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Distinct hypothalamic involvement in the amyotrophic lateral sclerosis-frontotemporal dementia spectrum

Nga Yan Tse [a,b,1], Martina Bocchetta [c,1], Emily G. Todd [c], Emma M. Devenney [a,b], Sicong Tu [a,b], Jashelle Caga [a,b], John R. Hodges [a,b,d], Glenda M. Halliday [e], Muireann Irish [d], Matthew C. Kiernan [a,b,e], Olivier Piguet [d], Jonathan D. Rohrer [c], Rebekah M. Ahmed [a,b,f,*]

[a] The University of Sydney, Brain & Mind Centre, Sydney, Australia
[b] Royal Prince Alfred Hospital, Sydney, Australia
[c] Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, United Kingdom
[d] The University of Sydney, School of Psychology and Brain & Mind Centre, Sydney, Australia
[e] The University of Sydney, Sydney Medical School and Brain & Mind Centre, Sydney, Australia
[f] Memory and Cognition Clinic, Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Sydney, Australia

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ABSTRACT

Background: Hypothalamic dysregulation plays an established role in eating abnormalities in behavioural variant frontotemporal dementia (bvFTD) and amyotrophic lateral sclerosis (ALS). Its contribution to cognitive and behavioural impairments, however, remains unexplored.

Methods: Correlation between hypothalamic subregion atrophy and cognitive and behavioural impairments was examined in a large sample of 211 participants (52 pure ALS, 42 mixed ALS-FTD, 59 bvFTD, and 58 age- and education- matched healthy controls).

Results: Graded variation in hypothalamic involvement but relative sparing of the inferior tuberal region was evident across all patient groups. Bilateral anterior inferior, anterior superior, and posterior hypothalamic subregions were selectively implicated in memory, fluency and processing speed impairments in addition to apathy and abnormal eating habits, taking into account disease duration, age, sex, total intracranial volume, and acquisition parameters (all $p \leq .001$).

Conclusions: These findings revealed that subdivisions of the hypothalamus are differentially affected in the ALS-FTD spectrum and contribute to canonical cognitive and behavioural disturbances beyond eating abnormalities. The anterior superior and superior tuberal subregions containing the paraventricular nucleus (housing oxytocin-producing neurons) displayed the greatest volume loss in bvFTD and ALS-FTD, and ALS, respectively. Importantly, the inferior tuberal subregion housing the arcuate nucleus (containing different groups of neuroendocrine neurons) was selectively preserved across the ALS-FTD spectrum, supporting pathophysiological findings of discrete neuropeptide expression abnormalities that may underlie the pathogenesis of autonomic and metabolic abnormalities and potentially certain cognitive and behavioural symptom manifestations, representing avenues for more refined symptomatic treatment targets.

1. Introduction

The hypothalamus is integral to metabolic, autonomic, and endocrine functions governing vital bodily functions (Vercruysse et al., 2018; Van Der Klaauw and Farooqi, 2015; Coll et al., 2007). Hypothalamic alterations are increasingly recognised in neurogenerative diseases including frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) (Vercruysse et al., 2018). Specifically, hypothalamic atrophy has been reported in bvFTD (Piguet et al., 2011; Bocchetta et al., 2015; Ahmed et al., 2015; Shapiro et al., 2022) and ALS (Gorges et al., 2017) relative to healthy controls. Pre-symptomatic carriers of genetic abnormalities associated with FTD and ALS [i.e., mutations in the microtubule-associated protein tau (*MAPT*) and progranulin (*GRN*; hexanucleotide expansion of the chromosome 9 open reading frame 72

* Corresponding author at: Brain and Mind Centre, University of Sydney, 94 Mallet St Camperdown, NSW 2050, Australia.
E-mail address: Rebekah.ahmed@sydney.edu.au (R.M. Ahmed).
[1] Reflects equal contribution to work.

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(*C9orf72*)] display significant volume loss in the hypothalamus compared to healthy controls, suggesting early hypothalamic involvement that may already occur prior to symptom onset (Gorges et al., 2017; Bocchetta et al., 2021). Histopathological evidence of TDP-43 deposition (Cykowski et al., 2014; Gabery et al., 2021) and loss of orexin- and oxytocin- producing neurons (Gabery et al., 2021) in the hypothalamus has been documented in ALS, alongside limited responsiveness to drugs targeting the hypothalamic melanocortin system (Vercruysse et al., 2016).

Consistent with its fundamental role in energy metabolism, feeding and satiety, aberrant hypothalamic functions have been linked with abnormal eating behaviour in bvFTD (Perry et al., 2014; Piguet et al., 2011; Bocchetta et al., 2015; Ahmed et al., 2015). In bvFTD patients, changes in levels of neuropeptides produced by the hypothalamus including reduced orexin (Çoban et al., 2013) and higher agouti-related peptide (AgRP) (Ahmed et al., 2015) have been reported, and the hypothalamic melanocortin system has been implicated in increased preference for high-fat foods (Ahmed et al., 2021). In ALS, an association has been reported between lower body mass index (BMI) and hypothalamic volume loss (Gorges et al., 2017). Together, hypothalamic disturbances plays a critical role in the manifestation of metabolic and eating abnormalities across the ALS-FTD spectrum with implications for survival (Lindauer et al., 2013; Dupuis et al., 2008; Ahmed et al., 2017).

Importantly, however, the hypothalamus is not one unitary structure, but rather comprises different nuclei subserving distinct functions (Vercruysse et al., 2018). Examination of the hypothalamus as a whole therefore precludes a thorough understanding of the differential contribution of hypothalamic subregions to symptom characteristics in the ALS-FTD spectrum. To our knowledge, few studies have attempted to understand how subdivisions of the hypothalamus are affected in these syndromes. Employing manual segmentation, Gorges et al. (2017) reported atrophy in both the anterior and posterior parts of the hypothalamus across sporadic ALS, symptomatic and presymptomatic mutation carriers. Further subdividing the hypothalamus into anterior superior, anterior inferior, superior tuberal, inferior tuberal and posterior subregions, recent studies reported findings of significantly lower volume primarily concentrated in bilateral anterior inferior, anterior superior, superior tuberal and posterior regions across all variants of FTD (Bocchetta et al., 2015; Shapiro et al., 2022) and symptomatic and presymptomatic carriers of *C9orf72* repeat expansions, as well as *MAPT* and *GRN* mutations (Bocchetta et al., 2021), pointing towards relative preservation of the inferior tuberal subregion.

