RESEARCH ARTICLE

Association of Changes in Cerebral and Hypothalamic Structure With Sleep Dysfunction in Patients With Genetic Frontotemporal Dementia

P. Tristin Best, MSc, John C. Van Swieten, MD, PhD, Lize Corrine Jiskoot, PhD, DClinPsy, Fermin Moreno, MD, PhD, Raquel Sánchez-Valle, MD, PhD, Robert Laforce, Jr., MD, PhD, Caroline Graff, MD, PhD, Mario Masellis, MD, PhD, Carmela Tartaglia, MD, James B. Rowe, PhD, Barbara Borroni, MD, Elizabeth Finger, MD, Matthis Synofzik, MD, Daniela Galimberti, PhD, Rik Vandenberghe, MD, PhD, Alexandre de Mendonça, MD, PhD, Christopher Butler, FRCP, PhD, Alexander Gerhard, MD, Isabelle Le Ber, MD, PhD, Pietro Tiraboschi, MD, Isabel Santana, MD, PhD, Florence Pasquier, MD, PhD, Johannes Levin, MD, Markus Otto, MD, Sandro Sorbi, MD, Harro Seelaar, MD, PhD, Arabella Bouzigues, MSc, David M. Cash, PhD, Lucy Louise Russell, PhD, Martina Bocchetta, PhD, Jonathan Daniel Rohrer, MRCP, Gabriel A. Devenyi, PhD, Mallar Chakravarty, PhD,* and Simon Ducharme, MD,* for the Genetic Frontotemporal Dementia Initiative (GENFI)

Correspondence
Mr. Best
paul.best@mail.mcgill.ca

Neurology® 2024;103:e209829. doi:10.1212/WNL.0000000000209829

Abstract

Background and Objectives

Sleep dysfunction is common in patients with neurodegenerative disorders; however, its neural underpinnings remain poorly characterized in genetic frontotemporal dementia (FTD). Hypothalamic nuclei important for sleep regulation may be related to this dysfunction. Thus, we examined changes in hypothalamic structure across the lifespan in patients with genetic FTD and whether these changes related to sleep dysfunction.

Methods

Data from the observational multisite Genetic Frontotemporal Dementia Initiative (GENFI) study were used. GENFI participants were adult members of a family with known pathogenic variants in the microtubule-associated protein tau (MAPT) or progranulin (GRN) genes or an expansion in the chromosome 9 open reading frame 72 (C9orf72) gene. Family members without a pathogenic variant served as controls. GENFI participants were followed annually, with up to 7 visits, and underwent clinical characterization, neuropsychological testing, biological sampling, and brain MRI. For our analyses, participants were included if they had at least 1 T1-weighted structural MRI scan available. Linear mixed-effect models were used to examine changes in sleep dysfunction, measured using the Cambridge Behavioural Inventory-Revised sleep subscale, volumetric changes in hypothalamic regions, and the associations between cortical and hypothalamic atrophy and sleep dysfunction.

Results

Participants included 491 adults with pathogenic genetic variants of FTD (27.9% symptomatic; median age: 49.4 years, 56.4%*F*) and 321 controls (median age: 44.2 years, 57.3%*F*). Pathogenic variant carriers showed greater sleep dysfunction across the adult lifespan (β = [0.25–0.34], $q < 0.005$) with MAPT carriers alone showing presymptomatic sleep changes (β = 0.34, $q = 0.005$). Cortical thinning in frontal and parietal regions was associated with greater

*These authors contributed to this work equally as co-senior authors.

From the Integrated Program in Neuroscience (P.T.B.), McGill, Montréal, Canada; Department of Neurology (J.C.V.S., H.S., L.C.J.), Erasmus Medical Centre, Rotterdam, Netherlands; Department of Neurology (F.M.), Donostia Universitary Hospital, San Sebastián, Spain; Institut D'Investigacións Biomèdiques August Pi I Sunyer (R.S.-V.), University of Barcelona, Spain; Faculté de Médecine (R.L.), Université Laval, Québec City, Canada; Department of Neurobiology (C.G.), Karolinska Institutet, Solna, Sweden; Sunnybrook Research Institute (M.M.), Toronto, Canada; Tanz Centre for Research in Neurodegenerative Diseases (C.T.), University of Toronto, Canada; Department of Clinical Neurosciences (J.B.R.), University of Cambridge, United Kingdom; Department of Clinical and Experimental Sciences (B.B.), University of Brescia, Italy; Department of Clinical Neurological Sciences (E.F.), University of Western Ontario, London, Canada; Hertie-Institute for Clinical Brain Research and Center of Neurology (M.S.), University of Tübingen, Germany; Neurology (D.G.), University of Milan, Italy; Department of Neurosciences (R.V.), KU Leuven, Belgium; Faculty of Medicine (A.M.), University of Lisbon, Portugal; Nuffield Department of Clinical Neurosciences (C.B.), University of Oxford, United Kingdom; Wolfson Molecular Imaging Centre (A.G.), University of Manchester, United Kingdom; Institut du Cerveau—ICM (I.L.B.), Hôpital Pitié-Salpêtrière, Paris, France; 31Fondazione IRCCS (P.T.), Istituto Neurologico Carlo Besta, Milan, Italy; Faculty of Medicine (I.S.), University of Coimbra, Portugal; Department of Neurology (F.P.), Université Lille, France; Department of Neurology (J.L.), Ludwig-Maximilians Universität München, Munich, Germany; Department of Neurology (M.O.), University of Ulm, Germany; Department of Neurofarba (S.S.), University of Florence, Italy; Department of Neurodegenerative Disease (A.B., D.M.C., L.L.R., M.B., J.D.R.), University College London, United Kingdom; and Department of Psychiatry (G.A.D., M.C., S.D.), McGill University, Montréal, Canada.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Coinvestigators are listed in the supplemental digital content available online at Neurology.org/N.

Glossary

FTD = frontotemporal dementia; **C9orf72** = chromosome 9 open reading frame 72; **GRN** = progranulin; **MAPT** = microtubule-associated protein tau; **AD** = Alzheimer disease; **REM** = rapid eye movement; **SCN** = suprachiasmatic nucleus; **SupTub** = superior tubular; **LHA** = lateral hypothalamic area; **MCH** = melanin-concentrating hormone; **MNI** = Montreal Neurological Institute; **OX** = orexin; **GENFI** = Genetic Frontotemporal Dementia Initiative; **CBI-R** = Cambridge Behavioural Inventory-Revised; **T1-w** = T1-weighted; **FDR** = false discovery rate; **CTh** = cortical thickness; **MMSE** = Mini-Mental State Examination; **TIV** = total intracranial volume; **VCP** = valosin-containing protein; **VLPO** = ventrolateral preoptic nucleus; **TBK-1** = TANK-binding kinase 1.

sleep disturbances in C9orf72 and GRN carriers ($q < 0.05$). MAPT carriers showed consistently significant volume loss over time across all sleep-relevant hypothalamic subunits ($\beta = [-0.56$ to $-0.39]$, $q < 0.005$), and reduced volumes in these subunits were related to increased sleep dysfunction ($\beta = [-0.20$ to $-0.16]$, $q < 0.05$).

Discussion

These findings suggest that sleep dysfunction in patients with genetic FTD may be attributable to atrophy in sleep-relevant hypothalamic subunits, with the most severe and consistent deficits observed in MAPT carriers. While biologically plausible, our statistical approach cannot confirm a causal link between atrophy and sleep disturbances.

