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## Neuroendocrine and neurotrophic signaling in Huntington's disease: Implications for pathogenic mechanisms and treatment strategies

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## Review article

# Neuroendocrine and neurotrophic signaling in Huntington's disease: Implications for pathogenic mechanisms and treatment strategies



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## ABSTRACT

Huntington's disease (HD) is a fatal neurodegenerative disease caused by an extended polyglutamine tract in the huntingtin protein. Circadian, sleep and hypothalamic-pituitary-adrenal (HPA) axis disturbances are observed in HD as early as 15 years before clinical disease onset. Disturbances in these key processes result in increased cortisol and altered melatonin release which may negatively impact on brain-derived neurotrophic factor (BDNF) expression and contribute to documented neuropathological and clinical disease features. This review describes the normal interactions between neurotrophic factors, the HPA-axis and circadian rhythm, as indicated by levels of BDNF, cortisol and melatonin, and the alterations in these intricately balanced networks in HD. We also discuss the implications of these alterations on the neurobiology of HD and the potential to result in hypothalamic, circadian, and sleep pathologies. Measurable alterations in these pathways provide targets that, if treated early, may reduce degeneration of brain structures. We therefore focus here on the means by which multidisciplinary therapy could be utilised as a non-pharmaceutical approach to restore the balance of these pathways.

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## 1. Introduction

Huntington's disease (HD) is a fatal autosomal dominant neurodegenerative disease caused by an expanded cytosine-adenine-guanine (CAG) repeat sequence in exon 1 of the Huntingtin gene (*HTT*) (The Huntington's Disease Collaborative Research Group, 1993). This expanded sequence encodes a mutant version of the protein, huntingtin (mHTT), which is associated with ubiquitous molecular and cellular anomalies, widespread neuronal dysfunction and cell loss (Kim et al., 2014) and the presentation of motor and non-motor features, including progressive impairments in motor control, cognitive function and mood (Tabrizi et al., 2013). Evidence also indicates that individuals suffer from sleep disturbances (Morton, 2013; Hansotia et al., 1985; Wiegand et al., 1991; Piano et al., 2015; Arnulf et al., 2008; Lazar et al., 2015a), autonomic abnormalities (e.g. hyperhidrosis, micturition disturbances, swallowing difficulties, sexual dysfunction, altered heart rate variability) (Andrich et al., 2002; Kopal et al., 2010) and metabolic irregularities (Browne et al., 1997; Mazziotto et al., 1987), with some non-motor features, such as cognitive and sleep abnormalities, emerging years before the onset of motor signs (Tabrizi et al., 2011; Lazar et al., 2015a).

Although the pathophysiology underlying the development and progression of these clinical features is complex, the accompanying alterations in neuroendocrine signalling, including cortisol (Aziz et al., 2009a; Hubers et al., 2015) and melatonin (Kallioliia et al., 2014; Aziz et al., 2009b) release, and changes in circadian rhythmicity (Morton et al., 2005; Aziz et al., 2010) suggest that the activity of the hypothalamic-pituitary-adrenal (HPA) axis and the suprachiasmatic nucleus (SCN) are impaired in HD (see Table 1 for summary of HD pathologies relevant to this review). Neuropathological changes including volume loss, the loss of orexin-releasing neurons and decreased protein levels of vasoactive intestinal peptide (VIP) and arginine vasopressin (AVP) in the hypothalamus support this supposition (Politis et al., 2008; Soneson et al., 2010; Petersén et al., 2005).

The HPA-axis is central to neuroendocrine signalling. Indeed, an intricate balance exists between neuroendocrine signalling and expression of neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF) (Issa et al., 2010; Smith et al., 1995a). In this review, we present for the first time the biological impact of HPA-axis dysfunction on circadian rhythm, neuroendocrine signalling, and neurotrophic factor support in HD (for a diagrammatic view, see Fig. 1). We also draw on existing evidence in animal models and patients with HD and other disorders to review non-pharmaceutical treatment strategies, particularly multidisciplinary therapy, exercise, cognitive therapy and social interaction, which may positively impact on HPA-axis dysfunction and potential downstream mechanisms and thereby delay disease onset in individuals with premanifest HD. Since candidate pharmaceutical treatment strategies for HD have been reviewed recently (Ross et al., 2014), here we detail non-pharmaceutical multidisciplinary approaches as they have been reported to exert beneficial effects on HPA-axis function, circadian rhythm and BDNF, are of minimal cost and can be implemented throughout life with few side effects.

### 1.1. Normal function of the HPA-axis and the SCN

The structures of the HPA-axis, including the hypothalamus, pituitary and adrenal glands, function in a tightly regulated manner to control responses to physiological and psychological stress, autonomic and immune functions and sleep-wake behaviour through the release of hormones, such as cortisol, in a circadian manner (Webster Marketon and Glaser, 2008; Ulrich-Lai and Herman, 2009; Steiger, 2002).

