Altered regional cerebral blood flow in idiopathic hypersomnia

Running title: Neuroimaging of idiopathic hypersomnia

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Abstract

Objectives: Idiopathic hypersomnia is characterized by excessive daytime sleepiness despite normal or long sleep time. Its pathophysiological mechanisms remain unclear. This pilot study aims at characterizing the neural correlates of idiopathic hypersomnia using single photon emission computed tomography.

Methods: Thirteen participants with idiopathic hypersomnia and sixteen healthy controls were scanned during resting wakefulness using a high-resolution single photon emission computed tomography scanner with ^{99m}Tc-ethyl cysteinate dimer to assess cerebral blood flow. The main analysis compared regional cerebral blood flow distribution between the two groups. Exploratory correlations between regional cerebral blood flow and clinical characteristics evaluated the functional correlates of those brain perfusion patterns. Significance was set at $p < 0.05$ after correction for multiple comparisons.

Results: Idiopathic hypersomnia participants showed regional cerebral blood flow decreases in medial prefrontal cortex, posterior cingulate cortex and putamen, as well as increases in amygdala and temporo-occipital cortices. Lower regional cerebral blood flow in the medial prefrontal cortex was associated with higher daytime sleepiness.

Conclusions: These preliminary findings suggest that idiopathic hypersomnia is characterized by functional alterations in brain areas involved in the modulation of vigilance states, which may contribute to the daytime symptoms of this condition. The distribution of regional cerebral blood flow changes was reminiscent of the patterns associated with normal non-rapid-eye-movement sleep, suggesting the possible presence of incomplete sleep-wake transitions. These abnormalities

were strikingly distinct from those induced by acute sleep deprivation, suggesting that the patterns seen here might reflect a trait associated with idiopathic hypersomnia rather than a non-specific state of sleepiness.

Keywords: idiopathic hypersomnia, single photon emission computed tomography, sleepiness, sleep disorders.

Statement of Significance

Idiopathic hypersomnia remains a poorly understood disorder, characterized by sleepiness and severe impact on quality of life. This article reports the first neuroimaging study of this disorder, showing altered brain perfusion in regions modulating sleep-wake states. These preliminary findings suggest that incomplete sleep-wake transitions might be involved in idiopathic hypersomnia. Future work, using larger samples, should investigate brain activity across the sleep-wake cycle to provide further support to this hypothesis, and perform comparisons with other subtypes of central hypersomnias such as narcolepsy with and without cataplexy in order to delineate the abnormal neural mechanisms specific to each subtype.

Introduction

Idiopathic hypersomnia (IH) is a disorder characterized by excessive daytime sleepiness, with difficulties waking up from sleep despite obtaining a sufficient quantity of night time sleep.[1] A majority of IH patients even display a long nocturnal sleep time (>11h).[2] The difficulty in waking is often accompanied by automatic behaviours, confusion, and repeated returns to sleep, a symptom called 'sleep drunkenness'. IH symptoms usually begin during adolescence or young adulthood. Its exact prevalence remains unclear [1], although one source suggests it to be around 0.3%.[3] This condition can have devastating consequences such as repeated job loss due to the inability to wake up in the morning, car accidents, cognitive impairment, loss of productivity and disrupted quality of life secondary to inappropriate sleep intrusions during daytime.[4] Treatment is symptomatic, and mainly relies on stimulant medications or melatonin.[5] Recent evidence also suggests a potential benefit of GABA-A receptors antagonists in IH.[6,7] All in all, it remains a poorly understood disorder with an unclear pathophysiology. Some hypotheses have been suggested, including the presence of an endogenous GABAergic mechanism that decreases vigilance in IH by enhancing GABA-A receptor signalling.[7,8]

Although IH shares some common features with other types of central hypersomnias such as narcolepsy (e.g., daytime sleepiness, short daytime sleep latencies), these conditions display a few distinctive clinical characteristics that set them apart. For instance, narcolepsy with cataplexy is characterized by rapid entries into rapid-eye-movement (REM) sleep (i.e. the so-called sleep-onset REM periods or SOREMPs), often associated with sleep paralysis and hypnagogic

hallucination, the presence of cataplexy (i.e. episodes of muscle atonia triggered by emotional stimulation) and a deficit of hypocretin-1 in the cerebrospinal fluid.[9] In contrast, IH is characterized by a lower number of SOREMPs, the absence of cataplexy and no consistent deficit in hypocretin-1.[10]

Several neuroimaging studies have been conducted in narcolepsy with cataplexy. For instance, both functional (e.g., Single Photon Emission Computed Tomography [SPECT] blood flow studies and positron emission tomography [PET] glucose metabolism studies during resting wakefulness)[11-13] and anatomical (e.g., Magnetic Resonance Imaging [MRI] morphometry)[14-16] neuroimaging studies demonstrated alterations in the hypothalamus, in line with anomalies of the hypocretin system. Alterations were also observed in other subcortical (e.g., thalamus, caudate) and cortical regions (e.g., superior frontal, inferior parietal, cingulate), possibly reflecting projection sites of hypocretinergic neurons as well as neural networks involved in vigilance states (i.e., default-mode network (DMN)).[17-19] In contrast, no neuroimaging study has yet been conducted in IH.

