sleep after sleep deprivation are separate also in humans, suggesting that they are mediated by different neurophysiological mechanisms [18]. It is possible that α<sub>2</sub>-containing GABA<sub>A</sub> receptors are involved in the generation of deep NREM sleep [19, 20].

In conclusion, pharmacological studies in genetically engineered mice and healthy humans suggest complex roles for distinct GABA<sub>A</sub> receptors and their subunits in the physiology and pharmacology of sleep.

### Functional neuroimaging of sedative-hypnotic medication effects during wakefulness

The clinical effects of ligands at BDZ binding sites not only consist of sedation and sleep induction, but also include anxiolysis, seizure suppression, and muscle relaxation. Moreover, they may also exert unwanted actions, including anterograde amnesia, addiction, dependence, and tolerance [7]. To better understand and eventually overcome the limitations of classical BDZ, research during the past two decades aimed to elucidate separable key functions of distinct GABA<sub>A</sub> receptor subtypes. Neuroimaging provides one promising approach to identify brain regions in which activity is affected by pharmacological agents. Localized effects of drugs may help to clarify their exact mechanisms of action in the brain, as well as to explain the clinical effects elicited in the patient.

At present, only a small number of placebo-controlled studies have examined the effects of sedative-hypnotics on brain activity in human subjects who are either awake or asleep. Experiments during wakefulness tend to use a combination of pharmacological and behavioral challenges during neuroimaging. This protocol enables researchers to clarify drug effects on regional brain activity during different states of cognitive activation. Behavioral tasks are selected to engage cognitive processes that are known to be influenced by the drug under investigation. For example, it is well established that acute BDZ administration in healthy volunteers produces dose-related decrements in episodic memory encoding, while leaving retrieval of previously encoded material intact (reviewed by [21]). As outlined above, GABA<sub>A</sub> receptors in the brain are known to be the initial sites of BDZ action. Nevertheless, the neural networks affected by BDZ administration during episodic encoding are yet to be clarified. It

is possible that they extend well beyond the sites of initial drug–receptor interactions.

## Benzodiazepines

Different neuroimaging techniques including PET and fMRI were used to investigate the effects of diazepam, midazolam, triazolam, and lorazepam on brain activity during episodic memory encoding in healthy volunteers [22–28]. There is some discrepancy amongst the studies in regions showing BDZ-induced deactivation during performance of this task. This has been related to methodological differences in terms of experimental design (e.g., between- vs. within-subject manipulation of dose), type of stimuli (e.g., words vs. face-name pairs), modality of stimuli presentation (visual vs. auditory), and the nature of the control task to which the encoding task was compared. For example, Mintzer *et al.* [27] investigated memory encoding by comparing brain activity during more elaborate encoding (semantic categorization of words) with that during less elaborate encoding (orthographic categorization of words). By contrast, other research groups used ‘resting-wakefulness’ as the control condition [23, 25]. These authors scanned blindfolded volunteers during the presentation of auditory tones, which they were instructed to ignore. Brain activation during resting wakefulness may reflect the ‘default mode network’ consisting of precuneus, lateral parietal, ventromedial prefrontal, mid-dorsolateral prefrontal, and anterior temporal regions [29, 30]. This network has a high metabolic rate during resting wakefulness, which reduces following the introduction of specific tasks. It is thought to play an important role in the modulation of conscious processes, awareness, mental representations of the self, and inferential processing of context-related information.

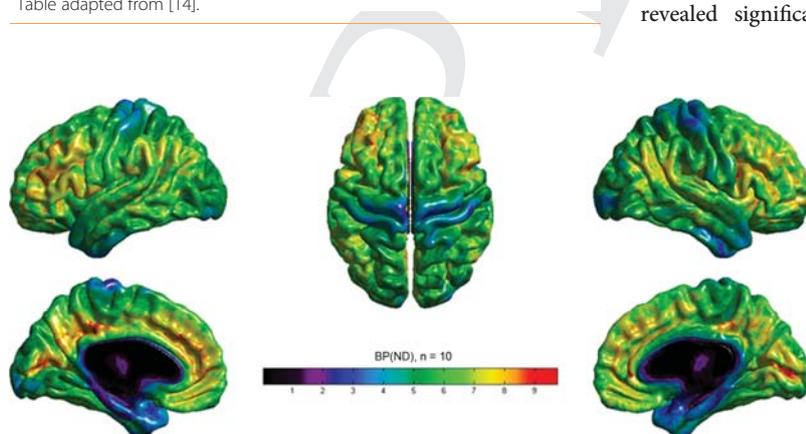
### Benzodiazepines (diazepam, midazolam, triazolam, lorazepam) induce deactivation of the prefrontal cortex and medial temporal lobe during episodic memory encoding