Introduction

Sleep disturbances are common and have been widely reported in frontotemporal dementia (FTD) with an estimated 33%–76% of patients with FTD experiencing some sort of sleep disturbance.[1] Sleep dysfunction is associated with reduced cognitive performance across the lifespan[2] and may contribute to caregiver distress.[3] Patients with genetic FTD, largely caused by pathogenic mutations in 1 of 3 fully penetrant autosomal dominant variations, chromosome 9 open reading frame 72 (C9orf72), progranulin (GRN), or microtubule-associated protein tau (MAPT),[4] may be at particular risk of experiencing sleep dysfunction. In MAPT carriers, severe sleep symptomatology has previously been observed in patients with FTD and animal models of the pathogenic mutations.[5,6] Furthermore, preclinical MAPT carriers have endorsed significantly greater sleep dysfunction relative to noncarriers, and these symptoms may precede the onset of core clinical symptoms.[7] Notably, rapid eye movement (REM) sleep behavior disorder has previously been associated with C9orf72 expansions.[8,9]

Hypothalamic atrophy is related to sleep dysfunction in neurodegenerative diseases. The hypothalamus contains several nuclei critical to the regulation of sleep and wakefulness, including the suprachiasmatic nucleus (SCN), the lateral hypothalamic area (LHA), and the ventrolateral preoptic nucleus (VLPO), and projects widely to the cortex.[10] The SCN serves as the circadian pacemaker, controlling the timing of sleep and wakefulness.[11] The LHA, by contrast, subserves feeding and sleep.[12] The LHA and adjacent zona incerta contain the cell bodies of neurons containing melanin-concentrating hormone (MCH).[12] MCH neurons are known to be activated during rapid eye movement sleep.[13,14] The LHA also contains wake promoting orexin ([OX]; also known as hypocretin) neurons, which are only found in the LHA and perifornical area.[12] Finally, the VLPO plays an important role in the maintenance of sleep and regulating sleep-wake cycles.[15] Given the importance of the hypothalamus in the coordination of sleep and wakefulness, damage to it should have an outsized impact on sleep performance. This structure has been implicated in disordered sleep in Alzheimer disease (AD),[16] Parkinson disease,[17] and sporadic FTD,[18,19] and reduced OX-A levels in CSF in patients with FTD have been directly correlated with increased daytime somnolence.[20]

Previous work on sleep dysfunction in FTD has primarily been focused on patients with sporadic FTD. Previous investigations, however, have shown unique mutation-specific changes in brain structure with distinct relations to behavioral and psychiatric features in those with FTD-related mutations.[21] Comparatively, little work has been performed to examine the neural correlates of sleep disturbances in genetic FTD. This study aims to examine disordered sleep and the associations between hypothalamic structure and sleep dysfunction in genetic FTD.

Methods

Participants

All data were taken from data freeze 5 of the Genetic Frontotemporal Dementia Initiative (GENFI) study,[22] which includes participants tested between January 30, 2012, and May 31, 2019. A total of 1,108 participants have been recruited from 25 sites across the United Kingdom, the Netherlands, Belgium, France, Spain, Portugal, Italy, Germany, Sweden, Finland, and Canada. Participants were recruited at each site either through

clinical contacts or through those independently reaching out to study teams. Participants included adults with known pathogenic mutations causative of FTD alongside family members who did not carry a pathogenic variant who served as controls.

Symptom Assessment and Cambridge Behavioural Inventory

All participants underwent a standardized clinical and neuropsychological assessment as previously described.[23] A binary variable of symptomatic vs nonsymptomatic was defined by expert clinicians at the time of visit. Individuals were deemed "nonsymptomatic" should they not exhibit typical FTD symptoms or "symptomatic" should they exhibit these symptoms. Of particular interest to this project is the Cambridge Behavioural Inventory-Revised (CBI-R).[24] The CBI-R is a validated, informant-based questionnaire designed to assess and quantify behavioral and psychiatric symptoms common in neurodegenerative disorders within the previous 4 weeks.[24] Cognitively normal informants who know the participant well completed the CBI-R. Items were evaluated on a 5-point scale, from 0 to 4. This study focused on the CBI-R sleep subscale containing 2 items that assess (1) sleep disruption during the night (sleep is disturbed at night) and (2) excessive daytime somnolence (sleeps more by day than before [cat naps, etc]). A composite score, ranging from 0 to 8, of these 2 items was used as the measure of sleep dysfunction in this study.[24]

Image Processing

Acquisition

Participants were recruited and scanned at a GENFI2 site. All participants underwent whole-brain 1.1-mm isotropic resolution volumetric T1-weighted (T1-w) magnetic resonance imaging. MRI scans were acquired using a 3T scanner or 1.5T should 3T not be available. Scan protocols were designed at the outset of the study to harmonize across scanners and imaging sites as much as possible to ensure adequate matching between the scanners.[23] Volumetric T1-w MRI scans were acquired for 983 participants, of which 47 were acquired at 1.5T. Acquisition parameters were as follows: slice thickness 1.1 mm (1–1.2 mm), repetition time 2000 ms (6.6–2,400), echo time 2.9 ms (2.2–9 ms), flip angle 8 deg. (8–11), and number of slices 208 (140–208).

Raw Image Quality Control

Involuntary subject motion during MRI acquisition can cause imaging artifacts that can negatively affect the quality of the data.[25] Reduced image quality can bias derived cortical volumes and thickness estimates and reduce their reliability. To control for these imaging artifacts, quality control of the raw images was assessed using the guidelines developed in the Computational Brain Anatomy Laboratory.[26,27]

Preprocessing

Preprocessing of the raw T1-w images was completed using the minc-bpipe-library pipeline[28] to improve image quality and standardize the images that were used as inputs to the volumetric and cortical thickness (CTh) analyses. The minc-bpipe-pipeline allows supervision of each step through providing quality control images at several preprocessing stages and performs the following steps: (1) N4 bias field correction,[29] (2) registration of the image into Montreal Neurological Institute (MNI) space using bestlinereg,[30,31] (3) field-of-view standardization and brain orientation into MNI space using an inverse-affine transformation of an MNI space head mask, and (4) extraction of the brain using the BEaST technique.[32]

Cortical Thickness

Skull-striped preprocessed brain images derived from the minc-bpipe-library pipeline were used as inputs into the CIVET 2.1.1 pipeline[33] to extract CTh using the average ICBM152 model as the target of registration and a 30-mm surface-based blurring kernel. Outputs were quality controlled to ensure that the gray and white matter surface tissue classification and surface extraction were successful.

Volumetric Measurement of the Hypothalamus

The N4 bias field–corrected preprocessed brain images derived from the minc-bpipe-library were used as inputs for the hypothalamus segmentation. We used a convolutional neural network–based automated hypothalamus segmentation algorithm[34] to obtain volumes in 5 hypothalamic subunits: anterior-inferior (SCN and supraoptic nucleus), anterior-superior (preoptic area and paraventricular nucleus), posterior (mamillary body, posterior lateral hypothalamus, tuberomammillary nucleus), tubular inferior (infundibular nucleus, ventromedial nucleus, supraoptic nucleus, lateral tubular nucleus, tuberomammillary nucleus), and the tubular superior subunit (dorsomedial nucleus, paraventricular nucleus, anterior lateral hypothalamus). Compared with a sample of images manually segmented by an expert rater, given the relatively small size of the hypothalamus (~800 mm^3), the algorithm showed comparatively high Dice coefficients for the whole hypothalamus (0.83) and the posterior and tubular subunits (<0.80) and moderate Dice coefficients for the anterior subunits (<0.54).[34] While not as accurate as manual segmentation, this algorithm can provide reliable and accurate segmentation of the hypothalamus and its subregions in large data sets. Bilateral volumes, in mm^3, of the 5 hypothalamic subunits were extracted, and subunit volumes for each hemisphere were summed for subsequent analysis. Visual inspection of the segmentations was then performed to ensure adequate segmentation.

Statistics

CBI-R Statistical Analyses

Linear mixed-effect models (lmer from the lme4 1.1–14 package R 4.1.0) were used to test whether there were differences in the trajectories of sleep disturbances across the lifespan, as measured by scores on the CBI-R sleep subscale, in carriers of pathogenic variants causative of FTD compared with controls. This model (eq. 1) included pathogenic variant status, the participant's age at visit (to account for mutation-

specific changes across the lifespan), the interaction between these terms, and sex as fixed effects. Participant and family IDs, to account for potential clustering effects based on family membership, were included in the model as random effects.

$$\text{CBI-R Sleep} \sim \text{Pathogenic variant status}^{*}\text{Age at visit} + \text{Sex} + (1|\text{ID}) + (1|\text{Family ID}) \quad (1)$$

To confirm that these findings were not solely driven by symptomatic mutation carriers, additional analyses conducted separately for presymptomatic and symptomatic mutation carriers relative to controls were performed. These models, alongside the statistical models used for the hypothalamic analyses, were corrected for multiple comparisons, using the false discovery rate (FDR) with a threshold of $q \leq 0.05$ to control for the expected proportion of discoveries that are falsely rejected,[35,36] and as such, we will be reporting q-values.

