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N-acetyl-aspartyl-glutamate connects neuroinflammatory signatures to attention and working memory in people with HIV

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Abstract

Despite viral suppression, many people with HIV (PWH) experience persistent cognitive difficulties. We previously demonstrated that cerebrospinal fluid (CSF) *N*-acetyl-aspartyl-glutamate (NAAG) was associated with spatial attention and working memory. Here, we report that CSF NAAG also correlates with an inflammatory signature (MCSF, IL-15, MCP-1, sCD40L, IL-18, MMP-9) that relates to spatial attention and working memory. These results suggest that CSF NAAG may serve as an immunomodulatory biomarker relevant to cognition in PWH.

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Authors' contributions: L.H.R. and B.S.S. were responsible for study conceptualization; R.R. and J.A. were responsible for the development and analysis of CSF NAAG levels; H.R. and R.T.V. were responsible for the analysis of the CSF immune markers; R.T.V. also developed the immune panel and provided expertise in understanding the immune signatures; R.M.D. processed the computerized based cognitive data; A.C. conducted a literature review; L.H.R. was responsible for statistical analysis; J.M.C. contributed to the larger study design; L. H.R. and B.S.S. were responsible for manuscript writing and review. All authors have reviewed and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

Despite viral suppression, many people with HIV (PWH) experience cognitive difficulties in attention/working memory (WM) [1]. We recently reported that cerebrospinal fluid (CSF) concentrations of *N*-acetyl-aspartyl-glutamate (NAAG), a brain dipeptide that modulates glutamatergic neurotransmission via metabotropic glutamate receptor 3 (mGluR3; reviewed in [2]), were selectively associated with spatial attention/WM in 28 virally suppressed (VS)-PWH [3]. These findings extend prior magnetic resonance spectroscopy studies linking higher NAAG to better attention, WM, and executive function across neuropsychiatric conditions [4–6], including HIV [7], demonstrating that this relationship extends to CSF. However, the biological context of CSF NAAG in HIV remains poorly understood, including whether it reflects or modulates the neuroinflammatory milieu.

We extended our prior analysis by examining CSF NAAG and CSF inflammation associations in a subset of 15 VS-PWH (mean age 58.5 years [SD 10.9, range 39–76]; 67% male; 67% Black; 87% undetectable plasma viral load <20 cp/ml, two detectable at 45.6 and 65 cp/ml) from our original cohort [3] with available CSF inflammatory data. No additional selection criteria or subsampling were applied. The 15 participants were comparable to the full cohort in demographic (age, sex, race) and viral load, indicating that the subset was representative. NAAG concentrations were quantified using liquid chromatography–tandem mass spectrometry [3]. Neuroinflammatory markers were measured using multiplex immunoassays (U-PLEX, Meso Scale Discovery). Of the 37 markers assayed, 31 were detectable. Tumor necrosis factor (TNF)-, basic fibroblast growth factor, interferon (IFN)-inducible T-cell alpha chemoattractant, interleukin (IL)-29, IL-10, and macrophage inflammatory protein (MIP)-1 were undetectable or infrequently detected (IL-10, 46%, MIP-1, 20%). Figure 1, Supplemental Digital Content, http://links.lww.com/QAD/D727 shows the full distribution and detectability of analytes. The 31 analytes included *growth/trophic factors* [placental growth factor (PIGF), vascular endothelial growth factor (VEGF)-A, VEGF receptor (VEGFR)-1, tyrosine kinase with immunoglobulin and epidermal growth factor homology domains (Tie-2), brain-derived neurotrophic factor (BDNF)]; *cytokines*: [IL-6, IL-15, IL-18, IFN-, TNF-related apoptosis-inducing ligand (TRAIL)]; *chemokines*: [monokine induced by IFN-(MIG), IFN–induced protein (IP)-10, stromal cell-derived factor (SDF)-1, MIP-1β, MIP-3β, fractalkine, monocyte chemoattractant protein (MCP)-1]; *myeloid/microglial activation*: [macrophage colony-stimulating factor (M-CSF), sCD14, sCD163, soluble CD40 ligand (sCD40L)]; *endothelial/vascular injury*: [clusterin, cystatin C, vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM)]; *matrix remodeling/blood brain barrier integrity*: [matrix metalloproteinase (MMP)-2, MMP-9, von Willebrand factor (vWF)]; *acute-phase proteins* [C-reactive protein (CRP), serum amyloid A (SAA)]; and *neuronal injury*: neurofilament light chain (NfL). Many analytes are multifunctional and span multiple categories.

