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ORIGINAL ARTICLE

Sleep inertia measurement with the psychomotor vigilance task in idiopathic hypersomnia

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Abstract

Study Objectives: Sleep inertia is a frequent and disabling symptom in idiopathic hypersomnia (IH), but poorly defined and without objective measures. The study objective was to determine whether the psychomotor vigilance task (PVT) can reliably measure sleep inertia in patients with IH or other sleep disorders (non-IH).

Methods: A total of 62 (51 women, mean age: 27.7 ± 9.2) patients with IH and 140 (71 women, age: 33.3 ± 12.1) with non-IH (narcolepsy = 29, non-specified hypersomnolence [NSH] = 47, obstructive sleep apnea = 39, insomnia = 25) were included. Sleep inertia and sleep drunkenness in the last month (M-sleep inertia) and on PVT day (D-sleep inertia) were assessed with three items of the Idiopathic Hypersomnia Severity Scale (IHSS), in drug-free conditions. The PVT was performed four times (07:00 pm, 07:00 am, 07:30 am, and 11:00 am) and three metrics were used: lapses, mean 1/reaction time (RT), and slowest 10% 1/RT.

Results: Sleep inertia was more frequent in patients with IH than non-IH (56.5% and 43.6% with severe sleep inertia in the past month, including 24% and 12% with sleep drunkenness). Lapse number increase and slowest 10% 1/RT decrease, particularly at 07:00 am and 07:30 am, were proportional with M-sleep inertia severity, but regardless of sleep drunkenness and sleep disorders. Similar results were obtained when PVT results were compared in patients with/without D-sleep inertia, with the largest increase of the lapse number at 07:00 am and 07:30 am associated with severe sleep inertia and sleep drunkenness.

Conclusions: PVT is a reliable and objective measure of sleep inertia that might be useful for its characterization, management, and follow-up in patients with IH.

Statement of Significance

Three items of the Idiopathic Hypersomnia Severity Scale (IHSS) allow assessing self-reported sleep inertia and sleep drunkenness to characterize its frequency and duration. The psychomotor vigilance task (PVT) is a reliable and valid objective measure of sleep inertia, especially in idiopathic hypersomnia (IH), where this phenomenon is often very pronounced and disabling. IHSS and PVT may represent reliable instruments in clinical setting to optimize management and follow-up of patients with IH.

Key words: sleep inertia; sleep drunkenness; sleepiness; idiopathic hypersomnia; psychomotor vigilance test; idiopathic hypersomnia severity scale

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Introduction

Idiopathic hypersomnia (IH) is an orphan hypersomnolence disorder clinically characterized by three main symptoms: excessive daytime sleepiness (EDS), excessive quantity of sleep (EQS), and sleep inertia [1–5]. Sleep inertia refers to the difficulty to wake up and "getting going" after sleep (reduced vigilance and impaired performances), lasting from few minutes to hours [6]. Sometimes, patients may be also confused and unable to react adequately to external stimuli on awakening, a condition called sleep drunkenness. In IH, sleep inertia and sleep drunkenness are frequent (21%–55%) [4, 7–10] and may be severe and disabling, resulting in a significant impairment of the quality of life [11, 12].

Difficulty in awakening is a common experience in healthy subjects, especially in adolescents [13, 14], but may also be a dramatic phenomenon with dangerous consequences, particularly when performing tasks that require attention and decision-making [15, 16]. Sleep inertia may be observed under several conditions, such as sleep deprivation, delayed sleep phase syndrome, non-rapid eye movement (NREM) arousal disorders, sleep apnea, insomnia, mood disorders [1, 13, 14, 17], and less frequently in narcolepsy type 1 (NT1) [7]. However, the current assessment of sleep inertia is variable, not standardized and without measures of its frequency and duration. Moreover, different definitions are used to explore the difficulty in waking up, making hard the comparison among studies and disorders [7, 9, 10, 12, 13]. A 21-item self-report measure of sleep inertia was validated in the context of depression that may reflect mood dysregulation rather than sleep inertia [17]. We recently developed and validated the Idiopathic Hypersomnia Severity Scale (IHSS), a comprehensive self-report assessment scale of the three main IH symptoms and their consequences. This scale includes two questions on sleep inertia frequency and duration (i.e. great difficulty in waking up and the time duration to feel completely awake), and one on sleep drunkenness (i.e. confusion and clumsiness) after nighttime sleep [18].

Several studies on cognitive performances and neurophysiological correlates of sleep inertia have been performed in healthy subjects [6, 16], but only few in hypersomnolence conditions [19, 20]. To our best knowledge, no study evaluated sleep inertia upon nocturnal awakening in IH using standardized self-reported and objective measures. The psychomotor vigilance task (PVT) is an easy and short tool that is widely used to measure behavioral alertness and sustained attention by recording reaction times (RT) to visual (or auditory) stimuli [21]. PVT is very sensitive to sleepiness-related performance impairment in sleep-deprived conditions and in sleep disorders, but has never been tested in IH [22–24]. It has been reported that PVT performances are altered, particularly reaction speed more than accuracy, upon awakening from nocturnal sleep [25] and naps [26], reflecting a state of instability with altered alertness. This transition period from sleep to wakefulness leads to impaired cognitive performances (cognitive throughput and working memory) and reduced sustained attention, which are characteristics of sleep inertia [25].

In this study, we quantified self-reported sleep inertia using the IHSS and the PVT at awakening from nighttime sleep in patients with IH or other sleep disorders. The main objective of the study was to determine whether PVT is a reliable objective measure of sleep inertia in IH.

Methods

Subjects

Between 2016 and 2019, 202 patients older than 16 years of age (80 women, mean age: 31.60 ± 11.55 years), referred to the Sleep Unit and Reference National Center for Rare Hypersomnia Disorders in Montpellier, France were included in this study. They all underwent a standardized evaluation including sleep inertia, and polysomnography (PSG) and four PVT sessions during the same hospitalization in drug-free conditions. They also had a comprehensive clinical evaluation that included body mass index (BMI) (<25 kg/m^2: normal, ≥25 and <30 kg/m^2: overweight, ≥30 kg/m^2: obesity), detailed medical history by sleep experts with sleep disorder screening, Epworth Sleepiness Scale (ESS; score >10: EDS) [27], IHSS (14 items; score: 0–50) [18], and Beck Depression Inventory II (BDI-II; score ≤13: minimal, 14–19: mild, 20–63: moderate-severe depressive symptoms) [28] in only 161 patients.

This study was approved by the local ethics committees (Comité de Protection des Personnes, France: "Constitution of a cohort and of a clinical, neurophysiological and biological bank of rare hypersomnolence disorders"). Consent to participate was provided by all patients.

Self-reported sleep inertia and sleep drunkenness

Self-reported sleep inertia in the morning during the past month (M-sleep inertia) prior to PSG was assessed with two standardized questions from the IHSS (items 3 and 4): "Is it extremely difficult for you, or even impossible, to wake up in the morning without several alarm calls or the help of someone?" (score 3: always, 2: often, 1: sometimes, 0: never), "After a night sleep, how long does it take to feel like you are functioning properly (i.e. fully functional, both physically and intellectually) after getting out of bed?" (score 4: ≥2 h; 3: >1 h but <2 h; 2: between 30 min and 1 h; 1: <30 min; 0: I feel I am functioning properly as soon as I wake up). M-sleep inertia was defined as severe with a score ≥2 for both questions, absent with a score = 0 for both questions, and mild for the other scores. The presence of sleep drunkenness over the past month (M-sleep drunkenness) was defined by a score ≥2 for item 5 of the IHSS ("In the minutes after waking up, do you ever do irrational things and/or say irrational things, and/or are you very clumsy, for example, tripping, breaking, or dropping things?"; score 3: always; 2: often; 1: sometimes; 0: never).

Self-reported sleep inertia and sleep drunkenness were also evaluated on the day of the PVT assessment (D-sleep inertia, D-sleep drunkenness) with items 4 and 5 of the IHSS to assess their presence and duration (i.e. long D-sleep inertia if ≥30 min; presence of D-sleep drunkenness if ≥30 min).

