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Huntington's disease : hypothalamic, endocrine and metabolic aspects

Aziz, N.A.

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Chapter 4

Sleep and circadian rhythm alterations correlate with depression and cognitive impairment in Huntington's disease

N. Ahmad Aziz, MSc[1]; Galia V. Anguelova, BSc[1]; Johan Marinus, PhD[1]; Gert Jan Lammers, MD, PhD[1]; Raymund A.C. Roos, MD, PhD[1]

Parkinsonism Rel Disorders (accepted for publication)

[1] *Department of Neurology, Leiden University Medical Center, Leiden, the Netherlands*

ABSTRACT

Objective: Sleep disturbances are a prominent feature of Huntington's disease (HD) and can substantially impair patients' quality of life. However, sleep complaints and their association with other symptoms and signs of HD have not yet been assessed in large groups of patients or premanifest mutation carriers. Therefore, we aimed to (1) delineate the nature of subjective sleep disturbances, (2) identify important predictors of sleep impairment, and 3) evaluate the usefulness of the SCOPA-SLEEP questionnaire, a short instrument that can assess both daytime sleepiness (DS) and night-time sleep (NS), in a group of HD patients and premanifest mutation carriers. *Subjects & methods:* Using standardized questionnaires, DS, NS and depressed mood were assessed in 63 HD patients, 21 premanifest mutation carriers and 84 controls. *Results:* NS impairment was significantly more prevalent in HD patients compared with controls (58.1% *vs.* 34.9%, p=0.012), but DS was not (12.7% *vs.* 7.9%, p=0.560). Depression was the only independent predictor of NS impairment in HD patients, accounting for 19% of the variance. Compared with controls, both sleep onset latency and wake-up time were significantly delayed in HD patients. Moreover, in HD patients, later wake-up time was significantly associated with cognitive score (r=-0.43), total functional capacity (r=-0.54) and depressive symptoms (r=+0.47). The SCOPA-SLEEP questionnaire was a reliable and valid instrument for application in HD patients. *Conclusions:* HD is primarily accompanied by NS disturbances and a delayed sleep phase syndrome-like phenotype, which are associated with depression and lower cognitive as well as functional performance.

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat sequence in the gene encoding the protein huntingtin.[1] The disease is characterized by motor impairment, cognitive deterioration, behavioral problems and progressive weight loss.[1,2] However, disturbed sleep is also a prominent feature of the disease, substantially impairing the quality of life of both patients and caregivers.[3] Polysomnographic and actigraphic findings in small groups of HD patients have documented an increased sleep onset latency, sleep fragmentation and frequent nocturnal awakenings, reduced sleep efficiency, delayed and shortened rapid eye movement (REM) sleep, increased periodic leg movements, as well as circadian rhythm disturbances.[4-10] However, the exact nature of sleep complaints as well as their association with other symptoms and signs of the disease have not yet been studied in large groups of HD patients or premanifest mutation carriers.

Recently, it was shown that the sleep-wake disturbances in HD patients are partly reproduced in the transgenic R6/2 mouse model of the disease.[9] Importantly, cognitive decline and decay of learning in R6/2 mice were alleviated by pharmacological imposition of sleep, suggesting that a similar strategy might be of benefit to HD patients.[10,11] Moreover, apart from affecting alertness, attention, memory and executive control, lack of sleep is also considered a risk factor for developing depression.[12] Conversely, recent clinical findings indicate that treatment of depressive symptoms may reduce sleep disruption in a number of neurodegenerative and extrapyramidal conditions, especially Alzheimer's and Parkinson's disease.[13,14] However, in order to provide rationale for the evaluation of comparable approaches in HD, it is first necessary to assess the association between sleep disruption and both cognitive impairment and depressive symptoms in HD patients.

Characterization of sleep problems in HD patients as well as the identification of contributing factors are of paramount importance for the design and implementation of novel therapeutic strategies. Therefore, the aims of the present study were to (1) delineate the nature of subjective sleep disturbances in HD patients and premanifest mutation carriers in comparison with non-mutation carrying control subjects, and (2) to assess the relation between sleep and various clinical characteristics, including cognitive impairment and depressive symptoms, in order to identify important predictors of sleep disturbances in HD patients. In addition, we evaluated the reliability and validity of the SCOPA-SLEEP questionnaire, a very short instrument that can assess both daytime sleepiness and night-time sleep,[15] in patients with HD.

