Hypothalamic volume is associated with age, sex and cognitive function across lifespan: a comparative analysis of two large population-based cohort studies

Peng Xu,[a] Santiago Estrada,[a,b] Rika Etteldorf,[a] Dan Liu,[a] Mohammad Shahid,[a] Weiyi Zeng,[a] Deborah Früh,[a] Martin Reuter,[b,c,d] Monique M. B. Breteler,[a,e] and N. Ahmad Aziz[a,f,*]

[a]Population Health Sciences, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
[b]Artificial Intelligence in Medical Imaging, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
[c]A.A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Boston, MA, USA
[d]Department of Radiology, Harvard Medical School, Boston, MA, USA
[e]Institute for Medical Biometry, Informatics and Epidemiology (IMBIE), Faculty of Medicine, University of Bonn, Germany
[f]Department of Neurology, Faculty of Medicine, University of Bonn, Germany

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Summary

Background Emerging findings indicate that the hypothalamus, the body's principal homeostatic centre, plays a crucial role in modulating cognition, but comprehensive population-based studies are lacking.

Methods We used cross-sectional data from the Rhineland Study (N = 5812, 55.2 ± 13.6 years, 58% women) and the UK Biobank Imaging Study (UKB) (N = 45,076, 64.2 ± 7.7 years, 53% women), two large-scale population-based cohort studies. Volumes of hypothalamic structures were obtained from 3T structural magnetic resonance images through an automatic parcellation procedure (FastSurfer-HypVINN). The standardised cognitive domain scores were derived from extensive neuropsychological test batteries. We employed multivariable linear regression to assess associations of hypothalamic volumes with age, sex and cognitive performance.

Findings In older individuals, volumes of total, anterior and posterior hypothalamus, and mammillary bodies were smaller, while those of medial hypothalamus and tuberal region were larger. Larger medial hypothalamus volume was related to higher cortisol levels in older individuals, providing functional validation. Volumes of all hypothalamic structures were larger in men compared to women. In both sexes, larger volumes of total, anterior and posterior hypothalamus, and mammillary bodies were associated with better domain-specific cognitive performance, whereas larger volumes of medial hypothalamus and tuberal region were associated with worse domain-specific cognitive performance.

Interpretation We found strong age and sex effects on hypothalamic structures, as well as robust associations between these structures and domain-specific cognitive functions. Overall, these findings thus implicate specific hypothalamic subregions as potential therapeutic targets against age-associated cognitive decline.

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Keywords: Hypothalamus; Cognitive function; Brain imaging; Age-associated cognitive decline; Sexual dimorphism; Cortisol

Introduction

The human hypothalamus, located beneath the thalamus, is part of the diencephalon.[1] It has a complex and delicate architecture, consisting of dozens of interconnected nuclei and tracts, and plays an essential role in the regulation of a wide range of physiological, behavioural, and cognitive processes.[2–4] Moreover, accumulating neuropathological evidence points towards extensive hypothalamic involvement in various neurodegenerative disorders, including Alzheimer disease,[5] Parkinson disease,[6] Huntington disease,[7] frontotemporal dementia,[8] and amyotrophic lateral sclerosis.[9]

*Corresponding author. Population Health Sciences, German Center for Neurodegenerative Diseases (DZNE), Venusberg-Campus 1/99, 53127, Bonn, Germany.
E-mail address: Ahmad.Aziz@dzne.de (N.A. Aziz).

Research in context

Evidence before this study

We conducted a comprehensive search of PubMed for articles pertaining to the human hypothalamus in relation to age, sex, and cognitive function (from inception to October 24, 2024). The search terms included hypothalamus, suprachiasmatic nucleus, supraoptic nucleus, paraventricular nucleus, infundibular nucleus, median eminence, dorsomedial nucleus, ventromedial nucleus, tuberomammillary nucleus, tuberal nucleus, and mammillary body/bodies in combination with volume, age, sex, cognitive function/impairment, memory, dementia, and Alzheimer disease. Previously, several small-scaled studies provided preliminary and inconsistent estimates of age and sex effects on the volume of the total hypothalamus, or specific substructures, in adult (up to 506 cases) and pediatric populations (up to 700 cases). Additionally, several prior small-scaled studies reported an association between hypothalamic volume and cognitive performance in specific clinical populations, including neurodegenerative diseases and mood disorders (up to 151 cases), and between the volume of the mammillary bodies and memory (up to 63 cases). However, no previous population-based studies were found that investigated the volume of the hypothalamus and its substructures in relation to age, sex, and cognitive function across adult life span.

Added value of this study

We provide a comprehensive assessment of the volumes of the hypothalamus and its substructures in relation to age, sex and both general and domain-specific cognitive function in large-scale populations-based cohort studies. Notably, the findings from two independent cohorts were highly consistent, indicating strong age and sex effects on hypothalamic structures, as well as robust associations between these structures and domain-specific cognitive functions.

Implications of all the available evidence

The identification of strong age and sex-specific volumetric alterations in the human hypothalamus and its subregions across lifespan provides a detailed reference for future studies on the role of this critical structure in the pathogenesis of a range of neuropsychiatric, neuroendocrine, metabolic, as well as sleep and circadian rhythm disorders. In particular, our findings regarding the robust associations between the volumes of different hypothalamic substructures and domain-specific cognitive function have several direct implications: Firstly, we establish region-specific links between various hypothalamic structures and performance in different cognitive domains, which could be further assessed as potential imaging markers for early detection of cognitive decline. Secondly, these results reveal potential hypothalamic targets for the development of novel interventions aimed at preserving or enhancing domain-specific cognitive performance. Lastly, by establishing a robust association between the hypothalamus and cognitive function, our findings offer novel perspectives on the neuroanatomical basis of cognition, contributing to a better understanding of the pathogenesis of age-associated cognitive impairment.

Assessing hypothalamic structure and its phenotypic correlates across the lifespan could therefore provide novel insights into the neurobiological basis of age-associated dysregulation of a range of bodily functions, particularly those occurring in the context of age-related neurodegenerative diseases.[5–9]

Neuropathological studies have substantially advanced our understanding of the functional anatomy of different hypothalamic structures in humans.[4,10,11] However, limited sample sizes, peri- and post-mortem factors affecting brain tissue quality, application of a range of different neuropathological techniques, as well as limited availability of ante-mortem clinical data pose major challenges that remain to be overcome. Therefore, magnetic resonance imaging (MRI) studies have been increasingly employed to assess hypothalamic structure *in vivo*.[12–15] While these studies have provided preliminary estimates of age and sex effects on hypothalamic volume, the results have been inconsistent, likely due to inclusion of limited age ranges, small sample sizes, and pre-selection of specific (diseased) populations. Hence, more in-depth investigations of the structure of the hypothalamus in relation to age and sex in much larger populations are warranted for a better understanding of the role of this tiny, yet crucial brain structure in health and disease.

