



Assessing the impact of inflammation on limbic circuitry and its role in depression in older adults

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Background and objectives

- Inflammation is hypothesized to represent an important biological event increasing the likelihood of major depressive episodes. Yet, the impact of inflammation on the limbic, system involved in major depressive disorders, remains to be determined.
- In this study, we examined how inflammation measured in older adults at risk of Alzheimer's disease (AD) was related with a life history of major depression and the integrity of limbic circuitry.

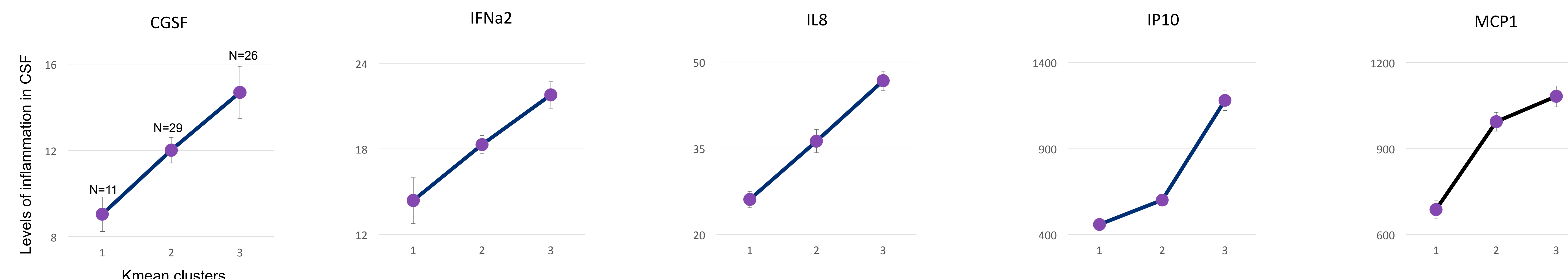
Method: Participants and markers of inflammation

- A total of 29 markers of inflammation were collected with lumbar puncture (LP) of cerebrospinal fluid (CSF) in 107 older adults of the PREVENT-AD cohort, which includes cognitively normal adults with a parental or multiple-sibling history of AD dementia.
- The CSF inflammatory markers were assayed using the Milliplex HCYTMAG60PMX29BK xMap kit (EMD-Millipore, Billerica, MA). Because several participants were below the assay range for several inflammatory markers and because some failed quality check for brain imaging, the final sample comprised 68 participants.
- Kmean clustering was applied to generate 3 groups of individuals based on their expressions of the 29 markers of inflammation (low, intermediate and high levels of inflammation).

