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Research report

Mind the gap – Interthalamic adhesions in prodromal and clinical Alzheimer's disease

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ABSTRACT

Background: The interthalamic adhesion (IA) is an anatomical bridge connecting the left and right thalamus. While prior studies have explored its prevalence and function in healthy populations, stroke, hydrocephalus, and schizophrenia, none have examined the IA in the context of Alzheimer's disease (AD). This study aims to analyse the prevalence of the IA in the prodromal to clinical AD continuum and evaluate the association with AD cerebrospinal fluid (CSF) biomarkers and thalamic, hippocampal, and ventricular volumes.
Method: IA prevalence was assessed in 542 MRIs from the Alzheimer's Disease Neuroimaging Initiative (ADNI), including healthy controls (HC), early mild cognitive impairment (EMCI), late MCI (LMCI), and AD patients. Inter-rater reliability was assessed with Cohen's Kappa, and a chi-squared test ($\chi 2$) examined rater differences. Binary and multinomial logistic regressions evaluated the effect of CSF biomarkers, volumes, and clinical data on IA prevalence and type.
Results: There were no significant differences in IA prevalence or variants across the four groups. The single IA was the most common type, while bilobar and double variants were less frequent. Post-hoc analysis, however, showed that AD CSF biomarker measures showed positive associations with the broad IA subtype in HC and EMCI.
Conclusion: The study found no overall differences in IA prevalence or its variants related to prodromal or clinical AD. Still, elevated Aβ42, p-Tau levels, and larger thalamic volume were linked to a higher likelihood of a broad IA. These findings suggest that the IA may be involved in prodromal AD pathophysiological processes.

1. Introduction

The interthalamic adhesion (IA), also anatomically referred to as massa intermedia, is a band of white matter tissue formed by neurons and/or neuropil connecting the median border of both thalami (Damle et al., 2017). It is located posterior to the foramen of Monro and anterior to the posterior commissure, emerging most commonly from the dorsomedial thalamic nucleus and spanning through the third ventricle (Borghei et al., 2020, 2021; Patra et al., 2022; Sahin et al., 2023; Vidal. et al., 2024). According to existing MRI studies, the prevalence of an IA

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

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ranges from 68 % to 98 % in the population, with an absence of an IA between 15 % and 20 % of the population (Borghei et al., 2021; Patra et al., 2022; Wong et al., 2021). This absence is more commonly found in males than in females (Borghei et al., 2021; Patra et al., 2022; Vidal et al., 2024), with larger IA found also in females compared to males (Damle et al., 2017).

The IA has four recognised anatomical variants: single, broad, double, and bilobar (Fig. 1). When present, the single IA is the most prevalent variant, with more than 60 % of cases having a single IA (Patra et al., 2022; Sahin et al., 2023; Vidal et al., 2024). In 18 % of cases, the IA can be present as a larger adhesion, referred to as broad IA, with the double IA being present in ~10 % of cases and the bilobar IA being even rarer (<10 %, (Tsutsumi et al., 2021)). The functional implication of the IA is still a matter of debate. Given that nearly one-fifth of the population has no IA, it was first proposed to be a vestigial part of the brain (Viller, 1887). However, more recent studies suggest that the IA may have functional relevance. For example, findings have related IA presence to attentional function in healthy individuals (Damle et al., 2017). More recently, a study in stroke and healthy participants suggested that the IA could play a compensatory mechanism rather than a specific cognitive function (Vidal et al., 2024). Thus, the question of the IA's functionality remains open.

To our knowledge, the presence or function of the IA in neurodegenerative conditions, such as Alzheimer's disease (AD), is completely unknown but might be of relevance. The thalamus is one of the earliest structures to be affected by AD pathophysiology. Neurofibrillary tangles are found in the anterodorsal thalamic nuclei concurrently with deposition in the transentorhinal cortex (Braak and Braak, 1991). Thalamic structural and functional changes in AD are early features, even in its prodromal stages (Aggleton et al., 2016; de Jong et al., 2008; Nestor et al., 2003). More recent studies have shown that thalamic nuclei changes are related to impaired episodic memory, executive function, attention deficits, and spatial navigation deficits in AD (Bernstein et al., 2021; Forno et al., 2023; Iglesias et al., 2018). Despite the role of the thalamus in AD, to our knowledge, no study has analysed the prevalence of the IA in the AD continuum.

Our study aims to analyse the prevalence of IA and its variants in the large ADNI database, including healthy controls (HC), early mild cognitive impairment (EMCI), late MCI (LMCI) and AD dementia patients. We will further compare the differences within the variants across the four groups. Finally, we will analyse the effects of cerebrospinal fluid (CSF) AD biomarker levels and brain volume changes as they relate to the prevalence of the IA and its variants. We expect to find a higher prevalence of robust IA adhesions (e.g., broad) in healthy ageing/early prodromal AD (HC/EMCI) and thinner IA adhesion (e.g., single or double) in late prodromal AD/clinical. We anticipate that variations in CSF biomarker levels and brain region volumes will influence the probability of observing an IA and its variants.

2. Material and methods

All data for this article were obtained from the ADNI database, including ADNI 1, ADNI GO, and ADNI 2 phases (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, including inclusion and exclusion criteria please see http://www.adni-info.org.

2.1. Imaging and descriptive data

Imaging data were searched through the ADNI database for all subjects imaged at baseline with a 3 Tesla scanner using an MPRAGE sequence. Participants were included if they were healthy controls (HC) or had a diagnosis of early MCI (EMCI), late MCI (LMCI), or AD. The total search led to 546 datasets. Demographic data, including age, sex, educational level, and cognitive and biomarker data for all datasets, were also downloaded. Cognitive data included the Montreal Cognitive Assessment (MoCA), the Mini-Mental State Examination (MMSE), the Clinical dementia rating (CDR), and the CDR sum of boxes (CDR-SB). Biomarkers included CSF levels of $A\beta_{42}$, total tau, and phosphorylated TAU (pTau). From this, two participants were excluded due to missing cognitive data. Also, two scans were excluded due to large thalamic lesions. This led to a final sample of 542 participants (HC n = 174, EMCI n = 182, LMCI n = 102, AD n = 84).