Given the paucity of knowledge about the pathophysiology of IH, this pilot study aimed at characterizing the neural correlates of this condition through assessments of regional cerebral blood flow (rCBF) distribution using SPECT with ^{99m}Tc-ethyl cysteinate dimer (ECD). We hypothesized that IH would be associated with altered rCBF in cortical areas involved in the modulation of vigilance states (e.g., DMN), while preserving the hypocretinergic system.

Materials and methods

Subjects

Thirteen adult (> 18 years old) participants with well-characterized IH were recruited from several sleep clinics in the Montreal area, as well as through advertisements in local patients associations. Inclusion criteria for IH followed the ICSD-3 diagnostic criteria[20]: 1. excessive daytime sleepiness present for at least 3 months; 2. daytime mean sleep latency < 8 min based on a multiple sleep latency test (MSLT; if the 24h-total sleep time was > 11h, then this criterion was not required); 3. absence of cataplexy; 4.number of SOREMPs < 2 on the MSLT; 5. absence of other causes of hypersomnia (e.g., other sleep or neurological disorders, hypersomnia related to the use of drugs or medications). Sixteen good sleepers matched for age were recruited as healthy controls (HC) through local advertisements. The following exclusion criteria were applied to all potential participants: 1. sleep disorders, other than IH, as assessed by a semi-structured interview and polysomnography (e.g., sleep apnea-hypopnea syndrome with apnea-hypopnea index > 5/h); 2. systemic or neurological diseases (e.g., diabetes, hypertension, dementia, stroke, epilepsy); 3. shift or night work; 4. psychiatric disorders according to standard criteria[21]; 5. history of head injury, encephalopathy, or intracranial surgery; 6. history of alcoholism or drug abuse. Psychotropic medications that could influence sleep and alertness (e.g., psychostimulants) were withdrawn at least one week before the start of the protocol and during the whole study procedure.

The study protocol was approved by ethics committees of the Hôpital du Sacré-Coeur de Montréal and the Regroupement Neuroimagerie Quebec - Centre de Recherche de l'Institut Universitaire de Gériatrie de Montréal. All participants provided written informed consent.

Clinical characteristics

Demographic and clinical characteristics of all participants were collected to provide insight into the significance of eventual rCBF differences. This included age, sex, level of education and disease duration as estimated by self-report of symptom onset. Daytime mean sleep latency, as an objective measure of sleepiness, and number of SOREMPs were extracted from the MSLT. Standardized questionnaires included: the Epworth Sleepiness Scale (ESS) for self-reported daytime sleepiness[22], the Pittsburgh Sleep Quality Index (PSQI) for overall sleep quality[23], the Beck Depression Inventory (BDI) for severity of depression symptoms[24], the Beck Anxiety Inventory (BAI) for severity of anxiety symptoms.[25] The Morningness-Eveningness Questionnaire (MEQ) was also included to evaluate participants' self-assessed chronotype.[26]

Demographic and clinical characteristics of both groups were compared using student *t* tests for continuous variables and chi-square tests for categorical variables.

SPECT data acquisition and analysis

SPECT scans with ^{99m}Tc-ECD were performed in a high-resolution SPECT scanner yielding a 2 mm FWHM resolution (NeuroFocus, NeuroPhysics, Shirley, MA). Both IH and HC groups were scanned during morning wakefulness. A freshly prepared unidose of 750 MBq of ^{99m}Tc-ECD was administered, followed by a saline flush of 30 cc, while the subject was lying awake in the preparation room. During the period of injection and neural distribution of the compound, subjects were instructed to relax and remain awake with their eyes open, and they were constantly monitored by a research assistant to ensure they maintained wakefulness. Approximately 30 min later, they were scanned in the SPECT scanner with a single static 30-min acquisition according to the manufacturer's prescribed procedure.

After standard reconstruction (filtered back projection, subtraction of 50 % of the Compton window from the peak window) and attenuation correction (noniterative Chang algorithm), SPECT data were processed using Statistical Parametric Mapping (SPM) 12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in Matlab (version R2014b). SPECT images were registered and spatially normalized to a SPM SPECT template. SPECT images were then smoothed with a 14-mm FWHM filter. To remove the effect of global differences on regional values among subjects, global normalization was performed using proportional scaling. The CBF images were normalized to the mean global CBF value. An explicit image-mask for the whole brain was applied in order to exclude non-brain tissue from analysis.

Our main analyses focused on the differences in rCBF between the two groups (IH and HC), which were assessed with SPM12 using a two-sample t-test. This allowed us to identify cerebral regions with decreased perfusion and those with increased perfusion in IH compared to HC. In order to investigate the potential impact of these rCBF differences, exploratory correlation analyses were performed in SPM12 as following: 1) across both groups between rCBF and each of the following clinical characteristics separately: ESS, PSQI, BDI and BAI, including age, sex and education as covariates; 2) within the IH group only between rCBF and mean sleep latency at the MSLT (objective daytime sleepiness), including age, sex, education and disease duration as covariates. For all contrasts, significance was set at $p < 0.05$ after Family-Wise Error (FWE) correction for multiple comparisons on small volumes of interest (SVC; sphere, 10 mm). This correction focuses on brain regions of interest, using coordinates reported in previous neuroimaging studies.[27-33] In line with our hypothesis, we focused on regions that have been shown involved in the modulation of vigilance states from neuroimaging studies of sleep and DMN changes with sleep and hypersomnolence. For localization of rCBF changes, significant results were overlaid on a template created by averaging the participants' MRI images that were obtained from a standard T1 MP-RAGE sequence (TR 2.53s, TE 1.64ms, voxel size 1x1x1mm, 176 slices, resolution of 1mm isotropic) using a 3-Tesla MRI scanner (Siemens, Magnetom TRIO). The MRI images were resampled to standardized stereotaxic space (non-linear ICBM152) using CIVET, an image processing pipeline.[34] In brief, each MRI image was corrected for field inhomogeneities,[35] and resampled to standardized stereotaxic space (linear ICBM152)[36,37]

using an affine transformation matrix estimated with nine parameters and a cross-correlation objective function, as well as a non-linear transformation matrix (non-linear ICBM152).[38] For visualization only (figures 1-3), the statistical threshold was set at $P < 0.01$.

