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Hyperactivity in patients with narcolepsy and idiopathic hypersomnia: an exploratory study

Caroline Dodson[1†], Karen Spruyt[2*†], Ciaran Considine[3], Emily Thompson[4], Osman S. Ipsiroglu[5], Kanika Bagai[4], Rosalia Silvestri[6], Barbara Couvadelli[7] and Arthur S. Walters[4]

Abstract

Introduction Patients with either Idiopathic Hypersomnia or Narcolepsy demonstrate excessive daytime somnolence (EDS) with resultant inattention mimicking Attention Deficit Hyperactivity Disorder (ADHD). Patients with ADHD also often express sleep problems including EDS. Thus, patients with ADHD and patients with idiopathic hypersomnia or narcolepsy may share inattention and daytime drowsiness as common features. However, it is not known whether EDS patients with idiopathic hypersomnia or narcolepsy also have increased movement (hyperactivity) like ADHD patients, the determination of which is the purpose of this study.

Methods We studied 12 patients (7 Narcolepsy type 2 and 5 Idiopathic Hypersomnia) with EDS as shown by Multiple Sleep Latency Test which served as the gold standard for entry into the study. Twelve subjects without symptoms of EDS served as the control group. None of the participants had a previous history of ADHD. Each participant underwent a one-hour session laying at 45 degrees with surveys about the need to move and actigraphy as an objective measure of movement.

Results Sleep-disordered patients with EDS reported more symptoms of inattention and hyperactivity on the ADHD Self-Report Scale. At each of the time points patients with EDS had a clear trend to express the need to move more than controls on the Suggested Immobilization Test (SIT). For the total 60 min, a large effect size for the need to move during the SIT test was found between patients and controls (Cohen's $d = 0.61$, $p = 0.01$). Patients with EDS did not express a need to move more to combat drowsiness than controls, nor did actigraphy show any difference in objective movement between patients and controls during the SIT.

Conclusion Patients with EDS express inattention and a need to move more than controls. However, hyperactivity was not verified by objective measurement, nor did the EDS patients express a need to move to combat drowsiness more than controls. Thus, a hypothesis to be further tested, is whether narcolepsy and idiopathic hypersomnia may be more a model of the inattentive form of ADHD rather than the combined or inattentive/hyperactive form of ADHD. Further studies are needed to explore the relationship between EDS and hyperactivity.

Keywords Narcolepsy, Idiopathic hypersomnia, Attention-Deficit Hyperactivity Disorder (ADHD), Inattention, Hyperactivity, Hypoarousal, Sleepiness, Drowsiness, Somnolence, Suggested Immobilization Test (SIT)

[†]Caroline Dodson and Karen Spruyt shared first authorship.

*Correspondence:
Karen Spruyt
karen.spruyt@inserm.fr; karen.spruyt@u-paris.fr
Full list of author information is available at the end of the article

Introduction

Varying degrees of inattention and hyperactivity are diagnostic features of Attention Deficit Hyperactivity (ADHD). Studies in ADHD populations have put forward a hypo-arousal hypothesis explaining their inattention as well as their hyperactivity (Sikstrom and Soderlund 2007; Saad et al. 2018). Patients with ADHD also often express sleep problems including Excessive Daytime Somnolence (EDS) (Bioulac et al. 2015; Oosterloo et al. 2006). The reverse is also true. Patients with idiopathic hypersomnia (IH) or narcolepsy (N) sleep disorders demonstrate EDS as their core feature with resultant inattention (Oosterloo et al. 2006; Calhoun et al. 2012; Lecendreux et al. 2015; Modestino and Winchester 2013). Thus, patients with ADHD and patients with sleep disorders characterized by EDS may share inattention and daytime drowsiness as common features. However, it is not known whether sleep-disordered patients expressing EDS also have increased movement (hyperactivity) like ADHD patients, the determination of which is the purpose of this study.

A limited understanding of arousal dysregulation in ADHD exists (Irwin et al. 2020). A recent review concluded that particularly during resting state and during tasks requiring response regulation and sustained attention rather hypo- than hyperarousal might be underlying ADHD. For instance, increased power in slow (relative to fast) oscillations in EEG have been suggested (Barry et al. 2003). At the same time, it has been suggested in ADHD literature that such a hypo-arousal state is potentially compensated by hyperactive motor behaviors and sensation-seeking behavior. In children, preliminary findings highlighted the clinical importance of measures of movement intensity (Li et al. 2016).

To our knowledge, ours is the first study to objectively explore the co-occurrence or comorbid condition of hyperactivity in patients with sleep disorders characterized by EDS. We aimed to objectively measure a tendency toward hyperactivity in a standardized assessment setting in sleep-disordered patients with EDS. We hypothesize that sleep-disordered patients with EDS will show evidence of both inattentiveness and hyperactivity. If patients with EDS have hyperactivity, this could lead to important pathophysiological understandings and links between EDS and ADHD. Similarly, this would also suggest that treatment of the EDS might lead to improvement of hyperactivity, a connection which could be explored in future therapeutic studies.

