

Lower hypothalamic volume with lower body mass index is associated with shorter survival in patients with amyotrophic lateral sclerosis

Jeryn Chang¹  | Thomas B. Shaw^{2,3,4}  | Cory J. Holdom⁵  |
 Pamela A. McCombe^{2,6,7}  | Robert D. Henderson^{2,6,7}  | Jurgen Fripp⁸  |
 Markus Barth^{3,4}  | Christine C. Guo⁹  | Shyuan T. Ngo^{2,5,7}  | Frederik J. Steyn^{1,2,7}  |
 For the Alzheimer's Disease Neuroimaging Initiative^a

¹School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Saint Lucia, Australia

²Department of Neurology, Royal Brisbane and Women's Hospital, Herston, Australia

³Centre for Advanced Imaging, The University of Queensland, Saint Lucia, Australia

⁴School of Information Technology and Electrical Engineering, The University of Queensland, Saint Lucia, Australia

⁵Australian Institute of Bioengineering and Nanotechnology, The University of Queensland, Saint Lucia, Australia

⁶UQ Centre for Clinical Research, The University of Queensland, Herston, Australia

⁷Wesley Medical Research, The Wesley Hospital, Auchenflower, Australia

⁸CSIRO Health and Biosecurity, Herston, Australia

⁹ActiGraph, LLC, Pensacola, Florida, USA

Correspondence
 Frederik J. Steyn, School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Australia.
 Email: f.steyn@uq.edu.au

Abstract

Background and purpose: Weight loss in patients with amyotrophic lateral sclerosis (ALS) is associated with faster disease progression and shorter survival. Decreased hypothalamic volume is proposed to contribute to weight loss due to loss of appetite and/or hypermetabolism. We aimed to investigate the relationship between hypothalamic volume and body mass index (BMI) in ALS and Alzheimer's disease (AD), and the associations of hypothalamic volume with weight loss, appetite, metabolism and survival in patients with ALS.

Methods: We compared hypothalamic volumes from magnetic resonance imaging scans with BMI for patients with ALS ($n = 42$), patients with AD ($n = 167$) and non-neurodegenerative disease controls ($n = 527$). Hypothalamic volumes from patients with ALS were correlated with measures of appetite and metabolism, and change in anthropomorphic measures and disease outcomes.

Results: Lower hypothalamic volume was associated with lower and higher BMI in ALS (quadratic association; probability of direction = 0.96). This was not observed in AD patients or controls. Hypothalamic volume was not associated with loss of appetite ($p = 0.58$) or hypermetabolism ($p = 0.49$). Patients with lower BMI and lower hypothalamic volume tended to lose weight ($p = 0.08$) and fat mass ($p = 0.06$) over the course of their disease, and presented with an increased risk of earlier death (hazard ratio [HR] 3.16, $p = 0.03$). Lower hypothalamic volume alone trended for greater risk of earlier death (HR 2.61, $p = 0.07$).

Conclusion: These observations suggest that lower hypothalamic volume in ALS contributes to positive and negative energy balance, and is not universally associated with loss

^aData used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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of appetite or hypermetabolism. Critically, lower hypothalamic volume with lower BMI was associated with weight loss and earlier death.

KEY WORDS

ALS, amyotrophic lateral sclerosis, hypothalamus, MRI, survival, weight loss

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the death of motor neurons in the brain and spinal cord. This results in worsening atrophy of voluntary muscles, paralysis, and death usually within 3 to 5 years from symptom onset [1]. Multiple factors contribute to disease outcome in ALS. Body mass index (BMI) is associated with survival [2] and weight loss prior to [3] or following [4] symptom onset is associated with faster disease progression and earlier death.

The aetiology for weight loss in ALS is multifactorial [5]. Patients with energy deficit early in the disease experience a loss of body and fat mass, which is associated with shorter survival [4, 6–8]. Weight loss in ALS is thought to result from negative energy balance from increased resting energy metabolism (hypermetabolism) [9, 10] and/or decreased caloric intake [11, 12]. Indeed, loss of appetite in ALS contributes to weight and fat loss as a consequence of reduced energy intake [13, 14]. Dysfunction of the hypothalamus, a brain structure critical for regulating energy intake and metabolism [15], is suggested to contribute to impaired energy homeostasis leading to weight loss in ALS [5]. Hypothalamic Tar DNA-binding protein 43 (TDP-43) inclusions, hypothalamus-specific neuronal loss, and atrophy of the hypothalamus are observed in patients with ALS [16]. Furthermore, reduced hypothalamic volume in patients with ALS is correlated with lower BMI [17]. Whether hypothalamic dysfunction contributes to loss of appetite, hypermetabolism, and/or weight loss in ALS remains unknown.

We compared and contrasted hypothalamic volumes relative to BMI in patients with ALS, patients with Alzheimer's disease (AD) and non-neurodegenerative disease controls (controls). For patients with ALS, we also investigated the relationship between hypothalamic volume, appetite, metabolism, disease progression and survival. A trend for lower hypothalamic volume was observed in patients with ALS and AD. For ALS, a quadratic association was observed between hypothalamic volume and BMI, whereby lower hypothalamic volumes were found in patients with lower or higher BMI. Lower hypothalamic volume in ALS was associated with greater risk for earlier death. Risk of earlier death increased when also considering lower BMI.

METHODS

Study design and participants

This study was approved by the University of Queensland, the Royal Brisbane and Women's Hospital (RBWH), and Uniting Care Health Human Research Ethics Committees (Australia). All

participants provided written, informed consent. The study design is illustrated in Figure 1. For prospective measures in ALS, 62 patients with ALS were enrolled via motor neurone disease (MND) clinics at the Wesley Hospital and the RBWH. Forty-eight patients who met the El Escorial criteria for probable or definite ALS [18] were invited to participate in imaging studies. Three patients received a final diagnosis of ALS and frontotemporal dementia (ALS-FTD). Imaging studies were conducted at the Herston Imaging Research Facility (EATT4MND project, $n = 37$) or at the University of Queensland Centre for Advanced Imaging facility (7TEA project, $n = 11$) [19]; data were collected using a 3-Tesla (3T) Siemens Prisma scanner or a 7-Tesla (7T) Siemens Magnetom scanner (Siemens Healthcare, Erlangen, Germany), respectively. Six patients failed to complete imaging. Exclusion criteria were use of gastrostomy, respiratory impairment where forced vital capacity was <60% of predicted, and/or a history of diabetes, as these could impact assessments of appetite and/or metabolism. For comparison with AD, imaging data from 423 patients were sourced from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset (<http://adni.loni.usc.edu/>; see supplemental text). Of these, 38 patients with AD were excluded based on ethnicity, and 210 were excluded based on age.