Results

Demographic, clinical and SPECT data were normally distributed based on Shapiro-Wilk tests. Demographic and clinical data for both groups are presented in Table 1. All recruited IH participants had a history of daily long sleep time (i.e. 24h-total sleep time > 11h). There were no significant differences in demographic characteristics (age, sex, and level of education) between the two groups. IH participants showed more severe daytime sleepiness (based on ESS) and worse sleep quality (based on PSQI). They also presented with higher depression and anxiety scores as compared to HC. Average MEQ scores were in the intermediate chronotype range for both groups, with no significant MEQ difference between groups.

Group comparison of SPECT data (Table 2, Fig.1) revealed that IH participants displayed significant rCBF decrease bilaterally in the medial prefrontal and posterior cingulate cortices, the putamen and the left cerebellum. In addition, IH participants showed a significant rCBF increase in the left amygdala as well as in the left inferior temporal and inferior occipital cortices.

Details on the significant correlations between rCBF and participants' clinical characteristics can be found in Table 3. Across both groups, lower rCBF in the medial prefrontal cortex was associated with higher self-reported daytime sleepiness as reflected by higher ESS scores; in the IH group, this medial prefrontal hypoperfusion was also associated with higher objective daytime sleepiness as reflected by lower daytime mean sleep latency on the MSLT (Fig. 2). Across both groups, lower rCBF in the right putamen was also associated with higher sleepiness measured by the ESS; in contrast, higher rCBF in the amygdala was associated with higher ESS-based sleepiness and depression symptoms as evaluated by the BDI. No significant correlation was observed between rCBF and the other clinical parameters (i.e. PSQI, BAI).

Complete SPECT results for group comparisons and correlations, including regions that were not significant after correction for multiple comparisons, can be found in tables S1 and S2 (supplementary material).

Discussion

Using functional neuroimaging with SPECT during resting wakefulness, this pilot study reported alterations in rCBF in participants with IH as compared to controls in regions encompassing portions of the DMN (medial prefrontal and posterior cingulate) as well as in the putamen, cerebellum and amygdala. Interestingly, rCBF anomalies, particularly in the medial prefrontal cortex, were correlated with daytime sleepiness severity, suggesting a possible link beween these alterations and IH clinical severity. These preliminary results constitute the first neuroimaging evidence of altered brain perfusion in IH.

When comparing the present results in IH with the results of previous SPECT and PET studies in narcolepsy with cataplexy[11-13], it seems that there could be a distinct distribution of deficits between both conditions, where narcolepsy with cataplexy has a broader extent of rCBF decreases including subcortical structures such as the hypothalamus and the thalamus, while IH deficits seem mainly concentrated on sub-regions of the DMN with a preservation of the hypothalamus, in line with the absence of hypocretin-1 loss in this condition.[2] Moreover, narcolepsy with cataplexy showed rCBF decreases in the gyrus rectus and paracentral gyri[12,13], whereas these regions were not affected in IH. This distinct distribution of deficits might relate to the differences in clinical characteristics between IH and narcolepsy with cataplexy. Further comparative studies with larger sample sizes are needed to evaluate the differences between these two conditions. Furthermore, there appears to be clinical commonalities between IH and other narcolepsy subtypes such as narcolepsy without cataplexy: in these two groups, there is

no history of cataplexy and no consistent deficit on hypocretin-1.[2] However, neuroimaging data in narcolepsy without cataplexy are very limited. The only neuroimaging study conducted in narcolepsy without cataplexy compared to HC found no significant structural changes in white matter, but did not assess structural or functional changes in grey matter.[39] Therefore, further neuroimaging studies are needed to compare these various types of central disorders of hypersomnolence in order to delineate the abnormal neural mechanisms specific to each subtype.

The mechanisms underlying the observed pattern of rCBF changes in the DMN remain to be clarified. The DMN is one of the most active networks during resting wakefulness and it is known to play a key role in controlling internal awareness and consciousness.[40] Moreover, within the DMN, the medial prefontal cortex was the region that showed the most prominent decrease in rCBF. This region has been shown to be widely connected with stuctures belonging to the ascending activating system.[41] It has also been shown that increasing medial prefrontal activity is associated with higher levels of arousal found in psychiatric conditions such as obsessive–compulsive disorder and post-traumatic stress disorder.[42,43] In addition, a structural MRI study in healthy individuals showed that a decreased volume of the medial prefrontal cortex was associated with higher levels of daytime sleepiness.[44] These studies suggest a role for the medial prefrontal cortex in controlling arousal during wakefulness, and thus lower activity in this region as suggested by decreased rCBF might be involved in reducing arousal levels in IH.

