Clinical and neuroradiological correlates of sleep in myotonic dystrophy type 1

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Abstract

Abnormalities of sleep are common in myotonic dystrophy type 1 (DM1), but few previous studies have combined polysomnography with detailed clinical measures and brain imaging. In the present study, domiciliary polysomnography, symptom questionnaires and cognitive evaluation were undertaken in 39 DM1-affected individuals. Structural brain MRI was completed in those without contra-indication (\(n=32\)). Polysomnograms were adequate for analysis in 36 participants. Sleep efficiency was reduced, and sleep architecture altered in keeping with previous studies. Twenty participants (56%) had moderate or severe sleep-disordered breathing (apnoea-hypopnoea index [AHI] \(\geq 15\)). In linear modelling, apnoeas were positively associated with increasing age and male sex. AHI \(\geq 15\) was further associated with greater daytime pCO\(_2\) and self-reported physical impairment, somnolence and fatigue. Percentage REM sleep was inversely associated with cerebral grey matter volume, stage 1 sleep was positively associated with occipital lobe volume and stage 2 sleep with amygdala volume. Hippocampus volume was positively correlated with self-reported fatigue and somnolence. Linear relationships were also observed between measures of sleep architecture and cognitive performance. Findings broadly support the hypothesis that changes in sleep architecture and excessive somnolence in DM1 reflect the primary disease process in the central nervous system.

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1. Introduction

Myotonic dystrophy type 1 (DM1) is a dominantly inherited, multisystem disorder resulting from pathological expansion of a CTG trinucleotide repeat in the \(DMPK\) gene [1]. DM1 is characterised by myotonia, weakness and wasting of skeletal muscle, with additional features including cataract, cardiac conduction abnormalities, male hypogonadism, and cognitive deficits. The phenotype is highly variable, spanning a clinical continuum from severe congenital to late adult-onset disease [2].

Issues relating to sleep and excessive daytime somnolence (EDS) are commonly reported by people with DM1, the
latter affecting up to 90% of individuals [3]. Patients describe increased sleep requirement, restless sleep, liability to doze in the daytime, and a lack of refreshment from sleep [4,5]. EDS may profoundly affect quality of life, potentially impacting work, home life and relationships with caregivers [6].

Level I attended polysomnography (PSG) and multiple sleep latency tests (MSLT) have been widely employed to characterise sleep abnormalities in DM1. Compared with controls, people with DM1 have increased total sleep time, but with greater fragmentation of sleep [7,8]. Sleep architecture is altered, including an increased proportion of total sleep time spent in slow wave and rapid eye movement (REM) stages of sleep [9,10]. The MSLT objectively confirms the presence of EDS [8,10], and additional features including sleep onset REM periods, cataplexy, sleep paralysis, lucid dreams and hypnagogic hallucinations have been reported [9–12].

Sleep-disordered breathing (SDB) is a frequent finding in DM1 and may be present despite normal daytime respiratory assessments [13–15]. Intriguingly, EDS can be observed in some patients who lack significant SDB, or may persist despite appropriate treatment of the same [5,9,12,14], suggesting SDB is not the principal driver of somnolence in this group.

Broadly, it is assumed that abnormalities of sleep architecture and EDS arise from the effects of DM1 on the central nervous system (CNS). Histological studies of brain reveal widespread changes in people with DM1, including the presence of neurofibrillary tangles, neuronal loss and gliosis [16]. Neuroimaging confirms marked structural brain changes, including widespread volume loss affecting white and grey matter, presence of T2-hyperintense lesions, and evidence of microstructural disruption of white matter on diffusion tensor imaging (DTI) [17]. Recent data also demonstrate that hippocampus and amygdala volumes appear larger in DM1 patients compared with controls [18]. No sizeable studies have previously combined neuroimaging with detailed phenotyping of sleep, and so the relationship between structural brain changes and abnormalities of sleep is currently poorly defined. Targeted therapies for somnolence symptoms are also lacking, although the ‘off-label’ use of modafinil in selected patients is supported by some clinicians [6].

In this context, we sought to describe the prevalence and characteristics of sleep abnormalities in a clinically well-characterised outpatient population with adult-onset DM1. Correlations of the sleep abnormalities were explored with self-reported symptom questionnaires, cognitive performance and regional brain volumes derived from MRI.