The paraventricular nucleus (PVN) releases corticotrophin releasing factor (CRF) into the hypophyseal portal system, where it stimulates the release of adrenocorticotrophic hormone (ACTH) from the corticotropes of the anterior pituitary (Rivier and Vale, 1983). ACTH is released into the systemic circulation and stimulates the adrenal cortex to release glucocorticoids, such as corticosterone in mice and cortisol in humans, which regulate responses to stress in central and peripheral systems. These glucocorticoids then provide negative feedback, inhibiting further release of CRF and ACTH by binding to glucocorticoid receptors (GRs) at the PVN and pituitary level, inhibiting further HPA-axis activation via glucocorticoid response elements (GREs) (Keller-Wood and Dallman, 1984).

Glucocorticoid release is subject to inputs from other brain regions, particularly the amygdala, stria terminalis and hippocampus, which are all regions fundamentally involved in emotional regulation and memory (Hauger and Dautzenberg, 2000). However the basal circadian release of glucocorticoids is facilitated by the connection between the PVN and SCN.

The SCN is located in the anterior hypothalamus and functions as the central circadian clock that is the principle site of circadian rhythm coordination in mammals (Nishino et al., 1976). The SCN receives information from the retina and other brain regions and synchronises the circadian rhythms of the organism emerging at cellular, physiological and behavioural levels to various zeitgebers, the most important of which is ambient light. Synchronization is mediated through neural and humoral signals. On a molecular level the circadian rhythm in mammals is based on an autoregulatory transcriptional-translational feedback mechanism involving *CLOCK* and *BMAL1* transcription factors and *PERIOD* (*PER1*, 2 and 3) and *CRYPTOCHROME* (*CRY1* and 2) core clock genes (Gekakis et al., 1998). This molecular clock regulates a considerable proportion of the human genome. Importantly, through its connections with the PVN and mediation of the HPA-axis, the SCN controls daily variations in melatonin and cortisol release which are involved, amongst other things, in sleep-wake behaviour and autonomic arousal regulation.

More specifically, activity of the SCN is synchronised to the environmental light-dark cycle directly through the retinal-hypothalamic tract and indirectly through the retinogeniculate pathways and conveys this information to other hypothalamic nuclei, the reticular formation and the pineal gland, coordinating the diurnal activities of these brain regions (Brzezinski, 1997). Melatonin coordinates circadian rhythms in response to the day-night cycle and initiates the thermoregulatory cascade, decreasing core body temperature to induce sleepiness (Brzezinski, 1997; Krauchi et al., 2000). The circadian variation of core body temperature is also associated with the internal structure of sleep, particularly with the circadian rhythm of REM (Dijk and Czeisler, 1995).

### 1.2. Stress and the role of cortisol

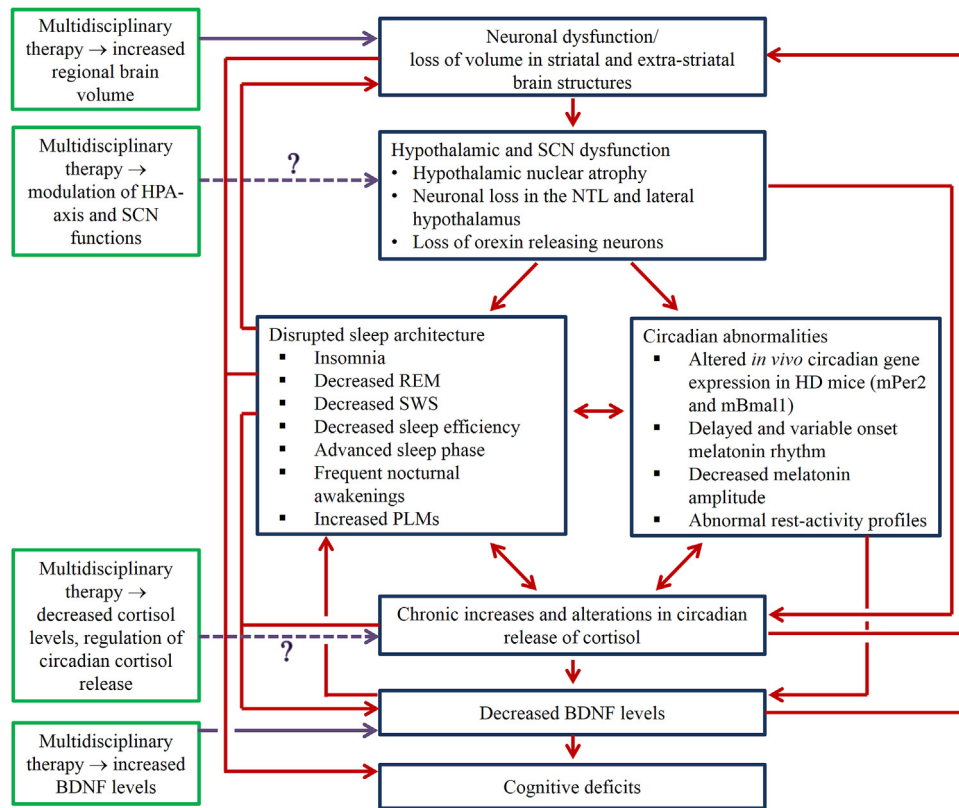
Cortisol secretion follows a circadian rhythm in individuals with normal sleep-wake cycles. Within the first 30 min of awakening, cortisol levels increase by up to 75% (Pruessner et al., 1997). Cortisol levels then tend to plateau and around midnight reach their nadir. There is large variation in circadian cortisol levels between individuals, however morning cortisol levels are relatively stable intra-individually, allowing for measurement of the cortisol awakening response (CAR), which serves as an indication of HPA-axis function and circadian rhythmicity (Stone et al., 2001).

