Sleep-wake cycle and 24-h motor activity in early-mid Huntington's disease patients: An actigraphy-based study

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ABSTRACT

BACKGROUND: Disrupted 24h sleep-wake and rest-activity cycles are known common features in Huntington disease (HD) patients; however, critical periods during the 24-hour cycle have been less studied.

OBJECTIVE: To analyse the differences between early-mid stage HD patients and healthy controls (HC) in sleep patterns and 24h motor activity by using actigraphic monitoring.

METHODS: Twenty HD patients (13 females; mean age ± SD 56.45±16.94) at early-mid stage of the disease and 20 HC were actigraphically monitored for a week. We applied the Functional Linear Modeling (FLM) to analyze motor activity from the actigraphic data. We analyzed parameters regarding both the time spent in bed and out of bed; get-up time (GUT); time in bed (TIB); midpoint of sleep (MS); sleep motor activity (SMA); sleep onset latency (SOL); total sleep time (TST); wake after sleep onset (WASO); sleep efficiency (SE); number and duration of awakenings (AWK); diurnal motor activity (DMA) and diurnal total sleep time (DTST).

RESULTS: Ten patients were in Stage I, 6 in Stage II and 4 in Stage III. HD patients presented lower SE and higher TIB, SOL, WASO, AWK and AWK > 5 minutes in comparison to HC. Moreover, higher motor activity was observed in patients with HD, in particular between 2:15 and 4:00 am, from around 40 minutes prior to bedtime until 20 minutes after bedtime, and from around 20 minutes prior to get-up time until 50 minutes after get-up time.

CONCLUSIONS: Actigraphy documented a specific 24h motor pattern in HD, potentially constituting a disease signature.

Keywords: Huntington disease; neurodegenerative diseases; sleep; circadian rhythms; actigraphy.

INTRODUCTION

Significant sleep disturbances and altered rest-activity patterns are present in 90% of patients with Huntington disease (HD).[1]

Changes in sleep architecture in HD consist of increased sleep and REM latencies, decreased sleep efficiency, decreased percentage of slow-wave (SWS) and REM sleep, and increased proportion of time spent in stage NREM1 and in wake after sleep onset.[1-3] Abnormal circadian rhythm patterns have been documented by actigraphic monitoring demonstrating altered rest-activity profiles and a delayed sleep phase in HD patients.[3-6] Circadian rhythms in HD patients have not been systematically studied until recently. Previous reports indicate that both pre- and symptomatic HD patients with sleep disturbances have significantly poorer neuropsychiatric outcomes and accelerated thalamic degeneration compared with patients without sleep disturbances.[4,7]

These results highlight the importance of assessing sleep and circadian rhythm disturbances in the management of HD, because a better characterization of the patterns of the sleep disturbances and circadian dysfunction using the wearable tools that could be potentially used in the everyday clinical practice may have important implications for the management of HD patients.[1-3]

Based on these premises, the aim of our study was to characterize sleep features and 24h rest-activity patterns in an early-mid stages of HD population, compared to healthy controls, by using actigraphic monitoring analysed with functional linear modeling (FLM) — a new technique, which allowed to directly compare actigraphic data from HD patients and controls, represented as continuous functions, leading to a precise determination of the time of the day when the two groups differed in motor activity.[8-10] Moreover, we focused on the wake-sleep[11] and sleep-wake[12] phase transitions.

METHODS

Participants

This cross-sectional study was conducted at the Institute of Neurological Sciences of Bologna (IRCCS Istituto delle Scienze Neurologiche di Bologna) between May 2018 and March 2019. Twenty subjects with manifest HD (13 females; mean age=56.45±16.94) were consecutively recruited during their scheduled follow-up visit at the Outpatient Clinic for Movement Disorders of the Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy. Inclusion criteria included a positive genetic test for HD, age over 18 years, a negative history for daily overuse of coffee (more than 3/day), alcohol (more than 2 units/day) and cigarettes (more than 15/day) and the absence of relevant concomitant pathologies, including sleep disorders and psychiatric diseases such as schizophrenia, major depressive and/or anxiety disorders according to DSM 5 criteria. The disease stage was defined based on the Total Functional Capacity subscore of the Unified Huntington's Disease Rating Scale (stage I included scores from 11 to 13; stage II: from 7 to 10; stage III: from 3 to 6; stage IV: 1 or 2; and stage V: score 0). Cognitive status was assessed using Verbal Fluency (VF), Symbol-Digit Modalities Test (SDMT), Stroop Word (W) and Color (C) tests and Clinical Dementia Rating (CDR). Psychopathological features were assessed by using the Problem Behaviours Assessment for HD - Short Version (PBA-s), including depression/anxiety symptoms, irritability, apathy, psychotic symptoms and executive functions. Clinical and socio-demographic data (age at evaluation, age and first symptom at onset, disease duration, medication status) were ascertained during an interview and collected in a database. All patients underwent home-based actigraphy recording for seven consecutive days.