Cognitive impairment is the hallmark of many age-associated neurodegenerative diseases.[16] Recent findings from animal experiments point towards a crucial role of the hypothalamus in the modulation of cognition, both directly through extensive projections to cortical and limbic regions and indirectly through regulation of mood, sleep/circadian rhythm, metabolism, and neuroendocrine outflow.[2–4,17,18] For example, as an important subregion of the hypothalamus and a key component of the circuit of Papez, the mammillary bodies are crucially implicated in the regulation of cognition, especially memory function, through their extensive connections to the hippocampus and other cortico-limbic structures.[19] However, despite consistent evidence from animal experiments for the critical role of the mammillary bodies for cognitive performance, results of human studies assessing the association between volumes of mammillary bodies and cognitive impairment are inconsistent.[20,21] These discrepancies likely arise from variations in the characteristics of the populations studied, including differences in age ranges and diagnostic groups. Similarly, recent animal

experiments indicate that disturbances of the hypothalamic orexinergic system could be implicated in the pathogenesis of both mild cognitive impairment and Alzheimer disease, potentially through modulation of amyloid-β dynamics.[22,23] Moreover, hyperactivation of the hypothalamic-pituitary-adrenal axis, which is under direct control of the corticotropin releasing factor-producing neurons of the hypothalamic paraventricular nucleus (PVN), has for long been implicated in the pathogenesis of age-associated cognitive decline.[24,25] Mounting evidence indicates that also other hypothalamic substructures could be related to cognitive function, including the lateral hypothalamus, the infundibular nucleus, and the supra-mammillary nucleus.[2,26] Nonetheless, the relevance of these findings for age-associated cognitive decline and neurodegenerative diseases in humans remains unclear as the association between hypothalamic structure and cognitive function has not been systematically assessed before in large well-characterised (population-based) cohorts.

To enable detailed assessment of the human hypothalamus in large cohorts, recently we developed a fully automatic, multi-modal parcellation procedure for accurate volumetric segmentation of the hypothalamus and its subregions on brain MRI.[27] Here, to address the aforementioned issues, we applied this automatic segmentation algorithm to the full brain imaging datasets of two independent large-scale population-based studies for cross-validation, i.e., the Rhineland Study and the UK Biobank Imaging Study. Specifically, we aimed to investigate the volumes of the human hypothalamus and its subregions in relation to age, sex, as well as detailed domain-specific measures of cognitive performance in the general population. Our findings indicate that the volumes of the hypothalamus and its subregions substantially vary with age, exhibit marked sex differences and are strongly related to both general and domain-specific cognitive function.

Methods

Study cohorts

The Rhineland Study (RS) is an ongoing population-based cohort study, recruiting inhabitants aged 30 years and above from two geographically defined areas in Bonn, Germany (www.rheinland-studie.de). The study's only exclusion criterion is an insufficient command of the German language required for providing informed consent. Participants are primarily Caucasians of European descent.[28] The study aims to contribute to the prevention, early detection and treatment of neurodegenerative and other age-related diseases. Participants undergo an ~8-h deep phenotyping assessment, including detailed brain imaging and standardised cognitive test batteries.

The UK Biobank Imaging Study (UKB) is part of the UK Biobank Study, an ongoing population-based cohort study collecting in-depth genetic and health information data on approximately half a million participants from across the United Kingdom. In 2014, the UK Biobank Study re-invited participants who had completed the baseline visit for an additional visit, involving detailed brain imaging and cognitive testing batteries. The selection of participation for this sub-study was based on protocols of the UK Biobank imaging enhancement.[29]

Our initial study population consisted of the first 8318 participants of the RS, and the 49,304 participants of the UKB who had completed the first imaging visit. We excluded 2180 individuals from the RS without brain imaging data. Subsequently, after visual quality control assessments, we excluded 326 individuals from the RS dataset and 4228 individuals from the UKB dataset due to insufficient image quality. This resulted in a final analytical sample size of 5812 (55.2 ± 13.6 years, age range: 30–95 years, 58% women) and 45,076 (64.2 ± 7.7 years, age range: 44–83 years, 53% women) participants from the RS (Supplementary Figure S1) and UKB cohorts (Supplementary Figure S2), respectively.

Imaging data

In RS, imaging data were obtained using two identical 3T MRI scanners equipped with 64-channel head-neck coils (MAGNETOM Prisma; Siemens Healthcare) at two examination facilities situated in Bonn, Germany.[30] Detailed information about the protocols and sequence parameters in RS are provided in Supplementary Table S1. MRI data in UKB were obtained from Siemens Skyra 3T scanners equipped with 32-channel head coils. Initially, a single scanner in Cheadle Manchester was dedicated to the UKB, followed by two further identical scanners in Newcastle and Reading.[31] The complete protocols and sequence parameters in UKB are available in the online documentation (biobank.ctsu.ox.ac.uk/crystal/crystal/docs/brain_mri.pdf).

We applied our automated deep learning-based method 'FastSurfer-HypVINN' for sub-segmentation of the hypothalamus on 0.8 mm isotropic T1- and T2-weighted images from RS, as well as 1.0 isotropic T1-weighted images from UKB. Importantly, we previously validated the performance of FastSurfer-HypVINN against ground-truth manual segmentations on MR images from both RS and UKB.[27] This pipeline segments the hypothalamus into six subregions on each side, including the anterior hypothalamus (AH), the medial hypothalamus (MH), the lateral hypothalamus (LH), the tuberal region (TBR), the posterior hypothalamus (PH), and the mammillary bodies (MMB).[27] Details about the neuroradiological definition of different hypothalamic structures are provided in Supplementary Table S2. Finally, total brain volume and estimated total intracranial volume (ETIV) for both datasets were

obtained using the FreeSurfer (version 6.0) standard processing pipeline.[32,33]

Demographic and cognitive data

Age and sex were based on self-reports. Level of education was assessed according to the International Standard Classification of Education 2011 (ISCED) (RS), or an educational attainment score based on the highest qualification level (UKB) as described previously.[34,35] In RS, four fluid cognitive domains were evaluated through multiple tests: working memory (Corsi Block-tapping Test and Digit Span Test), episodic memory (Auditory Verbal Learning and Memory Test (AVLT)), executive function (Word Fluency Task, Trail-Making Test B, and Anti-saccade Task), and processing speed (Trail-Making Test A and Pro-saccade Task).[36] Similarly, UKB employed seven tests for the assessment of the same cognitive domains: working memory (Numeric Memory Test), episodic memory (Paired Associate Learning Test and Pairs Matching Test), executive function (Trail-Making Test B), and processing speed (Trail-Making Test A, Reaction Time Test, Symbol Digit Substitution Test).[37] Detailed information regarding all cognitive tests included in the present study are provided in Supplementary Table S3. Given the relatively high proportion of missing cognitive measures in the UKB cohort, a comparison between participants with and without cognitive measures is provided in Supplementary Table S4. Missing cognitive data in the UKB primarily resulted from some tests being introduced later or limited to subsets of participants, with proportions of missingness ranging from 7% to 33% (more detailed information in this regard is provided in Supplementary Methods).