Despite the methodological differences, all but one study [24] revealed significant deactivation of the prefrontal cortex

**Table 51.1.** Relative functional effects of z-drugs at different GABA<sub>A</sub> receptors

z-drug	GABA <sub>A</sub> receptor subunit			
	α <sub>1</sub>	α <sub>2</sub>	α <sub>3</sub>	α <sub>5</sub>
<b>Zolpidem</b>				
Affinity	21x	1x	1x	Negligible
Potency	4–12x	2x	1x	Negligible
Efficacy	1x	1x	1x	Negligible
<b>Zaleplon</b>				
Affinity	4–17x	1–2x	1–2x	1x
Potency	3–33x	1–5x	1x	1–2x
Efficacy	1–2x	1x	2x	1x
<b>Zopiclone</b>				
Affinity	11x	7x	1x	2x
Potency	4–6x	1x	Conflicting data	4–6x
Efficacy	1x	1x	1x	1x
<b>Eszopiclone</b>				
Affinity	8x	5x	1x	8x
Potency	1x	4x	4–6x	10x
Efficacy	2x	4x	4x	1x

The lowest values for affinity, potency, and efficacy for each drug are assigned a reference value of 1x, and the other values for that drug characteristic are expressed relative to this. Table adapted from [14].



**Figure 51.2** High-resolution, mean parametric maps of <sup>18</sup>F-flumazenil binding potential [BP(ND)] in healthy adults. (Reproduced, with permission, from [11]).

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following BDZ administration during memory encoding. This region plays an important role in this step of episodic memory in humans (reviewed by [31]). It has been proposed that the prefrontal cortex is responsible for the initial control of reflective processes (e.g., selection and direction of processing resources, maintenance and manipulation of information) that ultimately lead to the transformation of sensory input into internal representations [31–33].

Another key region indicated in episodic memory is the medial temporal lobe (reviewed by [34]). There are large cortico-cortical direct reciprocal connections between the prefrontal cortex and the medial temporal lobe, passing through the uncinate fascicle, anterior temporal stem, and anterior corpus callosum [35]. Despite this, medial temporal structures have shown relative resistance to the effects of BDZ, with only two out of seven research papers revealing a significant deactivation within this region of interest during episodic memory encoding (hippocampus: [28]; parahippocampus: [27]). The medial temporal lobe is thought to bind together representations that were initially processed by the prefrontal cortex into a durable contextualized episodic memory trace [32, 33]. Thus, it is possible that the effects of BDZ on memory may be primarily mediated by impairment of encoding processes occurring in the prefrontal cortex, with relatively little effect on the integration or transfer of information to long-term memory [25].

### Z-drugs

#### Zolpidem reduces visual cortex activation by flashing checkerboard

Functional MRI was recently used to investigate the effect of zolpidem on brain function during wakefulness [36]. Acute oral administration of the drug reduced the robust activation of the visual system produced by the presentation of a flashing checkerboard. These findings agree with previous fMRI studies which showed that other positive GABA<sub>A</sub> receptor modulators, such as alcohol [37], reduced activation during visual cortex stimulation. The observed effects may result from synaptic inhibitory activity. Developmental studies in rats suggest high expression of  $\alpha_1$  subunits in adult primary visual cortex [38]. Nevertheless, the functional significance of the imaging findings in humans remains unknown. It could be related to reported distortions in visual perception attributed to the drug, including blurred vision and hallucinatory experiences [39].

#### Sedating antidepressants and melatonin

Functional neuroimaging methods were also applied to the study of non-GABAergic agents, including sedating antidepressants and melatonin.

An fMRI study conducted in healthy volunteers examined the effects of mirtazapine on brain activation associated with behavioral inhibition and reinforcement processing [40]. This sedating antidepressant enhanced activation in the right lateral orbitofrontal cortex during behavioral inhibition and in

both parietal cortices during reinforcement processing to monetary reward. Mirtazapine acts as an antagonist of 5-HT<sub>2A</sub> receptors and as an agonist of 5-HT<sub>1A</sub> receptors, suggesting that serotonin may play an important role in behavioral inhibition and reward processing. This effect may also underlie some of the therapeutic effects of serotonergic antidepressants [40].