In addition to its natural circadian rhythm, cortisol is released in response to physiological and psychological stress (Staufenbiel et al., 2013). Stress has many contributing factors and occurs when environmental demands surpass the individual's coping abilities (Fink, 2010). The response to stress, particularly adaptation, varies

**Table 1**  
Summary of HD pathologies relevant to this review article.

Pathologies in Huntington's disease	Evidence	References
HPA-axis and SCN pathologies	Mouse models: <ul style="list-style-type: none"> <li>• Hypothalamic degeneration, pituitary and adrenal pathologies</li> <li>• Loss of orexin-releasing neurons</li> </ul>	Petersén et al. (2005), Du et al. (2012), Sathasivam et al. (1999), Björkqvist et al. (2006)
	Premanifest HD <ul style="list-style-type: none"> <li>• Hypothalamic volume loss (shown by voxel-based morphometry)</li> </ul>	Soneson et al. (2010)
	Manifest HD: <ul style="list-style-type: none"> <li>• Hypothalamic volume loss (shown by voxel-based morphometry) Loss of neurons in the nucleus tuberalis lateralis (NTL) and lateral hypothalamus (at post-mortem)</li> <li>• Loss of orexin-releasing neurons (at post-mortem)</li> <li>• Decreased protein levels of vasoactive intestinal peptide (VIP) and arginine vasopressin (AVP) (at post-mortem)</li> </ul>	Petersén et al. (2005), Kremer et al. (1990, 1991), Douaud et al. (2006), Gabery et al. (2010), Kassubek et al. (2004), Aziz et al. (2008), van Wamelen et al. (2013)
Increased cortisol levels	Premanifest HD: <ul style="list-style-type: none"> <li>• Increases in the cortisol awakening response (CAR)</li> <li>• Increased daily cortisol output</li> </ul>	(Hubers et al., 2015; van Duijn et al., 2010)
Decreased BDNF	Mouse models: <ul style="list-style-type: none"> <li>• Decreased brain BDNF levels</li> </ul>	(Zuccato et al., 2005; Pang et al., 2006)
	Manifest HD: <ul style="list-style-type: none"> <li>• Reduction of between 53 and 82% of BDNF in the caudate and putamen (at post-mortem)</li> </ul>	(Ferrer et al., 2000)
Circadian rhythm disturbances	Mouse models: <ul style="list-style-type: none"> <li>• Breakdown in rest-activity cycle</li> <li>• Dysregulation of circadian gene expression, particularly in the SCN</li> <li>• Reduced circadian rhythm of spontaneous electrical activity in SCN neurons</li> </ul>	Morton et al. (2005), Kudo et al. (2011), Maywood et al. (2010)
	Manifest HD: <ul style="list-style-type: none"> <li>• Disturbances in rest-activity profiles</li> <li>• Abnormal day-night ratios</li> <li>• Altered sleep-wake timing</li> </ul>	Morton et al., (2005), Hurelbrink et al. (2005)
Alterations in melatonin release	Premanifest HD: <ul style="list-style-type: none"> <li>• Temporal spread of melatonin rise</li> </ul>	Kallioliia et al. (2014)
	Manifest HD: <ul style="list-style-type: none"> <li>• Decreased mean and acrophase melatonin levels</li> <li>• Temporal spread of melatonin rise</li> <li>• Delayed rise phase</li> </ul>	Kallioliia et al. (2014), Aziz et al. (2009b)
Sleep disturbances	Premanifest HD: <ul style="list-style-type: none"> <li>• Fragmented sleep profile</li> <li>• Decreased theta power during REM sleep</li> </ul>	Lazar et al. (2015a)
	Manifest HD: <ul style="list-style-type: none"> <li>• Insomnia</li> <li>• Decreased REM</li> <li>• Decreased slow wave sleep (SWS)</li> <li>• Decreased sleep efficiency</li> <li>• Advanced sleep phase</li> <li>• Frequent nocturnal awakenings</li> <li>• Increased periodic leg movements (PLMs)</li> </ul>	Morton (2013), Hansotia et al. (1985), Wiegand et al. (1991), Piano et al. (2015), Arnulf et al. (2008), Morton et al. (2005), Neutel et al. (2015)

Premanifest HD = individuals carrying the gene for Huntington's disease who do not yet display overt motor signs, however may exhibit mild cognitive decline and mood disturbances; Manifest HD = individuals carrying the Huntington's disease gene who display overt motor signs of disease, cognitive decline and mood disturbances; HD = Huntington's disease; HPA-axis = hypothalamic-pituitary-adrenal axis; BDNF = brain-derived neurotrophic factor; SCN = suprachiasmatic nucleus; REM = rapid eye movement