Cortisol levels

Cortisol levels were only available in a subset of participants (N = 1515) of the Rhineland Study (Supplementary Table S5). Cortisol concentrations were quantified in scalp hair samples through liquid chromatography tandem mass spectrometry using a steroid panel as described previously.[38] Scalp hair cortisol levels reflect the average amount of cortisol (in pg/mg) in the three months prior to the sampling date.

Menopausal status

Menopause status was only available in women (N = 2829) of the Rhineland Study, derived from self-reported information (Supplementary Table S6).

Ethics declarations

The protocol of Rhineland Study was approved by the ethics committee of the University of Bonn Medical Faculty (Ref: 338/15). The study is conducted according to the International Conference on Harmonization Good Clinical Practice standards (ICH-GCP), with written informed consent obtained in accordance with the Declaration of Helsinki. Approval for conducting UK biobank Study was received from the National Information Governance Board for Health and Social Care and the National Health Service North West Centre for Research Ethics Committee (Ref: 11/NW/0382). Every participant provided written informed consent.

Statistical analysis

Results are reported as mean ± standard deviation (SD) for continuous variables, and as counts and percentages for categorical variables, unless otherwise specified.

Age and sex

We used separate multivariable linear regression models to assess the association of each volumetric measure of the hypothalamus (dependent variable) with age and sex (independent variables). In these models, we included both a linear and a quadratic term for age (i.e., age and age^2) to assess potential nonlinear age effects, and an interaction term (i.e., age × sex) to evaluate potential age-by-sex interaction effects, while adjusting for ETIV to account for differences in head/brain size. All continuous variables were mean-centred to mitigate collinearity. In the event that the higher-order or interaction terms were not statistically significant, these terms were removed from the final models to obtain the most precise estimates for the main effects. For bilateral hypothalamic structures, we used the sum of the left and right sides as the outcome for conciseness, given that initial analyses per side did not reveal any lateralised effects (data not shown).

Cognition

Cognitive test scores with skewed distributions were log-transformed and, if applicable, inverted to ensure that higher values represented better cognitive performance. Subsequently, all cognitive test scores were Z-standardised to enable direct comparison of the effect sizes across multiple cognitive domains. To produce summary cognitive domain scores, we averaged the corresponding Z-scores of tests belonging to each cognitive domain (Supplementary Table S4). For producing an overall global cognition score, we averaged the Z-scores across all domains. As a sensitivity analysis, we also created an overall global cognition score using the first principal component of the Z-scores across all cognitive tests, which accounted for 34.7% (RS) and 34.8% (UKB) of the total variance in cognitive performance, as a summary measure (Supplementary Figure S3). Separate multivariable regression models were employed for each cognitive domain score (dependent variables) to evaluate their association with the volumes of different hypothalamic structures (independent variables), while adjusting for age, age^2, sex, education level, and ETIV. All effect sizes are reported as standardised effect sizes, i.e., indicating a change in SD of cognitive domain scores per SD change of volume. To illustrate and contextualise the magnitude of the effect sizes of the

associations between hypothalamic volumes and cognitive function, we compared them to those of the associations between age and cognitive function, using the fully adjusted models (i.e., cognitive measure ~ beta1 *volume + beta2*age + beta3*age2 + sex + education + ETIV; in which age was standardised to a mean zero and a standard deviation of one). We specifically compared 'beta1' to the sum of 'beta2 + beta3' (the latter can be interpreted as the age effect for an age one standard deviation higher than the sample mean age), to provide an intuitive illustration of the effect sizes for the associations between cognitive function and hypothalamic volumes.

Functional validation

For functional validation of the age effects on MH volume, we assessed the association between the volume of MH, which includes the corticotropin releasing factor-producing neurons of the PVN, and cortisol levels. To this end, we employed multivariable regression models with age, age^2, sex, MH volume (adjusted for ETIV) and its interaction with age as independent variables, and log-transformed cortisol levels (to account for the right skewed distribution of hair cortisol levels) as the dependent variable. To assess whether menopause status could partly account for the positive association between age and the volume of TBR, which contains gonadotropin-releasing hormone (GnRH) neurons, in women, we employed a multivariable regression model with menopausal status (i.e., pre- or postmenopausal), age, age^2, ETIV as independent variables, and TBR volume as dependent variable. In addition, as luteinizing hormone, a gonadotropin indicative of GnRH secretion, increases marked from 70 years onward in men,[39] we performed age-stratified analyses in men from both the RS and UKB cohorts, comparing those older and younger than 70 years (i.e., as proxies for high vs. low luteinizing hormone groups), while adjusting for ETIV.

All models were run in the two cohorts (i.e., RS and UKB) separately, including additional sensitivity analyses in which we excluded participants with known neurological diseases (including stroke, dementia, Parkinson disease, and multiple sclerosis). Following the traditional epidemiological definition, we defined confounders as those variables that are associated with the exposure as well as the outcome conditional upon the exposure, and are not in the causal path leading from the exposure to the outcome. Thus, we adjusted for sex and ETIV as covariates when focusing on the age effect, and age, age^2 and ETIV as covariates when focusing on the sex effect. Moreover, we adjusted for age, age^2, ETIV and education level when assessing the association between hypothalamic volumes and cognitive function. This approach aimed to minimize bias while avoiding overadjustment, ensuring model simplicity and interpretability. Statistical analyses were performed in R (base version 4.2.2). To assess the consistency of our findings, we compared all findings between the two cohort. To account for multiple comparisons, two-sided false discovery rate (FDR)-corrected P-values <0.05 were considered statistically significant.

Role of funders

The funders played no roles in the study design, data collection, data analysis, interpretation, or the writing of the manuscript.

Results

Demographics

The mean age of the study participants was 55.2 ± 13.6 years (58% women) in RS, and 64.2 years ± 7.7 (53% women) in UKB. Mean volumes of the total hypothalamus (TH) were 1124.2 ± 104.8 mm^3 in RS and 1102.1 ± 119.9 mm^3 in UKB (Table 1). On average, excluded participants were older, more often male, and had a lower education level compared to those included in the analytical sample (RS: Supplementary Table S7, UKB: Supplemental Table S8).

Age and sex effects on hypothalamic volumes

In both cohorts, the average volumes of TH, AH, PH and MMB were smaller in older individuals, while the average volumes of MH and TBR were larger in older individuals. Importantly, the association between hypothalamic volumes and age were curvilinear, indicating more pronounced volumetric differences with increasing age. The association between age and LH volume was weaker and inconsistent between the two datasets (Table 2 and Fig. 1).