Neurophysiological evaluation

All patients underwent a standard PSG (from 11:00 pm to 07:00 am) in the sleep laboratory that included electroencephalogram leads, electrooculogram, chin electromyogram, cannula/pressure transducer system, mouth thermistor, chest and abdominal bands, pulse oximeter, EMG electrodes on bilateral anterior tibialis muscles, and electrocardiogram. The studied PSG variables were: total sleep duration (TST), sleep efficiency,

percentage of N1, N2, N3, and rapid eye movement (REM), sleep latency, REM sleep latency, wake after sleep onset (WASO), apnea–hypopnea index (AHI), periodic leg movements during sleep (PLMS), and micro-arousal indexes [29–31]. Sleep apneas were defined as a drop in peak flow signal excursion by ≥90% for ≥10 s, and hypopneas as a drop in the peak flow signal excursion by ≥30% for ≥10 s associated with either a ≥3% desaturation and/or a micro-arousal [31]. Sleep-related respiratory events were classified in obstructive, central or mixed, and stratified in mild (AHI = 5–14.9/h), moderate (AHI = 15–29.9/h), and severe (AHI ≥ 30/h).

PSG recording was followed by a standard multiple sleep latency test (MSLT) in 101 patients and by a modified MSLT (forced awakening after 1 min of sleep) in 70 patients who also underwent a 32-h bed-rest PSG recording the day after [10]. All patients with PSG and modified MSLT had a PSG with standard MSLT within the last year. Moreover, 31 patients did not perform the MSLT and 13 patients performed the 32-h bed-rest PSG recording in a previous evaluation without PVT. All subjects were drug-free at the study time.

Constitution of groups

A total of 62 patients (51 women, mean age: 27.72 ± 9.18 years) had IH based on the ICSD-3 current [1] and alternative validated criteria [3, 10], namely complaint of EDS and/or EQS, mean sleep latency (MSL) ≤8 min and <2 SOREMPs on the standard MSLT (n = 27) and/or a TST ≥ 19 h on the 32-h bed-rest recording (n = 52, all with TST ≥ 11 h/24, 17 of them with MSL ≤ 8 min). No patient had cataplexies, AHI ≥ 15/h, or nighttime TST < 6 h on the PSG. They had not night or shiftwork, no sleep-deprived conditions (at least 7 h asleep per night) and no advanced or delayed sleep–wake phase disorders. Patients with non-IH sleep disorder (n = 140; 71 women, mean age: 33.32 ± 12.09 years) included: 29 patients with NT1 (all with EDS, typical cataplexy, and cerebrospinal fluid hypocretin-1 <110 pg/mL, except for one with intermediary levels = 123 pg/mL), 47 with non-specified hypersomnolence (NSH; i.e. complaint of EDS and/or EQS, AHI <5/h and TST ≥6 h on the PSG, but without diagnostic criteria of central hypersomnolence disorder: MSL >8 min for all subjects and TST <19 h for the 16 patients who underwent the 32-h bed-rest recording), 39 with obstructive sleep apnea syndrome (OSAS; mild, N = 26; moderate, N = 10; severe, N = 3), and 25 with insomnia and/or short TST (i.e. <6 h on the PSG) including 4 with clinically significant restless legs syndrome.

Psychomotor vigilance task

All patients underwent a visual PVT in the laboratory, at 07:00 pm before the PSG recording, and the next morning, at 07:00 am, 07:30 am, and 11:00 am, using the short 5-min PVT version [32–34]. Subjects were instructed to monitor the computer screen and press the response button as soon as the red millisecond-counter appeared which stopped the counter and displayed the RT in msec; stimuli were randomly presented. The following metrics, which are considered the most sensitive PVT outcomes [32–34], were computed: mean 1/ RT (or response speed), number of lapses (N Lapses; lapse = RT ≥500 msec) and slowest 10% 1/RT.

Statistical analysis

The sample was described using numbers and percentages for categorical variables, and means with standard deviation (*SD*) for continuous variables. The associations between clinical and PSG characteristics and severity of M- and D-sleep inertia were studied using multinomial regression logistic (four categories) or logistic regression (two categories). When comparisons were statistically significant in the four categories, two-by-two comparisons were performed with a correction for multiple comparisons using the Bonferroni method. Mixed-effect regression models were used to examine the PVT profiles by taking into account the repeated measures (four times) and the groups as function of sleep inertia. Participants were considered as random effects. Time periods, groups and their interaction with the time periods were considered as fixed effects. Significance was set at $p < 0.05$. Analyses were performed using SAS (version 9.4; SAS, Cary, NC).

Data availability statement

Raw data are available on request to the corresponding authors by any qualified investigator.

Results

Compared with the non-IH group (n = 140 patients), patients with IH (n = 62) were younger, more frequently women, had higher ESS scores, higher TST and sleep efficiency, lower WASO, N1%, micro-arousal index, and AHI on the PSG. BMI categories and BDI-II scores were comparable between groups.

Self-reported sleep inertia and sleep drunkenness

Overall, M-sleep inertia was observed in 174 (86.1%) patients, with mild and severe symptoms in 78 (38.6%) and 96 patients (47.5%; including 32 with sleep drunkenness, 15.8%; Table 1). All the patients reporting sleep drunkenness also had sleep inertia. Only 28 (13.9%) patients did not report sleep inertia. Among the 62 patients with IH, 57 (91.9%) had M-sleep inertia that was severe in 35 (56.5%; including 15 with sleep drunkenness, 24%). In the non-IH group (n = 140), 117 patients (83.6%) had M-sleep inertia that was severe in 61 (43.6%; including 17 with sleep drunkenness, 12%): 12 (48%) patients with insomnia, 27 (57.4%) with NSH, 6 (20.7%) with NT1, and 16 (41%) with OSAS.

Compared with patients without or with mild M-sleep inertia, patients with severe M-sleep inertia (with/without sleep drunkenness) had more often IH and NSH, less frequently NT1, and were less overweight, without differences in age and sex (Table 1). They also had higher total and partial (i.e. after exclusion of the three items related to sleep inertia and sleep drunkenness) IHSS, ESS, and BDI-II scores, longer MSL on the MSLT and lower WASO, AHI and micro-arousal index on the PSG, without association with the 32-h bed-rest TST.

PVT metrics and self-reported sleep inertia in the last month and on PVT day

Compared with patients without M-sleep inertia, the number of lapses markedly increased and the slowest 10% 1/RT

Table 1. Clinical and polysomnographic characteristics associated with self-reported sleep inertia over the past month (M-sleep inertia) in the whole sample (n = 202)