### 2. Materials and methods

#### 2.1. Recruitment and ethical approval

Subjects were recruited as part of the DM1-Neuro study, a cross-sectional study of CNS involvement in adults with DM1. The subjects presented here represent a subgroup within the previously reported study cohort of 46 affected individuals [19], who additionally consented to domiciliary PSG. Adults with DM1 attending the West of Scotland Clinical Genetics Service were contacted by letter and invited to participate. Recruitment was targeted to those with adult or late-onset DM1. Unequivocal onset of DM1-specific symptoms before age 16 years, or learning disability diagnosed in childhood were criteria for exclusion. Patients consistently using non-invasive ventilation were not asked to participate in the PSG portion of the study. The West of Scotland Research Ethics Committee 4 (Reference: WOS 15/WS/0189) approved the protocol. Participants provided written, informed consent, and the study was conducted according to the principles of the Declaration of Helsinki.

#### 2.2. Self-reported symptom measures and cognitive evaluation

Symptom questionnaires and neuropsychological tests were applied by a single operator (MJJ). Self-reported symptom questionnaires were: the Myotonic Dystrophy Health Index (MDHI), DM1-ActivC® and the Fatigue and Daytime Sleepiness scale (FDSS). The neuropsychological battery consisted of: the Stroop test (Golden and Freshwater, Stoelting Co; 2002); the five Trail Making Tests (TMT) from the Delis-Kaplan Executive Function System (D-KEFS™); the Block Design test from Weschler Abbreviated Scale of Intelligence – Second Edition (WASI II); the Edinburgh Cognitive and Behavioural ALS Screen (ECAS); and an FAS Controlled Oral Word Association Test. Further details of the cognitive evaluation have been previously reported [19].

#### 2.3. Polysomnography

Domiciliary American Academy of Sleep Medicine Level II unattended full polysomnography (PSG) was undertaken using the Embletta® MPR PG with ST+ proxy (Natus Incorporated, Pleasanton, CA) recording device. Level II unattended PSG measures essentially the same physiological parameters as an inpatient sleep laboratory study (Level I), but without video or the continuous presence of a technician. The device was configured to measure: electrocardiogram (two channels), subject position, electroencephalogram (EEG) at ten channels with electrodes placed according to the 10/20 system rules (F3, F4, T3, T4, Cz, Pz, C4, C3, O1, O2), two electro-oculogram (EOG) channels, three chin electromyogram (EMG) electrodes, and two EMG surface electrodes at both tibialis anterior. Airflow was measured by thermistor and nasal cannulae, and oxygen saturation (SaO₂) by digital oximetry. Respiratory effort was assessed by respiratory inductance-plethysmography chest and abdominal effort belts. This setup is consistent with SCOPER categorisation S₁ C₂ O₁ P₂ E₁ R₁, based on the Collop criteria for out-of-centre sleep study devices [20]. The operator attended the subject’s home around 20:00 on the evening of PSG to attach the equipment. The patient was asked to state their intended “lights off” time, in-keeping with usual bedtime. The device was set to record for 8 h from then.
alarms were used for wakening, and any sleep beyond 8 h was not recorded.

RemLogic™ software (Natus Medical Incorporated, USA) was used for analysis. Sleep studies were scored according to the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (Version 2.4) [21], with desaturations defined as a 4% or greater fall in SaO₂.

2.4. MRI

Participants attended a single MRI session at the Glasgow Clinical Research Facility. Height and weight were recorded prior to scanning. For patients who did not attend for MRI, self-reported height and weight were used. Imaging was undertaken using a 3T Siemens Prisma MRI scanner (Software version: VE11B. Erlangen, Germany), with a 20-channel head and neck receiver coil. Pertinent sequences for the analysis presented here were T1-w 3D MPRAGE (TR = 2300 ms, TE = 2 ms, TI = 900 ms, flip = 10°) and T2-w SPACE dark fluid (TR = 5000, TE = 386 ms, TI = 1800 ms, flip = 120°). The whole brain was imaged, both sequences had 1.1 mm³ voxels.

Images were processed using the BRAINSAutoWorkup pipeline, with regional volumes adjusted for intracranial volume using a power-proportion method as previously described [18].

