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# Dual pathway to tau-related neurodegeneration in amygdala subregions

**AMANDA ANNETTESDOTTER<sup>1</sup>**, KATJA SELEZNEVA<sup>1</sup>, AMANDA E. DENNING<sup>2</sup>, ANIKA WUESTEFELD<sup>1</sup>, SADHANA RAVIKUMAR<sup>2</sup>, RANJIT ITTYERAH<sup>2</sup>, LISA M. LEVORSE<sup>2</sup>, MADIGAN BEDARD<sup>2</sup>, EUNICE CHUNG<sup>2</sup>, JOHN L. ROBINSON<sup>2</sup>, THERESA SCHUCK<sup>2</sup>, EDWARD B. LEE<sup>2</sup>, SYDNEY LIM<sup>2</sup>, WINIFRED TROTMAN<sup>2</sup>, ALEJANDRA BAHENA<sup>2</sup>, DAVID J. IRWIN<sup>2</sup>, EMILIO ARTACHO-PÉRULA<sup>3</sup>, MARÍA DEL MAR ARROYO-JIMÉNEZ<sup>3</sup>, ALICIA VELA HORCAJADA<sup>3</sup>, ESTHER BUENDIA ROSADO<sup>3</sup>, NOEMÍ VILLASECA GONZÁLEZ<sup>3</sup>, MARIA MERCEDES IÑIGUEZ DE ONZOÑO MARTIN<sup>3</sup>, MARÍA PILAR MARCOS RABAL<sup>3</sup>, ANA MARÍA INSAUSTI-SERRANO<sup>3</sup>, MÓNICA MUÑOZ-LÓPEZ<sup>3</sup>, DAVID A. WOLK<sup>2</sup>, COREY T. MCMILLAN<sup>2</sup>, NICOLA SPOTORNO<sup>1</sup>, DANIEL T. OHM<sup>2</sup>, OSKAR HANSSON<sup>1</sup>, RICARDO INSAUSTI<sup>3</sup>, PAUL A. YUSHKEVICH<sup>2</sup>, & LAURA E.M. WISSE<sup>1</sup>

<sup>1</sup>Lund University, Lund, Sweden; <sup>2</sup>University of Pennsylvania, Philadelphia, USA; <sup>3</sup>University of Castilla-La Mancha, Albacete, Spain

## Background

- Tau pathology is associated with neurodegeneration and may contribute to neuronal loss not only through local toxic effects<sup>1</sup>, but also through degeneration of connections to other affected regions<sup>2</sup>.
- The amygdala is affected early by tau pathology<sup>3</sup> and has connections with other vulnerable MTL regions<sup>4</sup>.
- The contribution of local and distal tau pathology to neurodegeneration in the amygdala – across its overall structure and its subregions – remains unclear.

MTL=medial temporal lobe

## Aim

To link tau pathology in the amygdala and other MTL regions to structural measures of the amygdala and its subregions.

## Methods

- Volumes of the amygdala and its subregions (Figure 1)
- 9.4 tesla (0.2x0.2x0.2 mm<sup>3</sup>) postmortem MRI
- Manual segmentations

|                                            | N              |  |
|--------------------------------------------|----------------|--|
| <i>n</i> with subregional amygdala volumes | 69             |  |
| <i>n</i> with quantitative tau             | 70             |  |
| age at death                               | 78±11 [44–101] |  |
| females                                    | 30 [38%]       |  |
| cognitively impaired                       | 57 [73%]       |  |
| no/low ADNC <sup>a</sup>                   | 31 [40%]       |  |

<sup>a</sup>ABC score < 2

- Tau pathology measures

- Contralateral semi-quantitative ratings (0–3)

- in the amygdala, and other MTL regions: the dentate gyrus, Cornu Ammonis 1/subiculum (CA1/SUB), and entorhinal cortex (ERC)

- Ipsilateral quantitative tau burden (tangles and threads) from histology

- in the whole amygdala, and the lateral, basolateral/basomedial, cortical, and centromedial subregions

