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Consistently lower volumes across thalamus nuclei in very premature-born adults

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ABSTRACT

Lasting thalamus volume reduction after preterm birth is a prominent finding. However, whether thalamic nuclei volumes are affected differentially by preterm birth and whether nuclei aberrations are relevant for cognitive functioning remains unknown.

Using T1-weighted MR-images of 83 adults born very preterm (≤ 32 weeks' gestation; VP) and/or with very low body weight (≤ 1,500 g; VLBW) as well as of 92 full-term born (≥ 37 weeks' gestation) controls, we compared thalamic nuclei volumes of six subregions (anterior, lateral, ventral, intralaminar, medial, and pulvinar) across groups at the age of 26 years. To characterize the functional relevance of volume aberrations, cognitive performance was assessed by full-scale intelligence quotient using the Wechsler Adult Intelligence Scale and linked to volume reductions using multiple linear regression analyses.

Thalamic volumes were significantly lower across all examined nuclei in VP/VLBW adults compared to controls, suggesting an overall rather than focal impairment. Lower nuclei volumes were linked to higher intensity of neonatal treatment, indicating vulnerability to stress exposure after birth. Furthermore, we found that single results for lateral, medial, and pulvinar nuclei volumes were associated with full-scale intelligence quotient in preterm adults, albeit not surviving correction for multiple hypotheses testing.

These findings provide evidence that lower thalamic volume in preterm adults is observable across all subregions rather than focused on single nuclei. Data suggest the same mechanisms of aberrant thalamus development across all nuclei after premature birth.

1. Introduction

With a worldwide prevalence of about 11 % (Chawanpaiboon et al., 2019), preterm birth (i.e., birth before 37 weeks of gestation) is of considerable public health importance (Volpe, 2009a). Among other risks, such as increased mortality at birth, preterm birth entails a substantially increased risk for impaired neuro-cognitive development, including altered brain development (Breeman et al., 2015; Eryigit

Abbreviations: ANCOVA, Analysis of Covariance; BW, birth weight; eTIV, estimated total intracranial volume; FDR, False Discovery Rate; FT, full-term (≤ 37 weeks of gestation); GA, gestational age; INTI, intensity of neonatal treatment; IQ, intelligence quotient; VP, very preterm (≤ 32 weeks of gestation); VLBW, very low birth weight (≤ 1,500g).

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Madzwamuse et al., 2015; Nosarti et al., 2012; Volpe, 2009a; Wolke et al., 2019). For example, full-scale intelligence quotient (IQ) of adults born very preterm (≤ 32 weeks of gestation; VP) and/or with very low birth weight (≤ 1500 g; VLBW) was on average 12 IQ points lower compared to controls born full-term (Eves et al., 2021). Furthermore, aberrant neuro-cognitive development has been found to be mediated by the disrupted development of various brain processes at both the macroscopic and microscopic levels. On a microscopic level, prematurity-associated hypoxia-ischemia, hemorrhage, and inflammation affect the maturation of rapidly developing and therefore vulnerable cell populations, such as pre-oligodendrocytes and subplate neurons (Back et al., 2002; McClendon et al., 2017; Salmaso et al., 2014; Volpe, 2009a). On a macroscopic level, this manifests in widespread gray and white matter abnormalities, such as altered cortical architecture, impaired white matter integrity and connectivity, as well as lower cortical and subcortical volumes (Hedderich et al., 2020; D.M. 2021; Inder et al., 2023; Kelly et al., 2023; Menegaux et al., 2021; Molnár et al., 2019; Ruzok et al., 2022; Schmitz-Koep, Haller, et al., 2021, 2023, 2023; Schmitz-Koep, Zimmermann, et al., 2021; Volpe, 2019).

Among the various changes following preterm birth, deviated thalamocortical development is considered an important driver of neurodevelopmental disturbances after prematurity for two reasons (Wisnowski et al., 2015). First, the thalamus, consisting of several functionally different nuclei, is in its crucial developmental phase at the time of preterm birth. Its whole volume triples between 27 and 37 weeks of gestation (Makropoulos et al., 2016) and during this time, important thalamocortical connections are formed via the guidance of subplate neurons (Kostović et al., 2014; Kostović and Jovanov-Milošević, 2006; Kostović and Judaš, 2010; Volpe, 2009a). Second, thalamic nuclei are essential hubs for cortical networks relevant to multiple processes shown to be impaired after premature birth (Hwang et al., 2017). Indeed, thalamocortical connectivity as well as whole thalamus volume have been reported to be altered in preterm neonates (Ball et al., 2012, 2013), and children (Wisnowski et al., 2015; Zubiaurre-Elorza et al., 2012), but also in adolescents (Bjuland et al., 2014; Nosarti et al., 2014) and adults (Berndt et al., 2019; Menegaux et al., 2021; Meng et al., 2016; Pascoe et al., 2019).

While previous studies have shed light on the impact of preterm birth on the entire thalamus, it is unknown whether lower thalamic volume in preterm adults is driven by a selective effect on a few structures or a global impairment across all nuclei. Recent methodological advances in neuroimaging allow the reliable distinction of the structurally and functionally diverse nuclei of the thalamus on T1-weighted images (Iglesias et al., 2018), thus enabling us to address this question. As the pathological mechanisms of prematurity are widespread and involve multiple cortico-thalamic systems, we hypothesized that this pattern is reflected in a volume reduction in many thalamic nuclei rather than a focal impairment of a few. Furthermore, the thalamus, particularly the medial and pulvinar nuclei, is known to moderate cortical functions (Halassa, 2022; Hwang et al., 2022; Pergola et al., 2018; Sherman, 2016). Therefore, we hypothesized that lower volume of the medial and pulvinar nuclei might be linked to lower cognitive performance in VP/VLBW adults. To address these hypotheses, we determined thalamic nuclei volumes in 83 adults born very preterm or with very low body weight and in 92 age- and sex-matched full-term controls at 26 years of age and linked them with full-scale IQ by multiple regression analysis.

2. Methods and materials

2.1. Participants

The Bavarian Longitudinal Study (BLS) is a geographically defined, whole-population sample of neonatal at-risk children and healthy full-term (FT) controls. Subjects were followed from birth, between January 1985 and March 1986, into adulthood (Eryigit Madzwamuse et al., 2015; Wolke and Meyer, 1999). 682 infants were born very preterm (< 32 weeks of gestation; VP) and/or with very low birth weight (birth weight < 1500 g; VLBW). Informed written consent from a parent and/or legal guardian was obtained. Initially, 916 FT born infants born at the same obstetric hospitals and alive at the age of 6 were recruited. 350 of them were randomly selected as control subjects within the stratification variables of sex and family socioeconomic status to be comparable with the VP/VLBW sample. Of these, 411 VP/VLBW individuals and 308 controls were eligible for the 26-year follow-up assessment. 260 VP/VLBW subjects and 229 full-term controls participated in psychological assessments (Breeman et al., 2015). All subjects were screened for MR-related exclusion criteria, including (self--reported): claustrophobia, inability to lie still for > 30 min, unstable medical conditions (e.g., severe asthma), epilepsy, tinnitus, pregnancy, non-removable MRI-incompatible metal implants, and a history of severe CNS trauma or disease that would impair further analysis of the data. However, the most frequent reason not to perform the MRI exam was that subjects declined to participate.