T1-w 3D MPRAGE and the T2-w SPACE dark fluid sequences were also analysed using a Lesion Growth Algorithm (LGA) (http://www.applied-statistics.de/lst.html) [22], from the Lesion Segmentation Toolbox, from which the total volume of white matter hyperintensities were derived.

2.5. Capillary blood gas measurement

A capillary blood sample was obtained by skin-prick from the earlobe just prior to MRI scanning. One of two devices was used for all analyses: an ABL 77, or ABL 80 Flex (Radiometer Medical®). Both were used in routine clinical service at the Queen Elizabeth University Hospital, so were subject to appropriate calibration and maintenance.

2.6. Additional clinical data

Additional clinical data were obtained from electronic medical records relating to the subject’s review appointments with the West of Scotland Clinical Genetics Service. Data were extracted from the annual appointment most closely contemporaneous to PSG. All measures had been recorded by one of two clinicians; MJH or BB. Data extracted from electronic clinical records were: Muscle Impairment Rating Score (MIRS), Epworth sleepiness score, electrocardiogram (ECG) measures, liver function tests (LFTs) and haemoglobin A1c (HbA1c).

2.7. Measurement of CTG repeat expansion

CTG trinucleotide repeat length was measured by small-pool PCR (SP-PCR) as previously described [23], using the flanking primers DM-C and DM-DR. Four reactions, each using 300 pg blood genomic DNA template, were performed for each patient. CTG repeat lengths were estimated by comparison against DNA fragments of known length in the molecular weight marker. The lower boundary of the expanded molecules in SP-PCR was used to estimate the inherited, or “progenitor” allele length (ePAL).

2.8. Statistical analysis

Statistical analysis was undertaken using Statistical Package for the Social Sciences (SPSS, Version 24.0; IBM 2015), with the exception of linear regression analyses using BRAINSAutoWorkup data, which were undertaken using R statistical software (Version 1.1.453, 2009–2018 RStudio, Inc.).

Correlations of PSG and self-reported symptom measures with regional brain volumes were investigated by multivariable linear regression analysis. For group comparison between participants with AHI ≥ 15 and those < 15, the model used the volume of the brain region of interest (vROI) as the dependent variable, and the group by AHI (AHIgroup) as an explanatory variable, adjusted for age, sex and logePAL. An interaction term was used between age and logePAL, to reflect the age-dependent nature of somatic mosaicism [24]. The model is summarised as follows: \( vROI \sim age^{+}\logePAL+sex+AHIgroup \). Relationships between other sleep measures (PSG and self-reported measures) used the sleep measure under investigation as the dependent variable, and age, logePAL, sex and vROI as explanatory variables: \( Sleep\ measure \sim vROI+age^{+}\logePAL+sex \).

Linear associations of cognitive performance with sleep measures were explored using the linear model: \( Test\ score \sim age+sex+PSG\ measure \), where Test score = the patient’s score in a given cognitive assessment, and PSG measure = the variable under investigation.

Given the exploratory nature of the study, \( p \)-values are presented without adjustment for multiple testing.

2.9. Tissue banking

DNA and serum from consenting participants have been stored at the MRC Centre Biobank for Neuromuscular Diseases, Newcastle University, UK.

3. Results

3.1. Study acquisition and cohort demographics

PSG was completed as described in 39 subjects. Thirty-five gave data of adequate quality for analysis on the first attempt. Two failed because of inadequate EEG, and a third because the subject could not tolerate facial electrodes or nasal cannulae. A fourth study was affected by battery failure but was repeated with a successful outcome. Thirty-six PSG studies were therefore used for analysis. Demographic details of the study cohort are summarised in Table 1.
Table 1
Demographic details of the study cohort.

<table>
<thead>
<tr>
<th>Total with satisfactory PSG (n.)</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: n. (%)</td>
<td>22 (61.1)</td>
</tr>
<tr>
<td>Age (years): mean (SD)</td>
<td>49.0 (12.1)</td>
</tr>
<tr>
<td>MIRS: Ratio 1:2:3:4:5</td>
<td>3.6:7:19:1</td>
</tr>
<tr>
<td>BMI: mean (SD)</td>
<td>26.6 (4.6)</td>
</tr>
<tr>
<td>ePAL (number of CTG repeats): mean (SD)</td>
<td>237 (124)</td>
</tr>
</tbody>
</table>

3.2. Sleep efficiency and sleep architecture

The mean recording period (time in bed; TIB) was 478.9 min (SD 6.6), mean total sleep time (TST) was 352.9 min (SD 91.8), and total sleep period (TSP) was 450.0 min (SD 43.8).

