Neuroimaging of Narcolepsy

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Abstract: Neuroimaging techniques have refined the characterization of neural structures involved in the regulation of normal sleep-wake cycle in healthy humans. Yet brain imaging studies in patients with sleep disorders still remain scarce. In narcoleptic patients, structural and functional brain imaging studies have suggested the involvement of the hypothalamus in the pathophysiology of narcolepsy, plausibly consistent with an impairment of the hypocretin-orexin system. Some recent studies have further suggested that cataplexy, a key feature of the narcoleptic syndrome, might result from a dysfunction of the hypothalamus and its interactions with limbic structures. Other neuroimaging studies have focused on the assessment of neurotransmission and the effects of pharmacological treatment in narcoleptic patients. However, the neural correlates of some main symptoms of narcolepsy, such as sleep attacks, hypnagogic/hypnopompic hallucinations and sleep paralysis, are still unknown. In addition, the description of brain activity patterns during sleep in narcoleptic patients needs further investigation. Neuroimaging has proven to be a valuable tool for the study of sleep regulation and sleep disorders; its future developments will undoubtedly improve our understanding of the neural mechanisms underlying narcolepsy with cataplexy.

Keywords: Sleep, Narcolepsy, Cataplexy, Modafinil, Functional Neuroimaging, fMRI, PET, SPECT.

INTRODUCTION

Brain imaging offers a non-invasive approach to study the neural mechanisms of normal physiological functions as well as pathogenic processes in neurological diseases. Two broad categories of neuroimaging modalities are used. On the one hand, structural imaging allows detecting differences in brain morphology associated with a specific condition. In recent years, it has been demonstrated that differences that may not be identifiable by visual inspection can be revealed by using automated, statistical methods such as voxel-based morphometry (VBM). Based on high-resolution magnetic resonance imaging (MRI) scans, this technique compares tissue composition (grey and white matter) across all brain regions between groups. Proton magnetic resonance spectroscopy (^{1}H-MRS) is used to assess the regional brain content in different compounds such as N-acetylaspartate (NAA), Creatine (Cr) and Phosphocreatine (PCr), the ratio of which (NAA/Cr+PCr) provides a local measure of neuronal function (neuronal quantity or activity of existing neurons). On the other hand, functional imaging allows assessing regional brain activity between two separate conditions or in association with a specific physiological process. The main techniques, ranged in increasing order of spatial and temporal resolution, are single photon emission computed emission 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-hexamethylene-propyleneamine-oxime (^{99m}Tc-HMPAO) and ^{99m}technetium-ethylcysteinate dimer (^{99m}Tc-ECD), both indirect markers of regional cerebral blood flow (rCBF). PET shows the distribution of compounds labeled with positron-emitting isotopes. Commonly used PET isotopes are [^{15}O]-labeled water ($H_2{}^{15}O$), an indirect marker of rCBF, and [^{18}F]fluorodeoxyglucose (^{18}FDG), a marker of glucose metabolism. FMRI 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. The BOLD signal relies on the relative decrease in deoxyhemoglobin concentration that follows the local increase in cerebral blood flow in an activated brain area. Both SPECT and PET can also be coupled with synthetic ligands to specific receptors thereby allowing the comparison of the brain distribution of different neurotransmitters between conditions.

In healthy humans, functional neuroimaging has been successfully used to characterize the patterns of brain activity associated with the different stages of sleep. These studies mainly used PET to compare brain activity between non-rapid-eye-movement (NREM) sleep or rapid-eye-movement (REM) sleep and wakefulness. At a global level, it has been shown that brain glucose metabolism drops by approximately 40% during NREM sleep compared to wakefulness, while it remains at a similar level between REM sleep and waking [1]. At a regional level, only decreases in brain activity have been found during NREM sleep. These deactivations were located in the brainstem, thalamus, basal ganglia, hypothalamus, basal forebrain, prefrontal cortex, anterior cingulate cortex and precuneus [2-6]. Conversely, both regional increases (pontine tegmentum,

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thalamus, amygdala, hippocampus, anterior cingulate cortex, temporo-occipital areas, basal forebrain) and decreases (dorsolateral prefrontal cortex [DLPFC], posterior cingulate gyrus, precuneus and inferior parietal cortex) in brain activity have been found in association with REM sleep [2, 7, 8]. These patterns identify the neural structures involved in the generation or regulation of sleep stages. However, these early studies, based on an approach that averages brain activity over time periods of more than one minute, cannot account for activations related to short neural events or sleep microarchitecture, *i.e.* NREM sleep oscillations and REM sleep ocular saccades. Indeed, during NREM sleep, brain activity is organized by spontaneous coalescent cerebral rhythms: spindles and slow waves [9]. On electroencephalographic [EEG] recordings, spindles appear as waxing-and-waning oscillations at a frequency of about 11-15 Hz and duration of more than 500 ms, and are prominent during stage 2 of NREM sleep. During deeper stages of NREM sleep, they are progressively replaced by low frequency high amplitude waves at a frequency of 0.5-4 Hz (slow waves). Recently, combined EEG/fMRI studies have demonstrated that local increases in brain activity are associated with spindles (thalamus, anterior cingulate cortex, insula, superior temporal gyrus) [10] and slow waves (brainstem, cerebellum, precuneus, posterior cingulate gyrus, inferior frontal gyrus and parahippocampal gyrus) [11]. Besides showing the brain regions that participate in the generation or modulation of these essential rhythms of NREM sleep, these data also emphasize that NREM sleep is not only a stage of brain activity decrease, but is also characterized, on a refined temporal scale, by transient and phasic increases in brain activity. Phasic activity during REM sleep is characterized by ponto-geniculo-occipital (PGO) waves, named according to their most frequent sites of recording in animals, and closely related to the occurrence of REM sleep ocular saccades. Functional neuroimaging studies have shown that ocular saccades in humans are associated with brain activity in the pontine tegmentum, thalamus and occipital cortex [12-14], therefore providing further evidence that PGO waves can also be recorded in humans and organize brain activity during REM sleep.