**Fig. 1.** The interrelated consequences of HPA-axis and circadian rhythm disruption on BDNF expression and sleep and the implications on neurobiology. Disruption of the HPA-axis and circadian rhythmicity as a result of hypothalamic dysfunction facilitates alterations in cortisol release and disrupted sleep architecture. Conversely, disrupted sleep can lead to increased cortisol and negatively effect the circadian rhythm. Increased cortisol can also disrupt sleep architecture and the circadian rhythm. Circadian rhythm abnormalities and increased cortisol can negatively effect the release of BDNF and this, in turn, can induce cognitive deficits, disrupt sleep architecture and reduce neuronal support which can facilitate the loss of brain volume. Multidisciplinary therapy has the potential to favourably affect this mechanism at several levels. HPA axis = hypothalamic-pituitary-adrenal axis; SCN = suprachiasmatic nucleus; NTL = nucleus tuberalis lateralis; REM = rapid eye movement; SWS = slow wave sleep; PLMs = periodic leg movements; BDNF = brain-derived neurotrophic factor.

among individuals and is influenced by an individual's resilience (Russo et al., 2012). The biological processes that occur in order to allow the individual to adapt to environmental stressors are collectively termed allostasis and involve the release of cortisol and adrenalin among many other chemical mediators (Sterling and Eyer, 1988; Juster et al., 2010).

Cortisol acts to maintain blood pressure, mobilise energy resources and decrease inflammation (Fraser et al., 1999; Petrovsky et al., 1998; Peckett et al., 2011). Although individuals have the ability to adapt to these biological effects of cortisol, excessive or insufficient activation of the HPA-axis can contribute to maladaptive consequences, leading to pathology (McEwen and Stellar, 1993).

### 1.3. Pathological effects of chronic glucocorticoid release

Significant increases in the CAR and daily cortisol output have been documented in premanifest HD (preHD) compared to healthy controls and manifest HD (Hubers et al., 2015; van Duijn et al., 2010; Shirbin et al., 2013), which implies disruption of the circadian rhythm and therefore of the HPA-axis (Aziz et al., 2009a; Politis et al., 2008).

Disruption of the HPA-axis leads to altered circadian release of cortisol (Saper et al., 2005). Severe alterations in glucocorticoids have been shown to exacerbate excitotoxic processes in neurons, predominantly those of the hippocampus (Sapolsky et al., 1988; Crochemore et al., 2005; Sorrells et al., 2014; Stein-Behrens et al., 1994). Chronic exposure to glucocorticoids decreases neurogenesis, arborisation of dendrites and density of synapses in

the hippocampus and prefrontal cortex (PFC) (Crochemore et al., 2005; Tata et al., 2006) and results in abnormalities of the caudate, putamen and amygdala in animal models (Delgado y Palacios et al., 2014). Chronic stress has been shown to modulate the onset and progression of disease features in the R6/1 HD mouse model (Mo et al., 2014a,b). Higher glucocorticoid levels, such as those seen in post-traumatic stress disorder (PTSD), have also been linked to a loss of volume in the PFC and striatum and associated impairments in cognitive function and sleep homeostasis, which suggests that exacerbated cortisol levels, such as those observed in preHD, may accelerate the onset and progression of disease features, particularly cognitive and mood disturbances (Staufenbiel et al., 2013; Sapolsky, 1999). Chronically elevated cortisol levels have also been associated with reduced levels of BDNF in wild-type and schizophrenia rodent models and in humans in other clinical populations, including schizophrenia and major depressive disorder (Issa et al., 2010; Smith et al., 1995a). This reduction in BDNF could further exacerbate loss of volume in striatal and extra-striatal structures and further disrupt melatonin release and HPA-axis function. Such an association between chronic cortisol release and reduced BDNF requires further investigation in preHD for treatment strategies.

### 1.4. Effects of glucocorticoids on BDNF

BDNF is essential for survival, differentiation and outgrowth of neurons in the central and peripheral nervous systems and protects neurons from excitotoxin-induced degeneration (Bemelmans et al., 1999; Husson et al., 2005). BDNF is synthesised in cortical neurons

and delivered to the striatum via axonal transport of vesicles (Altar et al., 1997; Goodman et al., 1996). BDNF deficits have been documented in cell lines expressing mHTT and in brains of HD mouse models and patients at post-mortem (Ferrer et al., 2000; Gauthier et al., 2004; Zuccato et al., 2001, 2005). Analyses of post-mortem brain tissue of four HD subjects indicated regional BDNF deficits of between 53% and 82% in the caudate and putamen compared to age-matched controls (Ferrer et al., 2000; Gauthier et al., 2004), suggesting that volume loss in these regions may, at least in part, be mediated by a lack of neurotrophic factor support.

Significantly elevated glucocorticoids have been reported to decrease the expression of BDNF in animal models and other clinical populations (Issa et al., 2010; Smith et al., 1995a). Chronic stress in rodents induced by repeated restraint results in a negative correlation between plasma glucocorticoid levels and hippocampal BDNF mRNA expression (Murakami et al., 2005; Smith et al., 1995b). Furthermore, exogenous administration of glucocorticoids is associated with a transient, dose-dependent reduction in BDNF mRNA and protein in the hippocampus of adrenalectomized (ADX) rodent models (Hansson et al., 2006; Schaaf et al., 1998). However, five days of oral corticosterone treatment in the R6/1 HD mouse model did not significantly affect hippocampal BDNF expression, emphasising the need to characterise the effects of chronic elevated stress on BDNF levels in HD animal models and patients. It is conceivable that elevated glucocorticoid levels, as observed in preHD, contribute to decreased BDNF expression, thereby potentiating neuronal dysfunction and cell loss in cortical and sub-cortical brain structures.