Materials and methods

Procedure

This study was approved by the Vanderbilt University Medical Center IRB (#171008) and all subjects signed a consent form before enrollment. We recruited sleep-disordered patients diagnosed with narcolepsy and idiopathic hypersomnia from the Vanderbilt University Medical Center sleep clinic, each of whom had a history and physical examination by a sleep physician. By standard definition, patients with narcolepsy or idiopathic hypersomnia have EDS as objectively measured on a Multiple Sleep Latency Test (MSLT) which served as the gold standard for the measurement of EDS and was a pre-study requisite for entry into the study (Johns 1992). During the MSLT patients were for 2 weeks off of any stimulant or sedative medications which could result in any false negative or false positive results.

Narcolepsy and idiopathic hypersomnia

Narcolepsy is defined by a sleep onset latency of < 8 min and the additional presence of at least 2 sleep onset REM periods (SOREMS) on the MSLT or 1 SOREM on the MSLT and a REM latency < 15 min on the overnight polysomnogram (AAMS 2014). Idiopathic Hypersomnia was similarly defined by a sleep onset latency of < 8 min on the MSLT but in the absence of 2 SOREMS (AAMS 2014). Subjects who went back on their stimulant medications after the MSLT were not asked to come off their current medications, but had to express that their current regimen inadequately controlled their sleepiness. In addition, they had to be on stable dosages of their medication regimen for the previous two weeks before the current study. By MSLT criteria 7 patients with narcolepsy type 2 (i.e., without cataplexy) and 5 patients with idiopathic hypersomnia were entered into the study.

We also recruited 12 control subjects, without a history of EDS or known sleep disorder, from the Vanderbilt Research recruitment Email Distribution, which is an email distribution that goes to all Vanderbilt employees.

None of the EDS patients nor controls had a previous diagnosis of ADHD or any other sleep disorders. Subjects with sleep apnea, or at risk for sleep apnea (e.g., obese) as determined by either previous polysomnography with a baseline Apnea–Hypopnea Index (AHI of > 15) or a self-reported history of prominent snoring or awakenings associated with choking or gasping were excluded.

Assessment session

Participants arrived at the sleep lab of Vanderbilt Clinical Research Center at approximately 3 PM, to both control for the circadian aspect of drowsiness, as well as to sample participants at the typical maximum period of afternoon circadian drowsiness. Patients then underwent a 15-min quiet period to minimize the effect of varying levels of previous motor activity before the onset of active recording. Past medical history, medication, and sleep report information were collected which also documents

medication and caffeine intake within 24 h of the study and sleep the night before.

Measures

Before the onset of active recording participants completed several scales.

Epworth Sleepiness Scale (ESS) The ESS quantifies self-reported sleepiness over the previous two weeks. A score of greater than 10 raises concern, with a minimum score of 0 and a maximum score of 24. The original version has an internal consistency of 0.88 and strong discriminatory power for daytime sleepiness (Johns 1992, 2000).

The Insomnia Severity Index (ISI) The ISI quantifies the severity of insomnia symptoms (Kraepelien et al. 2021; Bastien et al. 2001). The internal consistency, of the original ISI, is 0.74. A total score ≥ 8 is considered a clinical cut-off, with total scores suggestive of clinical severity being: 0–7 = No clinically significant insomnia, 8–14 = Subthreshold insomnia, 15–21 = Clinical insomnia (moderate severity), 22–28 = Clinical insomnia (severe).

The Patient Health Questionnaire for Depression and Anxiety (PHQ-4) The original PhQ-4 quantifies the severity of recent anxiety and depression by combining an anxiety and depression scale showing good factorial and criterion validity (Kroenke et al. 2009). The total score is calculated by adding the scores for the four items which are rated as normal (0–2), mild (3–5), moderate (6–8), and severe (9–12). Higher scores suggest more functional impairment, disability days, and healthcare use. The clinical cut-off is equal to or greater than 3.

The Adult ADHD Self-Report Scale (ASRS) The ASRS quantifies ADHD symptoms (Kessler et al. 2005). The ASRS is an instrument consisting of the eighteen DSM-IV-TR criteria. We administered Part A of the measure, which contains the 6 items that demonstrate the most diagnostic accuracy in the publisher's validity studies. A score of 4 or more on the 6 items is indicative of a symptom profile highly consistent with an ADHD diagnosis in adults. Furthermore, the first 4 questions of the ASRS probe inattention, and the 5th and 6th questions probe hyperactivity.

Digit Vigilance Test (DVT) With the paper–pencil format of the DVT (Lewis 1995), a measure of sustained attention and psychomotor speed was administered. It involves a specific target number (6 or 9) appearing randomly within 59 rows of 35 single digits on two pages that need to be crossed out. Total time and total errors (commission + omission) are recorded.

The hyperactivity assessment Patients then underwent a Suggested Immobilization Test (SIT) (Hening et al. 1999; Montplaisir et al. 1998). The SIT was first developed by the group of Montplaisir as a way of measuring Periodic Limb Movements during wakefulness in the Restless Legs Syndrome (Montplaisir et al. 1998). However, we previously adapted the test to measure general body movements (Hening et al. 1999), a methodology that we again employ in the current study. During the SIT subjects are asked to report symptoms on Visual Analogue Scales (VAS) and objective movement data is recorded by actigraphy.