In sleep medicine, both structural and functional neuroimaging modalities have investigated the pathophysiology of various sleep disorders. Despite the constraints imposed by studies on patients (such as the presence of comorbidities and different pharmacological treatments, lower samples, etc.), neuroimaging has in several instances brought new theories or corroborated hypotheses on the mechanisms of these diseases. The contribution of neuroimaging to sleep medicine has been reviewed in detail elsewhere [15-18]. Here we focus on the brain imaging studies dedicated to narcolepsy. We will first review the structural findings evidenced by VBM and spectroscopy. Then we will describe the use of functional brain imaging techniques in narcoleptic patients, including SPECT, PET and fMRI studies acquired either during baseline waking state, active paradigms or after pharmacological treatment.

STRUCTURAL NEUROIMAGING OF NARCOLEPSY

Early reports have described the structural brain MRI of patients with narcolepsy. One study has reported the presence of bilateral T2 hyperintensities in the pons of 3 drug-resistant narcoleptic patients, thereby suggesting an involvement of pontine structures in the pathophysiology of narcolepsy [19]. However two other studies found no pontine lesions [20, 21], except in 2 patients also presenting with chronic arterial hypertension [21]. The latter finding therefore questions the specificity of pontine abnormalities, which actually might relate to non-specific vascular changes rather than narcolepsy *per se*.

VBM

A few studies have used VBM to systematically compare grey and white matter volumes between narcoleptic patients and healthy controls. Results from these studies are mostly inconsistent. One study found no difference in 15 patients presenting with narcolepsy-cataplexy and hypocretin-1 reduction compared to 15 age and sex matched healthy controls [22]. All other studies reported regional decreases in grey matter volumes, as summarized in Fig. (**1**). Two of these studies found decreases of cortical grey matter in 12 narcoleptic patients respectively in inferior temporal/frontal [23] and right prefrontal/frontomesial regions [24], possibly contributing to cognitive impairments such as attentional deficits experienced by narcoleptic patients [25]. Two other studies reported decreases of grey matter volume in the hypothalamus of respectively 29 [26] and 19 [27] narcoleptic patients, in addition with other grey matter reductions in the cerebellar vermis, superior temporal gyrus and right nucleus accumbens [26]. These observations suggest that neuronal losses may affect hypocretinergic structures (*i.e.*, hypothalamus) as well as some major sites of hypocretin projections (*i.e.*, nucleus accumbens). Discrepancies between the reported VBM studies might be due to differences in data preprocessing or patient sampling, *e.g.* disease duration or pharmacological treatment. The latter seems actually particularly variable from one study to another, which might influence the results and their significance, because it is difficult to disentangle the effects of the disease from those of the medication. For instance, while most patients were medicated for excessive daytime sleepiness (EDS) in two studies [22, 24], half of them were drug naïve in a third study [23]. This strongly suggests that future studies should cautiously select homogeneous groups of newly diagnosed and unmedicated patients with narcolepsy-cataplexy to reliably identify structural brain alterations specific to narcolepsy.

Spectroscopy

Local concentrations in a few metabolites have been assessed with ^{1}H-MRS, and the results are summarized in Table **1**.

Hypothalamic abnormalities in narcolepsy have been found in one ^{1}H-MRS study, which has demonstrated a decrease of NAA/Cr+PCr in the hypothalamus of 23 patients compared with 10 controls [28]. This reduced ratio might reflect a local neuronal loss, but might also be due to neuronal dysfunction in the hypothalamus. In agreement with earlier structural reports that found no specific lesion in the pons of narcoleptic patients [20, 21], another ^{1}H-MRS study described no significant change of NAA/Cr+PCr ratios in the ventral pons of 12 patients compared to 12 controls [29]. It is still unknown whether such metabolite changes can

be found in other subcortical structures and in cortical areas of narcoleptic patients.