A sample of 20 healthy controls (HC, 13 females; mean age=54.5±15.57) were recruited at the Laboratory of Applied Chronopsychology of the Department of Psychology "Renzo Canestrari", University of Bologna (Bologna, Italy). HC were recruited if they reported scores within the normal range at the Italian version[13] of the Mini Sleep Questionnaire[14] as well as if they referred to not take any medications able to interfere with sleep.

The samples of patients with HD and HC were balanced for sex (χ^2_1=0; p=1) and age (t_{38}=.38; p=.71).

The study was approved by our local Ethical Committee (Comitato Etico Interaziendale Bologna-Imola, CE-BI, code 17134/2017). All subjects gave written informed consent to the study protocol, in agreement with the Convention of Helsinki.

Actigraphy

In the current study, the actigraph model Micro MotionloggerWatch (Ambulatory Monitoring, Inc., Ardsley, NY, USA) was used. The actigraph is equipped with a thermal sensor that allows to understand when the device is no longer worn. The hardware consists of a triaxial accelerometer presenting sensitivity equal to or higher than 0.01 g. The sampling frequency is 32 Hz, with filters set to 2-3 Hz. The software Motionlogger Watchware (Ambulatory Monitoring, Inc., Ardsley, NY, USA) was used to initialize the actigraphs in zero crossing mode to collect motor activity data in 1 min epochs.

Actigraphic sleep/wake parameters

The Action W 2.7.1150 software (Ambulatory Monitoring, Inc., Ardsley, NY, USA) was used in order to calculate the actigraphic sleep/wake parameters of each recording day. Applying validated algorithms,[15] each epoch is classified as sleep or wake.

As regards the time spent in bed, the following actigraphic parameters were computed (see **Supplementary Figure 1**): 1) bedtime (BT), the clock time the participants went to bed trying to fall asleep; 2) get-up time (GUT), the clock time the participants got out of bed after a night's sleep; 3) time in bed (TIB), the time in minutes between BT and GUT; 4) midpoint of sleep (MS): the clock time that splits in half the TIB; 5) sleep motor activity (SMA), motor activity counts in 1 min epochs during the assumed sleep; 6) sleep onset latency (SOL), the time interval, in minutes, between the BT and the sleep onset (SO, first block of 20 consecutive sleep epochs including no more than one epoch of wake); 7) total sleep time (TST), the sum in minutes of the sleep epochs between SO and GUT; 8) wake after sleep onset (WASO), the sum in minutes of the wake epochs between SO and the last sleep offset; 9) sleep efficiency (SE), the ratio between TST and TIB multiplied by 100; 10) awakenings (AWK), number of awakenings; 11) number of awakenings longer than 5 minutes (AWK>5).

With reference to the time spent out of bed, the following actigraphic parameters were calculated: 1) diurnal motor activity (DMA), motor activity counts in 1 min epochs during the assumed wake period; 2) diurnal total sleep time (DTST), the sum in minutes of sleep epochs in the time interval between GUT and BT; 3) diurnal sleep episodes (NAP), number of sleep episodes occurring between GUT and BT; 4) number of diurnal sleep episodes lasting more than 5 minutes (NAP>5); 5) duration in minutes of the longest sleep episode (NAPD).

24h motor activity pattern

For each participant the software Action 4 (Ambulatory Monitoring, Inc., Ardsley, NY, USA) was used to extract the motor activity counts, minute by minute, over the 24h of each recording day in order to depict the mean 24h motor activity pattern.

Falling asleep patterns

For each recording day, using the data about bedtime obtained through the Action W 2.7.1150 software (Ambulatory Monitoring, Inc., Ardsley, NY, USA) and the output of the software Action 4 (Ambulatory Monitoring, Inc., Ardsley, NY, USA) on motor activity counts, minute by minute, over the 24h, we analyzed the falling asleep patterns extracting the motor activity counts from 120 minutes prior to bedtime up to 120 minutes after bedtime.