Cortical Thickness Statistical Analyses

To examine how changes in CTh related to measures of sleep disturbances, vertexwise linear mixed-effect models were used (vertexLmer from RMINC_1.5.2.2 package from R 3.6.3). This model (eq. 2) included pathogenic variant status, z-scored CBI-R sleep subscale scores, the interaction between the preceding terms, the participants' baseline age, sex, and z-scored Mini-Mental State Examination (MMSE) scores, as a global measure of disease severity, as fixed effects. Random effects included the participant ID and scanning site. Owing to nonconvergence, family ID was omitted from the CTh model. The resulting maps were corrected for multiple comparisons using FDR with a threshold of ≤ 0.05.

$$\text{CTh} \sim \text{Sex} + \text{Age at baseline} + \text{MMSE} + \text{Pathogenic variant status}^{*}\text{CBI-R sleep} + (1|\text{ID}) + (1|\text{Scanning site}) \quad (2)$$

Volumetric Hypothalamus Statistical Analyses

To examine changes in hypothalamic volume over time in mutation carriers compared with controls, linear mixed-effect models were used. This model (eq. 3) included pathogenetic variant status, participants' age at visit, the interaction between the preceding terms, sex, and total intracranial volume (TIV), to control for differences in brain size, as fixed effects. Random effects included the participant ID and scanning site. Again, owing to nonconvergence, family ID as a factor was omitted from the volumetric models.

$$\text{Volume} \sim \text{Sex} + \text{TIV} + \text{Age at Visit}^{*}\text{Pathogenetic variant status} + (1|\text{ID}) + (1|\text{Scanning site}) \quad (3)$$

To examine whether sleep dysfunction can be related to atrophy in the hypothalamus and its subunits in mutation carriers, linear mixed-effect models were used. This model (eq. 4) included pathogenetic variant status, z-scored CBI-R sleep subscale scores, the interaction between the preceding terms, baseline age, sex, z-scored MMSE scores, and TIV as fixed effects. Random effects included the participant ID and scanning site.

$$\text{Volume} \sim \text{Sex} + \text{Baseline age} + \text{MMSE} + \text{TIV} + \text{Pathogenetic variant Status}^{*}\text{CBI-R sleep} + (1|\text{ID}) + (1|\text{Scanning site}) \quad (4)$$

Standard Protocol Approvals, Registrations, and Patient Consents

All aspects of this study were approved by institutional review boards at each of the GENFI sites. Our site received the full approval from the McGill University Health Centre review ethics board (MPE-CUSM-15-942). Research was conducted according to the principles of the Declaration of Helsinki. All participants provided written informed consent.

Data Availability

Data access to GENFI is managed by a central data access committee that can be contacted through the study website.[37]

Results

Participants

From the 983 participants with at least 1 T1-weighted MR image, scans from 130 participants were discarded because of poor image quality. Eleven participants were excluded because they had a rarer mutation causative of FTD (i.e., valosin-containing protein or TBK-1). Additional 14 participants were excluded because of MR image preprocessing failure, leaving 828 participants (scans = 1,818), of whom 39 participants were scanned at 1.5T (scans = 52). These scans were processed to obtain volumes for the hypothalamic subunits and for CTh. Fifty scans from 16 participants were excluded because of poor segmentation of the hypothalamus, leaving 812 participants (scans = 1,768), of whom 33 were scanned at 1.5T (scans = 45). These data were used for all behavioral and hypothalamic analyses. Seven hundred and ninety-five participants (scans = 1,735; 49 scans from 36 participants at 1.5T) were included for CTh statistical analyses, because of 83 scans from 33 participants being excluded due to insufficient-quality surface extraction or tissue classification. While more scans at 1.5T failed the segmentation and cortical thickness pipelines, most of these scans passed our rigorous visual quality control measures to ensure adequate segmentation, tissue classification, and surface extraction. A summary of this process can be found in eFigure 1. Details regarding demographic and clinical information of the samples are listed in Tables 1 and 2.

CBI-R Sleep Analyses

Group comparisons on the CBI-R sleep subscale across the lifespan revealed significant differences between controls and all mutation carrier groups (C9orf72, $\beta = 0.32$, $q = 1.99 \times 10^{-4}$; GRN, $\beta = 0.25$, $q = 0.003$; MAPT, $\beta = 0.34$, $q = 0.003$) (Figure 1). Increased age was significantly associated with increased sleep

Table 1 Baseline Demographic and Clinical Characteristics in Pathogenic Variant Carriers and Healthy Controls Used for Behavioral and Hypothalamus Analyses

Characteristic	Controls, N = 321	C9orf72, N = 209	GRN, N = 196	MAPT, N = 86	*p* Value
Symptomatic, n (%)	—	68 (32.5)	46 (23.5)	23 (26.7)	0.122
Female, sex, n (%)	184 (57.3)	109 (52.2)	124 (63.3)	44 (51.2)	0.097
Age, y	45.9 (13.2)	50.2 (14.0)	50.0 (13.1)	45.0 (13.3)	<0.001
Education, y	14.3 (3.53)	13.8 (3.38)	14.0 (3.71)	14.1 (3.24)	0.359
MMSE, M	29.4 (1.09)	27.4 (4.23)	27.6 (4.64)	27.9 (3.88)	<0.001
CBI-R sleep	0.44 (0.98)	1.20 (1.90)	0.95 (1.64)	1.38 (1.90)	<0.001

Abbreviations: CBI-R = Cambridge Behavioural Inventory-Revised; C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-ssociated protein tau; MMSE = Mini-Mental State Examination.
Values are listed as means (SD) unless otherwise specified. Chi-squared or one-way analysis of variance was used to examine group differences for relevant variables.

scores compared with controls, suggesting greater sleep dysfunction across all mutation carrier groups relative to controls, with MAPT carriers exhibiting greater mean sleep scores across the lifespan. Furthermore, when examining presymptomatic and symptomatic participants separately, we observed significantly greater sleep dysfunction across all symptomatic mutation carrier groups, relative to controls (β = [0.94–1.02], q < 0.001) (eTable 1); however, only MAPT mutation carriers exhibited subtle albeit significantly greater sleep dysfunction in the presymptomatic cohort (β = 0.34, q = 0.005) (Table 3).

Hypothalamus Analyses

Group comparisons of hypothalamic volumes across the lifespan in mutation carriers and controls revealed significant differences between mutation carriers and controls. These results are presented in Figure 2. There were significant differences in the trajectories of bilateral hypothalamic volumes in all mutation carrier groups when compared with controls. Volumes in the anterior-superior subunit were significantly reduced in both C9orf72 expansion and MAPT mutation carrier groups (β = [−0.52 to −0.26], q < 0.001); however, the differences in GRN mutation carriers were not significant (β = −0.13, q = 0.087). We observed greater volume loss in the anterior-inferior subunit in C9orf72 expansion (β = −0.17, q = 0.029) and MAPT mutation (β = −0.39, q = 5.2×10^{-4}) carriers compared with controls. Again, there were no significant differences between the trajectories in GRN mutation carriers and controls (β = −0.08, q = 0.321). We observed greater volume loss in the posterior (β = [−0.56 to −0.30], q < 0.001) and SupTub (β = [−0.55 to −0.20], q < 0.005) subunits in all mutation carrier groups relative to controls. In contrast to other subunits, trajectories of volumes in the inferior tubular subunit in C9orf72 expansion and MAPT mutation carriers were not statistically different from those in controls (β = [−0.10 to −0.02], q > 0.05) while the subunit volume in GRN carriers were greater relative to controls (β = 0.19, q = 0.013).