METHODS

Design and participants

HD patients and premanifest mutation carriers were recruited from the outpatient clinic of the department of Neurology of the Leiden University Medical Center (LUMC) between June 2007 and December 2008. Control subjects were recruited over the same period and were randomly selected non-mutation carrying family members, partners or acquaintances of participating patients, employees at our department or their acquaintances. Exclusion criteria for both groups were the diagnosis of a preexistent primary sleep disorder or a disease of the central nervous system unrelated to HD. All patients and premanifest mutation carriers were

seen once or twice a year as part of their regular care. Three weeks before the scheduled yearly appointments two identical postal surveys containing standardized questionnaires were sent to these subjects. The forms in one of the surveys were completed by the patients or premanifest mutation carriers themselves (or by the primary caregivers on their behalf) while, whenever possible, the other survey had to be completed by a non-mutation carrying family member, the partner or an acquaintance. The patients and premanifest mutation carriers brought their survey to the scheduled appointment and simultaneously provided contact data for the control subject. When questionnaires were not fully completed or were not received within one month, subjects were reminded by phone. The study protocol was approved by the medical ethics committee of the LUMC and all participants provided written informed consent.

Measurement instruments

The clinical condition of HD patients was assessed according to the motor, cognitive, behavioral and functional subscales of the Unified Huntington Disease Rating Scale (UHDRS).[16] Premanifest status was defined as a score of <5 on the UHDRS motor subscale. The following standardized instruments were used in all subjects to assess sleep disturbances and depressive symptoms: Epworth's Sleepiness Scale (ESS) [range (0-24)][17], the Pittsburgh Sleep Quality Index (PSQI) [range (0-21)][18], the SCOPA-SLEEP[15], and the Beck Depression Inventory (BDI) [range (0-63]. The ESS evaluates daytime sleepiness; subjects must rate the chance of dozing off under eight different situations.[16] The PSQI primarily evaluates night-time sleep, consisting of 19 self-rated questions and five questions rated by the bed partner or roommate. The latter five questions are used for clinical information only and are not tabulated in the scoring of the PSQI.[18] Scores are first grouped in seven domains which assess subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.[18] The ESS and PSQI scales were included as they are frequently used and have previously been applied in small groups of HD patients.[6] The SCOPA-SLEEP questionnaire consists of two parts, one assessing daytime sleepiness (SCOPA-DS [range (0-18)]) and the other assessing night-time sleep (SCOPA-NS [range (0-15)]), and was originally developed for patients with Parkinson's disease.[15] However, since the items are not disease specific it can also be applied to other populations.[15] The SCOPA-SLEEP questionnaire was included as it is quick and easy to administer, and can assess sleep problems both during the day and night. In all questionnaires higher scores indicate more severe impairment.

Statistical Analysis

Mean differences between HD patients, premanifest mutation carriers, partners and other controls were assessed using χ^2-tests and one-way analysis of variance (ANOVA). Using multiple linear regression, group differences were also assessed after correction for differences in age, sex, body mass index (BMI), depressive symptoms and medication use (differentiating between sleep medications, antidepressants, neuroleptics and a rest group). In order to assess differences in usual bed and wake-up times (circular variables) between groups, we used pairwise Watson-Williams F-tests.[19] In HD patients, partial correlations, adjusting for age and sex, were used to assess the relation of each clinical variable — such as BMI, CAG repeat size and various UHDRS subscores — with sleep disturbances and timing. To identify which predictor variables were independently associated with sleep impairment in HD patients, we also used a stepwise regression procedure (an independent predictor

of sleep impairment is a variable that remains significantly associated with sleep impairment after adjustment for the effects of other significant predictor variables); this latter approach ensured minimization of type I error in identifying predictors of sleep impairment in HD. The reliability of all sleep scales in the patient group was assessed with Cronbach's α. Using Pearson's correlation coefficients, the construct validity of the SCOPA-SLEEP in HD patients was assessed by comparing responses on its day and night subdomains with those on the ESS and PSQI scales, respectively. All data are presented as means ± SD unless otherwise specified. All tests were two-tailed and values of $p < 0.05$ were considered significant. Programming was performed in SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL) and Oriana version 2.02 for circular statistics (Kovach Computing Services, Wales, UK).