Non-neurodegenerative disease control participants were included based on the absence of any cognitive or neurodegenerative disease. Forty-four control participants (EATT4MND, $n = 24$; 7TEA, $n = 20$) were recruited as a convenience sample of family, friends and colleagues of patients with ALS. A total of 898 controls were included from the ADNI dataset. One participant from EATT4MND was unable to complete imaging assessment, and 121 ADNI individuals were excluded based on ethnicity and 282 based on age.

Imaging data acquisition

The EATT4MND T1-weighted scans were obtained from a three-dimensional 1-mm³ isotropic MP2RAGE sequence (repetition time (TR)/echo time (TE)/inversion times (TIs)/acquisition time (TA) = 5000 ms/2.98 ms/701,2500 ms/9 m:02 s) [20], and the 7TEA T1-weighted scans were obtained using a 0.9-mm³ isotropic MP2RAGE sequence (TR/TE/TIs/TA = 4900 ms/3.1 ms/700,2700 ms/5 m:54 s) [21]. ADNI 3T images were acquired with either an anatomical 1-mm³ isotropic full-brain T1-weighted MP-RAGE or Accelerated IR-SPGR sequence. These scans were acquired during the ADNI1, ADNI2 and ADNI3 studies (additional acquisition parameters available at <http://adni.loni.usc.edu/>). After quality control (see Methods S1), 42 patients with ALS, 175 patients with AD, and 538 control datasets proceeded to segmentation.

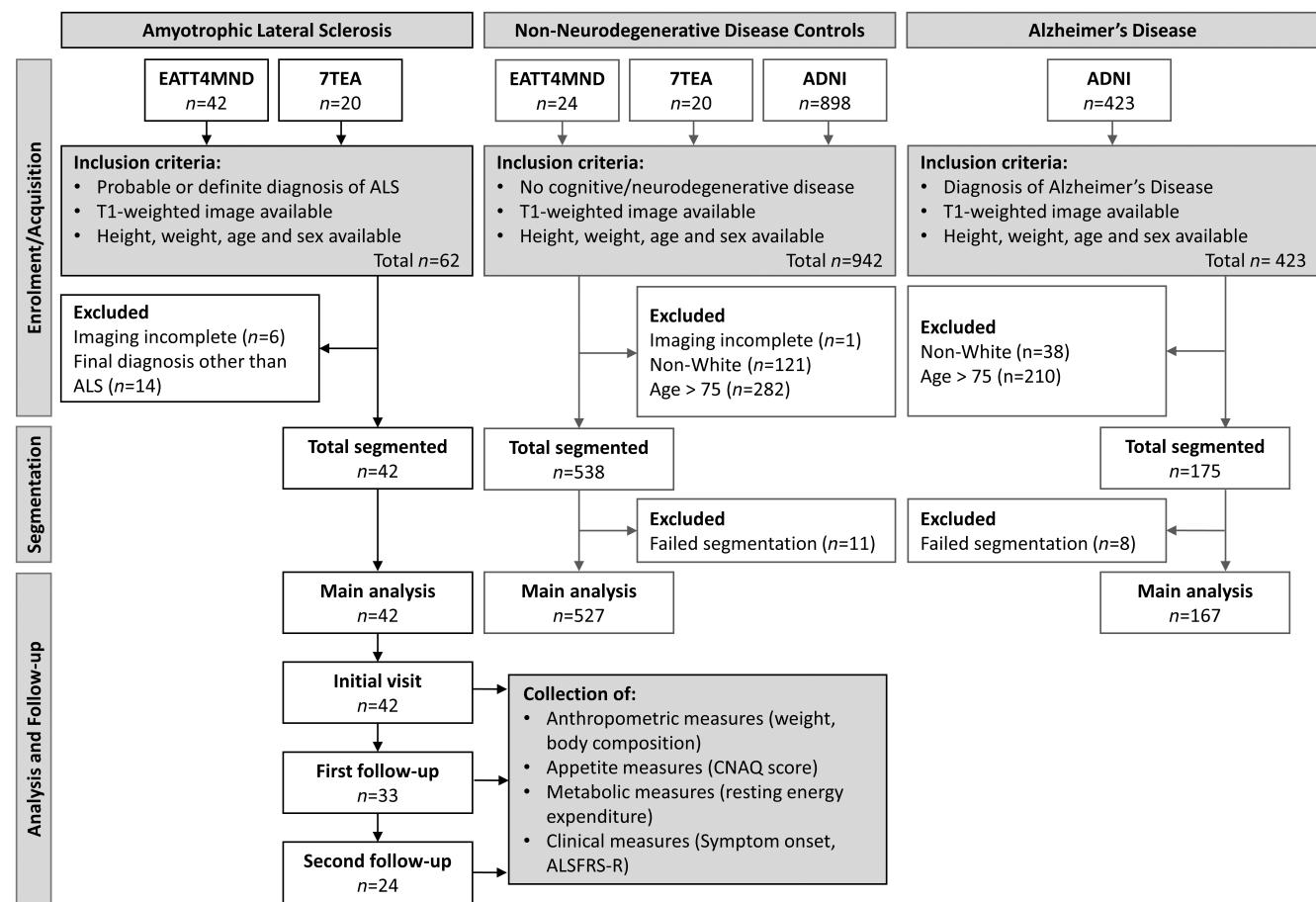


FIGURE 1 Participant inclusion diagram summarizing recruitment or acquisition, segmentation, and analysis. Participants were derived from three studies/datasets (Endocrine and Appetite Targets and Therapies for MND [EATT4MND]; neurobiology-informed diagnostic toolkit for neurodegenerative diseases [7TEA study]; Alzheimer's Disease Neuroimaging Initiative [ADNI]). Patients with amyotrophic lateral sclerosis (ALS) participated in baseline and follow-up research visits for the collection of anthropometric, appetite, metabolic, and clinical measures. ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; CNAQ, Council on Nutrition Appetite Questionnaire.

Segmentation

We established an Open Source Hypothalamic-Fornix (OSHy-X) atlas and tool for multi-atlas fusion segmentation for 3T and 7T data that relies on Joint Label Fusion [22] to extract hypothalamic and fornix volumes [23] (Figure 2). Validation of OSHy-X found excellent interrater scores, and outperformed FreeSurfer's segmentation of the hypothalamus [24, 25]. Automated segmentation was completed for all ALS patients; images from eight patients with AD and 11 controls failed segmentation.