Sleep efficiency describes the total sleep time (TST) as a proportion of TIB. In the general population, sleep efficiency decreases with age, with meta-analysis of several studies estimating an average of around 95% at age 20 years, to 80% at age 75 years [25]. The rate of decline is slightly greater in females compared with males. In our DMI cohort, sleep efficiency also reduced with age (p=0.005, Adj R²=0.187). This model improved with inclusion of sex in a multivariate model (p=0.006, Adj R²=0.223), with males exhibiting poorer sleep efficiency. A lack of internal controls and the possibility of a first-night effect precluded any definitive comparison with unaffected individuals, although lines of best fit are compared with control data derived from meta-analysis by Ohayon and colleagues [25] in Fig. 1.

Fig. 1. Sleep efficiency plotted against age.

Dotted line represents the expected age-related trend in unaffected individuals, derived from meta-analysis of multiple studies (Ohayon et al. n. = 3577) [25].

Subjects spent on average 7.3% (SD 4.4%) of TST in stage 1 sleep, 47.1% in stage 2 (SD 11.3%), 20.8% (SD 11.4%) in slow-wave sleep and 24.8% (SD 7.6) in REM sleep. Sleep architecture was widely variable between individual subjects, but trend lines suggest an overall decreased proportion of stage 2 sleep, and increased proportion of stage 1, slow wave and REM sleep compared with control data (Fig. 2).

Percentage of stage 1 sleep was inversely correlated with percentage of slow wave (p=0.034, Adj R²=0.100) and REM sleep (p=0.023, Adj R²=0.119), and was positively associated with sleep efficiency (p=0.002, Adj R²=0.235). Similarly, percentage of stage 2 sleep was inversely correlated with percentage of slow wave (p < 0.001, Adj R²=0.626) and REM sleep (p=0.013, Adj R²=0.144). There was a weak positive association between percentage of REM sleep and sleep efficiency (p=0.039, Adj R²=0.093).

3.3. Sleep disordered breathing

3.3.1. Prevalence and characteristics of sleep disordered breathing

Applying American Academy of Sleep Medicine (AASM) criteria for SDB (1999), five subjects (14%) had normal studies (apnoea-hypopnoea index; AHI < 5), 11 (31%) had mild SDB (AHI ≥ 5 to < 15), 10 (28%) had moderate SDB (AHI ≥ 15 to < 30) and 10 (28%) had severe SDB (AHI ≥ 30) (Supplementary Figure 1).

The most common events were obstructive hypopnoeas, with a mean incidence of 20.4/hour. Of 36 participants, 29 (80%) had five or more obstructive hypopnoeas per hour. Central apnoeas were the next most common event, with a mean incidence of 3.1/hour (SD 3.8). Obstructive
apnoeas, central hypopnoeas or mixed hypopnoeas were generally uncommon (Supplementary Table 1). There was an apparent sex effect which approached statistical significance, with central apnoeas and obstructive hypopnoeas occurring more frequently in males, \((p=0.052, \text{Cohen's } d=0.91\) and \(p=0.051, \text{Cohen's } d=0.71\) respectively).

3.3.2. Clinical factors associated with sleep-disordered breathing

Clinical factors associated with AHI were explored by linear regression. Because the distribution of both AHI and ePAL were skewed \((p < 0.05\) in Shapiro-Wilk test of normality), a transformation by logarithm with base 10 was undertaken, to give logAHI and logePAL \((p=0.235, p=0.904\) in Shapiro-Wilk test respectively). A stepwise linear regression analysis was performed, to investigate correlation of logAHI with covariates of sex, capacity for physical participation (DM1-ActivC® score), BMI and logePAL. Age + sex + DM1-ActivC® score + BMI emerged as the model with best fit \((\text{Adj } R^2=0.361)\). Beta coefficients and significance levels from this model are summarised in Table 2, showing that increasing age and male sex made the most significant contributions to the model. The effects of BMI and DM1-ActivC® score did not reach significance.

Correlations of logAHI with measures of sleep architecture were also explored. In linear models, logAHI was not detectably associated with sleep efficiency, or percentage of TST spent in stage 2, slow wave, or REM sleep. A weak, positive association was observed between logAHI and percentage of TST in stage 1 \((p=0.036, \text{ Adj } R^2=0.097)\).