Neural Correlates of CBI-R Sleep Scores

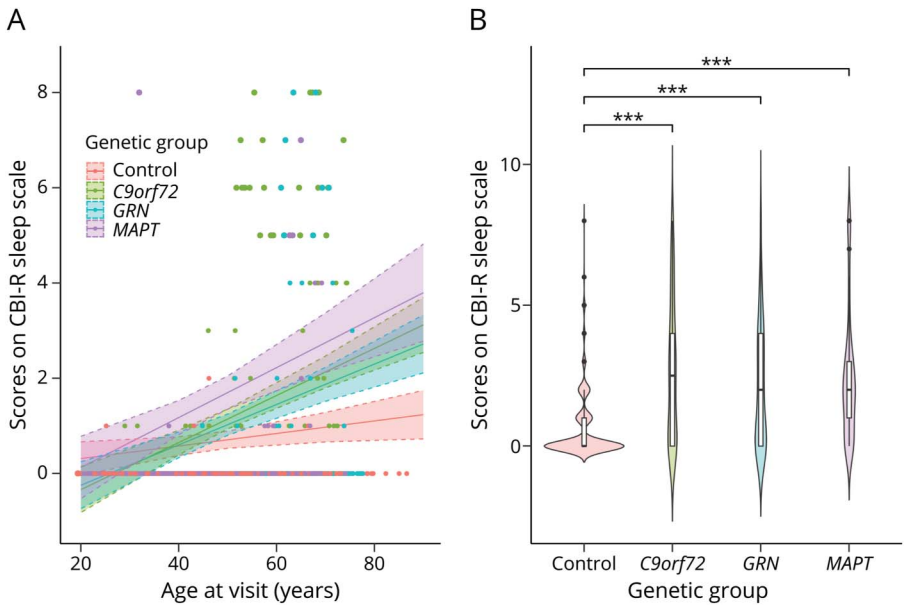
Associations between cortical thinning and scores on the CBI-R sleep scale are presented in Figure 3. In brief, greater scores on the CBI-R sleep scale, indicative of greater sleep dysfunction, are associated with increased atrophy in C9orf72

Table 2 Baseline Demographic and Clinical Characteristics in Pathogenic Variant Carriers and Healthy Controls Used for Cortical Thickness Analyses

Characteristic	Controls, N = 323	C9orf72, N = 191	GRN, N = 193	MAPT, N = 88	*p* Value
Symptomatic, n (%)	—	56 (29.3)	41 (21.2)	24 (27.3)	0.188
Female sex, n (%)	184 (57.0)	102 (53.4)	124 (64.2)	45 (51.1)	0.103
Age, y	45.5 (13.1)	49.0 (13.7)	49.3 (13.0)	44.7 (13.3)	<0.001
Education, y	14.3 (3.52)	13.9 (3.18)	14.0 (3.69)	14.0 (3.34)	0.262
MMSE, M	29.3 (1.13)	27.7 (3.99)	28.0 (3.84)	28.1 (3.49)	<0.001
CBI-R sleep	0.43 (0.97)	1.14 (1.84)	0.86 (1.50)	1.33 (1.79)	<0.001

Abbreviations: CBI-R = Cambridge Behavioural Inventory Revised; C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; MMSE = Mini-Mental State Examination.
Values are listed as means (SD) unless otherwise specified. Chi-squared or one-way analysis of variance was used to examine group differences for relevant variables.

Figure 1 Trajectories and Group Differences in CBI-R Sleep Subscale Scores in Genetic FTD



(A) Scores on the CBI-R sleep subscale across the adult lifespan: Model = CBI-R Sleep ~ Sex + Age at visit * Genetic Group + (1|Id) + (1|blinded family). (B) Scores on the CBI-R sleep subscale in symptomatic mutation carriers: Model = CBI-R Sleep ~ Sex + Age at visit + Genetic Group + (1|Id) + (1|blinded family). The dotted line represents 95% CIs, ***q < 0.001. CBI-R = Cambridge Behavioural Inventory-Revised; FTD = frontotemporal dementia.

expansion carriers in the left prefrontal, parietal, posterior cingulate cortex, and lateral temporal lobe, alongside some right prefrontal involvement. In GRN mutation carriers, greater scores on the CBI-R sleep scale are associated with cortical thinning in the right posterior frontal lobe and parietal lobe and with some posterior temporal lobe involvement. There were no significant associations between sleep measures and cortical thinning in MAPT mutation carriers.

Figure 4 presents associations between hypothalamic volumes and scores on the CBI-R sleep scale. In brief, both C9orf72 and MAPT carriers had significant associations between volumes in the SupTub region and scores on the CBI-R sleep scale, where lower volumes were associated with greater CBI-R sleep scores (β = −0.17, q = 0.002, and β = −0.16, q = 0.021, respectively).

Table 3 Linear Mixed-Effect Model of CBI-R Scores as a Function of Genetic Status and Demographic Variables in Presymptomatic Mutation Carriers

Predictor	β	95% CI	q Value
Intercept	0.02	−0.11 to 0.14	0.43
C9orf72	−0.11	−0.28 to 0.06	0.26
GRN	−0.005	−0.14 to 0.13	0.95
MAPT	0.34	0.12–0.57	0.005
Age at visit	0.11	0.05–0.17	0.001
Sex (male)	0.12	0.01–0.24	0.04

Abbreviations: β = standardized regression coefficient; C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau.

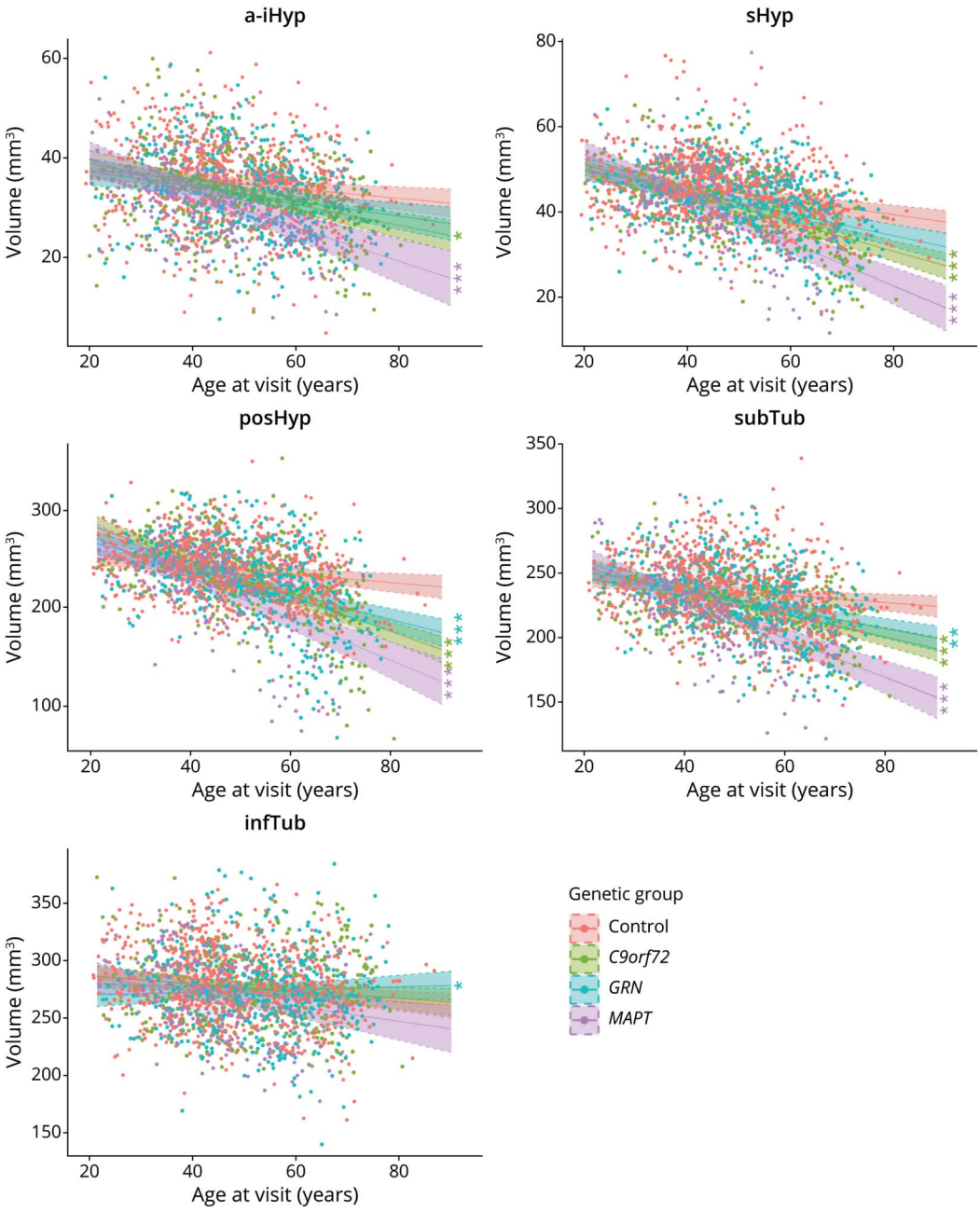
MAPT mutation carriers showed trends of associations between anterior-inferior volumes and scores on the CBI-R sleep scale, with greater scores being associated with reduced hypothalamic volumes (β = −0.16, q = 0.06). This association was not significant in C9orf72 expansion or GRN mutation carriers. Furthermore, greater CBI-R sleep scores were associated with reduced volumes in the posterior hypothalamic subunit across all mutation carrier groups (β = [−0.20 to −0.14], q < 0.003). Finally, there were no significant associations between anterior-superior subunit or tubular-inferior subunit volumes and scores on the CBI-R sleep scale that survived correction for multiple comparisons.

