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Huntington's disease : hypothalamic, endocrine and metabolic aspects

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Chapter 7

Increased hypothalamic-pituitary-adrenal axis activity in Huntington's disease

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ABSTRACT

Context: Huntington's disease (HD) is a fatal hereditary neurodegenerative disorder characterized by motor, cognitive and behavioral disturbances. Hypothalamic-pituitary-adrenal (HPA) axis dysfunction could contribute to a number of HD signs and symptoms, however, no data are available on cortisol diurnal variations and secretory dynamics in HD patients. *Objective:* To perform a detailed analysis of HPA axis function in HD patients in relation to clinical signs and symptoms. *Design, setting & participants:* Twenty-four hour cortisol secretion was studied in eight early-stage, medication-free HD patients and eight age-, sex- and body mass index (BMI)-matched controls in a clinical research laboratory. Cortisol levels were measured every 10-min. *Main outcome measures:* Multi-parameter auto-deconvolution and cosinor regression were applied to quantify basal, pulsatile and total cortisol secretion rates as well as diurnal variations in cortisol levels. *Results:* Total cortisol secretion rate and the amplitude of the diurnal cortisol profile were both significantly higher in HD patients compared with controls (3490 ± 320 *vs.* 2500 ± 220 nmol/L/24h, $p = 0.023$ and 111 ± 14 *vs.* 64 ± 8 nmol/L, $p = 0.012$, respectively). Cortisol concentrations in patients were particularly increased in the morning and early afternoon period. In HD patients, mean 24 h cortisol levels significantly correlated with total motor score, total functional capacity as well as BMI. *Conclusions:* HPA axis hyperactivity is an early feature of HD and is likely to result from a disturbed central glucocorticoid feedback due to hypothalamic pathology. HPA axis dysfunction may contribute to some signs and symptoms in HD patients.

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by an expanded CAG repeat size in the gene encoding the protein huntingtin.[1] The disease is characterized by chorea, cognitive deterioration, and psychiatric and behavioral problems.[1] Other debilitating but less well-known features of HD are weight loss, sleep disturbances and autonomic nervous system dysfunction, the causes of which are poorly understood.[2,3] However, as neuronal inclusions of mutant huntingtin, the neuropathological hallmark of HD, and substantial atrophy and cell loss have been reported in the hypothalamus of HD patients, neuroendocrine perturbations may be involved.[2,4-6]

Recently, progressive alterations in the hypothalamic-pituitary-adrenal (HPA) axis function were reported in the R6/2 mouse, the most widely used transgenic model of HD.[7] R6/2 mice show progressive increases in serum and urine corticosterone levels which is accompanied by a Cushing-like syndrome.[7] Increased urine and serum cortisol levels have also been reported in HD patients.[7-10] However, these studies applied a single or a few baseline measurements, which is clearly not adequate to assess either the pulsatile nature of cortisol secretion or its robust diurnal rhythmicity. Apart from mean levels, both the pulsatile secretion patterns and the diurnal variations are thought to be essential for normal hormone function.[11] Indeed, substantial diurnal rhythm disturbances, attributed to aberrant signaling by the suprachiasmatic nucleus (SCN), have been described in both HD patients and animal models.[12,13] As the activity of the suprachiasmatic nucleus, the body's master clock, is accurately reflected in the diurnal fluctuations of plasma cortisol levels,[14,15] we hypothesized that both the diurnal rhythmicity of plasma cortisol and its secretion pattern are likely to be perturbed in HD patients.

We tested this hypothesis by applying circadian rhythmicity analysis and deconvolution of 24 h plasma cortisol concentration profiles in both early stage HD patients and healthy matched controls.

SUBJECTS AND METHODS

Subjects

Eight early-stage HD patients and eight healthy control subjects, matched for age, sex, and body mass index (BMI), were enrolled in the study. Clinical details are summarized in **Table 1**. In the patient group, mutant CAG repeat size ranged between 41 and 50. The clinical diagnosis of HD was made by a neurologist specialized in movement disorders (R.A.C.R.). The Unified Huntington's Disease Rating Scale (UHDRS) was used to assess HD symptoms and signs.[16] All subjects were free of medication. Subjects were eligible for participation after exclusion of hypertension, any known (history of) pituitary disease, recent intentional weight change (>3 kg weight gain or loss within the last 3 months), and any other chronic conditions except HD. Written informed consent was obtained from all subjects. The study was approved by the ethics committee of the Leiden University Medical Center.