Awakening patterns

For each recording day, using the data about get-up time obtained through the Action W 2.7.1150 software (Ambulatory Monitoring, Inc., Ardsley, NY, USA) and the output of the software Action 4 (Ambulatory Monitoring, Inc., Ardsley, NY, USA) on motor activity counts, minute by minute over the 24h, we explored the awakening patterns extracting the motor activity counts from 120 minutes prior to the get-up time up to 120 minutes after the get-up time.

Procedure

Participants wore the actigraph around the non-dominant wrist for seven consecutive days. Furthermore, they were requested to push the event-marker button of the actigraph when they went to bed and switched off the lights attempting to sleep (bedtime), when they switched on the light after a night's sleep and got out of bed (get-up time) in addition to each time they removed and re-wore the device (for example, when they took a shower). Finally, they also filled in the sleep diary, day by day within 30 minutes from the get-up time. When participants forgot to push the event-marker button, the scorer referred to the replies to the questions on bedtime and get-up time reported in the sleep diary and simultaneously interpreted the information coming from the thermal sensor of the actigraph, in order to correctly define the time spent in bed for the actigraphic analyses.

Data analysis

To detect any significant differences between patients with HD and HC in the actigraphic sleep/wake parameters, a set of unpaired sample t-tests was performed with group (patients with HD and HC) as the independent variable and each actigraphic parameter as the dependent variable. Because of the multiple comparisons, the Bonferroni correction was applied leading to consider as significant p-values less than .003.

In order to investigate any differences in the 24h motor activity pattern between patients with HD and HC, the Functional Linear Modeling (FLM)[8-10] was applied. FLM extends standard linear regression to the analysis of smooth functions, which represent the 24h motor activity patterns. FLM replaces discrete activity values measured at each time unit by a function to model the data and reduce variability. The function represents the expected activity value at each time point measured. In FLM, the model regression coefficients and error term are functions. However, the comparisons between the two groups at each time point are non-independent and a correction for multiple testing is not needed. FLM does not test simultaneously different hypotheses, it tests each hypothesis separately (using different statistical tests). The p-value is calculated by counting the proportion of permutation F-values greater than the F-statistics for the observed pairing. In this study, the global critical value (obtained by the global test that yields a single number, which is the proportion of the maximized F-values from each permutation) is considered to identify the time points where differences between groups emerge because it represents a more conservative test.

The same statistical approach was used to detect a potentially different falling asleep pattern, regardless of the time the bedtime occurred, between patients with HD and HC. To this aim, FLM compared the functional forms of motor activity of patients with HD and HC within the time interval defined by the two hours prior to the bedtime and the two hours after the bedtime.

FLM was also applied to highlight a potentially different awakening pattern, regardless of the time the awakening occurred, between patients with HD and HC. To this end, FLM compared the functional forms of motor activity of patients with HD and HC within the time interval defined by the two hours prior to the get-up time and the two hours after the get-up time.

RESULTS

Patients

A total of 20 patients with manifest HD, with a genetically confirmed diagnosis, were recruited in our study (see **Supplementary Table 1**). The age of our population was of 56.45±16.94 years (mean ± SD) and the median CAG repeats on mutant allele was of 43 triplets (range: 38-60). The patients were evaluated clinically no more than a week before the study entry.

Our study included 10 patients in Stage I (TFC 11-13), 6 patients in Stage II (TFC 7-10) and 4 patients in Stage III (TFC 3-6).

Nine out of 20 patients (45%) showed cognitive involvement, scoring between 0.5-1 in the CDR scale (mild dementia). Fourteen (70%) showed anxiety and/or depressive symptoms, but none of those fulfilled the criteria of major depression.

Seven out of 20 patients (35%) were on neuroleptics, 4 (20%) on benzodiazepines, 9 (45%) on antidepressants. During the actigraphic recordings, patients continued taking their therapy to avoid any interference with their normal sleep-wake rhythm.

Actigraphic sleep parameters

Patients with HD presented significantly lower sleep efficiency (SE) and higher time in bed (TIB), sleep onset latency (SOL), wake after sleep onset (WASO), AWK and AWK > 5 compared to HC (**Table 1**). In addition, they showed a tendency towards a higher nocturnal sleep motor activity (SMA) compared to controls.

