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RESEARCH ARTICLE

Pupillometry to differentiate idiopathic hypersomnia from narcolepsy type 1

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Summary

Idiopathic hypersomnia is poorly diagnosed in the absence of biomarkers to distinguish it from other central hypersomnia subtypes. Given that light plays a main role in the regulation of sleep and wake, we explored the retinal melanopsin-based pupil response in patients with idiopathic hypersomnia and narcolepsy type 1, and healthy subjects. Twenty-seven patients with narcolepsy type 1 (women 59%, 36 ± 11.5 years old), 36 patients with idiopathic hypersomnia (women 83%, 27.2 ± 7.2 years old) with long total sleep time (> 11/24 hr), and 43 controls (women 58%, 30.6 ± 9.3 years old) were included in this study. All underwent a pupillometry protocol to assess pupil diameter, and the relative post-illumination pupil response to assess melanopsin-driven pupil responses in the light non-visual input pathway. Differences between groups were assessed using logistic regressions adjusted on age and sex. We found that patients with narcolepsy type 1 had a smaller baseline pupil diameter as compared with idiopathic hypersomnia and controls ($p < 0.05$). In addition, both narcolepsy type 1 and idiopathic hypersomnia groups had a smaller relative post-illumination pupil response (respectively, 31.6 ± 13.9% and 33.2 ± 9.9%) as compared with controls (38.7 ± 9.7%), suggesting a reduced melanopsin-mediated pupil response in both types of central hypersomnia ($p < 0.01$). Both narcolepsy type 1 and idiopathic hypersomnia showed a smaller melanopsin-mediated pupil response, and narcolepsy type 1, unlike idiopathic hypersomnia, also displayed a smaller basal pupil diameter. Importantly, we found that the basal pupil size permitted to well discriminate idiopathic hypersomnia from narcolepsy type 1 with a specificity = 66.67% and a sensitivity = 72.22%. Pupillometry may aid to multi-feature differentiation of central hypersomnia subtypes.

KEYWORDS
biomarkers, idiopathic hypersomnia, melanopsin-mediated pupil response, narcolepsy type 1, pupil diameter, pupillometry

1 | INTRODUCTION

According to the International Classification of Sleep Disorder (ICSD-3; American Academy of Sleep Medicine, 2014), central hypersomnia disorders include idiopathic hypersomnia (IH), narcolepsy type 1 (NT1) and type 2 (NT2), Kleine–Levin syndrome, hypersomnia associated with psychiatric disorders, and hypersomnia due to a medical disorder, medication or substance use. IH is a chronic sleep and wake disorder characterized by excessive daytime sleepiness (EDS), either a prolonged total sleep time on 24 hr (TST ≥ 11 hr on 24 hr) and/or a reduced mean sleep latency. Several hypotheses regarding the causes of IH have been raised, including deficiency of arousal systems (Arnulf et al., 2019), circadian (Landzberg & Trotti, 2019), homeostatic (Sforza et al., 2000), autonomic nervous (Sforza et al., 2016) or brain connectivity dysfunction (Dauvilliers et al., 2017), but its pathophysiology remains mostly unknown. To date, besides the approval of the Xywav by the US Food and Drug Administration, no medication has been approved by the European Medicines Agency for this disorder. Although IH is considered as a rare pathology with a prevalence estimated of about 0.05% (Billiard & Sonka, 2016), its true prevalence remains difficult to establish, first because there are many causes of sleepiness, but also due to the absence of biomarkers to distinguish IH from NT2 and other hypersomnia subtypes. In addition, changes over time of hypersomnia diagnostic criteria due to the evolution of international classifications participate in the difficulties met by clinicians to identify a clear phenotype of IH. Indeed, IH was initially split between IH with long sleep time versus without long sleep time (American Academy of Sleep Medicine, 2005), and later merged together in the current ICSD-3 (American Academy of Sleep Medicine, 2014). All this underscores the need to identify biomarkers of IH to have a better understanding of its pathophysiology and to clarify the spectrum of hypersomnia disorders, in order to provide tailored medical care.

Light plays a major role in the regulation of many brain functions such as sleep/wake regulation (LeGates et al., 2014; van der Meijden et al., 2016), circadian rhythms, mood and cognition (LeGates et al., 2014). Light affects alertness and sleep in two ways: directly in a circadian-independent fashion, and indirectly through clock entrainment and phase shifting of circadian rhythms (Hubbard et al., 2021). These non-visual effects of light are primarily mediated by melanopsin-based phototransduction. Melanopsin is a photopigment sensitive to short wavelength (Bailes & Lucas, 2013; peak sensitivity at 460–480 nm corresponding to blue light) expressed in the intrinsically photosensitive retinal ganglion cells (ipRGCs; Dacey et al., 2005). These neurons project towards several brain structures (Vandewalle et al., 2009), including the olivary pretectal nucleus involved in the regulation of the pupillary light reflex (Schmidt et al., 2011). In contrast to cones and rods, ipRGCs have slow-action kinetics and sustained response over time after exposure to blue light. The ipRGCs specific kinetic response can be observed after an exposure to blue light followed by darkness: the pupil remains constricted longer than it does after having been exposed to other wavelengths (Bailes & Lucas, 2013; Gamlin et al., 2007). This pupil response, named the post-illumination pupil response (PIPR), reflects the prolonged activity over time of the melanopsin-containing cells (Gamlin et al., 2007), and has been reported to be reduced in major depressive disorder (MDD; Laurenzo et al., 2016), seasonal affective disorder (SAD; Roecklein et al., 2013) and delayed sleep–wake phase disorder (Abbott et al., 2021). More recently, we showed for the first time that patients with IH with prolonged sleep time had reduced PIPR as compared with healthy subjects (Rach et al., 2022), indicating a lower reactivity of the melanopsinergic system. We suggested that a reduced sensitivity of the melanopsin system could lead to a phenotype of both decreased overall alertness and delayed sleep–wake timing in IH with long sleep time (Rach et al., 2022). This reduced ipRGCs integration of the light signal could also be present in individuals suffering from another hypersomnia subtype, and contribute to a "light-related vulnerability to sleepiness", but this has never been explored.