Participants are studied during wakefulness lying with the body up at 45 degrees for 60 min in a sleep lab bed with the SIT. The SIT is executed in normal room light, with windows blocked and the door closed to control for ambient light and noise. Participants are reminded, as appropriate, to lay quietly and try to resist falling asleep during the session. They are instructed to not ambulate around the room, eat, drink, read, watch television, or converse with technicians (aside from exchanging required information), to control for possible intra-participant activities that might serve to compensate for hypo-arousal. The research assistant was present and in case of drowsiness, the research assistant stimulated the patient to stay awake.

The subjective aspect: In our particular case, during these 60 min participants were asked to mark two visual analogue scales (VAS, i.e. line of 10 cm long) every 20 min (i.e. at 0, 20, 40, and 60-min marks). One of the VAS indicated the level of sleepiness perceived by the subject at each time point and the other asked the subject to indicate how intensely they felt the urge to move at each time point.

In addition, at each time point, the subjects also answered the open-ended question: "If you need to move, why do you need to move?" This open-ended question was counted as affirmative if at any time during the 20, 40, and 60 min period the subject said that they needed to move (NTM) to combat sleepiness.

The objective assessment: Actigraphy with the Philips Respironics Actiwatch-64 of the non-dominant hand served as a quantitative measure of movement throughout the procedure (Martin and Hakim 2011). The

mobility index was used as a key indicator, with higher values indicating more mobility.

Statistical analysis

Descriptive analyses are applied to describe sample characteristics. The 4 primary endpoints were (a) the total score on ASRS and each item, (b) the count of the affirmative response of the need to move to fight somnolence (NTM), (c) the score on the VAS measuring the urge to move, and (d) bin assessment of movement counts with the actigraphy.

Group differences were analyzed by Kruskal–Wallis ANOVA by Ranks (H) or Kolmogorov–Smirnov test (KS), and differences in proportions by Fisher exact 2-tailed (FE) or Maximum Likelihood Chi-square (ML Chi-square) test when appropriate. Spearman rank (r_s) correlations were applied to correlate the degree of sleepiness and urge to move of the VAS. Given the small sample sizes, we calculated Cohen's *d* (mean ± standard error), or the clinical effect size, and its power for the main outcomes. Statistical analyses were performed with Statistica version 13 (StatSoft, Inc. (2009), STATISTICA, Tulsa, OK). A *P*-value of $p < 0.05$ is considered statistically significant.

Results

Sample characteristics

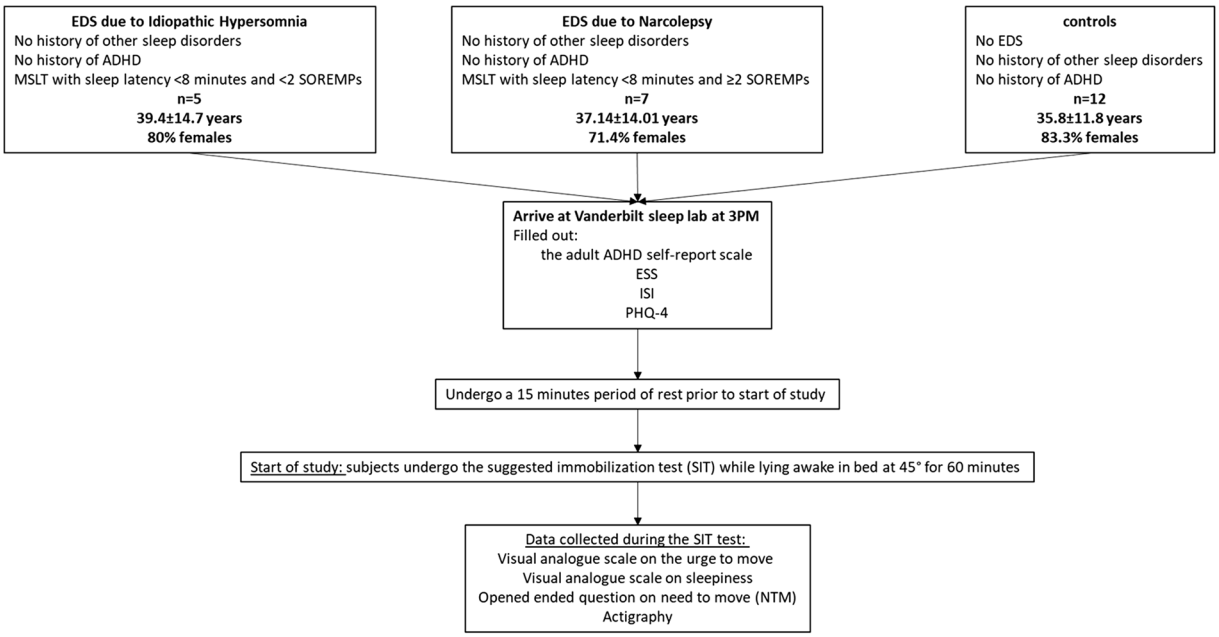
Figure 1 is the flowchart of participants. Groups did not differ in age ($(H = 2, N = 24) = 0.3$, $p = 0.88$) or gender (ML Chi-square(2) = 0.37, $p = 0.83$).