Our study sample, derived from the BLS, has been previously described in detail (Hedderich et al., 2019; Menegaux et al., 2021; Schmitz-Koep, Menegaux, Gaser, et al., 2023). 101 subjects born VP/VLBW and 111 full-term (FT) controls underwent MRI at 26 years of age (see Table 1). MRI examinations took place at two sites: the Department of Neuroradiology, Klinikum rechts der Isar, Technical University of Munich (N = 144), and the Department of Radiology, University Hospital of Bonn (N = 68). The study was carried out in accordance with the Declaration of Helsinki and approved by the local ethics committees of the Klinikum rechts der Isar, Technical University of Munich, and the University Hospital of Bonn. All participants gave written informed consent. They received travel expenses and a small payment for participation. In the following, a participant's sex refers to a binary classification (male/female) assigned at birth based on external anatomy.

To preview the results of both the MRI data and especially the segmentation quality control of the thalamic nuclei, several subjects had to be excluded (see next sections for detailed reasons), so that 83 VP/VLBW and 92 FT subjects could be included in the analyses.

2.2. Birth-related variables

Gestational age (GA) in weeks was deduced from maternal reports on the first day of the last menstrual period and serial ultrasounds during pregnancy. In cases that differed by two or more weeks, clinical assessment at birth following the Dubowitz method was applied (Dubowitz et al., 1970). Birth weight (BW) in grams and intensity of neonatal treatment (INTI), quantifying duration and intensity of medical intensive care treatment after birth, were acquired from obstetric records (Gutbrod, 2000; Wolke and Meyer, 1999). INTI was derived from daily assessments of care level, respiratory support, feeding dependency, and neurological status (including mobility, muscle tone, and neurological excitability). Each of the six variables was scored on a 4-point rating scale (0–3) by the method of Casaer and Eggermont (Casaer and Eggermont, 1985). Subsequently, INTI was computed as the mean score of daily ratings during the first ten days of life or until a stable clinical state was reached (total daily scores; 3 for three consecutive days), depending on which occurred first, ranging from 0 (best state) to 18 (worst state).

2.3. Behavioral variables

To assess global cognitive performance at the age of 26, before and independent of the MRI examination, study participants were asked to complete a short version of the "Wechsler Intelligenztest für Erwachsene", the German adaptation of the Wechsler Adult Intelligence Scale, third edition (von Aster et al., 2006). This test was administered by trained psychologists who were unfamiliar with group membership. Results were used to derive full-scale IQ estimates (Breeman et al., 2015;

Table 1
Demographical, clinical, and cognitive data. Data are listed for the final data sample after exclusion due to quality control.

	VP/VLBW ($n = 83$)			FT ($n = 92$)			*p*-value
	Mean/*n*	**SD**	**Range**	**Mean/*n***	**SD**	**Range**	
Sex assigned at birth (m/f)	43/40			53/39			0.537
Age (years)	26.7	±0.64	25.7–28.3	26.8	±0.77	25.5–28.9	0.431
GA (weeks)	30.4	±2.17	25–36	39.7	±1.01	37–41	**<0.001*****
BW (g)	1321	±319.0	730–2070	3399.3	±437.2	2120–4670	**<0.001*****
Harmonized eTIV (mm^3)	$1.56e^6$	$\pm0.15e^6$	$1.23e^6$–$1.86e^6$	$1.65e^6$	$\pm0.16e^6$	$1.29e^6$–$2.08e^6$	**<0.001*****
INTI (days)	11.8	±3.61	3.4–17.6	n.a.	n.a.	n.a.	n.a.
Full-Scale IQ[a]	98.15	±12.15	70–137	106.3	±13.7	77–143	**<0.001*****

Note: INTI is not applicable for healthy controls because there was no treatment in the neonatal intensive care unit after birth. Statistical comparisons: sex with χ^2 statistics; age, GA, BW, full-scale IQ with two-sample *t*-tests. Bold letters indicate statistical significance defined as $p < 0.05$. Asterisks indicate statistical significance defined as $p < 0.001$ (***).
Abbreviations: BW, birth weight; f, female; FT, full-term; GA, gestational age; INTI, Intensity of Neonatal Treatment; IQ, intelligence quotient; m, male; n.a., not applicable; SD, standard deviation; eTIV, estimated total intracranial volume; VP/VLBW, very preterm and/or very low birth weight.

Eryigit Madzwamuse et al., 2015).

2.4. MRI data acquisition

At both sites, Munich and Bonn, MRI data acquisition was performed on Philips Achieva 3 T TX systems or Philips Ingenia 3 T systems using an 8-channel SENSE head coil. Subject distribution among scanners was as follows: Bonn Achieva 3 T: 5 VP/VLBW, 12 FT, Bonn Ingenia 3 T: 33 VP/VLBW, 17 FT, Munich Achieva 3 T: 59 VP/VLBW, 65 FT, Munich Ingenia 3 T: 3 VP/VLBW, 17 FT. Across all scanners, sequence parameters were kept identical. Scanners were checked regularly to provide optimal scanning conditions, and MRI physicists at the University Hospital Bonn and Klinikum rechts der Isar regularly scanned imaging phantoms to ensure within-scanner signal stability over time. A high-resolution T1w 3D-MPRAGE sequence (TI= 1300 ms, TR= 7.7 ms, TE= 3.9 ms, flip angle= 15°, field of view= 256 mm × 256 mm, reconstruction matrix= 256 × 256, reconstructed isotropic voxel size= 1 mm^3) was acquired. All images were visually inspected for artifacts.

2.5. MRI data processing

Cortical reconstruction and quality control. Images saved as DICOMs were converted to NIfTI-format using *dcm2niix* (Li et al., 2016). T1w images were processed using FreeSurfer's cortical reconstruction process *recon-all* (version 7.3.2; http://surfer.nmr.mgh.harvard.edu/). In brief, artifact correction, skull stripping, normalization into standard space as well as cortical segmentation and parcellation were performed. One subject was excluded from further analyses since the *recon-all* algorithm failed repeatedly due to an issue with the Talairach transformation step. Reconstruction quality was assessed visually following FreeSurfer recommendations for version 7+ (https://surfer.nmr.mgh.harvard.edu/fswiki/QATools), which generates lateral and medial snapshots of the cortical reconstruction. Visual assessment was based on guidelines provided by the ENIGMA Working Group (https://enigma.ini.usc.edu/protocols/imaging-protocols/). All subjects passed this step of quality control and were included in further analyses. No subjects were excluded from the analysis.

