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Sleep and Huntington Disease: Polysomnographic Findings and Clinical Correlates

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Introduction

Huntington's disease (HD) is a progressive, fatal, neurodegenerative disorder caused by an abnormal expansion of a CAG repeat sequence in the gene encoding the protein huntingtin (HTT) on chromosome 4[1]. The cellular functions of HTT are still not completely understood[2-5]. Most available evidence suggests that HD arises predominantly from gain of a toxic function of mutant HTT[6, 7], that results in myriad molecular and pathophysiological features, including mitochondrial dysfunction, intracellular trafficking defects, abnormalities of protein folding and/or processing[8-10]. The disease is transmitted as a late onset autosomal dominant trait with age-dependent penetrance[11]. HD affects approximately 4–8 individuals per 100,000[12] and typically presents between 35 and 45 years of age, with an average survival of 15–25 years after disease onset[13]. Individuals at risk of inheriting the expanded CAG nucleotide can be identified before clinical onset by predictive genetic testing. Pathologic studies show a massive striatal neuronal cell death with up to 95% loss of GABAergic medium spiny projection neurons, which project to the globus pallidus and the substantia nigra, whereas large interneurons are selectively spared[14, 15]. However, neurodegeneration is more widespread, even long before the disease onset[16, 17], and includes a range of cortical and subcortical structures as well as a global brain shrinkage.

Clinical features of HD include progressive motor dysfunction, cognitive decline, and psychiatric disturbance[4, 18]. Motor signs include involuntary movements (chorea), that tipically worsens during walking, concentration and stress. With disease evolution chorea impairs gait balance and voluntary movements. The motor score of the Unified Huntington's Disease Rating Scale (UHDMRS) includes all motor systems affected and is a useful tool to assess patients and disease progression[1, 19]. A wide range of disorders of mental function and behavior occur at any time during the disease[20]. Cognitive changes are always present and can be present early in the disease[21-24]. The diagnosis is made on clinical examination, based on the

combination of motor, behavioural and cognitive symptoms in the setting of a family history of the disease[25]. A DNA test showing abnormal CAG expansion in the HTT gene can be used to confirm the diagnosis. Atrophy of the caudate nucleus on cerebral magnetic resonance imaging (MRI) supports the diagnosis. Although no curative treatment is available today, symptomatic treatment of chorea may be beneficial in some individuals, as it may have a favorable effect on motor function and quality of life[26, 27].

Sleep disturbances are frequent in HD patients. In a self or carer-completion questionnaire, 87.8% of patients reported sleep-related problems, rated as important by 61.7%; these disorders consisted mainly in restless limb movements, periodic jerks, nocturnal awakenings, daytime sleepiness and early awakening[28]. Disturbed sleep was a prominent feature of the advanced disease, substantially impairing the quality of life of both patients and caregivers[28]. Recently, Goodman et al[29] reported asymptomatic sleep changes since early stages, often long before motor disturbances. In this study, subjects remained significantly longer in bed, spent more time awake, had a marked reduction of deep sleep and rapid eye movement (REM), but none reported excessive daytime sleepiness (EDS). Moreover, patients had alterations in rest-activity cycles similar to those described in more advanced stages of the disease, suggesting that sleep abnormalities start early in the disease course and might represent crucial therapeutic target.

Polysomnography and actigraphy in small groups of HD patients have documented an increased sleep onset latency[30], sleep fragmentation and frequent nocturnal awakenings, reduced sleep efficiency, delayed and shortened REM sleep, increased periodic leg movements, as well as circadian rhythm disturbances[31-39]. Moreover, apart from affecting alertness, attention, memory and executive control, lack of sleep may also be considered as a

risk factor for developing depression[40]. However, sleep alterations as well as their association with other symptoms and signs of the disease have not been systematically studied in large groups of HD patients.

Aims of the study

The aims of the study were:

1) the primary aim of the study was to objectively evaluate sleep features in a large, single-center, population of HD patients by means of nocturnal, laboratory based video-polysomnography (V-PSG), and to correlate PSG findings with clinical parameters;

2) a secondary aim was to evaluate subjective sleep-related symptoms, and to test the clinical reliability of subjective sleep evaluation, based on a battery of sleep and psychometric questionnaires, by comparing the results with those obtained with the gold standard diagnostic tool, namely V-PSG;

3) finally, we decided to evaluate the EEG modifications in HD patients during the sleep-wake cycle, by means of the exact LOw REsolution Tomography (eLORETA) software and to evaluate correlations indexes between EEG power spectra and clinical features.

Patients and Methods

Patients

A cohort of 30 consecutive adult HD patients was enrolled, 16 women and 14 men, mean age was 57.3±12.2 years (range: 41-80 years). Patients were recruited at the Movement Disorders Center of the Catholic University in Rome from February to June 2014. The inclusion criteria were age>18 years, and diagnosis of HD. Diagnosis of HD was based, according to the established criteria[41], on clinical criteria and confirmed by genetic testing in 21/30 (70%). The 9 patients who refused to undergo genetic testing were definitely clinically affected by HD and had a familiar history of HD with at least one family member genetically confirmed. Fifteen patients were taking tetrabenazine, 18 were on neuroleptic treatment, 15 assumed antiepileptic drugs (AEDs) as mood stabilizers (prevalently valproic acid). Most patients (23/30) were assuming more than one drug.

								Treatment						
	Age	Sex	Neck	BMI	Disease duration	UHDMRS	CAG	TBZ	NLP	MTD	Li	BZD	AEDs	ADP
1	45	F	32,0	20,57	4	58	47	yes	no	no	yes	no	no	no
2	63	M	34,5	17,24		63		no	yes	no	yes	yes	no	no
3	60	F	31,0	19,98	1	12	40	no	no	yes	no	no	no	no
4	80	F	32,0	17,19	8	63	40	yes	yes	no	no	yes	no	yes
5	40	F	31,0	19,56	4	27	57	no	no	yes	no	no	no	no
6	60	F	35,0	15,43	14	103	45	yes	no	no	no	no	yes	no
7	49	M	39,0	22,89				no	no	no	no	no	no	no
8	59	F	34,0	27,55	18	57	45	no	yes	no	no	yes	yes	no
9	41	F	31,0	19,53	4	19	48	no	no	no	no	no	yes	no
10	78	M	37,5	19,84	10	69	42	no	no	no	no	no	yes	no
11	71	M	35,6	22,41	10	49	43	no	yes	yes	no	no	no	no
12	43	M	43,0	20,40	5	88		yes	yes	no	no	no	yes	no
13	53	F	32,0	17,58	7	78		yes	yes	yes	no	yes	yes	no
14	45	F	32,0	21,97	14	80		no	yes	yes	yes	no	yes	no
15	50	M	45,0	23,99	12	63	46	yes	yes	yes	no	yes	yes	no
16	52	M	37,0	21,51	12	36		no	yes	yes	no	no	no	no
17	75	F	34,0	24,65	11	36	40	yes	no	no	no	no	no	no
18	71	F	34,0	20,90	10	50		no	yes	yes	no	no	yes	no
19	68	F	33,0	32,87	6	39	41	no	yes	no	no	no	yes	no
20	57	F	38,0	22,03	10	75	43	yes	yes	yes	no	yes	no	yes
21	43	M	40,0	26,81	6	40		no	no	yes	no	no	no	no
22	61	F	37,0	28,30	8	61	44	yes	no	yes	no	no	no	no
23	48	F	33,0	15,43	13	89		yes	yes	no	no	no	yes	yes
24	56	M	40,5	24,49	8	31	44	no	yes	no	no	yes	yes	yes
25	43	M	38,5	23,27	12	68	52	yes	yes	yes	yes	no	yes	no
26	74	F	37,0	22,48	17	75	42	yes	yes	yes	no	no	no	no
27	78	M	40,0	21,13	18	61	43	yes	no	yes	no	no	no	no
28	51	M	40,0	25,88	6	20	43	no	yes	no	yes	no	yes	no
29	53	M	39,0	25,83	4	26	43	yes	no	no	no	no	no	no
30	52	M	34,0	16,98	12	75	43	yes	yes	no	no	no	yes	no
Mean	57,30		35,99	21,96	9,43	55,55	44,33							
SD	12,24		3,75	4,01	4,49	23,43	4,08							
Total		14M, 16F						15	18	14	5	7	15	3,00

In the EEG spectral analysis, a subgroup of 23 consecutive patients (belonging to the same cohort) was enrolled, including 14 women and 9 men, mean age was 57.0±12.4 years (range: 40-80 years)[42].

	Age	Gender	Disease duration	UHDMRS	CAG repeats
1	60	F	1	12	40
2	80	F	8	63	40
3	40	F	4	27	57
4	60	F	14	103	45
5	49	M	4	25	
6	59	F	18	57	45
7	41	F	4	19	48
8	43	M	5	88	
9	53	F	7	78	
10	45	F	14	80	
11	50	M	12	63	46
12	75	F	11	36	40
13	71	F	10	50	
14	68	F	6	39	41
15	57	F	10	75	43
16	43	M	6	40	
17	61	F	8	61	44
18	56	M	8	31	44
19	43	M	12	68	52
20	74	F	17	75	42
21	78	M	18	61	43
22	51	M	6	20	43
23	53	M	4	26	43
Mean	56,96		9,00	52,04	44,47
SD	12,43		4,83	25,10	4,45
Total		9M, 14F			

Control groups

Sleep scores and V-PSG findings in HD patients were compared with a control group of 30 healthy subjects matched for age and sex (14 men, 16 women, mean age 56.5±11.8 years, range 38 – 76).