Given that and to identify biomarkers of hypersomnia subtypes, we aimed to explore the melanopsin-mediated pupil response to light in individuals with NT1, IH with long sleep time and healthy subjects using a pupillometry method highly specific of melanopsin-based phototransduction (van der Meijden et al., 2015) to assess whether melanopsin-mediated pupil responses may help differentiating between different hypersomnia subtypes.

2 | METHODS

2.1 | Participants

Women and men aged 18 years or older with a diagnosis of IH ($n = 36$), NT1 ($n = 27$) or healthy controls ($n = 43$) were included between 2020 and 2022 at the Sleep Disorders Center of the University of Strasbourg. There is a major overlap of IH and control participants with our previous study, as several participants (28 IH patients and 29 healthy subjects) were also included in this work (Rach et al., 2022). Given the heterogeneity of IH phenotypes and in order to identify biomarkers of hypersomnia subtypes, only IH patients with prolonged sleep time were included in the study. The diagnostic criteria of IH with long sleep time were: (1) a subjective EDS ≥ 3 months long evaluated with the Epworth Sleepiness Scale (ESS score > 10); (2) a TST ≥ 660 min (> 11/24 hr) associated or not associated to a mean sleep latency during the multiple sleep latency tests (MSLT) ≤ 8 min with no more than one sleep onset in rapid eye movement (SOREM) period. The diagnostic criteria of NT1 were: (1) a subjective EDS ≥ 3 months evaluated with the ESS (ESS score > 10) or daily episodes of irrepressible need to sleep or daytime lapses into sleep; (2) a mean sleep latency during the MSLT ≤ 8 min with two SOREM periods or more (a SOREMP within 15 min of sleep onset on the preceding nocturnal polysomnography (PSG) can replace one of the SOREMPs on the MSLT) and the presence of cataplexy; or (3) reduced cerebrospinal fluid hypocretin-1 levels (≤ 110 pg ml^{-1}). Patients with IH and NT1 previously underwent a PSG examination (≤ 5 years prior to the inclusion) at the Sleep Disorders Center of the University of Strasbourg for three consecutive days to assess the

TST/24 hr (determined during a continuous video-PSG recording of 24 hr), SOREM and sleep latency at the MSLT, as well as microarousal index per hr, apnea–hypopnea index per hr (AHI), periodic limb movement index per hr (PLM).

Non-inclusion criteria for patients were sleep disorders other than IH with long sleep time or NT1 (circadian rhythm disorder, AHI > 15, PLM arousal/non-arousal index > 15 for the IH patients only), daytime sleepiness due to sleep debt (measured with sleep diary 2 weeks prior to hospitalization), sleep duration < 6 hr, past or current serious or unstable medical illness known to affect the phototransduction (neurodegenerative disorders, acquired hereditary retinal disorders, etc.), current psychiatric or medical disorders associated with hypersomnolence, use of light therapy in the last month, use of medications known to affect the vigilance (modafinil, sodium oxybate, pitolisant, methylphenidate, melatonin, and drugs containing dopamine or serotonin) and/or with known sympathetic or parasympathetic effects for less than 1 month or with dosage changes in the month prior to the evaluation, use of drug or substance abuse, travel across two timezones or more during the last 2 months prior to participation, shiftwork or self-imposed irregular sleep schedule within the last year, suicidal ideations, and pregnancy/breastfeeding.

Controls were recruited through advertisements (displayed at the Strasbourg University, shops, and online announcements). Supplementary inclusion criteria for this group were no history of sleep–wake disorders (assessed by several questionnaires described in the Table S1) or mood disorders reported at the clinical examination (as assessed by the Mini International Neuropsychiatric Interview—MINI 2.0; Lecrubier et al., 1997) and a body mass index (BMI) comprised between 18 and 30 kg m^{-2}. They also received an eye examination to exclude retinal dysfunction and dyschromatopsia.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants gave their written informed consent prior to their enrolment in the study (API, 2016 HUS n° 6791) and all procedures have been approved by a French Institutional Review Board on 19 November 2019 (Comité de Protection des Personnes Sud-Ouest et Outre-Mer, number 1-19-070 SI 5025).

2.2 | Procedures

Controls and patients who completed all inclusion and non-inclusion criteria gave their written informed consent prior to their enrolment in the study. The method has been described elsewhere in a previous published work (Rach et al., 2022). Participants completed a detailed medical and sleep history interview, a physical examination and a psychiatric interview (MINI 2.0; Lecrubier et al., 1997). Inspection of the pupillary light reflex ensured good pupil reactivity to light. Self-assessments were completed during breaks within the pupillometry testing, and included the ESS to assess daytime sleepiness (Johns, 1991), the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep difficulties (Buysse et al., 1989), the Pichot Questionnaire to assess fatigue (Gardenas, 2002), the Horne and Ostberg Morningness–Eveningness Questionnaire (MEQ) to assess chronotype (Horne & Östberg, 1977), the Structured Interview Guide for the Hamilton Depression scale—SAD version—Self Assessment (SIGH-SAD-SA) to determine depressive symptoms severity (Terman et al., 2009), the State and Trait Anxiety Questionnaires (STAI-YA and YB; Spielberger et al., 1983), and a visual analogue scale (VAS) to determine global subjective light sensitivity (Table S1).

2.3 | Pupillometry

Before the pupillometry, subjects were placed in a white polychromatic light (200 lux, light source = RGB-LED, broadband light emitted by fluorescent tubes from the ceiling guaranteeing an uniform illumination of the room) room for 30 min to allow the pupils to adapt to light, as previously described (Rach et al., 2022). Participants seated in front of the pupillometer build at the Netherlands Institute for Neuroscience, Amsterdam, The Netherlands (Abbott et al., 2021; van der Meijden et al., 2016). The protocol was conducted between 09:30 hours and 16:30 hours to avoid circadian variations in pupil responses (Zele et al., 2011). All stimuli were presented to the right eye placed at 5 cm of a light box (16 × 10 cm; light source = RGB-LED, Lamina, NT-43F0-09424 LED, Atlas, RGB, Farnell, Leeds, UK), and the consensual pupil diameter measurements were recorded from the left eye with an infrared camera (wavelength = 880 nm). Sampling frequency was 25 Hz. Data were extracted using R software (R version 4.0.5, 2021-03-31, R Foundation for Statistical Computing, Vienna, Austria).