Functional MRI was also used to investigate the effects of melatonin on brain activities during visual, auditory, and memory tasks, and their relation to the induction of sleepiness [41]. This study revealed that afternoon ingestion of melatonin, and not placebo, reduced task-related activity in the rostral medial aspect of the occipital cortex during a visual-search task, and in the auditory cortex during a music task. The effects correlated with subjective measurements of fatigue. In addition, melatonin enhanced the activation in the left parahippocampus in an autobiographic memory task. These results demonstrate melatonin's ability to modulate brain activity in a manner resembling enhanced sleep pressure, despite participants being fully awake. Melatonin may induce sleep anticipation in the brain, so that sleep-related processes begin before actual sleep initiation [41].

### Functional neuroimaging of sedative-hypnotic medication effects during sleep

The effects of pharmacological agents on regional brain activity during sleep can be investigated by employing neuroimaging and polysomnography simultaneously.

### Benzodiazepines

#### Triazolam reduces blood flow in the prefrontal cortex and amygdala in NREM sleep

In an H<sub>2</sub><sup>15</sup>O-PET study in healthy volunteers, regional cerebral blood flow (rCBF) in NREM sleep was assessed in response to the BDZ triazolam [42]. Volunteers underwent two experimental nights – one placebo and one triazolam. Each night, two scans in wakefulness were obtained in a control condition with eyes closed, after which subjects took a treatment capsule. During sleep, three scans in superficial NREM sleep (stage 2) and three scans in slow-wave sleep were performed between 11:00 pm and 2:00 am. The EEG was recorded throughout the imaging session and used to determine the sleep states.

Compared with placebo, triazolam reduced blood flow in NREM sleep in the basal forebrain and amygdaloid complexes [42]. These findings indicate that triazolam has its main impact on the basal forebrain, rather than on other wake-promoting regions, including distinct nuclei of the brainstem, hypothalamus, and thalamus. The hypnotic effect of triazolam may thus result mainly from inhibition of the forebrain control system for wakefulness. Other imaging data show that the basal forebrain is deactivated in deep NREM sleep in healthy

adults [43], possibly suggesting that deactivation of this region is involved in promoting physiological NREM sleep. The deactivation of the amygdaloid complexes, which contribute to emotional responses such as anxiety and fear, indicates that the anxiolytic effect of BDZ is also related to their hypnotic effect.

## Z-drugs

Two studies employed PET imaging, in a double-blind, placebo-controlled manner, to assess the effects of zolpidem on brain function during sleep in healthy adults. These studies suggest that zolpidem has complex and varied influences on regional brain activity.

### Studies in healthy volunteers

#### Zolpidem reduces regional cerebral glucose metabolic rate in the basal ganglia and limbic structures

Zolpidem induced changes in regional cerebral glucose metabolic rate as quantified with  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ FDG-PET) that varied directly with the plasma drug concentration [44]. These changes were unevenly distributed throughout the brain, and were greater in subcortical areas than lateral cortical areas. Specifically, compared with placebo, zolpidem elicited a reduction in absolute glucose metabolic rate in medial frontal cortical and cingulate regions, frontal white matter, putamen, thalamus, and hippocampus. Relative metabolic rate tended to decrease more on the left hemisphere than on the right hemisphere, and more in lateral temporal and occipital regions than in parietal and frontal regions. Within the right hemisphere, the paracentral lobule, medial frontal gyrus, frontal white matter, precuneus, posterior putamen, and midbrain showed relatively lower glucose metabolism. In the left hemisphere, lower glucose metabolism was seen in the posterior thalamus and anterior cingulate. Finally, zolpidem enhanced relative glucose metabolism in the right anterior thalamus, left frontal matter, and left superior colliculus.

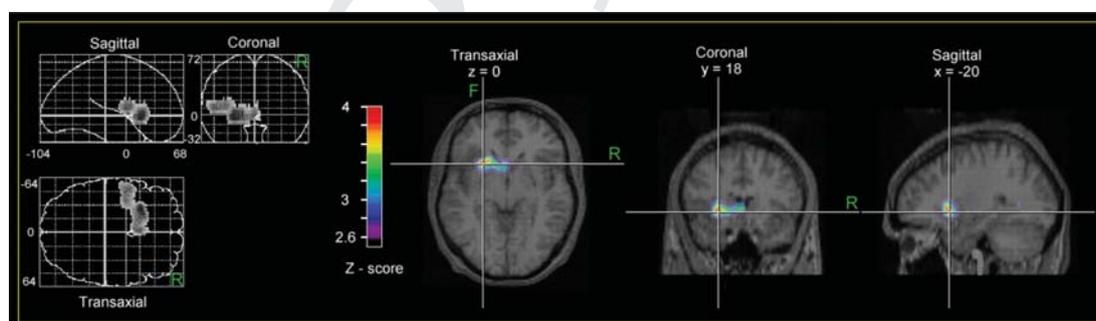
The present findings indicate that zolpidem reduces absolute and relative metabolic rates in the cingulate cortex in