In the EEG study, power spectra of HD patients were compared with those of a control group of 23 healthy subjects, matched for age and sex: 14 women and 9 men, mean age was 58.2±14.6 years (range: 38-81 years)[42]. Control subjects were healthy volunteers, without

subjective complaint of sleep disorders or diurnal symptoms consistent with sleep disruption. Controls underwent a full medical and neurological evaluation, and a hypnological interview to rule out present or previous history of sleep disorders. No subject in this group was taking Central Nervous System active drugs at the time of the study.

The study was approved by the local Ethical committee. All patients and control subjects were fully informed and all gave a written consent to participate.

Methods

Clinical and neurologic evaluation

All Patients underwent a medical and neurological examination, including measures of weight, height, body mass index (BMI) and neck circumference. The following clinical features were evaluated: disease duration, clinical severity (measured by means of the UHDMRS[43]), disease burden (calculated by the formula: CAG-35.5 X age[44]), number of CAG repeats, pharmacological treatments. In the present study the motor and behavioral symptoms did not allow the withdrawal of pharmacological therapies, which were kept unmodified during the evaluation period.

Subjective sleep evaluation

Sleep anamnesis was collected and questionnaires were administered by a sleep specialist. Subjective evaluation of sleep quality was performed by the validated Italian version of the Pittsburgh Sleep Quality Index (PSQI)[45]. A global score ≥5 was considered an indicator of poor sleep quality[46]. Sleep quality was also assessed by means of a specific questionnaire validated for HD patients (HDQ)[29]. This questionnaire evaluates 4 aspects of sleep: sleep quality, motor activity, abnormal motor behavior during sleep and other sleep disorders. Out of a total score of 19 points, scores of 0–3 represent the 'normal' range, while scores of 4–6 reflect 'mild' and scores of 7 and above indicate a 'significant' sleep disturbance which may merit further investigation and/or treatment.[29]

For the evaluation of EDS, two scales were used: the validated Italian version of the Epworth Sleepiness Scale (ESS)[47], and the Bologna questionnaire. The ESS is a validated, widely adopted questionnaire for the evaluation of sleepiness; the cut-off score for defining EDS was ESS=9. The Bologna questionnaire is a validated questionnaire which contains questions

concerning concepts such as “tiredness”, “resistible sleepiness”, “irresistible sleepiness” and “sudden sleep attacks”; the questionnaire divides patients in two groups, with “high risk” or “low risk” of EDS.[48]

An evaluation of the symptoms and clinical signs predictors of Obstructive Sleep Apnea syndrome (OSAS) was performed by means of the Berlin Questionnaire[49]. This evaluation included the measure of neck circumference, BMI, presence of habitual snoring, nocturia, morning headache, arterial hypertension, and apneas reported by the bed-partner. For diagnosis of RLS the validated four-item RLS criteria was used[50]. Fulfillment of all four criteria was required for diagnosis. The IRLLSG scale was administered to patients with positive RLS screening, in order to measure the severity of the disturbance. In order to evaluate the presence of REM sleep Behavior Disorder (RBD), the RBD questionnaire[51] was used.

Psychological functioning measures

The psychometric evaluation included the following scales: the Zung Anxiety Scale (SAS #54)[52], the short form of the Beck’s Depression Inventory (BDI-SF)[53], the Maudsley’s Obsessive Compulsive Inventory (MOCI[54]). The SAS #54 is a method of measuring levels of anxiety in patients who have anxiety-related symptoms. It uses a 4-point Likert-type scale, ranging from 1 to 4. The SAS contains 20 items with 15 increasing anxiety level questions and 5 items reverse scored. High scores correspond to higher levels of anxiety. The BDI-SF is a 13-item validated self-report instrument measuring characteristic attitudes and symptoms of depression over the previous two weeks. Scores >9 indicate mild to severe depression. The MOCI is a questionnaire with true-false format developed for evaluating the type of obsessive-compulsive symptoms and discriminating obsessive patients from other neurotic patients and from nonclinical people. The total score ranges between 0 (absence of symptoms) and 34

(maximum presence of symptoms). The MOCI has four subscales which measure the following traits: Checking, Cleaning, Slowness, and Doubting.

Objective sleep evaluation

Video-Polysomnography

Full-night, attended, laboratory-based V-PSGs were recorded in acclimatized, sound-proof rooms. Time of PSG recording was fixed (between 11 pm and 7 am). Recording montage included EEG leads applied to following locations: Fp1, Fp2, F3, Fz, F4, F7, F8, C3, Cz, C4, T3, T4, T5, T6, P3, Pz, P4, O1, O2; reference electrodes applied to the left (A1) and right (A2) mastoids; 2 EOG electrodes applied to the outer ocular cantus and referred to the contra-lateral mastoid, surface EMG of sub-mental and intercostal muscles, right and left anterior tibialis, right and left extensor communis carpi, airflow measured by thermocouple transducers, thoracic and abdominal effort, EKG and peripheral hemoglobin saturation measured by a sensor placed on a finger. Continuous audio and video recording was performed by means of infra-red cameras. Sleep recordings were analyzed on computer monitor, and sleep stages were visually classified according to the criteria of the American Academy of Sleep Medicine[55]. Sleep stage percentages were calculated related to Total Sleep Time (TST). The arousal indexes[56] (number of arousals per hour) were calculated for total sleep, NREM and REM stages.

The scoring of sleep-related respiratory events was performed visually, according to the criteria established by the AASM (2007)[57]. The analysis of the SpO_2 parameters was made with a dedicated software (Rembrandt SleepView-Medcare©). Oxygen desaturation events were defined as a fall in $SpO_2 \geq 3\%$. In the analysis of saturation, the following parameters were considered: baseline SpO_2, lowest SpO_2, Oxygen Desaturation Indexes (ODI) in total sleep, in

NREM and in REM. OSA was defined by the presence of an Apnea-Hypopnea Index (AHI) >5 events per hour of sleep (including obstructive and mixed events); Central Sleep Apnea (CSA) was defined by the presence of a Central Apnea-Hypopnea Index (CAHI) >5 events per hour of sleep. Periodic Limb Movements in Wake and Sleep (PLMW – PLMS) were scored according to established criteria[58], and PLM indexes were calculated for upper and lower limbs, and for wake, the entire sleep period, NREM and REM sleep. The cut-off value for abnormal PLM indexes during wake and sleep was 15 events/hour[58]. Additionally, the number of inter-movement intervals that were 10–90s long and all in sequences of at least 3, was divided by the total number of intervals to yield the periodicity index (PI); this index can vary between 0 (absence of periodicity, with none of the intervals having a length between 10 and 90s) to 1 (complete periodicity, with all intervals having a length between 10 and 90s)[59].

EEG

Continuous EEG recordings were performed during wake (before sleep) and during sleep. Periods of wake were detected visually, on the basis of the EEG trace and the simultaneous video recording. Epochs of EEG slowing, consistent with drowsiness, were detected visually and excluded from analysis. EEG was recorded by means of a Micromed System Plus digital EEGgraph (Micromed© S.p.A., Mogliano Veneto, TV, Italy). EEG montage included 19 standard scalp leads positioned according to the 10 - 20 system (recording sites: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). The reference electrodes were placed on the linked mastoids. Impedances were kept below 5KΩ before starting the recording and checked again at the end. In particular, impedances of the mastoids reference electrodes were checked to be identical. This electrode montage is considered as an adequate EEG spatial sampling for the estimation of cortical sources of eyes closed resting state EEG rhythms with the eLORETA software, since these rhythms are widely represented

across all human cerebral cortex in contrast to the circumscribed functional topography of event-related EEG changes (especially at high frequencies) in response to specific sensory or motor events[60]. Therefore, eyes closed resting state EEG rhythms can be properly sampled with a relatively low amount of electrodes, as opposed to the higher spatial sampling required to take into account to the detailed functional topography of event-related EEG activity. This relatively low-spatial sampling of EEG rhythms is in line with the fact that LORETA solutions are intrinsically maximally smoothed at source space, due to its regularization procedure[60, 61]. Sampling frequency was 256 Hz; analogic to digital conversion was made at 16 bit; pre-amplifiers amplitude range was ±3200 μV and low-frequency pre-filters were set at 0.15 Hz. The following bandpass filters were used: HFF = 0.2 Hz; LFF = 128 Hz. The line noise (in Italy: 50Hz) was removed by using a 50Hz notch filter. In the off-line analysis, rejection of artifacts (eye movements, blinks, muscular activations, respiratory or movement artifacts) was performed visually on the raw EEG trace, by posing a marker at the onset of the artifact signal and a further marker at the end of the artifact. Successively, the artifact segment (that is, the EEG signal interval included between the two markers) was deleted, and this cancellation involved all the EEG traces acquired within that interval. In this way, all the EEG intervals characterized by the presence of artifacts were excluded from the analysis. After artifact rejection, the remaining EEG intervals were exported into American Standard Code for Information Interchange (ASCII) files, and imported into the eLORETA software. We analyzed segments of EEG recorded in wake and during NREM and REM. The average length of each EEG segment analyzed were the following: wake=371±23 sec.; NREM=418±12 sec.; REM=379±34 sec.. Detailed method of PSG recording have been described previously[62]. All EEG analysis were performed by means of the eLORETA software[63].