Clinical protocol

Subjects were admitted to the Clinical Research Center for 24 h blood sampling. Two women (one patient and one control) were postmenopausal, the other women were studied in the early follicular phase of their menstrual cycle. A cannula was inserted into an antecubital vein 45 min before the start of blood sampling at 1630 h. Blood samples were collected with S-monovetten (Sarstedt, Etten-Leur, The Netherlands) from a three-way stopcock that was attached to a 0.9% NaCl and heparin (1 U/ml) infusion (500 ml/24 h) to keep the cannula from clotting. Sampling was performed through a long line to prevent sleep disruption by investigative manipulations. During 24 h, blood was collected in serum tubes at 10-min intervals. Blood was allowed to clot and, within 60 min of sampling, all tubes were centrifuged at 4000 rotations/min at 4 ºC for 20 min, and plasma was stored at -80 ºC until assay. Three standardized meals were served at 0900, 1300, and 1900 h (Nutridrink, 1.5 kcal/ml, 1500–1800 kcal/d; macronutrient composition per 100 ml: protein, 5 g; fat, 6.5 g; carbohydrate, 17.9 g; Nutricia, Zoetermeer, The Netherlands). Subjects remained sedentary except for bathroom visits. Twenty-four hour urine was collected for the determination of creatinine, catecholamines and cortisol concentrations. No daytime naps were allowed. Lights were switched off at 2300 h and, the next morning, subjects were awakened at 0730 h.

Body composition

Bioelectrical impedance analysis was used to assess lean body mass and fat percentage at 0800 h.

Assays

Plasma cortisol was measured by radioimmunoassay (GammaCoat™, DiaSorin, Stillwater, Minnesota, USA). The detection limit of the assay was 25 nmol/L, and the interassay variation ranged from 2 to 4%. Urine cortisol levels were assessed by the same assay after purification over a C18 column. Samples from each patient and matched control were handled in the same run. Urine creatinine was measured by a fully automated P 800 Modular system (Roche, Almere, the Netherlands). Urinary epinephrine, norepinephrine and dopamine concentrations were assessed by high performance liquid chromatography with electron capture detection (ESTA-Coulochem, Chelmsford, MA, USA).

Calculations and statistics

Deconvolution analysis. A recently developed, fully automatic, multi-parameter deconvolution procedure, *AutoDecon,* was used to estimate various specific measures of secretion and plasma disappearance rate of cortisol, considering all plasma hormone concentrations and their dose-dependent intra-sample variance simultaneously.[17] The *AutoDecon* process is a statistically based algorithm to test the significance of hormone secretion events, obviating the subjective nature of previously used deconvolution methods.[17] Apart from the initial concentration and the basal secretion rate, which both were initialized to zero, the *AutoDecon* algorithm requires only two approximations of the parameter values that are to be estimated: (1) The standard deviation of the Gaussian-shaped secretion events (Secretion*SD*) which is generally initialized as half of the data-sampling interval, and (2) a starting values for the elimination parameter, or hormone half-life.[17] Thus, for 10-min sampled data, the Secretion*SD* was initialized to 5-min together with a starting value for the cortisol half-life of 65-min.[18] To account for intrinsic errors in the estimates of hormone secretion and removal rates, the *AutoDecon* algorithm was then used to find the best fits for both parameters.[18] The following parameters

of the cortisol time series were estimated: number of secretory bursts, secretory burst half-duration (duration at half-maximal amplitude), mean mass secreted per burst, hormone half-life, basal secretion rate, pulsatile secretion rate, and total secretion rate.