- Thickness measures

- of MTL regions: CA1, CA1 white matter, subiculum, subiculum white matter, and ERC

- Statistical analysis

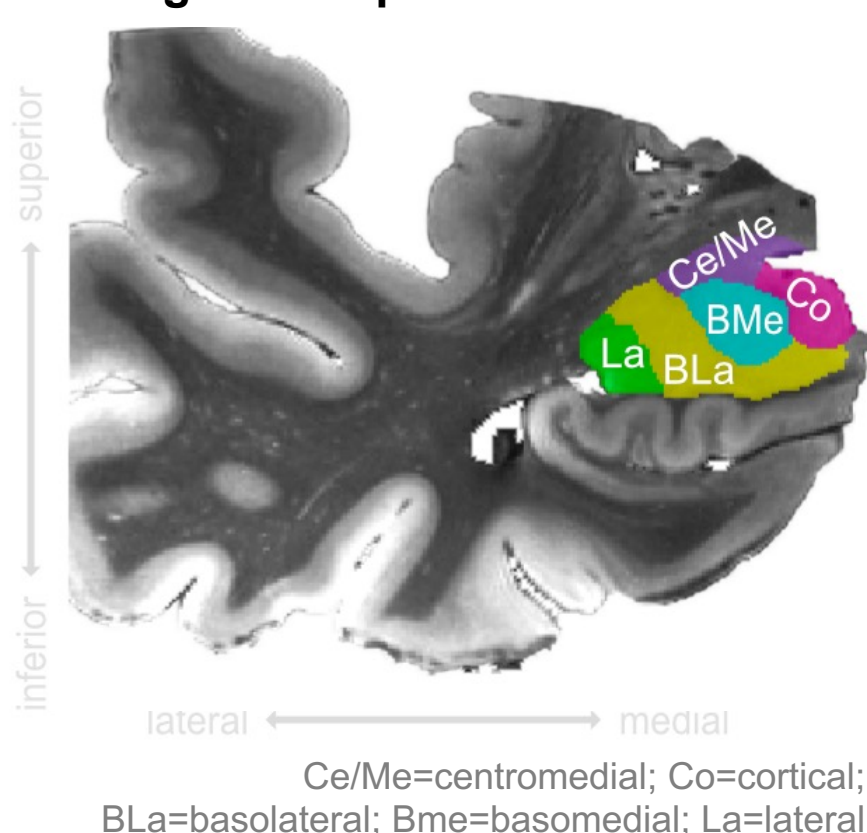
- partial Spearman rank correlations were used to test associations between semi-quantitative tau ratings and amygdala volumes, adjusting for age, sex, amyloid-β, α-synuclein, and TDP-43

- multiple linear regressions were used to test associations between quantitative tau burden and amygdala volumes, adjusting for age, sex, amyloid-β, α-synuclein, and TDP-43