Actigraphic wake parameters

Regarding the diurnal time, no significant differences were observed between patients with HD and HC (**Table 1**).

	HD patients	*HC*	*Statistics*	
			$t_{(38)}$	p^a
Sleep				
BT	*23:05 ± 1:57*	*23:56 ± 1:03*	*-1.70*	*.10*
GUT	*08:16 ± 1:18*	*07:23 ± 1:08*	*2.26*	*.03*
TIB	*548.86 ± 108.09*	*447.26 ± 58.92*	*3.69*	*<.001*
MS	*03:40 ± 1:23*	*03:40 ± 0:59*	*.04*	*.97*
SMA	*24.17 ± 15.75*	*12.28 ± 4.72*	*3.23*	*.003*
SOL	*21.61 ± 13.20*	*10.46 ± 4.27*	*3.59*	*<.001*
TST	*437.36 ± 103.25*	*417.49 ± 58.29*	*.75*	*.46*
WASO	*85.80 ± 51.31*	*17.23 ± 15.94*	*5.71*	*<.001*
SE	*79.65 ± 8.95*	*93.32 ± 4.30*	*-6.16*	*<.001*
AWK	*19.39 ± 9.20*	*6.89 ± 3.03*	*5.77*	*<.001*
AWK>5	*10.84 ± 5.63*	*3.31 ± 3.11*	*5.24*	*<.001*
Wake				
DMA	*190.85 ± 65.90*	*203.74 ± 25.72*	*-.82*	*.42*
DTST	*66.87 ± 56.02*	*37.31 ± 33.67*	*2.02*	*.05*
NAP	*5.58 ± 4.36*	*4.52 ± 4.49*	*.76*	*.45*
NAP>5	*4.03 ± 3.09*	*1.93 ± 1.94*	*2.57*	*.01*
NAPD	*28.44 ± 19.21*	*17.94 ± 15.82*	*1.89*	*.07*

Table 1. *Actigraphic sleep/wake measures observed in patients with Huntington disease (HD) and healthy controls (HC). Means, standard deviations, and statistics are reported with significant comparisons highlighted in italics.*

Note: BT=bedtime (h:min); GUT=get-up time (h:min); TIB=time in bed (min.); MS=midpoint of sleep (h:min); SMA=sleep motor activity (counts); SOL=sleep onset latency (min.); TST=total sleep time (min.); WASO=wake after sleep onset (min.); SE=sleep efficiency (%); AWK=awakenings (number); AWK>5=awakenings lasting more than 5 minutes (number); DMA=diurnal motor activity (counts); DTST=diurnal total sleep time (min.); NAP=diurnal sleep episodes (number); NAP>5=diurnal sleep episodes lasting more than 5 minutes (number); NAPD=duration of the longest sleep episode (min.).

[a] *Because of the multiple comparisons, the Bonferroni corrected p-value was less than .003.*

24h motor activity patterns

Comparing the 24h motor activity patterns of patients with HD and HC, a significantly higher motor activity was observed in patients with HD than HC between around 2:15 and 4:00 am (**Figure 1**).