In the larger sample with CSF inflammatory data (n=32), principal components analysis (PCA; varimax rotation with Kaiser normalization) identified eight neuroinflammatory signatures explaining 82.6% of total variance across all markers (italicized markers were negatively loaded): M-CSF/IL-15/MCP-1/*sCD40L*/IL-18/MMP-9 (12.9% variance); Tie-2/MMP-2/MIP-3β/IP-10 (12.3%); clusterin/cystatin C/ICAM/vWF/VCAM (12.1%), VEGF-A/PIGF/MIG/NFL/SDF-1/BDNF (12.0%); TRAIL/VEGFR-1/fractalkine (8.1%); CRP/SAA (7.5%); sCD14/sCD163 (6.4%); MIP-1β (5.8%); and IFN-/IL-6 (5.4%). Cognition was

assessed using an NIMH Research Domain Criteria-based cognitive battery with domain-specific factor scores derived from PCA [3]. The present analysis focused on spatial attention/WM. Pearson correlations were used to examine associations between CSF NAAG, neuroinflammatory signatures, and spatial attention/WM. Variable distributions were examined using histograms and Shapiro–Wilk tests to verify normality. Variables were normally distributed, supporting parametric tests. Given the small sample size and exploratory nature of this study, *P*-values were not adjusted for multiple comparisons, and results should be interpreted heuristically to guide future work.

CSF NAAG concentrations were associated with three neuroinflammatory signatures: M-CSF/IL-15/MCP-1/*sCD40L*/IL-18/MMP-9 (r=0.57, P=0.026), TRAIL/VEGFR-1/fractalkine (r=0.58, P=0.022), and CRP/SAA (r=0.60, P=0.019; Fig. 1). The only signature associated with both NAAG and spatial attention/WM was M-CSF/IL-15/MCP-1/*sCD40L*/IL-18/MMP-9 (r=0.56, P=0.031). Within this signature, IL-15 (r=0.786, P<0.001), MMP-9 (r=0.751, P=0.001), and M-CSF (r=0.607, P=0.016) correlated most strongly with NAAG, with MCP-1 (r=0.496, P=0.06) and IL-18 (r=0.42, P=0.11) not reaching significance. Spatial attention/WM was also associated with IL-15 (r=0.517, P=0.048), M-CSF (r=0.569, P=0.027), MCP-1 (r=0.549, P=0.034), and IL-18 (r=0.525, P=0.045). CSF NAAG remained associated with spatial attention/WM in this subset (r=0.59, P=0.02).

These exploratory findings suggest that NAAG is embedded within inflammatory pathways that converge with attention/WM. The implicated signature M-CSF/IL-15/MCP-1/*sCD40L*/IL-18/MMP-9 reflects coordinated myeloid recruitment (M-CSF, MCP-1), T-cell activation (IL-15, sCD40L, IL-18), and extracellular matrix remodeling (MMP-9) processes often linked to cognition in PWH (reviewed in [8]). At the individual-marker level, IL-15, MCSF, and MCP-1 were most strongly associated with NAAG and attention/WM, reinforcing the specificity of this inflammation–NAAG–cognition axis. Each marker has been implicated in functional equilibrium neuroimmune processes. IL-15 in neuroplasticity and neurogenesis [9,10], MCP-1 in immune surveillance and neurogenesis [11], and M-CSF in microglial maintenance and repair [12]. Whereas elevated neuroinflammation is typically associated with poorer cognition in PWH (reviewed in [13,14]), here higher levels of this signature were linked to higher NAAG and better attention/WM, suggesting that under viral suppression these pathways may act in compensatory or functional-equilibrium processes within the CNS. Alignment of these pathways with higher NAAG suggests that a coordinated immunometabolic state may facilitate preserved attention/WM in VS-PWH. The direction remains uncertain as proinflammatory activity may influence NAAG levels via upregulation of its catabolic enzyme, glutamate carboxypeptidase II (GCPII), while NAAG signaling through mGluR3 could in turn regulate inflammation and cognition. Although causality has not been established in humans, direct experimental evidence in preclinical models demonstrates that elevating NAAG or blocking its degradation by inhibiting GCPII reduces microglial activation and proinflammatory cytokine expression, supporting an anti-inflammatory and immunomodulatory role [15–17]. Whether this reflects a transient compensatory response or a stable protective phenotype remains to be determined. Other PCA-derived signatures reflected immune-regulatory, vascular, and neuroimmune signaling processes (5-TRAIL/VEGFR-1/fractalkine) and acute-phase systemic inflammation (6-CRP/SAA), but none associated with spatial attention/WM.

