Cognitive resilience against brain damage depends on white matter network connectivity: The Maastricht Study

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INTRODUCTION:

Brain damage is associated with cognitive decline and increased dementia risk [1]; however, there is heterogeneity in observed effect of brain damage on cognitive outcomes [2]. Differences in brain network connectivity may reflect the capability of the neurological substrate to compensate for brain damage and preserve cognitive function (cognitive resilience) [3]. We examined the associations between white matter connectivity, brain damage markers and cognition in a population sample of middle-aged individuals.

METHODS:

4759 participants from The Maastricht Study (age 59.2±8.7, 50.2% male) with available cognitive test and brain imaging data were assessed [4]. Brain volumes were quantified from structural MRI and taken as markers of atrophic damage. White matter hyperintensities (WMH), microbleeds and lacunar infarcts were visually assessed and combined into a vascular damage score. Log-transformed WMH volume was also assessed separately. Whole-brain connectivity statistics were derived from the average number and volume of white matter tracts connecting 94 segmented brain regions. Multivariable linear regression was used to investigate whether connectivity modified associations between brain damage and cognition, adjusted for a range of demographic and cardiometabolic risk factors.

RESULTS:

Atrophic (higher cerebrospinal fluid volume [B=-0.133, $p \leq 0.001$], lower gray [B=-0.095, $p \leq 0.001$] and white [B=-0.124, $p \leq 0.001$] matter volumes) and vascular damage markers (higher WMH volume [B=-0.082, $p \leq 0.001$], higher combined vascular damage score [B=-0.073, $p \leq 0.001$]) were associated with reduced cognition. A higher number of connections between brain regions was associated with better cognitive function (B=0.083, $p \leq 0.001$). Furthermore, connectivity moderated the negative association between damage and cognition ($\chi^2=8.64$, df=3, $p \leq 0.001$) in a dose-response fashion, such that individuals with high damage but strong connectivity showed normal cognitive function. A population-based estimate of damage-associated cognitive aging found that those with highest vascular damage score experienced 9.3 years accelerated cognitive aging, but a standard unit increase in connectivity moderated this by 7.0 years.

DISCUSSION:

Findings support the reserve hypothesis by showing that brain connectivity is associated with cognitive resilience. Findings were consistent across various brain damage markers and remained significant when adjusting for a wide range of relevant covariates. Further investigation into measures of brain network connectivity presents a promising avenue for studying determinants of resilience.

Keywords: cognitive resilience, white matter network connectivity, diffusion MRI

1. Livingston, G., et al., *Dementia prevention, intervention, and care: 2020 report of the Lancet Commission.* The Lancet, 2020. **396**(10248): p. 413-446.
2. Stern, Y., et al., *Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance.* Alzheimer's and Dementia, 2020. **16**: p. 1305-1311.
3. Stern, Y., *An approach to studying the neural correlates of reserve.* Brain Imaging and Behavior, 2017. **11**(2): p. 410-416.
4. Schram, M.T., et al., *The Maastricht Study: An extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities.* European Journal of Epidemiology, 2014. **29**(6): p. 439-451.