Neuroimaging of Narcolepsy and Primary Hypersomnias

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Summary

Advances in neuroimaging open up the possibility for new powerful tools to be developed that potentially can be applied to clinical populations to improve the diagnosis of neurological disorders, including sleep disorders. At present, the diagnosis of narcolepsy and primary hypersomnias is largely limited to subjective assessments and objective measurements of behavior and sleep physiology. In this review, we focus on recent neuroimaging findings that provide insight into the neural basis of narcolepsy and the primary hypersomnias Kleine-Levin syndrome and idiopathic hypersomnia. We describe the role of neuroimaging in confirming previous genetic, neurochemical and neurophysiological findings and highlight studies that permit a greater understanding of the symptoms of these sleep disorders. We conclude by considering some of the remaining challenges to overcome, the existing knowledge gaps and the potential role for neuroimaging in understanding the pathogenesis and clinical features of narcolepsy and primary hypersomnias.

Keywords

Hypersomnia, narcolepsy, Kleine-Levin Syndrome, sleep, neuroimaging, idiopathic hypersomnia, FDG-PET, fMRI, SPECT.

1. Introduction

Primary hypersomnia disorders are characterized by excessive daytime sleepiness (EDS), in some cases prolonged sleep duration, and pathogenesis that originates from the central nervous system (Black and others, 2004). In addition to sleep-related symptoms, a broad and complex collection of motor, perceptual, behavioral, and cognitive symptoms may be associated with one or several of these disorders (**Figure 1**). Examples of such symptoms are cataplexy (brief episodes of muscle weakness), hypnagogic hallucinations (fleeting perceptions or mentations during the transition to sleep), hyperphagia (compulsive eating), and cognitive impairment. This complex symptomatology makes diagnosis challenging. Here, we describe advances in neuroimaging that could open up the possibility for novel tools to be developed that potentially can be applied to improve the characterization and diagnosis of primary hypersomnias.

Specifically, in this review, we will focus on neuroimaging findings in three primary hypersomnias of central origin: 1) narcolepsy, 2) Kleine-Levin syndrome (KLS), and 3) idiopathic hypersomnia (IH). Narcolepsy appears in two forms, with cataplexy (type 1) and without cataplexy (type 2), and is characterized by sudden sleep attacks, fragmented night-time sleep, hypnagogic hallucinations and sleep paralysis. KLS is characterized by recurrent episodes of hypersomnia and may include behavioral, perceptual or cognitive disturbances, and dysregulation of eating and sexual behaviors. Finally, IH is determined by differential diagnosis of exclusion of other causes of EDS, and may include hypersomnolence with or without long sleep time and sleep inertia, or so called ‘sleep drunkenness’.

Narcolepsy type 1 is related to loss of specific neurons in the hypothalamus that produce orexin (also named hypocretin), which leads to disturbances in the brain's regulation of sleep and wakefulness. The pathogenesis of narcolepsy type 2 is less clear, but it may be related to partial loss of orexin neurons (Mahoney and others, 2019). Much less is known about the underlying cause of KLS and IH, but they are considered to be the result of disordered intrinsic sleep mechanisms (Bassetti, 2012) of central origin. By contrast, the more common secondary hypersomnias are caused by factors other than the brain's intrinsic regulation of sleep-wake mechanisms such as inadequate sleep hygiene, obstructive sleep apnea, or underlying neurological disorders, such as Alzheimer's disease, Parkinson's disease, epilepsy, stroke, or traumatic brain injury (Guilleminaul and Brooks, 2001; Haq and others, 2010; Billiard and Podesta, 2013). Primary hypersomnias are relatively rare, nevertheless, they can have serious health, social, and economic consequences for those who suffer from these debilitating conditions.

The diagnosis of narcolepsy and related hypersomnia conditions includes typically both subjective and objective assessments. Subjectively, estimation of sleep propensity (e.g., Epworth Sleepiness Scale), sleep need (e.g., sleep duration per 24 hours), and fatigue (e.g., Fatigue Severity Scale; Valko and others, 2008) are typically used to identify the presence of hypersomnia and/or somnolence. Objectively, the most common sleep-wake tests include assessments of sleep propensity (e.g., multiple sleep latency test; MSLT) and of the ability to stay awake (e.g., maintenance of wakefulness test) as well as wrist actigraphy that measures daily sleep-wake behavior (Bassetti, 2012). Polysomnography is employed to exclude other sleep disorders such as sleep apnea, but is often non-specific. Thus, there is a need for complimentary objective tools for clinicians to identify the definitive neuropathology and clinical features of hypersomnia disorders. Currently, neuroimaging techniques are not widely

94 employed to aid diagnosis, however, they represent a set of unique and powerful tools which
95 could provide insight into both the pathogenesis (e.g., genetic, neurochemical, and
96 electrophysiological) and into the clinical features (e.g., cataplexy, hypnagogic hallucinations,
97 hyperphagia, cognitive function). More specifically, techniques used to measure parameters
98 related to: 1) brain energy metabolism, perfusion, or neurotransmitter receptor distribution (e.g.,
99 positron emission tomography and single-photon emission computed tomography;
100 PET/SPECT), 2) neuronal network hemodynamics (e.g., functional magnetic resonance
101 imaging; fMRI), 3) metabolite concentration (e.g., magnetic resonance spectroscopy; MRS), 4)
102 grey/white matter distribution (e.g., voxel-based morphometry; VBM), and, 5) white matter
103 integrity (e.g., diffusion weighted imaging; DWI or diffusion tensor imaging; DTI) can be
104 applied to explain the neural basis of primary hypersomnia disorders of central origin (Maquet,
105 2005), and importantly, may even lead to novel methods for diagnosis and treatment.
106
107 The systematic investigation of hypersomnias using neuroimaging techniques is in its
108 infancy, and many gaps exist in our knowledge of these conditions. Previous reviews comprise
109 a combination of insomnia and hypersomnia disorders, or are more focused on treatment and
110 clinical outcomes (Desseilles and others, 2008; Engstrom and others, 2014). The present review
111 focuses only on neuroimaging of primary hypersomnia disorders including: narcolepsy, KLS,
112 and IH, as neuroimaging is particularly well-suited for understanding diseases of central origin.
113 Neuroimaging of treatment responses and secondary hypersomnias are beyond the scope of this
114 review and will not be included in the discussion. The major aims of this review are to: 1)
115 provide a comprehensive overview of the progress made by studies employing neuroimaging
116 to investigate the neural basis of narcolepsy, KLS, and IH, 2) gain insight into the pathogenesis
117 and clinical features of these disorders, 3) provide clinical insights that may provide unique

differential diagnostic information, 4) identify knowledge gaps, and, 5) suggest areas of future research.

2. Clinical features and pathogenesis of narcolepsy

Narcolepsy is a rare disorder primarily characterized by recurrent episodes of an irrepressible need to sleep, lapsing into sleep, or napping (DSM-5) (**Figure 1**). The sudden and irresistible character of the sleep attacks interferes with normal activities such as talking, working or driving. According to the third edition of the International Classification of Sleep Disorders (ICSD 3; Sateia 2014) the presence of cataplexy distinguishes between narcolepsy type 1 (with cataplexy), from narcolepsy type 2 (without cataplexy). Narcolepsy with cataplexy (type 1) is marked by a sudden loss of bilateral muscle tone or paralysis during wakefulness which is commonly elicited by strong emotions. The narcolepsy patient remains conscious and breath is unaltered during the cataplexy attack which ranges from a few seconds to several minutes. Common characteristics for both narcolepsy types are EDS, a mean sleep latency <8 min, and sleep-onset rapid eye movement (REM) periods, but in narcolepsy type 2, the EDS is less severe (Sateia, 2014) (**Figure 1**).