Discussion

The main findings of this project were threefold. First, we observed an increase in the prevalence and severity of sleep disturbances across the lifespan in all mutation carrier groups, particularly MAPT carriers. Furthermore, these differences between carriers and noncarriers precede onset of clinical symptoms in MAPT carriers. Second, we found significant differences in the trajectories of hypothalamic volumes. MAPT carriers showed pronounced volume differences across all hypothalamic subunits, save for the tubular inferior region. Measures of sleep dysfunction correlated with cortical thinning in frontal, parietal, and temporal lobes, but only in C9orf72 expansion and GRN mutation carriers. Finally, reduced hypothalamic volumes were related to sleep dysfunction in both C9orf72 and MAPT carriers, with MAPT carriers showing the strongest associations.

Our results indicate a differing evolution of sleep dysfunction across the lifespan in all mutation carrier groups compared with controls. As expected, we observed increased sleep disturbances as participants aged across all mutation carrier groups, with

Figure 2 Hypothalamic Subunit Volumes Across the Adult Lifespan in Genetic FTD

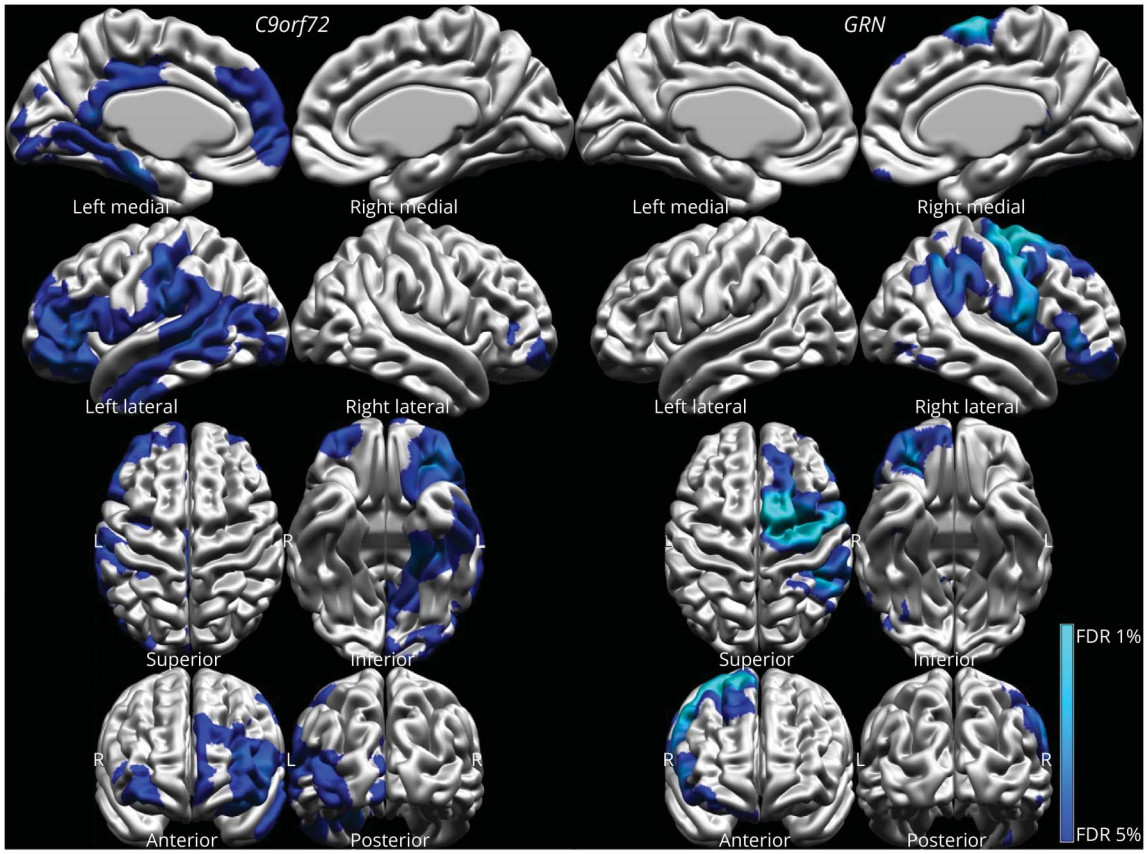


The dotted line represents 95% CIs. ***q < 0.001, **q < 0.01, *q < 0.05. Models = Vol ~ Sex + Total Intracranial Volume + CBI-R Sleep *Genetic Group + (1 | Id) + (1 | Scanning site). CBI-R = Cambridge Behavioural Inventory-Revised; FTD = frontotemporal dementia. a-iHyp = anterior inferior, a-sHyp = anterior superior, posHyp = posterior, subTub = superior tubular, infTub = inferior tubular.

increases in sleep symptomatology after onset of clinical symptoms. It is important to note that sleep dysfunction was more prominent in MAPT carriers compared with other mutation carriers and controls, corroborating previous suggestions that sleep dysfunction is more salient in MAPT carriers.[5,7] Only MAPT carriers alone exhibited greater sleep dysfunction than controls before the onset of clinical symptoms.

We found significant differences in the trajectories of hypothalamic volumes, with significant reductions in most of the measured subunits across the lifespan in mutation carriers compared with controls (Figure 2), including subunits containing nuclei (i.e., the SCN, LHA, and VLPO) relevant to the regulation of sleep and wakefulness. MAPT carriers showed the greatest volumetric changes across these subunits. This is in line with previous work demonstrating reduced hypothalamic volumes in symptomatic *MAPT* carriers in anterior and posterior regions, when compared to other mutation carrier groups.[38,39] Of interest, histopathologic work in bvFTD found that participants with tau pathologies had greater

Figure 3 Cortical Thinning Patterns Associated With Increased CBI-R Sleep Subscale Scores in C9orf72 and GRN Carriers Relative to Controls



