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Subjective sleep problems in Huntington's disease: A pilot investigation of the relationship to brain structure, neurocognitive, and neuropsychiatric function

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ABSTRACT

Subjective reports of sleep disturbance are a common feature of Huntington's disease (HD); however, there is limited research investigating the relationship between sleep problems with changes in brain and behaviour. This study aimed to investigate whether subjective reports of sleep problems in HD are associated with brain volume, neurocognitive decline, and neuropsychiatric symptoms. This retrospective pilot study used brain volume, neurocognitive and neuropsychiatric data from premanifest (pre-HD) and symptomatic HD (symp-HD). Subjective sleep problem was measured using the sleep item of the Beck's Depression Inventory-II (BDI-II). Pre-HD individuals reporting sleep problems had significantly poorer neuropsychiatric outcomes compared to those not reporting sleep problems. In the symp-HD group, those with sleep problems had significantly accelerated thalamic degeneration and poorer neuropsychiatric outcomes compared to those without sleep problems. There was no relationship between subjective sleep problems and neurocognitive measures. These findings suggest an association between subjective sleep disturbance, neuropathology, and development of neuropsychiatric symptoms in HD. Further studies using quantitative EEG-based monitoring of sleep in HD and changes in the brain and behaviour will be necessary to establish the causal nature of this relationship.

1. Introduction

Sleep disturbance is an early and pervasive feature of the neurodegenerative Huntington's disease (HD) [1], caused by an expanded CAG repeat in the huntingtin gene (HD Collaborative Research Group, 1993) [2]. Common sleep problems include insomnia, lower sleep efficacy, longer sleep latency, more frequent night-time waking and less slow-wave sleep [3,4]. Disturbed sleep can severely affect the quality of life of both patients and carers and can also exasperate neurocognitive and neuropsychiatric problems. In HD, there is ample evidence for robust structural brain changes, cognitive decline and psychiatric problems (see for example refs. [5–7]). However, how reports of sleep problems in HD may be associated with structural brain changes and neurocognitive and neuropsychiatric deficits remains unclear.

Neurodegenerative changes can be observed up to 20 years prior to clinical diagnosis of HD [5,7]. A number of studies have shown significant alterations in primary sleep regulating structures, including hypothalamus and thalamus [8,9], and secondary structures such as the striatum (caudate and putamen) in HD [5–8]. It is possible that structural brain changes might be influencing the sleep problems reported by HD individuals. Evidence for such a relationship can be found in studies that have shown narcolepsy-like episodes in transgenic mice models of HD with depleted orexin/hypocretin neurons in hypothalamus [10]. Importantly, orexin loss has also been reported in post-mortem hypothalamic tissue from HD patients [11,12]. Atrophy in secondary sleep regulating structure, such as caudate, is also associated with sleep disruption and reduced amount of slow-wave-sleep in HD [13], suggesting the important role of these brain structures in regulating sleep behaviour in HD.

Neurocognitive decline and neuropsychiatric symptoms in HD appear to run in parallel with the reported sleep problems. For example, the transgenic R6/2 HD mouse model showed cognitive decline that correlated with sleep and circadian disturbances [14]. In a study with both pre-HD and symp-HD individuals, a delayed sleep phase in symp-HD correlated with reduced cognitive performance [15]. Although sleep problems have been implicated in the development of psychiatric symptoms in healthy controls [16], there is no evidence to support an association with the neuropsychiatric profile of HD.

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This study sought to investigate whether structural brain atrophy, neurocognitive and neuropsychiatric dysfunction was associated with subjective reports of sleep problems in pre-HD and symp-HD individuals. We predicted that individuals with the mutant HD gene (both pre-HD and symp-HD) with reported sleep problems would show increased atrophy in sleep-critical brain structures, greater neurocognitive decline and neuropsychiatric symptoms compared with individuals who reported no sleep problems.

2. Methods

2.1. Participants

This study used retrospective data from the IMAGE-HD project, a longitudinal neuroimaging study in HD based in Melbourne, Australia [5,6,17–20]. The present study used cross-sectional data collected at study baseline (2008–2009) from participants in the pre-HD and symp-HD groups only [6,21]. One pre-HD and 4 symp-HD participants were excluded due to missing data and segmentation errors, leaving a total of 35 pre-HD and 32 symp-HD participants. All participants underwent a rigorous screening process prior to recruitment, and were free from brain injury, neurological and/or severe diagnosed psychiatric conditions other than HD. Detailed protocol used in the study can be obtained from previous publications [5,17,22–26]. The study was approved by Monash University and Melbourne Health Human Research Ethics Committees, and each participant gave written informed consent. Demographic details for the participants in the current investigation is provided in Table 1.