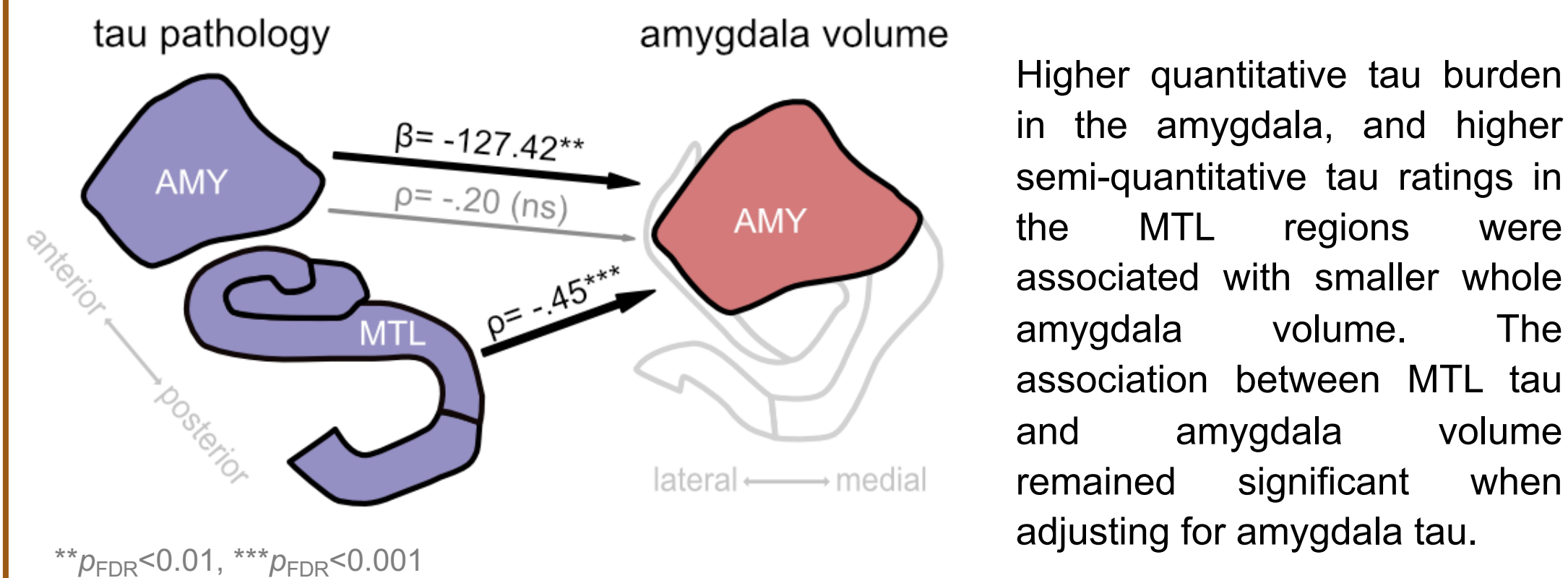
- mediation analysis was performed to test if MTL thickness was mediating associations between MTL tau and semi-quantitative whole amygdala volume

ADNC=Alzheimer's disease neuropathological change; MRI=magnetic resonance imaging

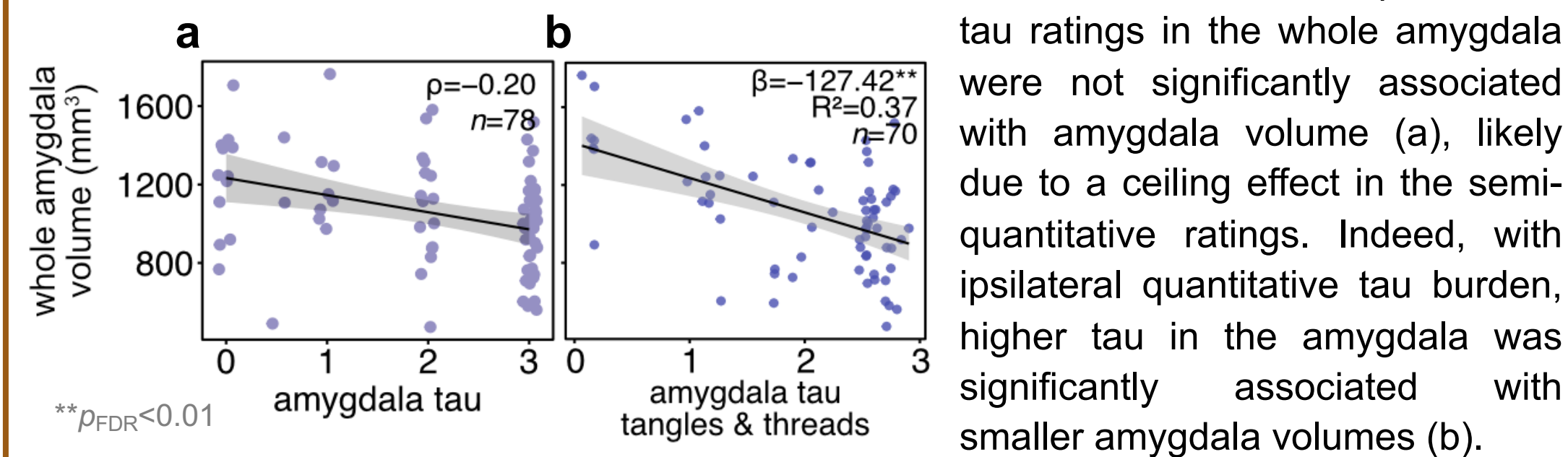
**Figure 1. segmented amygdala subregions on postmortem MRI**