eLORETA

For the estimation of cortical sources of EEG rhythms was used LORETA software as provided at http://www.unizh.ch/keyinst/NewLORETA/LORETA01.htm[63]. LORETA belongs to a family of linear inverse solution procedures modeling 3D distributions of EEG sources[61]. eLORETA computes 3D linear solutions for the EEG inverse problem within a three-shell spherical head model including scalp, skull, and brain compartments. LORETA solutions consist of voxel current density values able to predict EEG spectral power density at scalp electrodes. eLORETA is a reference-free method of EEG analysis, which allows to obtain the same source distribution for EEG data independently from the reference electrode. Estimated cortical sources of scalp EEG voltages are expected to reflect the synchronous synaptic neural currents of the pyramidal cortical neurons, which are associated to local field potentials. LORETA computes 3D linear solutions (LORETA solutions) for the EEG inverse problem within a three-shell spherical head model including scalp, skull, and brain compartments. The brain compartment is restricted to the cortical gray matter/hippocampus of a head model co-registered to the Talairach probability brain atlas and digitized at the Brain Imaging Center of the Montreal Neurological Institute[64]. eLORETA images represent the standardized electrical activity at each of 6239 cortical voxels (spatial resolution 5 mm) in Montreal Neurological Institute space. LORETA computes relative currents for z, x, and y components of any dipole.

Frequency analysis

EEG frequency analysis was performed by means of Fast Fourier Transform algorithm, with a 2 seconds interval on the EEG signal, in all scalp locations. The following frequency bands were considered: delta (0.5–4 Hz); theta (4.5–7.5 Hz); alpha (8–13.5 Hz); beta (14-30 Hz); gamma (30.5–60 Hz. For frequency analysis, monopolar EEG traces (each electrode referred to joint mastoids) were used. Topographic sources of EEG activities were determined

using the eLORETA software. The eLORETA software computes the current distribution throughout the brain volume. In order to find a solution for the 3-dimensional distribution of the EEG signal, the eLORETA method assumes that neighbouring neurons are simultaneously and synchronously activated. This assumption rests on evidence from single cell recordings in the brain that shows strong synchronization of adjacent neurons[65, 66]. The computational task is to select the smoothest of all possible 3-dimensional current distributions, a common procedure in signal processing[67, 68]. The result is a true 3-dimensional tomography, in which the localization of brain signals is preserved with a low amount of dispersion[63].

Statistical analysis

PSG data obtained in the patient group were compared to those obtained from controls. All sleep parameters and PSG measures were compared in these two groups by means of a non-parametric test (Mann-Whitney U-test). The threshold for significance was p=0.05. In case of multiples comparison, in order to avoid family-wise type I errors, a formal Bonferroni correction was applied to each family of comparisons, by dividing the limit of significance by the number of comparisons (for the ODI, 3 comparisons were made, in the conditions 'sleep', 'NREM' and 'REM', therefore the threshold level for significance was p=0.05/3=0.017; for the PLM indexes, 4 comparisons were made, in the conditions 'wake', 'sleep', 'NREM' and 'REM', therefore the threshold level for significance was p=0.05/4=0.0125). Moreover, within the HD group, we calculated the correlation indexes between sleep parameters and the clinical findings (UHDMRS, CAG repeats, disease duration). These correlations were evaluated by means of the Spearman correlation index: the critical value of the Spearman's ranked correlation coefficient was $\rho=0.362$, corresponding to a significance level $p<0.05$. Correlations were controlled for age differences.

The analysis of subjective sleep evaluation was performed in three successive steps: in the first step, we compared the results of the sleep evaluations performed by means of the different scales utilized, in order to evaluate the degree of agreement. In particular, we compared the measures of daytime sleepiness obtained with ESS with those of the Bologna Q; and we compared the measures of sleep quality obtained with PSQI vs HDQ. We measured the number of patients in which the results of the scales gave concordant or discordant results; 'concordant' were considered those cases in which both scales showed results above or below the cut-off. As for the HDQ, two different cut-off were considered: >3 ('mild sleep disorder') and >7 ('significant sleep disorder')[29]. Questionnaire results were further compared by an individual analysis to calculate the kappa statistic, which accounts for the amount of agreement expected.

In the second step, we compared the scores of sleep questionnaires with PSG data. For the PSQI and the HDQ, comparison were made with sleep efficiency index (SEI). 'Poor sleep' in subjective evaluation was defined as PSQI score ≥5 and HDQ≥3 or HDQ≥7; in objective evaluation 'poor sleep' was defined as SEI<82.7%, calculated as the mean-2 DS of a population of adult healthy controls recorded as normative data of our sleep laboratory. Moreover, to evaluate in deeper detail the sleep quality results, the sub-items of the PSQI scale were compared to PSG findings; in particular, the component C2 was compared to sleep latency (SL), C3 to Total Sleep Time (TST), C4 to SEI and C5 to the number of awakenings lasting > 1 minute (Aw). Again, the cut-off values were defined as the mean ± 2 DS of our controls. The following cut-off for PSG values were used: SL>48.8 minutes; TST<303.3 minutes; SEI<82.7%; Aw >7.9. For all these parameters we measured the kappa statistic; moreover, we computed the accuracy, sensitivity and specificity of each measure[69]. For these, we used the definitions set forth by Tilmanne et al. (2009)[70] to calculate accuracy, sensitivity and specificity[70]. When compared with PSG, a true positive (TP) indicates that the questionnaire identifies the disorder

correctly, a true negative (TN) indicates that the questionnaire identifies absence of disturbance, a false negative (FN) indicates that the scale misidentifies the disorder, and a false positive (FP) indicates that the scale identifies a unconsistant disorder. Accuracy is then defined as (TP + TN)/(TP + TN + FN + FP) and represents the agreement rate between PSG and the scale; sensitivity is defined as TP/(TP + FN) and represents the percentage of disorders identified correctly; and specificity is defined as TN/(TN + FP) and represents the percentage of subjects correctly identified as good sleepers. Finally, correlation were analyzed between sleep questionnaires (ESS, PSQI, HD, RBD), and clinical data and psychometric scores (age, disease duration, UHMDRS, number of CAG repeats, BDI, Zung-A and MOCI). These correlations were evaluated by means of the Spearman correlation index: the critical value of the Spearman's ranked correlation coefficient was $\rho(28)=0.375$, corresponding to a significance level $p<0.05$.

In the EEG study, power spectra were compared among conditions, for each frequency band. The conditions analyzed were three: wake, NREM, REM. All comparisons were performed by using the statistical non-parametric mapping methodology supplied by the LORETA software [71]. This methodology is based on the Fisher's permutation test: a subset of non-parametric statistics. In particular, this is a type of statistical significance test in which the distribution of the test statistic under the null hypothesis is obtained by calculating all possible values of the test statistic under rearrangements of the labels on the observed data points. Correction of significance for multiple testing was computed for the two comparisons between conditions for each frequency band: for the correction, we applied the non-parametric randomization procedure available in the LORETA program package [71]. T-level threshold were computed by the statistical software implemented in the LORETA, which correspond to threshold of statistical significance ($p<0.01$) for details see, [72, 73].

Finally, Spearman's rho correlation coefficients were computed as measures of correlation between EEG power spectra (in the Broadman Areas 4, bilaterally) and clinical

features (age, BMI, disease duration, disease burden, CAG repeats); the critical value of the Spearman' rho coefficient was $\rho(21)=0.41$, corresponding to $p=0.05$. All statistics were performed by means of the SYSTAT 12 software version 12.02.00 for Windows® (copyright SYSTAT® Software Inc. 2007). Correlation analyses were performed with the Statistical Package for Social Science (SPSS®) software version 19.

Results

Clinical and neurologic evaluation

The mean duration of the disease was 9.4±4.4 years, UHDMRS score was 55.5±23.4, CAG repeats were 44.3±4.1. Average BMI was 21.9±4.0 kg/m^2, neck circumference was 36.0±3.7 cm. In the control group, mean age was 56.5±11.8 years (range: 38-76), average BMI was 26.3±8.5 kg/m^2, neck circumference was 36.4±3.6 cm.