Thalamus nuclei segmentation and quality control. Next, the thalamus was segmented into 26 nuclei per hemisphere by applying a built-in thalamus segmentation pipeline developed by Iglesias and colleagues (Iglesias et al., 2018). Volumes in mm^3 were extracted for each subject and each nucleus directly from FreeSurfer. For quality assessment of the thalamus segmentation, we followed recent community standards (Sämann et al., 2022; Thalhammer et al., 2024; Weeland et al., 2022). Due to general poor segmentation results, the lateral and medial geniculate nuclei were excluded from further analyses. The limitans suprageniculate was also excluded due to its small size and the resulting vulnerability for inaccurate segmentation. The reticular nucleus was excluded due to its different developmental origin and functions. For each of the remaining 22 nuclei per hemisphere, the interquartile range (IQR) was calculated to determine statistical outliers (i.e., below Q1 – 1.5 * IQR or above Q3 + 1.5 * IQR). Segmentation quality of these outliers was visually inspected in Freeview. Subjects with five or more outliers were removed from further analyses ($n = 5$). As an additional quality measure, thalamus segmentation that deviated too much (i.e., more than 20 %, $n = 67$) from native (aseg) FreeSurfer segmentation of the thalamus were visually inspected. Moreover, about 5 % of randomly selected subjects ($n = 12$) were visually inspected for segmentation quality. By this means, a further 32 subjects were excluded from further analyses (i.e., due to shape inaccuracies: $n = 21$, posterior extension into neighboring structures: $n = 11$). In summary, 37 subjects were excluded due to high outlier numbers in nuclei volume and/or due to segmentation inaccuracies. The final sample included 83 VP/VLBW and 92 FT subjects (Table 1).

Scanner harmonization. Afterwards, nuclei volumes were retrospectively harmonized for site effects using NeuroCombat (version 0.2.12, in Python) (Fortin et al., 2018). Estimated total intracranial volume (eTIV) was adjusted, preserving biological variation related to diagnosis, sex, and age, whereas harmonized eTIV variance was additionally retained when harmonizing subregional thalamic measures. To assess the effect of scanner harmonization, several analyses of covariance (ANCOVA) were calculated. Before and after harmonization, one ANCOVA was performed for each thalamic subregion, with the respective subregional volume as dependent variable, scanner-ID (i.e., Bonn Achieva 3 T, Bonn Ingenia 3 T, Munich Achieva 3 T, Munich Ingenia 3 T) as independent variable as well as age, sex, and eTIV (unharmonized or harmonized, respectively) as covariates. Python's pingouin package (version 0.5.2) was used. Resulting F-values for each subregion before and after harmonization are visualized in Figure S1. Harmonization successfully removed variance attributed to the hardware.

Thalamic nuclei grouping into subregions. In accordance with prior literature (Iglesias et al., 2018; Thalhammer et al., 2024; Weeland et al., 2022), thalamic nuclei were grouped into six bilateral subregions: anterior, lateral, ventral, intralaminar, medial, and pulvinar (Fig. 1, Table 2). The volume values from either hemisphere were averaged for the final analysis. The analysis assessing group differences separately for both hemispheres can be found in the Supplement.

2.6. Statistical analysis

All statistical analyses were carried out in Python (version 3.9.13) using the following libraries: pandas (version 1.5.3), numpy (version 1.23.5), scipy (version 1.10.0), statsmodels (version 0.13.5), and pingouin (version 0.5.3). ComBat-harmonized values of the main outcome measure, thalamic subregion volume, were used for the analyses. All models were adjusted for age, sex, and harmonized eTIV. Normal distribution was assessed using histogram visualization and the Shapiro–Wilk test (Shapiro and Wilk, 1965).