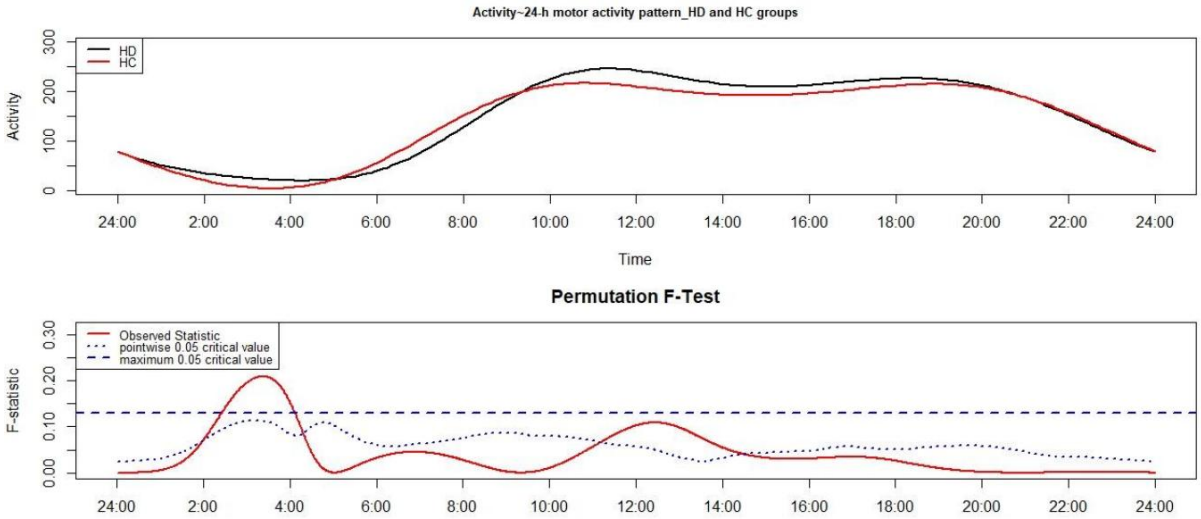

Figure 1. *Output of the Functional Linear Modeling (FLM) on the comparison between the 24h motor activity patterns of patients with HD and HC. The upper panel shows the functional forms of the 24h motor activity patterns observed in both groups. The lower panel reports the results of the statistical analyses aimed at comparing the motor activity between groups, minute-by-minute, over the 24h. Significant differences are observed when the red solid line (observed statistics) is above the blue dashed line (the global test of significance).*

Falling asleep patterns

The falling asleep pattern was significantly different between patients with HD and HC (**Figure 2**). More in detail, regardless of the specific time-of-day when the bedtime occurred, patients with HD presented significantly higher motor activity than HC starting from around 40 minutes prior to bedtime until 20 minutes after the bedtime. Furthermore, motor activity of patients with HD was significantly higher than motor activity of HC between about 40 and 75 minutes as well as between around 90 and 120 minutes after the bedtime.

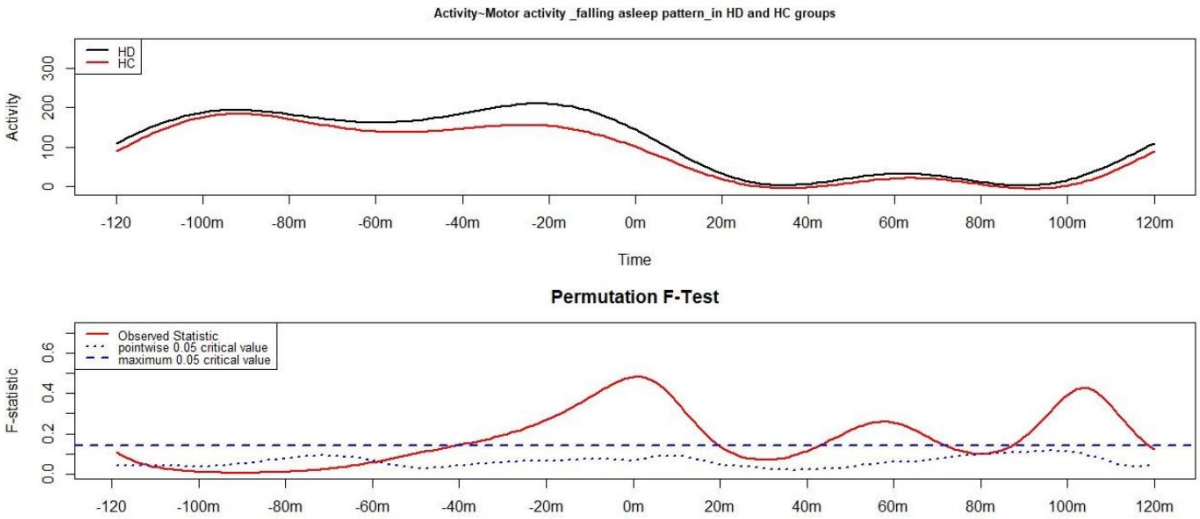

Figure 2. *Results of the Functional Linear Modeling (FLM) applied to the comparison of the motor activity, minute by minute, over the two hours prior to the bedtime and the two hours after bedtime, regardless of the specific time-of-day the bedtime occurred. The upper panel shows the functional forms of the motor activity patterns observed in patients with HD and HC starting from 120 minutes before (-120m) bedtime (0m) until 120 minutes after (120m) bedtime. The lower panel reports the results of the statistical comparisons minute by minute between groups in motor activity over this time interval, with significant results observed when the red solid line (observed statistics) is above the blue dashed line (global test of significance).*

Awakening patterns

As reported in **Figure 3**, the awakening pattern was significantly different between patients with HD and HC. More in detail, regardless of the specific time-of-day when the get-up time occurred, patients with HD presented significantly higher motor activity than HC starting from around 20 minutes prior to the get-up time until 50 minutes after the get-up time.