The pupil diameter was recorded through a pupillometry protocol divided in two parts. The first part of the protocol assessed the melanopsin-mediated pupil response with a validated protocol previously described (Rach et al., 2022; van der Meijden et al., 2015) that included 5 min of baseline darkness, 5 min of monochromatic red light (wavelength = 630 nm, luminance = 375 cd m^{-2}, retinal irradiance = 14.75 log photons cm^{-2} s^{-1}), 5 min of post-red darkness, 5 min of monochromatic blue light (wavelength = 470 nm, luminance = 375 cd m^{-2}, retinal irradiance = 14.75 log photons cm^{-2} s^{-1}) and 5 min of post-blue darkness. The second part of the pupillometry protocol allowed to explore the pupil response to green light, which remains today poorly investigated, and included 5 min of baseline darkness (green baseline), 5 min of monochromatic green light (wavelength = 520 nm, luminance = 375 cd m^{-2}, retinal irradiance = 14.75 log photons cm^{-2} s^{-1}), 5 min of post-green darkness. Given that large inter-individual differences exist in pupil relaxation time after exposure to blue light (van der Meijden et al., 2015), a break of 45 min was imposed between both parts of the pupillometry protocol to allow for the normalization of pupil diameter. As recommended, the first and last minutes of each 5-min period were excluded from analyses (Rach et al., 2022), and the pupil diameter (mm) was averaged on the three central minutes of each type of exposure. This validated protocol of successive prolonged red and blue light exposures allows

to maximize the contribution of ipRGCs to the pupil diameter (van der Meijden et al., 2018; Wong et al., 2005), and to minimize activity of cones and rods (Kardon et al., 2009). In order to quantify the functionality of ipRGCs (Roecklein et al., 2013), the PIPR, defined as the differences between baseline pupil diameter and the post-blue pupil diameter—also called sustained pupil diameter after blue light exposure (1), was calculated. As recommended (Kelbsch et al., 2019), we used the relative to baseline pupil diameter PIPR (2) to delete the influence of the basal pupil size on the results. In addition, the absolute PIPR (1) was calculated to facilitate comparison with other studies (Adhikari, Zele, & Feigl, 2015). These methods have been detailed and validated previously (van der Meijden et al., 2015). The red and green absolute (1) and relative (2) PIPR were also calculated in response to red and green lights.

1. Absolute PIPR (mm) = baseline pupil diameter – post-light exposure pupil diameter
2. Relative PIPR (%) = 100 * PIPR mm/baseline pupil diameter

In addition, an auditory version of the Psychomotor Vigilance Task (PVT), a validated task to assess sustained attention (Dinges & Powell, 1985), was performed during the three central minutes (Basner et al., 2011) of each 5-min block to measure vigilance throughout the pupillometry examination. Subjects had to rapidly press a button when they heard a sound (continuous 880-Hz tone) emitted at a random time by the pupilometer. The reaction time (ms) was recorded and averaged for each block. Reaction times superior to three times the within-subject SD were considered as false value and removed from the data set.

2.4 | Statistical analyses

In order to describe our population, we first compared groups (IH, NT1 and controls) regarding clinical characteristics (sex, age, BMI, sleepiness, fatigue, sleep quality and chronotype, depressive symptoms and anxiety questionnaires) using multinomial logistic regressions (with group as dependent factors and each clinical parameter separately as independent factor). PSG features, obtained for the IH and NT1 groups, were compared using binomial logistic regressions (group as dependent factor and each PSG feature as independent factor). Secondly, we investigated group differences in pupillometry features separately, using multinomial logistic regressions with group as dependent factor, and a pupillometry feature (PIPR, pupil diameter, PVT reaction time) as independent factor. Analyses included age and sex as covariates (and medication in Table S2) to adjust for previously reported age differences in melanopsin-mediated pupil response and pupil diameter (Adhikari, Pearson, et al., 2015; Tekin et al., 2018). In addition, linear mixed model was fitted to assess the effect of time throughout the pupillometry protocol on the PVT reaction time. Thirdly, we investigated the association between pupillometry features and clinical characteristics, using linear regressions with a pupillometry feature as dependent factor and clinical characteristics (age, sex, chronotype depressive symptoms, fatigue, sleepiness and PSG features) as independent factors. Those analyses were conducted within the whole population and separately by group. To assess if the association differed significantly by group, we also ran the model within the whole population adding group as an interaction factor. In addition, matrix of correlations were realised to test the association between PVT reaction time and pupillometry parameters in the whole population and in each group. Lastly, we investigated the diagnostic capabilities of the pupillometry features. Youden's index was used to determine optimal relative PIPR and baseline thresholds in the three models: IH versus NT1; NT1 versus controls; and IH versus controls. The diagnostic accuracy of these thresholds was expressed by the sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), receiver operating characteristic (ROC) area under the curve (AUC) and Youden's index. An AUC = 0.50 suggests no discrimination, 0.7 ≤ AUC <0.9 indicates an acceptable accuracy of the predictive model, 0.9 ≤ AUC <1 is very discriminating, and an AUC = 1 is a perfect discrimination (Swets, 1988).

Statistical analyses were conducted using the R software (R version 4.0.5, 2021-03-31, R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$ for all tests.