Furthermore, the possible involvement of an endogenous GABAergic mechanism has been suggested in the pathophysiology of IH, through the enhancement of GABA-A receptor signalling.[7,8] Interestingly, previous neuroimaging studies in healthy individuals reported an negative association between GABA levels and brain activation in areas belonging to the DMN such as the anterior cingulate and medial prefrontal cortices. In one of these studies, GABA concentration – as measured by magnetic resonance spectroscopy – correlated negatively with BOLD response in the anterior cingulate cortex during emotional processing.[45] In another study, midazolam – a GABA-A agonist – decreased rCBF level in the medial prefrontal and anterior cingulate cortices.[46] In this context, it could be speculated that our rCBF decreases in the DMN with IH might be related to a local increase of GABA neurotransmission underlying the decrease of vigilance. This hypothesis should be tested in future multimodal neuroimaging protocols.

Previous studies have also shown that regions within the DMN network display a reduction of brain perfusion and glucose metabolism from wakefulness to non-rapid-eye-movement (NREM) sleep in good sleepers,[27,31] in line with a need for homeostatic recovery in these regions that are highly active during wakefulness. Accordingly, we showed in a previous study that rCBF was decreased in the DMN and putamen during NREM sleep proportionally to the amount of EEG slow wave activity — a measure of sleep intensity — in good sleepers.[27] Interestingly, this rCBF distribution during NREM sleep was strikingly similar to the results reported here in IH during wakefulness (Fig. 3).

Such similarity of distribution might be interpreted as reflecting the possible intrusion of NREM sleep-like patterns into wakefulness in IH at the regional brain perfusion level. This interpretation could be tested in future protocols assessing brain responses across the sleep-wake cycle in IH subjects in comparison to good sleepers.

A few regions displayed increased rCBF in subjects with IH, including the amygdala. It is unlikely that this hyperperfusion was related to an acute emotional response since participants were in a resting state without any emotional-related task. Instead, this hyperperfusion might be related to altered mood levels in IH sufferers since higher rCBF in this region was associated with higher depression scores (Table 3). This observation is in agreement with previous findings showing an association between increased brain metabolism in the amygdala and depressive symptoms.[47,48] Interestingly, the predominantly left amygdalar hyperperfusion in IH is reminiscent of the increased glucose metabolism of the left amygdala reported during NREM sleep as compared to wakefulness in healthy individuals.[49] This common pattern is in line with the similarity of rCBF distribution between IH at wake and normal NREM sleep as discussed in the previous paragraph, and may thus support the presence of incomplete transitions from NREM sleep to wakefulness in IH. In contrast, alterations in the amygdala were not observed in narcolepsy with cataplexy during resting wakefulness in previous studies.[18] In narcolepsy with cataplexy, alterations in the amygdala have only been reported during task-related functional MRI in response to emotional stimuli.[50] This further supports the possibility of a differential alteration pattern between these two types of central hypersomnias. As for the hyperperfusion observed in temporo-occipital cortices, it may be related to an increased attentional drive to remain fully

awake and resist sleeping in IH compared to controls. These cortical regions are indeed part of the dorsal attentional network and were shown to play a role during an endogenous attentional task.[30]

Several limitations should be acknowledged in the present study. First, it was designed as a pilot investigation and based on a relatively limited sample size. Future neuroimaging studies are needed to replicate and confirm these findings in larger samples of IH. Secondly, we did not include actigraphic measurements as an objective screening for chronic sleep restriction (insufficient sleep syndrome) and circadian rhythm disorders. However, we performed a semi-structured interview and used questionnaires of chronotype to screen out for these conditions. In addition, all our recruited IH participants had a self-reported history of daily long sleep time (i.e. 24h-total sleep time > 11h), which limited the possibility of a chronic sleep restriction. Future studies should nevertheless include additional measures such as actigraphy to refine the phenotype description. Thirdly, there was no objective monitoring of alertness by polysomnography during the period of injection and brain distribution of the radio-labeled compound. The alertness of participants was still constantly assessed by a research assistant during that brief (2-3 minutes) period. The research assistant reported that none of the participants (either in the IH or control group) showed behavioral signs of sleep and that all of them kept their eyes open during the whole injection and distribution time, which supports our assumption that all participants remained awake during that period. However, we cannot

exclude that our results may have been influenced by some mixed effects even in the absence of obvious sleep, particularly involving a larger attentional effort to remain awake that IH participants may have presented as compared to HC during the SPECT procedure. Finally, it could be argued that rCBF changes observed in subjects with IH could represent a mere state effect of sleepiness in general rather than a trait pattern specific to this condition. This assumption, however, is not compatible with the effects observed after acute sleep deprivation. Indeed, in a previous study, we assessed the impact of a complete night of sleep deprivation on the distribution of rCBF during wakefulness using SPECT with ^{99m}Tc-ECD in various groups of participants, including a group of good sleepers.[51] In that group (n = 9), resting wakefulness following a complete night of sleep deprivation, compared to wakefulness following a normal night of sleep, was associated with rCBF decreases in various cortical areas (Fig. S1, supplementary material) which were strikingly distinct from the ones reported here in IH during resting wakefulness. Specifically, sleep deprivation was associated with lower rCBF in lateral fronto-temporal cortices, while IH is associated with rCBF decrease in medial cortical areas corresponding to portions of the DMN, as shown here. This suggests that inducing a state of sleepiness in good sleepers does not reproduce the rCBF changes observed in IH, which thus likely reflect a trait specific to the condition.