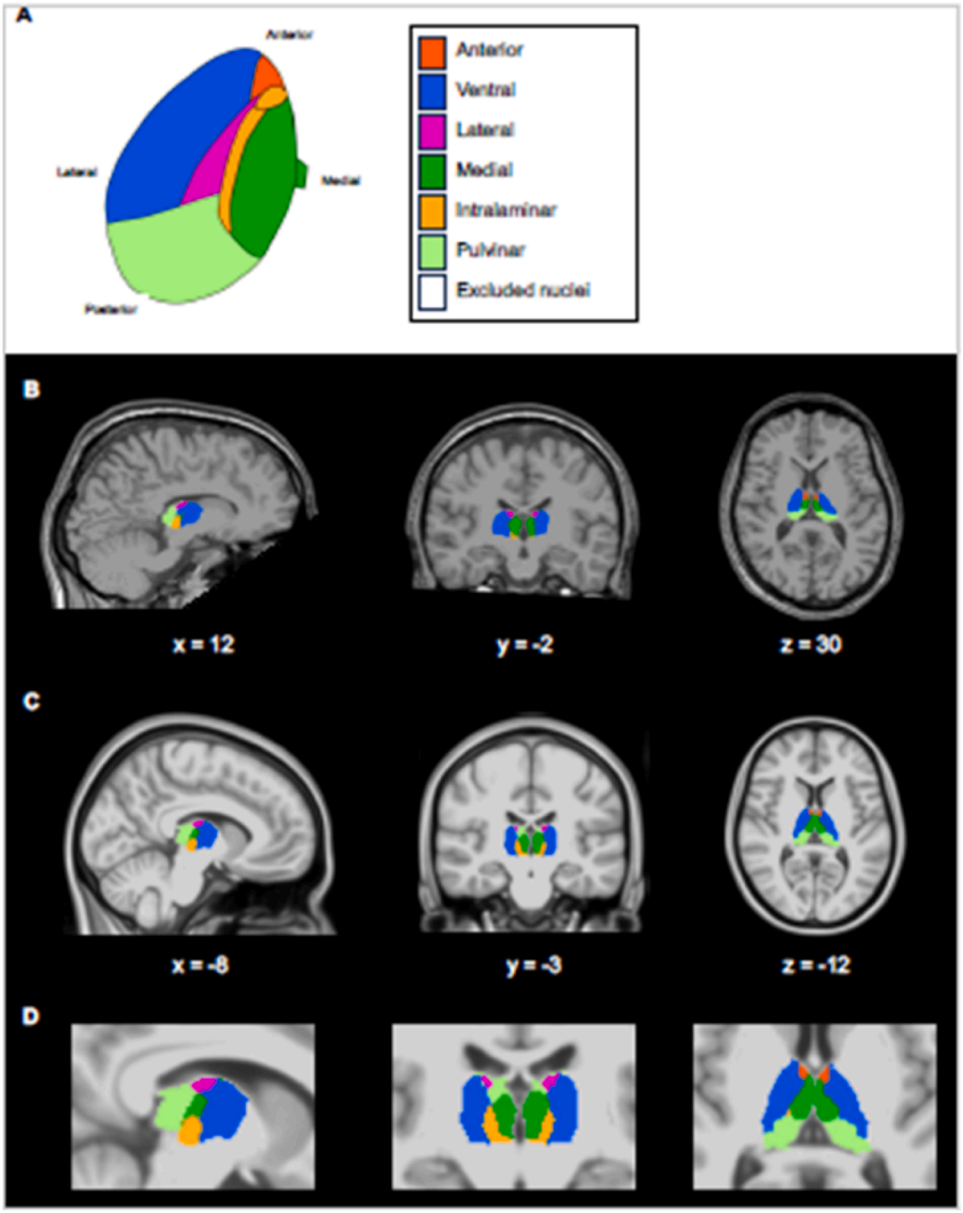

Fig. 1. Thalamic nuclei grouping based on segmentation in FreeSurfer. The thalami are segmented into 26 nuclei for each hemisphere, as listed in Table 2. (A) Based on literature recommendations (Iglesias et al., 2018; Weeland et al., 2022), thalamic nuclei were then grouped into six nuclei clusters per hemisphere (see Table 2): anterior (red), ventral (blue), lateral (pink), medial (dark green), intralaminar (orange), and pulvinar (light green). Excluded nuclei due to previous recommendations are summarized and shown in white. Panel (B) depicts an actual segmentation performed on a preterm male (GA= 27 weeks; BW= 1100 g) scanned in Bonn. In (C), thalamic subregions are overlaid on a bias-field corrected T1w image of the MNI152 template as obtained from FSL standards. Panel (D) depicts the same slices as shown in (C) but zoomed in on the thalamus. MNI Montreal Neurological Institute. Panel (A) was created with BioRender.com.

Statistical analysis of demographics. Group differences in age, GA, BW, and full-scale IQ were assessed with two-sample *t*-tests. A χ^2 test (*chi2_contingency* from scipy) was used to compare sex across groups.

Group comparison of thalamic subregion volume. To estimate group differences in thalamic volume between VP/VLBW and FT adults, ANCOVAs were performed. Mean volume of each of the six thalamic subregions served as the within-subject variable, whereas group was the between-subject variable. Sex, age, and harmonized eTIV were included as covariates. Cohen's d was used to estimate effect sizes.

Associations between thalamic subregion volume and degree of prematurity. General linear models were used to investigate whether thalamic subnuclei volumes in the VP/VLBW group were specifically related to prematurity dose. Mean volume of each thalamic subregion was entered as the dependent variable. GA, BW, or INTI was entered as a fixed factor, respectively, with sex, age, and harmonized eTIV as covariates.

Associations between thalamic subregion volume and cognitive performance. To explore the relationship between thalamic nuclei volume after preterm birth and cognitive performance, the extracted mean volumes of each preterm subject for each thalamic subregion were entered into a general linear model as independent variables with full-scale IQ as the dependent variable in the VP/VLBW group. Sex, age, and harmonized eTIV were entered as covariates. Subjects who did not undergo cognitive assessment were excluded from the analysis.

Thresholding and correction for multiple comparisons. Correction for multiple hypotheses testing was performed in Python per group using the False Discovery Rate (FDR) according to Benjamini and Hochberg (Benjamini and Hochberg, 1995). Statistical significance was defined as FDR-corrected $p < 0.05$.

Table 2
Thalamic nuclei grouping. In line with previous publications (Iglesias et al., 2018; Thalhammer et al., 2024; Weeland et al., 2022), thalamic subregions were defined incorporating the nuclei distinguished with the ThalamicNuclei pipeline (Iglesias et al., 2018) listed in the left column.

Thalamic regions	Included thalamic nuclei
Anterior	Anteroventral (AV)
Lateral	Laterodorsal (LD)
	Lateral posterior (LP)
Ventral	Ventral anterior (VA)
	Ventral anterior magnocellular (VAmc)
	Ventral lateral anterior (VLa)
	Ventral lateral posterior (VLp)
	Ventral posterolateral (VPL)
	Ventromedial (VM)
Intralaminar	Central medial (CeM)
	Central lateral (CL)
	Paracentral (Pc)
	Centromedian (CM)
	Parafascicular (Pf)
Medial	Paratenial (Pt)
	Reuniens (medial ventral) (MV-re)
	Mediodorsal medial magnocellular (MDm)
	Mediodorsal lateral parvocellular (MDl)
Pulvinar	Pulvinar anterior (PuA)
	Pulvinar medial (PuM)
	Pulvinar lateral (PuL)
	Pulvinar inferior (PuI)

3. Results

3.1. Sample characteristics

An overview of group demographic and clinical background variables is presented in Table 1. There was no significant difference between the VP/VLBW group and FT group regarding sex (χ^2_1= 0.38, p = 0.537) and age at scanning (t_{173}= 0.79, p = 0.431). By design of the study, VP/VLBW subjects had significantly lower GA (t_{172}= −36.7, p < 0.001) and BW (t_{172}= −35.5, p < 0.001). Furthermore, VP/VLBW subjects had significantly lower full-scale IQ scores (t_{167}= −5.12, p < 0.001) when compared to FT controls.

3.2. VP/VLBW adults show consistently lower volume across thalamic nuclei

To evaluate volumetric differences in thalamic subregions across VP/VLBW adults compared to FT controls, we performed a one-way ANCOVA adjusting for age, sex, and harmonized eTIV. Cohen's d was calculated to gauge effect size. There were significant group differences in all subregions examined (Fig. 2a, Table 3). More specifically, VP/VLBW subjects had on average significantly lower volumes in the anterior ($F_{1,173}$ = 10.807, p_{FDR} < 0.001), lateral ($F_{1,173}$ = 29.742, p_{FDR} < 0.001), ventral ($F_{1,173}$ = 34.459, p_{FDR} < 0.001), intralaminar ($F_{1,173}$ = 41.326, p_{FDR} < 0.001), medial ($F_{1,173}$ = 36.576, p_{FDR} < 0.001), and pulvinar ($F_{1,173}$ = 39.311, p_{FDR} < 0.001) subregions than FT controls. As a control analysis to rule out possible effects of averaging across hemispheres or nuclei groups, we also examined group differences for unilateral nuclei and separately for all included 22 nuclei. In agreement with the main analysis, we observed significantly lower volume (p_{FDR} < 0.05) for all six subregions of interest in both hemispheres (Supplementary Results, Supplementary Table S1) as well as for 41 of 44 nuclei (except left and right central lateral and right pulvinar; Supplementary Results, Supplementary Table S3). Additionally, whole thalamus volume of both hemispheres was lower in the VP/VLBW cohort compared to controls (Supplementary Results, Supplementary Table S2). The results are further not influenced by the method selected for TIV correction (see Supplementary Results, Supplementary Table S4) or whether neonatal intracranial hemorrhage was present (see Supplementary Results, Supplementary Table S5).

