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Cortisol and depression in pre-diagnosed and early stage Huntington's disease

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Summary Hypothalamic-pituitary-adrenal (HPA) axis dysfunction and depression have both been shown to occur in Huntington's disease (HD) gene carriers prior to diagnosis (pre-HD) and in diagnosed HD patients. However, the relationship between HPA axis dysfunction and the severity of depressive symptomatology in pre-HD and early-HD has not been systematically examined, despite morning hypercortisolism being a characteristic feature of some subtypes of idiopathic depression. The aim of this study was to investigate whether HPA axis function is related to levels of depression in pre-HD and early-HD. To assess HPA axis function we obtained salivary cortisol concentrations from 20 controls, 20 pre-HD, and 17 early-HD participants at four time points over a 24 h period. Depression symptoms were assessed using the Inventory of Depressive Symptomatology — Self-Report. Of the participants who were found not to be depressed, the early-HD group had significantly lower morning cortisol levels relative to pre-HD and controls. In contrast, the early-HD group with at least mild or greater levels of depression symptoms had a comparable cortisol concentration to pre-HD and controls. The results suggest that early-HD may be associated with hypocortisolism. However when depressed, a hyperactive HPA axis response may still be induced in early-HD and lead to cortisol levels that are similar to pre-HD and controls. Our study reveals that cortisol levels in HD may be modified by the presence or absence of depressive symptomatology. Depression may be an important factor for understanding how the HPA axis is affected in HD, particularly in the morning.

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1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease resulting from an unstable CAG expansion in the HTT gene (The Huntington's Disease Collaborative Research Group, 1993). The condition is characterised by a progressive manifestation of motor disability, cognitive impairment, and psychiatric disturbance. Depression is one of the earliest clinical signs of HD (Duff et al., 2007). One study reported that more than 30% of HD gene carriers initially presented for clinical attention with symptoms of depression in the absence of any neurological motor signs (Shiwach, 1994). Depression in HD is thought to reflect both environmental and endogenous aetiologies (Shiwach, 1994). The high rate of clinical depression in HD, particularly with closer proximity to motor onset, has not been completely explained by the knowledge of a gene-positive status, awareness of emerging neurological symptoms, or familial factors (Almqvist et al., 2003; Julien et al., 2007; van Duijn et al., 2008). It is likely that there is an organic component underlying HD depression.

In depression outside of the context of HD, a key pathological characteristics is hypothalamic-pituitary-adrenal (HPA) axis dysregulation (Gold et al., 1988). The HPA axis is the main physiological regulator of the body's stress response. HPA axis activity involves the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which stimulates adrenocorticotropic hormone (ACTH) release from the pituitary gland. This in turn triggers the production and secretion of cortisol from the adrenal cortex. A negative feedback system then suppresses CRH and ACTH releases. Depression can be associated with either increase or decrease in cortisol levels (Penninx et al., 2007). What is more, some studies report no abnormal HPA axis activity in the presence of a depressed mood (Watson et al., 2002). These inconsistencies may be in part because many factors affect the relationship between depression and cortisol levels, including the chronicity of depression, time of day, sleep quality and fatigue, emotional and physiological stress, physical state, and age. When depression is associated with HPA axis hyperactivity, this is most commonly observed shortly after waking (Sachar et al., 1973). Cortisol concentration is subject to circadian variation (Weitzman et al., 1971) with a marked spike in ACTH and cortisol levels on average 30 min after waking. This *cortisol awakening response* can be interpreted as reflecting the production capacity of the adrenal gland (Pruessner et al., 1997). Abnormally high morning cortisol is often considered a reliable physiological marker of depression (Bhagwagar et al., 2005; Hinkelmann et al., 2009).

With regard to HD, HPA hyperactivity has been identified in transgenic HD mice (Björkqvist et al., 2006), as well as in human HD (Aziz et al., 2009; Björkqvist et al., 2006; Heuser et al., 1991; Kurlan et al., 1988). Elevated cortisol has been recorded in morning blood samples of diagnosed HD patients compared to controls (Leblhuber et al., 1995; Saleh et al., 2009), and in morning saliva samples of pre-diagnosed HD (*pre-HD*) compared to diagnosed HD patients and controls (van Duijn et al., 2010). Only one study has undertaken 24-h HPA axis profiling in human HD, which showed abnormally high morning and afternoon cortisol in the plasma of early-stage HD patients (Aziz et al., 2009).

Despite several papers suggesting that depression in HD could be associated with abnormal HPA functioning (Björkqvist et al., 2006; for review, see Petersén and Björkqvist, 2006), and a broad acceptance that cortisol secretion is commonly altered in both HD and depression, there has been little systematic investigation of the relationship between HPA axis function and depression in HD. In two HD studies (each $n \leq 20$), circulating cortisol levels were not associated with a prior diagnosis of major depression (Heuser et al., 1991) or current depression ratings (Aziz et al., 2009). These studies, however, did not report how the severity of depressive symptomatology changed with diurnal variation in

Table 1 Demographics and clinical information.

		Early-HD (E)	Pre-HD (P)	Control (C)	*p* value	Group comparison[a]
Number of participants		19	20	20		
Demographic information						
Male	*n* (%)	10 (52.6%)	10 (50.0%)	9 (45.0%)	0.89	n.s.
Age (year)[b]	Mean (SE)	58.0 (2.3)	42.5 (2.8)	57.0 (2.7)	<0.001	P < C, E***
	Range	41.8–72.3	19.2–66.2	34.5–73.1	n/a	
Clinical information						
Disease burden	Mean (SE)	401.3 (14.5)	269.3 (22.2)	n/a	<0.001	E > P***
UHDRS Total Motor Score	Mean (SE)	30.1 (3.3)	3.6 (1.0)	2.6 (0.6)	<0.001	E > C, P***
Anti-depressants[c]	*n* (%)	13 (68.4%)	7 (35.0%)	1 (5.0%)	<0.001	E > C, P* P > C*
Current smoker	*n* (%)	3 (15.8%)	4 (20.0%)	2 (10.0%)	0.75	n.s.

Note: The identification of a group difference was based on a one-way analysis of variance or chi-squared tests, with Fischer's exact test applied where necessary to cell counts less than five. Tests were two-tailed. n/a: not applicable. n.s.: no significant difference.

[a] To investigate which groups differed significantly, post hoc group comparisons were undertaken using Bonferroni adjustment (for ANOVA) or standardised residuals (for chi-squared tests) where appropriate. Tests were two-tailed.

[b] Age at the time of assessment.

[c] Anti-depressant medications included tricyclics, selective serotonin-reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs).

* $p < 0.05$.

*** $p < 0.001$.