Conclusion

This pilot study shows that IH is characterized by specific rCBF alterations during resting wakefulness, encompassing regions belonging to the DMN (medial prefrontal, posterior cingulate). While these functional changes in IH seem distinct from those induced by sleep deprivation, they may also be reminiscent of the patterns characteristic of normal NREM sleep, thus pointing to the possible persistence of NREM sleep-like features during wakefulness in subjects affected by this disorder. These preliminary results constitute the first neuroimaging study of IH and suggest the presence of incomplete sleep-wake transitions as a possible mechanism underlying the clinical manifestations of IH.

Abbreviations list

IH: Idiopathic Hypersomnia

HC: Healthy Controls

SPECT: Single Photon Emission Computed Tomography

rCBF: regional Cerebral Blood Flow

ECD: Ethyl Cysteinate Dimer

PET: Positron Emission Tomography

MRI: Magnetic Resonance Imaging

BOLD: Blood Oxygenation Level Dependent

NREM: Non-Rapid-Eye-Movement

REM: Rapid-Eye-Movement

SVC: Small Volume Correction

MSLT: Multiple Sleep Latency Test

SOREMPs: Sleep-Onset REM (rapid eye movement) Periods

DMN: Default-Mode Network

ESS: Epworth Sleepiness Scale

PSQI: Pittsburgh Sleep Quality Index

BDI: Beck Depression Inventory

BAI: Beck Anxiety Inventory

MEQ: Morningness-Eveningness Questionnaire

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Author contributions

TTDV, JM, AZ, JPS designed the study. SB, FL and TTDV performed the experiments. SB, PG and TTDV performed the analyses. SB, TTDV and JM interpreted the results. SB and TTDV prepared and wrote the manuscript. All authors reviewed and commented on the manuscript.

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Table 1: Demographic and clinical characteristics of idiopathic hypersomnia (IH) participants compared to healthy controls (HC).

Parameters	IH (N = 13)	HC (N = 16)	p-value
Demographics:			
Age	33.31 ± 9.72	31.00 ± 9.47	0.526
Sex (M:F)	3:10	6:10	0.454
Education (years)	15.69 ± 2.72	16.38 ± 1.93	0.454
Clinical characteristics:			
Symptom duration (years)	11.46 ± 8.56	-	-
Mean sleep latency at MSLT (min)	7.28 ± 3.20	-	-
SOREMP at MSLT (Nb)	0.23 ± 0.44	-	-
AHI (Nb/h)	1.30 ± 1.39	0.70 ± 0.83	0.172
Epworth sleepiness scale	17.31 ± 4.25	4.75 ± 2.35	0.000*
Pittsburgh sleep quality index	4.84 ± 0.99	3.06 ± 1.12	0.000*
Beck depression inventory	9.61 ± 7.10	2.88 ± 3.03	0.002*
Beck anxiety inventory	9.64 ± 9.77	2.38 ± 3.16	0.025*
Morningness–eveningness questionnaire	48.77 ± 8.02	53.31 ± 10.14	0.189

Means ± standard deviations are presented and statistically compared for all parameters based on Student *t* test, except for Sex, which was based on Pearson's χ^2 test. Significant statistical differences at $P < 0.05$ are marked with an *.

Abbreviations: F: Female; M: Male; MSLT: Multiple sleep latency test; SOREMP: Sleep onset rapid eye movement sleep periods; AHI: Apnea–hypopnea index.

Table 2: Regional cerebral blood flow (rCBF) differences in idiopathic hypersomnia (IH) compared to healthy controls (HC).

Area	X	Y	Z	T	*P*
IH < HC					
Medial Prefrontal Cortex					
Left	-2	44	16	4.11	0.006[a]
Right	8	42	34	3.71	0.006[b]
Posterior Cingulate Cortex					
Left	-14	-58	32	2.86	0.038[c]
Right	12	-56	44	2.48	0.049[d]
Putamen					
Left	-18	-8	4	3.16	0.047[e]
Right	30	-6	12	2.98	0.042[f]
Cerebellum					
Left	-14	-66	-48	3.34	0.049[g]
IH > HC					
Amygdala					
Left	-10	-10	-24	2.93	0.017[h]
Inferior Temporal Gyrus					
Left	-44	-38	-16	3.97	0.047[i]
Inferior Occipital Gyrus					
Left	-46	-76	2	3.26	0.036[j]

X, Y, and Z coordinates (mm, in the MNI space) correspond to the local maxima of significant rCBF difference in IH compared to HC. T: T scores result from the statistical parametric analysis. *P*: Corrected P values (FWE correction) for multiple comparisons on small volumes (SVC) at 10 mm radius centred on corresponding published coordinates: a. (x, y, z: -2, 48, 8)[27]; b. (2, 48, 8)[27]; c. (-13, -65, 42)[28]; d. (13, -65, 42)[28]; e. (-20, -4, -8)[31]; f. (24, 8, 0)[31]; g. (-34, -78, -28)[52]; h. (-36, -36, -8)[49]; i. (-22, -8, 54)[33]; j. (-38, -78, -4)[28].

Table 3: Correlations between rCBF and clinical parameters.