2/5 IH and 4/7 N patients were off, while 3/5 IH and 3/7 N patients were on medications ($p = 0.014$) controlling sleepiness at the time of the assessment. Of the 6 EDS patients who remained on medications to manage hypersomnia, 1 was on amphetamines/dextroamphetamine (Adderall), 1 was on armodafinil (Nuvigil), 1 was on a combination of amphetamines/dextroamphetamines and armodafinil, 1 was on lisdexamfetamine (Vyvanse), 1 was on sodium oxybate (Xyrem) and 1 was on bupropion (Wellbutrin).

All measures were performed on all subjects except for actigraphy. There were 7 patients and 5 controls who had available actigraphy data. The rest were missing due to technical and logistical problems.

Sleep disorder and comorbidity evaluation

Table 1 tabulates the descriptive findings for the ESS score, ISI score, and PhQ-4 score for the 3 groups separately.



ADHD = Attention Deficit Hyperactivity Deficit, EDS = Excessive Daytime Somnolence, ESS = Epworth sleepiness scale, ISI = Insomnia Severity Index, PHQ-4 = Patient Health Questionnaire for Depression and Anxiety, MSLT = Multiple Sleep Latency Test, SOREMPS = Sleep Onset REM periods

Fig. 1 Flowchart of Participants and Procedure

Table 1 Descriptive Means ± standard deviations and proportions (%) above clinical cut-off score, of the ESS score, ISI score, PhQ-4 score, VAS sleepiness, and Digit Vigilance Test

Variable	[1] IH ($n=5$)	[2] Narcolepsy ($n=7$)	[3] Total patients ($n=12$)	[4] Control ($n=12$)	[1,2,4] Test-statistic	*p*-value	[3,4] Test-statistic *p*-value	[1,2] Test-statistic *p*-value
ESS total score	14.2 ± 4.8	11.9 ± 3.6	12.8 ± 4.1	4.8 ± 3.3	(H = 2, $N=24$) = 15.1	**0.0005**	**< 0.005**$^{\$}$	n.s.$^{\$}$
ESS cut-off > 10	80%	57.1%	66.7%	0%	ML Chi-square (2) = 16.0	**0.001**	**0.0003**$^{£}$	n.s.$^{£}$
ISI total score	11 ± 4.6	11.6 ± 5.6	11.3 ± 5	3.2 ± 2.6	(H = 2, $N=24$) = 14.5	**0.0007**	**< 0.005**$^{\$}$	n.s.$^{\$}$
ISI cut-off ≥ 8	60%	85.7%	75%	8.3%	ML Chi-square (2) = 13.3	**0.001**	**0.003**$^{£}$	n.s.$^{£}$
PhQ-4 total score	3.4 ± 3.8	3.1 ± 3.6	3.3 ± 3.5	0.6 ± 0.8	(H = 2, $N=24$) = 4.2	0.124	n.s.$^{\$}$	n.s.$^{\$}$
PhQ-4 clinical cut-off ≥ 3	60%	42.9%	50%	0%	ML Chi-square (2) = 10.7	**0.005**	**0.014**$^{£}$	n.s.$^{£}$
VAS Sleepiness 20-min	6.5 ± 2.7	5.5 ± 3.0	5.9 ± 2.8	2.5 ± 2.0	(H = 2, $N=24$) = 8.1	**0.017**	**< 0.05**$^{\$}$	n.s.$^{\$}$
VAS Sleepiness 40-min	8.0 ± 2.7	8.1 ± 2.3	8.0 ± 2.4	3.1 ± 2.4	(H = 2, $N=24$) = 11.7	**0.003**	**< 0 .005**$^{\$}$	n.s.$^{\$}$
VAS Sleepiness 60-min	7.9 ± 3.1	8.4 ± 2.3	8.2 ± 2.5	4.1 ± 3.5	(H = 2, $N=24$) = 9.4	**0.009**	**< 0 .01**$^{\$}$	n.s.$^{\$}$
DVT Red time (sec)	256.0 ± 131.3	168.4 ± 26.4	205 ± 93.3	198.7 ± 33.6	(H = 2, $N=24$) = 6.0	n.s.	n.s.$^{\$}$	n.s.$^{\$}$
DVT Red Total errors	1.0 ± 1.2	2.4 ± 2.1	1.8 ± 1.9	1.4 ± 1.4	(H = 2, $N=24$) = 1.9	n.s.	n.s.$^{\$}$	n.s.$^{\$}$
DVT Blue time (sec)	250.6 ± 133.7	174.0 ± 27.6	205.9 ± 92.0	199.6 ± 37.4	(H = 2, $N=24$) = 3.3	n.s.	n.s.$^{\$}$	n.s.$^{\$}$
DVT Blue Total errors	3.2 ± 2.6	2.4 ± 4.0	2.8 ± 3.3	3.5 ± 3.2	(H = 2, $N=24$) = 1.5	n.s.	n.s.$^{\$}$	n.s.$^{\$}$
DVT total time	507.2 ± 264.5	342.4 ± 53.3	411.1 ± 184.9	398.0 ± 70.7	(H = 2, $N=24$) = 4.5	n.s.	n.s.$^{\$}$	n.s.$^{\$}$
DVT Total errors	4.2 ± 2.6	4.9 ± 5.1	4.6 ± 4.1	4.8 ± 3.9	(H = 2, $N=4$) = 0.15	n.s.	n.s.$^{\$}$	n.s.$^{\$}$