The volume of the thalamus, the hippocampus, the lateral ventricle, the inferior lateral ventricle, and the third and fourth ventricles were estimated using Freesurfer v7.0.0 (https://surfer.nmr.mgh.harvard.edu/). Detailed Freesurfer preprocessing steps are reported elsewhere (Fischl et al., 2002). Total intracranial volumes (ICV) were calculated for each subject using Freesurfer's *recon -all* command. Volumes were normalised by dividing by the ICV, which resulted in ICV-adjusted values for statistical analysis.

2.2. IA and IA variants identification protocol

To prevent bias and ensure that raters were unaware of the diagnosis associated with each scan, the scans were blinded and then randomised. Two independent raters (GF and MH) characterised the presence, absence, and variant of IA following previously established protocols (Vidal et al., 2024). For n = 9 scans, both raters were unsure as to the subtype of the IA, for which a third expert rater (JV) was consulted, and their IA subtype recommendation was used for the analyses. Before rating the scans, both raters were trained by two expert raters on the identification of the presence or absence of an IA and their subtypes (JV,

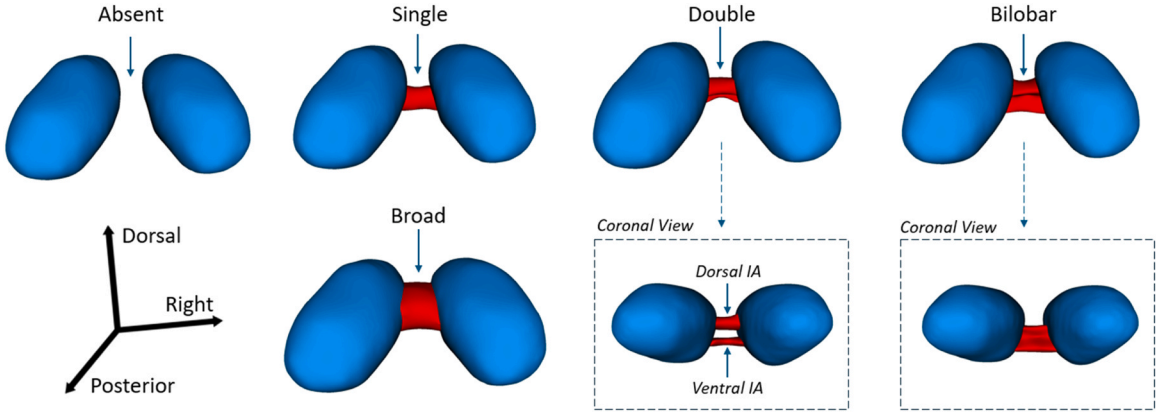

Fig. 1. Illustration of the different subtypes of interthalamic adhesions – Absent, Single, Broad, Double, and Bilobar.

EB). MRI images were reviewed using MRIcron software, starting with the axial slices and then sagittal and coronal slices to refine the characterisation of the IA. An IA was identified if a structure connecting both thalami was observed on at least one slice between the anterior and posterior commissure. Variants were classified as single, broad, bilobar, or double based on previously established criteria (Figs. 1, 2). For more detailed information on the characterisation of the presence or absence of an IA and the variant, please refer to the publicly available video protocol (Vidal et al., 2024)

2.3. Statistical analysis

Descriptive and cognitive data were checked for normality using the Shapiro-Wilk test. Differences in sex were analysed using a chi-squared test (χ^2). Age and educational level were compared between groups using one-way ANOVAs. Significant differences were only found for age; hence, age was used as a covariate for the IA analyses.

Inter-rating agreement on the presence, absence, and IA variant was assessed using Cohen's Kappa. Agreement values were interpreted as follows: ≤ 0 indicated no agreement; 0.01–0.20 as none to slight; 0.21–0.40 as fair; 0.41– 0.60 as moderate; 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement (McHugh, 2012). A Chi-squared test (χ^2) was then performed to analyse differences between raters in the IA assessment, both presence/absence and variants, across the four groups.

We conducted three parallel binary logistic regressions for the main IA analyses using the presence or absence of an IA as the dependent variable. The independent variables included AD biomarkers ($A\beta_{42}$, total tau, and pTau), cognitive measures (MoCA, MMSE, the CDR, and CDR-SB), brain volumes (hippocampus, thalamus, lateral and lateral inferior ventricles), and age. Additionally, three parallel multinomial logistic regressions were performed with IA variants as the dependent