		HD patients			Controls		
		Mean	**SD**	**Total**	**Mean**	**SD**	**Total**
Clinic and demographic data	**Age**	57,30	12,24		56,50	11,85	
	Gender			14M, 16F			14M, 16F
	Neck	35,99	3,75		36,37	3,60	
	BMI	21,96	4,01		26,27	8,54	
	Disease duration	9,43	4,49				
	UHDRS	55,55	23,43				
	CAG repeats	44,33	4,08				

Objective sleep evaluation

PSG – Sleep structure

Useful sleep recordings were obtained in all patients and controls. One patient showed an almost total insomnia (TST = 15 minutes). HD patients, as compared to controls (C), showed shorter TST (HD: 303±105 min, C: 406±51 min, p<0.001), reduced Sleep Efficiency Index (SEI; HD: 63±21%, C: 93±5%, p<0.001), increased number of awakenings (HD: 16±10, C: 5±3, p<0.001), and consequently augmented Wake After Sleep Onset (WASO; HD: 132±88 min, C: 40±29 min, p<0.001). Stages composition in HD was characterized by increased amount of N1

(HD: 15±9%, C: 9±7%, p=0.005), reduction of N3 (HD: 9±7%, C: 24±11%, p<0.001) and REM (HD: 10±7%, C: 19±5%, p<0.001). HD patients showed higher arousal indexes (number of events/hour) in total sleep (HD: 37±23, C: 14±5, p<0.001), in NREM (HD: 37±24, C: 14±5, p<0.001), and REM (HD: 31±29, C: 13±5, p=0.006).

PSG – Respiratory findings

Four patients presented PSG evidence of SDB: two had obstructive events (mild in one case, OAHI=5.9; and moderately severe in another, OHI=29.6 events/hour) and one had central events (CAHI=7.1 events/hour). One patient presented hemoglobin desaturations during sleep (ODI=16.7 events/hour) in absence of sleep-related respiratory events, possibly suggesting sleep-related hypoventilation. The patient with CSA and the patients with mild OSA had ESS scores above the cut-off. None of the subjects in the control group presented PSG findings consistent with SDB.

PSG – Motor activity, PLMS, RBD

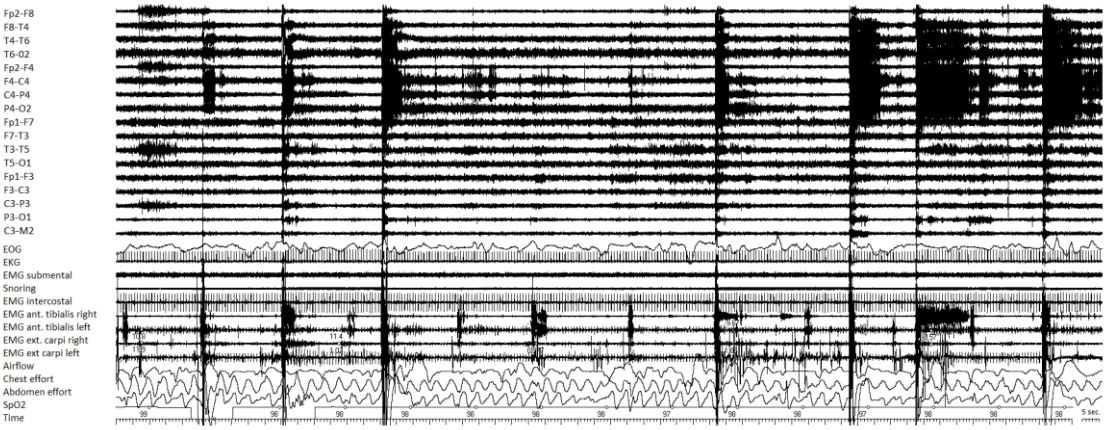
HD patients presented an overall increase of motor activity during wake and sleep. PLM were observed in all patients, both during pre-sleep wake and sleep. All patients, compared to controls, presented increased indexes of PLM at the lower limbs, during wake (PLMW; HD: 46±135, C: 0.5±1, p<0.001), total sleep (PLMS; HD: 18±19, C: 0.5±1, p<0.001), NREM (PLMS; HD: 18±19, C: 0.2±0.3, p<0.001) and REM (PLMS; HD: 15±24, C: 0.9±2, p=0.01). HD patients presented high indexes of PLM during wake and all sleep stages also in the upper limbs; recording of upper limbs PLM was not performed in the control group. Both upper and lower limbs PLM persisted during all sleep stages, but were consistently reduced during REM. No episode of RBD was observed in the V-PSG recordings; the two patients who had RBD-Q>5

did not show PSG evidence of RWA. None of the subjects in the control group presented PSG findings consistent with PLMS or RBD.

			Huntington		Controls		Mann-Whitney	
			Mean	DS	Mean	DS	U-test	p
Sleep structure		TIB	478,6	53,8	480,6	41,8	477,5	0,684
		TST	303,5	105,8	406,3	51,5	728,5	<0,001
		SPT	426,8	55,4	446,5	43,2	541,0	0,178
		SEI	63,5	20,8	92,9	5,1	872,5	<0,001
		SL	45,0	51,1	25,9	23,0	382,0	0,315
		Aw	16,3	10,0	4,7	3,2	71,0	<0,001
		WASO	132,2	88,1	40,2	29,5	110,0	<0,001
		REM	9,8	7,2	19,2	5,1	777,0	<0,001
		N1	14,6	8,9	9,0	7,3	261,0	0,005
		N2	36,7	17,9	38,9	11,6	445,0	0,941
		N3	9,0	7,4	23,8	10,7	801,0	<0,001
		Wake	29,6	21,0	24,8	44,1	232,0	0,001
		Arousal total	36,7	23,4	13,9	4,9	146,5	<0,001
		Arousal NREM	37,5	24,3	13,9	5,1	154,0	<0,001
		Arousal REM	31,1	29,4	13,5	4,7	263,5	0,006
Respiratory results	Central	Apneas	0,5	1,9	0,7	1,3	621,0	0,004
		Hypopneas	0,3	0,7	0,1	0,3	414,0	0,494
	Mixed	Apneas	0,0	0,0	0,1	0,3	540,5	0,024
		Hypopneas	0,0	0,0	0,0	0,0	465,0	0,317
	Obstructive	Apneas	0,5	1,3	1,0	1,6	605,0	0,012
		Hypopneas	1,1	4,7	1,3	1,7	622,5	0,006
	ODI	Total sleep	3,3	3,9	3,3	2,0	531,0	0,231
		NREM	3,0	3,6	2,7	1,8	535,5	0,206
		REM	5,8	9,6	5,3	3,3	574,5	0,063
PLM	Wake	Lower limbs	46,0	135,0	0,5	1,0	46,5	<0,001
	Sleep		17,6	19,5	0,5	1,4	0,0	<0,001
	NREM		17,9	19,2	0,2	0,3	2,0	<0,001
	REM		15,1	23,8	0,9	2,2	284,0	0,010
	Wake	Upper limbs	68,1	188,6	na	na		
	Sleep		20,9	27,6	na	na		
	NREM		21,5	27,6	na	na		
	REM		15,7	26,7	na	na		

Detailed results of PLM scoring, in patients and controls, in lower and upper limbs, and values of the periodicity index in HD patients during wake and sleep, are shown in the table below.

	Lower limbs						Upper limbs			
	Patients		Controls	Patients		Controls	Patients			
	PLMW	PI	PLMW	PLMS	PI	PLMS	PLMW	PI	PLMS	PI
1	12,0	0,582	0,1	15,6	0,824	0,1	72,2	0,672	34,4	0,714
2	58,8	0,737	0,2	19,0	0,732	0,0	82,0	0,882	3,9	0,699
3	13,2	0,755	0,3	1,3	0,986	0,0	45,2	0,769	5,6	0,852
4	13,5	0,792	1,2	16,6	0,841	1,0	13,0	0,659	85,3	0,869
5	89,6	0,820	0,6	3,2	0,679	1,1	170,5	0,771	52,5	0,904
6	8,1	0,907	0,3	3,8	0,852	0,2	54,1	0,848	35,6	0,836
7	90,5	0,647	0,0	21,7	0,846	0,0	71,9	0,849	11,5	0,871
8	11,1	0,794	0,0	22,3	0,736	0,0	44,8	0,659	1,6	0,869
9	8,8	0,742	0,0	4,0	0,759	0,1	82,3	0,793	37,2	0,941
10	147,8	0,702	0,1	112,4	0,789	0,2	28,9	0,777	8,3	0,867
11	59,9	0,658	0,2	6,3	0,765	0,0	72,3	0,817	5,0	0,751
12	13,0	0,872	0,3	17,0	0,739	0,0	52,4	0,802	64,0	0,749
13	52,4	0,716	0,4	6,0	0,744	0,0	49,0	0,894	5,3	0,768
14	50,9	0,735	1,0	19,8	0,825	0,0	43,5	0,911	14,1	0,730
15	55,3	0,614	0,0	16,2	0,691	1,3	80,5	0,912	1,4	0,758
16	49,4	0,714	0,0	2,1	0,894	1,2	57,3	0,900	3,3	0,698
17	36,9	0,751	0,3	16,6	0,735	0,0	91,0	0,514	1,0	0,891
18	8,1	0,717	0,3	16,6	0,769	0,0	53,5	0,899	22,0	0,864
19	71,0	0,810	0,2	17,1	0,781	0,3	106,5	0,872	4,6	0,854
20	50,9	0,832	0,0	16,1	0,746	4,2	82,9	0,733	14,0	0,803
21	75,0	0,863	0,0	17,7	0,779	0,0	134,0	0,758	18,6	0,694
22	54,0	0,865	2,3	24,4	0,719	3,2	49,5	0,652	29,4	0,657
23	67,6	0,766	1,0	2,4	0,698	0,0	52,7	0,843	3,5	0,912
24	13,1	0,816	1,2	5,5	0,841	0,0	60,6	0,901	5,5	0,851
25	124,0	0,751	0,0	23,3	0,867	0,0	113,5	0,752	64,3	0,764
26	42,5	0,824	0,0	19,0	0,906	0,0	42,3	0,847	27,5	0,781
27	37,6	0,735	2,1	21,2	0,867	0,2	41,8	0,865	28,6	0,753
28	42,4	0,614	0,6	18,3	0,899	0,1	80,5	0,789	30,2	0,779
29	10,6	0,698	0,0	22,9	0,847	0,5	54,6	0,764	2,1	0,801
30	11,2	0,751	1,2	20,6	0,901	0,3	58,7	0,698	6,6	0,659
Mean	46,0	0,753	0,5	17,6	0,802	0,5	68,1	0,793	20,9	0,798
SD	35,4	0,080	0,6	19,4	0,076	1,0	31,9	0,097	22,0	0,079