Diurnal rhythmicity analysis. Twenty-four-hour variations in plasma cortisol concentrations were assessed by cosinor regression, an algorithm that fits a cosine function to the data using repeated nonlinear regression.[19] This analysis estimates an acrophase, which is the clock time during the 24 h period at which hormone concentration is maximal; a mesor, which is the average value about which the diurnal rhythm oscillates; and an amplitude, which is half the difference between the peak and nadir values of the 24 h concentration series. Furthermore, in order to assess the effects of distinct circadian time frames on possible cortisol secretion differences between patients and controls more accurately, we divided the 24 h cortisol concentration series into six equal epochs in which we compared mean cortisol concentrations between patients and controls. The time epochs were defined as follows: (I) 1630 h – 2030 h, (II) 2030 h – 0030 h, (III) 0030 h – 0430 h, (IV) 0430 h – 0830 h, (V) 0830 h – 1230 h, and (VI) 1230 h – 1630 h.

Approximate entropy (ApEn). ApEn is a model-independent statistic used to quantify the regularity of a time series, in which is measured, within a predefined tolerance r given a pattern of window length m, the likelihood of a similar pattern in the next incremental window.[20] Greater regularity yields smaller ApEn values, whereas greater independence among sequential values of a time series yields larger ApEn values. ApEn parameters of m = 1 and r = 20% of the intra-series standard deviation were used, the statistical suitability of which has been established previously.[21] Data are also presented as normalized ApEn ratios, defined by the mean ratio of absolute ApEn to that of 1000 randomly shuffled versions of the same time series.

Statistical analysis. Results are expressed as mean ± standard error (SE) unless otherwise specified. Unpaired *t* tests were used to assess group differences. Repeated measures analysis of variance (ANOVA) was used to compare mean cortisol levels between patients and controls during specific time epochs within the circadian cycle. Spearman's correlation coefficient was applied to assess all correlations. All tests were two-tailed and significance level was set at $p < 0.05$. Statistical analyses were performed using SPSS for Windows (release 14.0, SPSS, Inc., Chicago, IL).

RESULTS

Subjects

The HD and the control group did not differ with respect to age, gender, BMI, body fat percentage, or lean body mass (all $p \geq 0.754$, **Table 1**).

Deconvolution analysis of cortisol time series

The average 24 h plasma cortisol concentration profiles of HD patients and controls are displayed in **Figure 1**. Illustrations of representative cortisol concentration profiles and corresponding secretion rate profiles in one HD and the matched control subject are presented in **Figure 2**. Deconvolution analysis showed that the total 24 h cortisol secretion rate was significantly higher in HD patients compared with controls (3490 ± 320 *vs.* 2500 ± 220 nmol/L/24 h, $p = 0.023$). In addition, there was also a trend for a higher total pulsatile cortisol secretion rate

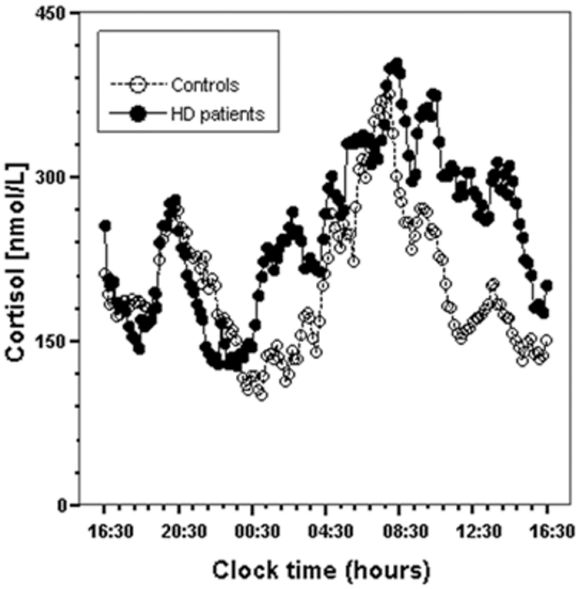
(2830 ± 330 *vs.* 2060 ± 180 nmol/L/24 h, p = 0.058). Basal cortisol secretion rate, number of secretion bursts, and mean hormone mass secreted per burst all tended to be higher as well, although these measures did not reach statistical significance (p ≥ 0.155). Details of all deconvolution-derived cortisol secretory kinetics are presented in **Table 2**.