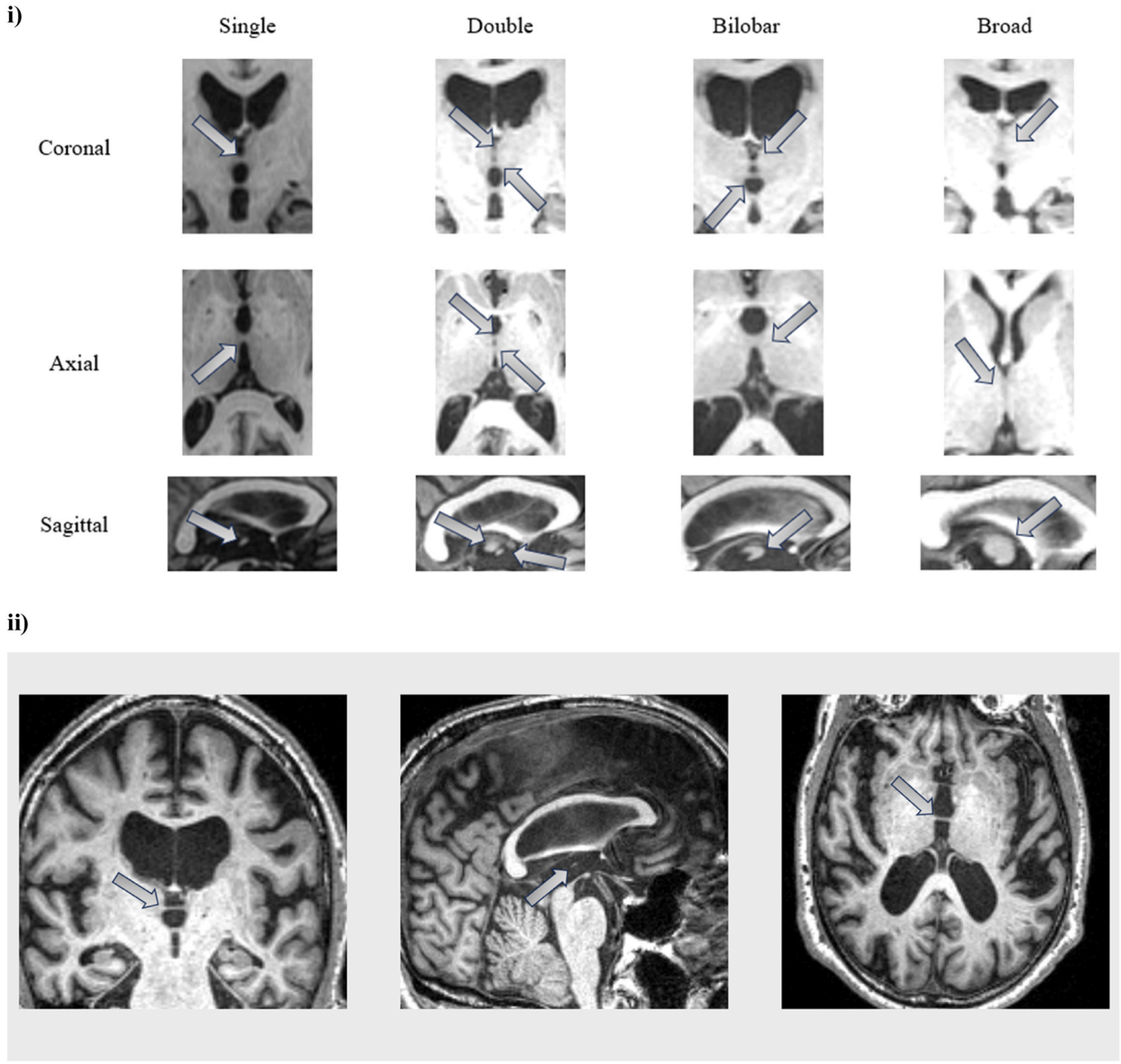

Fig. 2. Examples of IA variants. **Note.** i) IA variants in coronal, axial and sagittal cuts in healthy older people and ii) IA example in an AD patient with significant atrophy.

variable, using the same independent variables from the binary models. For this analysis, we excluded cases where both raters agreed on the absence of an IA and did not agree on the IA variants.

3. Results

3.1. Descriptive and imaging data

Detailed results are shown in Table 1. Overall, no significant differences were found between groups in terms of sex or level of education. As expected, significant differences were found between the four groups on the cognitive screening measures (MoCA, MMSE) and the clinical staging measure (CDR sum of boxes). The EMCI vs. LMCI contrast was the only contrast that showed no significant results in the CDR global comparison.

Significant volume differences were found in the hippocampus (HC vs LMCI [$p \leq 0.01$; $d = 0.188$]; HC vs AD [$p \leq 0.001$; $d = 0.245$]; EMCI vs LMCI [$p \leq 0.001$; $d = 0.140$]; EMCI vs AD [$p \leq 0.001$; $d = 0.259$]; LMIC vs AD [$p \leq 0.01$; $d = 0.130$]), and the inferior lateral ventricles (HC vs LMCI [$p \leq 0.001$; $d = -0.179$]; HC vs. AD [$p \leq 0.001$; $d = -0.317$]; EMCI vs. LMCI [$p \leq 0.001$; $d = -0.136$]; EMCI vs AD [$p \leq 0.001$; $d = -0.268$]; LMIC vs AD [$p \leq 0.01$; $d = -0.132$]) for all groups except for HC compared to EMCI. Both HC and EMCI showed significant differences with LMCI and AD in the volume of the lateral ventricles (HC vs LMCI [$p \leq 0.01$; $d = -0.105$]; HC vs AD [$p \leq 0.001$; $d = -0.186$]; EMCI vs LMCI [$p \leq 0.01$; $d = -0.116$]; EMCI vs AD [$p \leq 0.001$; $d = -0.194$]. AD showed significantly smaller overall thalamic volume compared to HC and EMCI (HC vs AD [$p \leq 0.01$; $d = 0.131$], EMCI vs AD [$p \leq 0.001$; $d = 0.147$]. Finally, AD showed significantly greater volume of the third ventricle compared to HC ($p \leq 0.001$; $d = -0.164$), EMCI ($p \leq 0.001$; $d = -0.163$), and LMCI ($p \leq 0.05$; $d = -0.097$) (See Fig. 3).

$A\beta_{42}$ levels significantly differed across all groups (HC vs EMCI [$p \leq 0.001$; $d = 0.099$]; HC vs LMCI [$p \leq 0.001$; $d = 0.228$]; HC vs AD [$p \leq 0.001$; $d = 0.324$]; EMCI vs LMCI [$p \leq 0.001$; $d = 0.137$]; EMCI vs AD [$p \leq 0.001$; $d = 0.259$]; LMIC vs AD [$p \leq 0.01$; $d = 0.165$]), whereas total and pTau levels differed for all groups except between HC and EMCI (total tau; HC vs LMCI [$p \leq 0.001$; $d = -0.135$]; HC vs AD [$p \leq 0.001$; $d = -0.317$]; EMCI vs LMCI [$p \leq 0.01$; $d = -0.102$]; EMCI vs AD [$p \leq 0.001$; $d = -0.280$]; LMIC vs AD [$p \leq 0.001$; $d = -0.155$]; (ptau; HC vs. LMCI [$p \leq 0.001$; $d = -0.151$]; HC vs. AD [$p \leq 0.001$; $d = -0.330$]; EMCI vs LMCI [$p \leq 0.01$; $d = -0.109$]; EMCI vs AD [$p \leq 0.001$; $d = -0.280$]; LMIC vs AD [$p \leq 0.001$; $d = -0.152$]).

3.2. IA assessment

Cohen's Kappa analysis showed an 'almost perfect' ($k = 0.938$) agreement between raters in the presence or absence of an IA. Within IA variants, the overall agreement was moderate ($k = 0.685$), with the double and bilobar variants as the lowest index (($k = 0.423$) and ($k = 0.437$), respectively) and the single with the highest agreement ($k = 0.828$) followed by the broad variant ($k = 0.734$) (Table 2).