While previous studies have offered preliminary insights into hypothalamic subregional changes in the ALS-FTD spectrum, several methodological issues warrant consideration. First, the existing studies are limited by small sample sizes and/or the exclusive focus on specific diagnostic groups. For example, Gorges et al. (2017) focussed solely on ALS, while the Bocchetta et al. (2015) study included only 18 bvFTD patients. In a more recent study, Bocchetta et al. (2021) examined a large sample of ALS and/or FTD-associated genetic mutation symptomatic carriers (Bocchetta et al., 2021), their sample consisted predominantly of bvFTD patients (n = 89) compared to other clinical phenotypes (i.e., 6 presenting with mixed ALS-FTD, 2 with ALS and 29 with other dementia syndromes) raising the question of whether the findings were primarily driven by the bvFTD phenotype. A similarly small sample of 7 ALS-FTD patients, but none with ALS, was included in Shapiro et al. (2022) examining hypothalamic subregional volumetry across FTD variants. The lack of inclusion of patients with concomitant ALS-FTD further limits our understanding of whether these findings also apply to this phenotype. This is of great clinical relevance given the high rate (10–15 %) of concomitant ALS-FTD (Burrell et al., 2016) (i.e., meeting diagnostic criteria for both ALS and FTD). Moreover, as the previous studies on hypothalamic changes in the ALS-FTD spectrum have focused on BMI and eating abnormalities, the potential contribution of hypothalamic subregions to other domains of cognition and behaviour remains to be established.

Here, we capitalise on advances in neuroimaging techniques that allow for precise parcellation of small subcortical brain regions to present the first detailed examination of hypothalamic subregion volume loss in a large and evenly distributed cohort of ALS, ALS-FTD and bvFTD patients. Our aims were to determine profiles of hypothalamic subregional changes across the ALS-FTD spectrum and to explore potential associations between hypothalamic subregion profiles and patterns of cognitive and behavioural impairment in each syndrome.

2. Material and methods

2.1. Participants

211 participants (52 ALS, 42 ALS-FTD, 59 bvFTD patients, and 58 healthy controls) were recruited from the FRONTIER Clinic and the FOREFRONT ALS and FTD Clinic, the multidisciplinary research clinics specialising in younger-onset dementias and motor neurodegenerative syndromes, respectively. Standard diagnostic assessment consisted of a medical and neurological examination, neuropsychological assessment, clinical interviews, and a structural brain MRI (Supplementary Fig. 1) (Kiernan et al., 2021, 2011). Diagnosis was determined by multidisciplinary consensus by a senior neurologist and clinical neuropsychologist according to the current clinical diagnostic criteria (Rascovsky et al., 2011; Strong et al., 2017; Shefner et al., 2020). Disease severity in ALS-FTD and bvFTD patients was measured by the Frontotemporal Dementia Rating Scale (FRS) (Mioshi et al., 2010), while functional impairment in ALS patients was measured using the revised ALS functional rating scale (ALSFRS-R) (Cedarbaum et al., 1999). All age – and education – matched healthy controls underwent clinical examination and scored above the cut-off for normal range (>88/100) on the third edition of the Addenbrooke's Cognitive Examination (ACE-III) (Hsieh et al., 2013), to ensure the absence of neurological, psychiatric or cognitive disturbance. Exclusion criteria for all participants included the presence of other dementia syndrome, psychiatric disorders, or a history of significant head injury.

2.2. Ethics approval

This study was approved by the Southeastern Sydney Local Health District and the University of New South Wales and University of Sydney ethics committees. All the participants or their person responsible provided written, informed consent in accordance with the Declaration of Helsinki.

2.3. Cognitive and behavioural measures

All cognitive and behavioural measures were completed within 3 months of MRI acquisition. Participants completed the ACE-III, comprising a total score as well as attention, memory, fluency, language, and visuospatial subdomain scores. Animal fluency (i.e., generating as many animal names as possible in one minute) was used as an indication of category fluency. The Trail Making Test (TMT) (Tombaugh, 2004) was administered to examine processing speed (Part A Time; TMT-A) and executive function (i.e., divided attention as reflected by Part B-A time difference; TMT B-A).

Carers of patients completed the revised version of the Cambridge Behavioural Inventory (CBI-R) (Wedderburn et al., 2008), which consists of a total score, and 10 subdomain scores for everyday memory, everyday skills, self-care skills, abnormal behaviour (i.e., behavioural disinhibition), mood changes, odd beliefs (i.e., delusion and hallucinations), abnormal eating habits, sleep changes, stereotypic behaviours (i.e., perseverative and ritualistic behaviours), and reduced motivation (i.e., apathy and inertia).

2.4. Blood sampling

All patients and controls underwent blood sampling to screen for the *C9orf72* repeat expansion, and *GRN* and *MAPT* mutations. Genomic DNA was extracted from peripheral blood lymphocytes. Proband DNA samples were then screened for the hexanucleotide repeat expansions in the *C9orf72* gene using a repeat primed polymerase chain reaction based on the protocol of Renton et al. (2011) Samples were scored as positive if they harboured an allele with more than 30 repeats. Sanger sequencing was performed to identify mutations in *GRN* and *MAPT*. *SOD1* gene mutations were screened in the ALS group.

2.5. Imaging

2.5.1. Brain imaging acquisition

The bvFTD and ALS-FTD group, and 50 controls underwent volumetric MRI on a 3T Philips Achieva scanner equipped with a standard 8-channel head coil using the following protocol: matrix 256 × 256, 200 slices, 1 mm^2 in-plane resolution, slice thickness = 1 mm, echo time = 2.6 ms, repetition time = 5.8 ms, flip angle = 8°. The ALS group and a separate group of control participants (n = 8) were scanned on a 3T General Electric (GE) scanner with a standard 8-channel head coil using the following protocol: matrix 256 × 256, 200 slices, 1 mm^2 in-plane resolution, slice thickness = 0.5 mm, echo time = 2.6 ms, repetition time = 5.8 ms, flip angle = 8°.

2.5.2. Brain volume analyses

We applied the segmentation tool of Billot et al. (2020) based on a deep convolutional neural network on volumetric MRI scans to parcellate the grey matter volumes of subregions of the hypothalamus including the whole left and right hypothalamus, as well as five subunits: (i) left and right anterior inferior (containing supraoptic nucleus); (ii) anterior superior (containing the paraventricular nucleus), (iii) inferior tuberal (containing the arcuate nucleus, the ventromedial nucleus and the posterior part of the supraoptic nucleus), (iv) superior tuberal (containing dorsomedial nucleus, the anterior part of the lateral hypothalamus, and the posterior part of the paraventricular nucleus); and (v) posterior (containing the posterior part of the lateral hypothalamus and the mammillary bodies).

