

Early-life second language experience confers lasting resilience of the medial temporal cortex to Alzheimer's biomarker burden in healthy aging

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1. Introduction

Second-language (L2) experience has been linked to a 4 to 5 year delay in dementia onset, but the **mechanism is debated**:

- **Resistance**: L2 experience reduces the accumulation of AD pathology itself (less amyloid/tau).
- **Resilience**: pathology accumulates equally, but the brain tolerates more of it before losing structure.
- Two open questions:
 - Is the L2 advantage **resistance or resilience**?
 - Does it require **ongoing** L2 use, or does **early-life** exposure suffice - even in people who stopped decades ago ("lapsed" L2 users)?

- **Hypothesis**: Early-life L2 frequency moderates the relationship between blood-based AD biomarkers and cortical thickness (a **resilience** signature), and this moderation persists in lapsed users, pointing to **developmental scaffolding** rather than an ongoing-exercise (training) effect.

Does early-life L2 experience leave a permanent structural trace - a reserve that outlasts the language itself?

2. Methods

Data	
Cohort	Definition of L2 experience
• ongoing CRC1436 cohort of cognitively healthy older adults (Z03 project) • N = 231 complete cases (structural MRI + plasma biomarkers + LEQ + covariates) • Mean age 71.3 yrs (SD 7.1); 47% female • L2 classification by LEQ (Lifetime of Experiences Questionnaire), score 1 = never ... 5 = weekly, 6 = daily, per early / mid / late life period	• Sustained L2: early and mid-life score ≥ 5 (N = 54) • Lapsed L2: early ≥ 5, mid-life < 5 (N = 91) • Low L2: early < 5 (N = 86) • High early-L2 (binary) = lapsed + sustained (N = 145)
MRI and AD pathology measurements	
• MRI: 0.8 mm MEMPRAGE, 3 T Siemens Skyra • FreeSurfer cortical thickness: Primary outcome: bilateral medial temporal cortical thickness • AD pathology index: We measured the Aβ1-42/1-40 ratio in the Aβ-IP eluates from plasma on the LUMIPULSE G platform (Fujirebio) and calculated the AT217-Term (Aβ1-40)/(Aβ1-42)*pTau217 as primary marker of AD pathology	
Statistical analyses	
• Linear models testing (a) resistance = group differences in AT217-Term; (b) resilience (L2 $\times$ AT217-Term interaction on thickness/GM volume). Adjusted for age, sex, education, and non-linguistic cognitive reserve (LEQ total minus L2 items). FDR-corrected across ROIs.	

3. Results

AD pathology - no indication of resistance

- General demographics were comparable with the exception of education - see Table 1
- Groups did **not** differ in AD biomarker burden
- $p = 0.94$, adjusted for age, sex, education, and non linguistic cognitive reserve [LEQ total minus L2 items] unadjusted Wilcoxon $p = 0.77$, N = 231