	Side	X	Y	Z	*R*	*P*
Negative correlation with ESS :						
Medial Prefrontal Cortex	L	-2	46	12	-0.80	0.013[a]
	R	10	40	24	-0.73	0.013[b]
Putamen	R	32	-6	12	-0.70	0.046[c]
Positive correlation with ESS :						
Amygdala	L	-8	-10	-20	0.80	0.050[d]
Positive correlation with MSL at MSLT:						
Medial Prefrontal Cortex	L	-14	46	-6	0.73	0.047[a]
	R	4	48	2	0.63	0.047[b]
Positive correlation with BDI :						
Amygdala	L	-10	-10	-22	0.79	0.006[d]

X, Y, and Z coordinates (mm, in the MNI space) correspond to the local maxima of significant correlation between rCBF and clinical parameters. *R*: Pearson's correlation coefficient. *P*: Corrected P values (FWE correction) for multiple comparisons on small volumes (SVC) at 10 mm radius centered on published coordinates: a. (x, y, z: -2, 48, 8)[27]; b. (2, 48, 8)[27]; c. (30, -11, 8)[31]; d. (-36, -36, -8)[49]. Abbreviations: L: Left; R: Right; ESS: Epworth sleepiness scale; MSL: Mean sleep latency; MSLT: Multiple sleep latency test; BDI: Beck depression inventory.

Figure Legends

Figure 1: Regional cerebral blood flow (rCBF) distribution in idiopathic hypersomnia (IH) participants compared to healthy controls (HC).

A. rCBF decreases in IH, were located in the medial prefrontal cortex (arrow), the posterior cingulate cortex (dashed arrow), and the putamen (arrow head).

B. rCBF increases in IH, were located in the amygdala (arrow), the inferior temporal gyrus (dashed arrow), and the inferior occipital gyrus (arrow head). The level of section is indicated on the top of each panel (X, Y and Z coordinates, in mm). The color scale indicates the range of T-values for each contrast. Results were overlaid on a template created by averaging the participants' MRI images and were significant at $p < 0.05$, after correction for multiple comparisons on 10-mm spherical volumes centered on published coordinates (see Table 2).

Figure 2: Regional cerebral blood flow (rCBF) in the right medial prefrontal cortex is correlated with self-reported and objective scores of daytime sleepiness.

A. (Left) The panel shows the location of the negative correlation between rCBF in the right medial prefrontal cortex and the Epworth sleepiness scale (ESS) scores across both groups. The level of section is indicated on the top of the panel. The color scale indicates the range of t values. Results were overlaid on a template created by averaging the participants' MRI images. (Right) Plot of the normalized rCBF responses in the right medial prefrontal cortex (x = 10 mm, y = 40 mm, z = 24 mm) in relation to ESS scores (i.e. rCBF decreases when ESS is higher, reflecting

higher self-reported sleepiness). Idiopathic hypersomnia (IH) participants are represented with red circles and healthy controls (HC) with blue circles. The black solid line is the linear regression.

B. (Left) The panel shows the location of the positive correlation between rCBF in the right medial prefrontal cortex and the scores of daytime mean sleep latency at the multiple sleep latency test (MSLT) in the IH group. (Right) Plot of the normalized rCBF responses in the right medial prefrontal cortex (x = 4 mm, y = 48 mm, z = 2 mm) in relation to the scores of daytime mean sleep latency at MSLT (i.e. rCBF decreases when the sleep latency is shorter, reflecting higher objective sleepiness).

Figure 3: Regional cerebral blood flow (rCBF) distribution in idiopathic hypersomnia (IH) during wakefulness and in good sleepers (GS) during non-rapid-eye-movement (NREM) sleep.

A. SPECT with 99mTc-ECD during resting wakefulness in 13 IH participants compared to 16 HC ($p^{corr} < 0.05$): rCBF decreases, in IH, were located in the medial prefrontal cortex (arrow) and the putamen (arrow head).

B. PET with $H_2{}^{15}O$ during NREM sleep in 23 GS ($p^{corr} < 0.05$): rCBF decreases, in proportion of slow wave activity, were located in the medial prefrontal cortex (arrow) and the putamen (arrow head). Note the *striking similarity* of distribution with IH (A). Panel B adapted from (Dang-Vu et al., 2005)[27] (Copyright (2005) with permission from Elsevier).

Figure 1.