proportion to its plasma concentration. In animals, this area is high in  $\alpha_1$ -containing GABA<sub>A</sub> receptors [38]. On the other hand, several regions that are also high in  $\alpha_1$  subtype receptors (e.g., fronto parietal and sensorimotor cortices) are apparently unaffected, whereas areas such as the thalamus and putamen with relatively few  $\alpha_1$  subunits show lower metabolism after zolpidem when compared with placebo. Thus, arguably the present findings may not fully reflect the mechanisms of action and clinical effects of zolpidem. The unusually low plasma concentrations of the drug may be partly responsible for this.

#### Zolpidem reduces regional cerebral blood flow in the basal ganglia and insula

PET imaging during sleep was also used to investigate changes in rCBF following administration of zolpidem [45]. The study revealed that zolpidem induced distinct changes in rCBF in sleep-deprived, healthy volunteers in combined stages 2 and 4 and REM sleep. More specifically, relative rCBF was lower after zolpidem than after placebo in the basal ganglia (left putamen and caudate) and in the insula, yet it was higher in the parietal cortex (the superior and inferior parietal lobules of the neocortex) (Figure 51.3). Analyzing only NREM sleep, similar blood flow differences were apparent, but did not reach significance. In REM sleep, rCBF in the anterior cingulate was lower after zolpidem than after placebo, whereas rCBF in the occipital and parietal cortices, parahippocampal gyrus, and cerebellum was higher.

The generalizability of these findings is limited by the possible confounding effects of sleep deprivation. However, it is noteworthy that reduced rCBF in slow-wave sleep relative to waking or to all other sleep stages has been reported for the basal ganglia, insula, and anterior cingulate cortex (see [43] for recent review). Thus, the present evidence indicates that zolpidem promotes changes in rCBF that are typical for slow-wave sleep [45]. The observation that some effects of zolpidem are related to those of deep sleep is in agreement with the drug-induced shortening of sleep latency and the decrease in combined arousal variables [18]. Moreover, the reduced rCBF in the putamen and cingulate cortex could be related to the



**Figure 51.3** Brain regions showing lower rCBF during sleep after zolpidem compared with placebo assessed by statistical parametric mapping. Results are displayed above a threshold of  $Z = 2.58$  ( $p < 0.005$  uncorrected,  $n = 8$ ). (Left) Statistical parametric map (SPM(Z)). The grey scale is arbitrary. (Right) Transaxial, coronal, and sagittal sections at a selected point of interest. The color scale for Z is indicated. (Reproduced, with permission, from [45]).

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findings of Gillin *et al.* [44] who revealed that zolpidem decreased absolute glucose metabolic rate in these regions. Equally, the zolpidem-induced changes in absolute glucose metabolism tended to be larger in the midline than in the lateral cortical areas – an observation that is in accordance with the present study, in which the parietal cortex exhibited a relative increase in rCBF [45].

### Studies in patients with neurological disorders

#### Zolpidem increases cerebral activity in patients suffering from neurological conditions

In the presence of brain injury, as opposed to healthy brain tissue, zolpidem has been shown to disproportionately enhance cerebral perfusion in areas that were hypoactive as a result of injury. This finding was demonstrated using single-photon emission computed tomography (SPECT) imaging in both neurologically diseased humans and baboons [46], and also using PET in a patient with postanoxic akinetic mutism [47]. Following zolpidem, the latter study revealed increased cerebral activity in the frontal cortex with both  $^{18}\text{F}$ -FDG PET (at resting state) and  $\text{H}_2^{15}\text{O}$ -PET in an activating condition relative to resting state. During cognitive activation (object naming), zolpidem elicited increased activation in the anterior cingulate and orbitofrontal cortices. Interestingly, behavioral parameters were also affected, but in an apparently paradoxical manner. More specifically, despite being a ‘sedating hypnotic,’ zolpidem induced a transient improvement in motor and cognitive performance. Similar findings were reported in studies involving patients suffering from various neurological conditions, including brain injury [48–50], stroke [51], and Parkinson’s disease [52], and in a patient in a vegetative state [53].