In addition to supporting normal neuronal functioning, BDNF is thought to be integral in the homeostatic regulation of sleep (Datta et al., 2015). Alterations in BDNF signalling as a result of irregular cortisol regulation may potentiate sleep deficits, which are evident early in HD. The interplay between glucocorticoids, neurotrophic factor support and sleep are not well understood but are likely to be important considerations in better understanding the interaction of the HPA-axis and circadian rhythm disruption as features of HD.

### 1.5. Pathologies of the HPA-axis and SCN in HD

mHTT causes progressive neuronal dysfunction and cell loss in striatal and extra-striatal regions, including the hypothalamic nuclei (Tabrizi et al., 2011; Li et al., 2000). Studies in mouse models report significant degeneration of the hypothalamus, as well as pituitary and adrenal pathologies (Du et al., 2012; Petersén and Björkqvist, 2006; Sathasivam et al., 1999; Björkqvist et al., 2006). Post-mortem and structural imaging studies in HD mutation carriers have reported volume loss in the hypothalamus, with significant hypothalamic nuclear atrophy, neuronal loss (particularly that of the nucleus tuberalis lateralis (NTL) and lateral hypothalamus (Kremer et al., 1990, 1991)) and microglial activation (Politis et al., 2008; Douaud et al., 2006; Gabery et al., 2010; Kassubek et al., 2004). Post-mortem studies have also reported loss of orexin-releasing neurons, responsible for innervating the SCN, in the hypothalamus in HD (Petersén et al., 2005; Aziz et al., 2008). Loss of this neuronal population is thought to contribute to circadian rhythm disturbances, HPA-axis dysfunction and subsequent alterations in cortisol release (Petersén et al., 2005). Moreover, HPA-axis dysregulation has been proposed as a contributing factor to comorbid depression in neurodegenerative diseases, including HD (for a comprehensive review, see Du and Pang, (2015)).

Hypothalamic atrophy has also been reported in preHD individuals using voxel-based morphometry (VBM) (Soneson et al., 2010). This may, at least in part, explain the observed alterations in cortisol release in preHD. A recent study, however, reported no hypothalamic volume loss in preHD individuals at a 12 month follow-up scan (Gabery et al., 2015). These conflicting findings reinforce the need

to better characterise hypothalamic and other regional volumetric changes in preHD, and determine whether such changes mediate or contribute to circadian rhythm disturbances and clinical features in HD.

### 1.6. Circadian rhythm disruption in HD

Circadian rhythmicity is progressively disrupted in HD, suggesting a possible bi-directional relationship with the neurodegenerative disease process (for a review see Videnovic et al. (2014)). Support for this notion comes from transgenic animal models of HD, such as in the R6/2, R6/1 and BACHD mice, which have shown that circadian disruption precedes the presentation of disease features (Morton et al., 2005; Kudo et al., 2011; Maywood et al., 2010). Furthermore, humans with manifest HD also display circadian rhythm abnormalities, with disturbances in rest-activity profiles and abnormal day-night ratios, as well as alterations in sleep-wake timing and melatonin and cortisol profiles (Morton et al., 2005; Videnovic et al., 2014; Hurelbrink et al., 2005). The neurobiology underlying these changes has yet to be clarified.

Several studies point to alterations in the SCN as being central to circadian disruptions in HD. For example, in the R6/2 mouse model of HD the rhythmic transcription of core clock genes in the SCN and other brain regions is disrupted *in vivo*, but then rescued when assessed in *in vitro* explants, suggesting that circadian deficits are due to alterations of the intrinsic circuitry of the SCN (Morton et al., 2005; Maywood et al., 2010). This is supported by a reduced circadian rhythm in spontaneous electrical activity in SCN neurons in BACHD transgenic mice (Kudo et al., 2011). Histopathological studies reveal reduced protein levels of VIP and AVP within the SCN of HD patients at post-mortem (van Wamelen et al., 2013). In transgenic animal models of HD, the decrease in VIP levels is associated with circadian disruption (Fahrenkrug et al., 2007). Recent evidence from Alzheimer's disease (AD) patients indicates that the number of VIP-expressing SCN neurons in the post-mortem brain correlates with circadian rhythm amplitude of motor activity (Wang et al., 2015).

Disruption of circadian rhythmicity has the potential to affect a broad range of molecular, cellular and physiological processes, most noticeably sleep (Lazar et al., 2015b; Archer et al., 2014). Disturbances in sleep are known to have multiple negative consequences on human physiology, including neuronal dysfunction and loss of brain volume (Joo et al., 2013), metabolic disturbances (Schmid et al., 2015), immune dysregulation (Irwin, 2002), impaired cardiovascular function (Zhong et al., 2005), cognitive impairments (Lo et al., 2012) and mood disturbances (Dinges et al., 1997). Sleep disturbance can, by itself, cause further disruption to circadian rhythmicity (Moller-Levet et al., 2013). It is highly likely that sleep and circadian disturbances are interrelated in HD.