RESULTS

Participants

In total, 168 subjects participated in this study (Table 1). Of these 84 were mutation carriers (63 had manifest HD and 21 were premanifest), and 84 were non-mutation carrying subjects. As sleep problems of the mutation carriers may affect the sleep quality of their partners, non-mutation carriers were further divided into a partner group and a group consisting of other controls (Table 1); in the remainder of this paper we will refer to these two groups as partners and controls, respectively. The four groups did not significantly differ with respect to age, sex, and BMI (all $p > 0.454$). Mutation carriers were significantly more depressed compared with non-carriers ($p < 0.001$), however, no difference between manifest and premanifest HD subjects was found ($p=0.106$). HD patients used significantly more antidepressants and neuroleptics compared to all other groups, while their use of sleep medication was significantly higher in comparison with controls only (Table 1).

Table 1. Characteristics of the study participants

	HD patients	Premanifest mutation carriers	Partners	Controls	*p*-value
No. of participants	63	21	21	63	-
Sex (% men)	46.0	42.9	47.6	41.3	0.972†
Age, mean (SD), yr	48.5 (10.7)	44.4 (8.7)	48.3 (9.1)	47.4 (10.5)	0.454‡
BMI, mean (SD)	25.3 (4.0)	25.5 (3.4)	25.5 (4.9)	25.3 (4.6)	0.991‡
BDI score, mean (SD)	11.8 (9.4)	8.1 (8.4)	4.3 (5.7)	4.4 (4.6)	<0.001‡
Sleep medication, n (%)	16 (25.4)	3 (14.3)	5 (23.8)	4 (6.3)	0.027†
Antidepressants, n (%)	23 (36.5)	1 (4.8)	4 (19.0)	1 (1.6)	<0.001†
Neuroleptics, n (%)	17 (27.0)	1 (4.8)	0	0	<0.001†
Other medication, n (%)	29 (46.0)	9 (42.9)	11 (52.4)	16 (25.0)	0.105†

†) χ^2-tests.

‡) One-way ANOVAs.

Legend: BDI = Beck's Depression Inventory; BMI = Body Mass Index; HD = Huntington's disease

Night-time sleep impairment

There were no significant differences in the global PSQI or SCOPA-NS scores between HD patients and premanifest subjects or between premanifest subjects and controls (Table 2). However, HD patients had significantly more night-time sleep impairment compared with controls as indicated by a higher percentage of patients having a PSQI score of 5 or higher (58.1% *vs.* 34.9%, p = 0.012), as well as by higher mean scores on both the PSQI and SCOPA-NS scales (Table 2). The differences in mean PSQI and SCOPA-NS scores remained significant when corrected for age, sex and BMI (β = 1.369, p = 0.037 for PSQI, and β = 1.44, p = 0.023 for SCOPA-NS (unstandardized coefficients)). In order to assess the nature of differences in sleep disturbances between groups, we also compared scores on the seven subdomains of the PSQI questionnaire separately (Table 2). HD patients experienced significantly more daytime dysfunction compared with premanifest subjects (p = 0.009). Moreover, compared with controls, HD patients had a significantly delayed sleep onset time, longer sleep duration, used more sleep medication and experienced more daytime dysfunction (Table 2). These findings remained significant when adjusted for age, sex and BMI (data not shown). Although there were no differences in usual bed time between groups, the usual wake-up time was significantly delayed in HD patients compared to both partners and controls (Table 2). There was also a trend towards a delayed wake-up time in premanifest subjects compared to controls (p=0.087).

Table 2. Sleep characteristics of the study population

	HD patients[†]	Premanifest mutation carriers[†]	Partners[†]	Controls[†]
PSQI global score	6.0 (3.9) [a]	5.2 (3.7)	5.3 (4.4)	4.7 (3.0)
Sleep quality	0.9 (0.9)	0.9 (0.9)	0.9 (0.9)	0.8 (0.6)
Sleep latency	1.3 (1.1) [a]	0.9 (0.9 (1.0)	1.0 (1.1)	0.8 (0.9)
Sleep duration	0.5 (0.8) [a, c]	0.8 (0.9)	1.1 (0.8)	0.8 (0.8)
Sleep efficiency	0.8 (1.1)	0.8 (1.1)	0.6 (1.0)	0.6 (1.0)
Sleep disturbances	1.2 (0.6)	1.1 (0.5)	1.1 (0.4)	1.1 (0.4)
Sleep medication	0.5 (1.1) [a]	0.3 (0.6)	0.5 (1.1)	0.1 (0.5)
Daytime dysfunction	0.8 (0.8) [a, b, c]	0.4 (0.5)	0.3 (0.4)	0.5 (0.6)
Usual bed time, hh:mm (circular SD)	22:54 (01:53)	23:32 (01:58)	23:28 (00:41)	23:14 (01:51)
Usual wake-up time, hh:mm (circular SE)	08:11 (01:36) [d, e]	07:40 (01:17)	07:07 (00:51)	07:06 (01:07)
SCOPA-NS	4.5 (4.0) [a]	3.4 (3.4)	3.8 (4.2)	3.1 (2.6)
ESS score	4.5 (4.2)	4.5 (3.9)	5.1 (3.7)	4.8 (3.5)
SCOPA-DS	3.1 (3.6)	2.6 (3.5)	2.8 (3.2)	2.5 (2.6)