As a further analysis of specificity, we extended our research question to evaluate consistent prematurity effects on thickness of cortical regions and on volume of subcortical nuclei, respectively. Whereas prematurity effects on regional cortical thickness is selective (i.e., only frontal, temporal, and parietal areas are affected), its effect on subcortical regions is non-selective but consistent across all regions (see Supplementary Methods and Results for details, Supplementary Figure S2). Thus, these findings suggest that there is a consistent volume reduction across all thalamic subregions in adults born VP/VLBW, which is non-specific in the sense that all other investigated subcortical regions also exhibit lower volume in prematurity.

Next, to verify whether the observed reductions in thalamic subregion volumes were specifically related to premature birth, we related thalamus subregion volumes with variables of preterm birth, namely INTI, GA, and BW (Table 4, Fig. 2b, Supplement). INTI was negatively associated with lower volume of all thalamic subregions except for the intralaminar region (anterior: t_{82} =−2.392 p_{FDR}= 0.023; lateral: t_{82}= −3.145, p_{FDR}= 0.004; ventral: t_{82}= −3.401, p_{FDR}= 0.003; medial: t_{82}= −2.963, p_{FDR}= 0.006; pulvinar: t_{82}= −3.430, p_{FDR}= 0.003). GA was significantly correlated with pulvinar subregional volume (t_{82}= 2.432, p_{unc}= 0.017; Supplementary Table S6), whereas BW was associated with anterior volume (t_{82}= −2.508, p_{unc} < 0.014; Supplementary Table S7), both only before FDR-correction. Overall, these results suggest that smaller thalamic subregion volumes of the VP/VLBW group are associated with the degree of prematurity, consistently for INTI, but only selectively for GA or BW.

3.3. Lateral, medial, and pulvinar volume reductions were related to worse cognitive performance in VP/VLBW adults

To explore the functional relevance of lower thalamic subregion volume in preterm-born adults, we ran general linear models with age, sex, and harmonized eTIV as covariates and full-scale IQ as a fixed factor in VP/VLBW subjects. Before FDR-correction, lateral (t_{79}= 2.068, p_{unc}= 0.042), medial (t_{79}= 2.179, p_{unc}= 0.032), and pulvinar (t_{79}= 2.130, p_{unc}= 0.036) thalamic subregions showed an association with full-scale IQ, which however was not significant after the correction for multiple hypotheses testing (Fig. 3, Table 5). When excluding VP/VLBW adults who had intracranial hemorrhage after birth, findings were shifted towards non-significance for the lateral, medial, and pulvinar nuclei, but also for the whole left and whole right thalamus (see Supplementary Results), suggesting a substantial link between neonatal brain injury, thalamic volumes, and cognitive outcome.

4. Discussion

Using T1w-MRI-based in vivo volumetry and clinical-cognitive assessment, we presented that volumes of all thalamic subregions examined are consistently lower in VP/VLBW adults compared to full-term peers, indicating a global impact of very preterm birth on the thalamus. This finding is further supported by the observed relationship between lower volumes and higher intensity of neonatal intensive treatment for most nuclei, suggesting that severity of medical-neurological complications affect thalamus nuclei development. Finally, there was an association between lateral, medial, and pulvinar volumes with reduced general cognitive performance, indicating relevance of these lower nuclei volumes for reduced cognitive functioning. Nonetheless, it is important to note that this finding did not survive FDR-correction. To the best of our knowledge, this is the first study demonstrating a consistent impact of prematurity on thalamus nuclei. Our findings support the model of widespread lasting effects of prematurity mediated by microscopic mechanisms such as hypoxia; furthermore, they suggest that impairment of the lateral, medial, and pulvinar nuclei may contribute to the lasting effects of prematurity on neurocognitive performance.

