**Introduction**

Functional neuroimaging techniques used to study narcolepsy include single-photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). SPECT shows the distribution of radioactive isotopes, the decay of which is associated with the emission of detectable single gamma photons. Examples of SPECT isotopes are \(^{99m}\)technetium-hexamethylpropylene amine oxime (\(^{99m}\)Tc-HMPAO) and \(^{99m}\)technetium-ethyl cysteinate dimer (\(^{99m}\)Tc-ECD), both indirect markers of regional cerebral blood flow (rCBF). PET shows the distribution of compounds labeled with positron-emitting isotopes, such as \(^{15}\)O-labeled water (H\(_2\)\(^{15}\)O), an indirect marker of rCBF, and \(^{18}\)F-fluorodeoxyglucose (\(^{18}\)F-FDG), a marker of glucose metabolism (CMRglu). Functional MRI measures the variations in brain perfusion related to neural activity, using a method based on the assessment of the BOLD (blood oxygen level-dependent) signal. SPECT and PET can also be coupled with synthetic ligands to specific receptors of interest, in order to investigate neuromodulatory changes associated with a condition.

In this chapter, we will review functional brain imaging studies conducted in narcoleptic patients and evaluating different pathophysiological aspects of the disorder: (1) neurotransmission studies targeting the cholinergic, serotonergic, and dopaminergic systems (PET/SPECT); (2) the distribution of brain activity across the sleep-wake cycle (PET/SPECT); (3) the neural circuits involved in emotional and reward processing (fMRI).

**Neurotransmission in narcolepsy**

The role of various neurotransmitters in the pathophysiology of narcolepsy has been explored using PET or SPECT coupled with specific ligands: acetylcholine (ACh), serotonin (5-HT), and dopamine (DA). Results are summarized in Table 27.1.

Only one study evaluated ACh function in narcolepsy. PET coupled with \(^{11}\)C]-methyl-4-piperidyl-benzilate (\(^{11}\)C-NMPB) was used to target muscarinic ACh receptors. No difference in muscarinic ACh binding was found in the pons, thalamus, striatum, and cerebral cortex of 11 patients compared with 21 controls [1].

Likewise there is a single work assessing 5-HT neurotransmission in narcolepsy. PET with \(^{2}\)H-methoxyphenyl-(N-2'-pyridinyl)-p-\(^{18}\)F-fluoro-benzamidoethylpiperazine (\(^{18}\)F-MPPF) was employed to study 5-HT\(_{1A}\) receptors. This study conducted on 14 patients showed an increase of 5-HT\(_{1A}\) binding – particularly in the anterior cingulate, temporal, and mesio-temporal cortices – during sleep compared with wakefulness [2]. However, no control group was recruited, which prevents from confirming the specificity of this result to narcolepsy.

More interest was devoted to DA neurotransmission in narcolepsy. Several studies are available with either PET or SPECT. Studies of presynaptic DA transporter binding converge to demonstrate no significant modification in narcoleptic patients, either with \(^{123}\)I-(N-(3-iodopropene-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) tropane (\(^{123}\)I-IPT) SPECT [3] or \(^{11}\)C-2β-carbomethoxy-3β-(4-fluorophenyl) tropane (\(^{11}\)C-CFT) PET [4]. As for postsynaptic D\(_2\)-receptor binding, only one study found a significant change between patients and controls: SPECT using \(^{123}\)I-ido benzamide (\(^{123}\)I-IBZM) demonstrated a D\(_2\) binding increase in the striatum of seven narcoleptic patients [3]. In addition, a positive correlation was observed between striatal D\(_2\) binding and the incidence of sleep attacks and cataplexy. However, other SPECT studies with IBZM [5, 6], as well as PET studies with \(^{11}\)C]raclopride [7, 8] or N-(3-[\(^{18}\)F]fluoropropyl)-spiperone (FPSP) [9] did not confirm striatal changes in D\(_2\) binding.

Altogether, available neuroimaging data do not consistently support the involvement of a neuromodulatory deficit in ACh, 5-HT, or DA systems for the pathophysiology of narcolepsy.