### 1.7. Melatonin and sleep disturbance in HD

Melatonin promotes the onset of sleep by inducing the thermoregulatory cascade (Krauchi et al., 2000). Significant decreases in mean and acrophase (times of peak rhythm) melatonin levels have been reported in manifest HD, with trends towards decreased melatonin levels in preHD (Kallioliia et al., 2014). A temporal shift in melatonin release has also been documented in HD mutation carriers, which could explain documented sleep disturbances (Kallioliia et al., 2014). The morning rise phase of melatonin has also been shown to be delayed in HD individuals (Aziz et al., 2009b), which provides a mechanism underlying the delayed sleep-wake timing reported to occur in these patients (Aziz et al., 2010; Goodman et al., 2010). The precise mechanism responsible for the decrease or delayed melatonin levels observed in HD is unclear, but could

potentially be attributed to the progressive neuronal dysfunction in the SCN (Kallioli et al., 2014; van Wamelen et al., 2013).

Disrupted or restricted sleep leads to increased activity of the HPA-axis (Meerlo et al., 2008). Acute sleep deprivation is associated with increased sympathetic activation, reflected by increases in heart rate and blood pressure (Zhong et al., 2005) and has been described as a chronic stressor that can elevate glucocorticoids and exacerbate disease pathways, such as neuronal dysfunction and degeneration (McEwen, 2006; Leproult et al., 1997). It is also important to note that disturbances in sleep, particularly disruption of slow wave sleep and decreased sleep duration, result in declines in cognitive and motor performance, as well as altered mood (Ferrie et al., 2011; Mander et al., 2013a,b, 2015).

Studies in animal models have shown that sleep deficits can negatively affect hippocampal function, and can lead to impaired synaptic plasticity (long-term potentiation) and changes in N-Methyl-D-Aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor signalling and fluctuations in levels of glutamate, a ligand for these receptors (Ravassard et al., 2009; Kopp et al., 2006). Sleep has been reported to promote the formation of branch-specific dendritic spines following motor learning in mice, with disruption of non-REM (NREM) sleep preventing the formation of branch-specific dendritic spines (Yang et al., 2014). Furthermore, sleep has been shown to drive clearance of neurotoxic waste from the central nervous system in mice and disruption of sleep could potentially facilitate accumulation of these substances (Xie et al., 2013). Sleep deficits have also been shown to negatively affect executive functions associated with the PFC, such as working memory and lateral thinking, likely due to the differential activation of adenosine receptors and disruption of synaptic homeostasis (Lo et al., 2012; Harrison and Horne, 1998; Florian et al., 2011). Loss of volume of the frontal, temporal and parietal cortices are associated with sleep deficits (Sexton et al., 2014) and could also affect executive functions associated with these regions.

Sleep disturbances have been reported in manifest HD, with several studies reporting insomnia, decreased REM, slow wave sleep and sleep efficiency, advanced sleep phase, frequent nocturnal awakenings and increased periodic leg movements (PLMs) (Hansotia et al., 1985; Wiegand et al., 1991; Piano et al., 2015; Arnulf et al., 2008; Morton et al., 2005; Neutel et al., 2015). Furthermore, a recent study by Lazar et al. (2015a,b) showed that sleep disruption is evident in preHD, characterised by a fragmented sleep profile and a decrease in theta power during REM sleep (Lazar et al., 2015a). These features were associated with disease burden score. It is notable that sleep deficits seem to appear at a time when cognitive impairments also start to emerge, indicating a potential relationship between these disease features.

Sleep deficits are of particular interest in HD, as cognitive functions associated with both the hippocampus and PFC are affected in this population before disease onset (Tabrizi et al., 2011), and can be negatively impacted by sleep disturbances, as well as increased glucocorticoids (Blagrove et al., 1995; Oei et al., 2006; Belanoff et al., 2001). Ultimately, alterations in circadian rhythm marked by changes in the molecular clock and facilitated by hypothalamic and SCN pathologies, could result in changes in melatonin release and increased cortisol levels, with resultant sleep disturbances, which are likely to potentiate neurodegeneration and associated changes in cognitive and motor deficits and mood disturbances in HD.

### 1.8. Environmental enrichment: a comprehensive non-pharmaceutical strategy to reduce the impact of circadian rhythm disturbances and HPA-axis dysfunction in HD

Several non-pharmaceutical strategies have been employed to ameliorate circadian and HPA-axis dysfunctions in mouse models

of HD, including bright light and behavioural therapy (Cuesta et al., 2014) and environmental enrichment (EE). EE is an experimental approach reported to change intrinsic and behavioural rest-activity circadian rhythmicity and glucocorticoid release and has been widely studied in transgenic and drug-induced AD, Parkinson's disease (PD) and HD mouse models (reviewed in (Nithianantharajah and Hannan, 2006)). EE employs exercise, cognitive and sensory stimulation to promote neurogenesis and improve cognitive and behavioural function, motor features and overall pathological processes underpinning these clinical features (Nithianantharajah and Hannan, 2006; Hannan, 2014; Lazic et al., 2006).