The total intracranial volume (TIV) was computed using SPM 12 v6470 (Statistical Parametric Mapping, Welcome Trust Centre for Neuroimaging, London, UK) running under MATLAB R2014b (Math Works, MA, USA) (Malone et al., 2015).

Stringent visual quality checks were conducted on all scans and segmentations to ensure suitable quality (i.e., motion, other imaging artefacts, pathology unlikely to be attributed to FTD or ALS and incorrect anatomical labelling). One ALS and one bvFTD participant were removed from the analyses due to motion artefacts.

2.6. Statistical analyses

Data were analysed using SPSS Statistics, version 26.0 (IBM, Armonk, NY). The statistical significance level was set at p <.05 for all analyses unless otherwise specified. One-way analysis of variance (ANOVA) was used to examine differences in demographic (i.e., age and education years) and cognitive variables (i.e., ACE-III total and subdomain scores, TMT-A and B-A time) between all groups, as well as variables specific to patient groups (i.e., disease duration and CBI-R total and subdomain scores) followed by Sidak post-hoc tests. In the case of violation of heterogeneity of variance based on Levene's test results, Welch's F was used and followed by Games–Howell post hoc tests. Categorical variables (i.e., sex, and *C9orf72* expansion and *GRN/MAPT* mutation status) were examined using chi-squared tests.

In order to account for the influence of the use of two different MRI scanners and acquisition protocols, whole-brain volume, as well as the significant difference in sex distribution, the hypothalamic raw volumes were first converted into w scores using the following formula: w score = [(observed volume in patient) − (predicted patient volume)]/(square root of the residual variance in controls), where the predicted patient volume and the residual variance were estimated from a linear regression model conducted on the volumes of the controls with the effect of age, sex, total intracranial volume, acquisition protocol and scanner type included as covariates. This not only controls for the potential confounding effects on hypothalamic volumes but also allows for direct comparisons across groups for all subsequent analyses (Bocchetta et al., 2022) with a w score of −1.96 corresponding to the 2.5th percentile of the controls, −1.65 to the 5th percentile and −1.04 to the 15th percentile, respectively.

One-sample t-tests were then conducted to test whether the derived w scores for each clinical group were each significantly different from 0, indicating the mean in the clinical group was below the mean of w scores in healthy controls. Despite the relatively small number of patients harbouring genetic abnormalities in the current cohort, one-sample t-tests were also performed within each genetic subgroup (i.e., ALS-FTD *C9orf72*, bvFTD *C9orf72* and bvFTD *GRN* and *MAPT*) in order to examine the potential influence of genetic status on hypothalamic volume. One-way ANOVA was conducted to compare the w scores between all clinical groups followed by Sidak post-hoc tests. Partial correlation was performed with all patient groups combined to explore associations between w scores, and cognitive and behavioural variables, with disease duration included as a covariate. Statistical significance was set at a conservative level of $p \leq .001$ to minimise the risk of Type I errors.

3. Results

3.1. Demographics

No significant group differences were identified in education level or age across cohorts (Table 1), however, sex distribution differed significantly in the ALS (a greater distribution of male participants; p =.005) relative to the control group (a greater proportion of female participants; p <.001). As may be expected, direct comparison of the patient groups revealed significantly longer disease duration in bvFTD compared to both ALS-FTD (p =.001) and ALS (p <.001) groups. In terms of genetic status, 12 bvFTD patients, 13 ALS-FTD, and one ALS patients harboured the *C9orf72* repeat expansion, while 5 bvFTD patients harboured a *GRN* or *MAPT* mutation. Chi-squared tests did not reveal any significant differences in the distribution of *GRN/MAPT* mutations, although a lower proportion of *C9orf72* repeat expansion carriers in ALS (p <.001), and a higher proportion of *C9orf72* repeat expansion carriers in ALS-FTD (p =.009) were observed relative to the other clinical groups. *SOD1* gene mutations were not found in the ALS group.

3.1.1. Cognitive profiles

Relative to controls and the ALS group, both bvFTD and ALS-FTD groups demonstrated significantly lower ACE-III total scores (both p <.001; Table 1) indicating a poorer level of global cognitive functioning (with no significant differences between the bvFTD and ALS-FTD groups). This profile of disproportionate cognitive impairment in the bvFTD and ALS-FTD groups was also evident across all ACE-III subdomain scores (all p values ≤.007). Of note, the ALS-FTD group performed more poorly on the ACE-III language subdomain compared to bvFTD patients (p <.001). ALS patients and controls consistently outperformed bvFTD and ALS-FTD on additional measures of processing speed (TMT-A; all p values ≤.002) and executive function (TMT-B-A; all p values ≤.04), with no significant differences evident between ALS and controls (all p values >0.05). Commensurate with previous literature, these findings indicate global cognitive impairment in bvFTD and ALS-FTD, compared to ALS patients and healthy controls.

3.1.2. Behavioural profiles

Relative to the ALS group, bvFTD and ALS-FTD showed significantly

Table 1
Demographic, clinical, and behavioural characteristics of study participants.