Bold are significant results at $p < 0.05$. Percentages represent the number of subjects above the clinical cut-off of all questionnaires

DVT Digit Vigilance Test; *ESS* Epworth Sleepiness Scale (cut-off > 10); *IH* Idiopathic Hypersomnia, *ISI* Insomnia Severity Index (cut-off ≥ 8), *H* Kruskal–Wallis ANOVA by ranks; *ML Chi-square[degrees of freedom = (2)]* Maximum Likelihood Chi-square; *PhQ-4* Patient Health Questionnaire for Depression and Anxiety (cut-off ≥ 3); *VAS* Visual Analogue Scale

$^{£}$ Fisher exact

$^{\$}$ Kolmogorov–Smirnov Test

Epworth sleepiness scale

The average ESS scores documented that patients were significantly sleepier than controls ($p=0.0005$) (Table 1). More patients score above the clinical cut-off (> 10) on the ESS and none of the control subjects scored above the clinical cut-off (> 10) on the ESS ($p=0.001$) (Table 1).

The insomnia severity index

The average ISI scores also showed that patients had more insomnia than controls ($p=0.0007$)(Table 1). More patients, in particular N, scored above the clinical cut-off on the ISI ($p=0.001$)(Table 1). Regarding severity of insomnia, proportions across groups were significantly different (ML Chi-square (6) = 17.0, $p=0.009$); i.e., for IH: No clinically significant insomnia: 2/5 (40%), Subthreshold insomnia: 1/5 (20%), Clinical insomnia (moderate severity): 2/5 (40%), and for N: No clinically significant insomnia: 1/7 (14.3%), Subthreshold insomnia: 4/7 (57.1%), Clinical insomnia (moderate severity): 1/7 (14.3%), Clinical insomnia (severe): 1/7 (14.3%), and one control subject showed Subthreshold insomnia: 1/12 (8.3%).

The patient health questionnaire for depression and anxiety

The average PhQ-4 scores indicated no group differences ($p=0.124$)(Table 1). However, more patients have a score above the clinical cut-off (≥ 3) on the PhQ-4 ($p=0.005$) (Table 1). Proportions in terms of severity, for the IH:

Normal: 2/5 (40%), Mild: 2/5 (40%), Severe: 1/5(20%), for the N: Normal: 4/7 (57.1%), Mild: 2/7 (28.6%) and Severe: 1/7(14.3%) and for controls: Normal: 12/12 (100%)(ML Chi-square (4) = 10.7, $p = 0.03$) were different across groups.

Comparison between IH and N groups showed no difference in terms of mean scores on sleepiness (VAS), the severity of insomnia or anxiety, and depression scores (Table 1, KS results).

ADHD evaluation

Adult ADHD Self-Report Scale

Despite the absent history of ADHD, patients showed more prominent ADHD features based on the ASRS sum score ($p = 0.005$)(Table 2) and proportions above the clinical cut-offs, particularly the IH. Table 2 shows the total sum score and the proportion above the clinical cut-off ≥ 1 for each item. Group differences were found for 3 inattentive and 1 hyperactive item, with particularly more IH subjects scoring above the clinical cut-off. The post-hoc Cohen's *d* effect size for the ASRS total score difference between the patient and control group (Cohen's $d = 1.7$, $p = 0.0003$) achieved a power of 97.5%.

Digit vigilance test

DVT showed no group differences (Table 1). Therefore, cognitive processes associated with sustained attention and visual search are comparable between our groups.

Hyperactivity evaluation during the SIT

Patients with EDS expressed a clear tendency to want to move more than controls on the VAS assessing the urge to move at 20 min, 40 min, 60 min, and for the entire 60 min combined (Table 3). Although the numeric values for the patients are higher at each of these time points, each individually did not meet statistical significance. On the other hand, the post-hoc total effect size difference for the total 60 min between the patient and control group (Cohen's $d = 0.61$, p-value = 0.01) of this repeated assessment achieved a power of 77%. In other words, the distribution of individual data points shows an overlap that does not reach statistical significance yet the average relative to the pooled variance (i.e., regardless of sample size) for the total 60 min showed a clinical significance per Cohen's *d* (p-value = 0.01).

In neither of the patient groups was the urge to move associated with their degree of sleepiness per VAS: i.e., *for IH*: 20-min $r_s = 0.4$, $p = 0.45$; 40-min $r_s = 0.8$, $p = 0.09$; 60-min $r_s = 0.1$, $p = 0.86$ and *for N*: 20-min $r_s = 0.2$, $p = 0.69$; 40-min $r_s = 0.4$, $p = 0.43$; except the 60-min $r_s = 0.8$, $p = 0.03$. Yet, in the *control group* the 60-min value was particularly highly correlated: i.e., 20-min $r_s = 0.2$, $p = 0.60$; 40-min $r_s = 0.7$, $p = 0.02$; 60-min $r_s = 0.8$, $p = 0.001$.