Volumes of all seven hypothalamic structures were significantly larger in men compared to women in both RS and UKB, independent of ETIV. However, for volumes of four hypothalamic structures (TH, AH, PH, and MMB), we found that although younger men have larger hypothalamic volumes, the differences of these volumes between men and women were smaller in older individuals. In contrast, the sex difference in TBR volume was larger in older individuals (Table 2 and Fig. 1). To better illustrate the curvilinear age and age–sex interaction effects for most hypothalamic structures, we also performed stratified analyses (Supplementary Tables S9 and S10). A visual summary of the effects of age and sex on volumes of different hypothalamic structures is provided in Supplementary Figure S4.

Cognitive correlates

Larger total hypothalamus volumes were associated with better global cognition (β ± standard error (SE): 0.025 ± 0.017 [RS] and 0.026 ± 0.007 [UKB], both P < 0.013). Specifically in each subregion, larger PH volumes were associated with better global cognition (0.036 ± 0.014 [RS] and 0.028 ± 0.006 [UKB], both P < 0.001), and executive function (0.053 ± 0.021 [RS] and 0.039 ± 0.011 [UKB], both P < 0.001) (Fig. 2 and

	Rhineland study N = 5812	UK biobank imaging study N = 45,076	P-value
Age, years	55.2 (13.6)	64.2 (7.7)	<0.001[a]
Age range, years	30–95	44–83	
Sex			<0.001[a]
Women	3362 (58%)	23,950 (53%)	
Men	2450 (42%)	21,126 (47%)	
Education level[b]			<0.001[c]
High	3793 (66%)	21,811 (49%)	
Middle	1869 (32%)	19,935 (45%)	
Low	95 (1.7%)	2855 (6.4%)	
Neurological diseases[d]	113 (1.9%)	746 (1.7%)	<0.001[e]
ETIV, ml	1548.8 (147.8)	1466.7 (158.7)	<0.001[f]
TBV, ml	1103.6 (117.7)	1108.6 (107.5)	<0.001[g]
Volumes, mm^3			
Total Hypothalamus (TH)	1124.2 (104.8)	1102.1 (119.9)	<0.001[g]
Anterior Hypothalamus (AH)	272.3 (46.4)	221.0 (51.5)	<0.001[g]
Medial Hypothalamus (MH)	104.0 (26.0)	111.0 (29.8)	<0.001[g]
Tuberal Region (TBR)	43.3 (9.6)	44.7 (10.0)	0.57[g]
Lateral Hypothalamus (LH)	135.6 (21.3)	139.8 (25.4)	<0.001[g]
Posterior Hypothalamus (PH)	368.4 (45.3)	368.9 (57.3)	<0.001[g]
Mammillary Bodies (MMB)	209.5 (26.7)	216.7 (29.8)	<0.001[g]

Data are shown as mean (SD) or n (%) for continuous and categorical variables, respectively. Abbreviations: ETIV, estimated total intracranial volume; ISCED, International Standard Classification of Education; SD, standard deviation; TBV, total brain volume. [a]P-values were obtained from Welch's Two Sample t-test for continuous variables and from Pearson's Chi-squared test for categorical variables. [b]Education level in the Rhineland Study was defined as follows: High (ISCED-11 levels 6–8), Middle (ISCED-11 levels 3–5), and Low (ISCED-11 levels 0–2). In the UK Biobank Imaging Study, it was classified as: High (equal to or higher than college level, Middle (secondary education level), and Low (below secondary level). These two classifications are generally equivalent. [c]P-value was obtained from a cumulative link model while adjusting for age and sex. [d]Neurological diseases included stroke, Parkinson disease, dementia, and multiple sclerosis. [e]P-values were obtained from a logistic regression model while adjusting for age and sex. [f]P-values were obtained from multivariable linear regression model while adjusting for sex. [g]P-values were obtained from multivariable linear regression model while adjusting for age, age^2, sex and ETIV.

Table 1: **Characteristics of the analytical sample from the Rhineland Study and the UK Biobank Imaging Study.**

Supplementary Table S11). Larger MMB were associated with better episodic memory (0.046 ± 0.023 [RS] and 0.011 ± 0.008 [UKB], both P < 0.012), while larger AH volumes were related to better executive function (0.030 ± 0.018 [RS] and 0.026 ± 0.011 [UKB], both P < 0.006). Conversely, a larger TBR volume was associated with worse global cognition (–0.038 ± 0.014 [RS] and –0.011 ± 0.006 [UKB], both P < 0.002), executive function (–0.058 ± 0.020 [RS] and –0.020 ± 0.011 [UKB], both P < 0.006), as well as processing speed (–0.026 ± 0.020 [RS] and –0.020 ± 0.007 [UKB], both P < 0.03). Similarly, a larger MH volume was associated with worse executive function (–0.033 ± 0.018 [RS] and –0.029 ± 0.011 [UKB], both P < 0.003) (Fig. 2, Supplementary Table S11). The summary of subregion-specific cognitive correlates is provided in Fig. 3. Additionally, we observed significantly positive interactions between age and MMB volume for executive function in both cohorts, indicating that the executive function decrease with age is less pronounced in individuals with larger MMBs. The relative effect sizes for associations between cognition and most hypothalamic volumes were around 4–15% of the total age effects on cognition. Detailed information is provided in Supplementary Table S12.

Despite not reaching statistical significance in both datasets, most other associations of hypothalamic structural volumes and cognitive test scores were also directionally consistent between RS and UKB (Fig. 2). Except for LH, all hypothalamic structural volumes were significantly associated with global cognition, executive function and processing speed in UKB, which was also largely confirmed in RS. Conversely, volumes of TH, TBR, PH, and MMB were significantly associated with