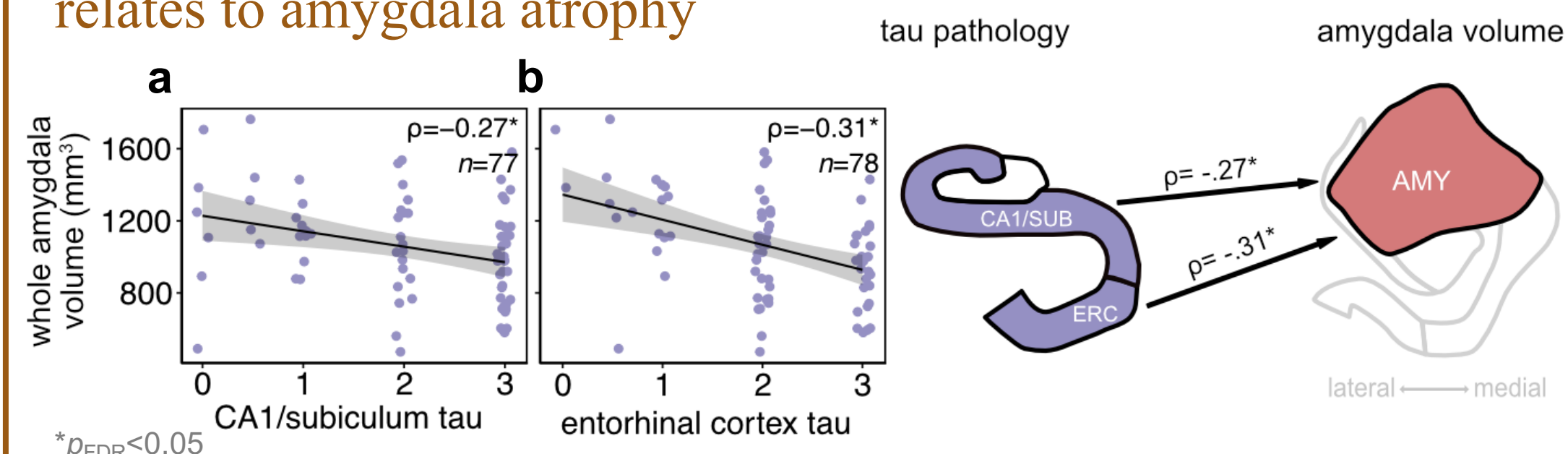
### 1. Higher tau in the amygdala and MTL is associated with smaller whole amygdala volume