No significant differences were found between the groups for the presence or absence of IA ($\chi^2 = 2.206$; p-value = 0.531). Additionally, no significant differences in variant distribution were observed when an IA was present across the four groups ($\chi^2 = 13.018$; p-value = 0.161).

3.3. Logistic regressions

Results from the binary logistic regression are detailed in Table 3.

Table 1
Descriptive Data.

	HC Mean (SD)	EMCI Mean (SD)	LMCI Mean (SD)	AD Mean (SD)	HC vs EMCI ES	HC vs LMCI ES	HC vs AD ES	EMCI vs LMCI ES	EMCI vs AD ES	LMCI vs AD ES
Age	73 (6.018)	70 (7.002)	72 (7.733)	74 (8.321)	0.111***	0.033	−0.069	−0.081	−0.159***	−0.105
Sex (M:F)	88:86	82:100	51:51	35:49	0.876	0.0	1.463	0.459	0.148	0.973
Education	16 (2.601)	16 (2.676)	16 (2.510)	15 (2.671)	−0.036	−0.133	−0.016	−0.151	−0.048	0.037
CDGLOBAL	0.003 (0.038)	0.497 (0.037)	0.505 (0.050)	0.798 (0.281)	−0.500***	−0.500***	−0.500***	−0.500	−0.500***	−0.496***
CDRSB	0.032 (0.133)	1.374 (0.808)	1.696 (1.003)	4.494 (1.757)	−0.498***	−0.499***	−0.500***	−0.176**	−0.465***	−0.436***
MMSE	29 (1.176)	28 (1.488)	27 (1.862)	23 (2.227)	−0.028***	0.140***	0.476***	0.057***	0.460***	0.407***
MOCA	27 (2.315)	26 (2.816)	24 (3.160)	19 (5.424)	0.051***	0.200***	0.407***	0.099***	0.360***	0.281***
Hippocampus_TIV	0.0068 (0.0008)	0.0068 (0.0009)	0.0065 (0.0008)	0.0007 (0.0061)	−0.024	0.118**	0.245***	0.140***	0.259***	0.130**
Inf-Lat-Vent_TIV	0.001 (0.0005)	0.001 (0.0006)	0.0014 (0.0008)	0.002 (0.0018)	−0.040	−0.179***	−0.317***	−0.136***	−0.268***	−0.132**
Lateral-Ventricle_TIV	0.0231 (0.0105)	0.0226 (0.0104)	0.0278 (0.013)	0.03 (0.012)	0.016	−0.105**	−0.186***	−0.116**	−0.194***	−0.063
Thalamus_TIV	0.0086 (0.0011)	0.0087 (0.0011)	0.0084 (0.0009)	0.0008 (0.008)	−0.017	0.060	0.131**	0.075	0.147***	0.068
3rd-Ventricle_TIV	0.0011 (0.0004)	0.0011 (0.0004)	0.0012 (0.0004)	0.0014 (0.0004)	0.007	−0.057	−0.164***	−0.059	−0.163***	−0.097*
4th-Ventricle_TIV	0.0012 (0.0003)	0.0012 (0.0003)	0.0013 (0.0004)	0.0012 (0.0003)	0.036	−0.030	−0.009	−0.063	−0.043	0.019
ABETA42	1382.997 (681.324)	1164.680 (602.103)	895.986 (446.848)	724.110 (421.044)	0.099***	0.228***	0.324***	0.137***	0.259***	0.165***
TAU	238.955 (90.407)	258.759 (126.616)	299.719 (133.113)	376.443 (145.347)	−0.028	−0.135***	−0.317***	−0.102**	−0.280***	−0.155***
PTAU	21.945 (9.351)	24.751 (14.457)	29.243 (14.546)	36.948 (15.444)	−0.036	−0.151***	−0.330***	−0.109**	−0.280***	−0.152***

Note. HC: Healthy controls; EMCI: Early mild cognitive impairment; LMCI: Late cognitive impairment; AD: Alzheimer's disease; ES: Effect size; CDGLOBAL: Clinical dementia rating global score; CDRSB: Clinical dementia rating sum of boxes; MMSE: Mini-mental state examination; MOCA: Montreal cognitive assessment; TIV: Total intracranial volume; ABETA42: CSF $A\beta_{42}$ levels; TAU: CSF Total tau levels; PTAU: CSF phosphorylated tau levels. Contrast between groups in Sex are represented by χ^2. Adjusted $p \leq 0.05$*; $p \leq 0.01$**; $p \leq 0.001$***