	A. Absent M-sleep inertia N = 28	B. Mild M-sleep inertia N = 78	C. Severe M-sleep inertia without sleep drunkenness N = 64	D. Severe M-sleep inertia with sleep drunkenness N = 32			Absent/mild M-sleep inertia N = 106	Severe M-sleep inertia N = 96	
Variables	n(%)	n(%)	n(%)	n(%)	p	Post hoc comparisons	n(%)	n(%)	p
Diagnosis					0.07				0.02
IH	5(17.86)	22(28.21)	20(31.25)	15(46.88)			27(25.47)	35(36.46)	
Insomnia	2(7.14)	11(14.10)	10(15.63)	2(6.25)			13(12.26)	12(12.50)	
NSH	5(17.86)	15(19.23)	18(28.13)	9(28.13)			20(18.87)	27(28.13)	
Narcolepsy	6(21.43)	17(21.79)	4(6.25)	2(6.25)			23(21.70)	6(6.25)	
OSAS	10(35.71)	13(16.67)	12(18.75)	4(12.50)			23(21.70)	16(16.67)	
Sex, women	12(42.86)	47(60.26)	41(64.06)	22(68.75)	0.19		59(55.66)	63(65.63)	0.15
Age, years*	37.09(±11.90)	31.32(±11.95)	30.97(±11.68)	28.77(±8.57)	0.05		32.84(±12.15)	30.24(±10.74)	0.11
BMI, kg/m^2					0.08				0.03
<25	19(67.86)	40(51.28)	43(67.19)	27(84.38)			59(55.66)	70(72.92)	
25–30	6(21.43)	27(34.62)	13(20.31)	3(9.38)			33(31.13)	16(16.67)	
≥30	3(10.71)	11(14.10)	8(12.50)	2(6.25)			14(13.21)	10(10.42)	
ESS score*	12.39(±5.45)	13.26(±5.62)	13.60(±4.82)	14.91(±4.57)	0.29		13.03(±5.56)	14.04(±4.75)	0.17
ESS score, >10	18(64.29)	55(70.51)	50(80.65)	28(87.50)	0.11		73(68.87)	78(82.98)	0.02
Total IHSS score*	19.30(±7.38)	27.09(±7.90)	32.29(±6.16)	35.97(±6.52)	<0.0001	A<B<C,D	25.36 (±8.40)	33.68(±6.51)	<0.0001
Partial IHSS score*	19.30(±7.38)	24.86(±7.46)	27.10(±5.74)	30.48(±5.89)	<0.0001	A<B,C;B<D	23.62(±7.76)	28.38(±5.99)	<0.0001
BDI-II score*	11.31(±6.96)	11.55(±7.91)	16.44(±10.57)	16.18(±9.57)	0.02	-	11.50(±7.68)	16.34(±10.15)	0.002
BDI-II score					0.08				0.005
<14	10(62.50)	40(66.67)	19(39.58)	12(42.86)			50(65.79)	31(40.79)	
14–20	4(25.00)	9(15.00)	10(20.83)	6(21.43)			13(17.11)	16(21.05)	
≥ 20	2(12.50)	11(18.33)	19(39.58)	10(35.71)			13(17.11)	29(38.16)	
MSL on MSLT, min*	10.17 (±5.06)	9.71 (±5.01)	12.42(±4.56)	11.94(±4.50)	0.02	B<C	9.83 (±5.00)	12.24(±4.52)	0.002
MSL on MSLT, ≤8 min	8 (36.36)	26(41.27)	10(18.18)	6(19.35)	0.03	B>C	34(40.00)	16(18.60)	0.003
Sleep duration, min*	419.14(±47.18)	425.18(±60.47)	420.94(±57.89)	433.75(±60.94)	0.73		423.58(±57.11)	425.21(±58.92)	0.84
Sleep efficiency, % *	84.42(±9.12)	84.17(±10.91)	84.53(±9.79)	86.52(±9.26)	0.73		84.23(±10.43)	85.20(±9.62)	0.50
Sleep latency, min*	13.50(±15.04)	15.13(±16.71)	19.97(±16.92)	17.63(±12.61)	0.22		14.70(±16.23)	19.19(±15.59)	0.05
REM sleep latency, min*	91.68(±78.49)	78.77(±52.10)	89.38(±50.45)	95.38(±48.58)	0.44		82.21(±60.13)	91.38(±49.66)	0.24
WASO, min*	56.46(±45.46)	59.27(±49.47)	47.61(±38.77)	40.56(±36.34)	0.18		58.53(±48.25)	45.26(±37.93)	0.04
Stage 1, %*	5.94(±5.67)	5.64(±4.01)	6.13(±5.29)	4.77(±4.17)	0.60		5.72(±4.48)	5.68(±4.97)	0.95
Stage 2, %*	55.12(±7.62)	54.05(±8.22)	51.88(±9.05)	54.12(±6.17)	0.25		54.34(±8.04)	52.63(±8.24)	0.14
Slow wave sleep, %*	17.83(±6.82)	19.37(±5.84)	20.59(±7.09)	20.25(±5.96)	0.27		18.96(±6.12)	20.47(±6.70)	0.10
REM sleep, %*	21.09(±6.15)	20.93(±6.53)	21.38(±6.06)	20.82(±3.92)	0.96		20.97(±6.40)	21.20(±5.42)	0.79
PLMS index/h*	3.79(±6.61)	5.59(±14.52)	3.84(±7.00)	6.62(±9.78)	0.61		5.11(±12.91)	4.76(±8.09)	0.82
AHI*	10.44(±18.66)	5.53(±7.68)	3.51(±4.97)	3.21(±4.52)	0.03	-	6.83(±11.73)	3.41(±4.80)	0.01
Micro-arousal index/h*	18.42(±15.31)	14.67(±7.40)	11.32(±5.66)	12.62(±7.03)	0.005	A,B>C	15.66(±10.16)	11.75(±6.14)	0.002
32-h bed rest TST, h* (n = 83)	20.29(±1.91)	19.78(±3.20)	19.71(±3.03)	20.30(±2.84)	0.89		19.85(±3.03)	19.96(±2.93)	0.87

*Quantitative variables are expressed as means (± standard deviation).

NSH, non-specified hypersomnolence; OSAS, obstructive sleep apnea syndrome; BMI, body mass index; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; BDI-II, Beck Depression Inventory II; MSL, mean sleep latency; MSLT, multiple sleep latency test; WASO, wake after sleep onset; REM, rapid eye movement; PLMS, periodic limb movements during sleep; AHI, apnea–hypopnea index; TST, total sleep time.

decreased at 07:00 am and 07:30 am proportionally with the severity of M-sleep inertia ($p_{Period \times Group}$ =0.02 for lapses, $p_{Period \times Group}$ =0.03 for slowest 10% 1/RT) after adjustment for age (Figure 1, A). No period × group difference was found for the mean 1/RT; however, the mean 1/RT over the four sessions significantly changed among groups with lower values at 07:00 am and 07:30 am (p_{Period} < 0.0001). PVT profiles were not different between patients with severe M-sleep inertia with/without sleep drunkenness.

Based on the sleep inertia assessment on PVT day, compared with patients without or with short D-sleep inertia (n = 86), patients with long D-sleep inertia (with/without sleep drunkenness; n = 116) had more frequently IH and less frequently NT1, had higher IHSS and BDI-II scores, and longer nighttime sleep latency on the PSG (Table 2). The PVT metric profiles of patients without D-sleep inertia and with short/long (with and without sleep drunkenness) were similar to those of patients with/without M-sleep inertia, but only the number of lapses showed