	Cohort	Age effects	Age^2 effects	Sex effects	Age and sex interaction
Total Hypothalamus	RS	−1.04 (−1.21, −0.88)[a]	−0.074 (−0.082, −0.065)[a]	62.04 (57.69, 66.39)[a]	−1.06 (−1.32, −0.81)[a]
	UKB	−3.82 (−4.98, −3.66)[a]	−0.160 (−0.174, −0.147)[a]	71.45 (69.32, 73.57)[a]	−1.71 (−1.94, −1.48)[a]
Anterior Hypothalamus	RS	−1.20 (−1.30, −1.11)[a]	−0.025 (−0.029, −0.020)[a]	16.68 (14.14, 19.21)[a]	−0.31 (−0.46, −0.16)[a]
	UKB	−1.94 (−2.02, −1.86)[a]	−0.055 (−0.062, −0.048)[a]	18.79 (17.71, 19.86)[a]	−0.25 (−0.37, −0.14)[a]
Tuberal region	RS	0.33 (0.31, 0.35)[a]	0.003 (0.002, 0.004)[a]	3.53 (3.04, 4.02)[a]	0.03 (0.00, 0.06)[a]
	UKB	0.21 (0.19, 0.22)[a]	0.001 (−0.001, 0.002)	4.06 (3.86, 4.26)[a]	0.06 (0.04, 0.09)[a]
Medial Hypothalamus	RS	0.65 (0.61, 0.69)[a]	0.011 (0.008, 0.014)[a]	6.33 (4.88, 7.79)[a]	0.01 (−0.07, 0.10)
	UKB	0.68 (0.64, 0.71)[a]	0.019 (0.015, 0.023)[a]	4.98 (4.37, 5.58)[a]	0.02 (−0.05, 0.08)
Lateral Hypothalamus	RS	0.12 (0.08, 0.15)[a]	0.000 (−0.002, 0.002)	4.34 (3.11, 5.57)[a]	−0.04 (−0.12, 0.03)
	UKB	−0.14 (−0.18, −0.10)[a]	−0.012 (−0.015, −0.008)[a]	5.80 (5.28, 6.32)[a]	−0.20 (−0.25, −0.14)[a]
Posterior Hypothalamus	RS	−0.80 (−0.89, −0.72)[a]	−0.047 (−0.051, −0.042)[a]	22.12 (19.90, 24.33)[a]	−0.59 (−0.72, −0.46)[a]
	UKB	−2.13 (−2.21, −2.05)[a]	−0.085 (−0.092, −0.077)[a]	27.25 (26.13, 28.37)[a]	−0.97 (−1.09, −0.85)[a]
Mammillary bodies	RS	−0.14 (−0.20, −0.09)[a]	−0.016 (−0.019, −0.014)[a]	9.03 (7.57, 10.49)[a]	−0.16 (−0.24, −0.07)[a]
	UKB	−0.49 (−0.53, −0.44)[a]	−0.029 (−0.033, −0.025)[a]	10.58 (9.97, 11.18)[a]	−0.37 (−0.43, −0.30)[a]

All results were obtained from the following model: volume ~ age + age^2 + sex + age × sex + estimated total intracranial volume. Findings are reported as unstandardised effect estimates (95% confidence intervals). Volumes of hypothalamic structures are indicated in cubic millimeters (mm^3). Age is indicated in years, and women constitute the reference group. RS, Rhineland Study; UKB, UK Biobank Imaging Study. The numbers of participants 5812 in RS and 45,076 in UKB. [a]These associations were statistically significant (false discovery rate-corrected P-value <0.05).

Table 2: **Age and sex effects on volumes of hypothalamic structures.**

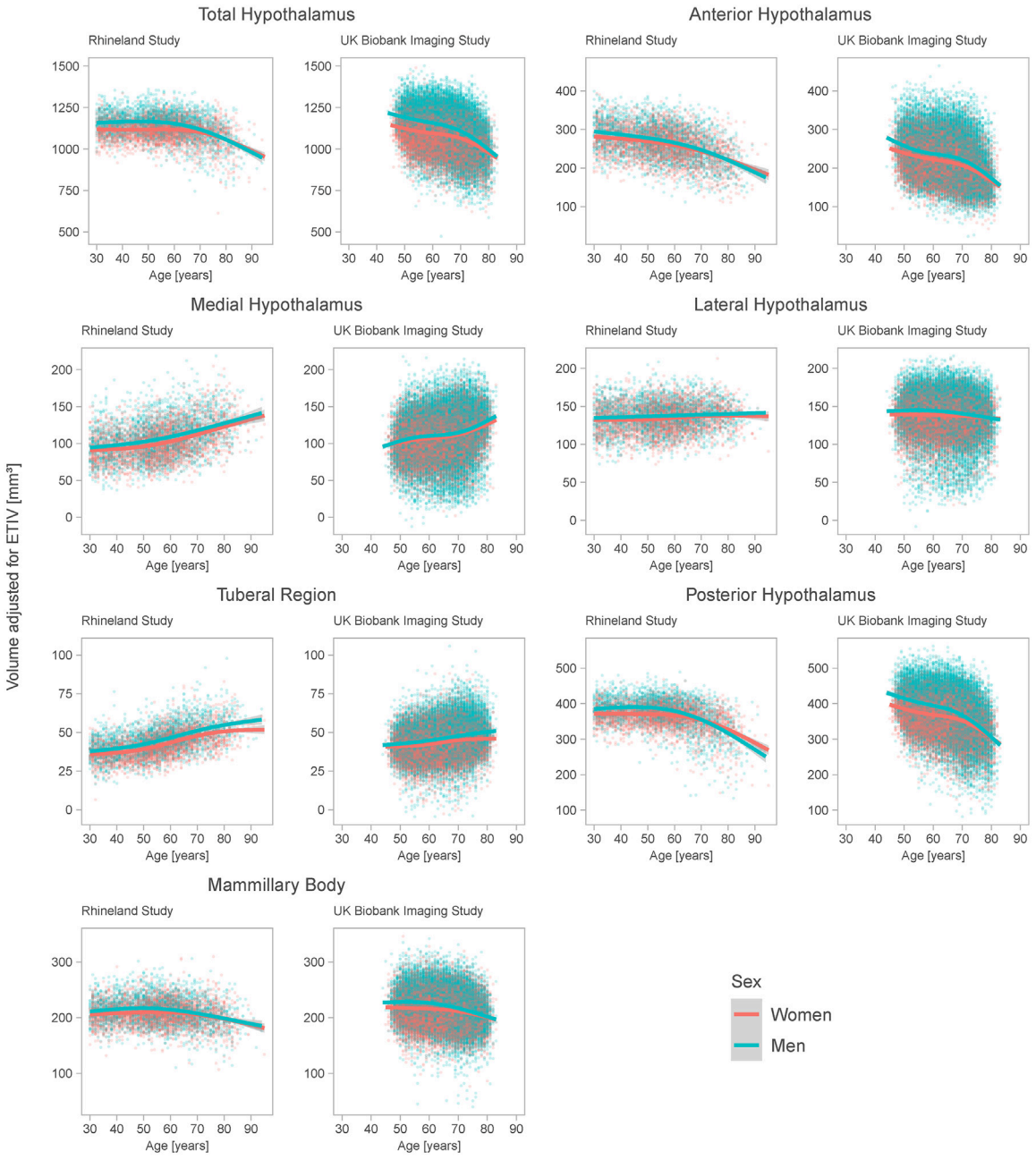

Fig. 1: **The associations of age and sex with volumes of hypothalamic structures in the Rhineland Study and the UK Biobank Imaging Study cohorts.** Volumes of hypothalamic structures in cubic millimeters (mm^3) were adjusted for estimated total intracranial volume. Plots on the left side indicate results from the Rhineland Study (N = 5812), while those on the right side indicate results from the UK Biobank Imaging Study (N = 45,076). Each point represents one participant coloured by sex (red for women and green for men). Overlapping points have a darker colour. The trend curves are based on spline regression with four degrees of freedom.

episodic memory in RS, with only the relationship with MMB also reaching statistical significance in UKB. For UKB, participants without missing data on cognitive domain score were younger and had a lower education level compared to those with non-missing data (Supplementary Table S4).