Subjective sleep evaluation

Twenty-nine subject were evaluate for sleepiness (one subject did not perform the Bologna Q). ESS score was above the cut-off in 6 subjects, Bologna Q detected 'high risk' of EDS in 7 cases. Thirty subjects were evaluated for sleep quality. PSQI score was above the cut-off in 18 subjects. Using a HDQ score cut-off =3 ('mild sleep disorder'), 10 subjects were poor sleepers. Two patients fulfilled the diagnostic criteria for RLS, and two had scores above the cut-off in the RBD-Q. The Berlin questionnaire identified 8 patients with high risk of OSAS (26.6%). The RBDQ identified 2 patients with scores above the cut-off value = 5, suggesting high risk of RBD.

	HDQ	PSQI	Bologna Q	Epworth	Berlin scale	IRLSSG criteria	IRLSSG score	RBD Q
1	9	14	low	14	high	0		9
2	2	3	low	2	low	0		1
3	1	6	low	0	low	0		1
4	13	18	high	9	low	0		4
5	3	4	low	0	low	0		1
6	5	13	high	21	high	0		3
7	8	11	low	5	low	4	11	5
8	2	4	low	6	low	0		2
9	4	10	low	2	low	0		1
10	2	7	high	3	low	0		1
11	2	3	low	3	low	0		1
12	2	6	high	4	high	0		1
13	3	9	low	1	low	0		5
14	5	5	low	6	low	0		1
15		16		11	low	0		2
16	2	4	low	6	high	0		1
17	1	5	low	10	high	0		1
18	1	5	low	4	low	0		2
19	4	7	high	14	low	0		3
20	2	4	low	7	low	0		1
21	1	5	low	7	low	0		1
22	3	6	low	3	high	0		1
23	1	2	low	3	low	0		1
24	12	17	high	14	low	0		6
25	4	4	low	6	low	4	9	5
26	3	3	high	14	high	0		1
27	4	9	low	6	high	0		2
28	1	4	low	3	low	0		1
29	1	1	low	3	low	0		2
30	2	3	low	3	low	0		2
Mean	3,55	6,93		6,33		0,27		2,27
SD	3,17	4,62		5,02		1,01		1,96

As concern the concordance between scales, the EDS results were concordant in 24, and discordant in 5. The Cohen-K was 0.505, which suggests a 'discrete' concordance between the two scales. When we compared concordant (C) vs non-concordant subjects (NC), we observed that the NC subgroup had higher scores for depression (BDI score, C=4.8±4.6; NC=14.2±6.9; p=0.0008) and anxiety (Zung score, C=29.2±5.3; NC=36.4±9.2; p=0.024); no differences were computed for all the other clinical and subjective parameters.

In the evaluation of sleep quality, the results were concordant with the PSQI in 20 subjects. The Cohen-K was 0.375, which suggests a 'poor' concordance between the two scales. Using a HDQ score cut-off =7 ('significant sleep disorder'), 4 subjects were poor sleepers. The results were concordant with the PSQI in 16 subjects. The Cohen-K was 0.186, which again suggests a 'poor' concordance between the two scales.

	Concordant	Discordant	Cohen k	Accuracy	Sensibility	Specificity
Bologna Q vs ESS	24	5	0,505			
PSQI vs HDQ (cut-off=3)	20	10	0,375			
PSQI vs HDQ (cut-off=7)	16	14	0,186			
PSQI vs SEI	18	12	0,062	0,600	0,167	0,889
HDQ (cut-off=3) vs SEI	14	16	0,143	0,467	0,200	1,000
PSQI components						
C2 vs SL	13	17	0,045	0,433	0,750	0,318
C3 vs TST	15	15	-0,027	0,500	0,524	0,444
C4 vs SEI	18	12	0,062	0,600	0,167	0,889
C5 vs Aw	25	5	-0,056	0,833	0,000	0,862

Subjective vs objective measures

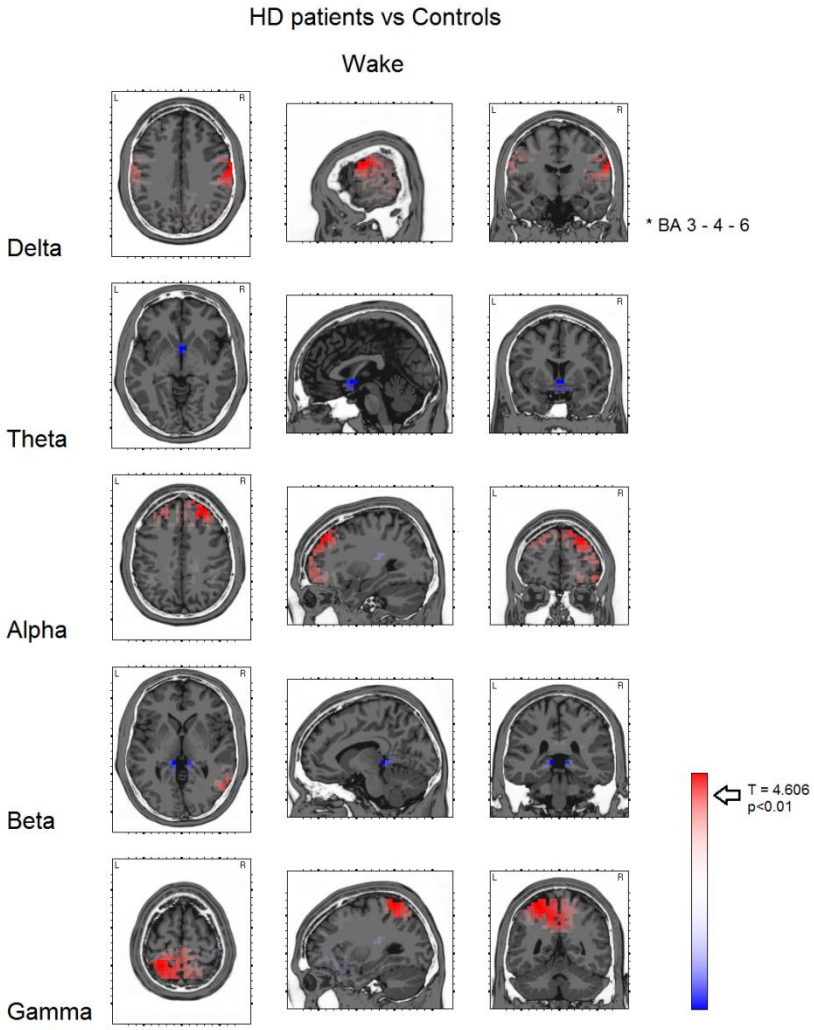
We measured the agreement of the subjective scales with objective data obtained from PSG recording. In particular, we compared the subjective sleep quality with the SEI; in this analysis, we used the HDQ cut-off =3, since it had showed a better concordance with the PSQI. At PSG evaluation, poor sleep was detected in 26 subject. Eighteen subjects were concordant with the PSQI evaluation, and 14 subjects were concordant with the HDQ. The Cohen-K between PSG and HDQ was 0.143, and between PSG and PSQI it was 0.062, suggesting 'poor' concordance between both scales and PSG. Furthermore, we matched the results of PSQI subcomponents with PSG scores. All comparisons showed poor or totally absent concordance between PSQI components and PSG findings; C4 and C5 showed a relatively high specificity (C4=0.889; C5=0.862) but low sensibility (C4=0.167; C5=0.000) with respect to PSG results, and C2 had the highest values of sensibility (0.750). Overall, C5 had the highest accuracy (0.833). The Berlin questionnaire identified 8 patients with high risk of OSAS (26.6%), whereas PSG showed that only 2 (6.6%) had PSG findings consistent with OSA; these data do not differ from the prevalence data observed in the general population[50, 74]. The RBDQ identified 2 patients with scores above the cut-off value = 5, suggesting high risk of RBD, not confirmed by V-PSG.