Table 1. Characteristics of the study population

	HD patients†	Controls†	p-value‡
Male/female	5/3	5/3	-
Age (y)	46.3 (3.8)	47.6 (3.6)	0.804
BMI	23.9 (1.1)	24.2 (0.7)	0.829
Fat (%)	25.4 (2.8)	25.8 (2.7)	0.927
Lean body mass (kg)	57.1 (3.6)	55.5 (3.3)	0.754
BDI score	7.0 (1.8)	3.3 (0.8)	0.085
Mutant CAG repeat size	44.9 (1.0)	-	-
Disease duration (y)	5.1 (1.1)	-	-
UHDRS motor score	20.3 (6.4)	-	-
UHDRS behavioral score	10.5 (4.7)	-	-
TFC score	11.8 (0.8)	-	-

†) Values are indicated as mean (SE).
‡) Differences between groups were assessed by unpaired t-tests.
Abbreviations: BDI = Beck Depression Inventory; BMI = Body Mass Index; TFC = Total Functional Capacity; UHDRS = Unified Huntington's Disease Rating Scale.

Figure 1. Mean plasma cortisol concentrations in HD and control subjects. *Sampling started at 1630 h and was continued at 10-min intervals for 24 h.*



Diurnal rhythmicity analysis

The results of the cosinor analysis of plasma cortisol concentration series are listed in **Table 3**. The acrophase of the cosine fit occurred in the early morning for both patients and controls and was not significantly different. However, the amplitude of the cosine function describing the diurnal plasma cortisol oscillations round the mean was significantly higher in HD patients compared with controls (111 ± 14 *vs.* 64 ± 8 nmol/L, p = 0.012). There was also a trend for a higher mesor in HD patients than in controls (p = 0.099). Repeated measures ANOVA demonstrated that the mean plasma cortisol concentrations were significantly higher in HD patients compared with controls during epochs V (i.e. 0830 h – 1230 h; 320 ± 20 *vs.* 220 ± 20 nmol/L, p = 0.002) and VI (i.e. 1230 h – 1630 h; 250 ± 20 *vs.* 160 ± 20 nmol/L, p = 0.007), but not during epochs I to IV (i.e. 1630 h – 0830 h; all p ≥ 0.133). Therefore, using the deconvolution best fit models, we estimated pulsatile and total cortisol secretion rates for epochs I-IV and V-VI separately. This analysis revealed that while pulsatile and total cortisol secretion rates did not significantly differ between HD and control subjects during the 1630 h to 0830 h period (pulsatile secretion: 1860 ± 290 *vs.*