[†]) All data are indicated as mean total or subscores (SD)
[a]) $p < 0.05$ with respect to controls (ANOVA)
[b]) $p < 0.05$ with respect to premanifest mutation carriers (ANOVA)
[c]) $p < 0.05$ with respect to partners (ANOVA)
[d]) $p < 0.01$ with respect to controls (Watson-Williams F-test)
[e]) $p < 0.01$ with respect to partners (Watson-Williams F-test)

Legend: ESS = Epworth's Sleepiness Scale; HD = Huntington's disease; PSQI = Pittsburgh Sleep Quality Index; SCOPA-DS = Scales for outcomes in Parkinson's disease-daytime sleep; SCOPA-NS = Scales for outcomes in Parkinson's disease-night-time sleep

As there were substantial differences in depressive symptoms between HD patients and controls, we repeated the analyses while correcting for the BDI score. After correction for the BDI score, differences in night-time sleep impairment between patients and controls became non-significant ($p > 0.912$ for differences in both PSQI and SCOPA-NS scores). This relation remained similar when also corrected for use of sleep medication, antidepressants, neuroleptics, and other drugs.

Daytime sleepiness

There were no significant differences in mean ESS or SCOPA-DS scores between groups (Table 2). Correction for age, sex, BMI, depression and medication use did not change the results. Only 12.7% of HD patients had a ESS score of 10 or higher as compared to 7.9% of controls ($p = 0.560$).

Reliability and validity of SCOPA-SLEEP in HD patients

The Cronbach's α for SCOPA-NS was 0.89, which was higher than that for PSQI, with the corrected item-total correlations ranging from 0.44 to 0.88 (Table 3). Moreover, the scores on the SCOPA-NS and PSQI scales were highly correlated ($r = +0.77$, $p < 0.001$). Using the PSQI cutoff value of 4/5 to discriminate between good and bad sleepers as an external criterion for SCOPA-NS resulted in an area under the receiver operating characteristic curve of 0.85, with an optimal cutoff at 3/4, yielding a sensitivity of 0.81 and a specificity of 0.77. The Cronbach's α for SCOPA-DS was 0.85, which was also higher than that of the comparable instrument ESS (Table 3). However, item 4 on the SCOPA-DS questionnaire had a corrected item-total correlation of zero as there were no HD patients who reported falling asleep while talking (Table 3), indicating that this question is not suitable for an HD population. The other corrected item-total correlations of SCOPA-DS were relatively high and ranged from 0.61 to 0.86 (Table 3). There was also a strong correlation between scores on the SCOPA-DS and ESS questionnaires ($r = +0.75$, $p < 0.001$). Applying the ESS cutoff value of 9/10 to detect excessive daytime sleepiness as an external criterion for SCOPA-DS led

Table 3. Reliability of sleep scales in HD patients

	Cronbach's α	Corrected item-total correlations
SCOPA-NS	0.89	0.44 – 0.88
1: Difficulty falling asleep		0.79
2: Been awake too often		0.81
3: Lying awake too long		0.88
4: Waking too early		0.44
5: Had too little sleep		0.76
PSQI	0.72	-0.01 – 0.74
SCOPA-DS	0.85	0.00 – 0.86
1: Falling asleep unexpectedly		0.76
2: Falling asleep while sitting		0.86
3: Falling asleep while watching TV		0.61
4: Falling asleep while talking		0.00
5: Difficulty staying awake		0.74
6: Falling asleep considered a problem		0.66
ESS	0.77	0.69 – 0.77

Legend: ESS = Epworth's Sleepiness Scale; HD = Huntington's disease; PSQI = Pittsburgh Sleep Quality Index; SCOPA-DS = Scales for outcomes in Parkinson's disease-daytime sleep; SCOPA-NS = Scales for outcomes in Parkinson's disease-night-time sleep

to an area under the receiver operating characteristic curve of 0.92, with an optimal cutoff at 3/4, yielding a sensitivity of 1.0 and a specificity of 0.78.