**Brain perfusion and glucose metabolism in narcolepsy**

Several functional neuroimaging studies were conducted to evaluate the distribution of brain activity during wakefulness and sleep in narcolepsy. Three of them described CMRglu [10, 11] and rCBF [12] patterns during resting wakefulness. Only preliminary reports compared rCBF values between sleep and waking [13, 14].

In a first PET study with \(^{18}\)F-FDG PET, CMRglu during baseline wakefulness was compared between 24 narcoleptic patients and 24 healthy subjects [10]. Significant decreases were observed in the posterior hypothalamus and medio-dorsal thalamus of patients. In this study, three patients had narcolepsy without cataplexy, and four were treated with medications (stimulants, antidepressants). In addition, no electroencephalographic (EEG) recording was carried out to objectively monitor...
Section 5: Neuroimaging of sleep disorders

Table 27.1. SPECT- and PET-ligand studies in narcolepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging</th>
<th>Target</th>
<th>Number of pat./ctrl.</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudo et al. [1]</td>
<td>PET 11C-NMPB</td>
<td>ACh (muscarinic)</td>
<td>11/21</td>
<td>None</td>
<td>No change</td>
</tr>
<tr>
<td>Derry et al. [2]</td>
<td>PET 18F-MPPF</td>
<td>SHT1A</td>
<td>14/0</td>
<td>12/14</td>
<td>N/A (no control group)</td>
</tr>
<tr>
<td>Eisensehr et al. [3]</td>
<td>SPECT IPT</td>
<td>DA (transporter)</td>
<td>7/7</td>
<td>None</td>
<td>No change</td>
</tr>
<tr>
<td>Rinne et al. [4]</td>
<td>PET 11C-CFT</td>
<td>DA (transporter)</td>
<td>10/15</td>
<td>None</td>
<td>No change</td>
</tr>
<tr>
<td>Eisensehr et al. [3]</td>
<td>SPECT 123I-IBZM</td>
<td>DA (D2)</td>
<td>7/7</td>
<td>None</td>
<td>Increase in striatum</td>
</tr>
<tr>
<td>Hublin et al. [5]</td>
<td>SPECT 123I-IBZM</td>
<td>DA (D2)</td>
<td>6/8</td>
<td>None</td>
<td>No change</td>
</tr>
<tr>
<td>Staedt et al. [6]</td>
<td>SPECT 123I-IBZM</td>
<td>DA (D2)</td>
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<td>No change</td>
</tr>
<tr>
<td>Khan et al. [7]</td>
<td>PET [11C]raclopride</td>
<td>DA (D2)</td>
<td>17/32</td>
<td>12/17</td>
<td>No change</td>
</tr>
<tr>
<td>Rinne et al. [8]</td>
<td>PET [11C]raclopride</td>
<td>DA (D2)</td>
<td>7/7</td>
<td>6/7</td>
<td>No change</td>
</tr>
<tr>
<td>MacFarlane et al. [9]</td>
<td>PET FPSP</td>
<td>DA (D2)</td>
<td>6/6</td>
<td>None</td>
<td>No change</td>
</tr>
</tbody>
</table>

N/A = not available.

Figure 27.1 Brain perfusion decreases during wakefulness in narcolepsy. Brain mapping of the regions where cerebral perfusion is decreased in narcoleptic patients compared to normal subjects (99mTc-ECD SPECT). Results are overlaid on T1 MRI, and are significant at FDR-corrected P < 0.05. (A) Significant hypoperfusion was observed in right posterior occipital lobe (arrowhead) and in the right parahippocampal gyrus (short arrow). Bilateral cingulate gyri and white matters in bilateral middle frontal gyri (long arrow) showed decreased cerebral perfusion. (B) Hypoperfusion was evident in bilateral posterior thalami (arrowhead) and in the white matters of the bilateral postcentral and supramarginal gyri (short arrow). (C) In the sagittal view of right hemisphere, significant hypoperfusion was observed in the caudate nucleus (arrowhead), in the subcallosal gyrus (short arrow), the cingulate gyrus extending along corpus callosum (long arrow), and in the parahippocampal gyrus (dotted arrow). (D) 3-dimensional rendering view showing decreased cerebral perfusion in bilateral paracentral areas (arrowhead) and superior/middle frontal gyri (short arrow). The frontal lobe is on the right and the occipital lobe on the left. (Reprinted from Neuroimage; Vol. 28(2); Yeon Joo E, Hong SB, Tae WS, Kim JH, Han SJ, Cho YW, Yoon CH, Lee SJ, Lee MH, Lee KH, Kim MH, Kim BT, Kim L. “Cerebral perfusion abnormality in narcolepsy with cataplexy”, pp 410–16, Copyright 2005, with permission from Elsevier.)