3 | RESULTS

The clinical characteristics of patients with hypersomnia and healthy subjects are presented in Tables 1 and 2. Thirty-six (83% female, $N = 30$) patients with IH with long sleep time, 27 patients with NT1 (59% female, $N = 16$) and 43 healthy subjects (58% female, $N = 25$) were included. The prevalence of women was higher in the IH group ($p < 0.05$), and the BMI was higher in the NT1 group ($p < 0.01$) as compared with others. In addition, patients with NT1 were older than patients with IH and controls (respectively, 8.8 years and 5.4 years older in mean, $p < 0.05$). Six patients with NT1 had lumbar puncture with a reduced hypocretin level (< 110 pg ml^{-1}) for all of them. Ophthalmological examination of healthy subjects was normal, and patients reported no ocular disease. Among patients with NT1, seven patients were under psychostimulant medication for more than 1 month (four modafinil, three pitolisant), and one patient was under sodium oxybate for more than 1 month. All patients had an AHI < 15, except one patient with NT1 who had an AHI = 22. All patients with IH had a PLM arousal/non-arousal index < 15, whereas 10 patients with NT1 had a PLM arousal/non-arousal index > 15.

As expected, both hypersomnia groups obtained higher subjective sleepiness (ESS), higher fatigue (Pichot), lower sleep quality scores (PSQI), higher self-rated depression symptoms (SIGH-SAD-SA) and higher state/trait anxiety scores (STAI-YA/YB) than controls ($p < 0.001$). Among patients with IH with long sleep time, seven had a mean sleep latency obtained at the MSLT ≤ 8 min. Participants in the IH group obtained lower scores at the MEQ as compared with other groups indicating a later chronotype ($p < 0.01$). More specifically, 48%

TABLE 1 Clinical and sociodemographic characteristics for IH with long sleep time, NT1 and control groups

	IH patients *N* (%) or mean ± SD	NT1 patients *N* (%) or mean ± SD	Control *N* (%) or mean ± SD
N	36	27	43
Sex (women)	30 (83.33%)[a,c]	16 (59.25%)[a]	25 (58.14%)
BMI	22.75 ± 3.37[a]	26.49 ± 6.08[a,b]	21.95 ± 2.69
Age	27.20 ± 7.17[a]	36.01 ± 11.55[a,b]	30.62 ± 9.35
Chronotype (MEQ)	47.34 ± 11.98[a,c]	56.08 ± 8.90[a]	57.74 ± 11.31
Sleepiness (ESS)	13.36 ± 3.54[c]	14.81 ± 5.29[b]	6.76 ± 3.31
Pichot fatigue score	16.06 ± 7.11[c]	14.41 ± 8.02[b]	2.91 ± 2.71
Sleep quality (PSQI)	5.32 ± 2.42[c]	6.68 ± 3.45[b]	2.30 ± 1.47
Severity of depressive symptoms score (SIGH-SAD-SA)	13.47 ± 8.69[c]	16.42 ± 9.92[b]	4.95 ± 4.07
Atypical score balance in percent (SIGH-SAD-SA)	40.24 ± 22.28[c]	38.9 ± 18.73	28.07 ± 28.65
State Anxiety (STAI-YA)	36.22 ± 11.89[c]	38.0 ± 11.94[b]	27.37 ± 7.35
Trait Anxiety (STAI-YB)	41.83 ± 11.83[c]	45.04 ± 13.47[b]	30.7 ± 7.79
Subjective light sensitivity (VAS)	61.11 ± 25.04	49.4 ± 22.52	54.44 ± 23.64
Photoperiod (hr)	11.92 ± 2.33	11.19 ± 1.75	12.10 ± 2.16

Note: Significant logistic regression between groups ($p < 0.05$).
Abbreviations: BMI, body mass index; Controls, healthy subjects; ESS, Epworth Sleepiness Scale; IH, patients with long sleep time idiopathic hypersomnia; MEQ, Morningness–Eveningness Questionnaire; *N*, size; NT1, patients with narcolepsy type 1; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; SIGH-SAD-SA, Structured Interview Guide For the Hamilton Depression Scale—Seasonal Affective Disorder version—Self Assessment; STAI, State and Trait Anxiety Questionnaires; VAS, visual analogue scale.
[a]Between NT1 and IH.
[b]Between NT1 and Control.
[c]Between IH and Control.

TABLE 2 Comparison of clinical and PSG characteristics for IH with long sleep time and NT1 groups

	IH patients *N* (%) or mean ± SD	NT1 patients *N* (%) or mean ± SD	IH versus NT1 β (SE)
N	36	27	
AHI (hr)	2.55 ± 2.82	6.9 ± 11.81	0.13 (0.07)
Microarousal index (hr)	13.98 ± 6.78	18.46 ± 11.63	0.06 (0.03)
PLM index (hr)	6.68 ± 9.04	14.14 ± 12.64	0.07 (0.03)*
TST/24 hr	744.8 ± 62.89	569.9 ± 173.44	−0.014 (0.004)***
Mean sleep latency (MSLT)	11.95 ± 4.00	4.53 ± 1.97	−1.44 (0.51)**
Number of SOREM (MSLT)	0.18 ± 0.52	2.93 ± 2.40	2.13 (0.59)**

Note: Significant logistic regression between IH and NT1 groups.
Abbreviations: AHI, apnea–hypopnea index; β (SE), logistic regression coefficient (standard error); Controls, healthy subjects; IH, patients with long sleep time idiopathic hypersomnia; MSLT, multiple sleep latency tests; *N*, size; NT1, patients with narcolepsy type 1; PLM, periodic limb movement; SD, standard deviation; SOREM, sleep-onset rapid eye movement; TST/24 hr, total sleep time on 24 hr.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

of IH patients, 54% of NT1 patients and 43% of healthy subjects had a neutral subjective chronotype; 11% of IH patients, 34% of NT1 patients and 39% of healthy subjects had a moderate morning type; 34% of IH patients, 5% of NT1 patients and 7% of healthy subjects had a moderate evening type; 3% of IH patients, 7% of NT1 patients and 9% of healthy subjects had definitely a morning type; 4% of IH patients, 0% of NT1 patients and 2% of healthy subjects had definitely an evening type. Finally, no between-group differences were observed in the photoperiod at the time of the test and subjective light sensitivity.