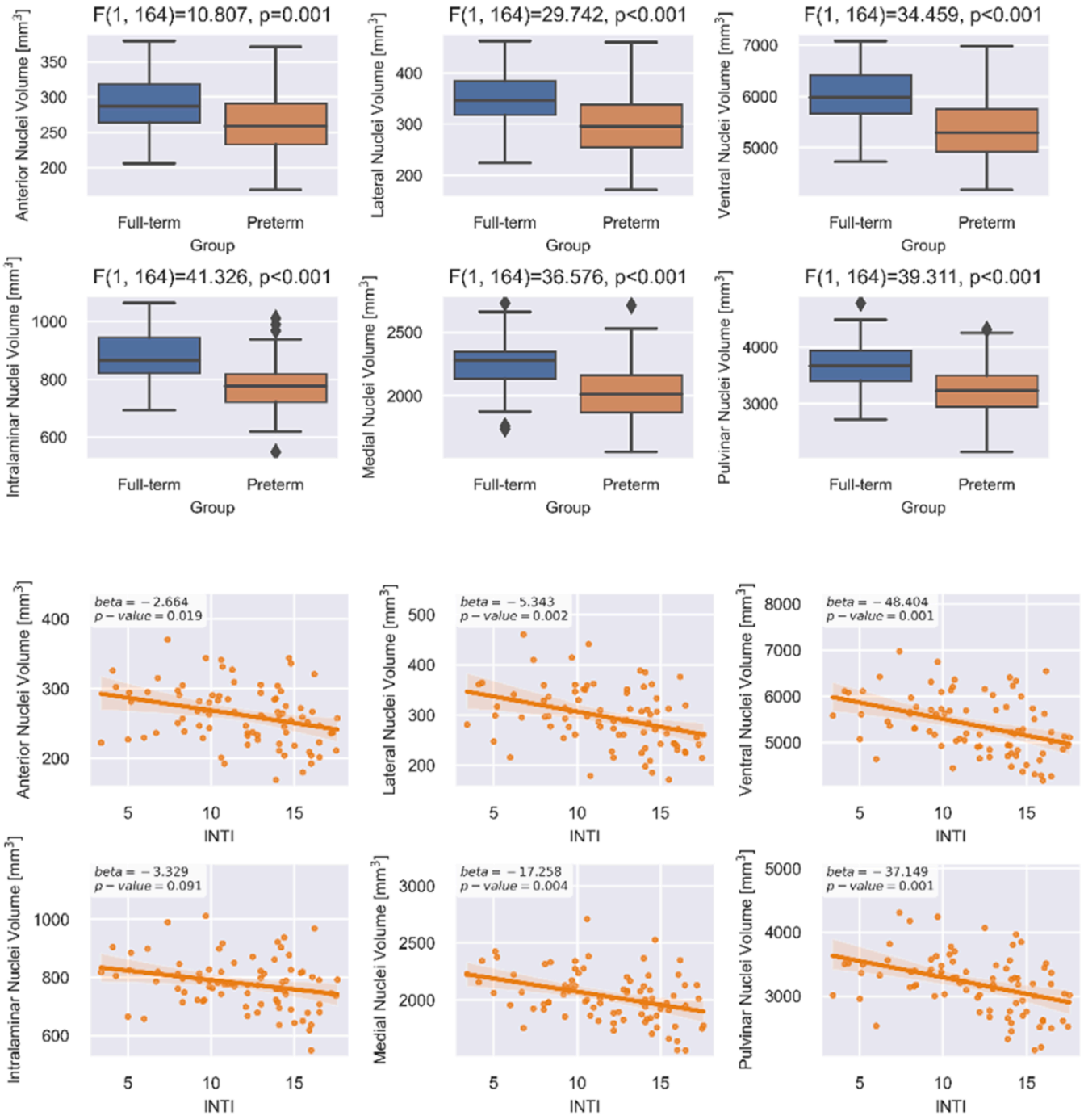

Fig. 2. Volumetric differences in thalamic subregions and their association with INTI. (A) VP/VLBW individuals show consistently lower volume across all thalamic subregions compared to FT controls. (B) INTI of VP/VLBW subjects significantly correlates with the volume of all thalamic subregions except the intralaminar nuclei. * $p_{unc} < 0.05$, ** $p_{unc} < 0.01$. FT, full-term; INTI, intensity of neonatal treatment; VP/VLBW, very preterm and/or very low birth weight.

4.1. Consistently lower volumes across thalamic nuclei in VP/VLBW adults

As a principal finding, we demonstrated that thalamic nuclei volumes are smaller in VP/VLBW adults than in term-born controls in all subregions examined, implying that prematurity has a global rather than a local impact on the thalamus. Beyond, we found such global effect on further subcortical regions such as caudate or putamen but not on cortical regions, where cortical thickness of only selected regions is aberrant. These findings are in line with previous results in the present (Grothe et al., 2017; Meng et al., 2016; Schmitz-Koep et al., 2020; Schmitz-Koep, Zimmermann, et al., 2021) and other preterm adolescent or adult cohorts (Bjuland et al., 2013; Nam et al., 2015; Nosarti et al., 2014; Pascoe et al., 2019), showing cortical thickness abnormalities in limited cortical areas, as opposed to global volume abnormalities of the subcortex. Minor differences in the affected regions may stem from different inclusion criteria, analysis methods, as well as heterogeneity between subjects. Regarding the outcome of thalamus changes, our results align with previous literature in preterm neonates (Ball et al., 2012), children (Chau et al., 2019; Loh et al., 2017; Zubiaurre-Elorza et al., 2012), and adults as well (Bjuland et al., 2014; Kuula et al., 2022; Meng et al., 2016; Pascoe et al., 2019), showing decreased volume of the

Table 3
Group-based volumetric analysis of the thalamic subregions.

Region	$F_{1,164}$	p-value	p_{FDR}	Cohen's d
Anterior	10.807	**0.001****	**0.001****	−0.72
Lateral	29.742	**<0.001*****	**<0.001*****	−1.00
Ventral	34.459	**<0.001*****	**<0.001*****	−1.12
Intralaminar	41.326	**<0.001*****	**<0.001*****	−1.14
Medial	36.576	**<0.001*****	**<0.001*****	−1.13
Pulvinar	39.311	**<0.001*****	**<0.001*****	−1.14

Note: A one-way ANCOVA adjusted for age, sex, and harmonized eTIV was conducted. Bold letters indicate statistical significance defined as $p < 0.05$, uncorrected and $p < 0.05$, FDR-corrected. Asterisks indicate statistical significance defined as $p < 0.001$ (***).
Abbreviations: FDR, false-discovery rate.

Table 4
Association of regional thalamic volume with intensity of neonatal treatment in VP/VLBW adults.

Region	t_{75}	β-coefficient	R-squared	p-value	p_{FDR}
Anterior	−2.392	−2.66	0.34	**0.019***	**0.023***
Lateral	−3.145	−5.34	0.24	**0.002****	**0.004****
Ventral	−3.401	−48.40	0.53	**0.001****	**0.003****
Intralaminar	−1.714	−3.32	0.53	0.091	0.091
Medial	−2.963	−17.26	0.34	**0.004****	**0.006****
Pulvinar	−3.430	−37.15	0.47	**<0.001****	**0.003****

Note: A general linear model was run with age, sex, and harmonized eTIV as covariates. Bold letters indicate statistical significance defined as $p < 0.05$, uncorrected and $p < 0.05$, FDR-corrected. Asterisks indicate statistical significance defined as $p < 0.001$ (***), $p < 0.01$ (**), and $p < 0.05$ (*), respectively.
Abbreviations: FDR, false-discovery rate; VP/VLBW, very preterm and/or very low body weight.

entire thalamus. In contrast to the rather large body of literature investigating the entire thalamus, studies on the volume of nuclei in preterm infants are still lacking. Some advances using combined thalamic nuclei shape and pose analysis (Lao et al., 2016) or deformation-based morphometry (Duerden et al., 2018) in preterm neonates have suggested specific regional abnormalities in the anterior and lateral thalamus, respectively. The difference between these studies, which found a local reduction in a few subregions, and our global results could be due to the differences in the methods and metrics used to determine the thalamic nuclei aberrations.

Overall, the present findings support the hypothesis that the reduction in thalamic volume after prematurity is due to a general shift in the developmental trajectory rather than a specific vulnerability of a few systems or nuclei. This could result from secondary degeneration of gray matter structures due to the degeneration of axons following primary brain damage such as white matter injury, hemorrhage (Inder et al., 2023; Volpe, 2009b), or the dysmaturation of subplate neurons (McClendon et al., 2017; Volpe, 2009a). Subplate neurons are particularly relevant for the correct formation of thalamocortical connectivity since they act as a scaffold for thalamic inputs to innervate cortical layer 4 (Ghosh et al., 1990; Hoerder-Suabedissen and Molnár, 2015; Kanold and Luhmann, 2010). Using the percent contrast of gray-to-white matter signal intensities as a proxy for cortical microstructure, we have previously shown in the same sample of preterm-born adults that projection fractions representing cortical layer 4 (DeFelipe et al., 2002; Wagstyl et al., 2020) are affected by prematurity (Schmitz-Koep, Menegaux, Zimmermann, et al., 2023). In line with these findings, thalamocortical connectivity has been demonstrated to be aberrant in preterm-born adults (Berndt et al., 2019; Menegaux et al., 2021). We speculate that the lower thalamic nuclei volumes may be the secondary consequence of these connectivity changes.