Anthropometric, appetite and metabolic measures

For patients with ALS, anthropometric, appetite, metabolic and clinical measures of disease progression were collected on the day of the scan, or sourced from parallel studies. For inclusion as baseline measures, data had to be collected within 3 months of the imaging visit. Measurements were collected at an average of 4.20 ± 3.35 monthly intervals for up to 59.66 months. A cumulative total of 637.71 months of follow-up data was collected (17.24 ± 15.08 months' follow-up/patient).

Body composition (fat mass and fat-free mass) was determined using the BodPod system (Cosmed USA Inc.) [26, 27]. Resting energy expenditure was assessed via indirect calorimetry (Cosmed Quark RM respirometer) [27]. The metabolic index was calculated as the percentage of measured resting energy expenditure relative to predicted resting energy expenditure. Patients with a metabolic index equal to or greater than 120% were considered to be hypermetabolic [9]. Appetite was assessed using the Council on Nutrition Appetite Questionnaire (CNAQ), as done previously [28]. A score of 28 or lower was suggestive of loss of appetite with the potential to lead to weight loss. Disease severity was inferred from the ALS Functional Rating Scale-Revised (ALSFRS-R) [29]. Change in ALSFRS-R score since disease onset (Δ FRS) was calculated as the difference between the maximum ALSFRS-R score (48 points) divided by the months elapsed since symptom onset.

Statistical analysis

All statistical analyses were conducted using R (V.4.1.0) [30]. Where sample variance and distribution assumptions were satisfied,

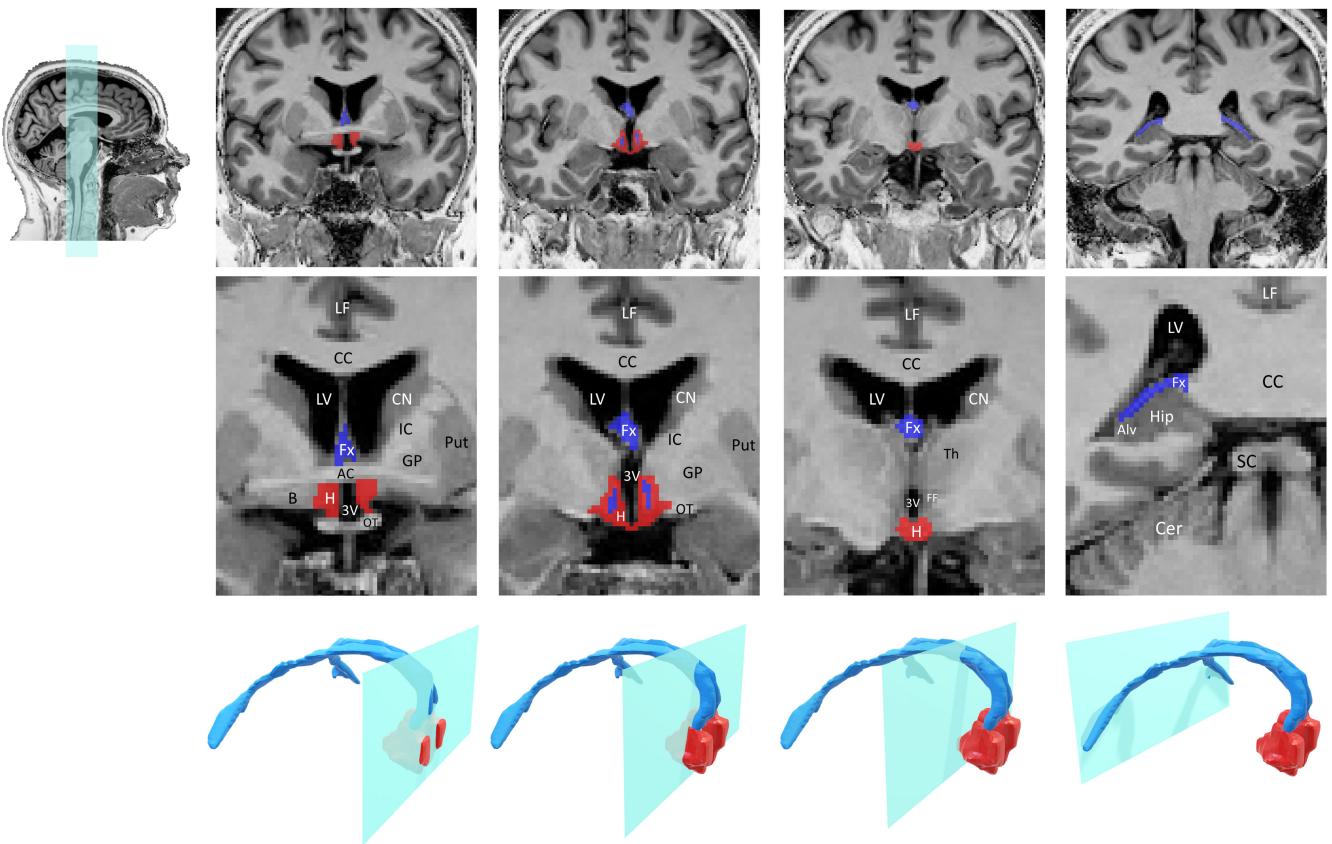


FIGURE 2 Manual segmentation of the hypothalamus and fornix. Manual segmentation of the hypothalamus (red) and fornix (blue). A detailed coronal view of the segmented hypothalamus and fornix, and key landmarks are illustrated in the first and second rows. The locations of representative coronal slices are indicated in the third row. The representative images shown are obtained from a male control participant in their 70s. 3V, third ventricle; AC, anterior commissure; Alv, alveus; B, diagonal band of Broca; CC, corpus callosum; Cer, cerebellum; CN, caudate nucleus; FF, fields of Forel; Fx, fornix; GP, globus pallidus; Hip, hippocampus proper; H, hypothalamus; IC, internal capsule; LF, longitudinal fissure; LV, lateral ventricle; OT, optic tract; Put, putamen; SC, superior colliculus; Th, thalamus.

multiple comparisons were conducted using the Kruskal-Wallis test, analysis of variance or a chi-squared test. Pairwise comparisons, including post hoc tests, were conducted with Wilcoxon rank-sum, Welch's t-test or chi-squared tests; and *p* values were Bonferroni-corrected for multiple comparisons.

Raw brain volumes were normalized against total intracranial volume by calculating their quotient and multiplying with a scaling factor (mean total intracranial volume), which were used in all subsequent analyses. For all analyses of brain volumes, the effect of dataset was treated as a covariate to account for differences in field strength and sequence used, such as partial voluming effects in 3T images.