Given the small and specific nature of the patient samples in these studies, it is difficult to extrapolate the findings to other patients suffering from neurological disorders. Moreover, the neuronal mechanism underlying this paradoxical effect of zolpidem remains unknown. Nonetheless, some authors suggest that zolpidem may reverse the diaschisis phenomenon (i.e., loss of function in a portion of the brain that is at a distance from the site of injury, but neurally connected), which prompts a recovery of cortical activity [48–50]. As proposed by Brefel-Courbon *et al.* [47], the stimulation of GABA function by zolpidem could interact with cortical-subcortical loops originating from the anterior cingulate and orbitofrontal cortices, which leads to disinhibition and thalamocortical over activity [54]. The improvement of function in the limbic loops could be related to both the reversal of a cortical-subcortical diaschisis, as well as to the improvement in motivational processes, which are necessary for speech and movement.

#### Eszopiclone may reduce glucose metabolism in the pontine and midbrain reticular activating system in patients with insomnia

Functional neuroimaging in patients with sleep disorders can provide clues to the underlying pathophysiology, as well as to the role of specific brain regions in generating and

maintaining sleep. Imaging findings support the concept that persistent activity in distinct arousal networks, particularly continuous activation of the precuneus, is linked to impaired sleep quality in patients with insomnia [55, 56]. With regards to pharmacological interventions, sedative-hypnotics may provide an antidote to the proposed CNS hyperarousal seen in these patients during sleep. The current literature lacks placebo-controlled neuroimaging experiments that investigate the effects of hypnotics on brain activity in insomnia subjects. However, a preliminary, open-labeled study employed  $^{18}\text{F}$ -FDG PET to assess the effects of eszopiclone, the S-enantiomer of the cyclopyrrolone, zopiclone, in eight individuals with primary insomnia [57]. Regarding its affinity, potency, and efficacy at different GABA<sub>A</sub> receptor subtypes (Table 51.1), this hypnotic can be considered to act preferentially at  $\alpha_2/\alpha_3$  receptors [14]. Subjective measures of sleep, sleep quality, mood, and next-morning alertness improved from pre- to post-treatment. In addition, the reduction in relative regional glucose metabolism from waking to NREM sleep in an arousal network originating in the pontine reticular formation and ascending into the midbrain, subthalamic nucleus, thalamus, and cerebellum was more pronounced following eszopiclone than before. Related neo cortical areas, including the orbitofrontal cortex, superior temporal lobe, right paracentral lobule of the posterior medial frontal lobe, right precuneus, dorsal cingulate gyrus, and parts of the frontal lobe showed a similar interaction with treatment. Reductions in relative metabolism after treatment were found in similar regions during sleep, but not in wakefulness. Thus, eszopiclone reverses a pattern of hyperarousal seen in insomnia patients in NREM sleep. The authors suggested that the inhibitory action of the drug focuses mainly on a CNS arousal neural network within sleep that includes the pontine and midbrain reticular activating system [57]. This research further validates the essential role of these structures in generating and maintaining sleep [55].

### Conclusions and perspectives

Neuroimaging studies employing PET and fMRI have consistently found reduced brain activity in physiological slow-wave sleep when compared with wakefulness (see [43] for comprehensive recent review). The regional reductions in brain activity span cortical (prefrontal cortex, anterior cingulate cortex, and precuneus) and subcortical structures (brainstem, thalamus, basal ganglia, basal forebrain) (Table 51.2), including neuronal populations involved in awakening and arousal, as well as areas that are highly active during wakefulness. Insomnia is characterized by difficulty initiating sleep, repeated awakenings with difficulty returning to sleep, or non-restorative/poor sleep quality [56]. Examining glucose metabolic rate with  $^{18}\text{F}$ -FDG PET in wakefulness and NREM sleep revealed that patients with insomnia exhibit a smaller decrease than controls in relative glucose metabolism from waking to NREM sleep in the brainstem reticular core and hypothalamus [58]. These findings support the concept that

**Table 51.2.** Summary of regional changes in brain activity in slow-wave sleep when compared with wakefulness, and of effects of sedative-hypnotics in resting wakefulness and NREM sleep