3.4. Clinical correlates of moderate to severe sleep disordered breathing

In the general population, a threshold of AHI \(\geq 15\) is typically used for consideration of treatment in symptomatic patients with obstructive sleep apnoea (OSA) \([26]\). To identify measures that may be useful in the clinic setting to predict presence of clinically significant SDB, a group comparison was undertaken between participants with AHI < 15, and those with AHI \(\geq 15\) \((\text{Table 3})\). Patients with AHI \(\geq 15\) tended to report more physical limitation on DM1-ActivC® \((p=0.003\) and the MDHI mobility subscore \((p=0.007)\), more fatigue on FDSS \((p=0.022)\) and the MDHI fatigue subscale \((p=0.006)\), and more problems with sleep in the MDHI sleep subscale \((p=0.027)\). Mean pCO2 was also significantly higher in the AHI \(\geq 15/h\) group \((p=0.021)\). However, no measure in isolation was strongly discriminatory between the two groups \((\text{Fig. 3})\).

We also sought to explore whether clinically significant SDB was independently associated with evidence of organ dysfunction in DM1. In a group comparison, adjusted for age, sex, BMI and ePAL, estimated marginal means appeared higher for liver transaminases, HbA1c, PR interval and
QRS duration in the AHI ≥ 15 group, though none of these effects reached statistical significance (Supplementary Table 2).

Group comparison was also undertaken between regional brain volumes in patients with AHI ≥ 15 and those < 15 (AHIgroup). Quality of segmentation was inadequate in one individual, whose data were excluded from structural brain analyses. The effect of AHIgroup was not significant for any of the regions assessed (Supplementary Figure 2). Volume of white matter lesions (expressed as % of total intracranial volume) measured by the LGA was also compared between AHI groups by one-way ANCOVA, adjusted for age, sex and ePAL. There was no significant difference between groups (estimated marginal mean = 1.88 [95% CI 0.68 to 3.09] versus 2.07 [95% CI 1.12 to 3.02], p = 0.821).

3.5. Neuroradiological correlates of sleep architecture and self-reported somnolence

Relationships between sleep measures and segmented vROI were explored by multivariate linear regression analysis as described. Standardised Beta coefficients for each vROI using this model are summarised in Fig. 4.

Percentage of stage 1 sleep was significantly associated with volume of occipital lobe (p = 0.024), including both grey and white matter segments (p = 0.021 and 0.04 respectively). Percentage of stage 2 sleep was positively associated with amygdala volume (p = 0.022). No regions reached significance in association with percentage of slow wave sleep. Percentage of REM sleep was inversely associated with cerebral grey matter volume, and positively associated with...
CSF volume (which represents an indirect, inverse measure of whole-brain volume; \( p = 0.046 \) and 0.023 respectively). vROI did not show any significant relationships with either sleep efficiency or AHI.

Although the effect of few vROI met statistical significance in this model, it is noteworthy that positive Beta values were consistently present for all cortical structures (whole cerebrum, as well as frontal, occipital, parietal and temporal lobes individually) in relation to stage 1 and 2 sleep, and negative Beta values in relation to slow wave and REM sleep.

Structural correlations with self-reported outcome measures relating to somnolence and/or fatigue were also explored using the same statistical model (Fig. 5). As would be expected, there was significant co-linearity between each of the four self-reported measures investigated (FDSS, Epworth score, MDHI fatigue subscale, MDHI sleep subscale; data not shown). Using this model, Epworth score was positively associated with cerebrospinal fluid volume (\( p < 0.001 \)) and inversely related to corpus callosum volume (\( p < 0.05 \)). For all self-reported somnolence scales, somnolence symptoms were positively associated with hippocampus volume (\( p < 0.05 \)). FDSS was additionally positively associated with caudate volume (\( p < 0.05 \)).

Of note, in univariate analysis, none of these four self-reported outcome measures was significantly correlated with sleep efficiency or percentage of each stage of sleep, with the exception of a weak positive correlation between the percentage of slow wave sleep and MDHI fatigue score (\( p = 0.03, \text{Adj R}^2 = 0.102 \)).