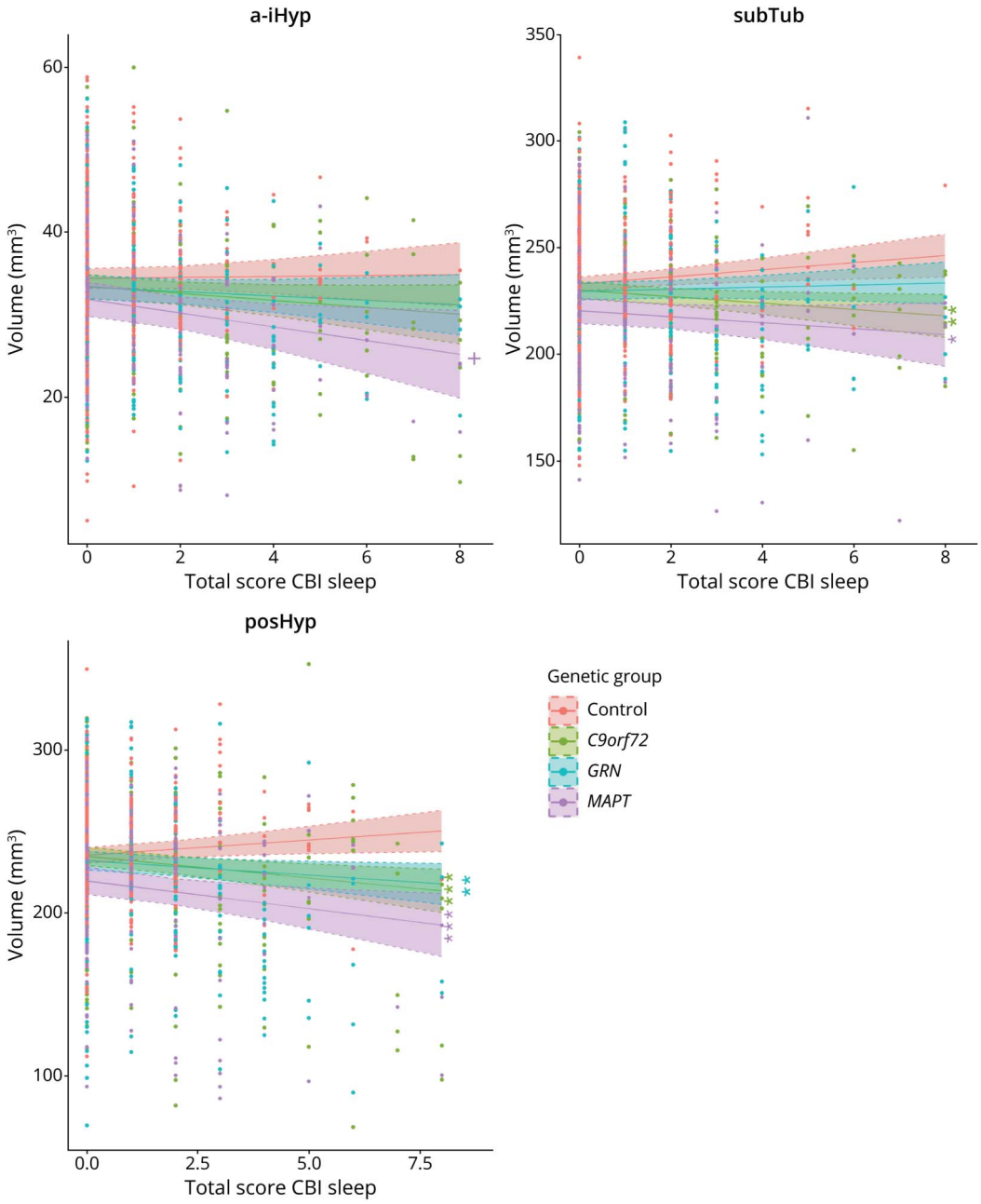
Model = CTh ~ Sex + Age at Visit + MMSE + CBI-R Sleep * Genetic Group + (1|Id) + (1| Scanning Site). FDR = false discovery rate; GRN = progranulin.

abnormal protein deposition in the hypothalamus compared with those with TDP-43 pathologies. Furthermore, they found that increased atrophy and neuronal loss in these regions,[40] suggesting tau pathology, as seen in MAPT carriers, may differentially affect hypothalamic integrity. Another study had found no TDP-43 deposition in the SCN in C9orf72 expansion carriers; however, dipeptide repeat protein inclusions were observed, suggesting a differential mechanism of hypothalamic atrophy unique to C9orf72 expansion carriers. The inferior tubular subunit, the sole preserved region in this study, has been shown to be preserved in sporadic bvFTD and FTD associated to *MAPT* mutations and *C9orf72* expansions,[39] although it seems to be implicated later in the disease course in MAPT mutation carriers.[38] Further in vivo imaging combined with ex vivo histopathologic work would be useful to elucidate the differential underpinnings of the observed hypothalamic atrophy.

We observed a significant association between cortical thinning and sleep symptomatology in C9orf72 expansion carriers and GRN mutation carriers, however not in MAPT (Figure 3). Adverse sleep symptomatology has been associated with atrophy patterns largely overlapping with those observed in GRN mutation and C9orf72 expansion carriers,[41] namely in the medial and lateral prefrontal cortex. The frontal cortex is suspected to be one of the key regulatory structures of non-REM sleep.[41] Reduced slow wave activity during non-REM sleep has also been associated with structural changes in the medial frontal cortex, and this may be driven by reduced frontal lobe-hippocampal connectivity.[42] This study cannot speak to this hypothesis, and thus, future work should seek to encompass a wider spectrum of subcortical structures in their analyses to address this lingering question. The absence of association between CTh and CBI-R sleep scores in MAPT carriers was unexpected because MAPT carriers endorsed the most severe sleep symptomatology and showed cortical thinning in regions previously linked with sleep disturbances, namely the medial prefrontal cortex, anterior cingulate cortex, and anterior medial lobes.[41-43] This discrepancy suggests that the sleep symptomatology observed in MAPT carriers may be driven primarily by hypothalamic alterations.

We observed significant associations between hypothalamic structure and our measure of sleep dysfunction in C9orf72 and MAPT carriers. 3 hypothalamic subunits, posterior, anterior-inferior, and SupTub, containing nuclei important to the regulation of sleep and wakefulness, that is, the SCN and LHA,[11,12] were significantly correlated with sleep

Figure 4 Associations Between Hypothalamic Subunit Volumes and Scores on the CBI-R Sleep Subscale



The dotted line represents 95% CIs. ***q < 0.001, **q < 0.01, *q < 0.05, +q = 0.06. Models = Volume ~ Sex + Age at visit + Total Intracranial Volume + MMSE + CBI-R sleep subscale *Genetic Group + (1 | Id) + (1 | Scanning Site). a-iHyp = anterior inferior, posHyp = posterior, subTub = superior tubular.

disturbances. However, despite significant volumetric changes in the anterior-superior subunit, which contains the VLPO, there were no significant associations between these volumes and sleep dysfunction. Furthermore, the subunit with no expected association with sleep dysfunction (i.e., inferior-tubular subunit) was not significantly related to sleep disturbances. Together, these findings suggest that structural changes in the SCN and LHA may be driving the adverse sleep symptoms observed in these mutation carriers. This is further corroborated through MAPT mutation carriers exhibiting the greatest hypothalamic atrophy and the most severe sleep symptomatology. Of interest, atrophy in the posterior subunit of the hypothalamus, which contains the posterior regions of the LHA, was significantly associated with sleep dysfunction across all mutation carrier groups. This suggests a role of orexigenic neurons in sleep symptomatology in FTD-related mutation carriers. Reduced OX-A levels in plasma and CSF have previously been associated with sleep disturbances in sporadic FTD.[19,20] Orexin has been a neuropeptide of interest regarding sleep in FTD,[44,45] and its dysregulation may instigate downstream alterations in other neurotransmitter pathways affected in the condition

contributing to other symptoms.[45] As such, these findings highlight the need for more in-depth research on orexigenic systems in FTD-related mutation carriers and as a potential target for pharmacologic interventions.

We acknowledge that there are limitations to this study. First, the CBI-R sleep subscale provides a limited and aggregate assessment of sleep dysfunction derived from the informant report rather than objective measures such as polysomnography or actigraphy. Given the limited nature of the behavioral assessment, where sleep dysfunction may mean too much or too little sleep, for this study, we were unable to provide a precise assessment of the neurobiological correlates of specific sleep deficits in patients with genetic FTD. As such, future projects should aim to assess objective measures (e.g., polysomnography) of sleep dysfunction in this population. Several medications commonly used in FTD, such as sertraline and quetiapine, may also affect sleep dysfunction.[46] We were unable to account for these in our analyses; however, it would be beneficial for future work to examine the role of medications in sleep dysfunction in genetic FTD.

It is important to note that this study contained a limited number of MAPT mutation carriers, representing approximately 17.5% of the mutation carriers in this sample. This is expected given that MAPT mutations seem to be the least frequently observed worldwide (23.2%) compared with GRN mutations (34.6.1%) and C9orf72 expansions (42.1%).[47] Future work with a larger sample of MAPT mutation carriers, however, would be needed to confirm the observations made in this study.

Finally, although we have examined volumetric changes in individual subunits of the hypothalamus, due to the limitations of structural MR imaging, examining volumetric change in individual nuclei was outside the scope of this study. The hypothalamus comprised a number of cytoarchitectonically distinguishable nuclei, within a very small structure, roughly 4 cm^3, and accounting for 0.3% of the human brain.[48] As such, imaging and subsequent segmentation of these nuclei are outside the purview of this study. This methodological limitation could be addressed in future studies, through imaging these structures at a higher field strength (e.g., 7T), allowing for better spatial resolution and integrating high-definition MR imaging with postmortem histologic analysis of these subunits.