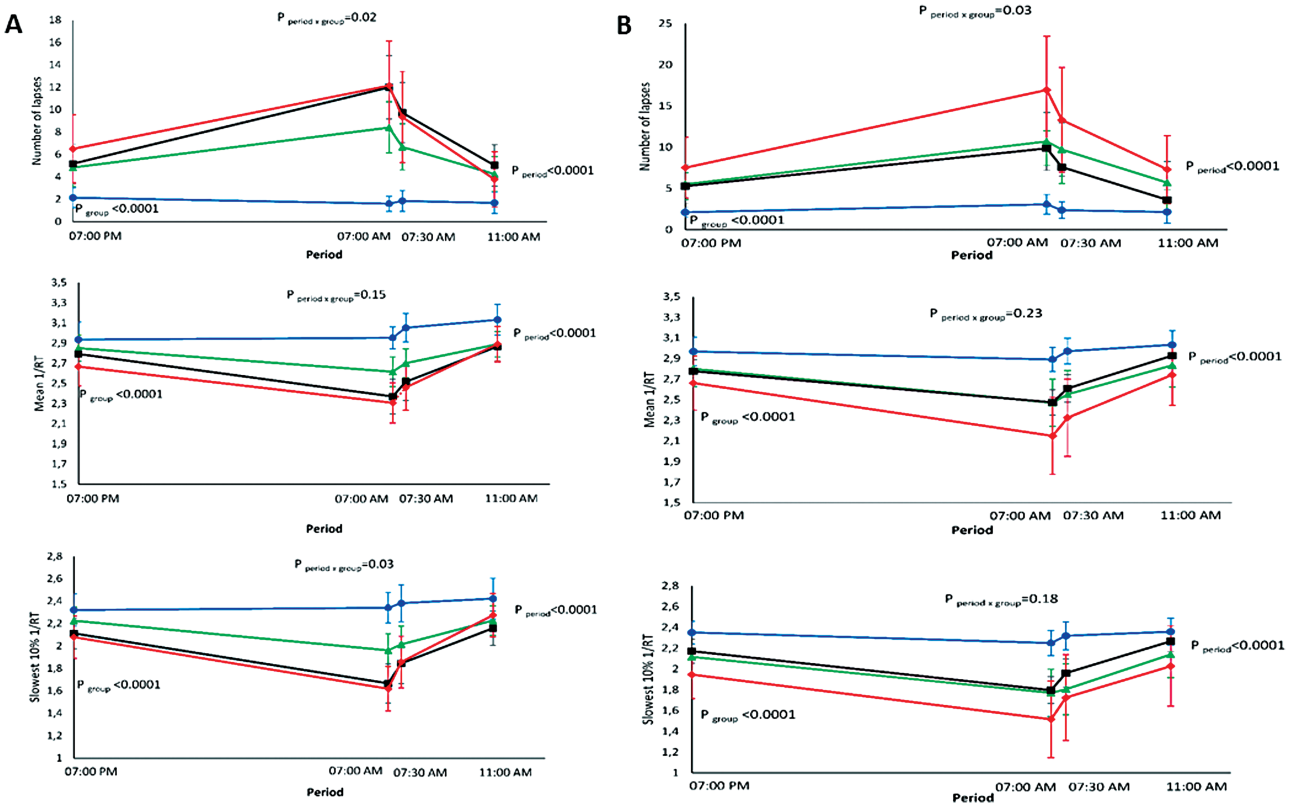

Figure 1. PVT metric profile across the four sessions in function of the severity of self-reported sleep inertia in the whole sample, adjusted for age. (A) M-sleep inertia: no M-sleep inertia (n = 28; blue line), mild M-sleep inertia (n = 78; green line), severe M-sleep inertia without sleep drunkenness (n = 64; black line), severe M-sleep inertia with sleep drunkenness (n = 32; red line). (B) D-sleep inertia: No D-sleep inertia (n = 45; blue line), Short D-sleep inertia (n = 41; green line), Long D-sleep inertia without sleep drunkenness (n = 97; black line), Long D-sleep inertia with sleep drunkenness (n = 19; red line).

a significant period × group interaction ($p_{\text{Period} \times \text{Group}}$ =0.03), with the greatest increase at 07:00 am and 07:30 am in patients with severe D-sleep inertia and sleep drunkenness (adjustment for age; Figure 1, B).

The PVT profile over the four sessions did not differ between patients with MSL above and below the standard 8-min cutoff (MSL ≤ 8 min, N = 50/171) and the 19-h TST cutoff (TST ≥ 19 h, N = 52/83) on the 32-h bed-rest recording. PVT metrics were not different between patients who slept (n = 132) or not (n = 39) during the 9:00 am-MSLT session and those who performed or not (n = 31) this test, nor as function of the BDI-II scores (≤13; 14–19; 20–63; data not shown).

Comparison of PVT metrics in function of the sleep disorder and self-reported sleep inertia

Compared with patients in the non-IH group without M-sleep inertia, patients with IH and severe M-sleep inertia were more frequently women and younger, had higher total and partial IHSS scores, and lower micro-arousal index on the PSG after adjustment for age and sex (Table 3). The PVT profile (four sessions) differed between groups with higher number of lapses and a decrease of the slowest 10% 1/RT ($p_{\text{Period} \times \text{Group}}$ = 0.0002 and 0.01, respectively) particularly at 07:00 am and 07:30 am in patients with IH and severe M-sleep inertia (adjustment for age and sex). The mean 1/RT tended to decrease ($p_{\text{Period} \times \text{Group}}$ = 0.05) in the IH with severe M-sleep inertia group (Figure 2). Similar results were obtained when comparing the clinical and PSG profiles in the non-IH/without D-sleep inertia and IH/with long D-sleep inertia groups (Table 3), with PVT metric alterations at 07:00 am and 07:30 am ($p_{\text{Period} \times \text{Group}}$ = 0.001 for number of lapses, $p_{\text{Period} \times \text{Group}}$ = 0.03 for slowest 10%1/RT, $p_{\text{Period} \times \text{Group}}$ = 0.07 for mean 1/RT; data not shown).

Finally, comparison of the non-IH with severe M-sleep inertia and IH with severe M-sleep inertia groups showed that patients with IH were more frequently women and younger, had shorter MSL, higher TST and sleep efficiency on the PSG, and higher TST on the 32-h bed-rest recording. Similarly, sleep latency and WASO on the PSG tended to be lower in patients with IH and severe M-sleep (Table 4). The PVT profile over the four sessions was comparable between groups (p_{period} < 0.0001) (adjustment for age and sex; Figure 3). Similar clinical and PSG differences (Table 4) and PVT profiles were found for the IH and non-IH groups with long D-sleep inertia ($p_{\text{Period} \times \text{Group}}$ = 0.79 for number of lapses, $p_{\text{Period} \times \text{Group}}$ = 0.92 for mean 1/RT and $p_{\text{Period} \times \text{Group}}$ =0.75 for slowest 10% 1/RT; data not shown). Among patients with severe M- and long D-sleep inertia, PVT profiles were similar when patients with IH were compared with those with NT1, NSH, OSAS and insomnia.

Discussion

In this study, we measured behavioral alertness and sustained attention using the PVT (four measurements) in patients with IH or other sleep disorders with and without self-reported sleep inertia and sleep drunkenness assessed by three items of the IHSS.

Table 2. Clinical and polysomnographic characteristics associated with sleep inertia assessed on PVT day (D-sleep inertia) in the whole sample (*n* = 202)

	A. No D-sleep inertia N = 45	B. Short D-sleep inertia N = 41	C. Long D-sleep inertia without sleep drunkenness N = 97	D. Long D-sleep inertia with sleep drunkenness N = 19			Absent/ short D-sleep inertia N = 86	Long D-sleep inertia N = 116	
Variables	n(%)	n(%)	n(%)	n(%)	p	Post hoc comparisons	n(%)	n(%)	p
Diagnosis					NA				0.01
IH	10(22.22)	8(19.51)	36(37.11)	8(42.11)			18(20.93)	44(37.93)	
Insomnia	4(8.89)	5(12.20)	12(12.37)	4(21.05)			9(10.47)	16(13.79)	
NSH	7(15.56)	15(36.59)	22(22.68)	3(15.79)			22(25.58)	25(21.55)	
Narcolepsy	12(26.67)	8(19.51)	8(8.25)	1(5.26)			20(23.26)	9(7.76)	
OSAS	12(26.67)	5(12.20)	19(19.59)	3(15.79)			17(19.77)	22(18.97)	
Sex, women	28(62.22)	24(58.54)	56(57.73)	14(73.68)	0.62		52(60.47)	70(60.34)	0.99
Age, years*	36.93(±13.57)	28.50(±10.74)	30.21(±10.50)	32.79(±9.45)	0.005	A>B,C	32.91(±12.95)	30.63(±10.34)	0.17
BMI, kg/m^2					NA				0.10
<25	25(55.56)	23(56.10)	67(69.07)	14(73.68)			48(55.81)	81(69.83)	
25–30	12(26.67)	12(29.27)	21(21.65)	4(21.05)			24(27.91)	25(21.55)	
≥30	8(17.78)	6(14.63)	9(9.28)	1(5.26)			14(16.28)	10(8.62)	
ESS score*	12.56(±5.07)	13.26(±5.36)	13.60(±5.07)	15.79(±5.61)	0.16		12.88(±5.19)	13.96(±5.20)	0.15
ESS score,>10	31(68.89)	27(69.23)	77(79.38)	16(84.21)	0.33		58(69.05)	93(80.17)	0.07
Total IHSS score*	21.05(±8.33)	29.38(±7.16)	31.35(±6.79)	37.59(±5.87)	<0.0001	A<B;C<D	24.86(±8.81)	32.39(±7.02)	<0.0001
Partial IHSS*	19.55(±7.50)	26.56(±6.59)	27.19(±5.92)	32.29(±5.47)	<0.0001	A<B;C<D	22.76(±7.88)	28.04(±6.13)	<0.0001
BDI-II score*	11.48(±6.42)	12.15(±8.97)	14.43(±9.18)	20.13(±12.54)	0.03	-	11.84(±7.84)	15.39(±9.98)	0.02
BDI-II score					0.24				0.07
<14	19(65.52)	19(55.88)	38(51.35)	5(33.33)			38(60.32)	43(48.31)	
14–20	7(24.14)	7(20.59)	11(14.86)	4(26.67)			14(22.22)	15(16.85)	
≥20	3(10.34)	8(23.53)	25(33.78)	6(40.00)			11(17.46)	31(34.83)	
MSL on MSLT, min*	10.00(±5.59)	10.58(±4.58)	11.42(±4.82)	12.63(±4.07)	0.27		10.29(±5.07)	11.60(±4.71)	0.08
MSL on MSLT,≤8min	15(41.67)	10(27.03)	22(26.51)	3(20.00)	0.31		25(34.25)	25(25.51)	0.22
Sleep duration, min*	419.24(±52.25)	437.22(±45.29)	428.45 (±55.39)	387.79(±88.39)	0.02	-	427.81(±49.60)	421.79(±63.35)	0.46
Sleep efficiency, %*	83.80(±10.55)	86.76(±7.53)	85.47(±8.99)	78.35(±15.42)	0.03	-	85.21(±9.30)	84.30(±10.57)	0.52
Sleep latency, min*	14.67(±17.00)	12.68(±9.71)	17.41(±14.57)	27.95(±25.38)	0.01	B<D	13.72(±13.97)	19.14(±17.13)	0.02
REM sleep latency, min*	87.44(±70.09)	78.83(±51.28)	84.96(±46.10)	110.89(±66.76)	0.25		83.34(±61.64)	89.02(±50.44)	0.47
WASO, min*	58.84(±52.14)	53.10(±41.62)	45.57(±36.74)	68.63(±57.75)	0.14		56.10(±47.24)	49.34(±41.50)	0.28
Stage1,%*	5.70(±4.89)	5.04(±2.90)	5.69(±5.00)	7.18(±5.79)	0.49		5.38(±4.06)	5.94(±5.14)	0.41
Stage2,%*	54.22(±9.03)	52.46(±8.45)	54.12(±7.78)	51.14(±7.22)	0.38		53.38(±8.75)	53.63(±7.74)	0.83
Slow wave sleep, %*	19.47(±7.64)	20.49(±5.62)	19.10(±6.29)	21.38(±5.67)	0.43		19.96(±6.73)	19.47(±6.22)	0.60
REM sleep, %*	20.60(±5.96)	21.99(±7.07)	21.07(±5.19)	20.29(±7.04)	0.66		21.26(±6.51)	20.95(±5.51)	0.71
PLMS index/h*	4.89(±10.23)	7.47(±17.21)	4.53(±8.31)	1.77(±3.03)	0.28		6.12(±13.97)	4.08(±7.76)	0.21
AHI*	8.66(±15.58)	4.09(±7.20)	4.57(±5.97)	2.66(±3.96)	0.08		6.48(±12.47)	4.26(±5.72)	0.12
Micro-arousal index/h*	16.90(±13.32)	13.35(±6.26)	12.80(±6.69)	12.57(±7.26)	0.12		15.21(±10.66)	12.76(±6.76)	0.06
32-h bedrest TST, h* (*n* = 83)	20.70(±2.17)	18.54(±3.43)	20.12(±3.05)	20.16(±2.09)	0.25		19.45(±3.11)	20.13(±2.89)	0.34