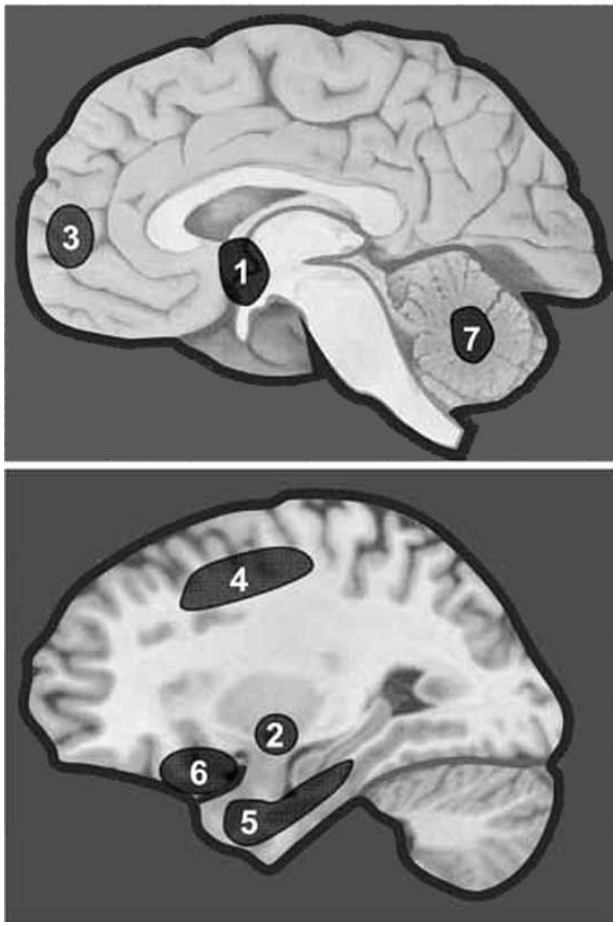

Fig. (1). Structural abnormalities in narcolepsy. This figure summarizes the grey matter decreases found in narcoleptic patients with voxel-based-morphometry (VBM) (upper panel = medial view; lower panel = lateral view). These decreases affect (**1**) the hypothalamus, (**2**) the right nucleus accumbens, (**3**) the medial prefrontal cortex, (**4**) the right prefrontal cortex, (**5**) the inferior temporal gyrus, (**6**) the inferior frontal gyrus, and (**7**) the cerebellar vermis. Adapted from Desseilles *et al*., SLEEP 2008.

Regional concentrations of other brain metabolites were also assessed with ^{1}H-MRS. One study reported the absolute levels of gamma aminobutyric acid (GABA) and glutamate (Glu) in the medial prefrontal cortex and basal ganglia of 17 narcoleptic patients with cataplexy compared to 17 healthy controls [30]. They found no difference in Glu levels in both areas and for GABA level in the basal ganglia, but a higher GABA concentration in the medial prefrontal cortex of patients. Because GABA is a major inhibitory neurotransmitter, this result may be consistent with the decrease in blood flow [31] and glucose metabolism [32] reported in the medial prefrontal cortex of narcoleptic patients during wakefulness (see below, section *Regional brain activity across the sleep-wake cycle in narcolepsy*). Several limitations of this study should however be mentioned, such as the low signal-to-noise ratio of the GABA signal with ^{1}H-MRS, the heterogeneous sample of narcoleptics including only 6 drug-naïve out of 17 patients, and the absence of control for the level of vigilance during scanning (12 patients slept and 5 were awake during data acquisition). To our knowledge, GABA and Glu levels in brain areas other than basal ganglia and medial prefrontal cortex have not yet been reported for narcoleptic patients.

FUNCTIONAL NEUROIMAGING OF NARCOLEPSY

Neurotransmission in Narcolepsy: SPECT and PET Ligand Studies

Using PET or SPECT coupled with specific ligands, the role of three neurotransmitters in the pathophysiology of narcolepsy has been probed: acetylcholine (ACh), serotonin (5-HT), and dopamine (DA). Results are summarized in Table **2**.

The cholinergic system was studied using PET coupled with [^{11}C]N-methyl-4-piperidyl-benzilate ([^{11}C]NMPB), that targets muscarinic ACh receptors. This study found no difference of muscarinic ACh binding in the pons, thalamus, striatum and cerebral cortex of 11 drug-naïve patients compared with 21 controls [33]. Therefore, available neuroimaging data do not support an involvement of ACh in narcolepsy.

Serotonergic neurotransmission was assessed in 14 narcoleptic patients using 2'-Methoxyphenyl-(*N*-2'-pyridinyl) -*p*-^{18}F-fluoro-benzamidoethylpiperazine (^{18}F-MPPF), a PET ligand to 5HT-1A receptors [34]. This study showed that the 5HT-1A binding was increased at a global and a regional level (anterior cingulate, temporal and mesio-temporal cortices) during sleep compared to wakefulness, but failed to demonstrate whether this effect was specific to narcolepsy, because no control group was included. Such higher receptor availability (*i.e.* decreased endogenous 5-HT release) during sleep might not be specific of the disease, as 5-HT is known to promote waking and suppress (REM) sleep [35].

Additional studies have investigated DA

Table 1. Spectroscopy (^{1}H-MRS) Studies in Narcolepsy

Study	Metabolite	Number of pat./ctrl.	Cataplexy	Treatment	Results
Lodi *et al*. (2004)	NAA/Cr + PCr	23/10	10/23	16/23	Decrease in hypothalamus
Ellis *et al*. (1998)	NAA/Cr + PCr	12/12	All	Not available	No change (brainstem)
Kim *et al*. (2008)	Glu	17/17	All	11/17	No change
Kim *et al*. (2008)	GABA	17/17	All	11/17	Increase in medial prefrontal

From left to right: reference of the study, brain metabolite assessed, number of patients and controls studied, proportion of patients with a history of cataplexy, proportion of patients exposed to medication for narcolepsy, and main result of the study.

neurotransmission in narcolepsy, but their results are mostly inconsistent. One SPECT study using [^{123}I](*S*)-2-hydroxy-3-iodo-6-methoxy-([1-ethyl-2-pyrrolidinyl]methyl)benzamide (IBZM) demonstrated an increase in postsynaptic D2-receptor binding in the striatum of 7 drug naïve narcoleptic patients (compared to 7 controls) and a significant positive correlation of this binding with the incidence of sleep attacks and cataplexy [36]. By contrast, results from other IBZM SPECT [37, 38], as well as from [^{11}C]-raclopride [39, 40] and N-(3-[^{18}F]fluoropropyl)-spiperone (FPSP) [41] PET studies did not show such enhancement of D2 binding in the basal ganglia. Reasons for this discrepancy remain unclear. The D2 changes observed by Eisensehr and colleagues [36] may not be attributed to the effects of treatment as all patients were unmedicated for EDS and/or cataplexy. Their significance is however weakened by the low sample of patients (n=7) included in the study. Results on striatal presynaptic DA transporter are more convergent, with no significant alteration evidenced in narcoleptic patients, when using [^{123}I](*N*)-(3-iodopropene-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl)tropane (IPT) SPECT [36] or [^{11}C]-2β-carbomethoxy-3β-(4-fluorophenyl)tropane ([^{11}C]-CFT) PET [42]. Altogether, the available neuroimaging studies do not consistently support a primary impairment of the DA system in narcolepsy.