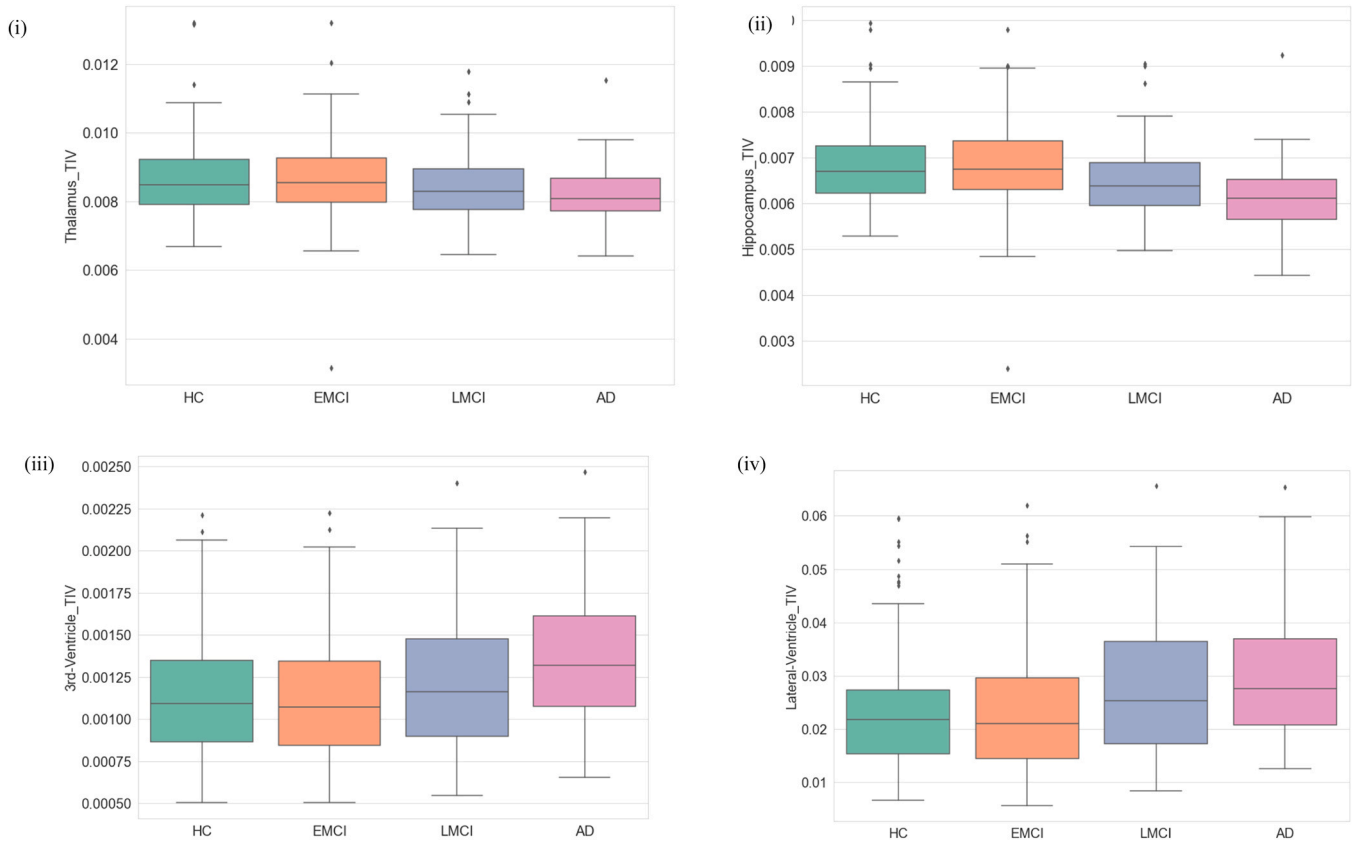

Fig. 3. Brain volume changes across ADNI cohort. **Note.** (i) Thalamus normalized TIV volume in the four groups; (ii) Hippocampal normalized TIV volumes in the four groups; (iii) 3rd Ventricle normalized TIV volumes in the four groups; (iv) Lateral Ventricle normalized TIV volumes in the four groups.

Table 2
Inter-rater agreement of the absence, presence or IA anatomical variant.

IA	Cohen's Kappa
Presence/Absence	0.938
Single	0.828
Double	0.423
Bilobar	0.437
Broad	0.734
Overall Subtypes	0.685

Note. Cohen's Kappa < 0: No agreement (or worse than chance); 0.01 – 0.20: Slight agreement; 0.21 – 0.40: Fair agreement; 0.41 – 0.60: Moderate agreement; 0.61 – 0.80: Substantial agreement; 0.81 – 1.00: Almost perfect agreement.

Table 3
Consensus Frequency Type of the IA in the AD continuum.

Group	Single	Double	Bilobar	Broad	Consensus / Total
HC	71 (63.96 %)	9 (8.11 %)	8 (7.21 %)	23 (20.72 %)	111/133
EMCI	77 (65.81 %)	10 (8.55 %)	7 (5.98 %)	23 (19.66 %)	117/148
LMCI	48 (73.84 %)	2 (3.08 %)	2 (3.08 %)	13 (20 %)	65/78
AD	36 (80 %)	2 (4.44 %)	5 (11.11 %)	2 (4.44 %)	45/62

Note. HC: healthy controls; EMCI: early mild cognitive impairment; LMCI: late mild cognitive impairment; AD: Alzheimer's disease

Our results revealed that ventricle volumes were associated with the presence/absence of an IA. Higher lateral ($\beta = 47.87$, $p \leq 0.01$) and inferior lateral ventricle ($\beta = 848.16$, $p \leq 0.001$) volumes were associated with an increased probability of IA presence. In contrast, increased 3rd ventricle volume ($\beta = -4604.83.16$, $p \leq 0.001$) decreased the likelihood of an IA. Thalamic volume showed a trend toward significant ($\beta = 603.00$, $p = 0.062$), indicating that greater thalamic volumes increased the probability of IA presence. By contrast, no significant effects were observed for hippocampal volume, AD biomarkers, cognitive measures, or age as to the presence or absence of IA.

Results from the multinomial logistic regression are detailed in Table 4. Our results showed that an increased 3rd ventricle volume decreased the probability of all IA variants (single ($\beta = -3474.59$, $p \leq 0.001$), double ($\beta = -6422.58$, $p \leq 0.001$), broad ($\beta = -1105e{+}04$, $p \leq 0.001$), bilobar ($\beta = -7791.98$, $p \leq 0.001$)). Conversely, larger inferior ($\beta = 50.19$, $p \leq 0.01$) and inferior lateral ventricle volumes ($\beta = 658.24$, $p \leq 0.01$) increase the probability of the single IA variant. Additionally, larger thalamic volumes increase the probability of a broad IA ($\beta = 1763.18$, $p \leq 0.05$) (Fig. 4).

Further, older age increases the likelihood of the double ($\beta = 0.99$, $p \leq 0.05$) and bilobar ($\beta = 0.9$, $p \leq 0.05$) IA variants. AD biomarkers showed that $A\beta_{42}$ CSF levels ($\beta = 0.0007$, $p \leq 0.05$) were significantly related to the broad IA variant only. More specifically, higher $A\beta_{42}$ levels increase the probability of a broad IA variant. Interestingly, when age was removed from the model, higher levels of pTau increased the likelihood to have a broad IA ($\beta = 0.1444$, $p \leq 0.05$), whereas total tau levels decreased the probability ($\beta = -0.135$, $p = 0.091$).

The IA variants did not significantly relate to hippocampal volumes.

To better understand the mechanisms of thalamic volume and AD CSF biomarkers with the broad IA across groups, we performed two specific post-hoc multinomial logistic regression analyses. Our post-hoc analysis revealed that, although no differences were found in the IA

Table 4
Binary logistic regression on the of IA presence vs absence.