In summary, this study has shown that the hypothalamic structure is involved in sleep dysfunction in FTD-related mutation carriers. Sleep dysfunction was common across mutation carrier groups but may be more severe in MAPT mutation carriers and increases after the onset of clinical symptoms. While cortical thinning in C9orf72 expansion and GRN mutation carriers correlates with increased sleep dysfunction, the increased severity of sleep dysfunction observed in MAPT carriers may be attributable to increased hypothalamic atrophy. These findings highlight the potential role of the orexigenic system in sleep dysfunction in carriers in genetic FTD. This study provides evidence that underlying neurodegenerative changes in the hypothalamus relate to sleep dysfunction in those with these mutations. This may inform the neurobiology of sleep disturbances in other related neurodegenerative disorders such as AD and Parkinson disease where sleep disturbances are common.[49]

Acknowledgment

The views expressed in this paper are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Study Funding

This research was undertaken thanks in part to funding from the Canada First Research Excellence Fund, awarded to McGill University for the Healthy Brains for Healthy Lives initiative. GENFI was also supported by the MRC UK GENFI grant (MR/M023664/1), the Italian Ministry of Health (CoEN015 and Ricerca Corrente), the Canadian Institutes of Health Research as part of a Centres of Excellence in Neurodegeneration grant, a Canadian Institutes of Health Research operating grant, the Alzheimer's Society grant (AS-PG-16-007), the Bluefield Project and the JPND GENFI-PROX grant (2019–02248). This work was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC 2145 SyNergy–ID 390857198). Several authors of this publication (JCvS, MS, RSV, AD, MO, JDR) are members of the European Reference Network for Rare Neurologic Diseases (ERN-RND)—Project ID No 739510. This work was also funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy within the framework of the Munich Cluster for Systems Neurology (EXC2145 SyNergy–ID 390857198), and by the NIHR Cambridge Biomedical Research Centre (BRC-1215-20014).

Disclosure

M. Bocchetta is supported by a Fellowship award from the Alzheimer's Society, UK (AS-JF-19a-004-517), and the UK Dementia Research Institute which receives its funding from DRI Ltd., funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK. J.D. Rohrer is an MRC Clinician Scientist (MR/M008525/1) and has received funding from the NIHR Rare Diseases Translational Research Collaboration (BRC149/NS/MH), the Bluefield Project and the Association for Frontotemporal Degeneration. The other authors report no disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* March 19, 2024. Accepted in final form October 2, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Linda Hershey, MD, PhD, FAAN.

Appendix 1 Authors

Name	Location	Contribution
P. Tristin Best, MSc	Integrated Program in Neuroscience, McGill, Montréal, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
John C. Van Swieten, MD, PhD	Department of Neurology, Erasmus Medical Centre, Rotterdam, Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Lize Corrine Jiskoot, PhD, DClinPsy	Department of Neurology, Erasmus Medical Centre, Rotterdam, Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Fermin Moreno, MD, PhD	Department of Neurology, Donostia Universitary Hospital, San Sebastián, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Raquel Sánchez-Valle, MD, PhD	Institut D'Investigacións Biomèdiques August Pi I Sunyer, University of Barcelona, Spain	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Robert Laforce, MD, PhD	Faculté de Médecine, Université Laval, Québec City, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Caroline Graff, MD, PhD	Department of Neurobiology, Karolinska Institutet, Solna, Sweden	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Mario Masellis, MD, PhD	Sunnybrook Research Institute, University of Toronto, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Carmela Tartaglia, MD	Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
James B. Rowe, PhD	Department of Clinical Neurosciences, University of Cambridge, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Barbara Borroni, MD	Department of Clinical and Experimental Sciences, University of Brescia, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Elizabeth Finger, MD	Department of Clinical Neurological Sciences, University of Western Ontario, London, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Matthis Synofzik, MD	Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Daniela Galimberti, PhD	Neurology, University of Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Rik Vandenberghe, MD, PhD	Department of Neurosciences, KU Leuven, Belgium	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Alexandre de Mendonça, MD, PhD	Faculty of Medicine, University of Lisbon, Portugal	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Christopher Butler, FRCP, PhD	Nuffield Department of Clinical Neurosciences, University of Oxford, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Alexander Gerhard, MD	Wolfson Molecular Imaging Centre, University of Manchester, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Isabelle Le Ber, MD, PhD	Institut du Cerveau—ICM, Hôpital Pitié-Salpêtrière, Paris, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Pietro Tiraboschi, MD	31Fondazione IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Isabel Santana, MD, PhD	Faculty of Medicine, University of Coimbra, Portugal	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Florence Pasquier, MD, PhD	Department of Neurology, Université Lille, france	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Johannes Levin, MD	Department of Neurology, Ludwig-Maximilians Universität München, Munich, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Markus Otto, MD	Department of Neurology, University of Ulm, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Continued

Appendix 1 *(continued)*

Name	Location	Contribution
Sandro Sorbi, MD	Department of Neurofarba, University of Florence, Italy	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Harro Seelaar, MD, PhD	Department of Neurology, Erasmus Medical Centre, Rotterdam, Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Arabella Bouzigues, MSc	Department of Neurodegenerative Disease, University College London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
David M. Cash, PhD	Department of Neurodegenerative Disease, University College London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Lucy Louise Russell, PhD	Department of Neurodegenerative Disease, University College London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Martina Bocchetta, PhD	Department of Neurodegenerative Disease, University College London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Jonathan Daniel Rohrer, MRCP	Department of Neurodegenerative Disease, University College London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Gabriel A. Devenyi, PhD	Department of Psychiatry, McGill University, Montréal, Canada	Analysis or interpretation of data
Mallar Chakravarty, PhD	Department of Psychiatry, McGill University, Montréal, Canada	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
Simon Ducharme, MD	Department of Psychiatry, McGill University, Montréal, Canada	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

Appendix 2 Coinvestigators

Coinvestigators are listed at Neurology.org/N.