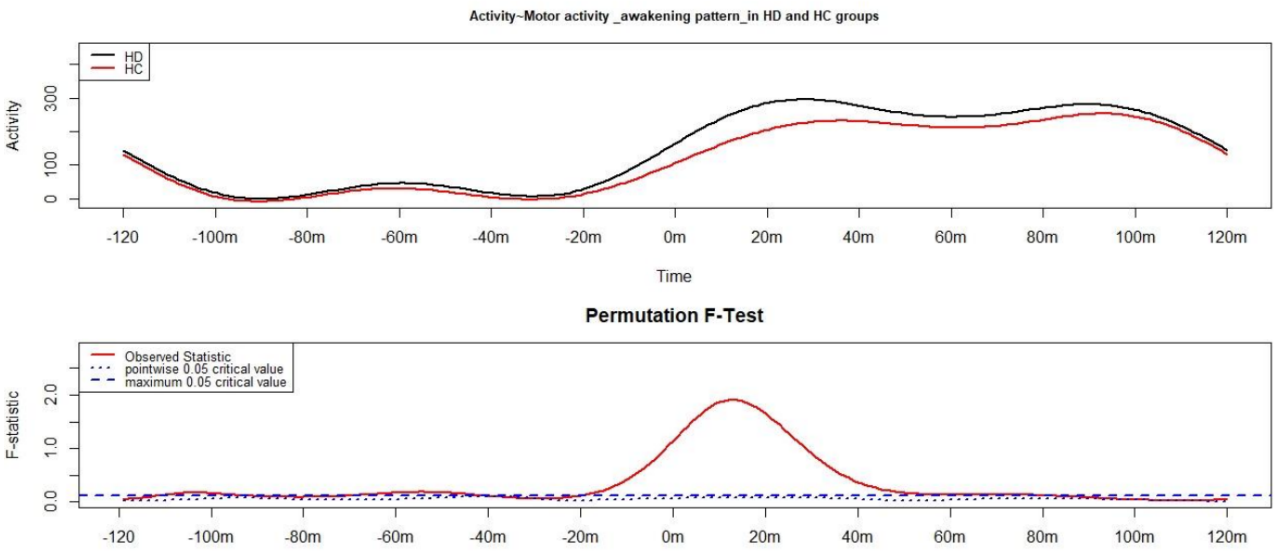

Figure 3. *Results of the Functional Linear Modeling (FLM) applied to the comparison of the motor activity, minute by minute, over the two hours prior to the get-up time and the two hours after the get-up time, regardless of the specific time-of-day the get-up time occurred. The upper panel shows the functional forms of the motor activity pattern observed in patients with HD and HC starting from 120 minutes before (-120m) the get-up time (0m) until 120 minutes after (120m) the get-up time. The lower panel reports the results of the statistical comparisons minute by minute between groups in motor activity over this time interval, with significant results observed when the red solid line (observed statistic) is above the blue dashed line (global test of significance).*

DISCUSSION

The one-week actigraphic monitoring provided objective evaluation for a prolonged time, allowing us to obtain reproducible data in several days of monitoring.[16] In line with data from the literature, our study conducted on early-mid stage HD patients confirmed a decreased sleep efficiency and a significant increase in the number of awakenings and time spent awake after sleep onset as characteristic sleep features in HD patients in comparison to a control group.[1,2,17] Sleep alterations in HD may occur not only in the advanced disease stages, but also in pre-manifest or in early stages of the disease. On the other hand, in HD patients, a progressively worsening sleep disorder was shown to be independent of CAG repeat length.[1] Sleep impairment has different determinants, including neurodegeneration, high nocturnal motor activity, the presence of concomitant cognitive deficits and psychiatric disorders, especially depression and anxiety. As in other degenerative diseases, such as Alzheimer disease and Parkinson disease, also in HD sleep structure disruption could be a direct consequence of

neurodegeneration as several brain areas—including the network involved in sleep organization and circadian oscillation—are affected by neurodegenerative processes.[17] The complex network involved in sleep-wake regulation is known to have a caudorostral organization, from reticular formation controlling the vigilance levels to rostral pons and caudal midbrain controlling REM sleep and thalamus controlling NREM sleep.[18] Any alteration that intervenes to interrupt this network causes alterations in the sleep structure.