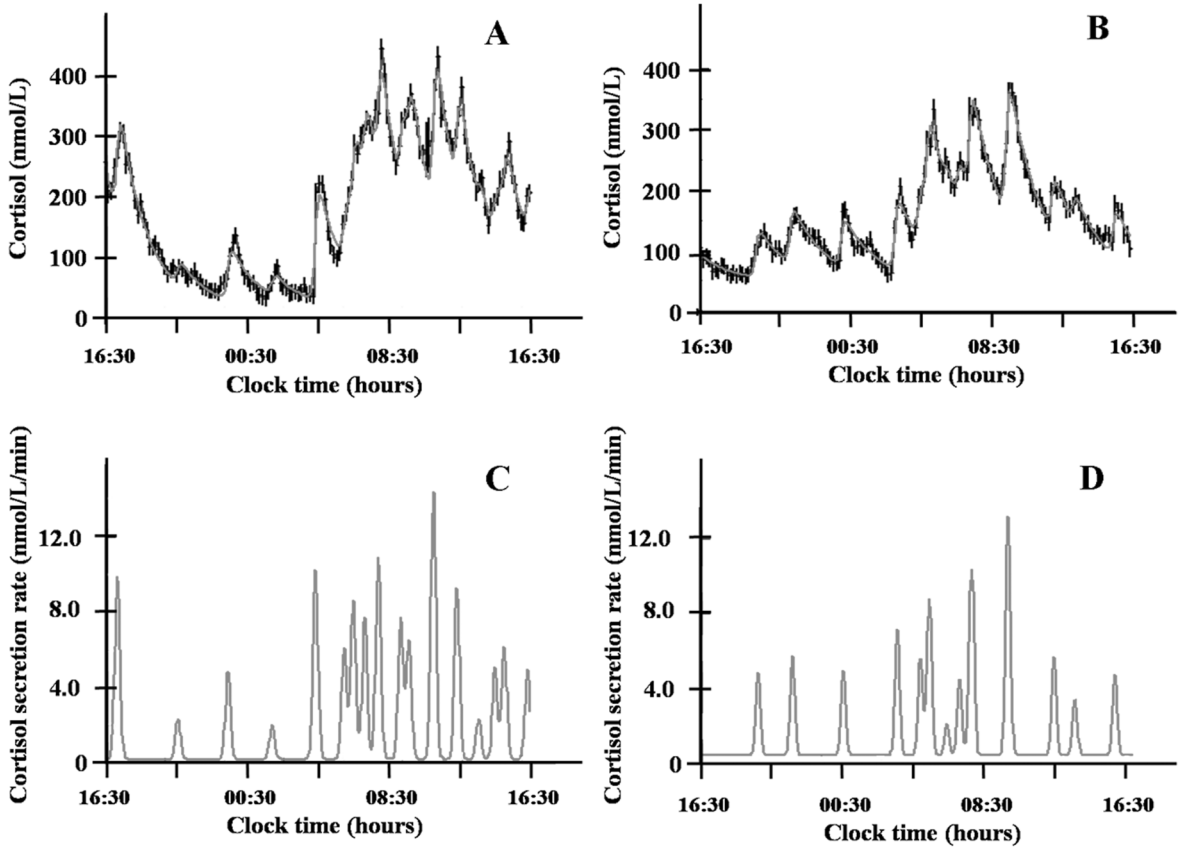
Table 2. Deconvolution analysis of 24 h plasma cortisol concentrations.

	HD patients†	Controls†	p-value‡
Half-life (min)	69.5 ± 5.1	79.6 ± 5.1	0.187
Pulse half-duration (min)	22.1 ± 4.2	15.5 ± 3.2	0.241
Pulse frequency (no./24 h)	14.4 ± 1.3	14.1 ± 0.5	0.863
Mean mass secreted per pulse (nmol/L)	250 ± 30	200 ± 20	0.155
Basal production rate (nmol/L/24 h)	0.45 ± 0.13	0.31 ± 0.06	0.340
Pulsatile production rate (nmol/L/24 h)	2830 ± 330	2060 ± 180	0.058
Total production rate (nmol/L/24 h)	3490 ± 320	2500 ± 220	0.023*
Percent pulsatile (%)	81 ± 5.1	83 ± 3.4	0.760

†) Values are indicated as mean ± SE.

‡) Differences between groups were assessed by unpaired t-tests: * $p < 0.05$

Figure 2. Deconvolution analysis of cortisol time-series. *The AutoDecon deconvolution analysis provided excellent fits to the data of individual subjects. Representative 24 h cortisol concentration profiles with fitted curves in a patient with HD (A) and the matched control subject (B). The lower panel depicts the corresponding deconvolution estimated secretory profiles in the same patient (C) and control (D).*



1540 ± 200 nmol/L/24 h, p = 0.382; total secretion: 2300 ± 290 *vs.* 1840 ± 210 nmol/L/24 h, p = 0.277), they were almost two-fold higher in HD patients during the 0830 h to 1630 h period (pulsatile secretion: 970 ± 90 *vs.* 510 ± 60 nmol/L/24 h, p = 0.001; total secretion: 1190 ± 80 *vs.* 660 ± 70 nmol/L/24 h, p << 0.001).

Regularity of plasma cortisol concentration time series

The ApEn values of the plasma cortisol time series in HD patients were not significantly different from those in controls (0.94 ± 0.08 vs. 0.90 ± 0.06, p = 0.673). The same held for ApEn ratios (0.51 ± 0.04 vs. 0.49 ± 0.03, p = 0.789).