*Quantitative variables are expressed as means (± standard deviation).

NSH, non-specified hypersomnolence; OSAS, obstructive sleep apnea syndrome; BMI, body mass index; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; BDI-II, Beck Depression Inventory II; MSL, mean sleep latency; MSLT, multiple sleep latency test; NA, not applicable; WASO, wake after sleep onset; REM, rapid eye movement; PLMS, periodic limb movements during sleep; AHI, apnea–hypopnea index; TST, total sleep time.

Sleep inertia was frequently reported by patients with IH and other sleep disorders (56.5% and 43.6% with severe sleep inertia in the past month, including 24% and 12% with sleep drunkenness, respectively). PVT metrics showed a marked increase of lapses and decrease of slowest 10% 1/RT, particularly at 07:00 am and 07:30 am, which increased with the sleep inertia severity, regardless of the presence of sleep drunkenness and the sleep disorder type. We obtained similar results when patients were grouped in function of the sleep inertia severity on PVT day, with the largest increase of lapses at 07:00 am and 07:30 am in patients with long sleep inertia and sleep drunkenness, regardless of the sleep disorder.

Sleep inertia is a frequent and disabling symptom in IH, but it is often underestimated by physicians, and is not included in the ICSD3 [1,3,6]. In IH, sleep inertia may be severe and long-lasting, and is sometimes associated with confusion, disorientation and clumsiness (i.e. sleep drunkenness that may be more problematic than EDS) [1, 2, 4–6]. Currently, there is no pathophysiological explanation for sleep inertia in IH. Several neuroimaging and electrophysiological studies in healthy subjects showed that sleep inertia, triggered by sleep deprivation, reflects a delay in transitioning from sleep to wake with slower reactivation of regions related to higher order processes necessary for cognitive tasks [6, 16, 35–39]. In protocols of forced awakening after a 3-min nap, event-related potentials are delayed or even replaced by high-amplitude negative waves that reflects the persistence of an NREM sleep-like state

Table 3. Clinical and polysomnographic comparisons between patients with IH and severe sleep inertia over the past month (M-sleep inertia) and on PVT day (D-sleep inertia) and patients with other sleep disorders (non-IH) without sleep inertia

	Non-IH without M-sleep inertia N = 23	IH with severe M-sleep inertia N = 35	Model 0	Model 1	Non-IH without D-sleep inertia N = 35	IH with long D-sleep inertia N = 44	Model 0	Model 1
Variables	n(%)	n(%)	p	p	n(%)	n(%)	p	p
Sex, women	8(34.78)	29(82.86)	0.0004		19(54.29)	35(79.55)	0.02	
Age, years*	37.41(±12.56)	27.16(±8.68)	0.002		39.22(±13.54)	28.02(±9.18)	0.0003	
BMI, kg/m^2			0.57	0.34			0.09	0.20
<25	16(69.57)	28(80.00)			19(54.29)	34(77.27)		
25–30	5(21.74)	4(11.43)			9(25.71)	7(15.91)		
≥30	2(8.70)	3(8.57)			7(20.00)	3(6.82)		
ESS score*	11.39(±5.33)	15.21(±4.10)	0.007	0.10	11.77(±5.29)	14.80(±4.60)	0.01	0.04
ESS score, >10	13(56.52)	32(94.12)	0.003	0.06	21(60.00)	39(88.64)	0.005	0.19
Total IHSS score*	18.13(±7.80)	35.10(±7.23)	0.0004	0.001	19.76(±8.53)	33.62(±7.39)	<0.0001	0.0001
Partial IHSS score*	18.13(±7.80)	29.63(±6.77)	0.0009	0.004	18.28(±7.76)	29.00(±6.65)	<0.0001	0.0003
BDI-II score*	11.17(±6.93)	16.29(±10.44)	0.12		13.15(±5.67)	14.68(±10.04)	0.52	0.92
BDI-II score			0.41	0.42			0.44	0.66
<14	8(66.67)	15(44.12)			12 (60.00)	22(50.00)		
14–20	2(16.67)	8(23.53)			5 (25.00)	9(20.45)		
≥ 20	2(16.67)	11(32.35)			3 (15.00)	13(29.55)		
MSL on MSLT, min*	10.99(±5.44)	9.86(±3.63)	0.37	0.48	10.67(±6.13)	9.56(±3.67)	0.34	0.43
MSL on MSLT, ≤8 min	4(23.53)	12(34.29)	0.43	0.52	9(34.62)	17(38.64)	0.74	0.56
Sleep duration, min*	410.04(±45.69)	447.14(±45.16)	0.009	0.36	411.86(±55.47)	452.50(±42.22)	0.002	0.09
Sleep efficiency, % *	82.51(±8.92)	88.86(±5.32)	0.005	0.05	81.27(±10.62)	88.90(±5.20)	0.0008	0.01
Sleep latency, min*	14.43(±16.03)	15.74(±12.91)	0.73	0.84	15.37(±18.68)	15.41(±12.60)	0.99	0.60
REM sleep latency, min*	89.57(±85.09)	95.51(±46.38)	0.73	0.06	87.34(±77.99)	93.07(±44.48)	0.68	0.17
WASO, min*	64.43(±46.41)	33.66(±22.79)	0.006	0.07	70.17(±53.90)	35.07(±22.91)	0.0009	0.01
Stage 1, %*	6.74(±5.93)	4.66(±3.13)	0.14	0.24	6.35(±5.27)	4.71(±2.96)	0.11	0.23
Stage 2, %*	54.51(±8.02)	51.61(±5.54)	0.11	0.75	53.45(±9.75)	53.29(±6.67)	0.93	0.95
Slow wave sleep, %*	17.59(±7.32)	21.77(±5.47)	0.02	0.37	19.32(±8.51)	20.53(±6.03)	0.46	0.68
REM sleep, %*	21.16(±6.53)	21.94(±4.34)	0.58	0.92	20.86(±6.39)	21.47(±3.94)	0.60	0.73
PLMS index/h*	3.81(±6.57)	4.21(±9.12)	0.85	0.82	5.54(±11.21)	4.25(±8.31)	0.56	0.46
AHI*	11.91(±20.22)	1.75(±2.05)	0.008	0.19	10.56(±17.11)	2.39(±2.88)	0.004	0.14
Micro-arousal index/h*	20.05(±16.39)	10.04(±4.25)	0.0009	0.01	18.88(±14.38)	11.32(±6.40)	0.005	0.03

*Quantitative variables are expressed as means (± Standard deviation).