By integrating neurometabolic and neuroimmune biomarkers, these results extend our prior observation of domain specificity in the NAAG–attention/WM link and highlight a potentially mechanistic inflammation–NAAG–cognition axis. Although limited by sample size, lack of controls, and exploratory correlational analyses, the convergence of NAAG and neuroinflammation on attention/WM underscores the value of domain-specific rather than global cognition. Associations suggest that in VS-PWH, certain neuroimmune mediators may act in functional-equilibrium rather than a pathogenic manner, supporting cognition through coordination with NAAG. Longitudinal studies in larger cohorts are needed to determine whether NAAG mediates the cognitive effects of neuroinflammation, whether neuroinflammation mediates NAAG's impact on cognition, or whether bidirectional influences operate over time. Such work could position NAAG as both a neurometabolic and immunomodulatory biomarker, informing precision diagnostics and glutamatergic- or immune-targeted therapies in neuroHIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

The datasets generated and/or analyzed during the current study are available from the corresponding authors upon reasonable request.

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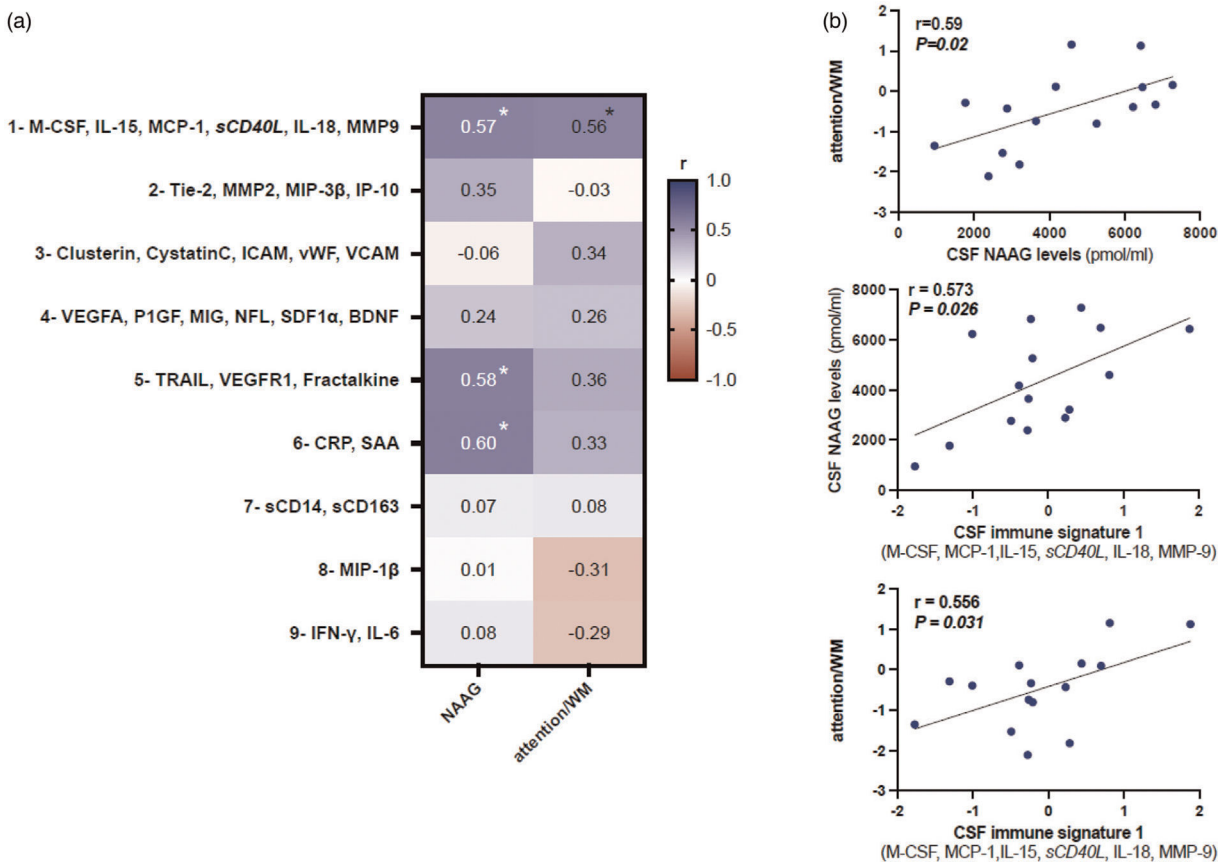

Fig. 1. Heatmap of correlations between cerebrospinal fluid (CSF) NAAG, eight PCA-derived neuroinflammatory signatures, and spatial attention/working memory (WM) in virally suppressed people with HIV (PWH, a).

Each cell represents the Pearson correlation coefficient (*r*), with color intensity indicating strength and direction of the correlation (green = positive, pink = negative). Asterisks denote statistical significance (**P* < 0.05). Among the eight signatures, only the M-CSF/IL-15/MCP-1/*sCD40L*/IL-18/MMP-9 signature was significantly related to both CSF NAAG and spatial attention/WM (b).