Sleep paralysis, hypnogogic hallucinations and disturbed nighttime sleep with frequent awakenings and fragmented sleep are other common symptoms in narcolepsy. Unlike KLS and IH, the symptoms in narcolepsy patients are usually relieved by short refreshing naps (Nishino, 2007). Narcolepsy also has a negative impact on cognition, as some patients report memory problems (Sturzenegger and Basseti, 2004), and have deficits in vigilance and sustained attention (Fulda and Schulz, 2001; Naumann and others, 2006). This broad range of symptoms is probably due to the intrinsic multifactorial pathogenesis of this syndrome, ranging from

genetic factors to environmental triggers (Miller and others, 2013; Scrima, 2010). A strong association of narcolepsy with a specific human leukocyte antigen (HLA) subtype (DQB1*0602) has been found (Faraco and Mignot, 2011), suggesting that an autoimmune process may be involved (Liblau and others, 2015).

Regarding the pathogenesis of narcolepsy, a role for the lateral hypothalamus was first suggested in 1931 by Von Economo (1931), and subsequently expanded on by Aldrich and Naylor (1989) who reported that symptomatic narcolepsy was associated with diencephalic lesions. Later, these findings were confirmed by post-mortem studies demonstrating an 85-95% cell loss of orexin-secreting neurons located in the latero-dorsal hypothalamus in patients with narcolepsy (Liblau and others, 2015; Peyron and others, 2000; Thannickal and others, 2000; Dauvilliers and others, 2014b). Although orexin deficiency represents a pathophysiological sign of narcolepsy, in rare cases narcolepsy type I patients show normal levels of orexin (Kanbayashi and others, 2002; Overeem and others, 2011). Signs of reactive gliosis have also been found in the hypothalamus and in orexin projection areas (Thannickal and others, 2003; Thannickal and others, 2009), a feature common to many neurodegenerative diseases (Cavaliere and others, 2007; Papa and others, 2014). These findings were confirmed later by Feneberg and others (2013) who found an elevated concentration of glial fibrillary acid protein, an indicator of astrogliosisneuropathology, in patients with narcolepsy-cataplexy.

In line with orexin neuron degeneration in the hypothalamus, the orexin concentration in cerebrospinal fluid (CSF) of narcolepsy type 1 patients is also reduced (Mignot and others, 2002). However, up to 90% of the patients with narcolepsy without cataplexy (type 2) have normal CSF orexin levels (Mahoney and others, 2019).

Orexinergic neurons receive inputs from brain areas involved in sleep-wake control, appetite control and reward. The orexin-secreting neurons of the hypothalamus are involved in the control of wakefulness, via the inhibition of the ventro-lateral preoptic nucleus of the hypothalamus (Didato and Nobili, 2009). Orexin neurons of the lateral thalamus project to brainstem nuclei involved in promoting arousal (Gotter and others, 2012). In particular, a primary projection of orexin neurons are the tubero-mammillary nuclei that, in turn, project to the prefrontal cortex, thalamus and other subcortical structures, and are normally active during wake and progressively less active during sleep (**Figure 2**).

While hypothalamic orexin neuron loss is now strongly implicated as a trigger for all symptoms, in most cases of narcolepsy with cataplexy, the cause of the wide-ranging clinical symptoms remains unclear and the diagnosis is mainly based on the result of MSLT and CSF orexin concentrations. Neuroimaging techniques are now beginning to be used for investigations of the neural basis of these wide-ranging symptoms and pathogenic factors in narcolepsy. For the past decade, an increasing number of neuroimaging studies have been performed to identify the structural and functional abnormalities of narcolepsy, and also in order to pinpoint differences between narcolepsy with and without cataplexy. However, the results have been controversial (Thannickal and others, 2009; Dang-Vu, 2013) (**Table 1**).

2.1 Neuroimaging of narcolepsy

2.1.1 Hypothalamus and orexin network involvement in narcolepsy

As described above, the hypothalamus and the orexin network are central to narcolepsy pathogenesis (**Figure 2**). In narcolepsy, hypoconnectivity of the hypothalamus and its

direct/indirect projection sites, including ponto-mesencephalic structures (e.g., reticular formation and locus coeruleus), subcortical regions (e.g., hippocampus, amygdala and basal ganglia), and cortical regions (e.g., frontal and temporal cortices) have been identified (**Figure 3**). Several of these brain areas are connected to the so-called orexin network (**Figure 2**), supporting the findings of orexin deficiency in narcolepsy. Additional imaging support for a hypothalamic orexin dysfunction in the pathogenesis of idiopathic narcolepsy comes from a recent DWI study (Menzler and others, 2012) that identified asymmetric microstructural white matter changes in the hypothalamus of eight patients with idiopathic narcolepsy with cataplexy, as compared to healthy controls.

These results are consistent with the morphological abnormalities reported by VBM studies that demonstrated significant gray matter reduction in bilateral hypothalami in narcolepsy with cataplexy (Draganski and others, 2002; Joo and others, 2009; Kim and others, 2009; Weng and others, 2015), suggesting atrophy of the hypothalamus as an underlying cause of cataplexy in patients with narcolepsy (Buskova and others, 2006). These results are consistent with Thannickal and others (2009) who in a postmortem study, found selective orexin cell degeneration in patients with cataplexy whereas no loss was observed in non-cataplexic patients. However, grey matter reduction has not always been confirmed (Brenneis and others, 2005; Kaufmann and others, 2002; Overeem and others, 2003), thus warranting further investigation.

In addition, SPECT imaging has revealed reduced regional cerebral blood flow (CBF) in the hypothalamus and thalamus of 25 narcolepsy patients with cataplexy during wakefulness (Joo and others, 2005). MRS has shown reduced hypothalamic NAA/creatine-phosphocreatine ratio (Lodi and others, 2004), confirming that hypothalamic neuronal loss is a pathogenetic

feature in narcolepsy. However, incongruent results have been reported from 18-fluorodeoxiglucose (FDG-PET) metabolism alterations of the hypothalamus in narcolepsy patients (Joo and others, 2004; Dauvilliers and others, 2010). For example, Joo and others (2004) found reduced hypothalamic metabolism in 24 narcolepsy-cataplexy patients during wakefulness, while Dauvilliers and others (2010) found significant hypometabolism specifically during cataplexy attacks. Several important factors may explain this incongruity, such as the selection criteria for healthy controls, the inclusion of patients with/without cataplexy, age differences, and possible drug interactions. Thus highlighting the complexity and challenges of studying the neural basis of narcolepsy systematically, using neuroimaging techniques, and otherwise.

In summary, recent developments in structural and functional neuroimaging techniques have provided insight into the pathology of the hypothalamus and specifically, deficient function in the orexin network in narcolepsy. However, technical challenges are inherent when imaging small structures such as the hypothalamus, (e.g., susceptibility and cardiac output artifacts), along with potentially confounding individual differences which remain to be satisfactorily disentangled from core symptomology. Furthermore, although MRI represents the goal-standard modality in evaluating the hypothalamic region, spatial resolution and the need of dedicated acquisition protocols often limit hypothalamus investigation.