	Controls (n = 58)	ALS (n = 52)	ALS-FTD (n = 42)	bvFTD (n = 59)	F	p	Post-hoc
Sex (M/F)	24/33	42/10	31/11	39/20	20.213[a]	<.001	ALS (more M participants) & Controls (more F participants)
Age (years)	63.60(10.75)	60.33 (10.72)	64.29(8.23)	61.92(8.35)	1.682	.172	–
Education (years)	13.40(2.59)	12.82 (2.58)	12.68(3.16)	12.38(3.06)	1.259	.290	–
Disease severity							
Disease duration (months)	–	28.1 (26.52)	33.38(22.174)	60.25(49.33)	9.202[b]	<.001	bvFTD > ALS, ALS-FTD
ALSFRS-R score	–	40.81 (5.10)	–	–	–	–	–
FRS Stage (Very Mild/Mild, Moderate, Severe, Very Severe)	–	–	5,20,8,0*	0,27,24,4*	–	–	–
C9orf72 abnormality	–	1	13	12	13.340[a]	.001	ALS (fewer *C9orf72*) & ALS-FTD (more *C9orf72*)
MAPT or GRN mutations	–	–	0	5	3.811[a]	.051	–
SOD1 mutations	–	0	–	–	–	–	–
ACE-III Total (/100)	94.58(3.42)	92.42 (5.42)	72.44(14.35)	76.84(15.65)	51.995[b]	<.001	Controls, ALS > bvFTD, ALS-FTD
ACE-Attention (/18)	17.17(0.91)	16.87 (1.66)	15.01(2.89)	14.84(2.83)	17.278[b]	<.001	Controls, ALS > bvFTD, ALS-FTD
ACE-Memory (/26)	24.68(1.62)	23.22 (4.26)	19.15(5.06)	18.85(5.39)	33.075[b]	<.001	Controls, ALS > bvFTD, ALS-FTD
ACE-Fluency (/14)	12.13(1.62)	11.25 (2.23)	5.37(3.85)	6.86(3.94)	58.409[b]	<.001	Controls, ALS > bvFTD, ALS-FTD
ACE-Language (/26)	25.12(0.94)	24.47 (1.94)	19.30(4.58)	22.31(4.31)	28.246[b]	<.001	Controls, ALS > bvFTD, ALS-FTD bvFTD > ALS-FTD
ACE-Visuospatial (/16)	15.50(0.87)	15.48 (0.91)	13.82(2.08)	14.02(2.58)	12.923[b]	<.001	Controls, ALS > bvFTD, ALS-FTD
TMT-A Time (seconds)	32.73(10.99)	33.54 (12.22)	62.94(28.36)	63.33(58.17)	16.539[b]	<.001	bvFTD, ALS-FTD > Controls, ALS
TMT-B-A Time (seconds)	37.89(19.32)	53.63 (42.14)	112.90(86.83)	110.00 (103.29)	11.947[b]	<.001	bvFTD, ALS-FTD > Controls, ALS
CBI-R Total	–	26.47 (20.72)	43.21(31.08)	64.54(29.33)	24.934[b]	<.001	bvFTD > ALS, ALS-FTD ALS-FTD > ALS
Memory	–	11.13 (13.11)	32.23(24.46)	43.07(21.26)	45.386[b]	<.001	bvFTD, ALS-FTD > ALS
Everyday skills	–	17.05 (29.53)	19.45(20.26)	30.53(25.92)	3.980	.021	bvFTD > ALS
Self-care skills	–	19.95 (29.77)	7.81(15.93)	16.00(25.51)	3.496[b]	.035	–
Mood changes	–	15.04 (15.61)	20.00(20.23)	29.24(22.22)	7.020[b]	.001	bvFTD > ALS
Odd beliefs	–	0.20(1.30)	5.00(12.20)	9.89(17.13)	12.183[b]	<.001	bvFTD,ALS-FTD > ALS
Abnormal behaviours	–	7.22 (11.64)	21.15(22.40)	36.30(23.33)	34.791[b]	<.001	bvFTD, ALS-FTD > ALS bvFTD > ALS-FTD
Eating habits	–	8.07 (12.15)	21.88(27.63)	41.31(30.31)	29.687[b]	<.001	bvFTD, ALS-FTD > ALS bvFTD > ALS-FTD
Sleep	–	29.81 (27.75)	25.94(25.85)	43.22(25.14)	6.074	.003	bvFTD > ALS, ALS-FTD
Stereotypic and motor behaviours	–	7.50 (12.03)	32.03(30.89)	41.07(28.82)	37.370[b]	<.001	bvFTD, ALS-FTD > ALS
Reduced motivation	–	13.05 (18.23)	32.17(29.37)	58.22(30.23)	43.152[b]	<.001	bvFTD, ALS-FTD > ALS bvFTD > ALS-FTD

Means (Standard Deviation).
[a]Chi-square value. [b]Welch's F value.
*FRS was not routinely administered at the FOREFRONT ALS and FTD Clinic and therefore this information was not available for the 9 ALS-FTD and 4 bvFTD patients recruited through the FOREFRONT ALS and FTD Clinic.
ACE-III = the third edition of the Addenbrooke's Cognitive Examination; ALS = amyotrophic lateral sclerosis; ALSFRS-R = the revised ALS functional rating scale; ALS-FTD = amyotrophic lateral sclerosis-frontotemporal dementia; bvFTD = behavioural-variant frontotemporal Dementia; CBI-R = the revised Cambridge Behavioural Inventory; F = Female; FRS = Frontotemporal Dementia Rating Scale; M = Male; TMT = Trail Making Test.

greater impairment across overall behavioural disturbances (CBI-R total score; p <.001 and p =.027; Table 1) and most CBI-R subdomains including everyday memory difficulties (both p values <.001), odd beliefs (p <.001 and p =.046), abnormal behaviours (p <.001 and p =.003), eating habits (p <.001 and p =.015), stereotypic and motor behaviours (both p values <.001), reduced motivation (p <.001 and p =.002), everyday skills (bvFTD > ALS p <.035), mood disturbances (bvFTD > ALS p =.001) and sleep changes (bvFTD > ALS p =.041).

Disproportionate impairments were further evident in bvFTD relative to ALS-FTD in terms of overall behavioural disturbances (CBI-R total; p =.003) as well as specific domains of abnormal behaviours (p =.005), eating habits (p =.004), sleep changes (p =.005) and reduced motivation (p <.001). These findings indicate a graded variation in behavioural abnormalities across the ALS-FTD spectrum, most pronounced in bvFTD.

3.2. Imaging results

3.2.1. Patterns of hypothalamic volumetric loss relative to controls

3.2.1.1. ALS vs. controls. ALS patients demonstrated significantly lower volumes in the bilateral superior tuberal (p <.001; Table 2 and Figs. 1 and 2) subregions and higher volumes in the left inferior tuberal (p =.001) subregion.

3.2.1.2. ALS-FTD vs. controls. ALS-FTD patients demonstrated widespread atrophy across all hypothalamic subregions with the exception of the bilateral inferior tuberal regions (all p values <.001; Table 2 and Figs. 1 and 2) in comparison to controls.

W scores <15th percentile were identified in the bilateral anterior inferior and posterior subregions, with more severe atrophy as reflected by *w* scores <10th revealed in the bilateral anterior superior hypothalamus.

3.2.1.3. bvFTD vs. controls. Compared to controls, bvFTD patients demonstrated a hypothalamic atrophy profile similar to that observed in the ALS-FTD group characterised by significant atrophy across all hypothalamic subregions with the exception of the bilateral inferior tuberal regions (all p values <.001; Table 2 and Figs. 1 and 2).

Specifically, *W* scores <15th percentile of the controls were found in the bilateral anterior inferior and posterior and right anterior superior subregions, while more severe atrophy as indicated by *w* scores <10th was revealed in the left anterior superior hypothalamus (Fig. 1).

Taken together, relative preservation of the bilateral inferior tuberal subregions was observed across the ALS-FTD spectrum with the greatest extent of volume loss identified in the anterior superior followed by anterior inferior and posterior hypothalamic subregions.