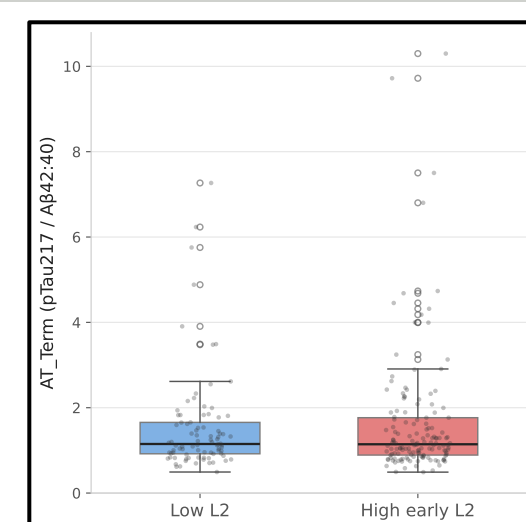


Fig. 1: No resistance: AD biomarker burden is equivalent across L2 groups

Neuroimaging - Resilience of the medial temporal cortex

- **Data indicate that early L2 confers resilience against AD pathology (Fig. 2, panel A)**
- Significant **L2 $\times$ AT217-Term interaction** on medial temporal cortical thickness ($t = 3.61$, $p_{FDR} = 0.004$):
 - In **Low-L2** participants, higher pathology predicted **thinner** medial temporal cortex
 - In **High early-L2** participants, thickness was **unaffected** across the pathology range
- **Lasting effects are present even in lapsed users (Fig. 2, panel B)**
- The resilience effect held in **both** trajectory groups:
 - Lapsed L2 (stopped after early adulthood): $p < 0.001$
 - Sustained L2 (continued into mid-life): $p = 0.010$