2.1.2 Brainstem involvement in narcolepsy

The brainstem contains nuclei which are important for arousal and REM sleep (Jouvet and other, 1967; Bier and others, 1994) and that regulate the networks responsible for the behavioral and physiological switch between wake and sleep (**Figure 2**); for excellent reviews

on sleep-wake mechanisms see (Saper & Fuller, 2017; Saper and others, 2001). Reports on narcolepsy-cataplexy patients with vascular/non-specific brainstem lesions suggest that the brainstem, which receives descending output from hypothalamic orexin neurons (Fernandez and others, 1995; Scrima and others, 1998; Reynolds and Roy, 2011), plays a crucial role in the pathogenesis of narcolepsy. A vascular origin for these lesions is consistent with the observation that many narcolepsy patients have long-standing hypertension (Frey and Heiserman, 1997; Ohayon, 2013; Pepin and others, 2014; Cohen and others, 2018), while a degenerative hypothesis has been postulated for patients with familial narcolepsy (Stepièn and others, 2010). More recently, lesions of the lower ascending reticular activating system have been detected in post-traumatic cases of narcolepsy (*n.b.,* not specified if with or without cataplexy) (Jang and others, 2016).

Among the earliest studies, Meyer and others (1980) reported lower brainstem activity detected by SPECT, both in awake and sleep states in narcolepsy patients. Using DTI, Menzler and others (2012) found white matter changes in N=8 narcolepsy-cataplexy patients in the mesencephalon, pons, and the medulla. These results were confirmed by a recent study by Juvodden and others (2018) who found widespread changes in white matter tracts including the brainstem, thus suggesting brainstem involvement in narcolepsy type 1. Additionally, others have reported alterations of several DWI parameters (e.g., increased mean diffusivity values without fractional anisotropy changes) in the ventral tegmental area and the dorsal raphe nuclei of patients with narcolepsy-cataplexy (Scherfler and others, 2012). A recent study by Drissi and others (2019) found signs of lower levels of neuromelanin in the rostral reticular formation of the brainstem. Altogether, wide ranging functional and structural neuroimaging techniques have provided complimentary data to suggest functional and anatomical changes of the brainstem may underlie the symptoms of narcolepsy.

2.1.3 Cortical and subcortical involvement in narcolepsy

Contradictory results have been reported about cortical and subcortical alterations in narcolepsy patients. One study in patients with narcolepsy-cataplexy compared to healthy controls revealed significant gray matter reductions in several cortical areas, including temporal and frontal regions, e.g., bilateral frontopolar, superior frontal, right superior temporal and left inferior temporal cortices (Joo and others, 2009). A recent coordinate-based meta-analysis identified significant regional gray matter reduction in the basal ganglia, anterior cingulate cortex, bilateral frontal and the right superior temporal cortices (Weng and others, 2015) (**Figure 3**). However, another meta-analysis on the same sample revealed no grey matter atrophy (Tanasescu and others, 2015). Using an improved approach of Signed Differential Mapping, Zhong and others (2016) confirmed gray matter alterations mainly in the bilateral hypothalamus, thalamus, basal ganglia, and also in the right inferior frontal gyrus. Moreover, cortical thickness in prefrontal areas has been found to be inversely correlated with the severity of narcolepsy (Schaer and others, 2012). Interestingly, many of these regions receive input from hypothalamic orexin-neurons (Kaufmann and others, 2002), providing further support that the role of the hypothalamus and orexin dysfunction in narcolepsy can be visualized by neuroimaging methods.

VBM studies showing reduced grey matter in subcortical areas such as the nucleus accumbens in narcoleptic patients suggest the involvement of other subcortical projection sites of the orexin system, such as the basal ganglia (Draganski and others, 2002; Joo and others, 2009). Moreover, several studies have compared brain patterns during wakefulness, with or without cataplexy attacks, revealing 99mTc-ECD SPECT hypoperfusion in basal ganglia and

cingulate cortex of narcolepsy patients (Chabas and others, 2007; Hong and others, 2006b) which has also been confirmed by fMRI studies (Schwartz and others, 2008; Reiss and others, 2008). In addition, findings obtained through PET/SPECT studies have supported a role for striatal dopaminergic transmission in narcolepsy patients (Aldrich and others, 1993; Eisensehr and others, 2003; Rinne and others, 1995). A recent longitudinal study (Jeon and others, 2018) conducted on patients with narcolepsy-cataplexy demonstrated significant progressive cortical thinning in prefrontal, superior temporal, insula and cingulate cortices, which was also related to age and regional thinning that accompany disease progression.

A DWI study in patients with narcolepsy-cataplexy (Scherfler and others, 2012) showed microstructural disruption of white matter bundles in cortical regions including fronto-temporal (orbitofrontal, inferior temporal) and anterior cingulate regions (Draganski and others, 2002; Joo and others, 2009; Brenneis and others, 2005). These results have recently been confirmed by a tract-based spatial statistics study reporting significant decreases in fractional anisotropy of white matter of the bilateral anterior cingulate, orbitofrontal area, frontal lobe, as well as the left anterior and medial thalamus in drug-naive narcolepsy patients with cataplexy (Park and others, 2016). Moreover, mean diffusivity values of bilateral frontal and right superior parietal cortices correlated positively with depressive mood in these patients (Park and others, 2016). Another study revealed reduced grey matter density in the superior temporal gyrus of narcolepsy patients (in a mixed sample of patients with and without cataplexy) (Kaufmann and others, 2002), a region also related to hypnagogic hallucinations in other conditions like schizophrenia. Furtehrmore, in a mixed sample of cataplexy and non-cataplexy patients Tezer and others (2018) observed reduced fractional anisotropy in the cerebellum, thalami, corpus callosum, parahippocampal gyrus and temporal white matter. Non-cataplexy participants also had decreased fractional anisotropy in the white matter of the midbrain. Recently, in a study

employing tract-based white matter analysis, Park and others (2019) reported reduced fractional anisotropy in the inferior fronto-occipital fasciculus, and in the associative tract connecting occipital, temporal, parietal and frontal lobes (Martino an others, 2010). This alteration in white matter fibers was also related to both clinical and neurophysiological symptoms. Taken together, these results suggest that white matter abnormalities may help to explain some of the core symptoms observed in narcolepsy and support a role of the fronto-occipital fasciculus in sleep-wake regulation in narcolepsy-cataplexy patients.

2.2 Cataplexy in narcolepsy

Cataplexy attacks are often brought on by strong emotional triggers, mainly positive emotions and particularly when laughing (Krahn and others, 2005). In some cases however, cataplexy can occur without any obvious stimulus. Generally, strong emotions activate orexin neurons and the loss of these neurons in narcolepsy patients causes a destabilization within the motor control system, eliciting muscle weakness or paralysis.

Neuroimaging studies employing PET have provided insights into cataplexy symptoms in narcolepsy, as revealed by hypermetabolism in the pre- and postcentral gyrus during cataplexy attacks in two patients (Dauvilliers and others, 2010) (**Figure 3**). In addition, regional CBF alterations in the cingulate cortex, parahippocampal gyrus, and other limbic regions (Joo and others, 2005) have been linked to cataplexy, and may explain the emotional nature of the trigger for cataplexy attacks. These limbic changes in narcolepsy-cataplexy patients (Joo and others, 2005; Joo and others, 2009) are also thought to be related to memory disturbances and mood alterations. It has also been found that (Nakamura and others, 2013) patients with narcolepsy-cataplexy have higher apparent diffusion coefficient (ADC) values in the right

inferior frontal gyrus compared to participants without cataplexy, suggesting that this region may be involved in cataplexy. In addition, compared to healthy controls, narcolepsy-cataplexy patients had higher ADC values in the left inferior frontal gyrus, parahippocampal gyrus and amygdala,and lower ADC values in the left postcentral gyrus. Both patients with and without cataplexy differed in fractional anisotropy values in the precuneus. Thus, neuroimaging has provided valuable insight into the functional and structural abnormalities that explain cataplexy symptoms in narcolepsy.