Dependent Variable		IA Presence vs Absence		
Model 1	Independent Variables	β	p-value	95 % CI
	Intercept	3.3661	0.003	1.11; 5.62
	$A\beta_{42}$	0.0002	0.510	−0.00; 0.00
	TAU	0.0022	0.670	−0.01; 0.01
	PTAU	−0.0022	0.963	−0.09; 0.09
	Age	**−0.0385**	**0.011**	**−0.07; −0.01**
Model 2	Intercept	5.0324	0.021	0.77; 9.29
	MoCA	−0.0330	0.386	−0.11; 0.04
	MMSE	−0.0046	0.943	−0.13; 0.12
	CDGLOBAL	0.1724	0.783	−1.05; 1.39
	CDRSB	−0.0374	0.339	−0.37; 0.13
	Age	**−0.0374**	**0.015**	**−0.07; - 0.01**
Model 3	Intercept	−0.4425	0.841	−4.76; 3.87
	Lateral Ventricle	**47.8657**	**0.004**	**15.319; 80.41**
	Inferior Lateral Ventricle	**848.1640**	**0.001**	**346.68; 1349.65**
	Thalamus	*603.0004*	*0.062*	*−31.391; 1237.39*
	Hippocampus	−242.4827	0.529	−996.757; 511.79
	Third Ventricle	**−4604.8331**	**0.001**	**−5622.29; −3587.37**
	Age	0.0247	0.216	−0.01; 0.06

Note. All volumes are adjusted for total intracranial volumes. IA: Interthalamic adhesion; $A\beta_{42}$: CSF $A\beta_{42}$ levels; TAU: CSF Total tau levels; PTAU: CSF phosphorylated tau levels. MOCA: Montreal cognitive assessment; MMSE: Mini-mental state examination; CDGLOBAL: Clinical dementia rating global score; CDRSB: Clinical dementia rating sum of boxes. Significant predictors are highlighted in **bold.** *Italic represents a trend toward significant.*

variant distribution across groups, AD showed a significant lower probability of having a broad IA compared to HC ($\beta = 0.674$, $p \leq 0.05$) and EMCI ($\beta = 0.556$, $p \leq 0.05$). Additionally, a trend toward significance was observed compared to LMIC ($\beta = 0.496$, $p = 0.085$).

Finally, we split the groups into healthy ageing/early prodromal AD (HC/EMCI) and late prodromal AD/clinical AD (LMCI/AD) to specifically understand how AD CSF mechanisms relate to thalamic volume. Our results showed that higher $A\beta_{42}$ were related with bigger thalamic volume in both groups (HC/EMCI ($\beta = 2.333e\text{-}07$, $p \leq 0.05$); LMCI/AD ($\beta = 3.23e\text{-}07$, $p \leq 0.05$)), whereas p-Tau was exclusively related with bigger thalamic volume in the healthy ageing/early prodromal AD group ($\beta = 5.755e\text{-}05$, $p \leq 0.05$). Total Tau showed no significant effect for any of the groups. (Table 5)

4. Discussion

To our knowledge, this is the first study investigating interthalamic adhesions in prodromal and clinical dementia. Our results show that the detection of IAs in these cohorts is straightforward, with an inter-rater agreement on the presence or absence of an IA at an 'almost perfect' level. Within IA variants, the highest inter-rater agreement was for the single IA, while double and bilobar variants showed the lowest inter-rater agreements.

Interestingly, we did not find significant group differences (controls, MCI, AD) in the IA prevalence. This was unexpected, as it has been suggested that IA prevalence might decrease with age, or that the IA might even get ruptured in some cases with increasing ventricle enlargement (El Damaty et al., 2017). In addition, we anticipated a higher prevalence of thinner IA variants (i.e., single, double, or bilobar) in clinical AD compared to MCI or even controls, due to increasing thalamic atrophy and third ventricle widening in clinical AD. Still, post-hoc analyses showed a decreased probability of having a broad IA in AD compared to HC and EMCI. Interestingly, the probability of having a broad IA in LMCI compared to AD showed only a trend toward significance. These results suggest that the probability of supporting robust IA connectivity (broad IA) decreases as in LMCI and AD. A possibility is that the IA is directly affected by the AD pathological process, resulting in a loss of fibre integrity as the disease progresses. Future longitudinal studies should focus on analysing IA integrity throughout the continuum of AD, as our results are cross-sectional only.

Notably, the effects of AD biomarkers on IA variants may also support this hypothesis. Although no significant effect was found for the binary logistic regression analysis, a significant positive effect for $A\beta_{42}$ and the broad IA was found in the multinomial logistic analysis. Crucially, when age was removed from the model, p-Tau levels became statistically significant. Both biomarkers showed positive coefficients, indicating that higher levels of $A\beta_{42}$ and p-Tau increased the probability of a broad IA.

To understand the mechanism of AD biomarkers better, we split the groups into healthy ageing/early prodromal AD (HC/EMCI) versus late prodromal AD/clinical AD (LMCI/AD) to analyse the effects of $A\beta_{42}$, p-Tau, and total tau on the thalamic volumes specifically. Surprisingly, our results showed that increased $A\beta_{42}$ levels were related to bigger thalamic volume in both groups. Notably, increased p-Tau levels were exclusively significant for the healthy ageing/early prodromal AD group (HC and EMCI). These results suggest that p-Tau directly impacts the IA structure