	Brain structures (cortical regions, limbic and paralimbic structures, arousal centers)										References
	MPFC	Insula	Precuneus	BG	ACC	PHG	Amygdala	Hypothalamus	Thalamus	ARAS	
<b>Slow wave sleep vs. wakefulness:</b>											
rCBF (H <sub>2</sub> <sup>15</sup> O) in healthy volunteers	↓	↓	↓	↓	↓				↓	↓	[43, 55]
Glucose metabolism ( <sup>18</sup> F-FDG) in insomnia	↑	↑	↑		↑	↑	↑	↑	↑	↑	[56, 58]
<b>Resting wakefulness:</b>											
rCBF (H <sub>2</sub> <sup>15</sup> O) after midazolam	↓	↓		↓	↓				↓		[23, 25]
<b>NREM sleep:</b>											
rCBF (H <sub>2</sub> <sup>15</sup> O) after triazolam	↓	↓			↓					↓	[42]
Glucose metabolism ( <sup>18</sup> F-FDG) after zolpidem	↓		↓	↓	↓				↓		[44]
rCBF (H <sub>2</sub> <sup>15</sup> O) after zolpidem		↓		↓							[45]
Glucose metabolism ( <sup>18</sup> F-FDG) after eszopiclone in insomnia patients	↓		↓						↓	↓	[57]

↓ = decrease; ↑ = reduced decrease; some changes were only seen in one hemisphere. MPFC = medial prefrontal cortex; BG = basal ganglia; ACC = anterior cingulate cortex; PHG = parahippocampal gyrus; ARAS = ascending reticular arousal system (including brainstem and basal forebrain).

persistent activity in arousal networks may be linked to the impaired sleep quality in insomnia [55]. Drawing on human studies such as this, as well as on animal data, a neurobiological model of insomnia was recently proposed [56]. The authors postulate that insomnia is a disorder of sleep/wake regulation distinguished by ongoing wake-like activity in NREM sleep, which leads to simultaneous, and regionally specific, waking and sleeping neuronal activation. The model suggests that this persistent activity occurs in wake-active brain structures including distinct cortical regions, paralimbic cortex, thalamus, hypothalamus, and brainstem arousal centers.

The sedative-hypnotics midazolam, triazolam, and zolpidem reduce brain perfusion and/or glucose metabolism in healthy volunteers in restful wakefulness and NREM sleep in the medial prefrontal cortex, insula, basal ganglia, anterior cingulate cortex, and thalamus [23, 25, 42, 44, 45] (Table 51.2). These findings suggest that BDZ and z-drugs promote sleep by reducing arousal. Similar to their distinct changes in the sleep EEG referred to as “spectral BDZ signature” [12], these effects appear to be irrespective of chemical structure and differential affinity, potency, and efficacy at

different subtypes of GABA<sub>A</sub> receptors. Moreover, sedative-hypnotic medication-induced changes in glucose metabolism and blood flow may not reflect the distribution patterns of different GABA<sub>A</sub> receptors in the brain. Apart from the thalamus, the most consistent deactivation in healthy volunteers occurs in limbic and paralimbic structures involved in emotional responses such as anxiety and fear. These observations indicate that anxiolysis is related to the hypnotic effects of both BDZ and zolpidem. Besides, augmenting the actions of endogenous GABA may be involved in sleep-promoting circuits. In support of this notion, a GABAergic deficit was linked to chronic insomnia in a patient with a mutation in the β<sub>3</sub> subunit of GABA<sub>A</sub> receptors [59]. It may be possible in the future, to design multi-modal imaging studies to investigate possible causal relationships among neurocircuitry, regional GABA concentrations, and distinct GABA<sub>A</sub> receptor dynamics.

A global reduction of GABA was also suggested in the brains of insomnia patients with proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) [60]. Preliminary findings highlight the promising pharmacological intervention with eszopiclone for treating the regional cerebral disturbances seen in

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insomnia during sleep [56]. However, given the open-label protocol, the data should be interpreted with caution. Other research groups have investigated the effects of triazolam [41] and zolpidem [43, 44] on regional cerebral activity during sleep using blinded and placebo-controlled protocols. Their findings indicate that GABAergic hypnotics have the potential to ameliorate the cerebral over activity that is characteristic of insomnia. A caveat is that these studies were performed in healthy individuals with 'good' sleep, and thus it is inappropriate to generalize the findings to patients. Indeed, zolpidem appears to increase cerebral activity in a region- and disease-specific manner in patients with neurological disorders rather

than to decrease cerebral activity such as in healthy individuals. Going forward, in order to clarify the efficacy and mechanisms of action of sedating hypnotics in reducing CNS hyperarousal in insomnia, it is recommended that functional neuroimaging studies, of rigorous design, be employed to assess their effects on regional activity during sleep in insomniac samples.

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