The analysis between BMI and hypothalamic volume was conducted using Bayesian regression with Markov chain Monte Carlo estimations. Unlike classic linear regression, Bayesian regression offers a probabilistic distribution of parameters based on the given data [31]. The credible intervals (CIs) indicate the range of possible parameters around the median, given a probability; and the probability of direction (pd), ranging from 0.5 to 1, indicating the existence of an effect in a particular direction. Generally, a pd greater than 0.95 suggests the existence of an effect [32].

We used the *k*-means algorithm as a non-biased method to perform cluster analysis; three centroids were specified for the

algorithm to identify three subgroups of patients in our cohort. This maximizes variance between clusters whilst minimizing variance within the clusters. Linear mixed models were used for the analysis of longitudinal follow-up data, with participant intercepts and months treated as random effects. Aside from baseline comparisons, BMI was \log_2 -transformed to satisfy the assumption of normality. Survival analysis was illustrated using Kaplan-Meier plots, with hazard ratios calculated using Cox proportional hazards models. The significance threshold is set at *p* < 0.05 for all frequentist statistical analyses.

RESULTS

Demographics and comparisons of brain volumes between patients with ALS or AD and controls

Baseline comparison for demographics are presented in Table 1. Age (*p* < 0.01), sex (*p* < 0.01) and BMI (*p* < 0.01) differed among the cohorts. Whole brain volume was reduced in patients with AD (*p* = 0.04) when compared to controls. Additionally, total grey matter volume was reduced in patients with ALS (*p* < 0.01) and AD

TABLE 1 Baseline characteristics of patients with amyotrophic lateral sclerosis, patients with Alzheimer's disease and controls at time of assessment

| | ALS/Control/AD comparison ^a | | Alzheimer's disease (n = 167) | <i>p</i> ^d |
|---|--|-----------------------|----------------------------------|-----------------------|
| | ALS (n = 42) ^b | Controls (n = 527) | | |
| Demographics | | | | |
| Age, years | 59.64 (8.88) | 68.32 (5.56) | 68.38 (5.28) | <0.01 |
| Sex: female | 10 (23.81) | 304 (57.69) | 84 (50.3) | <0.01 |
| Anthropometric measures | | | | |
| Weight, kg | 80.71 (16.59) | 78.37 (17.24) | 75.69 (16.92) | 0.10 |
| BMI, kg/m ² | 26.56 (5.12) | 27.58 (5.38) | 26.41 (5.29) | <0.01 |
| Clinical measures | | | | |
| ΔFRS ^c | 0.56 (0.36) | — | — | — |
| Site of onset: bulbar | 11 (26.19) | — | — | — |
| Volumes, mm³; adjusted by dataset | | | | |
| Whole brain | 1252854.94 (55237.64) | 1259504.18 (46431.82) | 1248657.78 (46147.75) | <0.01 |
| Total grey matter | 512319.53 (42762.16) | 523830.32 (26359.47) | 488357.44 (30545.75) | <0.01 |
| Whole hypothalamus | 752.37 (90.17) | 771.2 (97.88) | 746.62 (121.29) | 0.06 |
| Left hypothalamus | 377.09 (48.06) | 386.64 (52.97) | 375.52 (64.62) | 0.12 |
| Right hypothalamus | 375.28 (46.82) | 384.56 (55.25) | 371.1 (65.55) | 0.03 |
| Whole fornix | 954.76 (134.83) | 983.26 (149.85) | 882.71 (164.83) | <0.01 |
| Left fornix | 484.82 (71.81) | 500.4 (84.3) | 450.35 (90.63) | <0.01 |
| Right fornix | 469.94 (73.97) | 482.85 (80.05) | 432.36 (91.39) | <0.01 |

Abbreviations: ΔFRS, change in Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised score since disease onset; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BMI, body mass index.

^aData presented as mean (SD) for continuous variables or *n* counts (%) for categorical variables.

^bFor patients with amyotrophic lateral sclerosis, the median (interquartile range) difference between the date of the scan and the baseline visit was 21 (11–30) days.

^cTwo participants with a baseline visit greater than 3 months from the date of their scan are not considered for these measures.

^dMulti-group comparisons were tested using the Kruskal-Wallis test for continuous variables and chi-squared test for categorical variables. Post hoc tests were conducted where multi-group comparisons reached significance; these results are presented in the text. Wilcoxon rank-sum tests were conducted for continuous variables and chi-squared tests for categorical variables.

(*p* < 0.01), however, patients with AD had lower total grey matter volume compared to patients with ALS (*p* < 0.01). We observed a trend for reduced hypothalamic volumes in ALS and AD patients (*p* = 0.06); for AD, only right hypothalamic volume was significantly lower (*p* = 0.04) when compared to controls. There were no sex differences in hypothalamic volume within any cohort (*p* = 0.68). Fornix volumes were lower in ALS and AD when compared to controls, however, this did not reach statistical significance in ALS. Patients with AD had lower fornix volumes compared to controls (*p* < 0.01) and trended for lower fornix volumes compared to patients with ALS (*p* = 0.07).

Bayesian regression models were used for comparison of hypothalamic volume with BMI for each cohort, with hypothalamic volume as the independent variable and log₂-transformed BMI as the dependent variable. Linear associations were not observed for patients with ALS (*pd* = 0.69), AD (*pd* = 0.77) or controls (*pd* = 0.92; Figure 3a,b). For patients with ALS, hypothalamic volume followed a quadratic association with BMI (*pd* = 0.96). This association was not observed in controls (*pd* = 0.54) or patients

with AD (*pd* = 0.77). As seen with the whole hypothalamus, separate models for each hemisphere suggest a quadratic association with BMI for patients with ALS (left hemisphere; *pd* = 0.95, right hemisphere: *pd* = 0.96) but not for controls or patients with AD (Figure S1). BMI is generally considered a proxy measure for fatness [33], therefore, we extended our analysis to also consider % fat mass; % fat mass in patients with ALS had neither a linear (*pd* = 0.89) nor a quadratic association (*pd* = 0.67) with hypothalamic volume.