2.3 Emotional processing in narcolepsy

Given that strong emotions trigger cataplexic attacks, the links to the emotional regulation and processing have been studied using neuroimaging in narcolepsy. Schwartz and others (2008) investigated emotional processing in narcolepsy-cataplexy patients, finding both reduced activation of the hypothalamus and increased activation of the amygdala in response to humorous pictures, suggesting abnormal functioning of the brain regions that support emotional processing. Reiss and others (2008) also reported increased activation in the hypothalamus in addition to increased activation of the ventral striatum and the right inferior frontal gyrus when narcolepsy patients looked at humorous cartoons. Amygdala and hypothalamus involvement has been consistently observed in narcolepsy, suggesting that alterations in emotional processing could underlie cataplexy attacks (Schiappa and others, 2018). In addition to the amygdala, Meletti and others (2015) found increased brain responses in the anterior cingulate cortex and motor cortices during laughter, and that cataplexy was associated with increased activation in both cortical and subcortical areas. However, surprisingly, a recent study by Juvodden and others (2019) did not observe any brain activation differences between patients and controls when watching funny vs. neutral movies.

Significant reductions of the absolute volume of the hippocampus (Joo and others, 2012; Kim and others, 2016; Křečková and others, 2018) and the amygdala (Brabec and others, 2011; Kim and others, 2016), possibly in relationship with abnormalities in emotional processing (Walker and van der Helm, 2009), have been observed in patients with narcolepsy-cataplexy. Furthermore, a report using proton resonance spectroscopy in narcolepsy patients with cataplexy, revealed myoinositol decrease in the amygdala (Poryazova and others, 2009). Laughter seems to be the most common emotion-related trigger for cataplexy. Some authors have hypothesized that the manipulation of emotion-related behaviors, such as emotional manifestations restrictions, could reduce the probability of prompting cataplexy attacks (Tucci and others, 2003; de Zambotti and others 2014), and may therefore have some therapeutic benefit to patients. Future funrtional neuroimaging studies could provide conclusive evidence to support the neurophysiological efficacy of such interventions.

Vaudano and others (2019) used fMRI to investigate the brain networks involved in spontaneous laughter in children with narcolepsy/cataplexy. They found that laughter without cataplexy engaged a network encompassing motor and thalamic nuclei, suggesting diencephalic role in preventing cataplexy induced by emotions. This was consistent with previous studies (Meletti an others, 2015) whereby laughter induced enhanced activity in the amygdala, nucleus accumbens and prefrontal cortex during cataplexy. Collectively, these neuroimaging studies suggest functional changes in limbic structures and associated areas may help explain the link between emotion processing and cataplexy in narcolepsy.

2.4 Cognitive function in narcolepsy

Evidence for cognitive dysfunctions in patients with narcolepsy remain controversial. The earliest studies mostly showed intact memory and executive function (Aguirre and others, 1985; Rogers and Rosenberg, 1990). More recent research has revealed attention and executive function deficits that are consistent with subjective cognitive complaints from patients which impact their daily living (Rieger an others, 2003; Moraes an others, 2012). Naumann and colleagues (2006) observed impairment of attention and executive function, but preserved memory in narcoleptics. There were no differences in neuropsychological performance between medicated and non-medicated patients, suggesting that these observations were not due to medication effects. Zamarian and et al (2015) investigated whether subjective cognitive complaints were related to cognitive deficits from neuropsychological and clinical assessments. They found reduced capacity for sustained attention, executive function and working memory. Interestingly, depression symptoms and daytime sleepiness were correlated with subjective but not objective attention deficits. Thus suggesting that depression and sleep disruption have an additional negative impact on cognitive complaints in patients, which may be independent of objective cognitive deficits associated with narcolepsy. A recent fMRI study on adolescents with narcolepsy (type 1) showed increased deactivation within the default mode network (DMN) during a working memory task without signs of reduced activation in the prefrontal cortex, and in the absence of performance deficits (Witt and et al, 2018). Furthermore, MRS revealed that cortical deactivation in the DMN was associated with increased glutamate and decreased GABA in patients, whereas the opposite pattern was observed in healthy controls (Witt and et al, 2018). These results were in concordance with a previous resting state fMRI and EEG study showing that adolescents with narcolepsy-cataplexy were less likely to spend time in an EEG microstate that was related to the DMN (Drissi and others, 2016). Taken together, these studies suggest that narcolepsy is characterized by a dysregulation of cognitive resources in favor of monitoring and sustaining attention over actual task performance.

Moreover, and importantly, when investigating the neural correlates of cognitive functions in narcolepsy, it must be considered that neuropsychological alterations could be ascribed to sleep deprivation, rather than pathology, representing therefore a secondary outcome of symptoms rather than a neural marker of the pathogenesis of the disorder. Bayard el at (2012) reported that both narcoleptic patients with and without cataplexy performed poorer than controls on reaction time and executive function tests. However, the severity of executive function impairment was found to be related to daytime sleepiness and to the number of sleep onset REM episodes. Given that loss of orexin neurons is observed in narcolepsy with cataplexy, including projections to regions that support executive function (Collette et al 2005), whereas orexin CSF levels are normal in the majority (70-90%) of patients without cataplexy (Kanbayashi an others, 2002), these results suggest that executive function impairments are unrelated to orexin deficiency *per se*, and rather, may be a secondary feature of narcolepsy associated with daytime sleepiness and the severity of sleep disturbances such as sleep onset REM periods.

2.5 Summary

A wide range of functional and structural neuroimaging techniques have been utilized to investigate the cortical and subcortical neural substrates affected in narcolepsy, providing compelling new evidence to help explain the neural basis of the variety and complexity of pathology and symptoms in narcolepsy. These studies have found structural and functional alterations in the orexin system and its widespread projections, especially in limbic regions related to cataplexy and emotional processing, and also in cortical regions related to cognitive complaints and reported deficits in narcolepsy. Several studies report findings of white matter

and brain stem alterations in narcolepsy. However, the imaging findings of abberreations in the hypothalamus are less conclusive due to technical challanges in hypothalamic imaging.

3. Clinical features and pathogenesis of KLS

KLS or periodic idiopathic hypersomnia is a rare sleep disorder, affecting 1-5 per million individuals (Frenette and Kushida, 2009). It occurs primarily in adolescents and young adults (Critchley, 1967) and affects males significantly more than females (Miglis and Guilleminault, 2014). KLS is characterized by recurrent episodes of EDS, usually accompanied by behavioral abnormalities, such as overeating, sexual disinhibition, mood changes, and cognitive disturbances (Arnulf, 2015) (**Figure 1**). In between EDS episodes, patients have normal sleep and behavior, however, persisting working memory deficits have been reported (Landtblom and others, 2002; Engström and others, 2009; Engström and others, 2013). The mean duration of the EDS episodes is 12 days, ranging widely from as short as 2 days to as many as 270 days and usually remits spontaneously after 8–10 years (Arnulf and others, 2005). The pathogenesis of KLS remains unknown, although an overrepresentation in the Jewish population has been reported, suggesting a genetic component for this condition (Arnulf and others, 2008). Structural neuroimaging is normal in KLS (Arnulf and others, 2008), suggesting important differences from narcolepsy, but a nonspecific slowing of background EEG activity has been detected in 70% of KLS patients during the symptomatic phase (Huang and others, 2008).

3.1. Neuroimaging of KLS

As compared to narcolepsy, far fewer neuroimaging studies have been conducted investigating the neural basis of KLS (**Table 2**). Several functional neuroimaging approaches have been applied to elucidate KLS aetiology and most neuroimaging data have been obtained from single case reports (Landtblom and others, 2002; Lu and others, 2000; Portilla and others, 2002; Arias and others, 2002; Haba-Rubio and others, 2012). Converging evidence obtained by PET-SPECT and fMRI identify the thalamus and frontotemporal areas as the structures significantly impacted in KLS, suggesting that despite certain overlapping symptoms with narcolepsy, neuroimaging may help reveal unique pathophysiology to help distinguish between primary hypersomnias.