3.6. Sleep and cognition

Neither logAHI nor AHIgroup were significantly associated with performance in any of the cognitive tests.
However, greater sleep efficiency was associated with higher D-KEFS motor contrast score ($p = 0.001$, Beta = 0.630).

Several correlations were observed between measures of sleep architecture and cognitive performance. Greater percentage of time in stage 1 sleep was associated with poorer performance in the D-KEFS number-letter switching trail ($p = 0.034$, Beta = −0.363) and block design standard score ($p = 0.046$, Beta = −0.345). Greater percentage of stage 2 sleep was associated with better performance in the Stroop word ($p = 0.045$, Beta = 0.368), Stroop colour ($p = 0.016$, Beta = 0.427), colour-word ($p = 0.025$, Beta = 0.398), and the D-KEFS number scanning task ($p = 0.002$, Beta = 0.534). Greater percentage of slow-wave sleep was associated with poorer performance in D-KEFS number scanning task ($p = 0.028$, Beta = −0.385). Higher percentage of total sleep time in REM sleep was associated with poorer performance in the Stroop colour ($p = 0.013$, Beta = −0.418), Stroop colour-word ($p = 0.035$, Beta = −0.357), D-KEFS number scanning ($p = 0.037$, Beta = −0.354), and ECAS executive ($p = 0.040$, Beta = −0.346) subtests.

4. Discussion

This study explored polysomnography, clinical outcome measures and structural brain imaging together in a moderate-sized cohort of adults with DM1. Findings confirm that abnormalities of sleep are common in this group of patients, including reduced sleep efficiency, changes in sleep architecture and frequent SDB. Abnormalities generally increased with age and, furthermore, male sex, daytime hypercapnoea, self-reported fatigue and physical impairment were positively associated with presence of SDB. Increased proportion of REM and slow-wave sleep at the expense of stage 2 sleep – changes considered to be characteristic of DM1 [9,10] – showed some association with cortical volume loss and cognitive performance. Increased hippocampal volume was associated with greater self-reported somnolence, measured by multiple tools.

This study used home recording level II PSG instead of inpatient studies, and did not take specific steps to account for first-night effect, nor record preceding
sleep diary or actigraphy. These could be considered methodological limitations, since laboratory-based recordings are generally considered the gold standard for sleep research while ambulatory studies are typically reserved for clinical applications [27]. However, it is also well-recognised that physical and cognitive disability represent significant barriers to participation amongst patients with DM1 [28], and so our approach represented a conscious effort to optimise engagement by minimising the burden of participation to study subjects. The sleep characteristics we identified in terms of sleep efficiency, architecture and SDB were broadly consistent with published literature in DM1 [8,9,15]. Furthermore, for the single subject in whom PSG was repeated because of battery failure, sleep efficiency was very similar between the first and second recordings (64.8 versus 64.7%). Taken together, these findings support the validity of unsupervised, ambulatory PSG as a means of capturing exploratory sleep data for research in DM1, although subsequent replication of findings with inpatient studies may still be desirable.

The pre-determined PSG measurement period of 8 h was an additional limitation of our PSG studies. This means that data were not obtained regarding whether any subjects had prolonged sleep periods. Future work to look at sleep patterns over longer periods in DM1 would be a valuable extension, and is increasingly feasible with the continued evolution of wrist-worn actigraphy devices [29].

The most striking finding from our PSG studies was the high prevalence of SDB, with at least mild SDB present in 86% of subjects. This is consistent with published data in a similar-sized cohort [9]. It has previously been observed that SDB occurs more frequently in DM1 than other disorders with a comparable pattern of muscle weakness [30], leading to speculation that central factors in addition to muscle

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Fig. 5. Relationship between self-reported somnolence and/or fatigue and regional brain volumes. Diamonds represent the estimated coefficients for the relationship between the given sleep measure, and each brain regional volume (y-axis), adjusted for age, logePAL and sex. Solid lines represent 95% confidence intervals. Coefficients reaching statistical significance at $p < 0.001$ are coloured red, and those at $p < 0.05$ are coloured green.
weakness may contribute to abnormalities of breathing. While some central apnoeas were observed, the great majority of events we detected were obstructive in nature. Furthermore, moderate to severe SDB was significantly associated with higher scores in the MDHI mobility subscale and DM1-ActivC© scores, favouring increasing muscle weakness as a major risk factor for SDB. Additional clinical characteristics associated with risk of SDB were increasing age, male sex, daytime hypercapnea and self-reported fatigue or somnolence. These insights can aid risk stratification of patients in clinical outpatient settings, and may support a rational approach to screening for SDB in DM1 cohorts. However, it should also be emphasised that no single clinical measure consistently distinguished patients with significant SDB from those without, and so a low threshold for sleep investigations remains appropriate for all patients with DM1.