The number of subjects who expressed the need to combat drowsiness from the open-ended question "If you need to move, why do you need to move?" (NTM) at 20-min. was 40% of IH, 42.86% of N and 16.67% of controls and was not different (ML Chi-square (2) = 1.8, $p = 0.39$); at 40-min. was 40% of IH, 42.86% of N and 33.33% of controls and was not different (ML Chi-square (2) = 0.2, $p = 0.91$); at 60-min. was 20% of IH, 42.86% of N and 16.67% of controls and was not different (ML Chi-square (2) = 1.6, $p = 0.45$). Similarly, the proportion of hypersomnia patients and controls who expressed a need to move to combat drowsiness (2/5 = 40% for IH, 3/7 = 42.86% for N, and 4/12 = 33.3% for controls) did not differ during the entire total 60-min. timeframe (ML Chi-square (2) = 0.2, $p = 0.91$). Nine subjects expressed a need to move to combat drowsiness over the entire course of the study (5/12 patients and 4/12 controls). Thus the total patient (5/9, 55.56%) versus control (4/9, 44.44%) group also did not differ over the entire course of the study in the proportion of subjects expressing a need to move to combat drowsiness (Fisher Exact $p = 1.000$).

For the VAS urge to move, a sensitivity analysis for the 6 EDS patients not on any medications to treat EDS versus 12 controls yielded similar results. When the 6 EDS patients off medication were directly compared to the 6 EDS patients on medication there were also no differences in the urge to move. An additional sensitivity analysis eliminating patients or controls with anxiety or depression on the PhQ-4 also yielded similar results. Upon excluding the patients on medication and re-analyzing the Table 1 similar differences were found between the remaining patient group (i.e., those not taking medication) and controls, which is suggestive that our findings on the total patient group ($n = 12$) are robust (see Supplementary Table 1).

Actigraphic movement evaluation during the SIT

Movement at 20-, 40- and 60-min was comparable across groups (Table 4). Cohen's *d* of this repeated assessment is 0.05 ± 0.34, which was underpowered. The narcolepsy with(out) and the control subjects with(out) actigraphy data were not different in terms of age, ASRS total score, VAS "urge to move".

Additionally, due to the missing data, a post-hoc comparison of the ASRS total score and VAS "urge to move" between groups (i.e., replicating analysis pursued in the total group), for those with available actigraphy data was performed. Total ASRS was significantly different [(H = 2, $N = 12$) = 7.45, $p = 0.024$; IH = 4.0 ± 1.2, $N = 2.5 \pm 2.1$ and control = 0.6 ± 0.9],

Table 2 Means ± standard deviations and proportions (n,%) above clinical cut-off score of the ASRS

Variable	[1] IH ($n=5$)	[2] Narcolepsy ($n=7$)	[3] Total patient ($n=12$)	[4] Control ($n=12$)	[1,2,4] Test statistic	*p*-value	[3,4] Test-statistic *p*-value	[1,2] Test-statistic *p*-value
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?	80%	57.1%	66.7%	8.3%	ML Chi-square (2) = 10.3	**0.006**	**0.009**[£]	n.s.[£]
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?	60%	71.4%	66.7%	8.3%	ML Chi-square (2) = 9.8	**0.008**	**0.009**[£]	n.s.[£]
3. How often do you have problems remembering appointments or obligations?	80%	42.9%	58.3%	8.3%	ML Chi-square (2) = 9.10	**0.01**	**0.027**[£]	n.s.[£]
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?	100%	71.4%	83.3%	41.7%	ML Chi-square (2) = 7.1	**0.03**	n.s.[£]	n.s.[£]
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?	60%	28.6%	41.7%	0%	ML Chi-square (2) = 9.5	**0.009**	**0.037**[£]	n.s.[£]
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?	20%	0%	8.3%	16.7%	ML Chi-square (2) = 2.3	0.32	n.s.[£]	n.s.[£]
ASRS total score	4.0 ± 1.2	2.7 ± 2.0	3.3 ± 1.8	0.8 ± 1.0	(H = 2, *N* = 24) = 10.4	**0.005**	**< 0.05**[$]	n.s.[$]
ASRS total score ≥ 4	80%	42.9%	58.3%	0%	ML Chi-square(2) = 14.4	**0.0007**	**0.004**[£]	n.s.[£]

Bold are significant results at $p < 0.05$. Percentages represent the number of subjects above the clinical cut-off of the individual questions

IH Idiopathic Hypersomnia, *ASRS* Adult ADHD Self-Report Scale (clinical cut-off ≥ 4 of total score, and ≥ 1 for each item); *H* Kruskal–Wallis ANOVA by ranks; *ML* Chi-square[degrees of freedom = (2)]: Maximum Likelihood Chi-square

[£] Fisher exact

[$] Kolmogorov–Smirnov Test

Table 3 Means ± standard deviations of the Visual Analogue Scale (cm) querying the urge to move during Suggested Immobilization Test (SIT)