3.2.2. Genetic subgroup analyses

Looking across the groups in terms of genetic status (Supplementary Fig. 2), a similar pattern of pervasive hypothalamic atrophy (most pronounced in the anterior superior subregion) but relative preservation of the bilateral inferior tuberal subregions were also revealed in ALS-FTD *C9orf72* (n = 13), bvFTD *C9orf72* (n = 12) and bvFTD *GRN* and *MAPT* (n = 5) subgroups, suggesting that the overall findings remained a robust finding regardless of genetic status.

3.2.3. Patterns of hypothalamic volume loss across ALS-FTD clinical syndromes

Direct comparisons between the patient groups revealed significantly lower volumes in bvFTD and ALS-FTD relative to ALS across all hypothalamic subregions except for the bilateral inferior and right superior tuberal regions (all p values ≤.001; Supplementary Table 1). No significant differences were identified between bvFTD and ALS-FTD, suggesting similar magnitude and distribution of hypothalamic subregional atrophy.

3.3. Correlations between hypothalamic volumes and cognitive dysfunction

Within the entire patient cohort (n = 151; Table 3), profiles of cognitive performance were found to correlate with atrophy in selective hypothalamic subregions after controlling for disease duration. Broadly, reduced volume of the anterior inferior and superior, and posterior hypothalamic subregions, was associated with poorer cognitive performance on predominantly memory and fluency subdomains of the ACE-III (all p values ≤.001), as well as poorer category fluency and processing speed (TMT-A; all p values ≤.001). Further, the absence of significant associations with ACE-III attention and visuospatial subdomain (with the exception of left anterior superior subregion) scores and divided attention (i.e., TMT-B-A; all p values >.001) was suggestive of a lack of involvement in attentional and visuospatial impairments.

3.4. Correlations between hypothalamic volumes and behavioural symptoms

Across the overall patient cohort (n = 151; Table 4), volumes of the anterior inferior and superior, and the posterior subregion were associated with behavioural disturbances after accounting for disease duration. These included everyday memory difficulties and reduced motivation (i.e., apathy and inertia) in addition to well-established eating habit changes (all p ≤ .001).

4. Discussion

While the hypothalamus is increasingly recognised as playing an established role in eating and energy metabolic abnormalities in ALS-FTD, limited attention has been given to its potential role in cognitive and behavioural disturbances. Moreover, the relatively small size of the hypothalamus has precluded fine-grained delineation of subregions, up until recently. Leveraging recent advancements in neuroimaging, we provide the first comprehensive characterisation of hypothalamic subregional profiles *in vivo* and their associated contribution to cognitive and behavioural deficits in a large well-characterised cohort of ALS, ALS-FTD and bvFTD patients. Overall, widespread hypothalamic atrophy with relative preservation of inferior tuberal subregions was evident across the ALS-FTD spectrum. The anterior inferior and superior, and posterior hypothalamic subregions were selectively implicated in

Table 2
Hypothalamic volume *W* scores in each individual diagnosis group relative to controls.

Hypothalamus Region	ALS (n = 51)	t	p	ALS-FTD (n = 42)	t	p	bvFTD (n = 58)	t	p
Anterior Inferior	0.48(1.55)	2.19	.033	−1.34(1.44)	−6.036	<.001	−1.22(1.55)	−6.004	<.001
Left	0.50(1.42)	2.518	.015	−1.13(1.19)	−6.151	<.001	−1.03(1.37)	−5.728	<.001
Right	0.31(1.50)	1.498	.14	−1.18(1.65)	−4.62	<.001	−1.08(1.55)	−5.336	<.001
Anterior superior	−0.22(1.04)	−1.494	.141	−1.69(1.36)	−8.053	<.001	−1.48(1.36)	−8.275	<.001
Left	−0.13(0.89)	−1.065	.292	−1.49(1.19)	−8.086	<.001	−1.49(1.29)	−8.769	<.001
Right	−0.25(1.16)	−1.532	.132	−1.54(1.45)	−6.899	<.001	−1.18(1.37)	−6.59	<.001
Posterior	0.00(1.11)	0.004	.996	−1.31(1.65)	−5.17	<.001	−1.35(1.50)	−6.862	<.001
Left	−0.09(1.13)	−0.567	.573	−1.27(1.58)	−5.223	<.001	−1.09(1.42)	−5.863	<.001
Right	0.08(1.00)	0.542	.59	−1.04(1.47)	−4.602	<.001	−1.26(1.39)	−6.877	<.001
Tuberal Inferior	0.35(0.95)	2.589	.013	0.24(1.31)	1.189	.241	0.09(1.09)	0.646	.521
Left	0.44(0.87)	3.612	.001	0.16(1.22)	0.854	.398	0.14(1.07)	1.012	.316
Right	0.19(1.14)	1.177	.245	0.29(1.41)	1.353	.184	0.02(1.12)	0.144	.886
Tuberal Superior	−0.53(0.63)	−6.006	<.001	−1.21(1.21)	−6.457	<.001	-0.87(0.81)	−8.15	<.001
Left	−0.45(0.69)	−4.644	<.001	−1.20(1.15)	−6.775	<.001	-0.87(0.89)	−7.437	<.001
Right	−0.53(0.70)	−5.391	<.001	−1.03(1.38)	−4.855	<.001	-0.74(0.84)	−6.669	<.001

*Values are Mean *w* scores (Standard Deviation) after controlling for the effect of age, sex, total intracranial volume, acquisition protocol and scanner type.
ALS = amyotrophic lateral sclerosis; ALS-FTD = amyotrophic lateral sclerosis-frontotemporal dementia; bvFTD = behavioural-variant frontotemporal dementia.