Cortisol and MH volume

Participants included in this analysis were younger and more often women compared to those excluded (Supplementary Table S5). There was an age-dependent association between MH volume and hair cortisol levels ($P \approx 0.020$ for MH volume × age

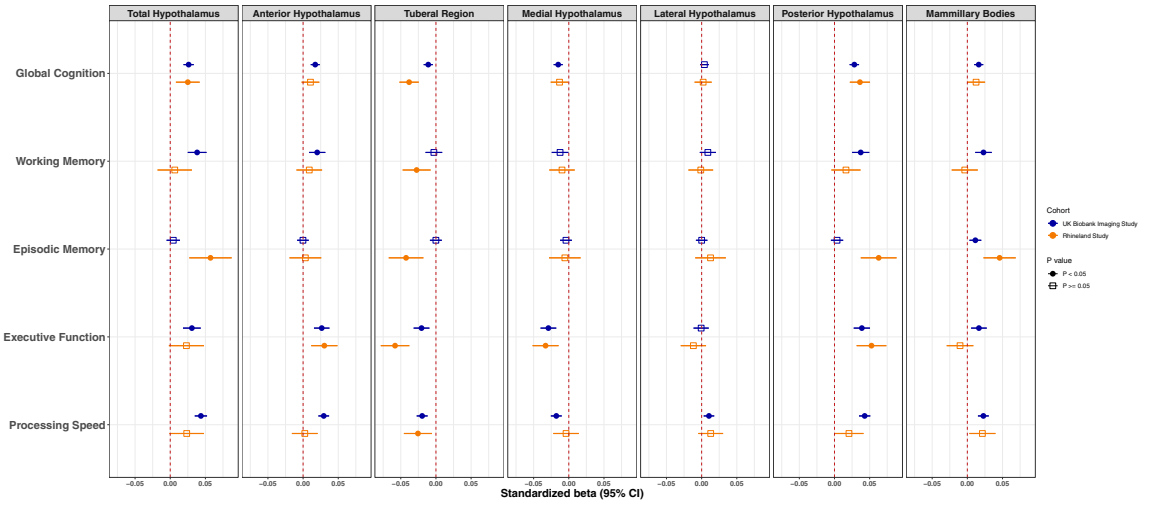

***Fig. 2:* Standardised associations of volumes of hypothalamic structures with domain-specific cognitive performance in the Rhineland Study and the UK Biobank Imaging Study.** The effect estimates were adjusted for age, age^2, sex, education level and estimated total intracranial volume. The solid circles represent the statistically significant point estimates (i.e., false discovery rate-corrected P-value <0.05), while the open squares represent the statistically non-significant ones. The number of participants for each cognitive domain were as follows (Rhineland Study; UK Biobank Imaging Study): global cognition (5708; 29,600), working memory (5732; 31,444), episodic memory (5748; 31,151), executive function (5728; 30,023), and processing speed (5743; 30,549).

interaction effect). Age stratified analysis, based on tertiles of the age distribution, revealed that although the association between MH volume and hair cortisol levels was not significant in the younger age groups (i.e., 30–48 years and 49–61 years), larger MH volumes were related to increased cortisol levels in the oldest age group (i.e., 62–95 years; 0.053 ± 0.021, P ≈ 0.011). This effect size amounts to about

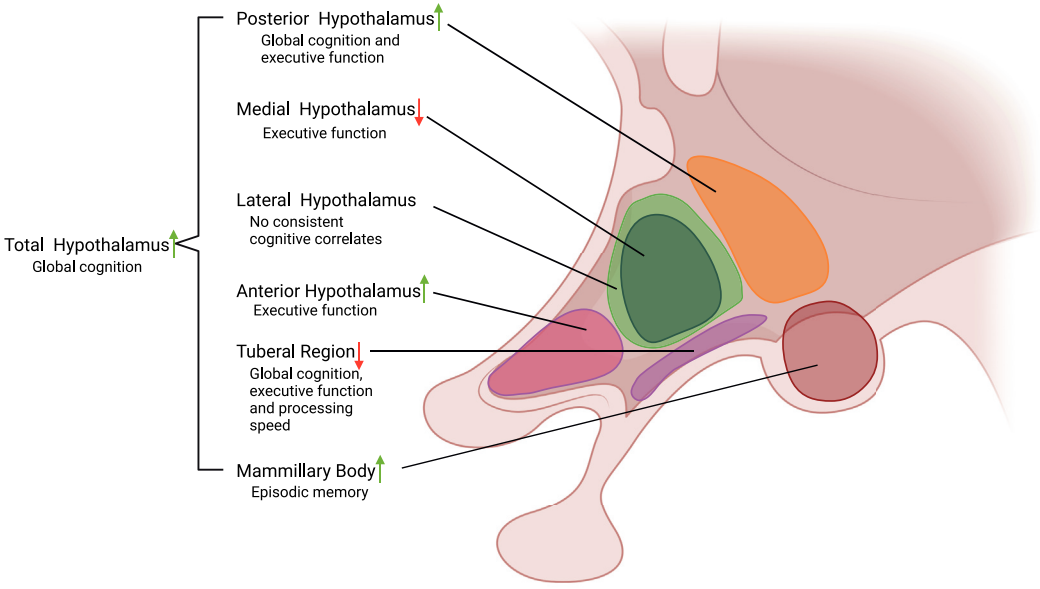

***Fig. 3:* Hypothalamic structures and their cognitive correlates.** The schematic figure shows the hypothalamus in a sagittal view, depicting the medial hypothalamus superimposed on the lateral part. All the statistically significant associations (i.e., false discovery rate-corrected P-value <0.05 in both cohorts) between volumes of different hypothalamic structures and cognitive domain scores are shown. The green upward arrows indicate that larger volumes were associated with better cognitive performance, whereas the red downward arrows indicate that larger volumes were related to worse cognitive performance. The figure was created with BioRender.

13% ± 5% increase in cortisol levels per SD increase of MH volume (Fig. 4).

Functional validation for age effects on TBR volume

Participants included in this analysis were on average younger (Supplementary Table S6). TBR volume was significantly larger in postmenopausal compared to premenopausal women (1.72 ± 0.52 mm^3, $P \approx 0.001$). Moreover, TBR volume was significantly larger in men older than 70 years compared to those 70 years and younger in both cohorts (9.64 ± 0.51 mm^3 [RS] and 3.65 ± 0.15 mm^3 [UKB], both $P < 0.001$).