3.1.1 Thalamic involvement in KLS

The thalamus modulates cortical arousal, influencing consciousness and regulating the cycle of sleep and wake states. It is conceived as a primary relay station of the brain encompassing the brainstem, hypothalamus, cortex, and in particular, thalamo-cortical interaction is fundamental for maintaining sleep and processing information in both REM and non-REM sleep (Larson-Prior and others, 2014).

Several authors (Hong and others, 2006a; Huang and others, 2005; Kas and others, 2014) report SPECT hypoperfusion in the thalamus of KLS patients during hypersomnia periods (Figure 4). However, regarding metabolism in the thalamus of KLS patients, divergent results have been reported (Figure 4; Table 2). In line with SPECT findings, a recent study showed PET hypometabolism in the thalamus, and also the hypothalamus, of a 15-year old KLS patient during a symptomatic period and also, even if less severe, during an asymptomatic period (Xie and others, 2016). On the other hand, two studies (Dauvilliers and others, 2014a;

Drouet and others, 2017) showed hypermetabolism in bilateral thalami, caudate nuclei, and lenticular nuclei during symptomatic periods as compared to asymptomatic periods. These results show that it is important to make a distinction between symptomatic vs. asymptomatic (i.e., following remission or between sleep episodes) periods in KLS.

During asymptomatic periods, an MRI study revealed abnormal relationships between NAA-levels (assessed by MRS) and fMRI-activity in the thalamus in KLS patients during a working memory task (Vigren and others, 2013). These results may help explain why working memory deficits are reported in KLS patients, although additional research is needed to better explain the relationship between NAA and the fMRI signal, whose links may be disparate or indirect. Another fMRI study in a small sample of KLS patients (Engström and others, 2009), later replicated in a larger group of patients (Engström and others, 2013), revealed increased activity in the thalamus and reduced frontal activity while performing a verbal working memory task. Yet another study by Jankowski and others (2013) demonstrated increased fMRI BOLD signal in the anterior and mediodorsal nuclei of the thalamus during a working memory task. However, a more recent study shows an inverse correlation between thalamic activation and working memory performance indicating that thalamic hyperactivation could be the result of overcompensation in high-performing KLS (Engström and others, 2014a). Nevertheless, these studies support a role of thalamic dysfunctions in the etiology of KLS, since it manifests alterations both in symptomatic and asymptomatic periods.

3.1.2 Brainstem involvement in KLS

One case study shows that the functional connectivity between the thalamus and the brainstem, mainly the dorsal pons, is reduced during periods of hypersomnia (Engström and

517 others, 2014b). However, asymptomatic KLS patients as compared to healthy controls showed
518 no difference in thalamic connectivity during rest. In addition, KLS patients had significantly
519 reduced functional connectivity between dorsal pons and the frontal eye field; an area of the
520 brain involved in cerebral control of eye movements but also involved in attention and working
521 memory (Engström and others, 2016). Given the lack of evidence, further neuroimaging
522 research investigating brainstem involvement in KLS is warranted.
523
524 ***3.1.3. Cortical involvement in KLS***
525
526 KLS patients show significant perfusion changes in the cerebral cortex most
527 prominently in the fronto-temporal cortex (Kas and others, 2014; Billings and others, 2011; Lo
528 and others, 2012) where fronto-temporal hypoperfusion has been observed also in
529 asymptomatic periods (Vigren and others, 2013; Vigren and others, 2014) (**Figure 4; Table 2**).
530 Kas and others (2014) observed significant hypoperfusion also in the parieto-temporal junction,
531 a region involved in complex cross-modal sensory integration (Seghier, 2013), in asymptomatic
532 KLS patients compared to healthy controls. Perfusion during symptomatic periods within the
533 parieto-temporal junction correlated strongly with the clinical scoring of several KLS-related
534 symptoms, such as depersonalization/derealization (Kas and others, 2014).
535
536 In addition to hypoperfusion in the fronto-temporal cortex and the parieto-temporal
537 junction, reduced perfusion in cortical associative areas, such as the orbito-frontal, anterior
538 cingulate and the insular cortices, have been reported in asymptomatic KLS patients (Kas and
539 others, 2014). Another study, comparing four drug-free male patients with typical KLS to
540 healthy controls, demonstrated an increased FDG-PET metabolism of fronto-temporal and
541 cingulate regions during the asymptomatic phase. Acquisitions during the symptomatic

episodes demonstrated a further hypermetabolism of orbito-frontal, motor, and insular areas (Dauvilliers and others, 2014a).

3.2 Summary

Neuroimaging studies of KLS have repeatedly found fronto-temporal hypoperfusion that also is persistent during asymptomatic periods (**Figure 4**). Previous imaging studies on subcortical involvement in KLS indicate that the thalamus has a key role during hypersomnia episodes, and also when patients are challenged with taxing working memory tasks. In between hypersomnia episodes, and during resting wakefulness, the thalamic involvement remains less clear, and remains to be fully elucidated.

4. Clinical features and pathogenesis of Idiopathic Hypersomnia

IH represents one of the most problematic diagnoses among virtually all sleep disorders, as it is primarily a diagnosis of exclusion. IH refers to a condition with significant daytime sleepiness not explained by other medical conditions, with a multiple sleep latency < 8 min, less than two sleep-onset REM periods, no cataplexy and no orexin deficiency. Two forms of IH are recognized, with and without a long sleep time (Sateia, 2014). As a result of a paucity of information on IH, it is only possible to hypothesize a prevalence, with estimates varying anywhere from 5.0% to 47.2% (see review of Billiard and Sonka, 2016).

Clinical manifestations are quite general and include symptoms called “sleep drunkenness” referred to difficulty in maintaining vigilance as a result of incomplete awakening, confusion and disorientation. Some disturbances such as headache, faintness,

567 temperature alterations and cardiac and gastroenteric problems accompany IH. Moreover, as in
568 other sleep disorders, memory and attention impairments have been reported (Vernet and
569 others, 2010). However, the lack for definite pathognomonic clinical features results in
570 uncertain diagnostic criteria that, in turn, complicate epidemiological and imaging studies
571 (Billiard and Sonka, 2016).
572
573 **4.1. Neuroimaging of Idiopathic Hypersomnia**
574
575 Neuroimaging research in IH is still in its infancy, with a very few studies having
576 investigated structural and functional correlates of this disorder (**Figure 5, Table 3**). Recently,
577 Boucetta and others (2017) conducted a SPECT study in thirteen participants, linking perfusion
578 with clinical information in IH. Two opposite patterns of CBF perfusion were identified: 1) a
579 reduction of rCBF in medial prefrontal cortex, posterior cingulate and left cerebellum, and by
580 contrast, 2) increased rCBF was observed in the left amygdala and in the inferior temporal and
581 occipital cortices. Furthermore, CBF alterations correlated with levels of sleepiness and
582 depression. Dauvilliers and others (2017) showed increased metabolism, measured by 18FDG-
583 PETin the insula and cingulate cortices and also in the caudate nucleus, in participants with IH
584 in a fully awake condition, compared to control participants. MRI structural data of possible
585 alterations in these patients are still lacking, and limited to a qualitative description in patients
586 with IH (Trotti and Bliwise, 2017). Even though available evidence is not sufficient to draw
587 strong conclusion about the neural basis of IH from neuroimaging studies, these pioneering
588 studies provide important first steps to a better understanding of the underlying causes, and may
589 provide a pathway to novel therapeutic interventions and treatments. Importantly, the lack of
590 evidence underlies the importance of the need for research in this area.
591

5. Conclusions and future directions

Even if there are similarities/overlap in symptoms in narcolepsy, KLS and IH, there are more unique clinical features to each syndrome **(Figure 1)**. The same can be said for the underlying pathogenesis and neural basis of these disorders, as visualized by the application of structural and functional neuroimaging techniques. Future studies employing functional connectivity approaches may reveal important insights into the functional networks impacted in hypersomnias. In particular, there is a paucity of neuroimaging studies KLS and IH, thus in contrast to narcolepsy, much less is known about the neural basis of these conditions, and the area is in great need for future research.