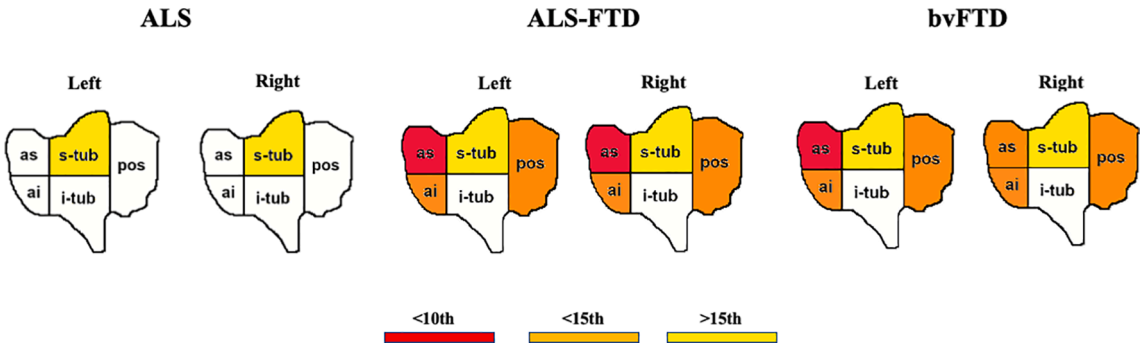

Fig. 1. Pattern of significant hypothalamic atrophy in ALS, ALS-FTD and bvFTD patients compared to healthy controls. The colour map indicates the percentile corresponding to the average *w* scores in each patient group, when these were statistically abnormal (i.e., significantly lower than 0) when compared to controls. Disease duration, age, sex, total intracranial volume, acquisition protocol, and scanner type were included as covariates in the computation of *w* scores. as = anterior superior (containing the paraventricular nucleus); ai = anterior inferior (containing supraoptic nucleus); ALS = amyotrophic lateral sclerosis; ALS-FTD = amyotrophic lateral sclerosis-frontotemporal dementia; bvFTD = behavioural-variant frontotemporal dementia; s-tub = superior tuberal (containing dorsomedial nucleus, the anterior part of the lateral hypothalamus, and the posterior part of the paraventricular nucleus); i-tub = inferior tuberal (containing the arcuate nucleus, the ventromedial nucleus and the posterior part of the supraoptic nucleus); pos = posterior (containing the posterior part of the lateral hypothalamus and the mammillary bodies). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

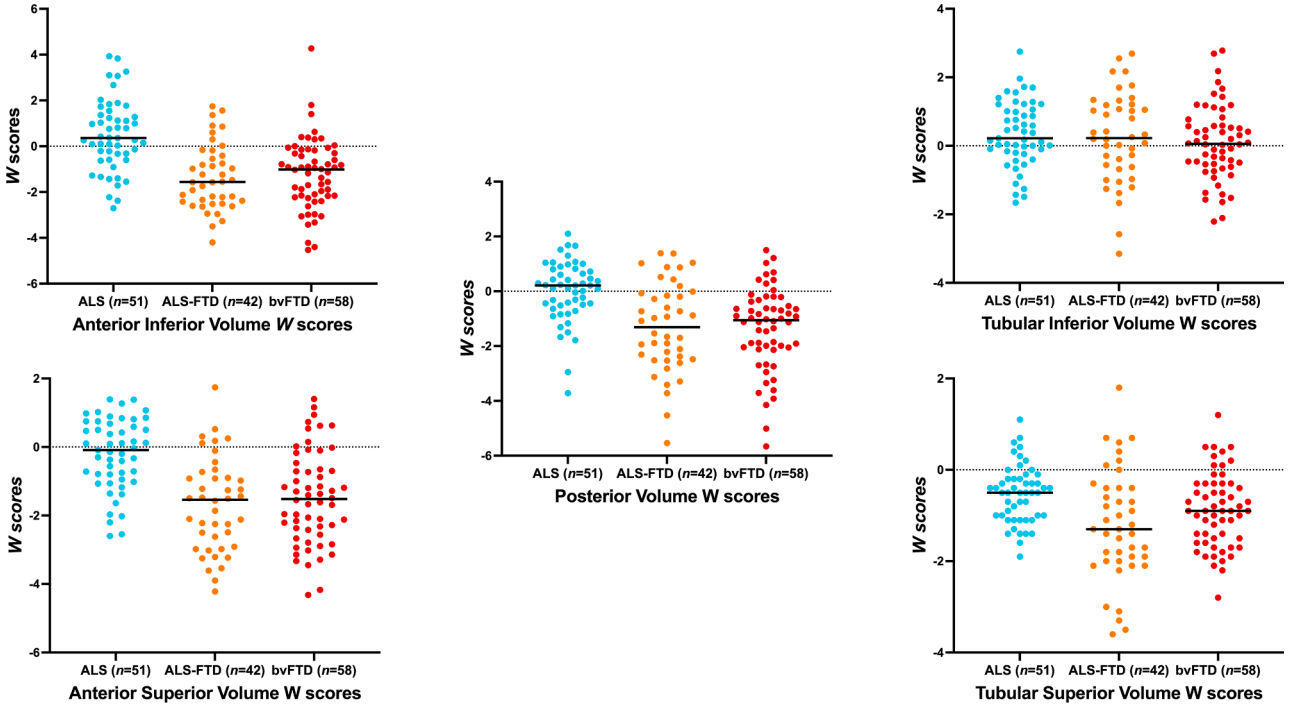

Fig. 2. Scatter plots demonstrating distribution of individual hypothalamic volume *W* scores within each diagnostic group across all 5 hypothalamic subregions. ALS = amyotrophic lateral sclerosis; ALS-FTD = amyotrophic lateral sclerosis-frontotemporal dementia; bvFTD = behavioural-variant frontotemporal dementia.

multiple domains of cognitive and behavioural disturbances over and beyond the effect of disease duration.

4.1. Patterns of hypothalamic atrophy across the ALS-FTD spectrum

Our main finding was of widespread hypothalamic atrophy across the bilateral anterior superior, anterior inferior, superior tuberal and posterior subregions in ALS-FTD and bvFTD groups, with greatest volume loss evident in the anterior superior region. While the previous finding of more pronounced hypothalamic atrophy in ALS-FTD compared to bvFTD patients (Shapiro et al., 2022) was not replicated in the current study, the bvFTD and ALS-FTD groups demonstrated comparable hypothalamic volumes despite a double disease-duration in the bvFTD group, providing largely converging evidence of more rapid hypothalamic degeneration in ALS-FTD. Moreover, we replicated previous findings of relatively preserved inferior tuberal subregions in our ALS-FTD and bvFTD patients (Bocchetta et al., 2015, 2021; Shapiro et al., 2022). Importantly, the extent of atrophy was comparable between ALS-FTD and bvFTD, pointing to hypothalamic involvement as a transdiagnostic feature across the ALS-FTD spectrum.

In the ALS group, reduction in hypothalamic volume was confined to the bilateral superior tuberal subregions, departing somewhat from previous findings of posterior hypothalamic atrophy. Methodological differences may go some way towards accounting for these discrepancies, as the Gorges et al. study conducted a coarse parcellation of the hypothalamus into two equal volumes along the anterior-posterior axis (Gorges et al., 2017), limiting comparability of findings. The posterior hypothalamus reported by Gorges et al. (2017) likely includes parts of the regions defined as superior tuberal subregions in the current study. The current study therefore consolidates and extends previous

Table 3
Partial correlations between hypothalamic volume *W* scores and cognitive variables across all diagnosis groups controlling for disease duration.