2.2. Procedures

2.2.1. Subjective report of sleep problems

Subjective sleep problem was measured using the sleep question on the Beck's Depression Inventory-Second Edition (BDI-II) [28]. Item-16 of the BDI-II is a question relating to sleep problems: a rating of 0 indicates no change in sleep pattern and a rating of 3 indicates the largest change in sleep pattern. Previous studies [e.g. [29]] have used and validated item-16 on the BDI as a subjective measure of sleep problems.

2.2.2. Neurocognitive and neuropsychiatric assessments

A detailed description of neurocognitive and neuropsychiatric assessments conducted in IMAGE-HD is provided in previous publications [5,17,22–26]. In this report, we used the cognitive and psychiatric measures reported to be most sensitive in HD. The Symbol Digit Modalities Test (SDMT) [30] and STROOP-WORD [31] were used as quantitative measures of executive function. Neuropsychiatric tests used in this report assessed anxiety and depression [Hospital Anxiety and Depression Scale] [32]. In addition, participants completed questionnaires associated with frontal-striatal dysfunction, including executive function and neuropsychiatric disturbances [Frontal Systems Behaviour Scale, FrSBe; [33]; Schedule of Obsessions, Compulsions and Psychological Impulses, SCOPI; [34]].

Table 1
Demographic data from participants included in the current investigation.

	Pre-HD (No sleep problems)	Pre-HD (Sleep problems)	Symp-HD (No sleep problems)	Symp-HD (Sleep problems)
N	18	17	18	14
Gender (M:F)	7:11	7:10	6:12	6:8
Age (years)	41.0 ± 9.7	42.4 ± 10.6	53.7 ± 9.4	50.7 ± 8.1
UHDRS-TMS	1.1 ± 1.2	0.6 ± 1.2	18.3 ± 9.5	17.5 ± 12.3
DBS	282.0 ± 53.6	257.5 ± 51.5	383.4 ± 65.5	371.4 ± 82.8
YTO	14.4 ± 6.9	16.6 ± 7.3	–	–
Duration of illness (years)	–	–	1.6 + 1.2	2.4 ± 1.9

Note: UHDRS-TMS: Unified Huntington's Disease Rating Scale – Total Motor Score; DBS: Disease Burden Score was estimated as (CAG − 35.5) ∗ age; YTO: Years to Onset (estimated using Langbehn [27] criteria). The values are presented as mean ± SD. There was no significant difference ($p > 0.05$) in any of the demographic variables between sleep problems and no sleep problems groups.

2.2.3. Image acquisition and processing of MRI data

Structural MRI data were acquired as part of the IMAGE-HD study. Volumetric analysis of caudate, thalamus, and hypothalamus in overall pre-HD, symp-HD, and controls were reported previously [6,21], which also describe the procedure used for segmenting the structures.

2.2.4. Statistical analysis

For both the pre-HD and symp-HD group separately, sleep data from the BDI-II was coded to reflect dichotomous sub groups: those who did not report sleep problems (indicated by a score of 0 in the BDI-II, item 16) and those who reported sleep problems (indicated by a score of >0 on the BDI-II, item 16). This resulted in a total of four groups: pre-HD no reported sleep problems (n = 18); pre-HD reported sleep problems (n = 17); symp-HD no reported sleep problems (n = 18); symp-HD reported sleep problems (n = 14).

Brain volume, and cognitive function were compared between individuals (pre-HD and symp-HD separately) reporting sleep problems and individuals not reporting sleep problems using independent sample *t*-tests (Mann-Whitney *U* tests were used for non normally distributed samples). Brain volumes were compared after correcting for intracranial volume using a power proportion method, recently developed for HD data [35]. Due to the exploratory nature of these analyses, between group differences were considered to be significant at $p \leq 0.05$ (uncorrected).

3. Results

3.1. Neurocognitive measures

In the both pre-HD (see Table 2) and symp-HD (see Table 3) groups, no significant differences were found between those with reported sleep problems and those without reported sleep problems on any neurocognitive measures.

3.2. Neuropsychiatric measures

In pre-HD (see Table 2), there was a significant difference between groups on total FrSBe, FrSBe disinhibition and HADS. Mean scores were higher in the reported sleep problems group compared to the no reported sleep problems group for each of these conditions with a medium effect size. Higher scores indicate greater neurobehavioural impairment.

In symp-HD (see Table 3), there was a significant difference between groups on the FrSBe apathy, disinhibition and executive dysfunction subscales. There was also a significant difference between groups on HADS anxiety and HADS depression scores.

3.3. Brain volumes

In pre-HD (Fig. 1, Table 4), no significant differences were found between those with reported sleep problems and those without reported sleep problems in any of the regions of interest.

In symp-HD, left, right, and total thalamic volumes were lower in the reported sleep problems group compared to the no reported sleep problems group. Other regions didn't show significant differences (Table 5).

4. Discussion

In the present study we report structural brain, neurocognitive, and neuropsychiatric differences in pre-HD and symp-HD individuals