EEG study[42]

Wake

Statistical analysis demonstrated significant differences (threshold T = ±4.606; $p<0.01$) in the wake EEG between patients and controls in the delta frequency band. In particular, a significant increase of delta power was observed, in HD patients, in the voxels corresponding

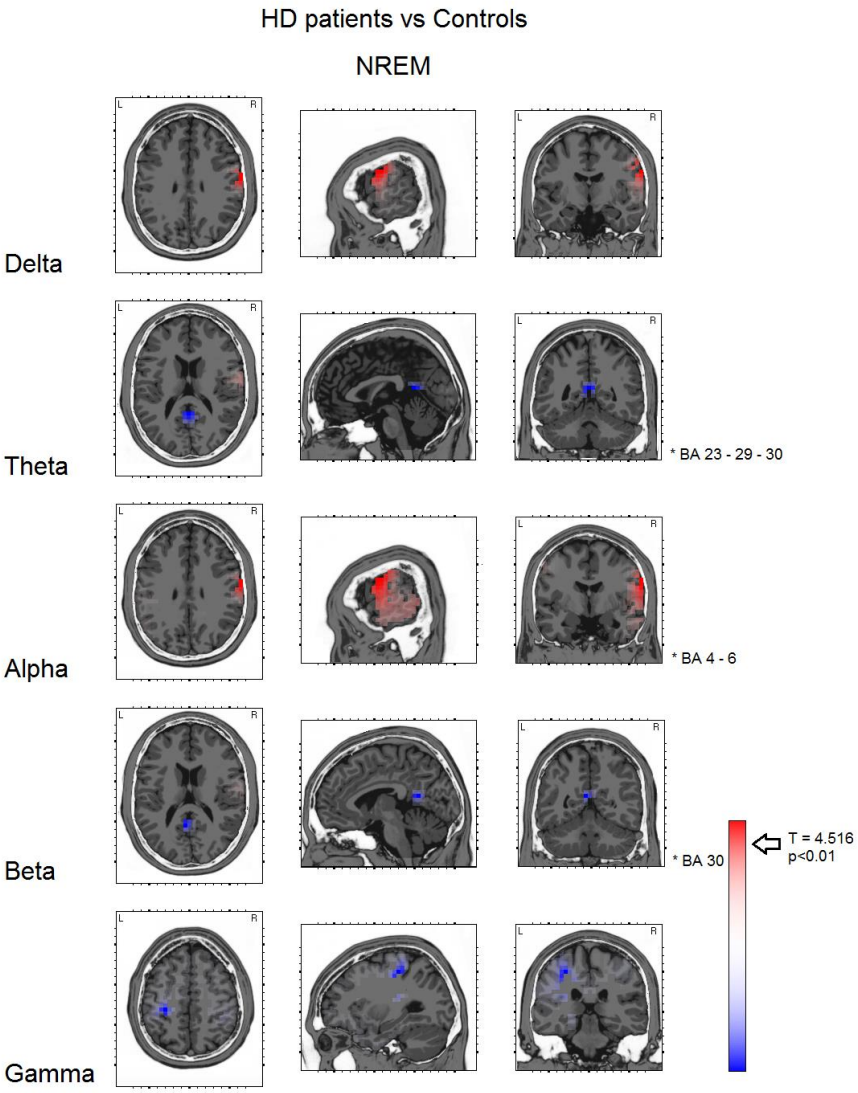
to the Broadman areas (BAs) 3, 4 and 6 bilaterally, with stronger significance on the right hemisphere. No significant differences, in wake, were detected in the other frequency bands.



NREM

In NREM sleep, HD patients showed a significant increase of the alpha power (threshold T = ±4.516; p<0.01) in the voxels corresponding to the BAs 4 and 6 bilaterally, again with stronger significance on the right hemisphere. HD patients also showed decreased theta power (threshold T = ±4.516; p<0.01) in the voxels corresponding to the BAs 23, 29 and 30

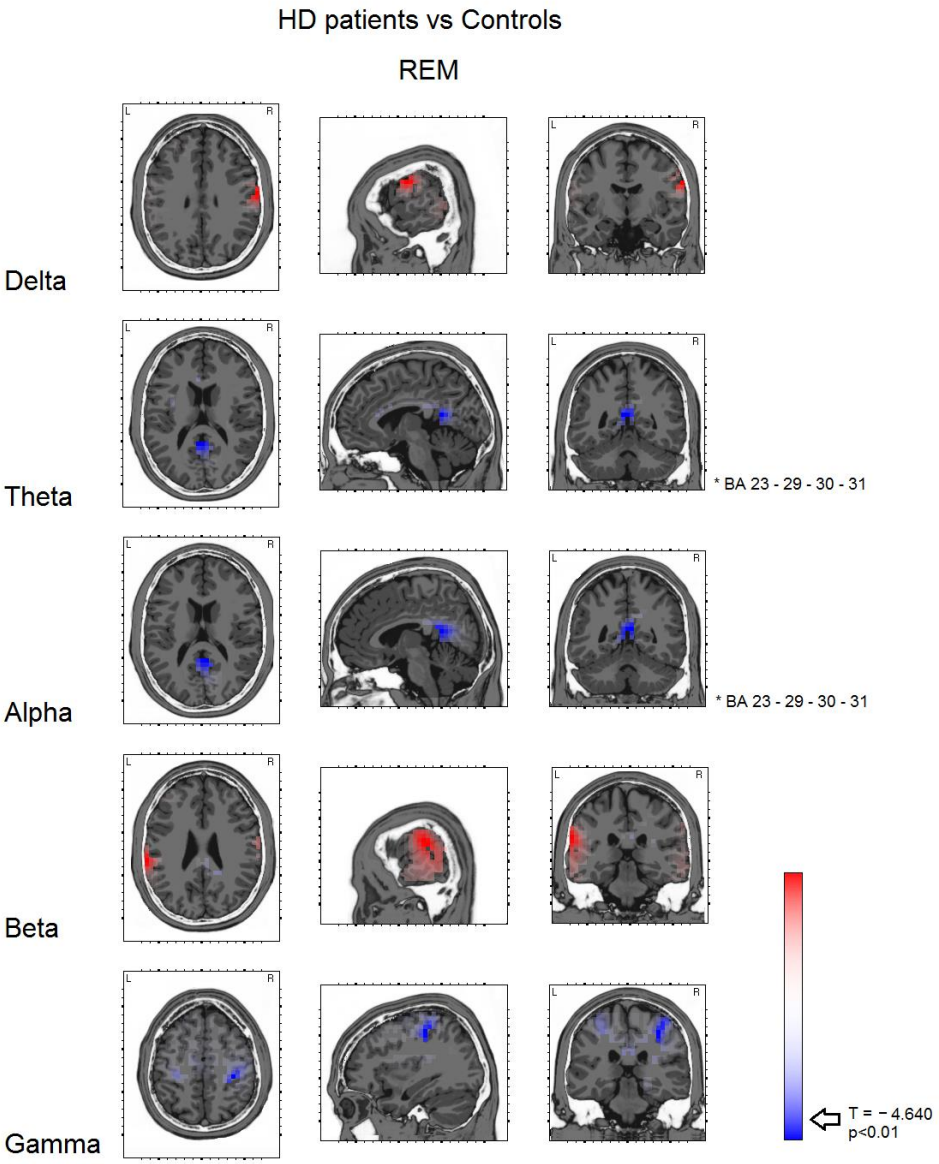
bilaterally. In the beta band, patients showed decreased power in the BA 30 in the left hemisphere (threshold T = ±4.516; p<0.01). No significant differences were detected in the delta and gamma frequency bands in NREM sleep.



REM

During REM, HD patients presented a significant decrease of the theta and alpha power (threshold T = ±4.640; p<0.01) in the voxels corresponding to the BAs 23, 29, 30 and 31

bilaterally. No significant differences were detected in the other frequency bands in REM sleep.



Clinical correlations

The analysis of correlations between clinical and sleep parameters showed that disease duration was significantly correlated with ESS score (Spearman ρ=0.420; p<0.02) but

not with PSG scores. UHDMRS correlated positively with the ESS score (Spearman ρ=0.475; p<0.005), and negatively with REM percentage (Spearman ρ=-0.524; p<0.002). No correlation between number of CAG repeats and sleep results was observed. The main clinical parameters (age, disease duration, clinical severity and CAG repeats) did not show any significant correlation with sleep scales. Conversely, all subjective sleep scores showed significant positive correlations with BDI, Zung-A and MOCI scores. In the EEG study, spectral power in Broadman Area 4 was significantly associated with: i) age and disease duration (in Wake), ii) BMI and disease duration (in REM); iii) UHDMRS (in NREM). No correlation were observed between EEG power spectra and CAG repeats.

	Wake								REM								NREM							
	δ		θ		α		β		δ		θ		α		β		δ		θ		α		β	
	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R
Age			+	+	+																			
BMI	-	-							-	-	-	-												
Disease duration	+	+	+	+			+						+	+							+			
Disease burden																								
UHDMRS		+																+	+	+	+	+	+	
CAG repeats																								

Effect of drug treatment

Finally, in order to rule out the effect of pharmacological treatment, the HD group was split into 2 subgroups: patients taking neuroleptics or benzodiazepines, which can potentially affect sleep measures (n=18), and patient not assuming these drugs (n=12). The comparison

did not show any significant difference between the subgroups, in any of the clinical and PSG variables. Also the comparison of PLM indexes between patients taking the different class of drugs did not show any significant difference.

Discussion

The present paper describes the largest cohort of HD patients enrolled so far for a polysomnographic sleep study.