None of the regional brain volumes measured correlated significantly with AHI, either in linear models or group comparison. In the general population, obstructive sleep apnoea syndrome (OSAS) has been linked to changes in hippocampal volume [31], as well as regional alterations in grey and white matter volumes [32,33]. The power of the present study to detect structural correlations was limited by sample size, as well as a confounding effect of heterogeneity within the sample with respect to factors including age and CTG repeat length, and so our findings do not exclude SDB as potentially contributing to structural brain changes in DM1. OSAS in the general population is also linked to morbidity affecting multiple body symptoms, including cardiovascular risk [34], insulin resistance [35] and fatty liver disease [36]. Despite this, the contribution of untreated SDB to morbidity in DM1 patients remains poorly defined. Larger studies to explore the clinical correlations of SDB, as well as defining the therapeutic impact of positive airway pressure (PAP) ventilation [37,38], remain areas of considerable unmet need to guide strategies for screening and treatment of SDB in DM1.

The neurobiology underlying changes in sleep architecture in DM1 likewise remains largely unknown. In normal physiology, transition between each stage of the sleep cycle, as well as maintenance of wakefulness, engages neurotransmitter systems in many anatomical locations, including brainstem, thalamus, hypothalamus, basal forebrain, and cortex [39]. In the present study, few structural correlations with measures of sleep efficiency and architecture reached statistical significance. This may again reflect limited power due to size and clinical heterogeneity of the sample. Nonetheless, it seems remarkable that the majority of regions, including all cortical segments, showed a positive contribution to the model in relation to stage 1 and 2 sleep, and a negative effect with respect to slow wave and REM sleep. This observation could support a more general causal relationship between the progressive, widespread structural brain changes that occur due to the primary disease process in DM1, and the characteristic changes in sleep architecture.

Despite having well-defined functional roles both in the regulation of sleep and breathing, we did not detect any significant clinical correlations between sleep measures and brainstem volume. Histopathological changes within the brainstem have been previously described in post-mortem studies of DM1 patients [40,41], and changes in this region may additionally provide a substrate for central hypoventilation and apnoeas observed in some patients. It should be emphasised that the volumetric measures we obtained do not offer data relating to microstructural changes affecting specific tracts, and so future studies should exploit additional imaging modalities such as DTI tractography, which may reveal further structural correlations.

We have previously demonstrated increased volume of hippocampus and amygdala in patients with DM1 compared with controls [18]. Enlargement of the hippocampus has also been described in OSAS cohorts, where it is hypothesised to result from the acute effects of hypoxic injury [42]. We did not observe any significant relationship between AHI and hippocampus volume, and so the cause of the increased volume in DM1 remains unclear. Intriguingly, reduced hippocampal volume has been associated with increased somnolence in OSAS [43], while we observed a positive relationship between volumes and self-reported somnolence and/or fatigue. This finding would support the hypothesis that the increase in volume observed in DM1 represents a pathological process. It should also be emphasised that subjects in our study were sampled only at a single timepoint. It is possible that an increased volume in response to acute injury could be followed by subsequent atrophy, which could account for the reduced hippocampal volume identified in a previous DM1 study which applied a voxel-based morphometry approach [44]. It is noteworthy that hippocampal changes in OSAS may be reversible with appropriate treatment [45], and so longitudinal studies examining volumetric changes with the initiation of CPAP or other treatments would also be a pertinent extension of this observation.

Preceding studies exploring neuroradiological correlations of self-reported fatigue and/or somnolence in DM1 have described various correlations using a range of imaging modalities. Greater symptoms have variously been associated with: increased fractional anisotropy [46], reduced white matter integrity of the superior longitudinal fasciculus and cingulum [47], volume decrease in the middle cerebellar peduncles, pons, midbrain and the right medio-frontal cortex [48], increased magnetic susceptibility of deep grey matter nuclei [49], increased white matter lesion load, ventral diencephalon and pallidum volume loss [50] and echogenicity of the mesencephalic raphe on transcranial sonography [51]. Self-reported scales in DM1 must be interpreted with some caution, since impaired disease-awareness is a well-recognised consequence of CNS involvement [52]. Nonetheless, our study is comparatively well-powered in relation to many preceding studies, and contributes a volume-based parcellation approach, which has rarely been applied previously in DM1.