Variable	[1] IH ($n=5$)	[2] Narcolepsy ($n=7$)	[3] Total patient ($n=12$)	[4] Control ($n=12$)	[1,2,4] Kruskal–Wallis ANOVA by Ranks, (H = 2, $N=24$) =	*p*-value	[3,4] Kolmogorov–Smirnov test *p*-value	[1,2] Kolmogorov–Smirnov test *p*-value
Urge to move 20-min	3.3 ± 4.6	3.3 ± 3.8	3.3 ± 4.0	1.3 ± 0.9	0.3	0.88	n.s.	n.s.
Urge to move 40-min	3.3 ± 4.2	4.3 ± 4.3	3.9 ± 4.1	2.4 ± 1.9	0.1	0.94	n.s.	n.s.
Urge to move 60-min	3.7 ± 5.0	5.4 ± 5.0	4.7 ± 4.8	2.2 ± 2.0	0.9	0.63	n.s.	n.s.
Total 60 min	2.7 ± 3.6	3.7 ± 3.7	3.3 ± 3.5	1.6 ± 1.1	0.5	0.78	n.s.	n.s

Bold are significant results at $p < 0.05$

n.s. Non-significant; Numbers represent averages ± standard deviations on a visual analogue scale of 10 cm long

IH Idiopathic Hypersomnia; H: Kruskal–Wallis ANOVA by ranks

Table 4 Means ± standard deviations of the actigraphic mobility index (%)

	[1] IH ($n=5$)	[2] Narcolepsy ($n=2$)	[3] Total patient ($n=7$)	[4] Control ($n=5$)	[1,2,4] Kruskal–Wallis ANOVA by Ranks, (H = 2, $N=12$) =	*p*-value	[3,4] Kolmogorov–Smirnov test *p*-value	[1,2] Kolmogorov–Smirnov test *p*-value
the first 20-min. bin	6.0 ± 1.3	5.6 ± 0.5	5.9 ± 1.1	5.6 ± 0.7	0.3	0.84	n.s.	n.s.
the second 20-min. bin	7.6 ± 5.1	5.7 ± 0.2	7.1 ± 4.3	7.6 ± 3.9	0.6	0.75	n.s.	n.s.
the third 20-min. bin	6.2 ± 1.7	7.1 ± 2.9	6.4 ± 1.9	14.7 ± 19.8	0.01	0.99	n.s.	n.s.
Total 60 min	2.1 ± 0.7	2.0 ± 0.3	2.1 ± 0.6	2.4 ± 1.1	0.1	0.94	n.s.	n.s.

IH Idiopathic Hypersomnia, *n.s* Non-significant

similar to the total group results. The VAS urge to move was not different, similar to the findings in the total group; i.e., at 20 min [(H = 2, $N=12$) = 0.25, $p=0.88$; IH = 3.3 ± 4.6, $N=4.5 \pm 6.4$ and control = 1.4 ± 0.8], at 40 min [(H = 2, $N=12$) = 0.17, $p=0.9178$; IH = 3.3 ± 4.2, $N=5.0 \pm 7.1$ and control = 2.8 ± 1.7], and at 60 min [(H = 2, $N=12$) = 0.45, $p=0.80$; IH = 3.7 ± 5.0, $N=5.0 \pm 7.1$ and control = 2.6 ± 2.1].

Adjusted *p*-value interpretation

With an adjusted p-value ≤ 0.001, the total scores of ESS, ISI (Table 1) and the total ASRS clinical cut-off score (Table 2) still demonstrated group differences. For the ASRS, the percentage of subjects above the clinical severity cut-off remains notable in both sleep-disordered groups, and particularly for the IH group (Table 2).

Discussion

In this study, the ADHD Severity Rating Scale (ASRS) rating scale suggested that patients with EDS had statistically significant evidence of both inattention and hyperactivity akin to that seen in ADHD patients. These results were similar to those obtained from the previous literature (Oosterloo et al. 2006; Calhoun et al. 2012; Lecendreux et al. 2015; Modestino and Winchester 2013). In addition, on the VAS administered during the SIT, patients with EDS expressed a clear tendency to want to move more than controls which reached significance for a total of 60 min with a large effect size. Patients did not express the need to move to combat drowsiness more than controls. There were no differences in objective movement as measured by actigraphic data collected during the SIT. These pilot data are a preliminary indication that hyperactivity,

here expressed as a need to move, needs further investigation as a separate entity in sleep-disordered patients with excessive daytime somnolence.

The hypo-arousal hypothesis postulated for ADHD might be an appropriate model for sleep-disordered patients with EDS. However, based on our pilot data of sleep-disordered patients with EDS, their potential hyperactive motricity remains questionable. But since EDS in IH and N does not lead objectively to hyperactivity, one implication of the results is that if sleep-disordered patients with EDS present with both inattentiveness and hyperactivity, treating their EDS alone might not necessarily result in improvement of the hyperactivity.

Arousal is governed by interactions between the peripheral and central nervous systems, in which the autonomic nervous system is a core component. Hence we may postulate that the control over the muscle fibers might be affected in those with arousal disorders such as EDS. A trend towards hyperactivity in the IH, and to a lesser extent in N, might be present given the amount of variation in our pilot data, particularly for the subjective report of the urge to move. More advanced measurement of movement, its frequency or intensity, in patients with EDS may further elucidate such a potential trend. Resting state measures may improve phenotyping EDS. For instance, Calhoun et al. (Calhoun et al. 2012), upon dividing a cohort into those with and without EDS by parental report demonstrate that those with EDS met significantly more of the diagnostic criteria required for the diagnosis of ADHD.