3.1 | Pupillometry features comparisons

Table 3 shows the comparisons between the 36 IH, 27 NT1 and 43 controls on pupillometry features, with age and sex used as

TABLE 3 Pairwise comparisons of IH versus Control, NT1 versus Controls, and IH versus NT1 on pupillometry measurements

	IH patients mean ± SD	NT1 patients mean ± SD	Controls mean ± SD	IH versus control β (SE)	NT1 versus control β (SE)	IH versus NT1 β (SE)
N	36	27	43			
Averaged pupil diameter (mm)						
Baseline	5.25 ± 1.06	4.10 ± 1.22	5.21 ± 1.36	−0.04 (0.19)	−0.57 (0.24)*	−0.52 (0.25)*
Red	3.04 ± 0.43	2.69 ± 0.53	2.95 ± 0.49	−0.27 (0.5)	−1.00 (0.59)***	−1.27 (0.64)*
Post-red	5.46 ± 1.19	4.42 ± 1.33	5.45 ± 1.26	−0.11 (0.19)	−0.62 (0.24)**	−0.51 (0.25)*
Blue	2.12 ± 0.22	1.90 ± 0.27	2.03 ± 0.27	0.81 (0.99)	−1.60 (1.1)	−2.41 (1.22)*
Post-blue	3.47 ± 0.65	2.87 ± 0.59	3.11 ± 0.65	0.68 (0.39)[t]	−0.46 (0.45)	−1.13 (0.49)*
PIPR						
Relative blue PIPR (%)	33.18 ± 9.99	30.73 ± 13.31	38.70 ± 9.71	0.05 (0.02)*	−0.07 (0.03)**	−0.02 (0.03)
Absolute blue PIPR (mm)	1.78 ± 0.72	1.43 ± 0.89	2.09 ± 0.93	0.45 (0.29)	−0.88 (0.33)**	−0.43 (0.36)
Relative red PIPR (%)	−3.9 ± 9.34	−3.17 ± 14.24	−6.13 ± 13.26	0.02 (0.02)	0.01 (0.02)	−0.01 (0.02)
Absolute red PIPR (mm)	−0.20 ± 0.45	−0.12 ± 0.52	−0.24 ± 0.59	0.39 (0.47)	0.29 (0.49)	−0.09 (0.56)

Note: Age and sex were included as possible confounding covariates in the logistic regression analyses. Significant logistic regression between groups.
Abbreviations: β (SE), logistic regression coefficient (standard error); Baseline, pupil diameter during basal darkness; Blue, pupil diameter during blue light exposure; Controls, healthy subjects; IH, patients with long sleep time idiopathic hypersomnia; *N*, size; NT1, patients with narcolepsy type 1; PIPR, post-illumination pupil response; Post-blue, pupil diameter after blue light exposure; Post-red; pupil diameter after red light exposure; Red, pupil diameter during red light exposure; SD, standard deviation.
*$p < 0.05$.**$p < 0.01$.***$p < 0.1$.

covariates in the analyses. Figure 1(a) represents the pupil diameter evolution through the pupillometry protocol.

3.1.1 | NT1 and IH versus controls

Patients with NT1 showed a significant reduced mean pupil size at baseline ($p = 0.016$) as compared with controls (Figure 2a; Table 3).

Concerning melanopsin-pupil response, both IH and NT1 groups showed a significantly lower relative PIPR (Figure 2b) as compared with controls (NT1 versus controls: $p = 0.006$; IH versus controls: $p = 0.043$), and the absolute PIPR was reduced in the NT1 group as compared with controls (NT1 versus controls: $p = 0.009$) but not in the IH group ($p > 0.05$). These differences were maintained when medication was added as a covariate in the logistic regression model (Table S2), and when patients with medication were excluded from the analyses (Table S3). Similar results were obtained with the green light protocol between NT1 patients and healthy subjects (see Table S4 for details).

The averaged PVT reaction time in both NT1 and IH groups was higher as compared with controls (all $p < 0.001$; Table S5) for each exposure condition (Figure 1b). The PVT reaction time did not vary throughout the pupillometry protocol in all groups (mixed linear models results are detailed in Appendix S6).

3.1.2 | IH versus NT1

The NT1 patients had reduced pupil size as compared with IH patients at baseline ($p = 0.038$) and throughout the protocol (Table 3). No significant differences were observed between IH and NT1 when comparing the blue relative and absolute PIPR.

3.2 | Relation between pupillometry and clinical parameters

Age was negatively associated to baseline pupil diameter in the whole population ($\beta = -0.04 \pm 0.01$, $p = 0.001$) and in the control group ($\beta = -0.04 \pm 0.02$, $p = 0.047$). However, age did not explain the pupillometry differences between groups, as this parameter was added as covariate in the analyses. Sleepiness, fatigue and depression were negatively correlated to the relative PIPR in the whole population (respectively: $\beta = -0.57 \pm 0.20$, $p = 0.005$; $\beta = -0.42 \pm 0.12$, $p = 0.0007$ and $\beta = -0.29 \pm 0.12$, $p = 0.021$). Sleepiness was also negatively correlated with baseline pupil diameter in the whole population ($\beta = -0.06 \pm 0.02$, $p = 0.009$). In addition, the PVT reaction time was negatively correlated to the pupil diameter and to the blue PIPR in the whole population and in the NT1 group ($p < 0.05$), but not in the IH and control groups ($p > 0.05$; Appendix S8). Other sociodemographic, medication and sleep parameters described earlier did not explain the between-group differences and were not significantly correlated with the relative/absolute PIPR and the pupil diameter in each group (all $p > 0.05$; Table S7).