Regional Brain Activity across the Sleep-Wake Cycle in Narcolepsy

Surprisingly, only few studies have examined the distribution of brain activity in narcoleptic patients during waking or during the different stages of sleep. Two studies, conducted by the same group, have described the regional patterns of brain glucose metabolism [32] and blood flow [31] during resting wakefulness (Fig. **2**). Two other studies have compared brain activity assessed by cerebral blood flow during waking and sleep [43, 44].

In a first study, conducted with ^{18}FDG PET, Joo and collaborators compared brain glucose metabolism during baseline waking in 24 narcoleptic and 24 healthy subjects [32]. They demonstrated that narcoleptics displayed a significant decrease of brain activity in the posterior hypothalamus and mediodorsal thalamus, and nearly significant decreases in various cortical areas (superior frontal gyrus, inferior parietal lobule, supramarginal gyrus, precuneus). However, the sample of patients in this study was clinically heterogeneous as 3 patients had no cataplexy, and 4 patients had taken stimulant and/or antidepressant medication (stopped a few days before scanning). In addition, no objective monitoring of their state of vigilance was conducted while the patients were scanned. In a second study, the same group conducted a ^{99m}Tc-ECD SPECT to compare rCBF in narcoleptics (n=25) and healthy controls (n=25) during wakefulness [31]. This time, all patients also suffered from cataplectic attacks. In addition, they were all newly diagnosed, and had no history of pharmacological treatment for EDS or cataplexy. The subjects' level of vigilance was objectively monitored with EEG during scanning. The results of this study revealed a decreased perfusion of hypothalamus, thalamus, caudate and multiple cortical areas (superior/middle frontal gyri, postcentral gyrus, parahippocampal gyrus, cingulate cortex) in narcoleptic patients. While the results from both studies are not exactly similar (especially for the distribution of cortical activity), they suggest a dysfunction of thalamic and hypothalamic structures in narcolepsy. A major issue is however the control of the state of vigilance, which is absent in the first study. In the SPECT study, the monitoring of wakefulness is carried out with EEG, but it actually shows that narcoleptic subjects tended to fall asleep a few minutes after the isotope injection (6.7 ± 3.6 min. [range 4-10]) while no control subject slept within the first 10 minutes after the injection. Therefore, the deactivations reported by Joo and collaborators might also reflect, at least partially, differences in vigilance states (*i.e.* sleep versus wake) between patients and controls, rather than a specific effect of the disease. Indeed some of the reported areas (thalamus, hypothalamus, cingulate cortex) are also brain structures known to decrease their activity during NREM sleep compared to wakefulness in normal subjects [4, 6, 45].

Table 2. SPECT- and PET-Ligand Studies in Narcolepsy

Study	Imaging	Target	Number of pat./ctrl.	Treatment	Results
Sudo *et al.* (1998)	PET ^{11}CNMPB	ACh (muscarinic)	11/21	none	No change
Derry *et al.* (2005)	PET ^{18}F-MPPF	5HT-1A	14/0	12/14	N/A (no control group)
Eisensehr *et al.* (2003)	SPECT IBZM	DA (D2)	7/7	none	Increase in striatum
Hublin *et al.* (1994)	SPECT IBZM	DA (D2)	6/8	none	No change
Staedt *et al.* (1996)	SPECT IBZM	DA (D2)	10/10	none	No change
Khan *et al.* (1994)	PET [^{11}C]-raclopride	DA (D2)	17/32	12/17	No change
Rinne *et al.* (1995)	PET [^{11}C]-raclopride	DA (D2)	7/7	6/7	No change
MacFarlane *et al.* (1997)	PET FPSP	DA (D2)	6/6	none	No change
Eisensehr *et al.* (2003)	SPECT IPT	DA (transporter)	7/7	none	No change
Rinne *et al.* (2004)	PET [^{11}C]-CFT	DA (transporter)	10/15	none	No change

From left to right: reference of the study, modality of brain imaging, targeted neurotransmitter, number of patients and controls studied, proportion of patients exposed to medication for narcolepsy, and main result of the study.