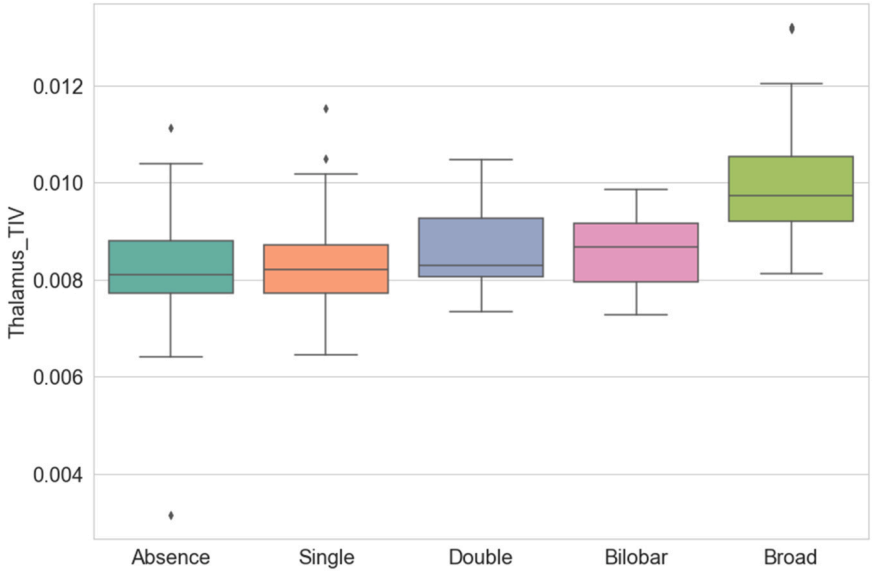

Fig. 4. Thalamic volume across IA variants. **Note.** Mean thalamic volume across IA variants and when IA is absent.

Table 5
Multinomial logistic regression on the IA variant.

Dependent Variable		IA variant											
		Single			Double			Bilobar			Broad		
Model 1	Independent Variables	β	p-value	95 % CI	β	p-value	95 % CI	β	p-value	95 % CI	β	p-value	95 % CI
	Intercept	0.99	0.436	−1.51; 3.49	−2.04	0.432	−7.13; 3.05	−1.49	0.579	−6.74; 3.77	**10.22**	**0.000**	**6.49; 13.94**
	$A\beta_{42}$	−5.84e−05	0.786	−0.00; 0.00	0.00	0.609	−0.00; 0.00	−2.31e−05	0.957	−0.00; 0.00	**0.00**	**0.024**	**9.08e−05; 0.00**
	TAU	0.00	0.543	−0.01; 0.01	−0.00	0.892	−0.02; 0.02	0.01	0.333	−0.01; 0.03	−0.01	0.247	−0.03; 0.01
	PTAU	−0.02	0.636	−0.12; 0.08	0.04	0.686	−0.15; 0.22	−0.05	0.620	−0.21; 0.13	0.12	0.111	−0.03; 0.26
	Age	−0.01	0.649	−0.04; 0.03	−0.01	0.851	−0.07; 0.06	−0.02	0.516	−0.09; 0.05	**−0.17**	**0.000**	**−0.23; −0.12**
Model 2	Intercept	1.65	0.350	−1.81; 5.10	−0.02	0.995	−7.23; 7.19	−3.36	0.407	−11.31; 4.58	−2.91	0.308	−8.52; 2.69
	MoCA	−0.02	0.663	−0.09; 0.06	−0.07	0.374	−0.23; 0.09	−0.12	0.173	−0.28; 0.05	0.01	0.844	−0.11; 0.13
	MMSE	−0.02	0.789	−0.15; 0.12	0.02	0.883	−0.26; 0.30	0.17	0.286	−0.14; 0.47	0.07	0.510	−0.14; 0.28
	CDGLOBAL	0.32	0.634	−0.99; 1.62	−0.77	0.574	−3.45; 1.92	0.15	0.917	−2.59; 2.88	0.88	0.342	−0.93; 2.69
	CDRSB	−0.11	0.414	−0.37; 0.15	−0.09	0.774	−0.66; 0.49	−0.14	0.650	−0.73; 0.45	−0.32	0.146	−0.74; 0.11
	Age	1.65	0.350	−1.81; 5.10	−0.02	0.995	−7.23; 7.19	−3.36	0.407	−11.31; 4.58	−2.91	0.308	−8.52; 2.69
Model 3	Intercept	0.16	0.942	−4.21; 4.54	−6.65	0.139	−15.46; 2.16	−4.27	0.358	−13.37; 4.83	−3.17	0.473	−11.84; 5.49
	Lateral Ventricle	**50.19**	**0.002**	**18.37; 82.01**	55.63	0.107	−11.98; 123.25	25.95	0.495	−48.55; 100.44	47.16	0.297	−41.46; 135.78
	Inferior Lateral Ventricle	**658.24**	**0.009**	**165.12; 1151.36**	64.55	0.922	−1229.89; 1358.99	*1029.32*	*0.056*	*−25.85; 2084.48*	211.24	0.802	−1439.55; 1862.03
	Thalamus	481.56	0.152	−176.94; 1140.05	205.14	0.768	−1156.16; 1566.44	−416.48	0.578	−1885.04; 1052.09	**1763.18**	**0.011**	**407.63; 3118.74**
	Hippocampus	−354.03	0.370	−1127.99; 419.94	346.04	0.691	−1359.49; 2051.56	1016.31	0.274	−806.39; 2839.02	−359.34	0.670	−2014.58; 1295.89
	Third Ventricle	**−3474.59**	**0.001**	**−4493.84; −2455.35**	**−6422.58**	**0.001**	**−8879.09; −3966.07**	**−7791.98**	**0.001**	**−10500; −5120.31**	**−11950**	**0.001**	**−15200; −8659.69**
	Age	0.0174	0.388	−0.02; 0.06	**0.09**	**0.017**	**0.02; 0.18**	**0.0921**	**0.037**	**0.005; 0.18**	−0.0001	0.997	−0.08; 0.08

Note. All volumes are adjusted for total intracranial volumes. $A\beta_{42}$: CSF $A\beta_{42}$ levels; TAU: CSF Total tau levels; PTAU: CSF phosphorylated tau levels. MOCA: Montreal cognitive assessment; MMSE: Mini-mental state examination; CDGLOBAL: Clinical dementia rating global score; CDRSB: Clinical dementia rating sum of boxes. Significant predictors are highlighted in **bold.** *Italic represents a trend toward significant.*

in the early stages of the disease, losing its effect in more advanced disease stages. While $A\beta_{42}$ levels are still within the normal range, increased accumulation of intracellular neurofibrillary tangles in the IA could lead to neuronal and synaptic loss (Iqbal et al., 2010; Zhang et al., 2021). This could explain why it is less probable to find robust IA connectivity (e.g., broad IA) in LMCI and AD. Our result suggests that this process impacts IA but not to the extent that the IA is completely lost with increased disease pathophysiology and associated atrophy (Fig. 2). Notwithstanding, this remains speculative at this stage, and future studies need to confirm this interpretation.