The application of neuroimaging techniques to better understand the neural basis of narcolepsy and primary hypersomnias presents some unusual challenges. Importantly, a distinction must be made between studies in which functional imaging data are acquired during wake and those obtained during sleep. While imaging during wake represents the easiest and most feasible approach in a clinical context, imaging during sleep remains the most informative, especially at single subject level, although technically very challenging, and likely restricted to research activities only, rather than clinical practice. Further complicating this endeavor, is the fact that simultaneous EEG and MRI would be necessary to properly distinguish between wake and sleep states during functional brain imaging. Future studies should also differentiate the characteritics of a disease (i.e., trait) from the consequences of a disease (i.e., state). This is especially important in sleep disorders where sleepiness can have a profound impact on cognitive function and behavior as a result of sleep deprivation *per se*. Nevertheless, the use of neuroimaging in sleep medicine has already increased our knowledge about sleep disorders, in particular for narcolepsy.

For now, the application of neuroimaging to determine the severity of narcolepsy and primary hypersomnias, aid diagnosis, and ascertain prognostic outcomes is mostly limited to the research laboratory. Recently, the introduction of hybrid PET/MR scanners may increase our efficacy to investigate brain structure and function in several conditions, employing the complementary contribution of both the modalities (Aiello and others, 2016; Tahmasian and others, 2015). This multimodal approach might be a valuable clinical tool in future studies of glymphatic system, recently implicated in the removal of potentially neurotoxic waste products during sleep (Xie and others, 2013) and potentially involved in pathophysiology of sleep disorders (Mander and others, 2016). In this context, neuroimaging tools integrated with genetic, neurochemical, and neurophysiological assessment in a radiogenomic scenario (Rutman and Kuo, 2009) could enable the elucidation of the neural basis of EDS, unrefreshing or excessive nocturnal sleep, and other cognitive and emotional symptoms associated with narcolepsy and primary hypersomnias.

Practice Points

Different neuroimaging techniques have demonstrated:

1. The role of orexin network deficiency in narcolepsy;

2. The key role of the thalamus in KLS during hypersomnia episodes;

3. The correlation of different and complex symptoms with the cortical and subcortical involvement in both narcolepsy and KLS.

Research Agenda

1. Neuroimaging techniques should be applied to larger and more homogeneous cohorts of patients, considering medication status sleep-wake state and, mainly for KLS, the disease phase.

2. A multimodal integrated approach should be preferred, considering the complementarity of different imaging modalities.

3. More studies should integrate neuroimaging tools with genetic, neurochemical and neurophysiological assessment to improve diagnosis of narcolepsy and hypersomnia conditions.

4. More neuroimaging studies, focusing on brain metabolism, structural and functional characteristics are needed to investigate the neural basis of idiopathic hypersomnia. This could provide a valuable diagnostic tool to improve differential diagnosis of IH.

652 **Conflict of Interest Statement:**

653 The research was conducted in the absence of any commercial or financial relationships that
654 could be considered potential conflict of interest.

655

656 **Author Contributions:**

657 Carlo Cavaliere wrote the initial manuscript draft. Mariachiara Longarzo, Stuart Fogel, Maria
658 Engström and Andrea Soddu contributed and revised the manuscript.

659

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Figures

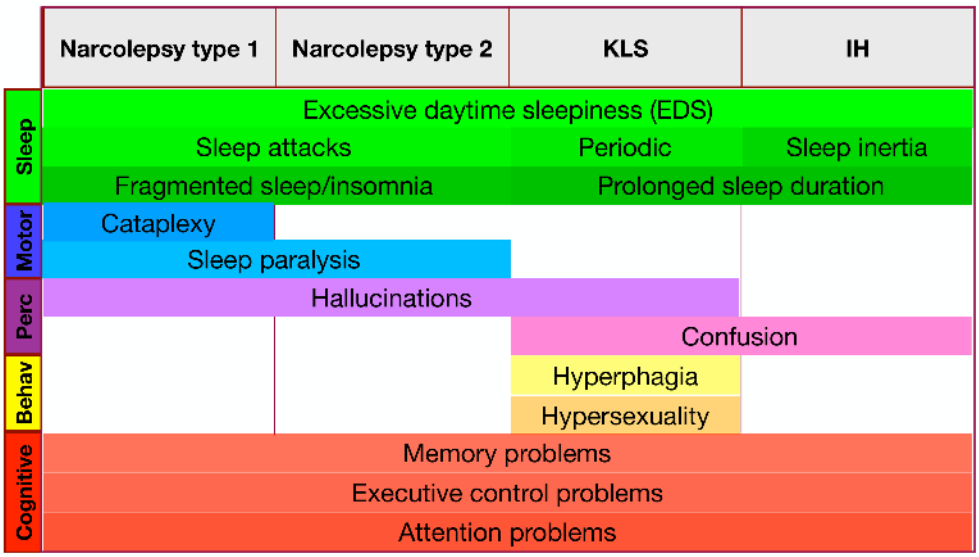

Figure 1. Schematic overview of symptoms in narcolepsy, KLS and IH. The figure shows sleep (green), motor (blue), perceptual (perc; purple), behavioural (behave; yellow), and cognitive (red) symptoms in narcolepsy type 1 and 2, Kleine-Levins syndrome (KLS), and idiopathic hypersomnia (IH).

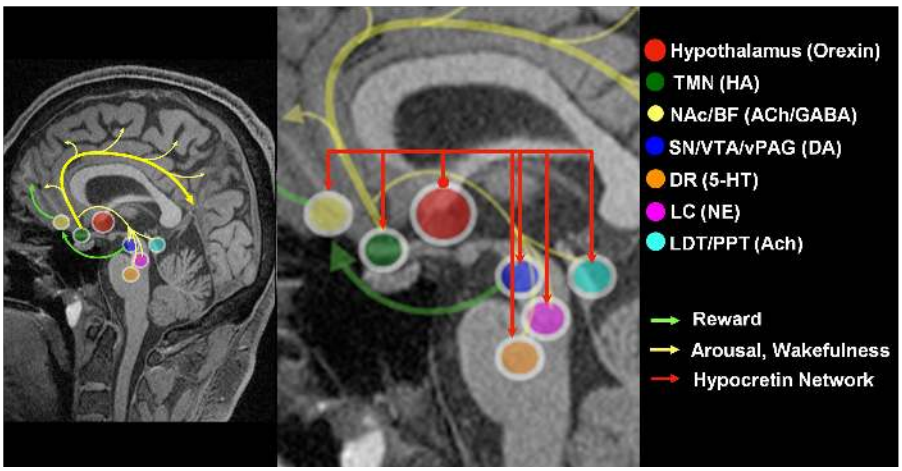

Figure 2. Left: mesolimbic pathway (green arrow) sustaining reward, and mesocortical pathway (yellow arrows) sustaining wakefulness/arousal are shown. **Middle:** orexincircuitry that from the hypothalamic area (red circle) projects to accumbens nucleus/basal forebrain (Nac/BF - yellow circle), tubero-mammilary nucleus (TMN - green circle), dorsal raphe (DR - orange circle), substantia nigra/ventral tegmental area/ventral periacqueductal gray

(SN/VTA/vPAG - blu circle), locus coeruleus (LC - purple circle), and laterodorsal tegmental nucleus/peduncolopontine tegmental nucleus (LDT/PPT - cyan circle). **Right:** Legend for neurotransmitters in each brain region.