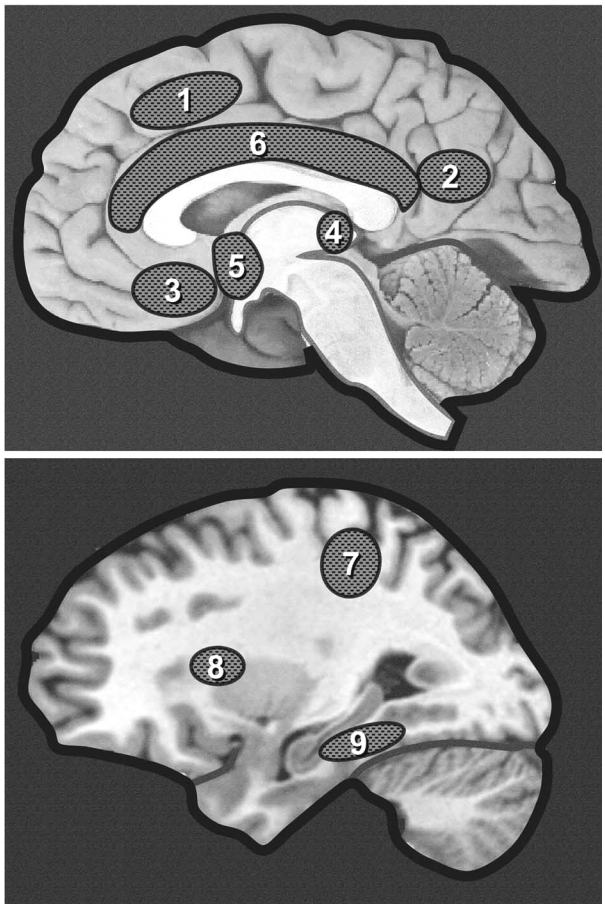

Fig. (2). Brain activity decreases during wakefulness in narcolepsy. This figure summarizes the regional brain activity decreases found in narcoleptic patients during resting wakefulness (upper panel = medial view; lower panel = lateral view). These decreases affect (**1**) the superior frontal gyrus, (**2**) the inferior parietal lobule, (**3**) the rectal/subcallosal gyrus, (**4**) the dorsal thalamus, (**5**) the hypothalamus, (**6**) the cingulate cortex, (**7**) the postcentral/supramaginal gyrus, (**8**) the caudate nucleus, and (**9**) the parahippocampal gyrus. Adapted from Desseilles *et al*., SLEEP 2008.

In an early study, Meyer and collaborators used ^{133}Xe inhalation to assess rCBF during wakefulness and sleep in narcoleptic subjects [43]. They showed that narcoleptics had a lower activity in the brainstem and cerebellum during wakefulness than controls, while, during sleep compared to wakefulness, brain activity increased in the patients across multiple brain areas including temporo-parietal regions. In contrast, using ^{99m}Tc-HMPAO SPECT, Asenbaum and colleagues did not find any significant difference in regional brain activity between wakefulness and REM sleep in 6 narcoleptic patients [44]. However, this study did not compare the patients to a control group. Results from both these functional brain imaging studies conducted during sleep in narcolepsy are still very preliminary, and no consistent conclusion can thus be drawn on the activity of the narcoleptic brain during sleep at the moment. Further studies, using state-of-the-art functional neuroimaging techniques, should reassess the patterns of brain activity during sleep in larger samples of narcoleptic patients compared to healthy controls.

Neural Correlates of Emotional Processing and Cataplexy in Narcoleptic Patients

Cataplexy is a frequent symptom in narcoleptic patients. It is characterized by a sudden loss of muscle tone usually triggered by strong emotional experience. Cataplexy may be limited to few muscular groups or result in a generalized atonia. In humans, the neural correlates of cataplexy have only been assessed by two preliminary reports. In both studies, the cataplexy attacks involved generalized atonia. On the one hand, Chabas and coworkers described the brain perfusion changes associated with cataplexy in one single patient, using ^{99m}Tc-ECD SPECT [46]. This 68-year-old woman suffered from status cataplecticus following the withdrawal of antidepressant medication used to treat cataplexy, but was still treated with modafinil at the time of scanning. Compared to a non-cataplectic waking condition, the cataplectic episode in this patient was associated with activation of the orbitofrontal cortex, the cingulate gyrus, the right putamen and right temporal cortex. No concurrent EEG monitoring of the state of vigilance was assessed in both conditions. The reported cataplectic episode was unusual in the sense that it was not triggered by any emotional stimuli. On the other hand, using the same imaging modality, Hong and colleagues reported the activation patterns in two narcoleptic patients during cataplexy compared to a baseline waking condition [47]. One of the two patients also suffered from obstructive sleep apnea. In contrast to the previous study, cataplexy was triggered by emotional stimulation, the quality of which however differed between the two patients (laughing in one patient, and sad story in the other). An advantage of this study was the simultaneous EEG monitoring, ensuring that the patients were still awake during the cataplectic attack. The results demonstrated increased activity in the brainstem, thalamus, basal ganglia, amygdala, hippocampus, cingulate and sensorimotor cortices, but also regional deactivations in the prefrontal and occipital cortex. They could also record REM sleep in one of the patients and comparison between cataplexy and REM sleep actually showed results quite similar to those of cataplexy versus waking. Interestingly, some brain activity patterns found during cataplexy are also those characteristic of normal REM sleep [7, 48] (activation of brainstem, thalamus, amygdala, cingulate cortex; deactivation of prefrontal cortex), suggesting some commonalities in the generators of both conditions. Enhanced activity in the amygdala and cingulate gyrus may also relate to the emotionality of the cataplectic trigger. The interpretation of these findings is however obscured by the very low number of patients, the heterogeneity of the cataplexy (*e.g.* type of triggering stimulation), concurrent pharmacological treatment (*e.g.* modafinil) or medical condition (*e.g.* sleep apnea), and the absence of comparison with healthy controls. Future studies using well-designed protocols on larger and more homogeneous samples of patients compared to controls are needed to reach consistent results and identify the neural structures associated with cataplexy. The lack of predictability of cataplectic attacks in experimental settings however makes it very difficult to investigate this condition with functional neuroimaging techniques.