Few preceding studies have explored the relationship between sleep and cognition in DM1. Our findings are in-keeping with those of previous authors [53,54], who
concluded that fragmentation of sleep due to SDB is not the primary explanation for impaired cognitive performance. Instead, we observed linear associations between measures of sleep architecture and cognitive function. This again could support a model in which both cognitive deficits and sleep abnormalities each represent phenotypic consequences of a common disease process affecting the CNS. Some of the most significant correlations were observed between stage 2 sleep, and cognitive tests which rely on basic processing speed such as the Stroop colour task, and the number-scanning portion of the Trail Making Test. Of note, the thalamus plays a key role in maintenance of stage 2 sleep [55], and thalamic atrophy has been linked to slowing of processing speed in normal ageing [56]. These observations suggest there may also be value in further exploration of the role of the thalamus and thalamocortical projections in both sleep and cognition in DM1.

A definitive pharmacological therapy for the treatment of EDS in DM1 is presently lacking, though wakefulness-promoting agent modafinil has been widely used. Small studies generally support its safety in DM1, but with variable evidence of efficacy [57–62]. The majority of respondents in a large UK survey of DM1-affected families reported a symptomatic benefit [6]. Nonetheless, due to a lack of robust trial data, no psychostimulant is formally recommended for use in myotonic dystrophy [57], and so access to the drug is likely to vary with local prescribing practices.

The mechanism of action of modafinil is not fully understood, but is thought to include activation of central dopaminergic and orexinergic systems, with an indirect effect on histaminergic tone [63]. While such drugs may not modify the underlying disease process, lessening the social impact of EDS still has clear potential to improve quality of life. Further work within the DM1 research community should therefore include the identification and evaluation of centrally-acting therapies for symptomatic treatment, with the aim of producing high-level randomised-control data to facilitate access to any agents that show efficacy.

Finally, future studies should also consider that mechanisms separate from structural brain change may contribute to EDS and altered sleep architecture in DM1 patients. Exploration of endocrine factors, particularly those related to circadian rhythm [64,65], as well as the potential impacts of dysregulation of alternative splicing [66] on neurotransmitter systems should be considered for future studies of sleep in DM1, and may reveal potential therapeutic targets.

5. Conclusions

In conclusion, our data confirm that SDB and changes in sleep architecture are common in adult outpatients with DM1. Increasing age, male sex, self-reported physical impairment, fatigue and sleepiness, as well as increased daytime pCO2 were associated with SDB, which may aid identification of those at-risk in the clinic setting. Clarification of the clinical significance of untreated SDB represents a major priority for future DM1 work. Our results support an association between altered sleep architecture and primary CNS changes in DM1, and suggest a significant relationship between pathological enlargement of the hippocampus and somnolence symptoms. Further work is required to define more detailed structural correlations. Future studies of sleep in DM1 should be well-powered, and utilise a range of imaging modalities as well as considering other aspects of the neurobiology of sleep to improve understanding of this important aspect of the disease and identify new strategies for treatment.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Conflicts of interest

Within the last five years Professor Monckton has been a scientific consultant and/or received an honoraria/stock options/grants from AMO Pharma, Charles River, LoQuis23, Small Molecule RNA, Triplet Therapeutics and Vertex Pharmaceuticals. Professor Monckton also had research contracts with AMO Pharma and Vertex Pharmaceuticals. Professor Monckton has received research grants/contracts from the European Union, CHDI, European Huntington Disease Network, Huntington Disease Society of America, National Institute of Health, Muscular Dystrophy UK and the Myotonic Dystrophy Support Group. Professor Monckton is on the Scientific Advisory Board of Myotonic (formerly the Myotonic Dystrophy Foundation) and EuroDyMA (European Dystrophia Myotonica Association), is a scientific advisor to the Myotonic Dystrophy Support Group and is a vice president of Muscular Dystrophy UK.; The remaining authors have no conflicts to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jmnd.2022.02.003.

Appendix A.

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References