#### 1.1. Local amygdala tau burden is associated with smaller amygdala volumes

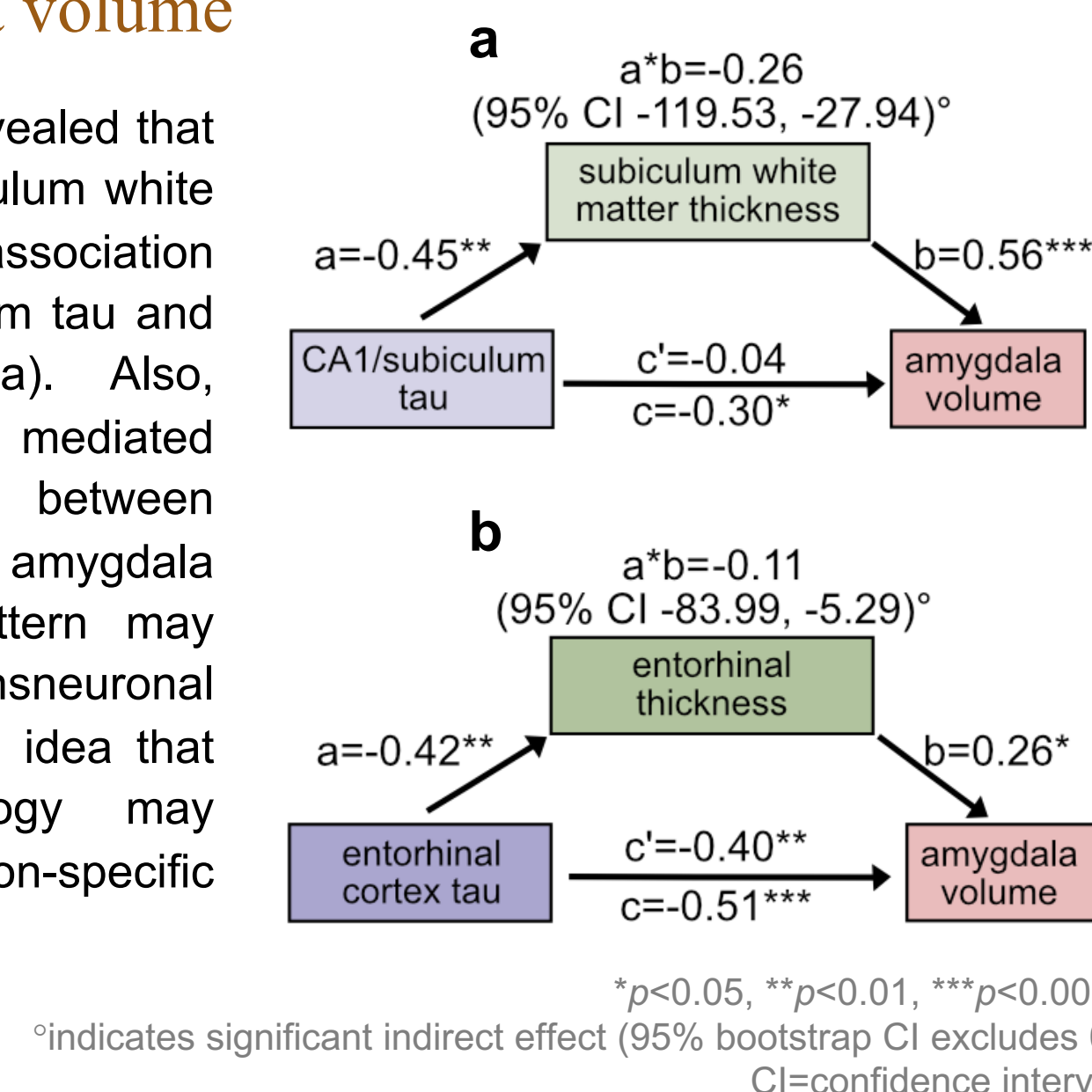


#### 1.2. Tau accumulation in structurally connected MTL regions relates to amygdala atrophy



#### 1.3. Thickness mediates associations between MTL tau and amygdala volume

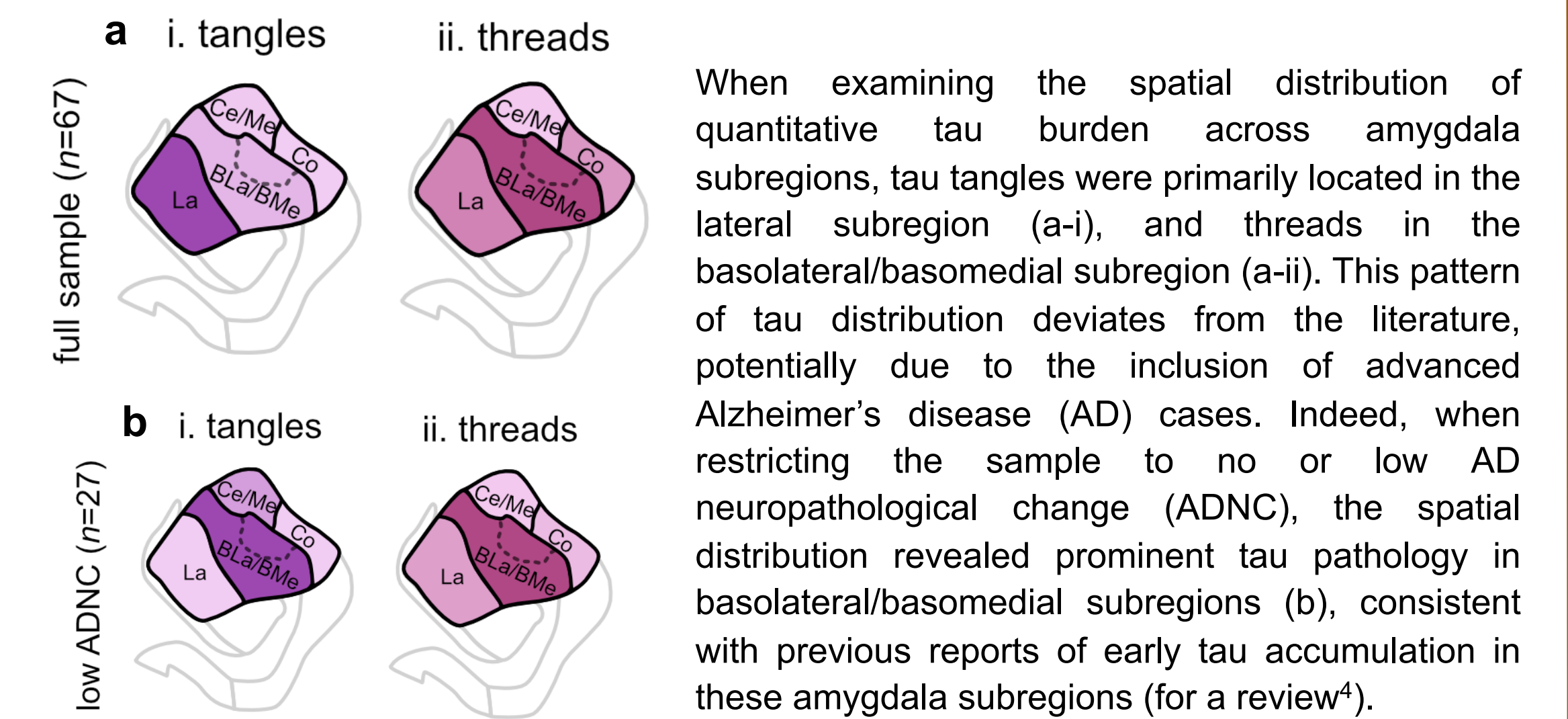
Mediation analyses revealed that thickness of the subiculum white matter mediated the association between CA1/subiculum tau and amygdala volume (a). Also, entorhinal thickness mediated the association between entorhinal tau and amygdala volume (b). This pattern may reflect retrograde transneuronal effects, supporting the idea that network-level pathology may contribute to region-specific neurodegeneration.