3.3 | Accuracy of the predictive models

The cut-off values, sensitivity, specificity, PPV, NPV and the ROC AUC of the relative PIPR and the baseline pupil diameter are

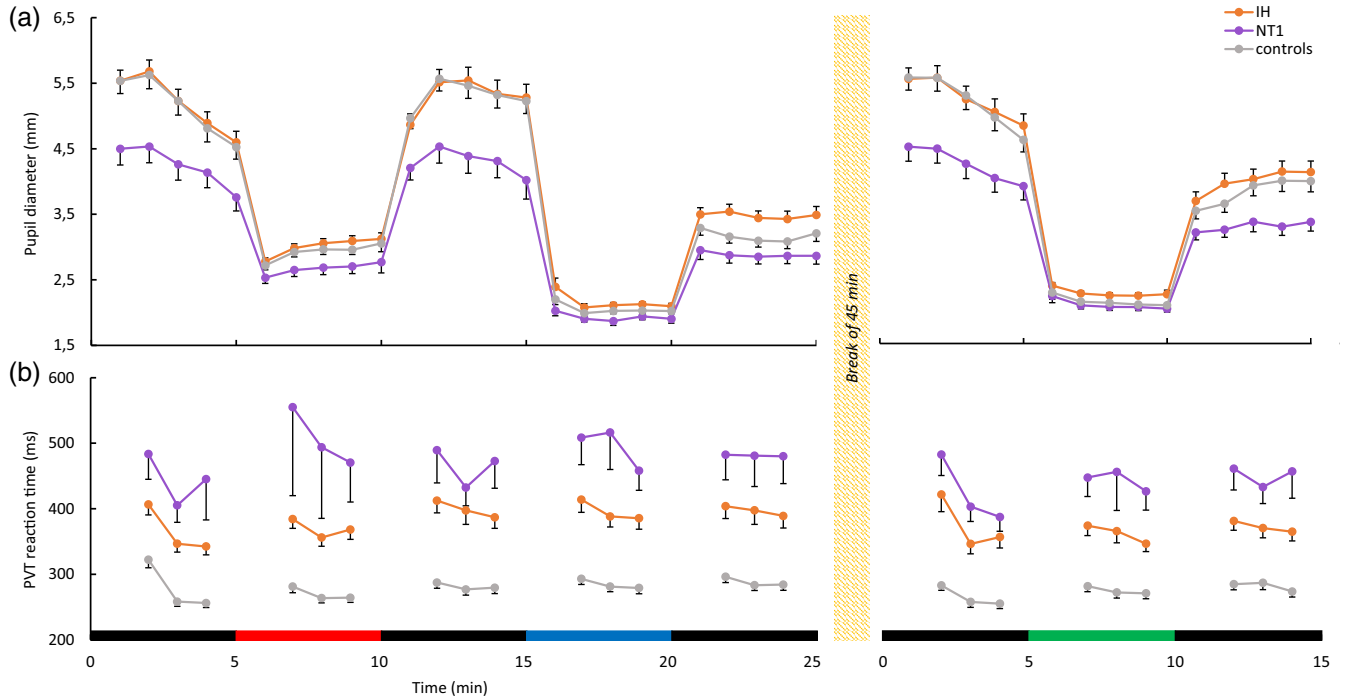

FIGURE 1 Variation of pupil diameter and vigilance throughout the pupillometry protocol. The narcolepsy type 1 (NT1) are represented in purple, patients with idiopathic hypersomnia with long sleep time (IH) in orange, and controls in grey. The bottom bar indicates the light exposure sequence: black: darkness; red: monochromatic red light (luminance: 375 cd m^{-2}, retinal irradiance: 14.75 log photons cm^{-2} s^{-1}); blue: monochromatic blue light (luminance: 375 cd m^{-2}, retinal irradiance: 14.57 log photons cm^{-2} s^{-1}); and green: monochromatic green light (luminance: 375 cd m^{-2}, retinal irradiance: 14.57 log photons cm^{-2} s^{-1}). (a) Pupillometry tracing. Each point represents the mean pupil size in mm per min ± SEM. NT1 display smaller pupil diameter compared with IH and controls throughout the protocol. (b) The Psychomotor Vigilance Task (PVT). Each point represents the mean reaction time per min ± SEM in ms. PVT was conducted during the three central minutes of each exposure condition, and showed an increased reaction time (ms) in patients with IH and NT1 as compared with controls

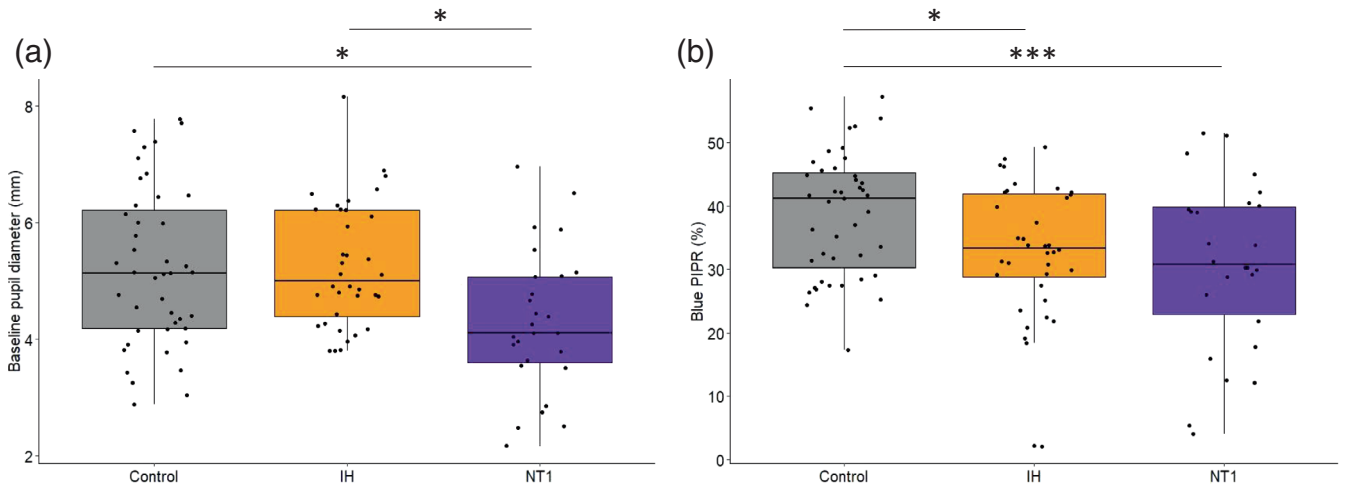

FIGURE 2 Baseline pupil diameter and relative post-illumination pupil response (PIPR) in patients with idiopathic hypersomnia (IH), narcolepsy type 1 (NT1) and controls. IH: patients with long sleep time hypersomnia; NT1: patients with narcolepsy type 1; Control: healthy subjects. (a) Boxplot of baseline pupil diameter by group. Each dot represents a subject's average pupil size in the three central minutes of the baseline period. The baseline pupil diameter was reduced in patients with NT1 as compared with controls, and with patients with IH (*$p < 0.05$). (b) Boxplot of the relative PIPR. Each dot represents a subject's PIPR. The relative PIPR was reduced in patients with NT1 and IH as compared with controls (*$p < 0.05$ and ***$p < 0.001$)