Urine analysis

Table 3. Cosinor analysis of diurnal cortisol concentrations.

	HD patients†	Controls†	p-value‡
Amplitude (nmol/L)	111 ± 14	64 ± 8	0.012*
Mesor (nmol/L)	233 ± 24	186 ± 11	0.099
Acrophase (hh:mm)	07:26 ± 01:46	05:25 ± 02:19	0.503

†) Values are indicated as mean ± SE.
‡) Differences between groups were assessed by unpaired t-tests: * p < 0.05

Urine cortisol levels were also higher in HD patients, although the difference failed to reach statistical significance due to substantial inter-individual variability (114 ± 26 *vs.* 82 ± 13 nmol/L; p = 0.302). There were no significant differences in urinary adrenalin, noradrenalin and dopamine levels (all p ≥ 0.10).

Table 4. Clinical correlates of cortisol levels in Huntington's disease patients

	Mean 24 h cortisol level [nmol/L]†
Motor score	0.74 (0.037) *
Behavioral score	-0.11 (0.779)
BDI score	0.15 (0.733)
TFC	-0.88 (0.004) **
BMI	-0.52 (0.037) *
CAG repeat size	0.20 (0.643)

†) Values are indicated as Spearman's (p-value): * p < 0.05, ** p < 0.01
Abbreviations: AUC = Area Under the Curve; BDI = Beck Depression Inventory; BMI = Body Mass Index; TFC = Total Functional Assessment; UHDRS = Unified Huntington's Disease Rating Scale.

Cortisol levels in relation to clinical phenotype

In HD patients, mean 24 h cortisol concentration significantly correlated with total motor score, total functional capacity and BMI (**Table 4**).

Cortisol levels in relation to mutant CAG repeat size

Although mutant CAG repeat size was not significantly related to mean cortisol levels (**Table 4**), it did significantly correlate with both 24 h pulsatile cortisol secretion rate (r = 0.76, p =

0.030) and pulse half duration (r = 0.85, p = 0.007). There were also trends for the associations between CAG repeat size and mean cortisol mass secreted per burst (r = 0.68, p = 0.062) and total 24 h cortisol secretion rate (r = 0.61, p = 0.108).

DISCUSSION

We present the first detailed description of cortisol secretory dynamics in patients with HD. We found that the total 24 h cortisol production rates were significantly elevated in HD patients. The increase in cortisol production was primarily confined to the morning and early afternoon period. In addition, circadian rhythmicity analysis revealed a significantly higher amplitude of the diurnal cortisol concentration profile in HD patients. These findings point towards a disturbed central glucocorticoid feedback regulation in HD patients and indicate that HPA axis dysfunction is an early feature of the disease.

The negative feedback inhibition of cortisol production is regulated by two receptor subtypes in the brain: The high-affinity mineralocorticoid receptors (MRs) in the hippocampus that determine basal cortisol levels, and the low-affinity glucocorticoid receptors (GRs) in the hypothalamus (primarily the paraventricular nucleus (PVN)), pituitary, cortex and elsewhere in the brain, that constrain cortisol secretion during the circadian peak or acute stress.[22] Cortisol preferentially binds to high-affinity receptors before filling low-affinity receptors.[23] Therefore, the effect of MRs predominates in the early nocturnal period when cortisol levels are low, whereas the effect of GRs dominates in the morning, when cortisol levels are highest.[22] As in HD patients the differences in cortisol levels were mainly confined to the morning and early afternoon period, disturbed GR function is likely to underlie increased cortisol production in HD patients. Our hypothesis of diminished hypothalamic feedback as the primary cause of elevated plasma cortisol levels in HD patients would imply either decreased regularity (i.e. increased ApEn) of plasma cortisol concentration time series and/or decreased coupling between ACTH and cortisol secretion.[24] As cortisol ApEn did not differ between HD patients and controls, our findings are consistent with decreased coupling between ACTH and cortisol secretion in HD, however, additional experiments are required to confirm or refute this hypothesis.