## Results

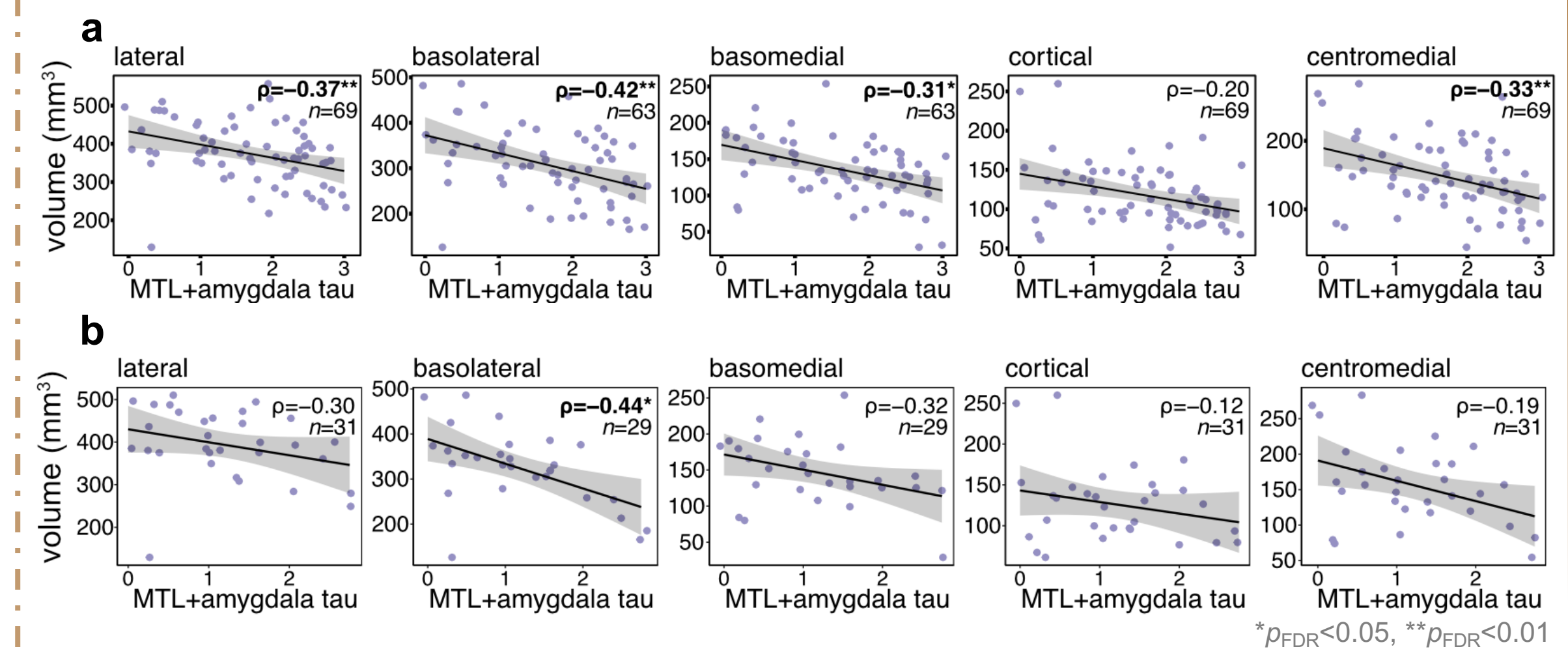
### 2. Higher MTL tau is associated with smaller volume across multiple amygdala subregions

#### 2.1. Spatial distribution of tau burden in amygdala subregions



#### 2.2. Hints of a more restrictive pattern of tau-related subregional neurodegeneration in early AD stages

In the full sample, higher MTL + amygdala tau ratings were associated with smaller volumes of all amygdala subregions, except the cortical (a). In the no/low ADNC subsample, higher tau was associated with smaller volume only in the basolateral subregion (b).



## Conclusions

- Higher tau burden both within the amygdala and in connected MTL regions was associated with smaller amygdala volumes.
- This supports a network-oriented view of tau-related amygdala neurodegeneration, where pathology may contribute to degeneration not only locally, but also across anatomically connected brain regions.
- This suggests that the pathways leading to MRI-visible atrophy are more complex than previously thought.
- A better understanding of the complex interplay of tau with neurodegeneration may improve prediction of atrophy and associated cognitive and behavioral symptoms.

MRI=magnetic resonance imaging; MTL=medial temporal lobe

### References:

<sup>1</sup>Moloney et al., 2021, *Alzheimers Dement*; <sup>2</sup>Cowan, 1970, *Contemporary Research Methods in Neuroanatomy*; <sup>3</sup>Braak & Braak, 1991, *Acta Neuropathol*; <sup>4</sup>Stouffer et al., 2023, *Brain*



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### contact:

✉ amanda.annettesdotter@med.lu.se