presented in Table 4 for each model (IH versus NT1, NT1 versus controls, IH versus controls). IH was used as positive class in models that compared IH versus NT1 and IH versus controls, and NT1 was used as positive class in the model that compared NT1 versus controls. The direction of the positive class relative to the cut-off point for the baseline and the relative PIPR are indicated in Table 4. Importantly,

TABLE 4 Sensitivity and specificity of the pupillometry parameters to discriminate IH from NT1, NT1 from controls, and IH from controls

Groups	Positive class	Cut point	YI	Sn (%)	Sp (%)	PPV (%)	NPV (%)	AUC
IH versus NT1	IH							
Baseline (mm)	≥	4.72	0.39	72.22	66.67	74.29	64.29	0.725
Blue PIPR (%)	≥	18.38	0.20	97.22	23.08	63.64	85.71	0.554
NT1 versus controls	NT1							
Baseline (mm)	≤	5.07	0.31	77.78	53.49	51.22	79.31	0.69
Blue PIPR (%)	≤	40.46	0.34	80.77	53.49	51.22	82.14	0.669
IH versus controls	IH							
Baseline (mm)	≥	4.72	0.14	72.22	41.86	50.98	64.29	0.516
Blue PIPR (%)	≤	34.97	0.27	63.89	62.79	58.97	67.5	0.636

Note: ≥ and ≤ indicate the direction of the positive class variables relative to cut point. An AUC > 0.70 indicates a good accuracy of the predictive model (Swets, 1988).

Abbreviations: AUC, area under the ROC curve; Controls, healthy subjects; blue PIPR (%), blue relative to baseline post-illumination pupil response; baseline: basal pupil diameter (mm); IH, patients with long sleep time idiopathic hypersomnia; NT1, patients with narcolepsy type 1; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; Sn, sensitivity; Sp, specificity; YI, Youden's index.

we found that the baseline pupil diameter permitted to well discriminate IH from NT1 with an AUC > 0.70.

4 | DISCUSSION

Major differences were found in pupillometry measures between NT1, IH and controls. Indeed, we found that patients with NT1 displayed smaller pupil size throughout the protocol as compared with patients with IH, and compared with healthy subjects. Patients with IH and NT1 obtained reduced relative PIPR as compared with healthy subjects, indicating a lower melanopsin response associated with both hypersomnia subtypes. Interestingly, sociodemographic, sleep and vigilance parameters did not explain these between-group differences.

To our knowledge, this is the first study to compare melanopsin-based pupil response to light between IH with prolonged sleep time, NT1 and healthy subjects. The reduced relative PIPR shows a less sustained pupil constriction amplitude after exposure to blue light in both hypersomnia subtypes as compared with healthy subjects, confirming our previous results obtained in smaller samples of patients with IH with prolonged sleep time and healthy subjects (Rach et al., 2022). In addition, this is the first evidence of a reduced sensitivity to blue light in NT1.

Patients with NT1 also showed reduced sensitivity to green light, more likely explained by the wavelength spectrum to which melanopsin is sensitive, which overlaps also the green colour. In addition, the sustained pupil constriction obtained after exposure to green light was visually quite similar to those obtained after exposure to blue light, suggesting that the melanopsin system may also react to green light. In this way, it was shown that the effects of green and blue lights were reduced in mouse in the absence of melanopsin (Bourgin & Hubbard, 2016). M cones and rods may also be involved in this pupil response, as it was recently shown that they were involved in the activation of non-visual brains structures (Schoonderwoerd et al., 2022).

In line with our results, one study showed reduced pupil size in NT1 (Pressman et al., 1984), while others described rapid oscillations of the pupil size, called hippus (Yoss et al., 1970), suggesting an autonomic nervous system imbalance. Because the pupil dynamic is mediated by the parasympathetic and sympathetic nervous systems, respectively, in favour of pupil constriction and pupil dilation (Loewenfeld & Lowenstein, 1999), the pupillary light reflex has been useful in discovering autonomic impairments (Bär et al., 2004). Reduced pupil diameter as found in NT1 may suggest an increased parasympathetic modulation contrasting with studies describing normal (Fronczek et al., 2008) or increased (Grimaldi et al., 2010) sympathetic activation. The low level of hypocretin-1 in NT1 has been proposed as a key factor responsible for autonomic impairments (Kayaba et al., 2003). Hypothalamic hypocretin neurons project to central and peripheral structures involved in the sympathetic pathway activation [the paraventricular nucleus (PVN), and the sympathetic preganglionic neurons of the spinal cord] leading to pupil dilation (Loewenfeld & Lowenstein, 1999). In parallel, the locus coeruleus, an arousal-promoting brain structure receiving direct-projections from the hypocretin neurons and the PVN, inhibits the parasympathetic pathway, which is in favour of pupil constriction (Loewenfeld & Lowenstein, 1999). Thus, hypocretin deficiency induces a decrease of the sympathetic activation (Kayaba et al., 2003) in parallel to a decrease inhibition of the parasympathetic pathway conducting to pupil size decrease (Samson et al., 2005). Contrary to NT1, the pupil dynamic did not reflect autonomic imbalance in IH as the basal pupil size was similar to healthy subjects. This is surprising because vegetative symptoms, such as headache, migraine or orthostatic hypotension, have been reported in non-hypocretin-deficiency sleep disorders (Arnulf et al., 2019) including IH, in favour of an increased parasympathetic function (Sforza et al., 2016). In addition, high sleepiness has been characterized by an unstable drift of central sympathetic activation as found in NT1 (Benarroch, 2020). Older studies have described an association between small pupil size and low levels of alertness, whereas a high pupil size was associated with high levels of cognitive

effort (Pressman et al., 1984; Yoss et al., 1970). In our study, similar correlations were found between the pupil diameter and the subjective sleepiness obtained at the ESS in the whole population, as well as between pupil diameter and PVT reaction time in the whole population and in the NT1 group. These results suggest that the baseline pupil diameter is a good indicator of sleepiness in NT1 but not in IH, more likely because patients with IH display a lower level of sleepiness.