As described in the literature, our patients showed a greater nocturnal motor activity in comparison with controls.[5,6] The relationship between higher nocturnal motor activity in HD patients and sleep remains a common matter of debate. Recent polysomnographic studies documented complex movements of upper and lower limbs, trunk, and often the whole body, with some periodicity during nighttime, associated with arousals in HD patients.[19,20] However, the discussion on the precise direction of this movements-arousals association is still ongoing: in particular, it has not yet been clarified if arousals, due to the intrinsic sleep fragmentation of HD, lead to the reappearance of usual daytime dyskinesias, or if sleep-related movements, such as possible atypical periodic movements, disrupt sleep continuity leading to a higher number of arousals. Moreover, the actigraphic estimates in HD patients should be used with caution due to the reduced agreement, previously reported in literature,[21] between wakefulness during the night detected through actigraphy and concurrent electroencephalographic recordings in HD patients. In particular, the actigraphy may have overestimated WASO and AWK due to abnormal movements in sleep in HD patients.

In our study, less than half of the patients had cognitive impairment. In HD patients, cognitive decline and psychiatric symptoms have been strongly correlated with a disruption of frontocortical–striatal and frontocortical–amygdala loops.[22] Frontal cortex degeneration is involved in neurochemical pathways regulating sleep and its degeneration may be one pathophysiological cause of concomitant sleep alterations and circadian dysregulation. Furthermore, none of our patients had a diagnosis of depressive disorder according to diagnostic criteria, while in the literature it is well-established that depressed HD patients had less preserved psychomotor functions and longer sleep time.[23]

Daytime overall motor activity detected by actigraphic monitoring showed no differences between HD patients and healthy controls, as previously reported by some but not all authors.[6] Some studies reported lower daytime motor activity in HD patients, but this ambiguous result is probably related to the particular HD subpopulations studied, with different ages and disease severity. In addition, the use of neuroleptic medications in HD patients was shown to reduce overall daytime activity in a 5-day actigraphic monitoring study[24] and depression itself is a

condition related to lower daytime activity in HD patients as demonstrated in a meta-analysis on 16 studies.[23] Moreover, concerning our results, it is not possible to exclude that the decreased overall motor activity during daytime in HD patients may be masked by registering excessive choreatic movements.

Our HD patients only showed a significant trend in the number of naps during daytime in comparison to controls. In two studies on 68 patients the authors reported more daytime sleepiness in HD patients both at pre-manifesting and early stages of the disease than healthy controls by using Epworth Sleepiness Scale (ESS).[25,26] The differences between our objective actigraphic findings and the subjective data reported in previous studies may be explained by the different type of tool used. A subjective tool (such as ESS) in patients with neurodegenerative disorders may be challenging due to the presence of possible confounders, such as impaired cognition, presence of anxiety and depression, and the influence of treatment with drugs with central effects.

Although previous studies showed a comparable 24h total motor activity in HD patients and healthy controls, by applying for the first time a new technique for actigraphic data analysis, we pointed out that motor activity in HD patients differed from controls in three specific periods during the 24 hours, particularly at falling asleep and awakening.[6] Our HD patients showed higher motor activity around bedtime (from 40 minutes prior until 120 minutes after), regardless of the specific time-of-day when the bedtime occurred. This specific moment of the transition from wakefulness to sleep, named "pre-dormitum", is characterized by gradual changes in cortical electroencephalographic (EEG) activity and in postural muscle tone.[18] Probably due to the degeneration of the network involved in sleep onset and stable maintenance, early-mid stage HD patients could show a prolonged pre-dormitum period with associated higher motor activity. Similarly, the high motor activity in HD patients around the awakening may be related to sleep-wake regulation network instability as a consequence of neurodegeneration.