The subjects’ vigilance state during the study. To address these limitations, the same group then conducted a 99mTc-ECD SPECT study during wakefulness in 25 patients and the same number of controls: this time, all patients had a history of cataplexy and no history of pharmacological treatment (for sleepiness or cataplexy) [12]. Moreover, EEG was available during the study to ensure that the subjects were fully awake during the procedure. The study found decreased rCBF in the hypothalamus and thalamus, in line with the 18F-FDG PET study. Additional significant decreases were also observed in the caudate, superior/middle frontal gyri, postcentral gyrus, parahippocampal gyrus, and cingulate cortex (Figure 27.1). A more recent study by another group used PET with 18F-FDG during wakefulness in 21 patients with narcolepsy and cataplexy, and 21 matched controls. In contrast with the two previous studies, no significant CMRglu decrease was found. Instead, increases were observed in the anterior and mid cingulate cortex, and in the right visual association cortex. As in the earlier 18F-FDG PET study, the two major limitations of these results are the inclusion of patients treated with psychostimulants and/or anticataplectic drugs (14 out of 21), and the absence of objective (EEG) monitoring of vigilance state.

In brief, with the exception of one 18F-FDG PET study that found increased CMRglu particularly in the cingulate cortex [11], other functional neuroimaging studies during wakefulness confirmed a hypothalamic dysfunction in narcoleptic patients, in agreement with a deficit in the hypocretin system [10, 12]. Other hypoperfusions (thalamus, caudate, prefrontal, and post-central cortices, limbic areas) might relate to clinical features associated with narcolepsy, such as altered emotional processing (see below) and attentional deficits.

As for the study of brain activity during sleep, early studies using 133Xe inhalation showed that narcoleptics compared with controls had a lower rCBF during wakefulness mostly in the brainstem-cerebellum region, while at sleep onset compared to wakefulness rCBF decreased in controls but increased in narcoleptic patients in the same region [13, 15]. In contrast, a 99mTc-HMPAO SPECT study did not find any rCBF difference between wakefulness and rapid eye movement (REM) sleep in narcoleptic patients [14]. As this last study did not include a control group, the specificity of this result to narcolepsy could not be established. Future studies, using state-of-the-art functional neuroimaging techniques, should reevaluate brain activity...
patterns during the different stages of sleep in narcoleptic patients compared with controls.

**Neural correlates of emotional processing in narcolepsy**

Processing of emotional information potentially plays an important role in narcolepsy–cataplexy. Indeed it is well known that emotions, particularly those with a positive component (jokes, laughter, etc.), can trigger cataplectic episodes. Functional MRI studies therefore assessed brain responses to humorous stimuli in narcoleptic patients. In a first study, 12 narcoleptics with cataplexy and 12 controls were scanned during presentation of humorous and neutral pictures [16]. In patients, pharmacological treatment was discontinued for at least 14 days prior to the fMRI session. Humorous pictures (compared to neutral pictures) were associated with an increased amygdala response together with a decreased response in the hypothalamus of patients compared to controls (Figure 27.2). In a second fMRI study, a similar paradigm was used in 10 narcoleptic patients with cataplexy compared to 12 healthy controls [17]. Medications were stopped for at least five days prior to the experiment. In agreement with the previous study, higher brain response to humorous cartoons were observed in several areas including the amygdala (as well as the inferior frontal gyrus, superior temporal gyrus, insula, nucleus accumbens) in narcoleptics compared to controls. However, fMRI response in the hypothalamus to humorous stimulation was not found decreased in this study, but rather increased.