Cataplexy is often triggered by emotions, and especially by positive stimuli such as jokes, laughter, etc. One could thus hypothesize that the processing of emotional stimulation is altered in narcoleptic patients, possibly contributing to the generation of cataplexy. Therefore, instead of directly studying unpredictable cataplectic attacks, two groups resorted to well-designed fMRI protocols to compare the neural responses to humorous stimuli between narcoleptics and healthy controls. Schwartz and colleagues scanned 12 narcoleptic patients and 12 healthy controls during presentation of humorous and neutral pictures [49]. All patients were known to also suffer from cataplexy and their pharmacological treatment was discontinued for at least 14 days before the experimental session. Contrasting the neural responses associated with humorous and neutral pictures demonstrated that the humorous pictures elicited increased activation of the amygdala and lower response of the hypothalamus in patients compared to controls (Fig. **3**). This result suggests a dysfunction of amygdalo-hypothalamic interactions during the processing of emotional information in narcoleptic patients, possibly underlying central mechanisms of cataplexy. A more recent study, conducted by Reiss and collaborators, used a similar paradigm to assess the neural correlates of humour processing in 10 narcoleptic patients compared to 12 healthy controls [50]. All patients were likewise known to have a history of cataplexy, five patients who had been treated with anti-narcoleptic drugs also stopped these medications (for at least 5 times the half-life of the longest half-life of the medication or five days minimum). In agreement with the study by Schwartz *et al*. they found a higher activation to humorous cartoons in narcoleptics compared to controls in several areas including the amygdala (and the inferior frontal gyrus, superior temporal gyrus, insula, nucleus accumbens). However, humour-related activity increase was also found in the hypothalamus, a result that is not consistent with the significant activity decrease in the patients' hypothalamus demonstrated by Schwartz *et al*. Whether differences in the stimuli used (funny pictures in Schwartz *et al*. versus cartoons with text in Reiss *et al*.) or differences in the subjective judgments of the humorous quality of the stimuli (patients with narcolepsy-cataplexy had similar humour ratings as controls in Schwartz *et al*. while patients rated significantly fewer humorous cartoons as funny in Reiss