Predictors of night-time sleep and daytime sleepiness in HD patients

As SCOPA-SLEEP appeared more reliable than PSQI and ESS for application in HD patients, we used scores on SCOPA-NS and SCOPA-DS to assess the relation between various clinical measures and sleep impairment in HD patients. Of all clinical measures tested, only the BDI score significantly correlated with both night-time sleep impairment and daytime sleepiness (Table 4). Moreover, stepwise regression also identified BDI score as the only independent predictor of night-time sleep impairment, accounting for 19% of the variation in sleep disturbances. However, BDI score was not independently associated with daytime sleepiness in HD patients (Table 4).

Table 4. Correlates of night-time sleep impairment and daytime sleepiness in HD patients

	SCOPA-NS score		SCOPA-DS score	
	Correlation† (r ; p-value)	**Stepwise regression† (effect; SE)**	**Correlation† (r ; p-value)**	**Stepwise regression † (effect (SE))**
BMI, kg/m²	-0.11 (0.404)	-	-0.09 (0.494)	-
CAG repeat no.	0.23 (0.094)	-	0.125 (0.363)	-
TFC score	0.01 (0.956)	-	0.05 (0.691)	-
Motor score	0.02 (0.876)	-	-0.25 (0.058)	-
Behavioral score	-0.01 (0.943)	-	0.01 (0.936)	-
Cognitive score	-0.07 (0.685)	-	0.187 (0.282)	-
BDI score	0.38 (0.002) **	0.16 (0.071) *	0.27 (0.033) *	-

†) All results are corrected for age and sex.
*) $p < 0.05$; **$p < 0.01$.

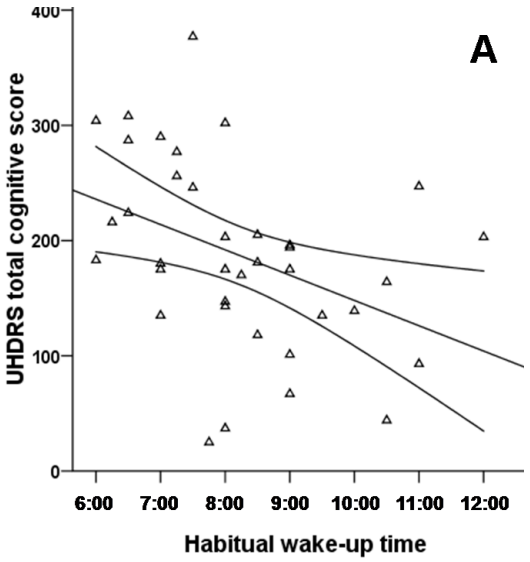
Legend: BDI = Beck's Depression Inventory; BMI = Body Mass Index; HD = Huntington's disease; ESS = Epworth's Sleepiness Scale; HD = Huntington's disease; PSQI = Pittsburgh Sleep Quality Index; SCOPA-DS = Scales for outcomes in Parkinson's disease-daytime sleep; SCOPA-NS = Scales for outcomes in Parkinson's disease-night-time sleep; TFC = Total Functional Capacity

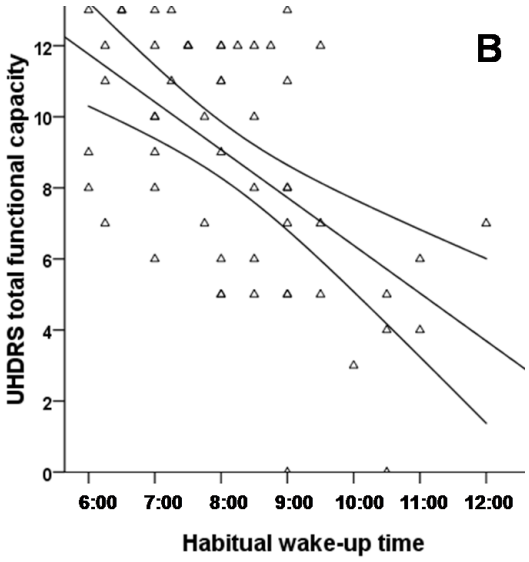
Circadian timing of sleep and cognition in HD patients

