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Effect of multidisciplinary rehabilitation on sleep outcomes in individuals with preclinical Huntington disease: an exploratory study

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Dear Editor. Sleep disturbances are an early feature of Huntington disease (HD), which worsen as the disease progresses. Studies have documented increased sleep fragmentation, decreased rapid eye-movement (REM) sleep, reduced sleep efficiency, insomnia and an increase in periodic leg movements (PLMs) in individuals with HD [1, 2]. Disturbances in sleep are thought to exacerbate cognitive impairments and may hasten subcortical neurodegeneration [3, 4]. Hence, management of sleep disturbances in individuals with HD is imperative.

Lifestyle interventions have been shown to positively affect sleep disturbances in individuals with insomnia and other neurodegenerative disorders. Improved sleep onset latency and efficiency have been reported in patients with insomnia after computerised cognitive training [5]. Also, the number of awakenings and time spent awake at night were found reduced in people with Alzheimer disease following sleep hygiene interventions. Sleep quality was improved in people with Parkinson disease after multidisciplinary rehabilitation [6]. However, no studies have evaluated the effect of multidisciplinary rehabilitation on sleep outcomes in individuals with HD.

This pilot study aimed to investigate the effect of a 9-month multidisciplinary rehabilitation program comprising exercise, cognitive training, sleep hygiene and nutrition guidance and socialisation on sleep architecture, sleep-related brain structures and sleep-dependent memory consolidation in individuals with preclinical HD. We hypothesized that multidisciplinary rehabilitation would improve sleep quality and architecture and that these improvements would be associated with maintenance of volume in sleep-related brain structures and improvement in sleep-dependent memory consolidation.

We included 16 individuals with the HD mutation in the study. Eligibility criteria included a cytosine-adenine-guanine repeat length $\geq$ 39, diagnostic confidence level on the Unified Huntington's Disease Rating Scale $\leq$ 2, total functional capacity score 13 [7] and the ability to safely engage in the intervention and provide written and informed consent. We excluded individuals if they had concomitant neurological, cardiovascular, sleep, metabolic or immunological conditions or performed regular shift work.

The multidisciplinary rehabilitation intervention consisted of 9 months of 3 times weekly supervised (1 exercise physiologist per 3-5 participants) aerobic and resistance training, computerised cognitive training, dual-task training, nutritional and sleep hygiene guidance and

social activities. To avoid general adaptation syndrome and overtraining, the intervention was divided into 6 distinct training blocks consisting of training (weeks 1-4), deloading (week 5) and recovery (week 6) phases. These rehabilitation approaches were selected on the basis of their demonstrated positive effects on sleep and neurological and cognitive outcomes in individuals with HD and in other clinical populations [5, 6, 8].

Before and after the intervention, participants underwent 1 night of in-laboratory polysomnography to evaluate sleep architecture. MRI was used to evaluate volume in caudate, putamen, pallidum, accumbens and thalamus structures. Sleep-dependent memory consolidation was assessed with the immediate (night of polysomnography) and delayed (morning after polysomnography) recall components of the Hopkins Verbal Learning Test-Revised (HVLT-R) to calculate memory retention.

The Shapiro-Wilk test was used to assess normality assumptions for all data. Categorical data are described with number (%) and were compared by chi-square test. Continuous data are described with mean (SD) or median (Q1-Q3) and were compared by paired-sample *t* test or Wilcoxon signed-rank tests as appropriate. A Holm-Bonferroni correction was applied to all clinical outcomes to account for multiple comparisons. Cohen's d was calculated to determine effect sizes for each outcome. Spearman correlation was used to examine correlations between changes in sleep outcomes and subcortical volumes and sleep-dependent memory consolidation. $P < 0.05$ was considered statistically significant. Statistical analyses involved using SPSS v24 (IBM Corp, Armonk, NY, USA).

Participant demographic and clinical characteristics are presented in Table 1. We found no significant changes in clinical disease outcomes, body mass index, use of psychotropic medications or anxiety or depression symptomatology throughout the study period. At baseline, the average relative percentage of REM sleep for the cohort was 17.16% (Table 2),

which was below the threshold considered healthy (21-30%) and indicates poor sleep quality [9]. However, after the 9-month intervention, the relative percentage of time spent in REM sleep increased to 25.38%, which indicates a positive effect on REM sleep. This change was accompanied by a significantly earlier bedtime and significantly increased total time spent in bed (Table 2). However, although care was taken to ensure participants were able to sleep and wake at times of their choosing, the effects on sleep timing may have been due to the laboratory environment.

We observed large and medium effect sizes for REM latency (time from sleep onset to the first REM sleep episode) and total sleep time after the intervention (Table 2), although these changes did not reach statistical significance. We observed small effect sizes for several other sleep outcomes, including number of awakenings, sleep latency, percentage of total sleep time spent in stage N2, number of arousals and PLM index but no significant changes in self-reported sleep quality or daytime sleepiness after the intervention (Table 2).

We performed volumetric analyses of brain regions relevant to HD and sleep-wake to determine whether changes in sleep were mediated by changes in regional brain volume. Right accumbens volume was significantly reduced after the intervention period ($p = 0.04$). No other differences were observed in subcortical structures throughout the intervention period. Change in accumbens volume was significantly correlated with PLM index ($r_s = -0.63$, $p = 0.016$) and percentage of N1 sleep ($r_s = 0.55$, $p = 0.039$) over the 9 months (9 months – baseline; Figure). However, because of no significant changes in PLM index or relative percentage of stage N1 sleep, this association may not be clinically relevant.

Increases in REM sleep did not appear to affect sleep-dependent memory consolidation, as indicated by a lack of change in total word recall, delayed word recall and word retention components of the HVLT-R (Table 2). This finding was unexpected, given the known role of

REM sleep in memory formation and consolidation [10]. However, in addition to REM sleep, non-REM (NREM) sleep has been suggested to play a vital role in sleep-dependent memory consolidation [11]. However, we found no changes in NREM sleep after the intervention period, which may explain in part the lack of changes in sleep-dependent memory consolidation. Also, the HVLT-R assessment may not have been sufficiently sensitive to detect changes in sleep-dependent memory consolidation. Previous studies have typically used the paired word association test [12], which may be more sensitive to changes in sleep-dependent memory consolidation and should be considered for future studies.

This study provides preliminary evidence that multidisciplinary rehabilitation may positively affect sleep architecture but may not ameliorate degeneration in sleep-related brain structures or improve sleep-dependent memory consolidation. Previous studies have reported greater sleep fragmentation and decreased REM sleep and total sleep time in individuals with HD [1, 2]. In the present study, relative REM sleep percentage increased to within healthy ranges after the intervention period. To our knowledge, this is the first study to report an increase in REM sleep in individuals with HD after a non-pharmaceutical intervention. This finding is of clinical interest, particularly given that REM sleep is thought to support neurogenesis and synaptogenesis and subsequently the maintenance of brain structures [10]. However, because of the non-controlled study design, these results must be interpreted with caution. Nevertheless, this study provides preliminary evidence that multidisciplinary rehabilitation may increase REM sleep to healthy ranges in individuals with preclinical HD and should be investigated further.

Conflict of interest. None declared.

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Legend

Figure. Percentage change in volume of the nucleus accumbens in individuals with preclinical Huntington disease after 9 months of a multidisciplinary rehabilitation in terms of change in (A) percentage of total sleep time (TST) spent in stage N1 ($n = 16$, $r_s = 0.55$, $p = 0.039$) and (B) periodic leg movement (PLM) index ($n = 16$, $r_s = -0.63$, $p = 0.016$).

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