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CSF cytokines show distinct associations with cognitive performance: CCL11 and IL-12 are negatively associated with MMSE scores, whereas IL-1ra and CCL5 present robust positive associations.

INTRODUCTION

Alzheimer’s disease (AD) is a prevalent neurodegenerative disorder characterized by progressive declines in cognitive and functional abilities, predominantly affecting older adults. AD is associated with prominent neuroinflammatory processes, in which chronic microglial overactivation leads to increased production of pro-inflammatory cytokines, immune signaling molecules that mediate communication among immune cells. Dysregulated cytokine production and sustained neuroinflammation contribute to neuronal damage, neurodegeneration, and the progression of cognitive impairment in AD.

We hypothesize that there are significant associations between CSF cytokine levels MMSE scores.

METHODS

**A. EXPERIMENTAL PROCEDURES**

**Figure 1. Experimental procedures workflow.** Schematic representation of the study design. (1) A cross-sectional approach was utilized. (2) Participants included 108 Brazilian older adults, (3) CSF samples were collected via lumbar puncture. (4) Biomarkers and multiple cytokines were quantified using the Luminex xMAP platform. (5) Cognitive performance was evaluated using the Mini-Mental State Examination (MMSE). (6) Associations between cytokines, AD biomarkers, and MMSE scores were explored using multiple linear regression models adjusted for age, sex, formal education, and APOE allele ε4 carrier status." adjusted for covariates (age, sex, formal education, and APOE ε4 status).

RESULTS

The multiple linear regression analyses demonstrated that CCL11 and IL-12 presented negative associations, while IL-1ra and CCL5 had substantial positive associations with MMSE scores. No significant associations were found between the other cytokines analyzed and MMSE scores. The network analysis showed that CCL11 had a strong positive interaction with CCL5 and positive mild interactions with IL-12 and pTau. Also, positive and mild interactions were found between IL-12 with CCL5 and IL-1ra.

**Table 1.** Adjusted associations between MMSE score and cytokines

| Variable         | B      | SD    | β     | p-value |
|------------------|--------|-------|-------|---------|
| Constant         | 15.438 | 8.600 |       | .076    |
| Sex              | -.908  | .731  | -.103 | .217    |
| Age              | -.107  | .054  | -.170 | .052    |
| Formal Education | .227   | .076  | .264  | .004*   |
| APOE ε4 carrier  | .913   | .828  | .104  | .274    |
| pTau             | -2.415 | .843  | -.290 | .005*   |
| Aβ42             | 2.074  | .775  | .241  | .009*   |
| CCL11            | -2.266 | .963  | -.241 | .021*   |
| IL-1ra           | 2.569  | .880  | .254  | .004*   |
| IL-12            | -.724  | .307  | -.202 | .021*   |
| CCL5             | 1.570  | .571  | .267  | .007*   |

Note: APOE: Apolipoprotein ε; B: regression slope or unstandardized coefficient, SD: standard deviation; β: standardized coefficient, indicates the effect of size; Sex: was defined as man and woman; MMSE: mini-mental state exam; IL: interleukin; IL-1ra: interleukin-1 receptor antagonist; CCL11: C–C motif chemokine ligand 11; CCL5: C–C motif chemokine ligand 5; (\*p<.05).

**Figure 2. Network of variables associated with MMSE.** Network representation of the variables that were significant predictors of MMSE in the regression model. The lines indicate correlations and the width representing force of correlation (the wider the line the stronger is the correlation). Blue lines indicate positive correlations while red lines indicate negative correlations. Abbreviations: MMSE: Minimental State Examination; IL: Interleukin; CCL5: C-C motif chemokine ligand 5; FE: Formal Education; APOE: Apolipoprotein E; Aβ42: Amyloid Beta 42; pTau: Phosphorylated Tau Protein.

CONCLUSION

- Our results suggest that cytokine activity is closely linked to cognitive impairment in AD, as reflected in MMSE performance in this Brazilian sample.
- Associations between cytokine levels and cognitive performance in AD, as assessed by the MMSE, highlighting the relevance of neuroinflammatory processes in AD.
- Future longitudinal studies integrating cytokine profiles with multimodal biomarkers are warranted to clarify temporal relationships and better characterize neuroinflammatory pathways involved in disease progression.

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OBJETIVE

This study investigated the cross-sectional associations between cerebrospinal fluid (CSF) cytokine levels and Mini-Mental State Examination (MMSE) scores in a sample of Brazilian older adults, adjusting for relevant covariates and Alzheimer’s disease biomarkers.

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