The results suggest that sleep is severely disrupted in HD patients. In particular, our HD patients had difficulties in initiating sleep (longer sleep latency than controls), and sleep was fragmented by frequent arousal and repeated, long lasting awakenings. As a result, sleep structure was characterized by increase of light sleep and decrease of deep sleep and REM. These findings, in particular REM sleep reduction, appear to be directly related with the clinical severity, measured by the UHDMRS. Concomitant sleep disorders were relatively uncommon in our sample. Two patients (6.6%) had symptoms of RLS, of mild-moderate severity; and two (6.6%) had PSG findings consistent with OSA. Daytime somnolence, measured by the ESS, was present in 8 patients (26.6%). Somnolence was present in 2/4 (50%) of the patients with PSG findings of SDB. These data do not differ from the prevalence data observed in the general population[50, 74]. This is in accordance with the result of a previous PSG study by Cuturic et al. (2009)[30]. In our sample, the prevalence of RBD was, once again, not different from that of the general population[75]. No episode of RBD was observed in the V-PSG recordings, and only two patients had, at the RBD-Q a score >5, which is considered the cut-off for the clinical suspicion of RBD. In V-PSG, these patients did not show RBD episodes or RWA. In our HD patients, nevertheless, motor activity during wake and sleep was considerably increased. All patients presented a variety of PLM during wake and sleep, involving both the upper and the lower limbs. PLMS persisted along all NREM sleep stages, and were markedly reduced during REM. Most PLM were associated with EEG arousals, suggesting that this motor activity may affect the structure of sleep. These data suggest that PLM may be a major pathogenic mechanism of sleep disruption and daytime sleepiness.

The present data are in accordance with some previous reports available in literature, which suggest that sleep is severely affected in HD[28, 29, 31, 32, 34, 36, 37]. Conversely, some data do not confirm previous findings. In particular, a previous study by Arnulf et al. (2008)[31] reported a higher prevalence of RBD in HD (up to 12%). In our sample, symptoms of RBD were reported in only two cases, and no episode of RBD was recorded in the V-PSG. As concerns the RBD-Q, it is known that this questionnaire, which has a high sensitivity for RBD, poorly discriminated patients with the most challenging differential diagnoses such as sleepwalking or epilepsy. Analogously, it may be conceived that the continuous motor activity of HD patients during sleep might mimic some RBD phenomena. Other relevant differences between our population and that described by Arnulf et al. concern the disease severity and the pharmacological treatment. Our patient were older, had longer disease duration and more severe motor impairment (mean UHDMRS score = 55.5 vs 25.4 in the Arnulf et al. study[31]). As a consequence of the clinical severity of our patients, we decided to perform the sleep study without any drug withdrawal. Even though this could bias some sleep measures, when we compared patients assuming neuroleptics or benzodiazepines with those assuming only amantadine or tetrabenazine, no difference was observed in clinical and sleep parameters. We observed in our HD patients a very high prevalence of PLM, both during pre-sleep wake and sleep, also involving upper limbs. Also in this respect, the greater clinical severity of our patients may account for the higher indexes of PLM as compared to that reported by Arnulf et al. Moreover, we decided to explore, in PSG, also the movements of the upper limbs, which were not recorded in previous studies. This technical issue may further explain the differences in PLM indexes. Recently, the role of caudate nucleus in sleep pathology has been evaluated[76]. Moreover, experimental animal models suggest that caudate lesions may induce behavioural restlessness and hyper-responsivity, consequent to failing of inhibitory modulation of sensory input[77]. Electrical stimulation of the caudate enhances cortical synchronization, inhibits

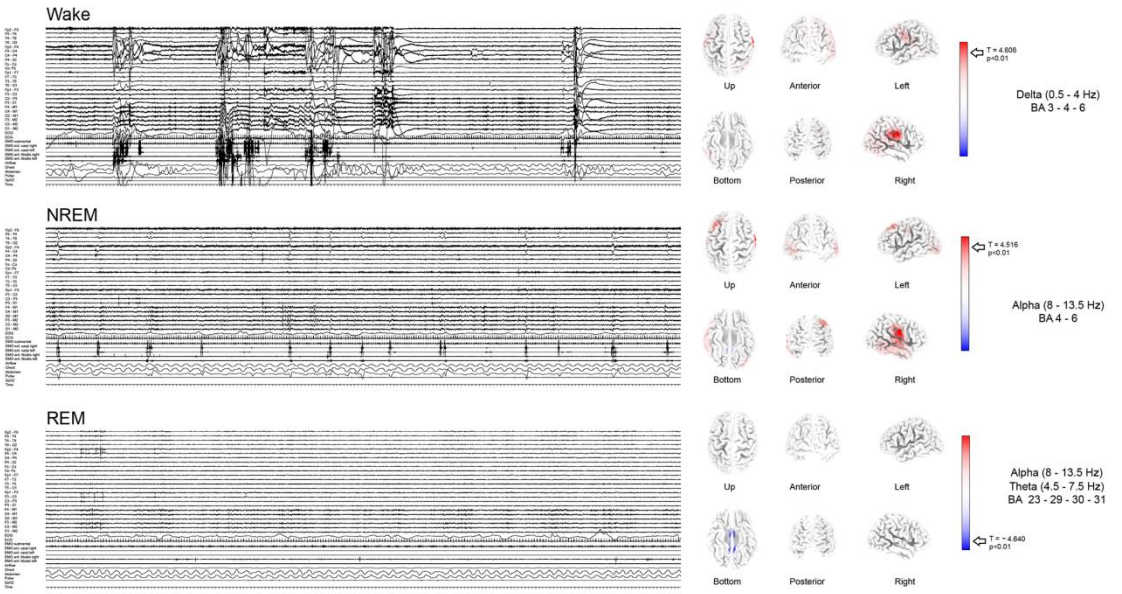
behavioural and autonomic nervous system responses to stimuli[78], and suppresses neuronal firing in the reticular formation, thalamus, hypothalamus and cortex[79]. Also in humans the stimulation of the caudate reduces cortical excitability[80]. Taken together, these data may suggest that the caudate degenerative process observed in HD account for the increased arousability, increased motor activity during wake and sleep (originating PLM), reduction of SWS and in particular of REM sleep and, overall, a general sleep disruption.[34, 35]

As concerns the subjective sleep evaluation, our data suggest, overall, that the subjective evaluation of sleep in HD patients shows a poor correlation with PSG results. As concern sleep quality, both the PSQI and the more specific HDQ showed relatively good specificity in detecting sleep disruption (in particular when this was evaluated by the SEI), but very low sensibility and, consequently, accuracy. Moreover, the two questionnaire presented a low degree of agreement (14/30 discordant subjects, Cohen k=0.186 with a 7-points HDQ cut-off, reduced to 10/30 discordant subjects, Cohen k=0.375 with a 3-points HDQ cut-off). Within the PSQI subcomponents, the C4 was the most specific (compared to SEI) while C5 was the most accurate (compared to awakenings). This suggests that the clinical application of these scales can lead to an underestimation of sleep disorders in HD patients. As concern the evaluation of EDS, the results of our scales could not be compared to the gold-standard procedure for EDS, that is MSLT, not performed in our study. Nevertheless, the scores of ESS and Bologna Q showed poor concordance, suggesting that different subjective methods used for evaluation of sleepiness can lead to different results (5/29 discordant subjects, Cohen k=0.505). Also the scales for OSA (Berlin Q) and RBD (RBD-Q) showed poor agreement with V-PSG data. This suggests that both these tools overestimate the prevalence of sleep disorders. Several elements could account for the discrepancies between subjective and objective data. In theory, these discrepancies could depend on age, gender, disease duration or severity

(expressed as UHMDRS), number of CAG repeats. When we compared these clinical data between the subgroups of 'concordant' (concordance of objective and subjective findings) and 'discordants' patients, we found no significant difference. Conversely, we observed that the 'discordant' subgroup showed high scores at the depression, anxiety and obsessive-compulsive scale. Moreover, we observed no correlation between clinical variables and subjective sleep scores, and, as opposite, significant direct correlations between the sleep and psychometric scales. This seems to suggest that the subjective perception of poor sleep, somnolence and presence of sleep disorders is deeply influenced by mood disorder, anxiety and obsessive-compulsive symptoms. Sleep quality and duration are often mispercepted in patients with sleep disorders. Such misperception usually consist in an underestimation of sleep, and only a small minority of poor sleepers overestimate their sleep. Our results suggest that at least a part of the HD population falls in this latter category. One possible explanation for this phenomenon is the anosognosia which HD patients develop in the course of their disease: people with HD may show reduced awareness of physical and mental changes in themselves[81].

The EEG study confirms that HD patients present significant EEG modification as compared to controls[42]. These modifications change across the wake and sleep stages. During wake, we observed an increase of delta activity, specifically localized on the sensory, motor and premotor areas (BAs 3, 4 and 6), bilaterally, with a right-side predominance. Conversely, during NREM sleep, the motor and premotor cortices (BAs 4 and 6) showed an increase of alpha activity. Finally, during REM sleep, no modifications of activity were observed in motor regions, while a diffuse decrease of alpha and theta power was seen in limbic structure, and particularly in the posterior cingulated cortex (BAs 23, 29, 30 and 31 bilaterally). These findings suggest that EEG modifications may be related to the motor dysfunction of HD.[25] The increased delta activity, during wake, might reflect a motor cortex dysfunction or, alternatively, an

increased inhibitory activity aimed to counterbalance the pathologic motor phenomena. Analogously, during NREM sleep, we observed an increase of alpha activity, which could represent the electrophysiological correlate of the sustained motor activity detected in PSG recording during NREM sleep[30, 31, 82].