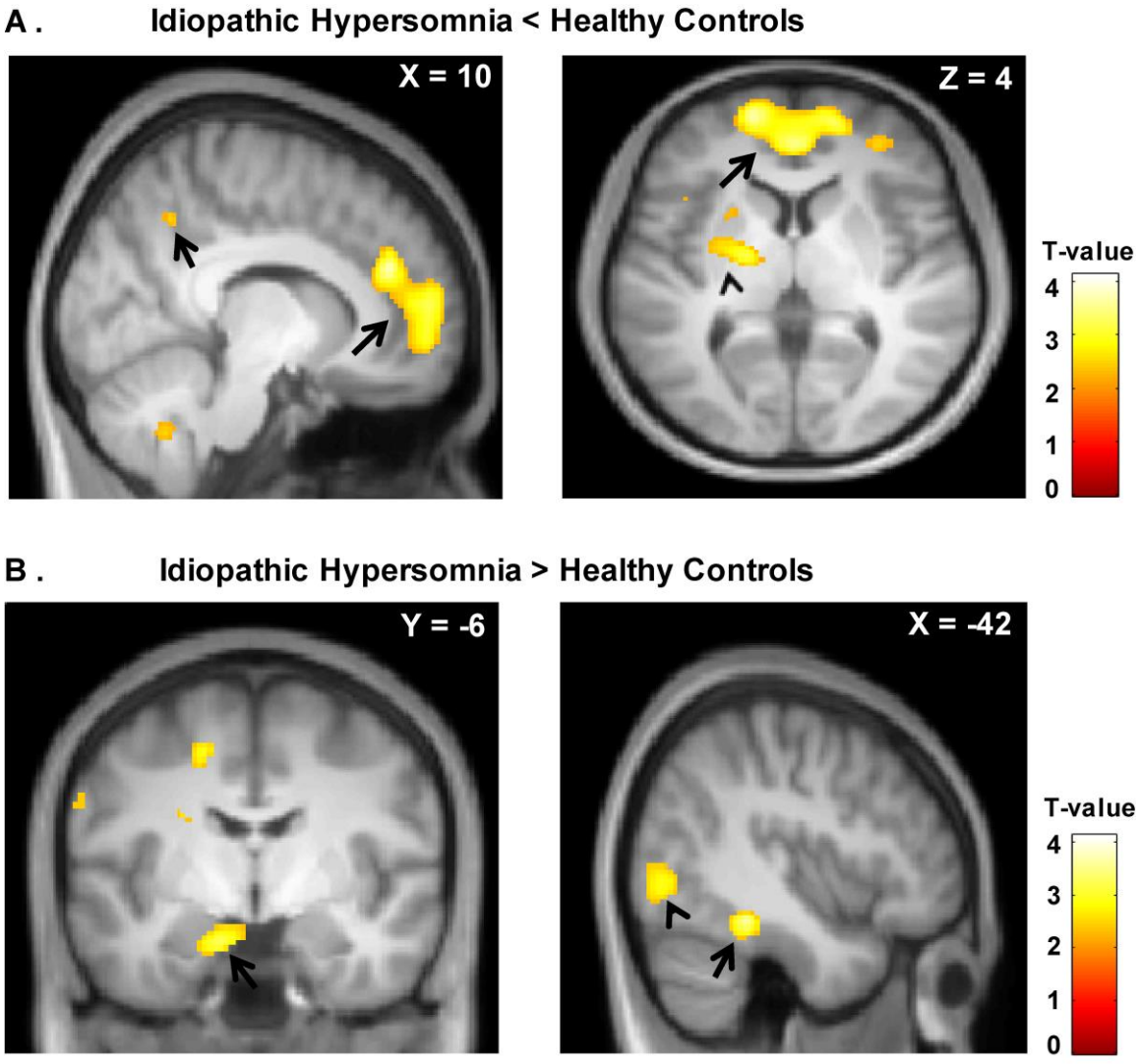

A .
Idiopathic Hypersomnia < Healthy Controls
X = 10
Z = 4
T-value
4
3
2
1
0
B .
Idiopathic Hypersomnia > Healthy Controls
Y = -6
X = -42
T-value
4
3
2
1
0

Figure 2.