Associations between hypothalamic volume and appetite and metabolism in patients with ALS

Loss of appetite (CNAQ score ≤ 28) was seen in 32.35% of patients with ALS. There were no differences in demographic or anthropometric measures between patients reporting intact appetite versus those reporting loss of appetite (Table S1). As observed previously [13], we found significant declines in body weight (*p* = 0.01), BMI (*p* = 0.02)

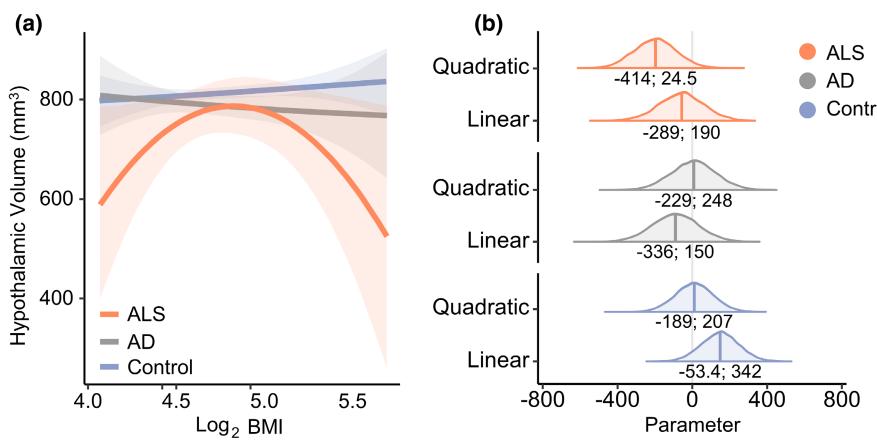


FIGURE 3 Fitted relationship between body mass index (BMI) and hypothalamic volume. (a) Fitted graph for the relationship between BMI and hypothalamic volume and (b) posterior distributions for the quadratic and linear terms for patients with amyotrophic lateral sclerosis (ALS), patients with Alzheimer's disease (AD) and non-neurodegenerative disease controls (controls). Shaded areas indicate 95% confidence interval (CI). For (b), 95% CIs are also indicated below each posterior distribution. Quadratic associations with BMI for both hypothalamic hemispheres are further illustrated in Figure S1.

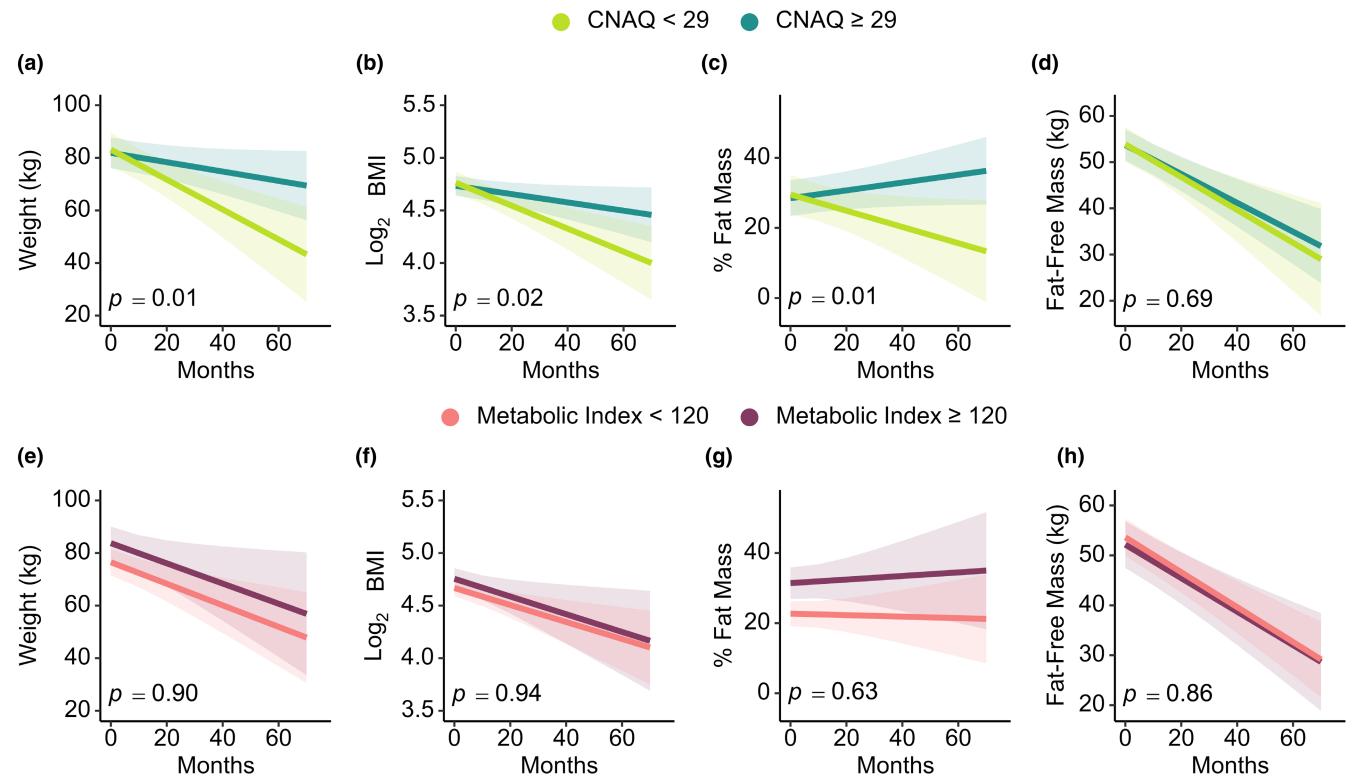
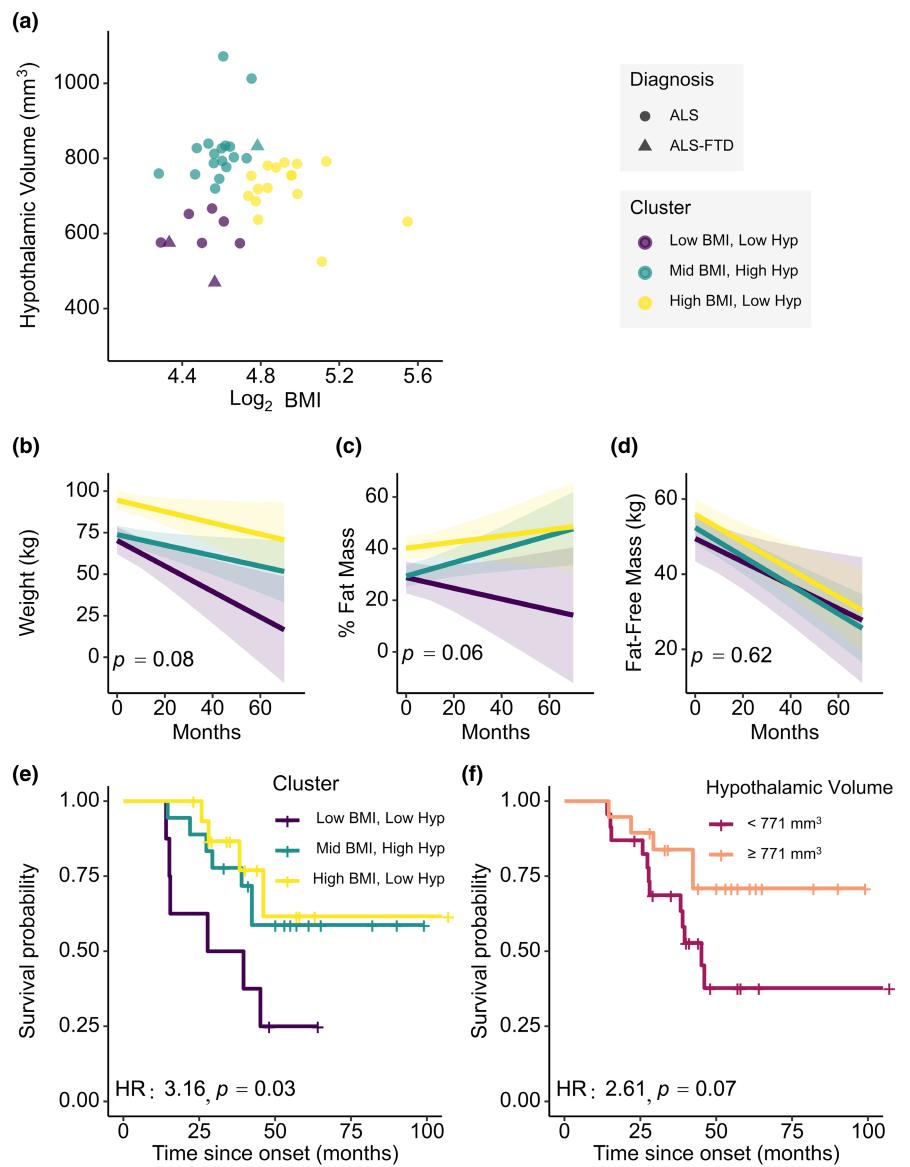