Additionally, there is evidence for thalamic injury as a primary event after preterm birth (Northington et al., 2001; Volpe, 2009b). Although most thalamic neurons are generated before 20 weeks of gestation (Bystron et al., 2008), GABAergic neurons develop later in the ventral telencephalic ganglionic eminence and subsequently migrate to the dorsal thalamus (Bystron et al., 2008; Letinic and Rakic, 2001). The concurrence of this event with preterm birth (Letinic and Rakic, 2001) hints at an increased vulnerability of thalamic GABAergic neurons to adverse events following preterm birth. Considering that 30 % of the neurons in every thalamic nucleus are GABAergic (Montero, 1986; Montero and Zempel, 1986), this may explain our findings of an overall lower volume.

The impact of prematurity on thalamic volume is supported by the relationship between reduced nuclei volumes and the intensity of neonatal treatment in the VP/VLBW group, i.e., the more intensive the postnatal treatment, the lower the volume of all nuclei (except intralaminar). Interestingly, the exposure of preterm neonates to intensive care unit methods has been linked to volume reductions of limbic system structures, including impaired thalamic growth (Chau et al., 2019; Duerden et al., 2018). This is supported by studies in preterm lambs, where prolonged positive pressure mechanical ventilation, one aspect of

Table 5
Association of regional thalamic volume with full-scale IQ in VP/VLBW adults.

Region	t_{79}	*β*-coefficient	*R*-squared	*p*-value	*p*-FDR
Anterior	0.287	0.10	0.31	0.775	0.775
Lateral	2.068	1.08	0.22	**0.042***	0.084
Ventral	1.914	8.71	0.50	0.059	0.089
Intralaminar	1.489	0.87	0.56	0.141	0.169
Medial	2.179	4.08	0.31	**0.032***	0.084
Pulvinar	2.130	7.40	0.45	**0.036***	0.084

Note: A generalized linear model was run with age, sex, and harmonized eTIV as covariates. Bold letters indicate statistical significance defined as $p < 0.05$, uncorrected and $p < 0.05$, FDR-corrected. Asterisks indicate statistical significance defined as $p < 0.05$ (*).
Abbreviations: FDR, false-discovery rate; VP/VLBW, very preterm and/or very low birth weight.

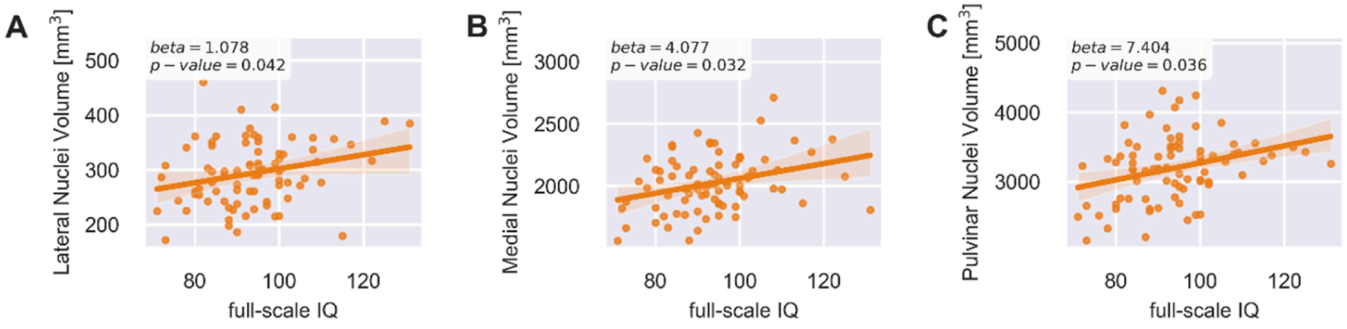

Fig. 3. Association between subregion volume with full-scale IQ in VP/VLBW subjects. Full-scale IQ significantly ($p_{unc} < 0.05$) correlates with the volume of the (A) lateral, (B) medial, and (C) pulvinar subregions, respectively, before correction for multiple comparisons. VP/VLBW, very preterm and/or very low birth weight.

INTI, was found to be associated with diffuse WM injury, particularly around the thalamus (Alahmari et al., 2017; Skiöld et al., 2014). The selective association between thalamic volume reductions and INTI rather than GA and BW may suggest that it is not the preterm birth itself, but rather the severity of the impairments it has left on an individual that is critical to the extent of thalamic volume reductions. In summary, this may indicate that the thalamus is particularly vulnerable to stress exposure in the neonatal care unit after preterm birth.

As thalamic nuclei volume was uniformly and lastingly reduced in prematurity and the thalamus is implicated in a variety of functions, aberrant nuclei volumes might be an interesting and relevant marker of prematurity effects on the brain. Thus, thalamus volume could be discussed as a general marker of lasting effects of preterm birth. So far, however, only group-based average results are available, which neglect individual heterogeneity after preterm birth (Dimitrova et al., 2020; R. 2021). To translate these findings into clinical practice, individual assessments of the thalamic nuclei will therefore be needed in the future, for example using normative modeling approaches (Dima et al., 2022; Marquand et al., 2016, 2019). Furthermore, these approaches might also be used to determine whether thalamic changes have the potential to stratify the effects of prematurity in individuals.

4.2. Functional relevance of consistently lower thalamus volumes for general cognitive performance

There was a trend towards significance for the association between lateral, medial, and pulvinar volumes and full-scale IQ in the VP/VLBW cohort, indicating that altered lateral, medial, and pulvinar volumes may contribute to the lasting effects of prematurity on cognitive performance. This section discusses factors that were not considered and that could lead to the at-trend results, followed by the conclusions drawn from these results.

There are multiple strands of evidence for a prominent role of the thalamus in cognitive performance (Halassa, 2022; K. Hwang et al., 2021, 2022; Sherman, 2016). For example, the medial nuclei have been attributed a major role in cognitive control in healthy individuals due to their extensive reciprocal connections with medial and lateral prefrontal cortices (Giguere and Goldman-Rakic, 1988; Halassa, 2022; Pergola et al., 2018) as well as their modulating activity on the connectivity between hippocampus and the medial prefrontal cortex (Georgescu et al., 2020; Yang et al., 2019). Studies in patients with focal lesions of the mediodorsal thalamus demonstrated its necessity in cognitive functioning (Hwang et al., 2020; 2021). Similarly, the pulvinar is known to control cortico-cortical communication (Saalmann et al., 2012; Shipp, 2003) and to be implicated in selective attention and visuospatial perception (Danziger et al., 2004; LaBerge and Buchsbaum, 1990; Menegaux et al., 2019; Saalmann et al., 2012; Saalmann and Kastner, 2011). After preterm birth, larger whole thalamus volumes at term-equivalent age were related to higher IQ at 7 years of age (Loh et al., 2017). Similarly, in another study, a relationship between impaired white matter integrity, which was associated with reduced thalamic volume, and full-scale IQ was demonstrated (Meng et al., 2016). This suggests that impaired integrity of the thalamus after preterm birth might be involved in overall intelligence deficits.