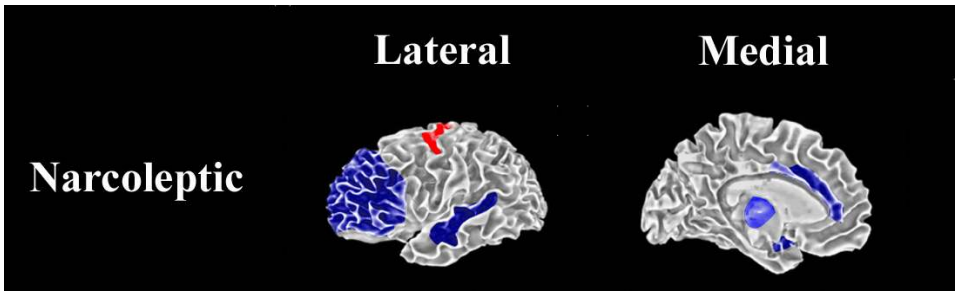

Figure 3. Schematic representation of the functional neuroanatomy of patients with narcolepsy. Regions colored in red are those in which there is a relative increase in neural activity compared to wake; those in blue correspond to relative decreases in neural activity, compared to wake. An hypofunction of several diencephalic and cortical areas is shown; conversely motor cortex is hyperactivated.

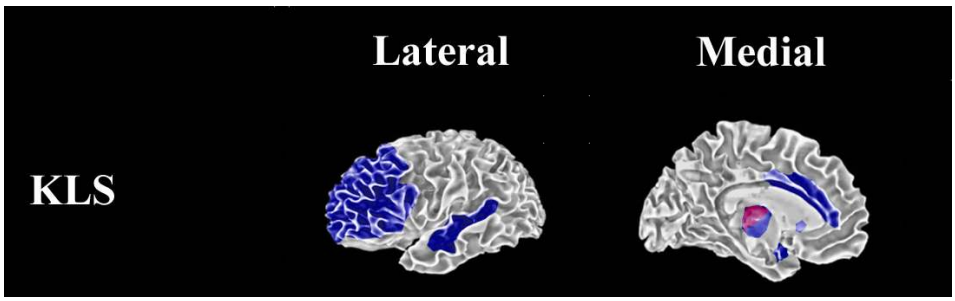

Figure 4. Schematic representation of the functional neuroanatomy of patients with KLS. Regions colored in red are those in which there is a relative increase in neural activity compared to wake; those in blue correspond to relative decreases in neural activity, compared to wake. An hypoactivation in the bilateral frontal and temporal lobes and diencephalic structures (thalami and hypothalamus).

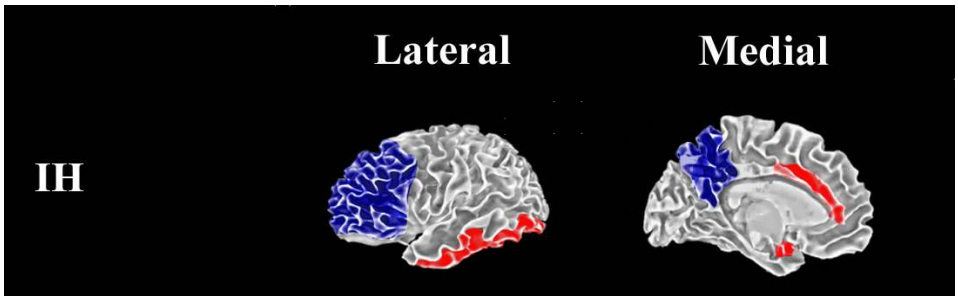

Figure 5. Schematic representation of the functional neuroanatomy of patients with IH. Regions colored in red are those in which there is a relative increase in neural activity compared to wake; those in blue correspond to relative decreases in neural activity, compared to wake. Ahypofunction of prefrontal and posterior cingulate cortices; hyperfunction of amygdala, anterior cingulate and temporo-parietal cortex. Abbreviations: KLS, Kleine-Levin syndrome; IH, Idiopathic hypersomnias. A, amygdala; B, basal forebrain; Ca, anterior cingulate gyrus; Cp, posterior cingulate gyrus and precuneus; F, prefrontal cortex (middle, inferior and orbito-frontal cortices); H, hypothalamus; M, motor cortex; P, parietal cortex; O, occipital-lateral cortex; Th, thalamus; T-O, temporo-occipital extrastriate cortex.

Tables:

Table.1. Neuroimaging findings in narcolepsy. MRI magnetic resonance imaging, MRS magnetic resonance spectroscopy, NAA N-acetylaspartate, MVol manual volumetry, VBM voxel-based-morphometry, DTI diffusion-tensor imaging, FA fractional anisotropy, fMRI functional magnetic resonance imaging, PET positron emission tomography, SPECT single photon emitted computed tomography.

From left to right: imaging analysis technique, reference, number of patients and controls studied, patients and imaging features, proportion of treated patients at the time of the imaging procedure, and main results of the study.

Technique	Reference	Number of patients/controls	Features	Number patients receiving treatment	Main findings
MRI	Frey and Heiserman, 1997 [45]	12	Cataplexy in 9.	12/12	Unspecific pontine lesions only in 2 hypertensive patients.
	Kim et al., 2016	33/31	Cataplexy in all.	n/a	Reduction in hippocampus and amygdala
	Křečková et al., 2018	48/37	Cataplexy in all	n/a	Reduction in hippocampus
MRI – MRS	Lodi et al., 2004 [33]	23/10	Cataplexy in 10.	16/23	Hypothalamic NAA/creatine-phosphocreatine reduction.
	Poryazova et al., 2009 [58]	14/14	Cataplexy in all.	None or off therapy at least 14 days before.	Metabolite decrease in amygdala and hypothalamus.
MRI – Mvol	Brabec et al., 2011 [54]	11/11	Cataplexy in all.	9/11	Reduction in Amygdala.
	Joo et al., 2012 [53]	36/36	Cataplexy in all.	None	Reduction in hippocampus.
MRI – VBM	Draganski et al., 2002 [34]	29/29	n/a	n/a	Reduction in hypothalamus, subcortical, and superior temporal areas.
	Kaufmann et al., 2002 [39]	12/32	Cataplexy in all.	6/12	Reduction in fronto-temporal areas.
	Overeem et al., 2003 [40]	15/15	Cataplexy in all.	13/15	None.

	Brenneis et al., 2005 [38]	12/12	Cataplexy in 11.	10/12	Reduction in prefrontal cortex.
	Buskovà et al., 2006 [ ]	19/16	Cataplexy in all.	9/19	Reduction in hypothalamic volume.
	Kim et al., 2009 [36]	17/17	Cataplexy in all.	11/17	Reduction in hypothalamus, brainstem, subcortical, and fronto-temporal areas.
	Joo et al., 2009 [35]	29/29	Cataplexy in all.	None	Reduction in thalami, subcortical, and fronto-temporal areas.
MRI - VBM/DTI	Scherfler et al., 2012 [48]	16/12	Cataplexy in all.	10/16	Alterations in hypothalamus, midbrain, and fronto-temporal areas.
MRI – DTI	Menzler et al., 2012 [41]	8/12	Cataplexy in all.	8/8	FA reduction in hypothalamus, brainstem, subcortical, and fronto-temporal areas.
	Nakamura et al., 2013 [ ]	24/12	Cataplexy in 12 MRI performed in awake condition	None	ADC values in patients with cataplexy was higher in frontal and parahippocampal gyri and amygdala; ADC was reduced in in postcentral gyrus. FA was different in precuneus.
MRI-DTI	Park et al., 2016 [51]	22/26	Cataplexy in all.	None	FA decrease in bilateral anterior cingulate, frontal lobe, anterior limb of the internal capsule and corpus callosum, as well as the left anterior and medial thalamus.
MRI – fMRI	Reiss et al., 2008 [61]	10/10	Cataplexy in all. Imaging protocol: Humorous versus non-humorous cartoons.	Off therapy	During task, increased activity in the limbic regions. Decrease of activity in the hypothalamus.