Sensitivity analysis

The associations of hypothalamic volumes and global cognitive function largely remained similar when the first principal component was used as a summary measure of overall cognitive function (Supplementary Figure S5). Similarly, exclusion of participants with known neurological diseases did not materially change the magnitude or the statistical significance of any of our findings (data not shown). Additionally, inclusion of UKB scanner site as a covariate in the models for the UKB dataset did not materially affect the results (Supplementary Figure S6). Based on these results and considering that the MRI scanners at both RS sites were identical in terms of hardware, parameter settings, and scanning protocols, we did not adjust for scanner sites in the analysis of RS data. This approach is consistent with previous publications using RS MRI data.[40,41]

Discussion

We present the combined findings of two large-scale population-based studies of the effects of age and sex on the volumes of the hypothalamus and its subregions, as well as the association of these hypothalamic structures with cognitive performance in the general population. We found strong region-specific age effects on the volumes of different hypothalamic structures. Although the volumes of most hypothalamic structures were smaller in older individuals, volumes of the medial and tuberal regions of the hypothalamus were significantly larger, a finding that we could directly functionally corroborate using hair cortisol levels in a subset of the participants. Similarly, the volumes of all hypothalamic structures exhibited substantial sex differences, even after accounting for differences in head size. Moreover, we discovered robust associations between the volumes of different hypothalamic subregions and domain-specific cognitive function. Importantly, our findings could readily be cross-validated between the two independent large-scale population-based cohorts, and were for the most part highly consistent between them.

In line with previous small-scale studies,[8,13] we found that the volumes of the hypothalamus and most of its subregions were smaller in older individuals. Another study reported higher mean diffusivity in the hypothalamus with older age, indicating structural degradation and neurodegeneration, which is also consistent with our findings.[42,43] However, unlike previous studies,[44]

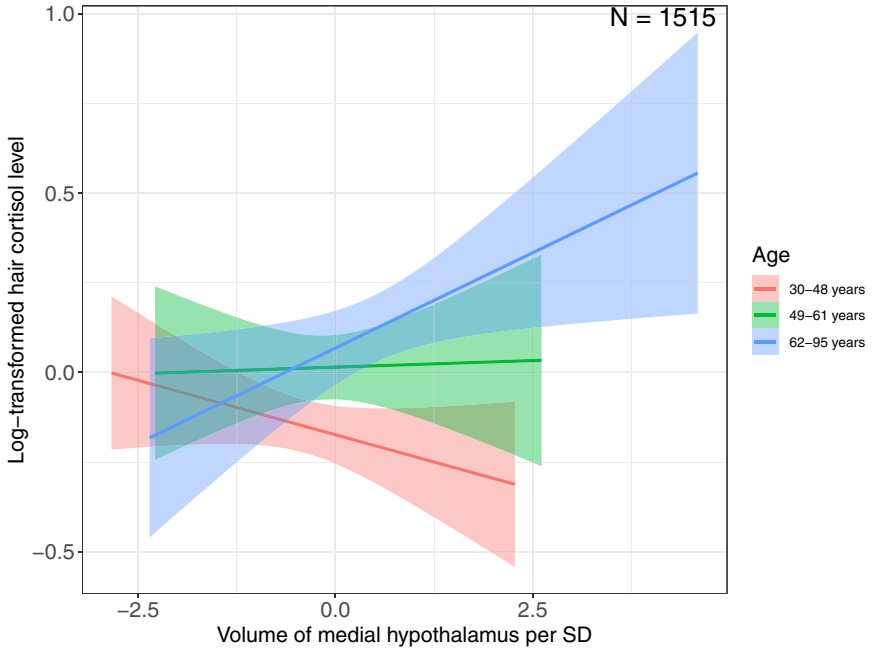

Fig. 4: **Association between volume of medial hypothalamus and hair cortisol levels stratified by age.** Lines represent the linear association between the volume of medial hypothalamus (adjusted for ETIV) and log-transformed hair cortisol levels for each tertile of age. The shaded areas represent the accompanying 95% confidence intervals of the mean. The number of participants in this analysis was 1515.

which largely focused on the volume of the entire hypothalamus, our region-specific analyses revealed that the volumes of two hypothalamic regions, i.e., MH and TBR were larger in older individuals. This finding could indicate potential resilience of specific hypothalamic regions to age-related neurodegeneration and brain atrophy. Indeed, previous neuropathological experiments found relatively stable neuronal counts and neuronal hypertrophy in the PVN of the hypothalamus, which is included in the MH region of our parcellations scheme, during both aging and neurodegenerative diseases.[45,46] Similarly, the volume of the arcuate nucleus, the rodent homologue of the human infundibular nucleus and the main part of the tuberal region, remained stable during aging in rats,[47] which also supports our findings. Alternatively, the observation that the number of microglial cells in the mediobasal hypothalamus is greater in mice suggests that pseudohypertrophy due to inflammation may also play a role.[48] Given that the corticotropin releasing factor-producing neurons of the PVN constitute the origin of the hypothalamic-pituitary-adrenal axis, through which secretion of the stress hormone cortisol is centrally regulated, we assessed whether MH volume was related to hair cortisol levels. Importantly, we found an age-dependent relationship between MH volume and hair cortisol levels, indicating a stronger association between MH volume and cortisol levels with advancing age. This result parallels reports of age-associated increases in cortisol secretion,[49] and provides direct functional validation for our observation of larger MH volume with age. Interestingly, hyperactivation of the hypothalamic-pituitary-adrenal axis has indeed been implicated in the pathogenesis of common age-associated neurodegenerative diseases like Alzheimer and Parkinson disease.[24] Similarly, prior studies discovered neuronal hypertrophy in the infundibular nucleus in older women compared to younger women,[50] and in older men compared to younger men.[51] These findings are likely due to the hypertrophy of GnRH neurons, which are located in TBR, potentially triggered by reduced negative feedback from sex hormones in older age. To corroborate this hypothesis, we evaluated differences in TBR volumes between pre- and postmenopausal women, as well as between men >70 vs. ≤70 years of age. We found significantly larger TBR volumes in postmenopausal women and older men, suggesting that age-related increases in gonadotropins may account for the larger TBR volume in older individuals. Together, these findings thus indicate that specific hypothalamic regions may possess resilience against age-associated neurodegeneration, and might even contribute to neuropathology elsewhere in the brain.

Our findings parallel those from previous small-scale studies indicating a relatively larger volume of the hypothalamus in men compared to women, even after adjusting for ETIV.[14] In addition, we extend previous findings by showing that these relative volumetric sex differences are not static, but exhibit substantial region-specific temporal dynamics across age. Indeed, for most hypothalamic regions the relative sex differences in volumetric measures diminished with advancing age, with the notable exception of TBR for which the volumetric sex difference increased with age. Interestingly, neuropathological experiments have found region-specific sexually dimorphic changes in both the size and number of different neuronal subpopulations of the hypothalamus, notably the supraoptic nucleus and the PVN.[52] These sexually dimorphic changes may be attributed to age-related changes in sex hormone levels, spanning the entire period from the intrauterine to postnatal phase, adulthood, and old age. Various hypothalamic nuclei are closely involved in the regulation of the stress response, dysregulation of which has been postulated to put women at an increased risk of both mood disorders and neurodegenerative diseases, especially Alzheimer disease.[53] Therefore, further studies aimed at delineating the sexually dimorphic role of the hypothalamus and its subregions could be instrumental in the elucidation of the neurobiological basis of sex differences in risk factors and causes of a range of (neuropsychiatric) disorders.