Still, in this study, we could show a significant link between whole left and right thalamus volume (see Supplementary Results) but not confirm a significant link between preterm lateral, medial, and pulvinar thalamic volume aberrations and cognitive outcome, which might be due to several reasons. First, the VP/VLBW cohort is rather well functioning, with IQ scores close to the fullterm participants, which underestimates true average differences (Kerr-Wilson et al., 2012; Lacalle et al., 2023; Rimol et al., 2023) and the impact of thalamic aberrations on cognition (Bjuland et al., 2014; Loh et al., 2017; Zubiaurre-Elorza et al., 2012). Second, only limited aspects of cognition are examined here. IQ is driven by several genetic, environmental, and socioeconomic factors (Franić et al., 2014; Shenkin et al., 2004). After preterm birth, it has been shown that IQ is highly heterogenous between subjects and that many brain areas contribute to an on-average IQ reduction (Eryigit Madzwamuse et al., 2015; Hedderich et al., 2019; Lacalle et al., 2023; Nosarti et al., 2008; Schmitz-Koep et al., 2020; Wolke et al., 2015). Therefore, thalamic volume could contribute to cognitive abilities but not determine them. Additionally, a sample of about hundred subjects might be too small to detect associations that might be highly heterogenous between subjects. Finally, the relation between full-scale IQ with lateral, medial, or pulvinar volume as well as with whole left or right thalamus volume, respectively, was lost when excluding subjects with neonatal intracranial hemorrhage, a severe form of neonatal brain injury. In line, a recent study in preterm children with white matter injury has suggested that thalamic volume and white matter injury interact to predict cognitive outcomes (Cayam-Rand et al., 2021).

Altogether, we hypothesized but could not conclusively demonstrate a relationship between thalamic volume and cognitive abilities in adulthood. To further elucidate this question, more studies that take into account various brain measurements and external factors are needed.

4.3. Strengths and limitations

This study is an extension of prior research on thalamus volume in VP/VLBW adults in several aspects: first, it focuses on single nuclei instead of the thalamus as a whole. Second, the pipeline applied to segment thalamic nuclei is well evaluated (Iglesias et al., 2018) and has been used repeatedly to estimate thalamic nuclei volumes in a variety of disorders (Huang et al., 2020; Mancini et al., 2020; Shin et al., 2019; Thalhammer et al., 2024; Weeland et al., 2022). Furthermore, cognitive testing was conducted by a trained neuropsychologist. By this means, a high-resolution, high-quality, well-justified analysis is provided. Third, methodological accuracy is provided since intensive quality control as well as the gold-standard procedure for adjustment of scanner effects, NeuroCombat (Fortin et al., 2018), were applied. Fourth, the relatively large data sample enhances the generalizability of the presented results. Lastly, the small age range of the study population in adulthood allows the assumption that chronological age differences are negligible.

Despite these strengths, we want to note several limitations of the current study. The VP/VLBW sample is biased towards participants with less neonatal complications and higher cognitive-behavioral functioning. Subjects with more birth complications in the initial Bavarian Longitudinal Study were more likely to drop out due to exclusion criteria for MRI (e.g., infantile cerebral palsy, the inability to lie still hypothetically due to underlying ADHD) and reject MRI assessment due to their stronger impairments. Given that the VP/VLBW sample's full-scale IQ is close to the normative average, generalizability of the results might be affected. Moreover, segmentation of thalamic nuclei is hindered by the poor contrast of thalamic margins on T1w images. Despite of our efforts to extensively review segmentation quality according to latest recommendations (Sämann et al., 2022; Weeland et al., 2022), we are aware that the anatomical relevance of the utilized pipeline has been questioned (Williams et al., 2022). In addition, we cannot eliminate the possibility that multi-site effects still influence our results, although recent standards to adjust for hardware effects have been applied (Fortin et al., 2018). However, as we demonstrate that these effects are not significant, large effects are not to be expected.

5. Conclusions

Our results show a general reduction of thalamic nuclei volumes in preterm-born adults associated with high neonatal treatment intensity. We interpret this as a vulnerability of all thalamic systems to higher stress and more severe consequences after preterm birth. A link between lateral, medial, and pulvinar volume reduction and full-scale IQ could be proposed but not finally concluded.

CRediT authorship contribution statement

Melissa Thalhammer: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Mehul Nimpal:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis. **Julia Schulz:** Writing – review & editing, Validation, Supervision, Conceptualization. **Veronica Meedt:** Writing – original draft, Methodology, Investigation, Formal analysis. **Aurore Menegaux:** Writing – review & editing, Data curation. **Benita Schmitz-Koep:** Writing – review & editing. **Marcel Daamen:** Writing – review & editing, Project administration. **Henning Boecker:** Writing – review & editing, Project administration. **Claus Zimmer:** Writing – review & editing, Resources. **Josef Priller:** Writing – review & editing. **Dieter Wolke:** Writing – review & editing, Project administration, Funding acquisition. **Peter Bartmann:** Writing – review & editing, Project administration, Funding acquisition. **Dennis Hedderich:** Writing – review & editing, Project administration, Funding acquisition. **Christian Sorg:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Melissa Thalhammer reports financial support was provided by Studienstiftung des deutschen Volkes. Christian Sorg reports financial support was provided by Deutsche Forschungsgemeinschaft (DFG). Peter Bartmann reports financial support was provided by German Federal Ministry of Education and Science. Dieter Wolke reports financial support was provided by German Federal Ministry of Education and Science. Dieter Wolke reports financial support was provided by EU Horizon 2020. Peter Bartmann reports financial support was provided by EU Horizon 2020. Christian Sorg reports financial support was provided by Commission for Clinical Research, Technical University of Munich. Benita Schmitz-Koep reports financial support was provided by Commission for Clinical Research, Technical University of Munich. Dennis Hedderich reports financial support was provided by Commission for Clinical Research, Technical University of Munich. If there are other authors, they 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 authors do not have permission to share data.

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Ethical approval and informed consent

The study was approved by the medical ethical board of the Klinikum rechts der Isar and the University Hospital Bonn; for a detailed description of the overall sample characteristics see Table 1.

Participants provided written consent to all conducted examinations.

Code availability

Code used to perform the main analyses can be found at https://github.com/Melissa1909/ThalamusVolumePrematurity.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2024.120732.

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