The first demonstration that EE could be beneficial in a genetic animal model involved HD mice (van Dellen et al., 2000) and demonstrated that EE could delay disease onset and progression displayed by improved motor function and preserved peristriatal brain structures. Ensuing investigations revealed that EE has cognitive and body composition benefits in R6/2 (Hockly et al., 2002) and N171 HD mice (Schilling et al., 2004), while also ameliorating cognitive deficits (Nithianantharajah et al., 2008) and affective (depressive-like) abnormalities in R6/1 mice (Pang et al., 2009; Renoir et al., 2013). Considering the more rapid disease progression of the R6/2 model compared to R6/1, this demonstrates that EE is effective in both rapid and more prolonged disease progression phenotypes.

EE has been reported to increase the length of neuronal dendrites in the dorsomedial nucleus of the hypothalamus, which is thought to play a role in the circadian control of sleep and waking behaviours (Chou et al., 2003), and alter stress reactivity in outbred rats (Francis et al., 2002; Mitra and Sapolsky, 2012), and in the female R6/1 mouse model, EE modulates HPA-axis activity (Du et al., 2012). Furthermore, circadian rhythm disturbances have also been ameliorated through bright light therapy and exercise in the R6/2 mouse model (Cuesta et al., 2014). This demonstrates that environmental interventions have the potential to modulate functions of the HPA-axis and the SCN in mouse models of HD and warrants further investigation into whether this can be recapitulated in the human HD population.

Moreover, EE in HD mice has been shown to rescue BDNF protein levels in the striatum and hippocampus (Spires et al., 2004), with associated delays in disease onset, including a reduction in cognitive decline (Nithianantharajah et al., 2008). These studies suggest that modulation of HPA-axis function and circadian rhythm facilitated by EE may, at least in part, rescue BDNF levels, ultimately contributing to neuroprotection and neurogenesis (Mattson, 2012).

Evidence suggests that physical activity in itself can be beneficial in delaying the progression of HD in mouse models. Pang et al. (2006) demonstrated that voluntary wheel running delayed onset of rear paw clapping, a feature of HD in mouse models, ameliorated cognitive deficits and also normalised rearing behaviour (Pang et al., 2006). Additionally, wheel running from a juvenile age (4 weeks) delayed onset of rear paw clapping and of deficits in motor coordination and rescued locomotor activity and exploratory behaviour (van Dellen et al., 2008). It has been suggested that some of the behavioural improvements resulting from voluntary physical activity are modulated by the upregulation of monoamines, such as serotonin, dopamine and nor-adrenaline, across several brain regions (Renoir et al., 2011). Interestingly, wheel running is associated with sex-dependent increases in BDNF expression, with only female HD mice exhibiting increases in BDNF following physical activity alone and male HD mice showing increases in BDNF only following EE (Zajac et al., 2010). This indicates that voluntary physical activity can up-regulate key molecules that modulate cognitive and behavioural changes in mouse models of HD in a sex-dependent manner.

Studies in several animal disease models have demonstrated the importance of social interaction in mediating the benefits of EE. For



example, co-housed AD APP/PS1 mouse models exhibit amelioration of memory deficits facilitated by increased BDNF-dependent neurogenesis in the hippocampus (Hsiao et al., 2014). Transgenic HD sheep exhibit circadian abnormalities when housed only with other HD flock, with circadian abnormalities absent in those HD gene positive sheep housed with wild-type sheep (Morton et al., 2014). Although physical activity and co-housing, when assessed alone, can produce positive outcomes in mouse models of HD, greater beneficial effects are observed when used in conjunction with other components of EE. Such findings demonstrate that environmental interventions have a positive impact on disease processes in animal models of HD and warrant further investigation into the translation of these programs into the human HD population.

### 1.9. Effects of multidisciplinary therapy on brain volume and potential biomarkers of HD in humans

Preclinical studies show that EE has positive effects on the pathological and clinical course of HD. However translation of EE from the laboratory to the clinic has proven difficult due to the strict parameters of the experimental model, such as diet and housing conditions. Several research teams have, nevertheless, begun to address some of these translational gaps using multidisciplinary therapy; a complex, interdisciplinary therapeutic approach comprising physical activity, cognitive stimulation and social interaction.

Studies evaluating the utility of multidisciplinary therapy have documented significant changes in grey matter volume, as well as improvements in memory, processing speed, balance and gait, mood and quality of life in patients with manifest HD (Thompson et al., 2013; Piira et al., 2013; Veenhuizen et al., 2011; Cruickshank et al., 2015). Recent data from our research programme has shown, in particular, that multidisciplinary therapy increases grey matter volume in the caudate tail and dorsolateral PFC in patients with manifest HD (Cruickshank et al., 2015). This therapy has also been reported to improve cognitive function, quality of life and depressive symptoms in patients with mild AD and cognitive impairment without dementia (Santos et al., 2015) and in PD, multidisciplinary therapy has been reported to improve motor performance, dyskinesias, balance and gait and slow disease progression (Frazzitta et al., 2013a, 2012, 2013b). The molecular mechanisms driving these neural and clinical changes are yet to be investigated. Several lines of evidence suggest, however, that multidisciplinary therapy may restore normal HPA-axis function, circadian rhythmicity and basal BDNF levels, promoting neural and clinical benefits in HD.