Yet another factor is that adults with ADHD show much more inattention than hyperactivity as opposed to children with ADHD where the hyperactivity component is more prominent (Gibbins et al. 2010). We did not have any subjects with pediatric ADHD in our current study. Therefore, we cannot exclude the possibility that, analogously, hyperactivity might be more prominent in children than in adults with EDS. It could therefore be possible that a study of children with narcolepsy and idiopathic hypersomnia would show a difference in hyperactivity between patients and controls. Differences between adults and children may be part of the reason that we did not find results for hyperactivity similar to those of Lecendreux, et al. (Lecendreux et al. 2015) whose study was in children as opposed to our study which was in adults.

This study of the relationship between ADHD to hypersomnia occurs in the context of other studies that have shown a relationship between ADHD to other sleep disorders. ADHD is associated with various sleep-related movement disorders, parasomnias, rhythmic movement disorders, disorders of partial arousal, circadian rhythm disorders, as well as hypersomnia (Walters et al. 2008). As with EDS, patients with other sleep disorders should be questioned about ADHD symptoms and vice versa. In the realm of our exploratory approach, the perceived hyperactivity as expressed in our small sample might be an overlooked clinical query.

There are some potential limitations of this study. However, given our small sample size, we have analyzed our data in multiple ways. Through Cohen's *d* analysis, an estimate that will not differ as a function of the sample size, we demonstrated the clinical differences as found through our non-parametric analyses. In addition, we interpreted findings with a more stringent p-value ≤ 0.001, confirming group differences. Through replication of analysis of our main objectives in the subsample with actigraphy data, we showed similar results as found in the total sample. Along with having a small sample size, we chose to monitor for an hour in the afternoon to account for circadian rhythm but limit assessment to that time point. Longer monitoring periods may yield greater disparity in movement over time. On the other hand, we did study all subjects at 3 pm which for most people is the average time for maximal circadian drowsiness. The actigraphic recording was obtained for 7 of the 12 patients and 5 of the 12 controls, which is another limitation. Video analysis of the accompanying movement was not able to be analyzed. Such an analysis will be the subject of a future study.

Conclusion

In this study, patients with Excessive Daytime Somnolence (EDS) due to either MSLT-diagnosed narcolepsy type 2 or idiopathic hypersomnia had inattention and hyperactivity symptoms per ADHD screening on the ADHD Self-Report Scale. During the SIT test, patients expressed a need to move more than controls on the visual analogue scale. However, since EDS was not associated with definite hyperactivity as measured by actigraphy in our sample, it would suggest that if patients present with comorbid EDS and hyperactivity symptoms, treating the EDS alone might not necessarily result in improvement of the hyperactivity.

Patients with EDS express inattention and a need to move more than controls. However, hyperactivity was not verified by objective measurement, nor did the EDS patients express a need to move to combat drowsiness more than controls. Narcolepsy and idiopathic hypersomnia might hypothetically be more a model of the inattentive form of ADHD rather than the combined or inattentive/hyperactive form of ADHD. However, because of the small sample size, and the risk of false negatives, our results should be interpreted with caution. Further studies are needed to explore the relationship between EDS and hyperactivity.

Studying the relationship between ADHD and EDS may lead to a better understanding of the pathophysiology of both ADHD and EDS. A good case–control study of the frequency of ADHD in the narcolepsy population is still needed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41606-023-00088-y.

Additional file 1: Supplementary Table 1. Descriptive Means±standard deviations and proportions (%) above clinical cut-off score, of the ESS score, ISI score, PhQ-4 score, VAS sleepiness, and Digit Vigilance Test per patients on/off medication.

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Authors' contributions
C.D., K.S. and A.S.W. wrote the main manuscript text. A.W.S and K.S. performed the statistical analysis and prepared tables and figures. All authors reviewed the manuscript.

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Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
The study was conducted according to the guidelines of the 1964 Declaration of Helsinki, and approved by the Vanderbilt University Medical Center IRB (#171008). All subjects signed a consent form before enrollment.

Consent to publication
Not applicable.

Competing interests
Arthur S. Walters M.D., Karen Spruyt Ph.D., Caroline Dodson B.S., Emily Thompson B.A., Kanika Bagai M.D., Rosali Silvestri M.D., Barbara Couvadelli M.D. PhD, Ciaran Considine PhD and Osman Ipsiroglu M.D. PhD have nothing to disclose.

Author details
[1]University of Miami - Miller School of Medicine, Miami, USA. [2]Université de Paris, NeuroDiderot INSERM, Bingen, 48 Bd Sérurier, 75019 Paris, France. [3]Behavioral & Cognitive Division, Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA. [4]Sleep Division, Department of Neurology, Vanderbilt University Medical Center, Nashville, TN, USA. [5]Sleep Wake-Behavior Clinic, Interdisciplinary Sleep Program, BC Children's Hospital, University of British Columbia CA, Vancouver, Canada. [6]Sleep Medicine Clinic, Department of Clinical and Experimental Medicine, Messina Medical School, AOU G Martino, Messina, Italy. [7]Neuroscience Department, Seton Hall University School of Health and Medical Services, Edison, New Jersey, USA.

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