	ACE Attention	ACE Memory	ACE Fluency	ACE Language	ACE Visuospatial	Category fluency	TMT-A	TMT-B-A
Anterior Inferior	0.171	0.25	0.343**	0.211	0.203	0.412**	−0.3**	−0.018
Left	0.206	0.259**	0.357**	0.24	0.223	0.423**	−0.344**	0.026
Right	0.113	0.204	0.276**	0.152	0.155	0.34**	−0.212	−0.057
Anterior superior	0.225	0.3**	0.362**	0.265**	0.271**	0.428**	−0.35**	−0.112
Left	0.227	0.326**	0.364**	0.289**	0.299**	0.417**	−0.365**	−0.151
Right	0.195	0.241	0.316**	0.213	0.214	0.382**	−0.294**	−0.069
Posterior	0.192	0.315**	0.296**	0.226	0.191	0.368**	−0.276**	−0.149
Left	0.175	0.314**	0.279**	0.262**	0.213	0.349**	−0.276**	−0.12
Right	0.185	0.281**	0.279**	0.171	0.152	0.346**	−0.247	−0.158
Tuberal Inferior	−0.129	−0.074	−0.154	−0.243	−0.175	−0.064	0.228	−0.006
Left	−0.075	−0.01	−0.041	−0.152	−0.122	0.015	0.161	−0.037
Right	−0.162	−0.126	−0.244	−0.297**	−0.2	−0.132	0.259	0.027
Tuberal Superior	0.204	0.223	0.166	0.159	0.12	0.184	−0.16	−0.168
	0.19	0.254	0.256	0.249	0.144	0.259**	−0.122	−0.17
Right	0.169	0.144	0.049	0.043	0.072	0.075	−0.154	−0.128

ACE = Addenbrooke's Cognitive Examination; TMT = Trail Making Test.
**$p \leq 0.001$.

Table 4
Partial correlations between hypothalamic volume *W* scores and CBI-R subdomain scores across all diagnosis groups controlling for disease duration.

	Memory	Everyday Skills	Self-Care Skills	Mood	Odd Beliefs	Abnormal Behaviour	Eating Habits	Sleep	Stereotypic Behaviour	Reduced Motivation
Anterior Inferior	−0.327**	−0.15	−0.055	−0.062	−0.181	−0.191	−0.31**	−0.046	−0.24	−0.225
Left	−0.355**	−0.186	−0.106	−0.066	−0.239	−0.211	−0.308**	−0.006	−0.223	−0.266**
Right	−0.251	−0.094	0.001	−0.049	−0.1	−0.142	−0.266**	−0.077	−0.22	−0.153
Anterior superior	−0.365**	−0.185	−0.059	−0.058	−0.171	−0.234	−0.318**	0.002	−0.309**	−0.238
Left	−0.402**	−0.162	−0.061	−0.126	−0.172	−0.281**	−0.351**	−0.01	−0.34**	−0.291**
Right	−0.285**	−0.178	−0.049	0.005	−0.147	−0.165	−0.248	0.012	−0.241	−0.162
Posterior	−0.345**	−0.138	−0.074	−0.033	−0.096	−0.215	−0.29**	−0.016	−0.22	−0.298**
Left	−0.338**	−0.113	−0.08	−0.024	−0.095	−0.178	−0.272**	0.003	−0.216	−0.296**
Right	−0.313**	−0.144	−0.061	−0.037	−0.087	−0.225	−0.275**	−0.031	−0.2	−0.267**
Tuberal Inferior	−0.062	0.085	0.137	0.02	0.156	−0.085	−0.06	−0.026	−0.156	−0.093
Left	−0.098	0.035	0.12	0.008	0.111	−0.12	−0.104	−0.03	−0.193	−0.134
Right	−0.016	0.122	0.131	0.028	0.176	−0.035	−0.007	−0.019	−0.092	−0.036
Tuberal Superior	−0.17	−0.038	0.159	0.032	−0.116	−0.138	−0.175	0.083	−0.245	−0.146
Left	−0.197	−0.052	0.192	−0.063	−0.183	−0.172	−0.163	−0.011	−0.286**	−0.187
Right	−0.105	−0.016	0.09	0.108	−0.027	−0.074	−0.142	0.144	−0.147	−0.074

CBI-R = the revised Cambridge Behavioural Inventory.
**$p \leq 0.001$.

investigations of hypothalamic alterations (Gorges et al., 2017; Cykowski et al., 2014; Gabery et al., 2021), and refines our understanding of selective hypothalamic involvement in ALS.

Overall, we found evidence of graded variation in hypothalamic involvement, with widespread and pronounced atrophy observed in bvFTD and ALS-FTD, selective involvement of the superior tuberal region in ALS, and relative sparing of the inferior tuberal region across all groups.

4.2. Associations with cognitive and behavioural functioning

After controlling for the effect of disease duration, bilateral anterior (including inferior and superior regions) and posterior hypothalamus was found to be involved in a wide range of cognitive functions, predominantly memory, fluency, and processing speed. A similar pattern of bilateral anterior inferior and superior and posterior subregional atrophy was associated with greater severity of behavioural disturbances including eating abnormalities and apathy/inertia (except for right anterior inferior and superior subregions). These findings offer novel and important insights that the hypothalamus contributes to the manifestation of cognitive and behavioural changes key to the ALS-FTD spectrum over and beyond well-established eating disturbance.

4.3. Potential mechanisms underlying differential hypothalamic involvement in ALS-FTD

The hypothalamus is known to be a dynamic integrative hub orchestrating inputs and outputs to and from other regions of the brain to regulate homeostasis of important neuroendocrine, metabolic and autonomic functions (Vercruysse et al., 2018; Van Der Klaauw and Farooqi, 2015; Coll et al., 2007). The observed widespread involvement of the hypothalamus in various cognitive and behavioural domains is in line with its rich connections to many parts of the brain involved in cognitive, emotional, and behavioural regulation. Specifically, studies using resting-state functional magnetic resonance imaging (fMRI) in healthy participants place the hypothalamus at the interface of several large-scale brain networks such as the Default Mode Network and Salience Network, through connectivity with the dorsal and ventral striatum, thalamus, brainstem, and higher-order cortical areas including orbitofrontal, cingulate (middle and posterior), and temporal cortices (Kullmann et al., 2014; Seeley et al., 2007). These regions are implicated in many higher-order cognitive functions including memory, decision-making, planning, and motivation (Shaw et al., 2021; Buckner et al., 2008), and align with the current findings of selective hypothalamic involvement in memory and executive function processes as well as

manifestation of apathy/inertia. Collectively, the hypothalamus appears particularly well positioned to bridge key physiological and psychological processes implicated in feeding behaviour, including cognition, motivation, and reward processing (Kullmann and Veit, 2021). Degeneration of the hypothalamus thus unsurprisingly gives rise to cognitive and behavioural changes in ALS-FTD, as a part of distributed neural networks underlying reward and motivation, appraisal and regulation of emotional salience, and goal-directed behaviour (Ahmed et al., 2016).