FIGURE 4 Longitudinal changes in body composition in patients with amyotrophic lateral sclerosis (ALS). Changes in (a) weight, (b) body mass index (BMI), (c) % fat mass and (d) fat-free mass in patients with ALS with loss of appetite (CNAQ ≤ 28) versus patients with intact appetite (Council on Nutrition Appetite Questionnaire [CNAQ] ≥ 28). Changes in (e) weight, (f) BMI, (g) % fat mass, and (h) fat-free mass in patients with ALS with hypermetabolism (metabolic index ≥ 120) versus patients who are not hypermetabolic (metabolic index < 120). The shaded areas indicate 95% confidence intervals.

and % fat mass ($p = 0.01$; Figure 4a–d) in patients with loss of appetite when compared to patients reporting intact appetite. There was no difference in hypothalamic ($p = 0.58$) or fornix ($p = 0.37$) volumes between patients reporting loss or intact appetite (Table S1). Moreover, there were no associations between CNAQ score and hypothalamic volume (linear: $pd = 0.54$; quadratic: $pd = 0.88$).

Hypermetabolism was observed in 39.5% of patients with ALS. Percent fat mass ($p = 0.02$) at baseline differed between patients who were hypermetabolic and those who were not (Table S2). Longitudinal analysis of body composition between patients with hypermetabolism versus patients who were not hypermetabolic (Figure 4e–h) showed no interaction effect for weight ($p = 0.90$),

FIGURE 5 Longitudinal and survival outcomes for patients with amyotrophic lateral sclerosis (ALS) clustered by hypothalamic volume and body mass index (BMI). (a) Patients with ALS are grouped into three clusters based on their hypothalamic (Hyp) volume and BMI. Longitudinal measures of (b) weight, (c) % fat mass and (d) fat-free mass are illustrated with shaded 95% confidence interval for each cluster. Kaplan–Meier plots illustrate the cumulative probability of survival between (e) the three clusters and between (f) lower and higher hypothalamic volume (dichotomized at the median). ALS-FTD, ALS and frontotemporal dementia.



BMI ($p = 0.94$), % fat mass ($p = 0.63$) or fat-free mass ($p = 0.86$). These results suggest that changes in weight and % fat mass in hypermetabolic patients occur independently of hypermetabolism, as reported previously [9]. There was no difference in hypothalamic volume between patients with hypermetabolism and patients who were not hypermetabolic ($p = 0.49$). Moreover, there were no associations between metabolic index and hypothalamic volume (linear: $pd = 0.75$; quadratic: $pd = 0.87$).

Our results suggest that reduced hypothalamic volume alone may not account for loss of appetite or hypermetabolism in patients with ALS.

Associations between BMI and hypothalamic volumes, and disease progression and survival in ALS

Follow-up analysis was conducted to identify patient outcomes relative to BMI and hypothalamic volume. Using k-means clustering, we identified three subgroups of patients: patients with a lower BMI and

a lower hypothalamic volume ($n = 8$); patients with an average BMI and a higher hypothalamic volume ($n = 18$); and patients with a higher BMI and a lower hypothalamic volume ($n = 16$; Figure 5a). Baseline comparisons among patients relative to these clusters are presented in Table 2. Inherent differences among patients across these clusters were observed for weight ($p < 0.01$), % fat mass ($p = 0.01$) and hypothalamic volume ($p < 0.01$). Alongside this, fornix volume was also significantly associated with the three clusters ($p < 0.01$), with the greatest fornix volume observed in patients with an average BMI and a higher hypothalamic volume. Whole brain ($p = 0.31$) and total grey matter volume ($p = 0.44$) did not differ among the three clusters. Measures of loss of appetite ($p = 0.28$) or the presence of hypermetabolism ($p = 0.80$) did not vary among the clusters.

Change in anthropometric outcomes among patients relative to these clusters (Figure 5b-d) revealed a faster rate of change in body weight within the lower BMI and lower hypothalamic volume cluster, when compared to the average rate of change in the remaining two clusters. The analyses suggest there was a greater loss of weight ($p = 0.08$; Figure 5b) and % fat mass ($p = 0.06$; Figure 5c) in patients