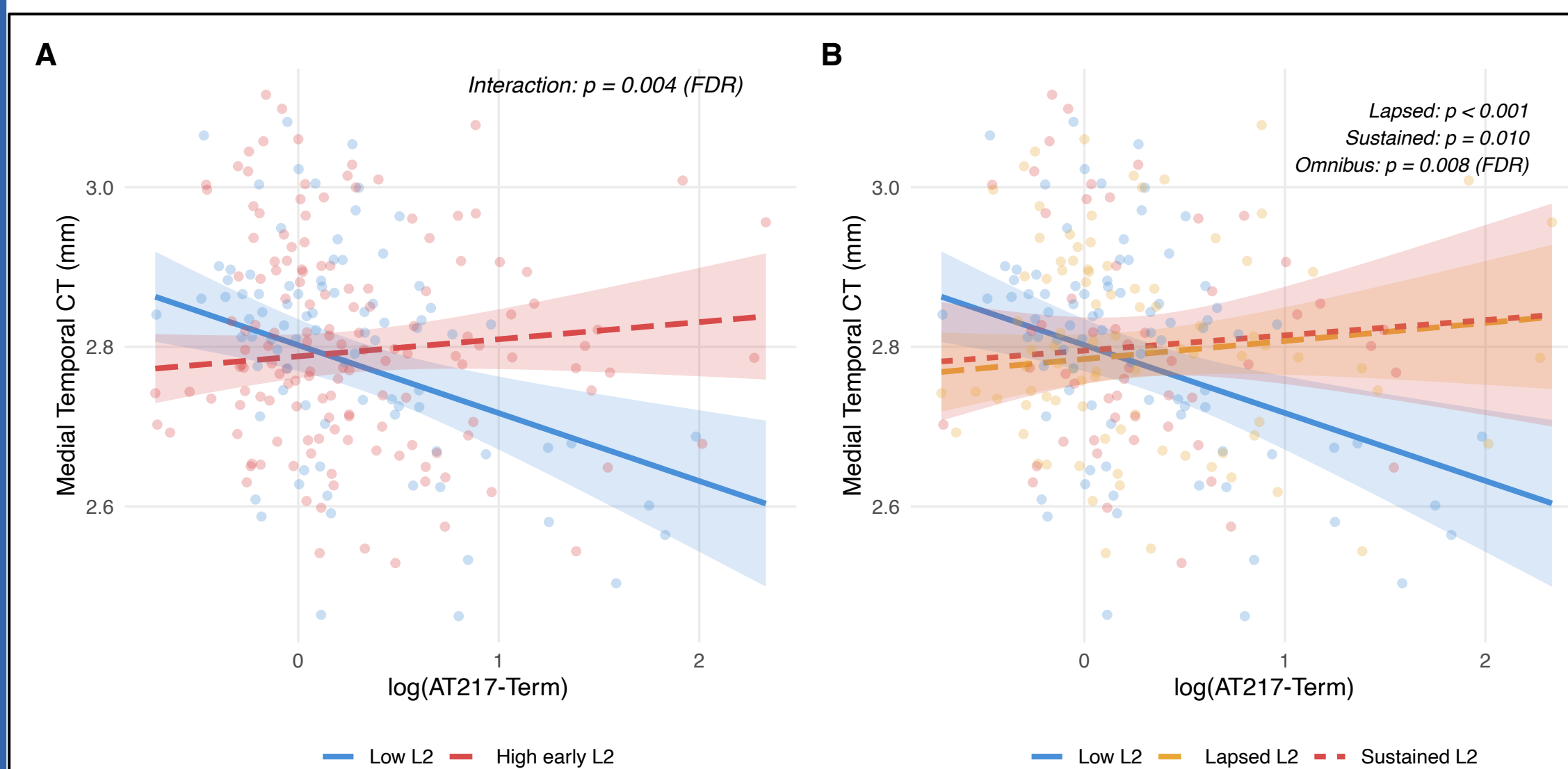


Fig. 2: (A) High vs. low early-L2. (B) By trajectory: lapsed ($p < 0.001$) and sustained ($p = 0.010$) both resilient; omnibus $p_{FDR} = 0.008$. Adjusted for age, sex, education, non-linguistic reserve.

3. Results (cont'd.)

Table 1. Participant characteristics by L2-use trajectory

	Total	Low L2	Lapsed L2	Sustained L2	p
N	231	86	91	54	
Age, years	71.3 (7.1)	71.2 (7.3)	70.9 (6.2)	72.3 (8.3)	0.485
Female, N (%)	108 (47%)	41 (48%)	40 (44%)	27 (50%)	0.762
Education, years	15.1 (2.3)	13.9 (2.2)	15.6 (1.9)	16.1 (2.4)	<0.001
CERAD-Plus total (z)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	0.6 (0.4)	0.019
AT217-Term, med [IQR]	1.14 [0.90-1.75]	1.15 [0.92-1.66]	1.11 [0.87-1.75]	1.18 [0.93-1.75]	0.772
ApoE $\epsilon\epsilon$, N (%)	52 (23%)	20 (24%)	20 (22%)	12 (22%)	0.974
LEQ total	101.3 (19.9)	91.2 (18.8)	104.4 (18.3)	112.0 (17.0)	<0.001
LEQ total (- L2 items)	97.0 (19.1)	89.3 (18.4)	100.4 (18.2)	103.8 (17.5)	<0.001
L2 early score	4.0 (1.7)	2.0 (1.0)	5.1 (0.4)	5.3 (0.5)	<0.001
Medial Temporal CT, mm	2.8 (0.1)	2.8 (0.1)	2.8 (0.1)	2.8 (0.1)	0.751
Hippocampal Vol, mm ³	3722 (374)	3730 (381)	3711 (355)	3731 (401)	0.931

Values: mean (SD), median [IQR] or N (%). P: ANOVA Kruskal-Wallis (AT-Term) or Chi². Sustained = early/mid ≥ 5 ; Lapsed = early ≥ 5 , mid < 5; Low = early < 5. AT217-Term = (A β 1-40)/(A β 1-42)*pTau217. CT = cortical thickness. LEQ = Lifetime of Experiences Questionnaire (- L2 = with L2 items removed).

4. Conclusion

- Early-life L2 experience does not prevent AD pathology from occurring
- However, our data suggest that early-life L2 experience is associated with preserved medial temporal cortical thickness despite elevated AD biomarkers
- The effect is specific to L2 experience and not explained by other cognitive-reserve components
- It persists in people who discontinued L2 use decades ago, consistent with developmental scaffolding: early-life L2 experience establishes lasting structural reserve that does not require ongoing use
- Together, these findings identify early-life L2 experience as a durable contributor to brain reserve, motivating longitudinal tests of whether preserved medial temporal structure delays cognitive decline

5. Outlook

- Better quantification and characterization of L2 use with finer-grained, more specific questionnaires capturing age of acquisition, proficiency, and switching frequency, not just use frequency
- Complementary structural analyses using different approaches, such as voxel-based morphometry (VBM), to confirm the medial temporal effect with a method independent of FreeSurfer
- Extension to diffusion MRI (DTI): to test whether the grey-matter resilience is mirrored in the white-matter tracts that connect the medial temporal lobe and language network (cingulum, uncinate, and inferior longitudinal fasciculi) which carry early AD pathology

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