References

1. McCarter SJ, St Louis EK, Boeve BF. Sleep disturbances in frontotemporal dementia. *Curr Neurol Neurosci Rep*. 2016. 16(9):85. doi:10.1007/s11910-016-0680-3
2. Scullin MK, Bliwise DL. Sleep, cognition, and normal aging: integrating a half century of multidisciplinary research. *Perspect Psychol Sci*. 2015;10(1):97-137. doi:10.1177/1745691614556680
3. Merrilees J, Hubbard E, Mastick J, Miller BL, Dowling GA. Sleep in persons with frontotemporal dementia and their family caregivers. *Nurs Res*. 2014;63(2):129-136. doi:10.1097/NNR.0000000000000024
4. Greaves CV, Rohrer JD. An update on genetic frontotemporal dementia. *J Neurol*. 2019;266(8):2075-2086. doi:10.1007/s00415-019-09363-4
5. Gemignani A, Pietrini P, Murrell JR, et al. Slow wave and rem sleep mechanisms are differently altered in hereditary pick disease associated with the TAU G389R mutation. *Arch Ital Biol*. 2005;143(1):65-79.
6. Koss DJ, Robinson L, Drever BD, et al. Mutant Tau knock-in mice display frontotemporal dementia relevant behaviour and histopathology. *Neurobiol Dis*. 2016;91:105-123. doi:10.1016/j.nbd.2016.03.002
7. Tavares TP, Mitchell DGV, Coleman KK, et al. Early symptoms in symptomatic and preclinical genetic frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry*. 2020;91(9):975-984. doi:10.1136/jnnp-2020-322987
8. Daoud H, Postuma RB, Bourassa CV, et al. C9orf72 repeat expansions in rapid eye movement sleep behaviour disorder. *Can J Neurol Sci*. 2014;41(6):759-762. doi:10.1017/cjn.2014.39
9. Sani TP, Bond RL, Marshall CR, et al. Sleep symptoms in syndromes of frontotemporal dementia and Alzheimer's disease: a proof-of-principle behavioural study. *eNeurologicalSci*. 2019;17:100212. doi:10.1016/j.ensci.2019.100212
10. Saper CB, Lowell BB. The hypothalamus. *Curr Biol*. 2014;24(23):R1111-R1116. doi:10.1016/j.cub.2014.10.023
11. Moore RY. Suprachiasmatic nucleus in sleep-wake regulation. *Sleep Med*. 2007;8(suppl 3):27-33. doi:10.1016/j.sleep.2007.10.003
12. Yamashita T, Yamanaka A. Lateral hypothalamic circuits for sleep-wake control. *Curr Opin Neurobiol*. 2017;44:94-100. doi:10.1016/j.conb.2017.03.020
13. Tsunematsu T, Ueno T, Tabuchi S, et al. Optogenetic manipulation of activity and temporally controlled cell-specific ablation reveal a role for MCH neurons in sleep/wake regulation. *J Neurosci*. 2014;34(20):6896-6909. doi:10.1523/JNEUROSCI.5344-13.2014
14. Jego S, Glasgow SD, Herrera CG, et al. Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus. *Nat Neurosci*. 2013;16(11):1637-1643. doi:10.1038/nn.3522
15. Arrigoni E, Fuller PM. The sleep-promoting ventrolateral preoptic nucleus: what have we learned over the past 25 years? *Int J Mol Sci*. 2022;23(6):2905. doi:10.3390/ijms23062905
16. Van Erum J, Van Dam D, De Deyn PP. Sleep and Alzheimer's disease: a pivotal role for the suprachiasmatic nucleus. *Sleep Med Rev*. 2018;40:17-27. doi:10.1016/j.smrv.2017.07.005
17. Kalaitzakis ME, Gentleman SM, Pearce RKB. Disturbed sleep in Parkinson's disease: anatomical and pathological correlates. *Neuropathol Appl Neurobiol*. 2013;39(6):644-653. doi:10.1111/nan.12024
18. Anderson KN, Hatfield C, Kipps C, Hastings M, Hodges JR. Disrupted sleep and circadian patterns in frontotemporal dementia. *Eur J Neurol*. 2009;16(3):317-323. doi:10.1111/j.1468-1331.2008.02414.x
19. Çoban A, Bilgiç B, Lohmann E, et al. Reduced orexin-A levels in frontotemporal dementia: possible association with sleep disturbance. *Am J Alzheimers Dis other Demen*. 2013;28(6):606-611. doi:10.1177/1533317513494453
20. Liguori C, Romigi A, Mercuri NB, et al. Cerebrospinal-fluid orexin levels and daytime somnolence in frontotemporal dementia. *J Neurol*. 2014;261(9):1832-1836. doi:10.1007/s00415-014-7455-z
21. Bussy A, Levy JP, Best T, et al. Cerebellar and subcortical atrophy contribute to psychiatric symptoms in frontotemporal dementia. *Hum Brain Mapp*. 2023;44(7):2684-2700. doi:10.1002/hbm.26220
22. The Genetic Frontotemporal Initiative. Accessed June 20, 2024. genfi.org
23. Rohrer JD, Nicholas JM, Cash DM, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *Lancet Neurol*. 2015;14(3):253-262. doi:10.1016/S1474-4422(14)70324-2
24. Wear HJ, Wedderburn CJ, Mioshi E, et al. The Cambridge behavioural inventory revised. *Demen Neuropsychologia*. 2008;2(2):102-107. doi:10.1590/S1980-57642009DN20200005
25. Reuter M, Tisdall MD, Qureshi A, Buckner RL, van der Kouwe AJW, Fischl B. Head motion during MRI acquisition reduces gray matter volume and thickness estimates. *Neuroimage*. 2015;107:107-115. doi:10.1016/j.neuroimage.2014.12.006
26. Bedford SA, Park MTM, Devenyi GA, et al. Large-scale analyses of the relationship between sex, age and intelligence quotient heterogeneity and cortical morphometry in autism spectrum disorder. *Mol Psychiatry*. 2020;25(3):614-628. doi:10.1038/s41380-019-0420-6
27. Computational Brain Anatomy Laboratory. Motion quality control (QC) manual. Accessed June 20, 2024. github.com/CoBrALab/documentation/wiki/Motion-Quality-Control-(QC)-Manual
28. Computational Brain Anatomy Laboratory. Accessed June 20, 2024. minc-bpipe-library. github.com/CoBrALab/minc-bpipe-library
29. Tustison NJ, Avants BB, Cook PA, et al. N4ITK: improved N3 bias correction. *IEEE Trans Med Imaging*. 2010;29(6):1310-1320. doi:10.1109/TMI.2010.2046908
30. Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr*. 1994;18(2):192-205. doi:10.1097/00004728-199403000-00005
31. Dadar M, Fonov VS, Collins DL, Alzheimer's Disease Neuroimaging Initiative. A comparison of publicly available linear MRI stereotaxic registration techniques. *Neuroimage*. 2018;174:191-200. doi:10.1016/j.neuroimage.2018.03.025
32. Eskildsen SF, Coupé P, Fonov V, et al. BEaST: brain extraction based on nonlocal segmentation technique. *Neuroimage*. 2012;59(3):2362-2373. doi:10.1016/j.neuroimage.2011.09.012

33. McConnell Brain Imaging Centre. Accessed June 20, 2024. *CIVET 2.1.1* bic.mni.mcgill.ca/ServicesSoftware/CIVET-2-1-0-Introduction
34. Billot B, Bocchetta M, Todd E, Dalca AV, Rohrer JD, Iglesias JE. Automated segmentation of the hypothalamus and associated subunits in brain MRI. *Neuroimage*. 2020;223:117287. doi:10.1016/j.neuroimage.2020.117287
35. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B: Stat Methodol.* 1995;57(1):289-300. doi:10.1111/j.2517-6161.1995.tb02031.x
36. Benjamini Y, Drai D, Elmer G, Kafkafi N, Golani I. Controlling the false discovery rate in behavior genetics research. *Behav Brain Res.* 2001;125(1-2):279-284. doi:10.1016/s0166-4328(01)00297-2
37. The Genetic Frontotemporal Initiative. GENFI—contact us. Accessed June 20, 2024. genfi.org/contact-us-2/
38. Bocchetta M, Todd EG, Peakman G, et al. Differential early subcortical involvement in genetic FTD within the GENFI cohort. *Neuroimage Clin.* 2021;30:102646. doi:10.1016/j.nicl.2021.102646
39. Bocchetta M, Gordon E, Manning E, et al. Detailed volumetric analysis of the hypothalamus in behavioral variant frontotemporal dementia. *J Neurol.* 2015;262(12):2635-2642. doi:10.1007/s00415-015-7885-2
40. Piguet O, Petersén A, Yin Ka Lam B, et al. Eating and hypothalamus changes in behavioral-variant frontotemporal dementia. *Ann Neurol.* 2011;69(2):312-319. doi:10.1002/ana.22244
41. Sexton CE, Storsve AB, Walhovd KB, Johansen-Berg H, Fjell AM. Poor sleep quality is associated with increased cortical atrophy in community-dwelling adults. *Neurology*. 2014;83(11):967-973. doi:10.1212/WNL.0000000000000774
42. Mander BA, Rao V, Lu B, et al. Prefrontal atrophy, disrupted NREM slow waves and impaired hippocampal-dependent memory in aging. *Nat Neurosci.* 2013;16(3):357-364. doi:10.1038/nn.3324
43. Ahmed MR, Halliday G, Hodges RJ. Hypothalamic symptoms of frontotemporal dementia disorders. *Handb Clin Neurol.* 2021;182:269-280.
44. Warren JD, Clark CN. A new hypnic paradigm of neurodegenerative proteinopathies. *Sleep Med.* 2017;32:282-283. doi:10.1016/j.sleep.2016.12.006
45. Hwang YT, Piguet O, Hodges JR, Grunstein R, Burrell JR. Sleep and orexin: a new paradigm for understanding behavioural-variant frontotemporal dementia? *Sleep Med Rev.* 2020;54:101361. doi:10.1016/j.smrv.2020.101361
46. Khoury R, Liu Y, Sheheryar Q, Grossberg GT. Pharmacotherapy for frontotemporal dementia. *CNS Drugs*. 2021;35(4):425-438. doi:10.1007/s40263-021-00813-0
47. Moore KM, Nicholas J, Grossman M, et al. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *Lancet Neurol.* 2020;19(2):145-156. doi:10.1016/S1474-4422(19)30394-1
48. Hofman MA, Swaab DF. The human hypothalamus: comparative morphometry and photoperiodic influences. *Prog Brain Res.* 1992;93:133-149. doi:10.1016/s0079-6123(08)64569-0
49. Vaou OE, Lin SH, Branson C, Auerbach S. Sleep and dementia. *Curr Sleep Med Rep*. 2018;4(2):134-142. doi:10.1007/s40675-018-0112-9