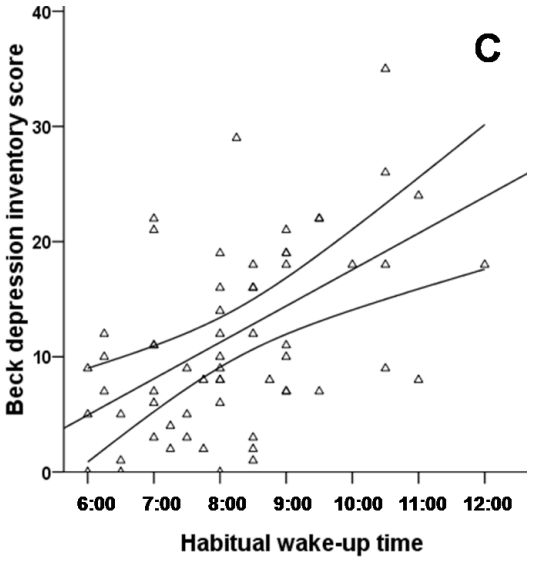
In order to assess whether circadian timing of sleep could affect cognitive functioning in HD patients, we examined the associations between usual bed and wake-up times and indices of cognitive performance in these subjects. UHDRS cognitive scores were available in 37 HD patients. Whereas the usual bed time was not significantly associated with the UHDRS cognitive scores, there were strong inverse associations between the usual wake-up time and the total cognitive score (r=-0.43, p=0.011; Figure 1A), and scores on the symbol digit modalities test (r=-0.45, p=0.003), and Stroop's colour naming (r=-0.47, p=0.005), word reading (r=-0.40, p=0.010), and interference (r=-0.56, p=0.001) tests. There was also a trend for the association between wake-up time and the verbal fluency test score (r=-0.30, p=0.076). In addition, the wake-up time was progressively

delayed with more severe total functional impairment (r=-0.54, p<0.001; Figure 1B) and more depressive symptoms (r=0.47, p<0.001; Figure 1C), but not with motor score, mutant CAG repeat or BMI (all p ≥ 0.083). As cognitive impairment and total functional capacity were highly correlated (r=+0.71, p<0.001), it was not possible to assess the association between wake-up time and cognitive score independent of functional impairment. Importantly, however, the association between wake-up time and total cognitive score remained significant even after correction for the BDI score (r=-0.34, p=0.047).

Figure 1. Habitual wake-up time is related to cognition, functional capacity and depression in HD patients. *Habitual wake-up time is delayed with more cognitive disability (A), more functional impairment (B), and more depressive symptoms (C) in patients with HD. The outer lines denote the 95% confidence interval of the mean.*







DISCUSSION

To our knowledge, this is largest cohort of HD patients and premanifest mutation carriers whose subjective sleep quality and daytime somnolence have been systematically assessed in relation to clinical symptoms and signs. Our findings indicate that while night-time sleep impairment is indeed more prevalent in HD patients, daytime sleepiness appears unlikely to be a major issue in HD. We also show that depression is the most important clinical predictor of sleep impairment in HD patients. Moreover, our findings suggest a delayed sleep phase syndrome (DSPS)-like circadian rhythm disorder in HD patients which appears to be associated with lower cognitive performance. These findings indicate that treatment of depressive symptoms and re-entrainment of the circadian rhythms could be evaluated as measures to enhance both sleep and cognitive functioning in HD patients.