TABLE 2 Baseline comparisons among cases with a lower body mass index (BMI) and a lower hypothalamic volume, cases with an average BMI and a higher hypothalamic volume, and cases with a higher BMI and a lower hypothalamic volume

| | Within case comparisons ^a | | | <i>p</i> ^b |
|--|--------------------------------------|-------------------------------|-------------------------------|-----------------------|
| | Low BMI, low hyp (n = 8) | Mid BMI, high hyp (n = 18) | High BMI, low hyp (n = 16) | |
| Demographics | | | | |
| Age, years | 63.28 (5.28) | 58.72 (9.57) | 59.57 (9.76) | 0.49 |
| Sex: female | 1 (12.5) | 5 (27.78) | 4 (25) | 0.69 |
| Anthropometric measures | | | | |
| Weight, kg | 71.00 (7.55) | 73.44 (8.76) | 92.92 (17.26) | <0.01 |
| Height, m | 1.77 (0.06) | 1.74 (0.07) | 1.73 (0.09) | 0.57 |
| BMI, kg/m ² | 22.68 (2.14) | 24.19 (1.87) | 30.92 (4.94) | <0.01 |
| % Fat mass ^c | 29.39 (7.04) | 30.86 (9.52) | 40.15 (9.13) | 0.01 |
| Fat-free mass, kg ^c | 49.67 (7.45) | 50.89 (10.67) | 54.86 (9.01) | 0.38 |
| Appetite/metabolic measures | | | | |
| Total CNAQ score ^c | 29.00 (3.54) | 29.5 (3.37) | 29.87 (2.33) | 0.84 |
| Appetite (CNAQ ≤28) ^c | 3 (60.00) | 3 (21.43) | 5 (33.33) | 0.28 |
| Energy expenditure, kcal ^c | 1535.14 (425.67) | 1657.82 (292.60) | 1877.36 (321.77) | 0.06 |
| Metabolic index ^c | 111.04 (21.32) | 118.93 (12.45) | 121.84 (17.45) | 0.36 |
| Hypermetabolic (metabolic index ≥120) ^c | 2 (28.57) | 7 (41.18) | 6 (42.86) | 0.80 |
| Clinical measures | | | | |
| ALSFRS-R ^c | 38.71 (5.28) | 38.28 (4.75) | 36.80 (6.68) | 0.68 |
| Bulbar sub-score | 9.43 (1.72) | 9.82 (2.04) | 10.20 (1.90) | 0.67 |
| Upper limb subscore | 5.86 (2.54) | 6.41 (2.12) | 6.00 (2.14) | 0.81 |
| Lower limb subscore | 5.71 (2.29) | 4.82 (2.07) | 3.73 (2.12) | 0.12 |
| Respiratory subscore | 11.86 (0.38) | 11.59 (0.71) | 11.13 (1.60) | 0.31 |
| Diagnostic delay, months | 10.36 (6.12) | 15.21 (7.24) | 13.02 (10.40) | 0.40 |
| Time since onset, months | 16.92 (7.78) | 23.13 (10.51) | 20.82 (8.87) | 0.31 |
| ΔFRS ^c | 0.70 (0.50) | 0.47 (0.28) | 0.59 (0.38) | 0.33 |
| Site of onset: bulbar | 4 (50.00) | 4 (22.22) | 3 (18.75) | 0.23 |
| Volumes, mm³ | | | | |
| Whole hypothalamus | 637.88 (52.41) | 916.16 (114.46) | 839.13 (97.91) | <0.01 |
| Left hypothalamus | 323.04 (38.39) | 470.52 (65.38) | 431.84 (53.47) | <0.01 |
| Right hypothalamus | 314.85 (20.07) | 445.64 (54.35) | 407.29 (49.00) | <0.01 |
| Whole fornix | 846.99 (129.71) | 1161.23 (181.94) | 1013.41 (106.56) | <0.01 |
| Left fornix | 421.16 (64.52) | 613.76 (88.94) | 538.51 (65.07) | <0.01 |
| Right fornix | 425.82 (79.03) | 547.47 (99.10) | 474.91 (61.44) | <0.01 |
| Whole brain | 470,507 (48,133) | 510,551 (57,297) | 494,757 (69,006) | 0.31 |
| Total grey matter | 1,153,219 (143,155) | 1,225,545 (103,684) | 1,224,419 (172,090) | 0.44 |

Abbreviations: ΔFRS, change in ALSFRS-R score since disease onset; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; BMI, body mass index; CNAQ, Council on Nutrition Appetite Questionnaire.

^aData presented as mean (SD) for continuous variables or *n* counts (%) for categorical variables.

^b*p* values for continuous variables were generated from a Kruskal–Wallis test or analysis of variance; chi-squared tests were conducted for categorical variables.

^cIndividual(s) with missing data for these baseline measures were not included in the statistical summaries and tests. Overall, the median (interquartile range) difference between the date of the scan and the baseline visit was 21 (11–30) days.

with lower BMI and lower hypothalamic volume. There was no interaction effect for change in fat-free mass (*p* = 0.62; Figure 5d) or total ALSFRS-R score (*p* = 0.49; data not illustrated).

A higher risk of earlier death was observed in patients with lower BMI and lower hypothalamic volume when compared to other patients (hazard ratio [HR] 3.16, confidence interval 1.15–8.68;

$p = 0.03$). Patients with a lower BMI and lower hypothalamic volume had a 3.16-fold increase in risk for earlier death (Figure 5e). BMI dichotomized at the median was not associated with greater risk of earlier death (data not illustrated; HR 1.1, confidence interval 0.42–2.91; $p = 0.85$), whereas, when considering hypothalamic volume alone, the results suggest a risk of earlier death (HR 2.61, confidence interval 0.91–7.44; $p = 0.07$; Figure 5f).

DISCUSSION

Impairments in hypothalamic function are thought to contribute to impaired energy homeostasis, leading to weight loss in patients with ALS [5]. This is important as greater weight loss in ALS is associated with faster disease progression and earlier death [3, 4]. Observations from the present study suggest that lower hypothalamic volume in ALS may not always be associated with energy deficit leading to weight loss. Greater weight loss and increased risk of earlier death were, however, observed in patients with ALS with lower hypothalamic volume and lower BMI. Therefore, deficits in hypothalamic function in ALS that contribute to weight loss may be of greater clinical concern.

Hypothalamic dysfunction corresponding to loss of hypothalamic volume is proposed across multiple neurodegenerative diseases, including in patients with ALS [5], AD [34] and behavioural-variant of frontotemporal dementia (bvFTD) [35, 36]. In AD, this is generally associated with weight loss, faster disease progression and shorter survival [37]. By contrast, impairment of hypothalamic function in bvFTD is thought to contribute to increased appetite and weight gain, and is associated with slower disease progression and lower risk for earlier death [35]. From these studies, one might assume that different neurodegenerative diseases differentially impact hypothalamic circuitries, resulting in select dysfunction of neuronal pathways that modulate positive or negative energy balance, culminating in weight gain or weight loss.

While demonstrating lower hypothalamic volume in patients with ALS and AD, we were unable to replicate prior studies showing linear associations between hypothalamic volume and BMI in ALS [17]. Rather, we found evidence for a quadratic relationship whereby lower hypothalamic volume was associated with lower and higher BMI. This appears to be disease-specific, as quadratic associations were not observed in patients with AD or in controls. While the results in patients with ALS can be explained by our inclusion of patients across a broader BMI range ($BMI 26.6 \pm 5.12 \text{ kg/m}^2$), whereas other studies seldom include patients with higher BMI ($16\text{--}37 \text{ kg/m}^2$ and $23.1 \pm 2.9 \text{ kg/m}^2$) [17, 38], a more pressing outcome is the suggestion that hypothalamic atrophy in ALS may not always contribute to weight loss. This would explain our finding that lower hypothalamic volume in patients with ALS was not universally associated with loss of appetite or hypermetabolism.