Impaired GR function may result from pathology of brain structures enriched in GRs, such as the hypothalamic PVN. Indeed, there are indications for PVN pathology in HD,[25,26] although additional quantitative morphometric studies are needed to pinpoint its exact nature.[2] Transcriptional dysregulation caused by mutant huntingtin might also play a role, while direct interaction of GRs with mutant huntingtin is unlikely as suggested by Diamond et al. [27] In turn, loss of GR function may aggravate HD pathology as aggregation and nuclear localization of mutant huntingtin fragments containing the expanded polyglutamine stretch can be modulated by the GR, a well-characterized transcriptional regulator.[27]The increased diurnal amplitude of plasma cortisol levels in HD patients is also likely to be centrally mediated, resulting from pathology of hypothalamic structures directly involved in the autonomic innervation of the adrenal cortex, namely the PVN and the SCN.[14,28] Utilizing a neuronal pathway between the SCN, the parvocellular subdivision of the PVN (containing both autonomic and CRH neurons), and the adrenal cortex,[28,29] the SCN is thought to exert an inhibitory effect on cortisol release.[30] Indeed, apart from PVN pathology,[2] there are also indications that the SCN is affected in HD. Marked disruption of expression of the circadian clock genes *mPer2*, *mBmal1*, and *prokineticin 2* in the SCN have been reported in the R6/2 mouse model of HD.[12,13] Furthermore, the expression levels of both vasoactive intestinal

polypeptide and its receptor VPAC2 in the SCN were recently shown to be decreased in the R6/2 mice.[31]

Our findings extend previous reports of increased cortisol levels in HD patients[7,9,10] and indicate that elevated plasma cortisol levels in HD subjects are secondary to a higher pulsatile cortisol production. Moreover, we found that pulsatile cortisol secretion, which is secondary to pulsatile ACTH release and is thus thought to reflect intermittent hypothalamic drive,[11] correlated with mutant CAG repeat size in HD patients. This finding suggests that increased cortisol secretion in HD is likely to result from central interference of the genetic mutation with HPA axis function rather than being secondary to other neuropsychiatric features of the disease. Even mildly elevated cortisol levels are associated with a number of clinically significant health effects as illustrated by findings of, e.g., plasma lipid disturbances, hypertension, insulin resistance, and impaired cognition in patients with subclinical Cushing's syndrome and major depressive disorder in whom cortisol elevations are not as great as in the classic Cushing's syndrome.[32-34] Therefore, despite the absence of obvious Cushingoid features in HD patients, increased cortisol production is likely to adversely affect their health. Moreover, although our patients were all in an early stage of the disease, we found significant correlations between mean 24 h plasma cortisol levels and the UHDRS total motor score, total functional capacity and BMI, indicating that increases in cortisol levels are likely to be progressive and may become even more clinically relevant in the latter stages of the disease. Indeed, HD patients exhibit a number of symptoms and signs that might partly be attributed to hypercortisolism, such as memory deficits, mood disturbances, skeletal muscle atrophy, impaired glucose tolerance and decreased hippocampal volume.[35-39] However, larger scale studies are needed to confirm an association between high cortisol levels and clinical phenotype in HD patients. This is important as antiglucocorticoid therapy may also hold therapeutic potential for HD patients.[40]

Limitations of this study are the absence of detailed data on ACTH secretion, and dynamic tests exploring the integrity of the HPA axis. Therefore, additional experiments exploring the 24 h ACTH secretion characteristics in association with cortisol levels are required and would thus allow for the calculation of the feedback and feed-forward coupling by the cross-ApEn metrics.[11] In addition, challenge tests such as the dexamethasone suppression test and the CRH test are needed to more fully assess feedback and/or feed-forward effects at various levels of control within the HPA ensemble in HD patients.[11]

In conclusion, we found that cortisol production rate is specifically increased in the morning and early afternoon period in early-stage, medication-free HD patients. Our findings indicate disturbed central glucocorticoid feedback in HD patients, which is likely to result from pathology of the SCN and PVN nuclei of the hypothalamus.

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