Model 0: crude association. Model 1: adjustment for age and sex.

BMI, body mass index; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; BDI-II, Beck Depression Inventory II; MSL, mean sleep latency; MSLT, multiple sleep latency test; WASO, wake after sleep onset; REM, rapid eye movement; PLMS, periodic limb movements during sleep; AHI, apnea–hypopnea index; TST, total sleep time.

at awakening in patients with IH and narcolepsy, but not in controls and in patients with hypersomnolence due to psychiatric disorders [19, 20]. Moreover, patients with IH have longer latency and reduced amplitude of cognitive evoked potentials (P300) than patients with narcolepsy [19, 20]. To better understand the mechanisms underlying sleep inertia in different conditions, first its clinical assessment and objective measurement need to be standardized. Among the few available instruments, the IHSS offers the opportunity to assess the frequency and duration of sleep inertia and related-sleep drunkenness in the past month [18]. Here, we found that 86% of patients (91.9% with IH and 83.6% of patients with other sleep disorders) reported sleep inertia in the last month. Sleep inertia was severe (i.e. frequent and for a duration ≥30 min) in 56.5% of patient with IH among whom 24% reported also sleep drunkenness, in line with previous studies [4, 7–9]. Both symptoms were more frequent in IH than in the other group, with low frequency in patients with NT1 and intermediate level in NSH. Patients with OSAS and insomnia are more likely to report fatigue and confusion at awakening, potentially linked to chronic sleep fragmentation [14, 40]. Conversely, in NT1, nighttime sleep and naps are often refreshing with infrequent sleep inertia [41]. Our study extended these findings by highlighting the frequent occurrence of severe sleep inertia with/without sleep drunkenness in patients with IH, and also in patients with non-specified hypersomnolence, a condition with similar clinical symptoms but not meeting the objective criteria for central hypersomnolence disorders based on the ICSD3 or alternative criteria [1, 3, 10].

Sleep inertia was associated with high ESS, IHSS (excluding the three related items of sleep inertia) and BDI-II scores, normal BMI, less objective daytime sleepiness, and less fragmented nocturnal sleep, as previously reported in patients with IH [8, 42]. Accordingly, patients with IH had the largest frequency and duration of sleep inertia, but also of undisturbed nocturnal sleep. Laboratory studies on healthy subjects found that cumulative disrupted sleep and sleep deprivation are associated with increased sleep inertia [43]. Similarly, sleep inertia reported by patients with OSAS and insomnia have been linked to sleep fragmentation and restriction [40, 44]. In a sample of patients with IH, sleep duration and sleep efficiency did not differ between patients with and without severe sleep inertia and sleep drunkenness [12]. Such discrepancies may relate to different assessments of sleep inertia and protocol settings with potential overlapping with morning fatigue, and different factors contributing to sleep inertia in function of the disorder. Patients with mood disorders frequently report sleep inertia [13, 14, 17], in line with our results showing associations between sleep inertia and depressive symptoms in patients with sleep disorders. However, it remains unclear whether sleep inertia in depression relates more to anhedonia or decreased motivation than to real sleep inertia [6]. Sleep inertia interacts with the homeostatic and circadian processes to influence performance

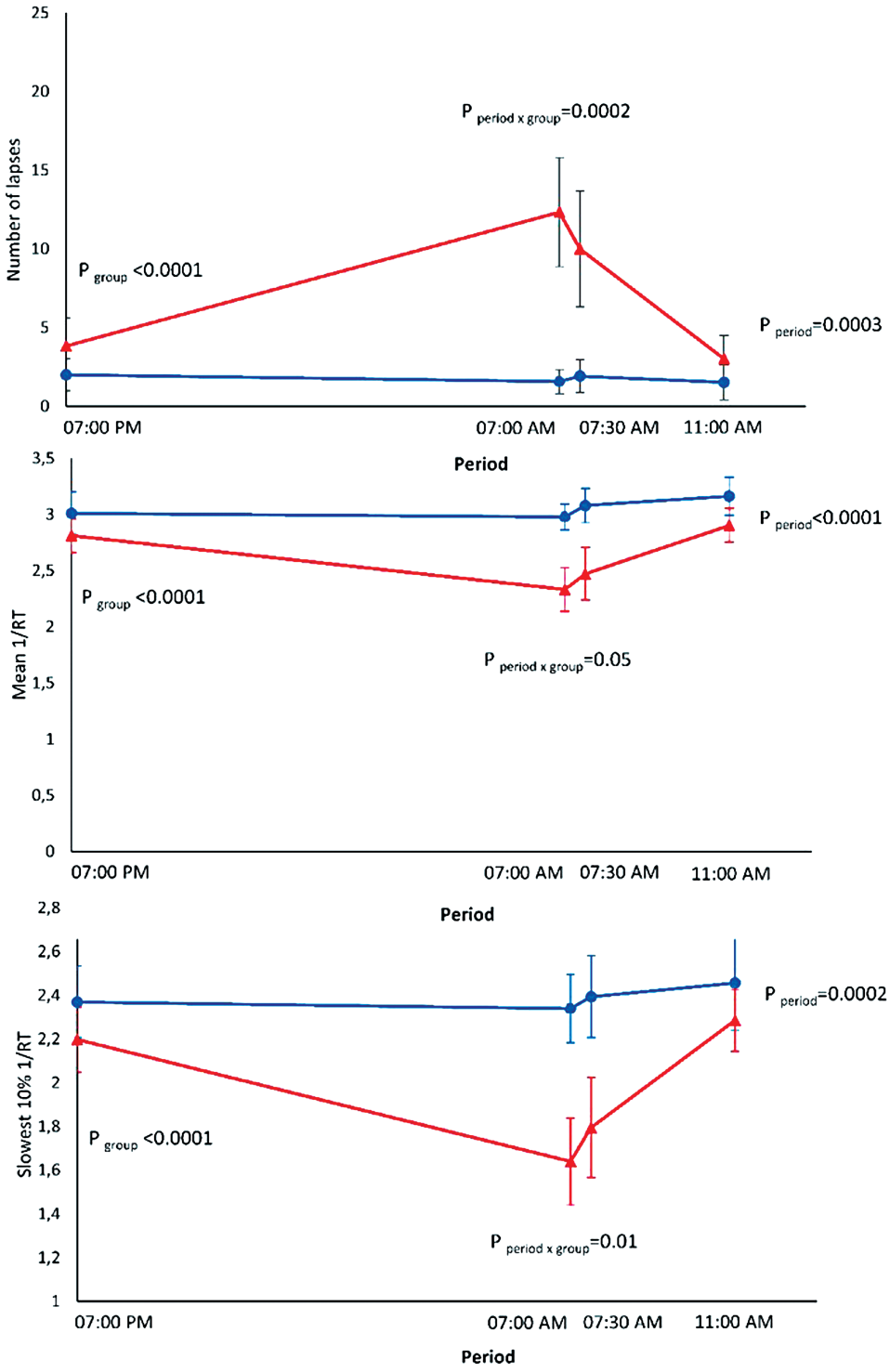

Figure 2. PVT metric profile across the four sessions in patients with IH and severe M-sleep inertia (n = 35; red line) compared with patients in the non-IH group without M-sleep inertia (n = 23; blue line), adjusted for age and sex.

immediately after awakening [6, 16]. Patients with IH are often young subjects, like those included in this study, a condition often associated with greater sleep inertia [6, 45]. Here, we did not find any association between sleep inertia and sex and age, although the mean age was below 40 years in all groups.. The clinical and polysomnographic parameters associated with M- and D-sleep inertia were very similar.