We discovered robust associations between the volumes of different hypothalamic subregions and domain-specific cognitive performance. Larger PH volume was consistently associated with better global cognition and executive function in both RS and UKB cohorts. Previous studies demonstrated the posterior hypothalamic area to be critical for synchronizing the theta rhythm,[54] which could enhance cognitive performance.[55] Moreover, this region harbors the supramammillary nucleus, which could modulate memory function through its extensive connections to the hippocampus.[2] We also found a strong relationship between MMB volume and episodic memory, which provides a more specific extension of previous studies that only examined general memory,[20,21,56] and highlights the role of the fornix-mammillary body circuit in regulating episodic memory function.[57] Similarly, a larger AH volume was related to better executive function, possibly due to the localization of the suprachiasmatic and the ventral preoptic nucleus within this region. These nuclei are crucial for the regulation of circadian rhythm and sleep,[58] which are strongly associated with better executive function.[59] Apart from their association with age, larger volumes of the MH and TBR regions were also related to worse age-adjusted cognitive function, including executive function and processing speed. Although the precise underlying mechanisms remain to be elucidated, hyperactivation of the hypothalamic-pituitary-adrenal axis may play an important role in mediating this association as high cortisol levels have been associated with an increased risk of (age-associated) cognitive decline and neurodegenerative diseases.[24,25] Moreover,

chemogenetic activation of Agrp neurons in the arcuate nucleus of mice reduced their cognitive performance, which also points towards an alternative pathway through which increased TBR volume could be linked to worse cognitive performance.[26] While the effect sizes observed for the associations of hypothalamic volumes and cognitive performance may appear small, the magnitude of these associations is consistent with those of other key brain structures involved in cognitive function such as the hippocampus.[60] These findings suggest that even small changes in hypothalamic subregions may have a clinically relevant impact on cognitive function. Additionally, these effect sizes were approximately 4–15% of the total age effects on cognitive performance, which is considerable. Given the highly complex architecture of the human hypothalamus and the lack of studies assessing its role in relation to cognition, more mechanistic experiments are warranted to elucidate the underlying neurobiological pathways that could account for the region-specific associations between different hypothalamic structures and performance on various cognitive domains.

Our study has both strengths and limitations. First, although most of our results were highly consistent between the RS and UKB cohorts, there were also some exceptions. In the RS cohort, we found more significant associations between hypothalamic volumes and episodic memory, which may be due to the tests used in RS (AVLT immediate and delayed recall), which are more comprehensive compared to those employed by UKB (paired associated learning and pairs matching). Conversely, more significant volumetric associations with processing speed were observed in UKB, potentially due to the more comprehensive set of test batteries employed for the assessment of this particular cognitive domain (including the Trail-Making Test A, Reaction Time Test, and Symbol Digit Substitution Test). Second, the findings involving the LH region were inconsistent. This could be due to technical challenges in accurately delineating the lateral boundaries of the hypothalamus, which are formed by diffuse white matter tracts, on MR images. This may have been further exacerbated by differing spatial imaging resolutions in the two cohorts.[27] Third, different cognitive tests were used in the two cohorts. To address this issue, we defined cognitive domain scores based on the nature of the tests employed. Importantly, except for the LH region, all our statistically significant results were directionally consistent between the two cohorts, supporting the robustness and generalizability of the findings. Fourth, participants with missing imaging data were excluded from the analyses, which may have resulted in selection bias. However, given that the included participants were generally younger and had a more favourable health profile, if anything, our findings are likely to have underestimated the magnitude of the true associations. Fifth, accumulating evidence indicates that obesity is associated with both hypothalamic microstructure and faster neurocognitive aging.[61–64] Direct assessment of the role of obesity as a potential modifier of the association between hypothalamic volume and cognitive function was beyond of the current paper, but will be explored in a future project. Lastly, due to the cross-sectional nature of our study, we could not assess the temporal dynamics between volumetric changes in hypothalamic structures and cognitive performance, which should be the focus of future longitudinal studies.

In conclusion, we found strong age and sex effects on volumes of different hypothalamic structures, as well as robust and region-specific associations between the volumes of these structures and performance on various cognitive domains. Thus, our findings implicate specific hypothalamic subregions as novel potential therapeutic targets against age-associated cognitive decline.

Contributors

PX, MMBB, and NAA conceptualised the project. The first draft of the manuscript was written by PX and NAA. Data were analysed by PX, SE, RE, DL, WZ, DF, and NAA. SE, MS, MR, and MMBB provided technical, statistical and methodological advice. PX, SE, RE, MS, MMBB and NAA accessed and verified the underlying data. All authors provided critical feedback and contributed to the writing and revision of the final version of the manuscript. All authors have read and approved the final version of the manuscript and confirm its accuracy and integrity.

Data sharing statement

The Rhineland Study's dataset is not publicly available because of data protection regulations. Access to data can be provided to scientists in accordance with the Rhineland Study's Data Use and Access Policy. Requests for further information or to access the Rhineland Study's dataset should be directed to rs-duac@dzne.de. All individual level data from the UK Biobank Imaging Study used in the current manuscript are available through the UK Biobank Resource (https://www.ukbiobank.ac.uk). This research has been conducted using the UK Biobank Resource under Application Number 82056.

Declaration of interests

MMBB reports the following declarations of interests: Co-PI of the project: Cluster of Excellence, "ImmunoSensation2—the immune sensory system" from German Research Funding Foundation (DFG); Grant number: EXC 2151–390873048. Co-PI of the project: Collaborative Research Center 1454 "Metaflammation & Cellular Programming", German Research Funding Foundation (DFG); Grant number: 43232535. Co-PI of the project: Competence Cluster in Nutrition Research, "Diet—Body—Brain (DietBB2)", German Ministry for Science and Education (BMBF); Grant number: 01EA1809C. PI of the project: "PreBeDem–Mit Prävention und Behandlung gegen Demenz", German Ministry for Science and Education (BMBF); Grant number: 01KX2230. Collaborator of the project: "Perceived Stress, inflammation, and the risk of neurodegeneration", Alzheimer Forschung Initiative (AFI); Grant number: #22017. Member of the Scientific Advisory Board, Central Institute of Mental Health, Mannheim, Germany. Member of the Advisory Board, Leibniz Institute on Aging–Fritz Lipmann Institute. Member of the Executive Board of the Cluster of Excellence ImmunoSensation2. NAA reports the following declarations of interests: European Research Council Grant (Number: 101041677) from the European Union. Profilbildung Grant for the project "InVirtuo 4.0" from Ministry of Culture and Science of the State of North Rhine-Westphalia, Germany. Chair of the Scientific and Bioethics Advisory Committee (2022–2024) and Executive Committee member (2024-present) of the European Huntington's Disease Network. Advisory Board member of the International Society for Neurodegenerative Diseases. Other co-authors report no relevant declarations of interests for this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105513.

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