As expected, sex did not affect the pupil size (Tekin et al., 2018). In congruence with previous studies (Adhikari, Pearson, et al., 2015), we found a negative correlation between age and baseline pupil size. However, we did not find an association between age and PIPR. This discrepancy with previous studies (Tekin et al., 2018; van der Meijden et al., 2016) could be explained by the homogeneity of age in our population. Nevertheless, age and sex did not explain the observed pupil response differences between groups, as both parameters were included as covariates in the logistic regression models. In addition, the relative PIPR was not associated with self-reported depression score in each group. This contrasts with studies describing a reduced PIPR in patients with MDD (Laurenzo et al., 2016); however, this is not surprising as patients did not meet cut-off criteria of MDD, although they obtained higher depression scores than healthy subjects as reported in the literature (Barateau et al., 2017). Similarly, self-reported chronotype did not explain the relative PIPR differences between groups as no extreme chronotype was found (morning or evening), although patients with IH displayed more evening chronotype, as expected (Vernet & Arnulf, 2009).

The main limitation of this study is the relatively small sample size. We observed high intra-individual variability, thus a large sample size is needed to fully comprehend group differences in pupillometry factors. A larger sample size would also allow considering other potential confounding factors, in addition to age and sex, such as medication intake. Indeed, the presence of medication in a few patients with NT1 could affect the pupil size, although we found that pupillometry differences were maintained when medication was added as a covariate in the analyses. Group differences could also have been confounded by the recent light history. However, groups did not differ in photoperiod. Another issue is whether a protocol of 25 min may be influenced by fatigue especially in patients with hypersomnia. For this purpose, the PVT realised throughout the protocol permitted to maintain them awake and allowed to confirm the absence of vigilance decline throughout the protocol as the reaction times were comparable between the five pupillometry blocks.

Overall, these results suggest altered functioning of the melanopsin system in both hypersomnia subtypes, as well as a reduced basal pupil size specific to the NT1 group. Thus, a poor integration of the light signal due to "hyposensitivity" of the ipRGCs system may lead, in a direct circadian-independent fashion, to lower stimulation of the waking system and/or a lower inhibition of brain structures involved in sleep promotion, and may participate in hypersomnolence phenotype described in IH and NT1. Likewise, the reduced pupil diameter due to hypocretin deficiency may contribute to the reduced ipRGCs integration of the light signal in favour of hypovigilance (Rach et al., 2022). These results suggest a "light-related vulnerability to sleepiness" in individuals suffering from NT1 and IH with two different pathophysiological mechanisms that have to be explored. Nevertheless, the reduced melanopsin sensitivity does not explain the prolonged sleep time in IH as no association was found between both parameters. Thus, the hypothesis of circadian impairments previously suggested in IH with long sleep time could participate to this symptom and need to be further explored.

The reduced melanopsin-specific PIPR may be an innovative trait marker of IH and NT1, and the global reduced pupil size in NT1 a marker of orexin deficiency. The pupillometry may be a promising tool to better diagnose central hypersomnia subtypes. Individually, baseline pupil size and PIPR are not sufficient to distinguish between IH, NT1 and controls given the specificity and sensitivity obtained. However, it could be a promising tool in combination with other biomarkers. We focused here on IH with long sleep time because the hypothesis of circadian impairments has been more associated with this phenotype. Thus, it will be interesting to compare the pupil reactivity of IH with long sleep time and NT1 to other central hypersomnia subtypes such as IH without prolonged TST and NT2. These steps will be necessary to validate them as objective biomarkers of central hypersomnia that are missing to classifications for IH. In addition, this could be completed by the exploration of cones and rods phototransduction, which participate in the non-visual effects of light (Tsai et al., 2009), using electroretinography for example.

In conclusion, these promising results provide a better understanding of the pathogenesis of IH and NT1, and call for further investigations aimed at investigating the underlying mechanisms of the pupil dynamic and melanopsin-mediated pupil response changes in IH and NT1, and in other hypersomnia subtypes in order to identify biomarkers of hypersomnia spectrum. Moreover, the dysfunction of pupil dynamic and melanopsin-based phototransduction observed in IH and NT1 suggest that exposure to natural or artificial light therapy might help and complement therapeutic approaches to improve wakefulness in both hypersomnia subtypes.

AUTHOR CONTRIBUTIONS

Héloïse Rach collected the data, conducted the pupillometry data processing and wrote the manuscript. Eve Reynaud contributed in planning and performing the analyses, and contributed to manuscript review and revisions. Ulker Kilic-Huck assisted with the study design and the funding, and contributed to manuscript review and revisions. Elisabeth Ruppert assisted with the study design and assisted with manuscript review. Henri Comtet assisted with the study design and assisted with manuscript review. Virginie Roy de Belleplaine contributed to the pupillometry assessments, as well as contributed to manuscript review and revision. Fanny Fuchs assisted with the study design, assisted with manuscript review, analyses and revisions, and collected part of the data. Eus J. W. Van Someren participated to the study design, and contributed to manuscript review and revisions. Pierre-A. Geoffroy assisted with the study design, assisted with data interpretation and critique, as well as contributed to manuscript review and revisions. Patrice Bourgin designed the study, secured

funding, and assisted with data interpretation and critique, as well as contributed to manuscript review and revisions.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest related to this work.

DATA AVAILABILITY STATEMENT

The data that support the findings will be available in upon request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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