PVT is among the most widely used measures of behavioral alertness, the most sensitive to sleep restriction, and the most reliable, with negligible aptitude and learning effects over repeated administrations [22]. PVT performances are stable across the 16 h of wakefulness except in case of sleep inertia in the first hour following awakenings [34]. The available studies used different PVT metrics as outcomes and different test durations. We

Table 4. Clinical and polysomnographic comparisons between patients with IH and patients with other sleep disorders (non-IH), all with severe sleep inertia over the past month (M-sleep inertia) and PVT day (D-sleep inertia)

	Non-IH with severe M-sleep inertia N = 61	IH with severe M-sleep inertia N = 35			Non-IH with long D-sleep inertia N = 72	IH with long D-sleep inertia N = 44		
			Model 0	Model 1			Model 0	Model 1
Variables	*n*(%)	*n*(%)	*p*	*p*	*n*(%)	*n*(%)	*p*	*p*
Sex, women	34(55.74)	29(82.86)	0.009		35(48.61)	35(79.55)	0.001	
Age, years*	32.00(±11.46)	27.16(±8.68)	0.04		32.23(±10.74)	28.02(±9.18)	0.04	
BMI, kg/m^2			0.49	0.57			0.40	0.52
<25	42(68.85)	28(80.00)			47(65.28)	34(77.27)		
25–30	12(19.67)	4(11.43)			18(25.00)	7(15.91)		
≥30	7(11.48)	3(8.57)			7(9.72)	3(6.82)		
ESS score*	13.38(±5.00)	15.21(±4.10)	0.08	0.04	13.44(±5.50)	14.80(±4.60)	0.18	0.17
ESS score, >10	46(76.67)	32(94.12)	0.05	0.06	54(75.00)	39(88.64)	0.08	0.10
Total IHSS score*	32.87(±5.98)	35.10(±7.23)	0.14	0.13	31.63(±6.72)	33.62(±7.39)	0.17	0.34
Partial IHSS score*	27.65(±5.43)	29.63(±6.77)	0.15	0.16	27.44(±5.76)	29.00(±6.65)	0.21	0.45
BDI-II score*	16.38(±10.03)	16.29(±10.44)	0.97	0.99	16.09(±9.98)	14.68(±10.04)	0.51	0.44
BDI-II score			0.64	0.70			0.50	0.57
<14	16(38.10)	15(44.12)			21(46.67)	22(50.00)		
14–20	8(19.05)	8(23.53)			6(13.33)	9(20.45)		
≥ 20	18(42.86)	11(32.35)			18(40.00)	13(29.55)		
MSL on MSLT, min*	13.88(±4.36)	9.86(±3.63)	0.0002	0.0002	13.27(±4.84)	9.56(±3.67)	0.0002	0.0003
MSL on MSLT, ≤8min	4(7.84)	12(34.29)	0.004	0.004	8(14.81)	17(38.64)	0.009	0.002
Sleep duration, min*	412.62(±62.44)	447.14(±45.16)	0.007	0.01	403.03(±66.92)	452.50(±42.22)	0.0001	0.0003
Sleep efficiency, % *	83.09(±10.86)	88.86(±5.32)	0.008	0.01	81.49(±11.98)	88.90(±5.20)	0.0007	0.001
Sleep latency, min*	21.16(±16.72)	15.74(±12.91)	0.11	0.06	21.42(±19.11)	15.41(±12.60)	0.07	0.05
REM sleep latency, min*	89.00(±51.67)	95.51(±46.38)	0.54	0.50	86.51(±53.95)	93.07(±44.48)	0.50	0.86
WASO, min*	51.92(±43.13)	33.66(±22.79)	0.03	0.05	58.07(±47.63)	35.07(±22.91)	0.006	0.02
Stage 1, %*	6.27(±5.71)	4.66(±3.13)	0.14	0.36	6.69(±6.00)	4.71(±2.96)	0.05	0.15
Stage 2, % *	53.21(±9.44)	51.61(±5.54)	0.36	0.24	53.84(±8.36)	53.29(±6.67)	0.71	0.72
Slow wave sleep, % *	19.73(±7.26)	21.77(±5.47)	0.15	0.26	18.83(±6.30)	20.53(±6.03)	0.16	0.49
REM sleep, % *	20.77(±5.95)	21.94(±4.34)	0.31	0.23	20.63(±6.28)	21.47(±3.94)	0.43	0.29
PLMS index/h *	5.08(±7.50)	4.21(±9.12)	0.61	0.94	3.97(±7.46)	4.25(±8.31)	0.85	0.78
AHI*	4.37(±5.62)	1.75(±2.05)	0.02	0.13	5.40(±6.66)	2.39(±2.88)	0.01	0.22
Micro-arousal index/h*	12.73(±6.85)	10.04(±4.25)	0.04	0.18	13.64(±6.86)	11.32(±6.40)	0.08	0.25
32-h bed-rest TST, h*	16.86(±1.11)	21.41(±2.32)	0.001	0.002	16.79(±1.34)	21.32(±2.30)	0.001	0.002

*Quantitative variables are expressed as means (± standard deviation).

Model 0: crude association. Model 1: adjustment for age and gender.

BMI, body mass index; ESS, Epworth Sleepiness Scale; IHSS, Idiopathic Hypersomnia Severity Scale; BDI-II, Beck Depression Inventory II; MSL, mean sleep latency; MSLT, multiple sleep latency test; WASO, wake after sleep onset; REM, rapid eye movement; PLMS, periodic limb movements during sleep; AHI, apnea–hypopnea index; TST, total sleep time.

chose three parameters, the number of lapses and the psychomotor speed (i.e. slowest 10% 1/RT and mean 1/RT), because they are more sensitive to sleep deprivation and alertness, unlike the most widely used outcomes (i.e. mean and median metrics) [32]. No specific PVT measure has been validated for sleep inertia; however, the chosen metrics better emphasize the slowing of the optimal and intermediate responses and decrease the long lapse contribution [32], and should better serve as PVT primary outcomes to quantify this phenomenon. As our protocol consisted of four repeated measurements (the night before at 07:00 pm as baseline, then at 07:00 am upon awakening after the PSG, 07:30 am to assess its duration, and 11:00 am to show its natural decline), we used a short PVT version (5 min) that represents a more practical alternative to the standard 10-min PVT [32–34]. The PVT performances at 07:00 am and 07:30 am were markedly impaired in patients with self-reported M-sleep inertia, especially the number of lapses and the slow response speed (slowest 10% 1/RT), and tended to worsen with the increasing severity of sleep inertia. Although not significant, the mean response speed (mean 1/RT) also showed a similar deteriorated profile at awakening (07:00 am and 07:30 am). The presence of D-sleep inertia also was associated with altered number of lapses. M-sleep inertia metrics (frequency and duration) were more associated with the PVT performances at awakening than D-sleep inertia, and this variability could be related to a sleep laboratory versus home effect. Conversely, the presence of sleep drunkenness on PVT day markedly affected the PVT performances (i.e. number of lapses) at 07:00 am and 07:30 am, which may reflect a particular behavioral state characterized by a different brain activity pattern during a lapse than during an appropriate response.

