Irritability and its Associations with Immuno-vascular Risk Factors in the Aging Brain

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BACKGROUND

- Neuropsychiatric symptoms have long been associated with immuno-vascular disorders.
- Age-associated neurovascular changes are pervasive and contribute to functional decline.
- Anecdotally, clinicians report increased irritability in patients with cerebrovascular disease (CVD).
  - Yet, very little evidence exists linking irritability to compromised cerebrovascular health.

AIM: *To examine the link between irritability and quantitative measures of immuno-vascular risk such as white matter integrity, systemic inflammation, and clinical vascular risk factors.*

METHODS

Measure of Neuropsychiatric Symptoms

- Neuropsychiatric Inventory Questionnaire (NPI-Q)
  - Irritability score: 0 – 3 (none, mild, moderate, severe)
  - Completed by an informant

Plasma-based Inflammatory Markers

- TNF-alpha (MesoScale Discovery)
- IL-6 (MesoScale Discovery)
- CRP (Quest Diagnostics)

Imaging

- 3T Siemens MRI scanner
  - DTI – measures of white matter integrity
    - Whole-brain fractional anisotropy (FA)
    - Whole-brain mean diffusivity (MD)

Measures of Clinical Vascular Risk Factors

- Systolic blood pressure
- Heart rate
- Body mass index (BMI)

Statistical Analysis

Multivariable linear regression models

- Controlling for:
  - Age
  - Sex
  - Education

Table 1. Study Participant Demographic and Clinical Characterization

n	175
Average Age (Range)	72 (52, 99)
Sex, % female	50.8%
Average Education (Range)	17.6 (12, 20)
Average MMSE (Range)	29 (23, 30)
CDR	(0 – 0.5), 97% 0
NPI Irritability Severity (n)	0: 152; 1: 19; 2: 4; 3: 0
Average Systolic BP (Range)	132 (99 – 183)
Average Heart Rate (Range)	67 (43 – 120)
Average BMI (Range)	26 (16, 37)

RESULTS

White Matter Microstructural Integrity

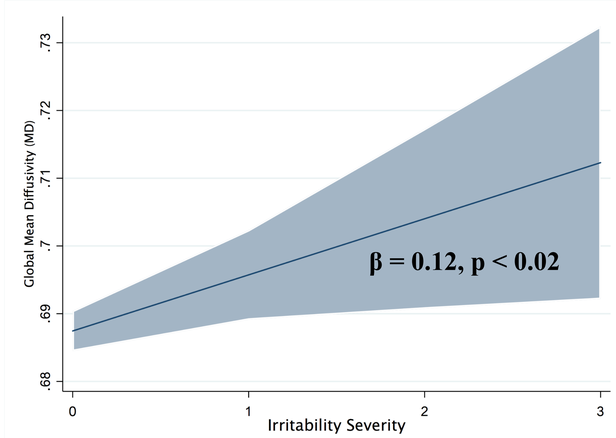

Figure 1. Greater mean diffusivity (MD), indicating compromised white matter microstructural integrity, is significantly associated with increased irritability severity.

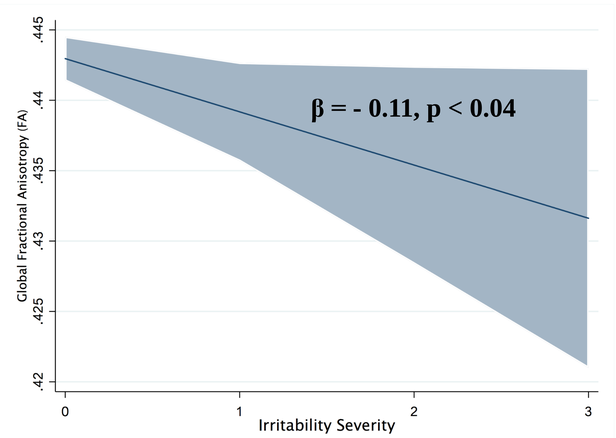

Figure 2. Lower fractional anisotropy (FA), indicating compromised white matter microstructural integrity, is significantly associated with increased irritability severity.

Systemic Inflammation

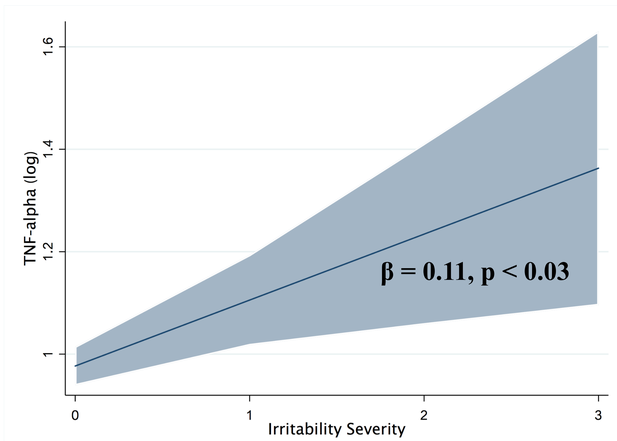

Figure 4. Greater levels of TNF-alpha, a proinflammatory cytokine and marker of systemic inflammation, is significantly correlated with increased irritability severity.

There were no statistically significant associations of irritability severity with white matter hyperintensities, Fazekas scores, CRP, or systolic BP (β range= 0.02 – 0.14, ps > 0.05)

CONCLUSIONS

- Neuropsychiatric symptoms are common comorbidities of neurodegeneration, and recent evidence suggests that they could be considered prodromal (Barnes et al., 2012)
- Our data indicate that irritability is linked with:
  1. compromised white matter microstructural integrity (*MD and FA*)
  2. molecular measures of systemic inflammation (*TNF-alpha*)
- There were only small, nonsignificant associations with traditional measures of cardiovascular health, i.e. systolic BP, heart rate, and BMI
  - This could be due to the following limitations in our cohort:
    - Our cohort lacks variability in systolic BP and irritability severity, as well as a low incidence of white matter disease
  - This could also indicate a lack of specificity in traditional clinical measures of vascular health
- Despite the restricted range of our typical aging cohort, we do see significant associations between irritability and white matter integrity as well as systemic inflammation
  - This could indicate that white matter integrity plays a nuanced role in mood and behavioral changes
  - Minor elevations in systemic inflammation could be enough to affect psychological experiences in older adults
- Inflammation and white matter changes are known risk factors for neurodegeneration, thus irritability may be a symptomatic harbinger of age-associated immuno-vascular dysregulation.
- Future research should aim to define the mechanisms related to the nuanced interplay between neuroinflammation and psychiatric symptomatology.

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