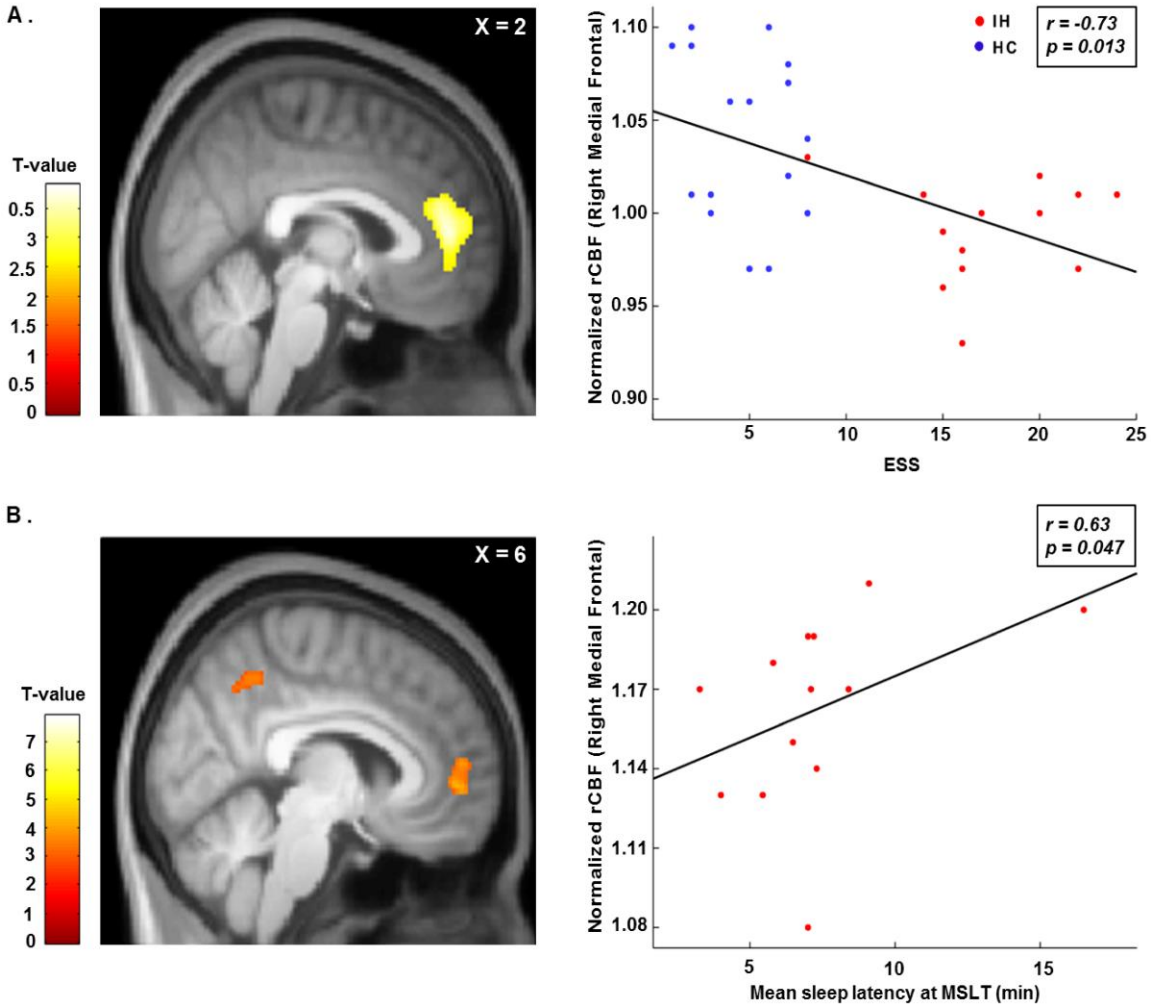
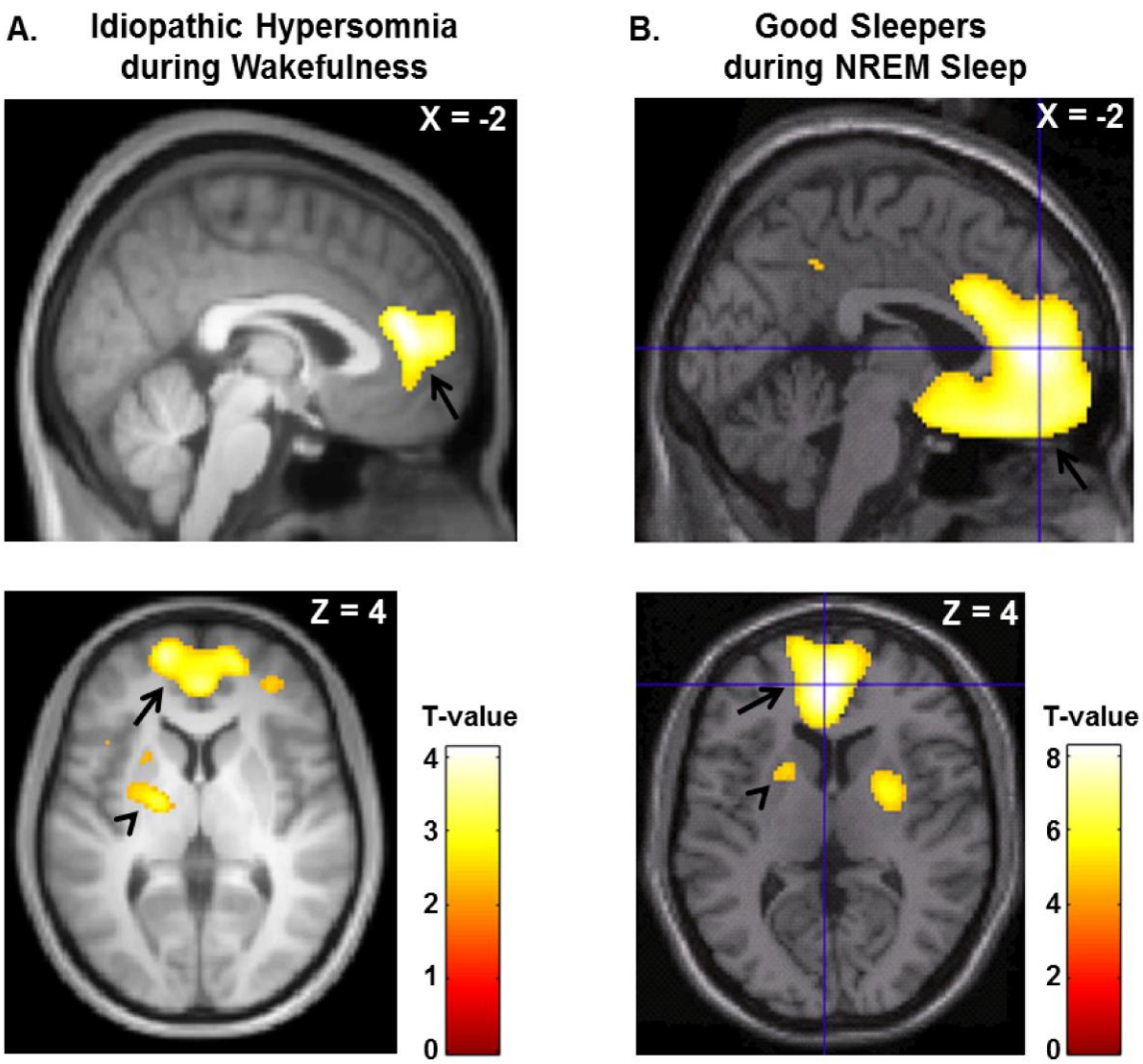


Figure 3.


A.
Idiopathic Hypersomnia
during Wakefulness
X = -2
Z = 4
T-value
4
3
2
1
0
B.
Good Sleepers
during NREM Sleep
X = -2
Z = 4
T-value
8
6
4
2
0