Measures of volume alone are insufficient to assess the complex nature of the hypothalamus in regulating energy balance, as this neglects disease-specific pathology that would differentially affect

cell-types within specific nuclei that modulate appetite and metabolism. TDP-43 inclusions are observed in post-mortem tissues from patients with ALS, and are thought to contribute to dysfunction of select cells within the hypothalamus [16]. Inflammation within the brain and spinal cord contributes to ALS pathogenesis [39], and in obesity, hypothalamic inflammation contributes to impaired nutrient sensing [40]. As such, inflammation could be a factor. Added to this complexity is the fact that ALS and FTD co-exist as extremes on a phenotypic spectrum of a single neurodegenerative disease, with patients sharing common genetic causes and pathological features of disease [41]. Weight loss and weight gain are observed across this ALS-FTD spectrum [42], and therefore one might further speculate that observations are representative of this broader disease spectrum.

Prior reports suggest that volume of the anterior-superior and the superior-tuberal hypothalamus is reduced in patients with ALS [38]. These regions implicitly include parts of the paraventricular nucleus (PVN) and lateral hypothalamus, which are key nuclei involved in the regulation of appetite and metabolism [15]. It has also been reported that PVN volume and orexin-producing neurons are decreased in patients with ALS, and that reductions in whole hypothalamic volume are associated with abnormal eating behaviour. However, no association between PVN volume and BMI has been observed [16], and direct comparisons with dedicated measures of appetite and metabolism were not made. Therefore, it remains unclear if dysfunction of specific hypothalamic circuitry contributes directly to changes in appetite and metabolism in ALS, and whether such changes are observed across all patients with ALS, or only a select number of patients across the ALS-FTD spectrum. To address this, more comprehensive investigations that consider volumetric and functional measures of hypothalamic ultrastructure, their constituent neuronal subtypes, and associations with physiology and behaviour (i.e., hypermetabolism and appetite) are needed.

Using a non-biased clustering approach, we identified three groups of ALS patients based on BMI and hypothalamic volume: patients with lower BMI and lower hypothalamic volume; patients with an average BMI and higher hypothalamic volume; and patients with higher BMI and lower hypothalamic volume. Results from within these groups show that patients with lower BMI and lower hypothalamic volumes trend towards losing % fat mass over the course of disease, whereas other patients maintain or gain % fat mass. As such, patients with lower hypothalamic volumes and lower BMI at study inclusion are at greater risk for continued energy deficit during the course of their disease. Critically, these individuals were also at greater risk for earlier death, suggesting that changes in hypothalamic volume leading to lower BMI could contribute to worse prognosis. We caution, however, that direct links between changes in BMI and energy deficit cannot be made. BMI is a poor indicator of fatness in patients with ALS [33], therefore, energy deficit is assumed from the greater loss of % fat mass in this cohort. Moreover, as hypothalamic volume did not correlate with % fat mass, any association with BMI is likely attributable to combined

changes in fat and fat-free mass. Of interest, we also found a greater risk for earlier death in patients with ALS with decreased hypothalamic volume alone, suggesting that risk for earlier death may occur independently of BMI.

We included assessments of fornix volume as this is associated with BMI in studies on obesity [43]. Fornix volume is lower in patients with AD [44], and TDP-43 inclusions have been observed in the fornix of patients with ALS [16]. As with the hypothalamus, we found significant variation of fornix volume across the three ALS patient clusters. Of interest, fornix volumes were lower in patients with lower hypothalamic volume and lower BMI. As a white matter tract that connects grey matter nuclei within the limbic system and beyond, physical changes of the fornix could contribute to altered brain function and behaviour in patients with ALS. While not directly addressed in the context of body weight regulation, observations set a precedent for more detailed studies that consider the role of the fornix in modulating the propagation of information between the hypothalamus and other brain structures that are involved in energy homeostasis in ALS.

This study has some limitations. While we established an automated pipeline for segmenting the hypothalamus for volumetric analysis [23], we were unable to confidently define functional sub-nuclei within the hypothalamus. This is mostly due to limitations associated with the contrast of T1-weighted MRI [45]. For direct comparisons of ALS hypothalamic volumes, and for assessments of hypothalamic volumes alongside BMI we also included disproportionately large sample sets from patients with AD and controls, when compared to ALS participants. To account for differences in sample size, we used a Bayesian linear model for the analysis of relationships between hypothalamic volume and BMI. The greater uncertainty that comes from low sample sizes (i.e., the number of patients enrolled in the 7TEA study) is represented in the statistical output and interpretation [46].

In summary, our findings suggest a complex role between hypothalamic volume and energy balance in ALS. The observations suggest that hypothalamic atrophy in ALS may not always contribute to weight loss, but that patients with hypothalamic dysfunction leading to weight loss are likely to be at greater risk for faster disease progression and earlier death. Early identification of these patients will help guide disease management. Further research into the ultrastructural and functional changes of the hypothalamus are needed to improve our understanding of the role of the hypothalamus in disease pathogenesis and of how specific deficits might impact energy homeostasis and survival.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest for this article.

DATA AVAILABILITY STATEMENT

Data for patients with ALS are not publicly available due to privacy/ethical restrictions. Data that support the findings of this study are available on request from the corresponding author. Imaging data from EATT4MND and 7TEA are available provided that these projects are acknowledged upon publication. Segmentation code can be found via our published software, OSHy-X (doi:10.21105/joss.04368).

ORCID

- Jeryn Chang  <https://orcid.org/0000-0002-6659-365X>
- Thomas B. Shaw  <https://orcid.org/0000-0003-2490-0532>
- Cory J. Holdom  <https://orcid.org/0000-0001-5972-6437>
- Pamela A. McCombe  <https://orcid.org/0000-0003-2704-8517>
- Robert D. Henderson  <https://orcid.org/0000-0002-2820-8183>
- Jurgen Fripp  <https://orcid.org/0000-0001-9705-0079>
- Markus Barth  <https://orcid.org/0000-0002-0520-1843>
- Christine C. Guo  <https://orcid.org/0000-0003-1530-0172>
- Shyuan T. Ngo  <https://orcid.org/0000-0002-1388-2108>
- Frederik J. Steyn  <https://orcid.org/0000-0002-4782-3608>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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