EE is capable of restoring normal HPA-axis function, circadian rhythmicity and basal BDNF levels in HD mouse models (Du et al., 2012; Cuesta et al., 2014; Zajac et al., 2010), with significant delays in peristriatal degeneration and cognitive and motor decline (Nithianantharajah et al., 2008; Pang et al., 2006; van Dellen et al., 2008), which could be facilitated by restoration of the HPA-axis and circadian rhythmicity and increases in BDNF levels. While these positive molecular changes are yet to be reported in patients with HD, evidence from other diseases suggests that multidisciplinary therapy may impact on the neuropathological and clinical course of the disease in a similar fashion to EE. For example, in PD multidisciplinary therapy has been reported to increase serum BDNF levels and lessen clinical burden in the early stages of the disease (Frazzitta et al., 2015, 2014).

The effects of multidisciplinary therapy on HPA-axis function, stress reactivity and circadian rhythmicity are yet to be investigated in any disease population. Furthermore, the effects of this therapy on BDNF in HD are also yet to be reported. However, the benefits of EE on the HPA-axis, BDNF levels and circadian rhythmicity in HD mouse models, both before disease features appear and following

onset, the increase in serum BDNF in PD patients and the increase in brain volume in manifest HD patients following multidisciplinary therapy, highlight the importance of assessing the effects of this therapy on HPA-axis function, circadian rhythmicity and BDNF levels in HD. It is conceivable that multidisciplinary therapy could regulate the HPA-axis, and possibly circadian rhythm, and increase BDNF levels, resulting in the positive brain changes observed in HD individuals following this therapy. Rationale for this can be seen in other populations when the effects of each of the components of multidisciplinary therapy are evaluated individually.

Physical activity, cognitive training and social interaction have a range of benefits on striatal and extra-striatal brain structures, HPA-axis function, circadian rhythm and BDNF levels. Higher physical activity levels are associated with increased hippocampal and PFC volume, accompanying improvements in memory in healthy older adults (Erickson et al., 2011; Colcombe et al., 2006) and increased BDNF levels (de Melo Coelho et al., 2014; Pereira et al., 2013). The latter could be mediated by the continual induction and eventual down-regulation of the stress response due to acute, transient increases in cortisol following exercise (Luger et al., 1987), leading to an adaptive stress response. The regulation of circadian rhythmicity and melatonin levels by exercise, indicated by shifts in onset and increases in peak melatonin release (Miyazaki et al., 2001; Buxton et al., 2003), could also facilitate an increase in BDNF and regulation of the HPA-axis, and lead to improvements in brain volume and associated functions.

Cognitive training has also been documented to increase grey matter volume in the cortex in regions involved in episodic memory in individuals with subjective memory impairment, a common risk factor for AD (Engvig et al., 2014). Furthermore, cognitive training has been shown to reduce stress-related symptoms and improve sleep onset latency and efficiency in individuals with stress-related exhaustion (Gavelin et al., 2015) and in older adults with insomnia (Haimov and Shatil, 2013), respectively. The regulation of stress symptoms and improved sleep efficiency could facilitate an increase in BDNF, which has been reported following cognitive training in individuals with PD (Angelucci et al., 2015).

Lastly, social interaction has been shown to increase whole brain volume, with associated improvements in visual attention and verbal learning (Mortimer et al., 2012). Social interaction attenuates the cortisol response to stressful stimuli, likely through coping or resiliency mechanisms (Kirschbaum et al., 1995), which is likely to facilitate the increase in BDNF observed in AD mouse models following social interaction (Hsiao et al., 2014).

These findings collectively indicate that lifestyle interventions could favourably impact on clinical and pathological aspects of HD. Indeed, evidence from animal models and human studies indicate that multidisciplinary therapy has significant potential to treat many of the clinical consequences of HPA-axis and circadian rhythm disturbances in HD. Such an approach may even have the potential to reduce the rate and/or forestall neuropathological changes that occur in individuals with preHD.

## 2. Conclusion

HD individuals exhibit a wide spectrum of clinical features indicative of degeneration in striatal and extra-striatal structures, including the hypothalamus. Hypothalamic pathologies are likely to result in HPA-axis dysfunction and circadian rhythm dysregulation, features which have been reported in HD mouse models and gene-positive individuals. The consequent increase in glucocorticoids and dysregulation of melatonin and sleep patterns are associated with decreased BDNF levels and have the potential to contribute to, or even exacerbate, disease processes. Much is still to be understood about the interaction between glucocorticoids,

BDNF and sleep. However, emerging evidence of potential strategies to ameliorate negative downstream consequences of these interactions, suggest a positive role for multidisciplinary therapy. Preliminary studies using such strategies have demonstrated favourable effects on HPA-axis and circadian rhythm disturbances in animal models of HD, as well as other clinical populations, however the effects of multidisciplinary therapy on HPA-axis dysfunction, circadian rhythmicity and BDNF levels in HD gene-positive individuals are yet to be investigated.

### Conflicts of interest

The authors declare no conflict of interest.

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