Not only positive emotional stimulation was assessed with fMRI in narcolepsy. Brain responses to unpleasant stimuli were also investigated in nine unmedicated narcoleptic patients with cataplexy and nine matched controls [18]. The task consisted in an aversive conditioning paradigm (visual conditioning stimuli and painful electrical stimulation). Results showed increased neural responses to conditioned stimuli in the amygdala and increased functional connectivity between the amygdala and medial prefrontal cortex in the control group but not in the narcolepsy group.

Altogether these studies suggest a dysfunction of amygdalo-hypothalamic and amygdalo-neocortical interactions during the processing of emotional information in narcoleptic patients, possibly underlying central mechanisms of cataplexy.

**Neural correlates of reward processing in narcolepsy**

Anticipation of reward (e.g., when playing games) constitutes a particular emotional experience prone to trigger cataplexy in humans [19], which suggests a potential involvement of the hypocretin system in reward brain circuits, and possible alterations of these circuits in narcolepsy with cataplexy. Accordingly, data in rodents show a close interplay between hypocretin neurons and reward-related brain regions, such as the nucleus accumbens and the DA ventral tegmental area [20–22]. In order to further evaluate a potential dysfunction of reward-related neural processes, an fMRI study was conducted in 12 unmedicated narcoleptic patients with clear-cut cataplexy and 12 matched healthy controls, while performing a task involving the mesolimbic and midbrain reward system [23]. This task consisted of a modified version of a monetary incentive delay task. Brain responses to high motivational cues included the ventral tegmental area in the control group, but not in the narcolepsy group. Responses to successful trials (compared to failed trials) revealed increased activity in the ventromedial prefrontal cortex and nucleus accumbens in the control group but not in the patients group. Likewise, increased

![Figure 27.2 Neural correlates of emotional processing in narcolepsy. Functional MRI response is decreased in the hypothalamus (A) and increased in the amygdala (B) during presentation of humorous pictures compared to neutral pictures, and more so in narcoleptic patients than in healthy controls (p < 0.001). (Adapted from Brain; Vol. 131(P2); S. Schwartza et al., “Abnormal activity in hypothalamus and amygdala during humour processing in human narcolepsy with cataplexy”; pp 514–522; Copyright 2008, with permission from Oxford University Press.)](image-url)
brain responses to successful positively cued trials were found in the nucleus accumbens and lateral prefrontal cortex in controls; in narcoleptics increased responses to these trials were found in the amygdala, consistent with reports of increased amygdala response to stimuli associated with highly positive emotions (see above). Finally, in the narcolepsy group, significant positive correlations were found between disease duration and fMRI responses to high motivational cues in the nucleus accumbens and ventromedial prefrontal cortex (Figure 27.3). Altogether these findings show evidence for a disruption of neural circuits involved in reward processing in narcolepsy. Furthermore, these data suggest a progressive functional recovery of reward-related brain structures in narcoleptic patients with longer disease duration.

**Conclusion**
Functional brain imaging studies in narcolepsy can be summarized as follows:

1. Narcolepsy is not associated with a specific alteration of the central cholinergic or dopaminergic activity.
2. Functional brain activity patterns of narcoleptic patients during resting wakefulness are characterized by abnormalities located in the hypothalamus – in agreement with a loss of hypocretinergic neurons in this disease – as well as in various cortical areas, possibly in relation with cognitive and attentional deficits encountered by these patients.
3. Altered emotional processing associated with cataplexy also involves a dysfunction of the hypothalamus, in addition to neural changes within limbic structures, in particular the amygdala.
4. Narcolepsy with cataplexy finally involves a dysfunction of neural circuits implicated in reward processing and encompassing the nucleus accumbens and the midbrain ventral tegmental area.

Further studies should investigate more closely brain activity changes across the sleep/wake cycle in narcoleptic patients. Indeed narcolepsy not only induces severe daytime symptoms, but is also frequently associated with sleep disruption, including changes in sleep microarchitecture [24, 25].

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