Method: Brain Imaging

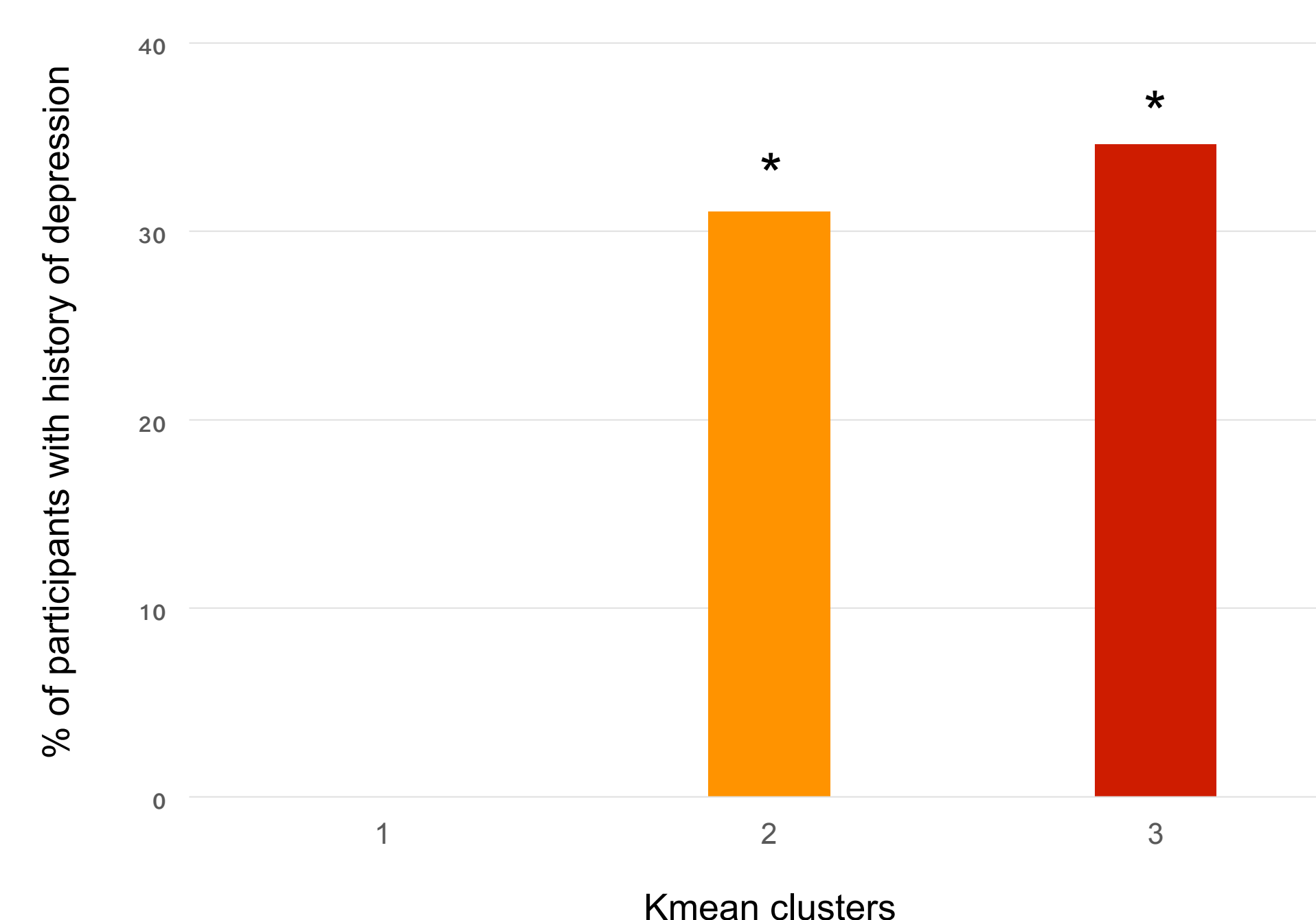
- Resting state functional magnetic resonance imaging (rsfMRI) was collected within one month after the LP was performed.
- rsfMRI analyses were restricted to correlation of the BOLD signal between 9 regions of interest (ROIs) delineating limbic circuitry. These ROIs were located in bilateral amygdala, nucleus accumbens, anterior hippocampus, posterior hippocampus, and one in the periaqueductal grey (PAG).
- The strength of the functional connectivity between these ROIs was linearly correlated with the participants' clusters using robust regressions.