Interestingly, the current findings replicate previous observations of the inferior tuberal subregion remaining relatively intact across the ALS-FTD spectrum. In terms of potential underlying mechanism, the inferior tuberal subregion includes the arcuate nucleus containing different groups of neuroendocrine neurons, among which, neuropeptide Y (NPY), AgRP, proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) neurons are centrally involved in regulation of feeding and energy expenditure (Parker and Bloom, 2012). Given that previous studies have reported high concentration of AgRP (Ahmed et al., 2015) and no significant changes in the density or morphology of NPY neurons (Piguet et al., 2011)in bvFTD, it may be that intact inferior tuberal subregions support the continued production of AgRP in the face of more global hypothalamic degeneration. Of particular interest, Shapiro et al. (Shapiro et al., 2022) similarly revealed that the inferior tuberal subregion represents the least affected subregion across the FTD spectrum, including bvFTD, ALS-FTD (despite a small sample size of 7), semantic variant and non-fluent variant primary progressive aphasia, as well as across *C9orf72* and *GRN* carriers. More widespread atrophy across the entire hypothalamus extending into the inferior tuberal region (although it remained the least affected with a relatively small volume reduction of only 10–13 %) was nonetheless observed in *MAPT* carriers as well as in patients with tauopathies, rather than TDP-43-opathies. This suggests that differential pathological mechanisms may underlie hypothalamic changes in tauopathies and TDP-43-opathies, however whether such generalised atrophy may be the result of advanced disease course remains unclear and requires replication in a larger cohort. Taken together, further histopathophysiological research exploring the distinct role of hypothalamic subregions containing various neuropeptide-producing neurons and neuropeptide receptors in the context of different pathological causes is clearly warranted.

In this context, the potential role of oxytocin is of interest given that the anterior superior subregion displayed the greatest atrophy in bvFTD and ALS-FTD, while the superior tuberal subregion was most affected in ALS. The anterior and superior tuberal subregions of the hypothalamus contain the paraventricular nucleus, which is responsible for the production of oxytocin (Kublaoui et al., 2008). Inhibition of oxytocin has been shown to increase feeding behaviour in mice and is associated with Prader-Willi syndrome characterised by insatiable hunger and related feeding behaviours (Atasoy et al., 2012). Further, relative to other neuropeptides synthesized in the paraventricular nucleus, oxytocin has been implicated as the main moderator for hyperphagic obesity compared to corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH) in mouse models (Kublaoui et al., 2008), suggesting its critical role in the regulation of food intake and appetite (Qin et al., 2018). Importantly, a significant loss of paraventricular oxytocin-producing neurons has been documented in a recent histopathological study of ALS patients (Gabery et al., 2021), supporting the key role of paraventricular pathology in metabolic symptom manifestations.

In line with this, there has been an increasing interest in the potential of oxytocin to enhance prosocial behaviour and ultimately as a symptomatic treatment for social deficits in FTD (Piguet et al., 2022). Significant improvement in carer-rated behavioural symptoms was observed following the administration of a single dose of intranasal oxytocin within the same day in bvFTD patients (Jesso et al., 2011). While this positive effect was not reported in another clinical trial involving a one-week course of intranasal oxytocin (Finger et al., 2015), elevated activation in limbic regions involved in emotional processing was identified following intranasal oxytocin administration in FTD patients in a fMRI study (Oliver et al., 2020), suggesting a neural modulatory effect.

Overall, while the above represents a simplified explanation, our findings of distinct structural hypothalamic abnormalities and their differential contribution to cognitive and behavioural disturbances highlight the need to investigate discrete neuropeptide expression abnormalities in ALS-FTD to progress alternative avenues for therapies.

4.4. Limitations and future directions

Several methodological limitations warrant discussion. Firstly, the absence of histopathological examination means that the direct relationship between hypothalamic subregion atrophy and neuropeptide expression remains to be established and should be considered in future studies where possible. Secondly, tasks assessing emotion processing and social cognitive function were not routinely administered to many of the ALS patients, preventing comparisons across all clinical groups. Given the hypothalamic connectivity to brain regions subserving emotional regulation and processing of emotional salience (Ahmed et al., 2016), future studies will benefit from the inclusion of such measures to comprehensively chart socioemotional changes and their relationship to hypothalamic subregion degeneration. Finally, resting-state fMRI data were not available for the ALS cohort recruited through the FOREFRONT ALS and FTD Clinic, it will therefore be beneficial for future investigations to incorporate resting-state fMRI across the ALS-FTD spectrum to examine alterations in hypothalamic subregion functional connectivity to detect early changes that may be present prior to the onset of prominent grey matter volume loss and, importantly, its relation to early cognitive and behavioural disturbances, given evidence of early hypothalamic involvement in pre-symptomatic genetic mutation carriers.

4.5. Conclusion

The hypothalamus has been traditionally regarded as primarily involved in energy metabolic and eating abnormalities in ALS-FTD. Using a novel neuroimaging technique, we provide a fine-grained parcellation of the hypothalamus to reveal graded variations in subregional atrophy across the ALS-FTD spectrum. Hypothalamic subregional atrophy was differentially associated with widespread cognitive and behavioural disturbances underscoring the impact of hypothalamic abnormalities beyond changes in eating and energy metabolism. Our findings demonstrate the importance of understanding how hypothalamic degeneration relates to the emergence of distinct clinical features across the ALS-FTD spectrum and offers new insights into potential neuropeptide expression abnormalities in ALS-FTD with therapeutic implications.

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CRediT authorship contribution statement

Nga Yan Tse: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Martina Bocchetta:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Emily G. Todd:** Formal analysis, Writing – original draft. **Emma M. Devenney:** Data curation, Writing – original draft. **Sicong Tu:** Data curation, Writing – original draft. **Jashelle Caga:** Data curation, Writing – original draft. **John R. Hodges:** Data curation, Writing – original draft. **Glenda M. Halliday:** Data curation, Writing – original draft. **Muireann Irish:** Supervision, Data curation, Writing – original draft. **Matthew C. Kiernan:** Supervision, Data curation, Writing – original draft. **Olivier Piguet:** Supervision, Data curation, Writing – original draft. **Jonathan D. Rohrer:** Conceptualization, Supervision, Formal analysis, Writing – original draft. **Rebekah M. Ahmed:** Conceptualization, Data curation, Supervision, Formal analysis, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103281.

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