In line with previous findings from a number of smaller-scale studies,[4-10] we found that night-time sleep disturbances are almost twice as common in HD patients compared to controls. Importantly, while the usual bed time did not differ between the groups, sleep onset latency as well as the usual wake-up time were both significantly delayed in HD patients, suggesting a phase-shift in the circadian sleep/wake cycle towards later hours. This finding is particularly interesting as recently we also found a delayed onset of the diurnal melatonin rise in a group of early-stage HD patients,[20] and is likewise suggestive of a DSPS-like circadian rhythm disorder. The pathophysiological basis of DSPS is presumed to lie within a slower endogenous clock with an abnormally long intrinsic circadian periodicity, resulting in a delayed phase position of the overt circadian rhythms, including those of melatonin and cortisol.[21] Interestingly, recently we reported an increased rate of early day cortisol production in HD patients as well, which may also be a manifestation of delayed circadian rhythms in HD.[22] Circadian rhythm disturbances in HD are likely to stem directly from pathology within the suprachiasmatic nucleus molecular oscillation, resulting from either the toxic effects of mutant huntingtin locally and/or arising from dysfunction of brain circuitry afferent to the suprachiasmatic nucleus,[9,10] but additional studies are needed to pinpoint the exact underlying cause. Although a delayed sleep onset has been described previously in smaller groups of HD patients[7,23,24], others have reported an earlier sleep onset and an advanced sleep phase.[4] However, the latter study included only 25 HD subjects (including 2 premanifest mutation carriers) and assessed bed and wake-up times during a single occasion in a laboratory setting, whereas we inquired about the usual bed and wake-up times in the previous month which are likely to be more representative of the habitual sleeping times.

Restoration of circadian rhythms by pharmacological imposition of sleep has been shown to improve cognition in R6/2 mice, suggesting that a similar strategy may be beneficial to HD patients.[10,11] As our findings are reminiscent of a DSPS-like phenotype in HD patients that is associated with cognitive impairment, another approach that may be evaluated in these patients is melatonin and/or bright light treatment at the appropriate times so as to phase advance the clock.[21,25,26] The administration of melatonin at the subjective dusk, and the use of bright light at the subjective dawn and avoidance of light in the subjective evening, could be used to phase advance the clock.[21,25] However, we could not detect a significant association between cognitive performance and night-time sleep disturbances in HD patients, suggesting that circadian rhythm alterations rather than sleep impairment *per se* are related to cognitive disability in these subjects. Nevertheless, the lack of an association

between night-time sleep and cognitive scores could also be due to the use of subjective measures of sleep quality in this study. As particularly REM sleep and deep sleep are thought to be implicated in neurobehavioral and cognitive performance,[27,28] and abnormalities have been reported in both of these sleep stages in HD,[4,7,29] future studies should focus on the exploration of the association between polysomnographic sleep measures and cognitive functioning in HD patients.

Depressed mood is highly prevalent in HD patients, with estimates ranging from 33 to 69%, and is an important determinant of their quality of life.[30,31] Here we demonstrate that depressed mood is also the most important clinical predictor of sleep disturbances in HD patients. This finding extends upon a previous report[6] by showing that the association between depressive symptoms and sleep impairment is independent from other symptoms and signs of the disease including motor, cognitive and functional impairment. However, due to the bidirectional association between depression and sleep disturbances, it is difficult to differentiate between cause and effect.[32] Depression is identified as the most frequent cause of chronic insomnia in both clinical and epidemiological studies,[33,34] and as many as three quarters of individuals with DSPS have a past or current history of depression.[35] Conversely, a number of longitudinal studies indicate that insomnia is a risk factor for developing both first-onset and recurrent depression.[32,36,37] The co-morbidity of depression and insomnia may be explained by changes in systems that are involved in both mood and sleep regulation, especially the serotonergic and noradrenergic systems.[38] Therefore, comprehensive treatment of depressive symptoms could help to resolve sleep complaints, whereas treatment of sleep problems and circadian rhythm alterations could help to bring about remission of depressive symptoms.[39] Thus, simultaneous treatment of depressive symptoms, sleep problems and circadian rhythm changes in HD patients should be evaluated in future studies as the effects may be synergistic with regard to both mood and sleep improvement.

In this study we also assessed the performance of the SCOPA-SLEEP questionnaire in HD patients. Both its night and day subdomains revealed a high degree of internal consistency in this population. Moreover, the correlation with other scales that assess similar constructs was strong, indicating good construct validity. As our findings primarily indicate night-time sleep problems in HD patients, particularly SCOPA-NS may prove to be valuable for application in these patients as it takes very little time to complete while its reliability and consistency in this population are actually higher than those of more extensive and time-consuming scales such as the PSQI.

In conclusion, our findings indicate mainly night-time sleep disturbances in HD patients and are suggestive of a DSPS-like phenotype associated with lower cognitive performance. Moreover, we identified depression as the principal predictor of sleep impairment in HD patients. As the mechanisms regulating sleep, mood and circadian rhythms show considerable overlap, comprehensive treatments aimed at alleviation of depressive symptoms and sleep impairment, as well as re-entrainment of circadian rhythms in HD patients may have synergistic effects and should be evaluated in future studies.

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