The significantly higher motor activity in patients with HD than in HC between around 2:15 and 4:00 am opens the way to some speculations. Polysomnographic studies have documented that HD patients spend less time in deep sleep (NREM3 sleep, N3). In 3 studies on 71 patients, HD subjects had a lower percentage of N3 sleep and a higher percentage of NREM1 sleep compared to healthy controls during the first part of the night.[19,27] A lower representation of N3 sleep in HD patients may lead to an increase of nighttime movements especially in the first part of the night, when N3 sleep physiologically predominates.[28] On the other hand, the increase in motor activity in HD patients at that particular time of the night could be the result of a circadian rhythm dysregulation. Circadian rhythm disturbances in HD could directly depend on a

pathology within the hypothalamic suprachiasmatic nucleus (SCN) possibly due to an abnormal interaction of mutant huntingtin with huntingtin-associated protein 1 (Hap-l), which is more abundantly expressed in the hypothalamus than in other brain regions.[5] These abnormalities were accompanied by a marked disruption of expression of the circadian clock genes in the SCN and other parts of the brain (e.g., motor cortex and striatum).[5] Disruption of the circadian rhythm is also reinforced by an increased morning cortisol output, reduced mean and acrophase concentrations, temporal spread of melatonin release[29,30] and by the loss of circadian blood pressure variability.[27] In transgenic animal models of HD, the disturbed night-day circadian rhythmicity worsens with disease progression indicating reduced diurnal patterns of activity, heart rate variability, and body temperature variability.[31,32] Moreover, PET and voxel based morphometric MRI studies documented a direct neuroimaging abnormality of HD patients' hypothalamus that occurred at least a decade before the clinical diagnosis.[33] In addition, in the pre-manifest stage of HD some authors documented an increased early cortisol production, suggesting an increased hypothalamic-pituitary-adrenal axis activity and a reduction of nocturnal concentrations, acrophase and amplitude of melatonin, indicating a potential phase shift in melatonin peak.[7-9] Thus, the occurrence of higher motor activity between 2:15 and 4:00 am in our patients may be related to a dysfunctional hormone release. High plasmatic levels of cortisol increased cortico-spinal tracts excitability,[34] possibly facilitating the emergence of movements during the night; in animal models, melatonin increases GABAergic tone facilitating the occurrence and the stabilization of sleep and suppressing sleep-related motor activity. A reduction in melatonin's concentration in HD patients may facilitate the emergence of motor activity by reducing overall GABAergic inhibition.[35]

Finally, it is impossible to exclude that a higher motor activity around bedtime may be explained by an increased in chorea due to routinary evening activities, as worsening of chorea with voluntary movements is a known phenomenon.

One of the strengths of our study is that the studied population consisted of HD patients homogeneously in an early and middle stage of the disease, in the absence of dementia or psychiatric disorders. We compared our patients with a control group of healthy subjects matched for age and sex; the one-week monitoring by means of actigraphy allowed us to obtain reproducible data in several days of monitoring.[16] Finally, we applied an innovative method of analysis of the actigraphic data, i.e., FLM, whose strength relies on determining "when", along the 24h scale, the two groups differ by directly representing data as directly comparable continuous functions.[8-10] At the same time, our study has some limitations. First, due to the strict exclusion criteria, we included a small population of patients; we did not measure any

circulating markers of the circadian clock (e.g., melatonin or cortisol levels) to provide an integration with motor activity patterns; for ethical reasons, we did not perform a complete washout of current medications of our patients; therefore, we were not able to exclude a possible influence of medications on sleep and motor activity; finally, employment status differed between HD patients (mostly unemployed) and HC (employed) and it may have had an impact on get up patterns and daytime sleep patterns.

CONCLUSIONS

Together with a reduction of sleep efficiency, a one-week 24h rest-activity actigraphic recording in early-mid HD patients documented a specific motor activity pattern characterized by a higher motor activity at falling asleep, awakening and between 2:15 and 4:00 am. This pattern potentially constitutes a signature of HD, especially in the early phases, indicating intrinsic circadian abnormalities of the disease. Further, videopolysomnographic studies in HD patients at different disease stages could be performed with particular attention to the sleep-wake transition, during the first part of the night and at awakening to confirm our data, characterizing the nature of the movements and their relationship with sleep stages including the possible changes during the course of the disease. There is growing evidence that sleep and circadian disorders are present in HD population and, correspondingly, increasing numbers of patients are seeking help for their sleep problems, particularly in the early stages. Furthermore, by increasing the number of patients, it would be interesting to compare HD patients with patients with other neurodegenerative diseases, such as Parkinson's disease, to see whether our findings are unique to HD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available within the article and its supplementary material.

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