PVT performances, especially number of lapses, were pronouncedly deteriorated in patients with IH and severe sleep inertia compared with all other patients without sleep inertia; however, PVT results were not different between patients with severe sleep inertia and with IH or other sleep disorders. We observed similar findings when using D-sleep inertia data, and also in patients with high versus normal daytime sleep propensity (i.e. MSL ≤ or >8 min at the MSLT) and long versus normal TST (TST ≥ or <19 h) on the 32-h bed-rest PSG recording. Altogether, the number of lapses at 07:00 am and 07:30 am should be considered as a valid objective measure of sleep inertia in the context of sleep disorders, in IH associated with its phenotypes with long or normal sleep time, and in other sleep disorders. However, sleep inertia, sleep drunkenness and altered PVT performances at awakenings may be absent and therefore are not necessary for the diagnosis of IH. Additional studies are needed to better define the factors associated with self-reported and objective sleep inertia in different sleep disorders and in IH. It remains unclear whether impaired responses in the lapses domain at awakening reflect a state instability with altered alertness due to inability of the

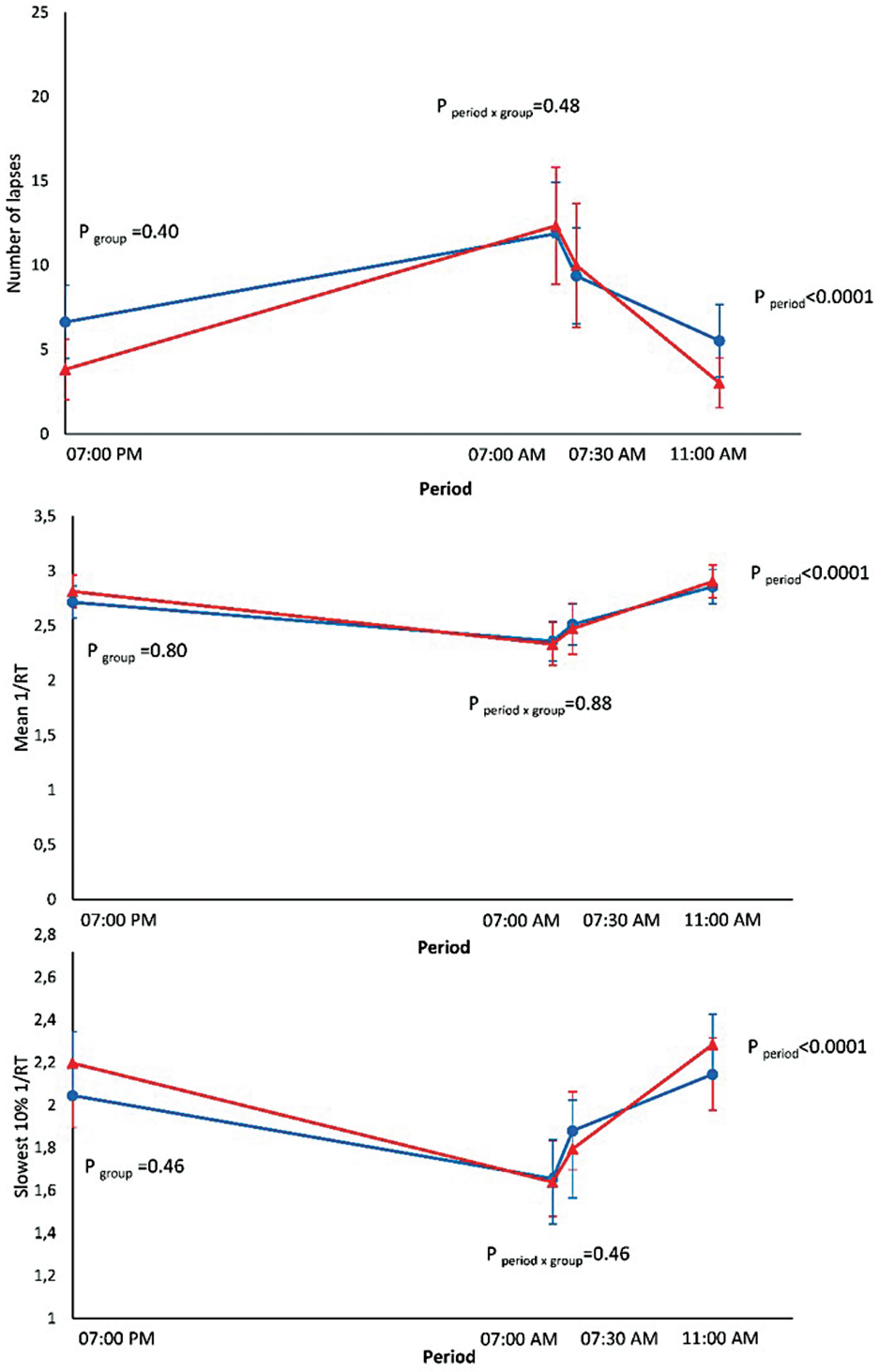

Figure 3. PVT metric profile across the four sessions in patients with IH (n = 35; red line) and other sleep disorders (non-IH; n = 61; blue line), all with severe M-sleep inertia, adjusted for age and sex.

arousal system to restore a complete and rapid awakening, or due to microsleeps induced by higher sleep pressure especially in patients with hypersomnolence [46]. The reason of the severe sleep inertia in IH is poorly understood. A deficiency in the wake-promoting system may predispose some patients to greater performance instability at awakening; however, recent data found no striking difference among cerebrospinal fluid monoamines, their metabolites and trace amine levels of patients with IH and patients without objective sleepiness [47]. Moreover, it has been hypothesized that awakening difficulties in patients with IH could be explained by a tendency toward a delayed sleep phase and excessive need for sleep that cannot be fulfilled, resulting in sleep deprivation [8, 45, 48–50]. We recently reported higher sleep efficiency and a trend to higher percentage of slow wave sleep in patients with IH, and proposed a standard for the diagnosis of clear-cut IH

that requires normal sleep continuity and architecture [10, 42]. Here, we did not analyze the association between the slow wave sleep amount close to awakening time (07:00 am) and the PVT performances. Further studies will focus on spectral analyses of EEG prior to wake time and their relationship to self-reported sleep inertia and sleep drunkenness, and to PVT performances in patients with IH.

Currently, no treatment is approved for IH [51]. Off-label treatments include stimulants and wake-promoting agents approved for narcolepsy, but often with limited efficacy on sleep inertia. Our results showed that sleep inertia may be self-reported with three items of IHSS and objectively assessed with the PVT at awakening. Moreover, as both PVT and IHSS are short and easy to perform, they are well-suited in clinical settings to optimize the management of patients with sleep inertia and to assess their responsiveness to sleep inertia treatments in randomized clinical trials [52].

This study has several limitations. We could not compare patients with IH with/without sleep inertia because only five patients with IH did not report sleep inertia. Moreover, we were also underpowered to study sleep inertia in function of the different IH phenotypes (with/without long sleep time) because only five patients had normal sleep duration on the extended bed-rest recording (three with mild and two with severe sleep inertia). We performed this study in the context of a sleep disorder diagnostic evaluation, thus explaining the diversity of non-IH sleep disorders that reflects the current clinical practice, and the lack of healthy controls. Also, we did not systematically assess circadian preferences and did not analyze the relationships between the usual wake-up time after spontaneous awakening and the PVT results. Conversely, we assessed PVT performances in a standardized procedure in the laboratory. We showed that altered PVT performances upon awakening lasted at least 30 min (PVT sessions: 07:00 am and 07:30 am) and were normal at 11:00 am; however, the lack of PVT sessions between 07:30 am and 11:00 am did not allow measuring the actual duration of objective sleep inertia. Also, we did not compare the sensitivity and specificity of the PVT values with sleep inertia given the complexity of the choices for defining the PVT threshold on that of 07:00 am versus 07:30 am, on that of single morning PVT or its comparison with the values of reference (i.e. 07:00 pm), and via comparisons between IH patients with severe sleep inertia and non IH patients without sleep inertia, or between all subjects with sleep inertia and those without. All these key analyzes will be reported in future publications. Finally, there are other neurobehavioral tests that may represent an alternative to the PVT or provide additional information, such as the sustained attention to response task [53]; however, comparing the performances of these two tests for sleep inertia measurement was out of the scope of the present study.

To conclude, we showed that three items of the IHSS allow assessing self-reported sleep inertia and sleep drunkenness in a standardized procedure to better characterize its frequency and duration in patients with IH and other sleep disorders. The PVT is a reliable and valid objective measure of sleep inertia that will help to better understand its biological correlates, especially in IH where this phenomenon is often very pronounced and disabling. Finally, both IHSS and PVT, with its feasibility and user acceptance, may represent reliable instruments in clinical setting to optimize IH management and follow-up.

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Author Contributions

E.E. participated in data acquisition, results interpretation, manuscript revision, and preliminary draft writing. A.L.R., R.L., N.B., S.C., and L.B. participated in the data acquisition and manuscript revision. I.J. participated in statistical analysis and results interpretation. Y.D. participated in study concept and design, data acquisition, results interpretation, manuscript revision, and drafting.

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