	Schwartz et al., 2008 [57]	12/12	Cataplexy in all. Imaging protocol: Humorous pictures versus resting.	None	During task, reduced hypothalamic and increased amygdala response to emotional stimuli.
	Ponz et al., 2010 [56]	12/12	Cataplexy in all. Imaging protocol: Reward expectancy task.	None	During task, increased activity in subcortical and limbic structures.
	Meletti et al., 2015	21	Cataplexy in all. Imaging protocol: patients scanned while viewing funny videos	None	Association between cataplexy and several cortical and subcortical areas.
	Drissi et al., 2016 [66]	16/16	Cataplexy in 15. Imaging protocol: Resting state.	16/16	Disruption of the default mode network.
	Witt et al., 2018	17/20	Cataplexy in 16 Imaging protocol: verbal working memory task	17/17	Increased deactivation of DMN during performance verbal working memory task.
	Juvodden et al., 2019	40/44	Cataplexy in all. Imaging protocol: Paradigm consisted in viewing short movies with a task	None	No differentiation in brain activation between fun and neutral movies.
	Xiao et al., 2018	26/30	Cataplexy in all Imaging protocol: Resting state	n/a	Abnormal functional connectivity in the executive and salience network
MRI – fMRI/MRS	Witt et al., 2017 [65]	17/20	Cataplexy in 16. Imaging protocol: Verbal working memory task.	17/17	During task, increased deactivation within the default mode network. Increased concentrations of Glutamate and decreased concentrations of GABA in the medial prefrontal cortex.

PET - 18FDG	Joo et al., 2004 [30]	24/24	n/a	n/a	Cerebral glucose hypometabolism of the hypothalamus-thalamus-orbitofrontal pathways
	Dauvilliers et al., 2010 [31]	21/21	Cataplexy in all. Imaging performed during wakefulness in all, and during cataplexy in 2 patients.	14/21	During cataplectic attacks, cerebral metabolism increased in primary somatosensory cortex, with a decrease in the hypothalamus.
SPECT	Meyer et al., 1980	13	Measurement of rCBF recorded during daytime sleep and wakefulness	None	Brainstem-cerebellar gray matter blood flow was reduced in the awake state
	Joo et al., 2005 [32]	25/25	Cataplexy in all. Imaging performed during waking state.	None	During wakefulness, hypoperfusion of the hypothalami, subcortical and fronto-parietal cortices.
	Hong et al., 2006 [60]	2	Cataplexy. Imaging performed during cataplexy and wakefulness phase (symptomatic vs asymptomatic phase).	n/a	During cataplexy, hyperperfusion of activation of amygdalo-cortico-basal ganglia-brainstem circuit
	Chabas et al., 2007 [59]	1	Cataplexy. Imaging performed during cataplexy and wakefulness phase (symptomatic vs asymptomatic phase).	n/a	During cataplexy, hyperactivity in normal non-rapid eye movement areas.

Table 2. Neuroimaging findings in KLS. MRI magnetic resonance imaging, MRS magnetic resonance spectroscopy, NAA N-acetylaspartate, MVol manual volumetry, VBM voxel-based-morphometry, DTI diffusion-tensor imaging, FA fractional anisotropy, fMRI functional magnetic resonance imaging, PET positron emission tomography, SPECT single photon emitted computed tomography. From left to right: imaging analysis technique, reference, number of patients and controls studied, patients and imaging features, proportion of treated patients at the time of the imaging procedure, and main results of the study.

Technique	Reference	Number of patients/controls	Features	Treatment	Main findings
MRI – MRS/fMRI	Vigren et al., 2013	14/15	Imaging protocol: Working memory task.Imaging performed during wakefulness.	None	Thalamic high fMRI-activation with low NAA-levels.
MRI - fMRI	Engstrom et al., 2009	8/12	Imaging protocol: reading span task.	1/8	Increased thalamic activity and reduced frontal activity.
	Engstrom et al., 2014	1/14	Resting state fMRI during both asymptomatic and hypersomnic periods.	n/a	Reduced functional connectivity between the brain stem and the thalamus during hypersomnia.
	Engstrom et al., 2014	18/26	Imaging protocol: listening span taskduring an asymptomatic state.	1/18	Reduced activation in the medial frontal and anterior cingulate cortices. Increased activation in the parietal and occipital cortices, the right putamen, and the left thalamus.
MRI/SPECT	Lu et a, 2000	1	n/a	n/a	Cystic lesion in the pineal region. Reduction in the hypothalamus.
	Landtblom et al., 2002	1	Imaging performed during relapse.	n/a	Large and asymmetric mamillary body.Fronto-temporal hypoperfusion close to symptomatic phase.
SPECT	Arias et al., 2002	1	n/a	Off therapy	Frontal hypoperfusion.

	Portilla et al., 2002	1	Imaging performed during sleep attack.	n/a	Hypoperfusion of temporal structures.
	Huang et al., 2005	7	Imaging performed during both symptomatic and asymptomatic periods.	n/a	Hypoperfusion of both thalami were seen only during the symptomatic period.
	Hong et al., 2006	1	Imaging protocol: during sleep attack and wakefulness (symptomatic vs asymptomatic phase).	n/a	Hypoperfusion in hypothalami, thalami, subcortical and fronto-temporal areas.
	Kas et al., 2014	41/11	Imaging protocol: during symptomatic (only 11 patients)and asymptomatic phase.	3/11 off therapy	Hypoperfusion in the orbito-frontal, the anterior cingulate, and the superior temporal and insular cortices, during wakefulness. Hypoperfusion in the dorsomedial prefrontal cortex and the parieto-temporal junction, during symptomatic periods.
	Vigren et al., 2014	24	Imaging protocol: between hypersomnia periods or after remission.	n/a	Hypoperfusion of fronto-temporal cortices in about 50% of patients.
PET - 18FDG	Dauvilliers et al., 2014	4/15	Imaging protocol: during sleep attack and wakefulness (symptomatic vs asymptomatic phase).	Off therapy	Hypermetabolism in sensory-motor cortex, thalamus and putamen. Hypometabolism in occipital and temporal gyri.
	Xie et al., 2016	1	Imaging protocol: during symptomatic and asymptomatic phase.	n/a	Hypometabolism in the thalamus and hypothalamus.

	Drouet et al., 2017	1	Imaging protocol: during symptomatic and asymptomatic phase.	n/a	Bilateral thalamostriatal hypermetabolism during symptomatic phase.

Table 3. Neuroimaging findings in IH. SPECT single photon emitted computed tomography, PET positron emission tomography. From left to right: imaging analysis technique, reference, number of patients and controls studied, patients and imaging features, proportion of treated patients at the time of the imaging procedure, and main results of the study.

Technique	Reference	Number of patients/controls	Features	Treatment	Main findings
SPECT	Bouccetta et al., 2017	13/16	Imaging performed during resting wakefulness.	n/a	Decreased CBF in prefrontal and cingulate cortices and putamen; Increased CBF in amygdala and temporo-occipital cortex.
PET - 18FDG	Dauvilliers et al., 2017	9/19	During the imaging all subjects were fully awake.	None	Increased metabolism in anterior and middle cingulate cortex and insula.