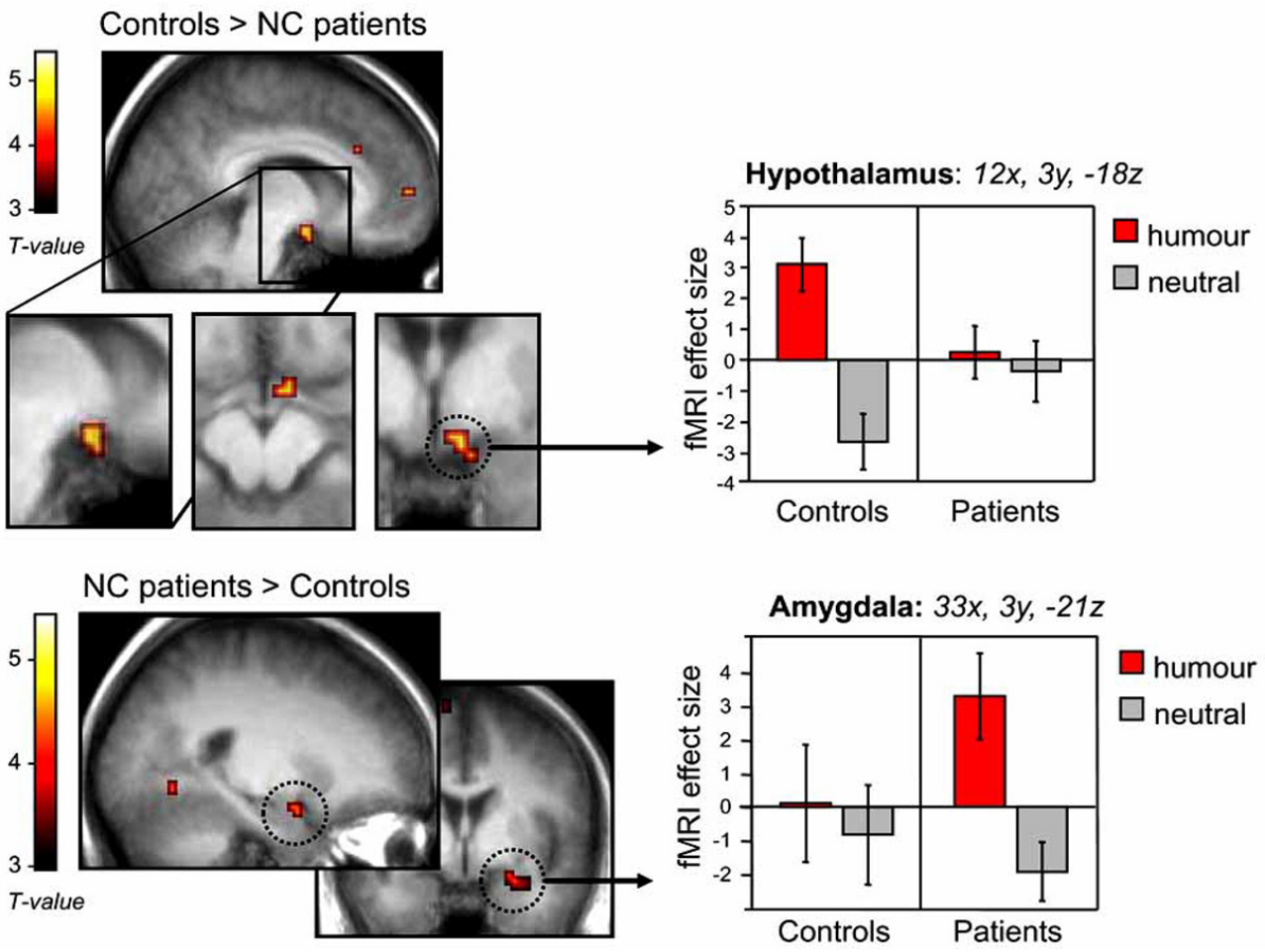

Fig. (3). Abnormal neural processing of emotional input in narcolepsy. The brain activity is dampened in the hypothalamus (upper panel) and increases in the amygdala (lower panel) during the presentation of humorous pictures compared to neutral pictures, and more in narcoleptic patients than in healthy controls. Adapted from Schwartz *et al.*, Brain 2008.

et al.) may explain these diverging results for the response in the hypothalamus remains to be settled.

Altogether, the reported brain activations associated with cataplexy are mainly based on single cases, which limits their significance. Nonetheless, studies on larger samples of patients have provided evidence that humour processing was affected in narcoleptic patients due to neural activity changes in specific brain structures. Although the direction of these changes is still ambiguous, the available results point to an involvement of the hypothalamus and amygdala in these dysfunctional networks. Because emotional stimulation and cataplexy are often associated, these studies suggest a role for limbic and hypothalamic structures in the generation of cataplexy.

Functional Imaging Effects of Treatment

Narcoleptic attacks can be efficiently prevented by the intake of stimulant medications. Amphetamines were among the earliest drugs used. Because of their side effects, they have been replaced in most cases by non-amphetamine stimulant medications, such as modafinil. Functional brain imaging reports studying the neural effects of these drugs are summarized in Table **3**.

The neural changes associated with the administration of amphetamines (single dose) in narcoleptic patients were studied in a preliminary fMRI report that assessed regional changes in brain activity associated with auditory and visual stimulation in 2 narcoleptic patients compared to 3 healthy controls [51]. Activation of the primary and association sensory cortices was larger after administration of a single dose of amphetamines in narcoleptics, but was reduced in controls after drug intake. Due to the low sample of subjects, this finding remains difficult to interpret.

Several studies investigated the functional brain changes associated with modafinil intake in humans. Joo *et al*. assessed changes in brain perfusion induced by a single dose of modafinil (400 mg) in 21 healthy subjects using ^{99m}Tc-ECD SPECT [52]. During wakefulness (as monitored by simultaneous EEG), modafinil compared to placebo triggered a higher activation of the pons and several cortical areas (including the prefrontal gyrus, insula, cingulate gyrus, left temporal and parahippocampal gyrus). These data suggest that modafinil influences neural networks involved in arousal, emotions and executive functions. The executive network activation is in agreement with an earlier fMRI study showing that a single dose of modafinil (200 mg) can counteract the negative effects of a single night of sleep deprivation on working memory (at a moderate level of task difficulty) in association with the recruitment of prefrontal and parietal executive areas [53].

The effects of modafinil have also been assessed in narcoleptic patients with fMRI. Ellis and colleagues probed the brain activations associated with visual and auditory stimulation in 8 narcoleptics and 8 healthy controls both before and after a single dose of modafinil (400 mg) [54]. They could not demonstrate any significant change between pre- and post-modafinil conditions in either controls or narcoleptics. Nevertheless, there was in both groups a negative correlation between the pre- and post-modafinil activation levels, suggesting that modafinil might still modulate brain reactivity to external stimulation.

Finally, two studies assessed brain activity changes induced by a prolonged administration of modafinil in narcoleptics during the baseline waking state. Using ^{18}FDG PET, Kim and collaborators scanned 8 narcoleptics and 8 healthy controls before and after 2 weeks of modafinil treatment [55]. In both pre- and post-treatment conditions,

Table 3. Functional Brain Imaging of Anti-Narcoleptic Drugs

Study	Howard *et al.* (1996)	Joo, Tae *et al.* (2008)	Ellis *et al.* (1999)	Kim *et al.* (2007)	Joo, Seo *et al.* (2008)
Imaging	fMRI	SPECT [99mTc]-ECD	fMRI	PET ^{18}FDG	SPECT [99mTc]-ECD
Drug	dexamphetamine	modafinil	modafinil	modafinil	modafinil
Dose (daily)	10 mg	400 mg	400 mg	100-400 mg	100-400 mg
Duration	single dose	single dose	single dose	2 weeks	4 weeks
Placebo	No	Yes	Yes	No	Yes
Paradigm	Visual-auditory	Waking rest	Visual-auditory	Waking rest	Waking rest
Number of pat./ctrl.	2/3	0/21	8/8	8/8	32/0
Cataplexy	All	N/A	All	6/8	All
Results	Larger activation in sensory cortex of patients	Increased activity in pons, prefrontal, insula, cingulate, left temporal and parahippocampal of healthy subjects	No significant change	Increased activity in left hippocampus of patients	Increased activity in prefrontal and decreased activity in precentral, hippocampus, fusiform and cerebellum of patients

From up to bottom: modality of brain imaging, studied drug, daily dose administered, duration of treatment with this drug, presence of a placebo condition, experimental paradigm, number of narcoleptic patients and healthy controls studied, proportion of patients with a history of cataplexy, and main results. N/A = non applicable.