Participants' clustering according to their levels of inflammation



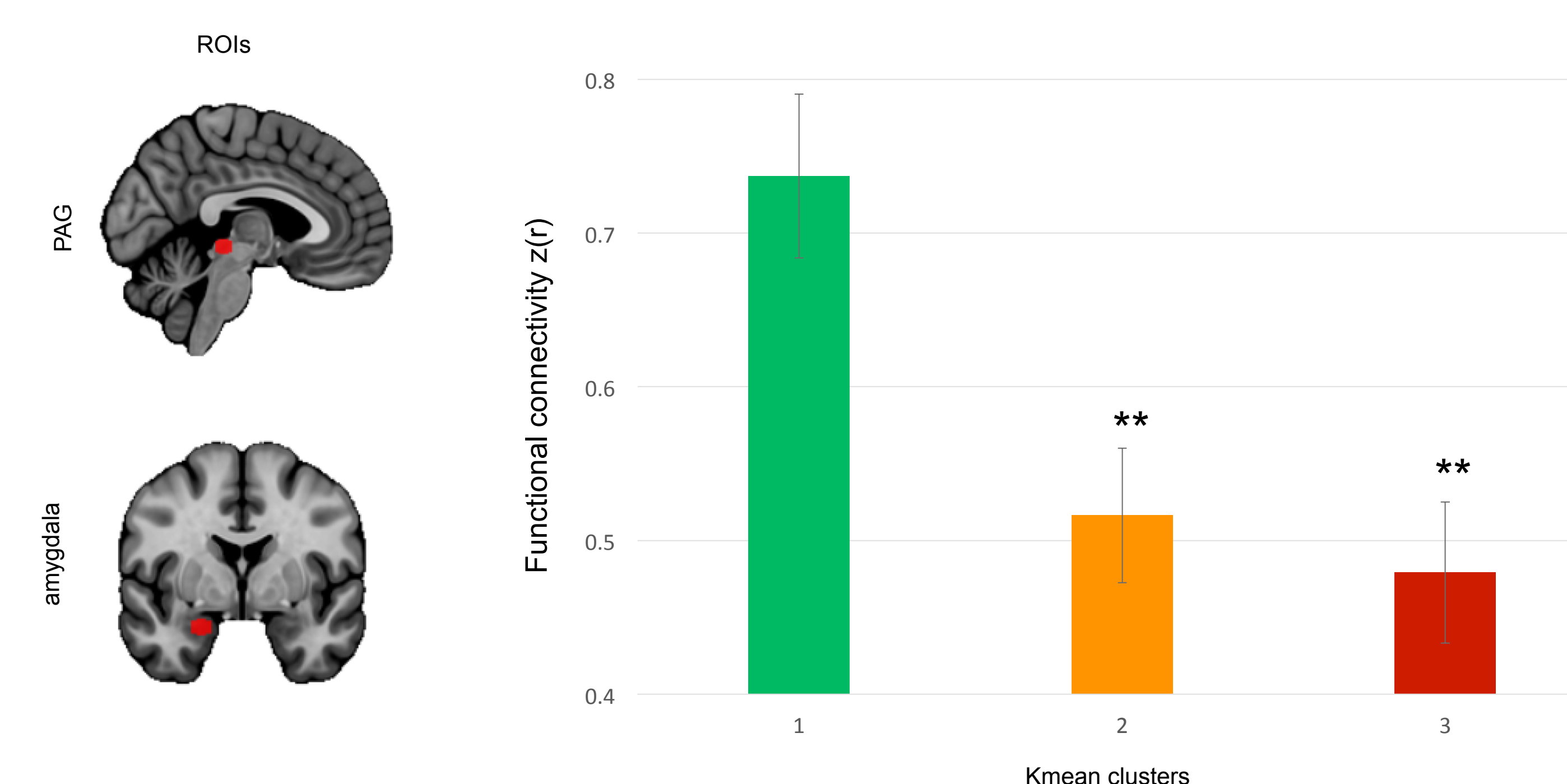
- Kmean clusters was performed on all 29 inflammatory markers. The figure displays five examples of markers with respect to each cluster (1: low; 2: intermediate; 3: high levels of inflammation).

Higher levels of inflammation in participants with history of depression



- The frequency of major episode of depression or burnout was lower in individuals with low inflammation compared to intermediate and high levels of inflammation ($\chi^2 > 4.4$; $ps < 0.037$).

Lower functional connectivity between PAG and amygdala in Clusters with higher inflammation



- Functional connectivity between the left amygdala and the PAG was related with the amount of inflammation after correcting for multiple comparisons ($F_{(2,63)} = 5.24$; $p = 0.002$).
- Post-hoc comparisons corrected for Bonferroni indicated that individuals with low inflammation showed higher connectivity than intermediate ($p = 0.027$) or high ($p = 0.007$) levels of inflammation.

Summary and Conclusions

- In older adults with a family history of AD, levels of inflammation were associated with a history of major episode of depression or burnout and with altered functional connectivity between the amygdala and the PAG.
- These findings are in line with the proposition that inflammation may alter functions of the emotion brain and therefore represents a risk factor for major episodes of depression.