The study design did not allow to evaluate drug-free HD patients; for this reason, some results could be biased by pharmacological effects. Most of our patients, for the treatment of involuntary movements, were assuming neuroleptics and tetrabenazine. Tetrabenazine is a drug whose effect on the scalp EEG have not been systematically investigated. Conversely, the effects of neuroleptics on the EEG are well known: both 'conventional' and 'atypical' antipsychotics may increase the high-frequency rhythms, namely alpha and beta power[83]. One half of the patient were on antiepileptic drugs (AEDs, in most cases sodium valproate - VPA), used not for seizures but as mood stabilizers. Chronic AEDs administration can increase EEG theta power, and can modify (either increase or decrease) alpha mean frequency[84]. Only few patients, at the moment of the study, were assuming

benzodiazepines (BZD). BZD can increase fast-frequency EEG components in wake and sleep, and can decrease theta and delta power during sleep[85]. Pharmacological effects on EEG are diffuse on the entire scalp, whereas most of the spectral modifications observed in our study were local; this suggests that the EEG modifications described are more likely due to the disease rather than to the treatments. Though HD is a degenerative disease which affects prominently sub-cortical structures and, in particular, the caudate nucleus, several morphological and neurophysiological data indicate that the brain cortex is diffusely involved[86-88]. In particular, cortical degeneration has been demonstrated in motor, pre-motor[89-91] and visual[88] areas. Functional compensation has been reported in early Alzheimer disease to offset neuronal loss; it is likely that such mechanism may also occur in other neurodegenerative diseases, particularly in HD[92]. Malejko et al. (2014) described, in HD patients, enhanced fMRI signalling in the striatum as well as in the orbitofrontal cortex/anterior insula, and interpreted these findings as the evidence for "*functional compensation in pre-manifest HD, which may suggest a defence mechanism in neuro-degeneration*"[92]. The PREDICT-HD study indicated that the prodromal phase of HD is associated with abnormal interhemispheric interactions among motor areas, and that these changes may contribute to increased motor symptoms and deficits in the executive control of movement[89]. Another study provided evidence of early compensatory activation (hyperactivation) of right-hemisphere inhibition and attention reorienting centers, despite an absence of cortical atrophy[93]. In our study, the EEG modifications observed in the motor areas were bilateral, though more evident on the right side (Figures 1, 2). Our results confirm that the response inhibition in HD is associated with altered functioning in brain networks that govern inhibition and motor control.[94] This hypothesis is further supported by the absence of EEG modifications in motor areas during REM, when the motor activity is markedly reduced[82] (Figure 4). EEG power spectra measured in the motor areas, during wake and sleep, showed significant correlations with several clinical

indexes (age, disease duration, burden, UHDMRS, BMI) which all reflect, directly or indirectly, the severity of the disease. When comparing our results with previous literature, however, it must be considered that in our study we did not enrol prodromal HD subjects. Moreover, HD patients showed modification of EEG activity in limbic areas (particularly in the posterior cingulate cortex) during sleep: these consisted in reduced theta and alpha power in REM, and reduced theta power in NREM. The slow oscillations occurring during NREM sleep and theta oscillations present during REM sleep have been considered of critical relevance for memory formation and consolidation.[95, 96] Therefore, these modification could be related to the memory impairment described in HD: it has been reported that the cingulate cortex undergoes structural degeneration during early stages of HD; and that cingulate dysfunction may contribute to deficits in mood, emotional processing, and visual working memory in HD.[97]

Several Authors have studied EEG features in HD and in presymptomatic subjects[98-117].

Author	Year	Patients	HD	Pre HD	Method	Sleep	Alpha	Beta	Theta	Delta	Other	Correlations
Patterson et al.	1948	26	no	26 'at risk'	EEG	no					Abnormalities in motor regions	Predictive
Harvald	1951	25	2	23	EEG	no	↓				low-voltage fast pattern	
Sem-Jacobsen et al.	1955	1	yes	no	ECoG	no	↓			↑		Evolution with age
Puca et al.	1965		yes	no	PSG	yes					↑ spindles	Clinical state
Chandler	1966	23	no	23	EEG	no						Predictive value
Scott et al.	1972	95	yes	no	EEG	no					Low voltage	Cortical atrophy
Sishta et al.	1974	16	yes	no	EEG	yes (barbiturates)	↓				Decreased spindles, K-complexes	No
Iakhno	1985	11	yes	no	Polygraphy	yes				↓	Increased spindles	Cortical atrophy
Pokrovskaia et al.	1988	93	yes	no	EEG	no	↓					Severity of disease
Streletz et al.	1990	10	yes	no	Q-EEG	no	↓		↑			Clinical stage of dementia
Bylsma et al.	1994	16	yes	no	Q-EEG	no	↓	↑	↓	↑		Neurological and cognitive impairment
Landau, Cannard	2003	1	yes	no	EEG	no	↓				Epileptiform activity	Juvenile variant
De Tommaso et al. Bellotti et al.	2003 2004	20	13	7 'at risk'	Q-EEG, FFT, artificial neural network	no	↓		↑	↑		CAG, clinical state
Ullrich et al.	2004	1	yes	no	EEG	no					Epileptiform activity	Juvenile variant
van der Hiele et al.	2007	16	no	yes	Q-EEG	no	↓		=			No
Hunter et al.	2010	27	24	3	Q-EEG	no	↓			↑		CAG, clinical state
Painold et al.	2010	55	yes	no	EEG mapping	no	↓	↓	↑	↑	Reduced global power	Cognitive and motor impairment
Painold et al.	2011	55	yes	no	LORETA	no	↓	↓	↓	↑		Cognitive and motor impairment
Ponomareva et al.	2014	29	no	yes	Q-EEG	no	↓		↓		Reduced alpha-theta border	CAG

Most Authors have described decrease of the alpha power[99, 100, 104, 106-111, 113-117] and increase of slow frequencies (delta and theta) [100, 107-109, 111, 114-116]. In a LORETA EEG study,

performed during controlled wake, Painfold et al. (2011)[116] observed that theta, alpha and beta power were diffusely decreased from early to late stages of the disease; whereas in the advanced disease stages patients showed a significant increase in delta power, mainly in the right orbitofrontal cortex[116]. Most studies have focused on correlations between EEG and clinical parameters. In previous studies, EEG modifications have been related to clinical state[101, 106, 109, 111, 114-116], cognitive impairment[107, 108, 115, 116], cortical atrophy[103, 105], CAG repeats[109, 111, 114, 117], evolution with age[100]. Other Authors have looked for a predictive value of EEG in subjects 'at risk' of developing HD[98, 102]. Most studies, anyway, focused on wake EEG, and only three reports, with small samples of HD patients, investigated EEG during spontaneous[101, 105] or induced[104] sleep with discordant results concerning the modifications of sleep spindles. When compared to previous literature, our study confirmed the increase in low-frequency bands power in HD patients during wake, but did not show confirm reduction in the alpha power. Comparable quantitative data on the sleep EEG in HD, to the best of our knowledge, are not available. The interpretation of the mechanism of sleep-related motor pattern is a clinically relevant issue in HD, since sleep disorders can worsen cognitive performance and quality of life. In this context, we believe that the definition of abnormalities in cortical activity, evaluated by means of scalp EEG, can help to understand the pathogenic mechanism of the motor disorder and can orient therapeutic strategies.

In conclusion, our EEG data suggest a defined pattern of motor cortex dysfunction during wake and sleep, which correlates with the clinical and polysomnographic evidence of increased motor activity during wake and NREM, and nearly absent motor abnormalities in REM. It could be hypothesized that EEG modifications reflect motor cortex impairment or, conversely, an effort to counterbalance abnormal motor output. Further studies, including modulation of cortical excitability, could help to understand the cortical neurophysiology of HD. As stated in the Methods, in moderate-to-severe HD patients, the presence of severe

motor, behavioural and psychiatric symptoms does not allow to withdraw pharmacological therapies; future studies are needed, which should enrol prodromal or mild HD subjects. We believe that characterization of these mechanisms of cortical motor control could support therapeutic strategies.

Conclusions

Though our results appear strikingly different from those reported in the previous papers of the French group[118-120], we believe that we may likely be describing the same phenomenon with different words. We agree that the complex of motor behavior observed during sleep in HD patients is not fully described by the term 'periodic limb movement', since it involves the trunk and often the whole body. Nevertheless our observations suggest that these abnormal motor activity, seen over long periods of time, show an evident periodicity. All the movements recorded in video-PSG are characterized by an EMG activation of the upper and lower limbs, sometimes followed by a sequence of more complex motor activation. Also, we fully agree that cortical arousals are strictly associated with such motor disorder. We suggest that periodic movements and concomitant arousal fluctuations may be explained as a an atypical periodic movement is sleep, occurring in patients with an extreme disregulation of motor control. The interpretation of the mechanism of sleep-related motor pattern in HD is relevant since it can orient therapeutic strategies[121].

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