

The association of tau and amyloid levels with representational similarity in the amygdala's reactivity to and recovery from negative stimuli in individuals at risk for Alzheimer's disease



Mingtong Liu¹, Tobey J. Bethausen^{1,2}, Lauren K. Gresham¹, Sterling C. Johnson^{1,2}, Stacey M. Schaefer¹

¹University of Wisconsin-Madison's Institute on Aging; ²University of Wisconsin School of Medicine and Public Health



Background

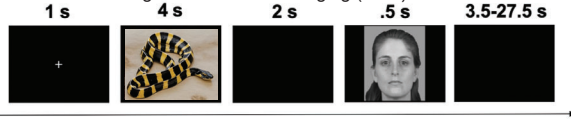
- Older adults at risk for Alzheimer's disease (AD) may show emotional differences before cognitive decline¹. Higher neuroticism, suggesting greater sensitivity to negative emotion, has been associated with a higher risk of AD².
- Amyloid and tau work together to drive healthy neurons into the diseased state.
- Existing studies suggest a relationship between self-reported emotional reactivity and amyloid burden, a crucial biomarker in predicting the development of Alzheimer's disease. For example, emotional reactivity, as measured by the revised NEO Personality Inventory, increases with age in adults who are later found to be amyloid-positive¹.
- Psychological well-being (PWB) has been indirectly linked to left amygdala persistence through daily affect: Those who exhibited less amygdala persistence, reported higher daily positive affect, which in turn, was associated with greater PWB³.
- This project examines whether tau and amyloid burden are related to
 - Brain reactivity to emotional stimuli (indicated by amygdala pattern similarity in response to negative compared to neutral images).
 - Brain measures of emotional recovery from negative stimuli (indicated by pattern similarity in the amygdala to negative pictures and the neutral faces that followed the negative pictures).
 - Functional connectivity in emotion regulation circuitry.
 - Psychological well-being.

Methods

Participants are from the Wisconsin Registry for Alzheimer Prevention⁴.

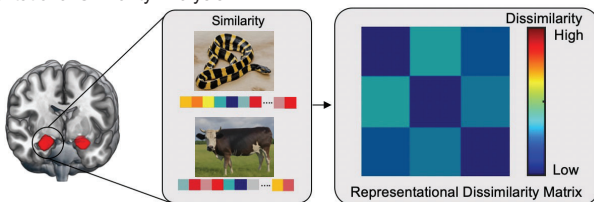
Participant Characteristic	All	Amyloid Negative (A-)	Amyloid Positive (A+)	Tau Negative (T-)	Tau Positive (T+)	Amyloid and Tau Positive (A+T+)
Sample Size	81	70	11	73	8	4
Mean Age	66.56	66.53	68.57	66.33	71.07	69.25
%Female	69%	69%	73%	67%	88%	100%
%BIPOC	6%	6%	9%	7%	0	0

Task-based functional magnetic resonance imaging (fMRI)

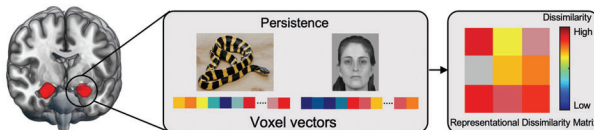


- 90 trials: 30 negative, 30 neutral, 30 positive emotional images (IAPS⁵) presented followed by a neutral faces.

Representational Similarity Analysis



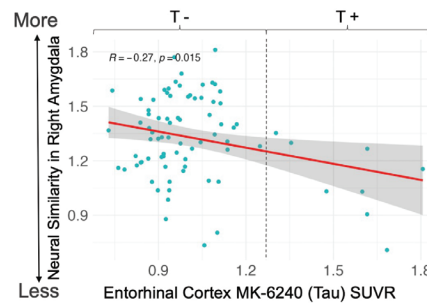
- Emotional reactivity: represented by the pattern similarity between negative compared to neutral images in the amygdala.



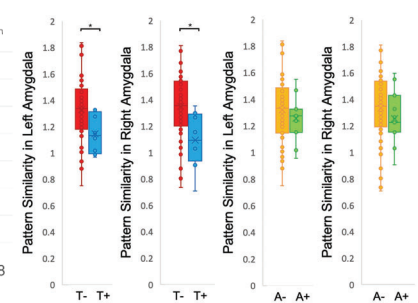
- Emotional recovery: represented by the pattern similarity between negative images and neutral faces that followed the negative images in the amygdala.

Research Question: Are amyloid and tau burden associated with fMRI indices of emotional reactivity to and recovery from negative stimuli in individuals at risk for Alzheimer's disease?