Leading on from this, our binary logistic results showed a positive trend, indicating that larger thalamic volumes increased the probability of an IA. A previous study in healthy people already showed that the presence of an IA was associated with increased thalamic volume (Damle et al., 2017). Our post-hoc analysis revealed that this effect was only significant for the broad variant. Crucially, the lateral and inferior lateral ventricle volumes showed a positive effect on the single IA, and the inferior lateral ventricle showed a positive trend toward significant for the bilobar IA. Increased age was also related with higher probability of a double and bilobar IA. This means that a larger thalamic volume increases the probability of a broad IA. On the contrary, larger ventricular volumes increases the probability of a single IA, whereas ageing increase the likelihood of a double or bilobar IA. Neurodegenerative diseases and ageing are associated with ventricular system enlargement (Curra et al., 2019) and thalamic shrinkage (Forno and Hornberger, 2023). Importantly, our results were consistent even with age as a covariate, suggesting that IA integrity is affected by ageing and AD pathological mechanisms. Our volumetric analyses align with our hypothesis, suggesting that ventricular system enlargement and thalamic shrinkage decrease the probability of finding larger IA. Evidence has already shown how ventricular dilatation can cause IA rupture due to hydrocephalus (El Damaty et al., 2017). Delineating the impact of tissue loss versus ventricular enlargement on the presence of IA and its extent is clearly another future direction that needs to be explored in MCI and AD.

In terms of ventricular enlargement, the 3rd ventricle was the most important predictor of an IA. Larger 3rd ventricle volume reduced the likelihood of the presence of an IA, and any of its IA variants. Interestingly, the lateral and inferior lateral ventricles increased the probability of a single IA variant. Ventricular enlargement can be a consequence of hippocampal atrophy (Apostolova et al., 2012) and has been related to pathological levels measured with AD biomarkers (Chou et al., 2009). Importantly, our results suggest that the absence of an IA and the single IA variant are more commonly seen with larger 3rd ventricle volumes. Probably, the positive effect of the lateral and inferior lateral ventricles in the single IA is the consequence of an enlarged ventricle system resulting in thinner adhesion of IAs as the disease progresses. Our volumetric analysis also suggests that the volumes of the ventricle may follow a progression, with the inferior lateral ventricle affected for EMCI, LMCI, and AD, the lateral ventricle affected for LMCI and AD, and the third ventricle only affected in AD.

In terms of prevalence, we replicated previous findings in healthy younger people and stroke patients that the single IA was the most prevalent IA variant across all images (Vidal. et al., 2024) with no significant differences across prodromal and clinical AD groups. Given that most of the population presents a single IA, it is logical to presume that the volume of the IA may shrink in dementia stages compared to healthy older adults. Thus, future studies are needed to determine whether the volume of the IA shrinks as a function of AD disease progression. The diameter and length of the IA could also be valuable metrics in future studies. Interestingly, in this regard, there was no effect on the clinical staging or cognitive measures in the presence or variant of an IA. The cognitive role of the IA in healthy controls is still a matter of debate. While some studies have found better performance on attention tests in participants with an IA (Borghei et al., 2020; Damle et al., 2017), others have failed in the attempt (Vidal et al., 2024). As has been previously

suggested, one plausible explanation for these conflicting findings is that the selection of the neuropsychological instrument is not sensitive enough to understand the role of an IA (Vidal. et al., 2024). A distinct possibility is that the cognitive domains assessed are not task-demanding of the IA. There have been suggestions that some aspects of the IA originates from the dorsomedial thalamic nucleus (Sahin et al., 2023), which has a crucial role in executive functions, memory and attention (Forno et al., 2023; Golden et al., 2016). A recent study reported that thalamic stroke patients with an IA performed better in executive tests (Vidal et al., 2024) compared to stroke patients with no IA. Therefore, our null results may be better explained due to the test selection, as clinical staging questionnaires or screening tests are not sensitive enough to detect an association between the IA and cognitive measures. Our analyses also showed that the bilobar and double variants had nearly identical distributions when considering the thalamus and third ventricle volumes. It is important to evaluate whether the distinction between these variants has functional significance or if it primarily reflects differences in the 'shape' of the adhesion only. If the latter is true, it may be worth reconsidering the classification and combining these variants, as this could provide more insight into their impact, such as their association with disease progression or staging.

Despite these novel findings, our study comes with limitations. First, using categorical variables may impact the robustness of the results. IA variants representing fewer cases (i.e., bilobar or double) may experience decreased statistical power, undermining the model's reliability. Second, the cross-sectional nature of our study limits our conclusions and raises several questions. We cannot be certain if the IA is directly affected by AD pathological mechanisms leading to changes in the IA variants from robust IA connectivity (broad) to thinner connectivity (i.e., single or double). Also, we cannot be certain how the IAs are affected by AD pathological mechanisms (i.e., p-Tau) with no volume or axonal integrity parameters. Future studies are required to conduct more in-depth volumetrics and pathophysiological investigations in prodromal and clinical AD. Importantly, as the single IA is the most prevalent in the population, an intriguing question is whether there are significant volume changes between groups within the same IA variant and whether the different IA subtypes have functional relevance or not. Finally, using robust techniques to measure axonal integrity will provide important answers if and how the IA variants are affected by AD pathophysiology.

5. Conclusions

In conclusion, this study provides novel results on the prevalence of IA variants across the AD continuum. Notably, IA was observed in most cases, regardless of the disease severity. The variants across groups showed no differences, with the single IA being the most prevalent across all groups. Importantly, elevated $A\beta_{42}$ and p-Tau levels and greater thalamic volume were associated with a higher likelihood of a broad IA. Although we cannot be certain that AD biomarkers directly affect IA integrity, our findings suggest that the IA may be related to AD pathology and disease progression.

CRediT authorship contribution statement

Gonzalo Forno: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Phoebe Rush:** Writing – review & editing, Visualization. **Vidal Julie P:** Writing – review & editing, Visualization, Methodology, Conceptualization. **Aggleton John P:** Writing – review & editing. **Rachel Tan:** Writing – review & editing. **Michael Hornberger:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Barbeau Emmanuel J:** Writing – review & editing, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Data availability

Data will be made available on request.

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