narcoleptics displayed segregated areas of hypometabolism compared to controls, including the brainstem, thalamus and mesio-temporal areas. The authors also demonstrated that left hippocampus was more activated during the post-treatment condition in narcoleptics, but did not contrast this effect with those observed in controls. Therefore, it is not possible to determine whether this post-modafinil hippocampal activation is specific to narcoleptic patients. Indeed, the SPECT study of Joo and colleagues suggested that modafinil can also increase activity of mesio-temporal areas in healthy subjects [52]. Other limitations of the Kim *et al*. study are the absence of a placebo condition and the lack of wake/sleep monitoring by EEG during and after the isotope injection. A second study was conducted by Joo and colleagues using ^{99m}Tc-ECD SPECT [56]. They studied a large sample of 32 narcoleptic patients treated with modafinil during 4 weeks compared to 21 placebo-treated patients. All subjects were monitored with EEG during the SPECT procedure. These results demonstrated that modafinil treatment increased brain activity in dorsolateral and medial aspects of prefrontal cortex, but also decreased the activity of precentral, hippocampal, fusiform and cerebellar regions. However, no group of healthy controls was included in this study, preventing any conclusion about the specificity of this effect to narcolepsy. Because the subjects not receiving modafinil had a shorter sleep latency after receiving the isotope (range 3-10 minutes) compared to the treated patients (range 6-15 minutes), some of the observed brain activity changes might also be due to some unspecific effects due to differences in vigilance levels rather than effects of modafinil *per se*. Indeed the post-modafinil activated prefrontal areas also belong to structures that are more active during wakefulness compared to NREM sleep in healthy subjects [57].

In summary, functional neuroimaging has successfully described the immediate effects of acute administration of modafinil on the brain activity of healthy subjects. No well-defined neural changes could be demonstrated with a single dose of modafinil in narcoleptic patients. Results obtained after several weeks of administration of modafinil are also still preliminary because none of these reports has studied the placebo-controlled effects of modafinil in a large sample of narcoleptic patients compared to healthy subjects.

CONCLUSION AND PERSPECTIVES

Brain imaging studies in narcoleptic patients have been conducted using different imaging modalities. Their results can be summarized as follows:

1. Narcolepsy is characterized by structural abnormalities located in the hypothalamus, in agreement with a loss of hypocretinergic neurons in this disease, as well as in various associative cortices, possibly in relation with the cognitive deficits encountered by patients.
2. Narcolepsy is not associated with a specific alteration of the central cholinergic or dopaminergic systems.
3. Functional brain activity patterns of narcoleptic patients during resting wakefulness parallel the changes demonstrated by structural imaging as they also indicate a dysfunction of the hypothalamus and multiple cortical areas.
4. Altered emotional processing associated with cataplexy also involves a dysfunction of the hypothalamus, in addition to neural changes within emotional-limbic structures.

On the one hand, future studies should address changes in brain activity associated with narcolepsy during the different stages of sleep using large samples of patients and controls. Such data would contribute to a better understanding of sleep regulation and disturbances in narcoleptic patients. On the other hand, functional MRI studies have begun to reveal the neural bases of emotion-triggered cataplexy. We proposed that similar approaches using dedicated experimental designs could also help understand the neural mechanisms underlying sleep attacks. The neural effects of medications used to treat narcolepsy and/or cataplexy should also be assessed in more detail using placebo-controlled protocols comparing patients and healthy volunteers.

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ABBREVIATIONS

Ach	=	Acetylcholine
BOLD	=	Blood Oxygen Level Dependent
[^{11}C]-CFT	=	[^{11}C]-2β-carbomethoxy-3β-(4-fluoro-phenyl)tropane
DA	=	Dopamine
DLPFC	=	DorsoLateral Prefrontal Cortex
EDS	=	Excessive Daytime Sleepiness
EEG	=	Electroencephalography
^{18}FDG	=	[^{18}F] FluoroDeoxyGlucose
^{18}F-MPPF	=	2'-Methoxyphenyl-(*N*-2'-pyridinyl)-*p*-^{18}F-fluoro-benzamidoethylpiperazine
fMRI	=	Functional Magnetic Resonance Imaging
FPSP	=	N-(3-[^{18}F]fluoropropyl)-spiperone
GABA	=	Gamma aminobutyric acid
Glu	=	Glutamate
^{1}H-MRS	=	Proton Magnetic Resonance Spectroscopy
$H_2{}^{15}O$	=	[^{15}O]-labeled water
IBZM	=	[^{123}I](*S*)-2-hydroxy-3-iodo-6-methoxy-([1-ethyl-2-pyrrolidinyl]methyl) benzamide
IPT	=	[^{123}I](*N*)-(3-iodopropene-2-yl)-2β-carbomethoxy-3β-(4-chlorophenyl) tropane

MRI	=	Magnetic Resonance Imaging
^{11C}NMPB	=	[^{11}C]N-methyl-4-piperidyl-benzilate
NREM	=	Non-Rapid-Eye-Movement
PET	=	Positron Emission Tomography
PGO	=	Ponto-Geniculo-Occipital
rCBF	=	Regional Cerebral Blood Flow
REM	=	Rapid-Eye-Movement
5-HT	=	Serotonin
SPECT	=	Single Photon Emission Computed Tomography
^{99m}Tc-ECD	=	^{99m}Technetium-EthylCysteinate Dimer
^{99m}Tc-HMPAO	=	^{99m}Technetium-HexaMethylene-PropyleneAmine-Oxime
VBM	=	Voxel-Based Morphometry
VMPFC	=	Ventro-Medial Prefrontal Cortex

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