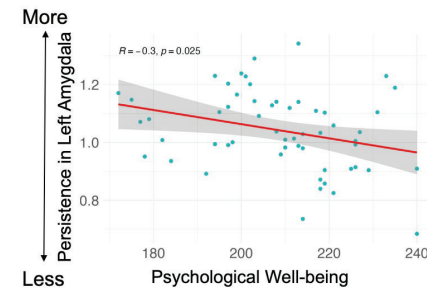
Results



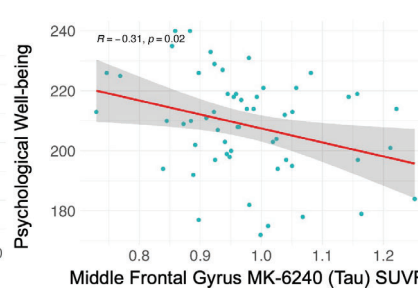
Greater tau burden in the entorhinal cortex is significantly related to less pattern similarity in right amygdala to negative and neutral images ($r = -0.27, p = 0.015$).



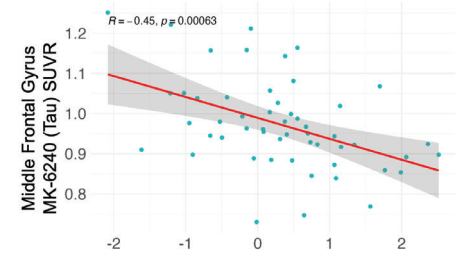
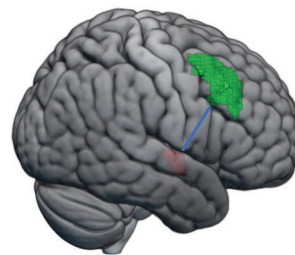
Pattern similarity in both left ($t(78) = 2.90, p = 0.014$) and right amygdala ($t(78) = 3.14, p = 0.013$) to negative and neutral images is greater in the T- group, compared with the T+ group.



Higher persistence in left amygdala activity patterns between negative images and neutral faces that followed the negative images is significantly related to lower psychological well-being ($r = -0.30, p = 0.025$).



Higher psychological well-being is significantly related to less tau in the middle frontal gyrus ($r = -0.31, p = 0.020$).



Connectivity between left amygdala and right middle frontal gyrus influenced by negative emotion persistence

Psychophysiological interactions (PPI) analysis shows that the connectivity between left amygdala and right middle frontal gyrus influenced by negative emotion persistence (Contrast of viewing neutral faces following negative images versus neutral faces following neutral images) is negatively associated with tau in middle frontal gyrus ($r = -0.45, p = 0.001$).

Conclusions

- Greater tau burden in the entorhinal cortex is significantly related to less neural similarity in right amygdala to negative and neutral images, suggesting a greater differentiation of the amygdala's response to negative vs. neutral images with higher tau.
- Higher tau in middle frontal gyrus and greater persistence in left amygdala response patterns from negative images to neutral stimuli that followed the negative images are both associated with lower levels of psychological well-being.
- Connectivity between left amygdala and right middle frontal gyrus (influenced by negative emotion persistence) is negatively associated with tau in middle frontal gyrus, suggesting less prefrontal regulation of amygdala activity.
- These findings provide evidence for associations between tau burden, fMRI indices of emotional reactivity and recovery, and psychological well-being in adults at risk for Alzheimer's disease.
- Future directions: Examine whether the fMRI indices of emotional reactivity and recovery predict future psychological well-being, accumulation of tau burden, and trajectories of cognitive decline to full clinical AD.

References & Funding

- Fredericks, C. A., Sturm, V. E., Brown, J. A., Hua, A. Y., Bilgel, M., Wong, D. F., Resnick, S. M., & Seeley, W. W. (2018). Early affective changes and increased connectivity in preclinical Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, 10(1), 471-479.
- Johansson, L., Guo, X., Duberstein, P. R., Hällström, T., Waern, M., Östling, S., & Skoog, I. (2014). Midlife personality and risk of Alzheimer disease and distress: A 38-year follow-up. *Neurology*, 83(17), 1538-1544.
- Puccetti, N. A., Schaefer, S. M., Van Reekum, C. M., Ong, A. D., Almeida, D. M., Ryff, C. D., Davidson, R. J., & Heller, A. S. (2021). Linking Amygdala Persistence to Real-World Emotional Experience and Psychological Well-Being. *The Journal of Neuroscience*, 41(16), 3721-3730.
- Johnson SC, Kosciak RL, Jonaitis EM, Clark LR, Mueller KD, Berman SE, Bendlin BB, Engelman CD, Okonkwo OC, Hogan KJ, Asthana S, Carlsson CM, Hermann BP, Sager MA. The Wisconsin Registry for Alzheimer's Prevention: A review of findings and current directions. *Alzheimers Dement (Amst)*. 2017 Dec 8;10:130-142.
- Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2008). International Affective Picture System (IAPS): Affective ratings of pictures and instruction manual. Gainesville, FL: University of Florida.
- Funding: This work was supported by R21MH113227 (jointly from NIMH & NIA) and U01AG077928 (NIA).