A Novel White Matter Tract-Based Index Links Brain Damage to Clinical and Cognitive Symptom in Multiple Sclerosis

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OBJECTIVE: Fatigue, depression, and cognitive deficits are common in multiple sclerosis (MS), but their link to brain damage remains unclear. We examined the association between local measures of disconnection, quantified by the **tract density index** (TDI), and clinical, cognitive, and biological markers (neurofilament light chain). We further assessed TDI effects on **global connectivity** using patient-specific disconnectomes and Hopf modeling.

RESULTS: TDI was positively associated with fatigue (FSS: p=0.0086) and depression (BDI-II: p=0.028), and negatively with executive functioning (p=0.030), independent of lesion volume/number and age (**Fig. 1**). Nonlinear analyses (generalized additive model) revealed a TDI cut-off (~48.7 fibers), below which stronger associations emerged with all clinical markers, including EDSS (**Fig. 2**). Global connectivity measures showed similar patterns at comparable TDI cut-offs. When dividing patients into high vs. low TDI involvement, significant differences in global connectivity were observed, with the high-involvement group showing greater alterations even after controlling for lesion volume, number and age (**Fig. 3**)

METHODS:

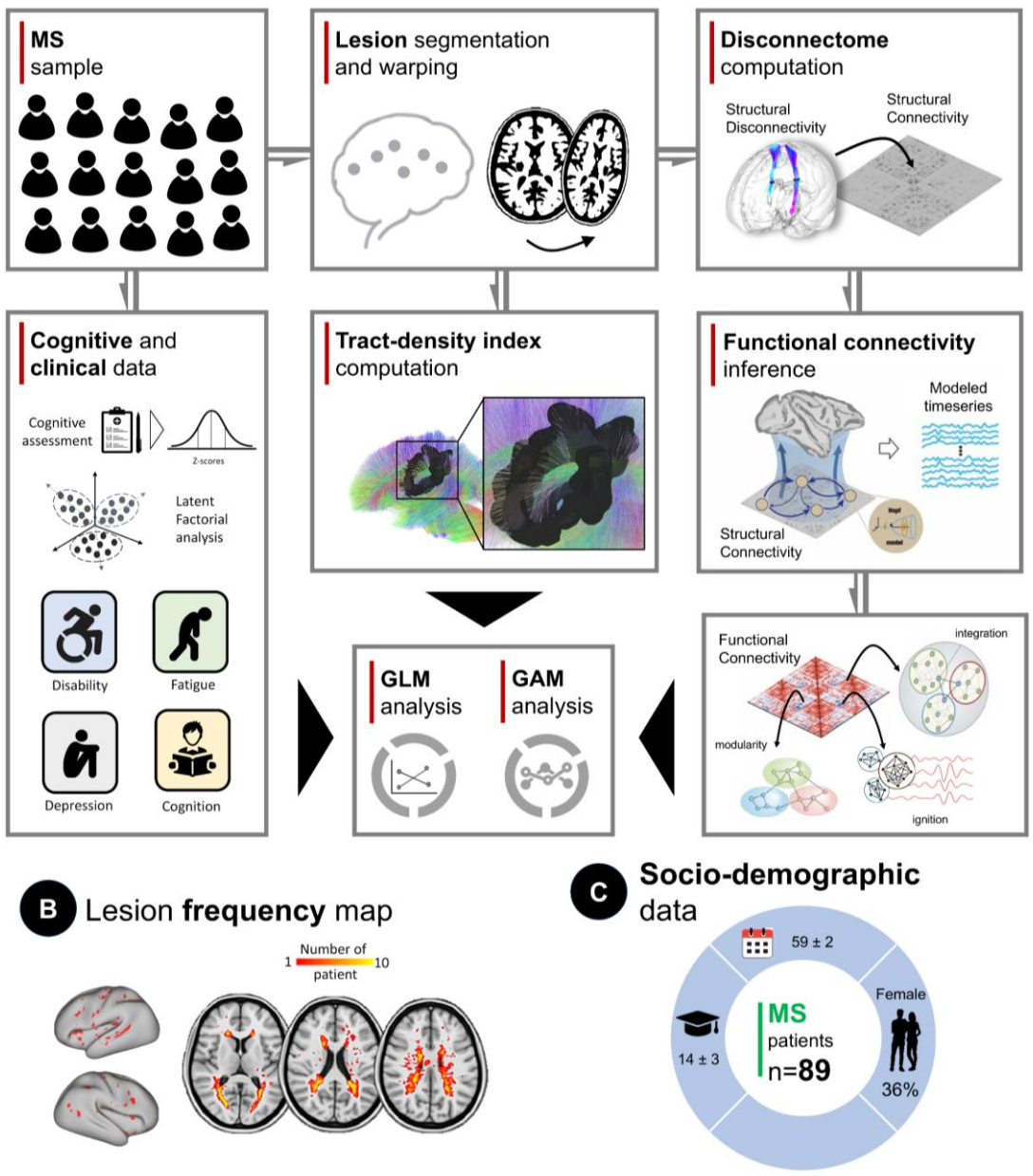


Fig. 1. TDI association with clinical and cognitive outcomes

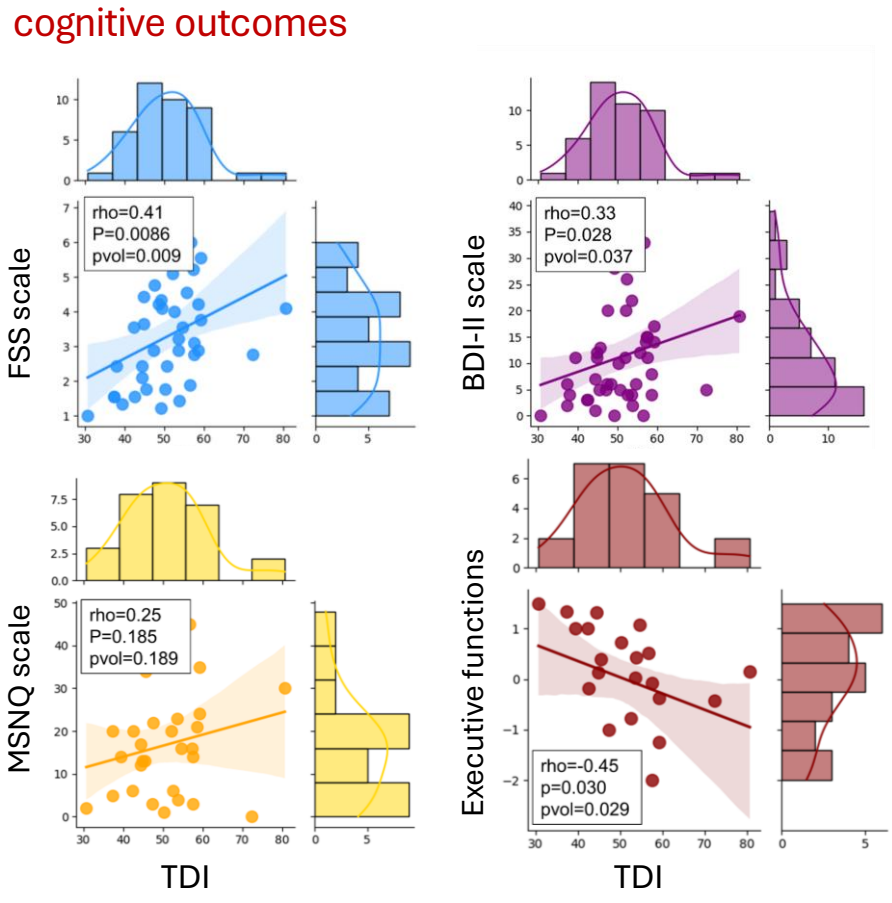


Fig. 2. TDI non-linear effects with global connectivity and clinical/biological outcomes

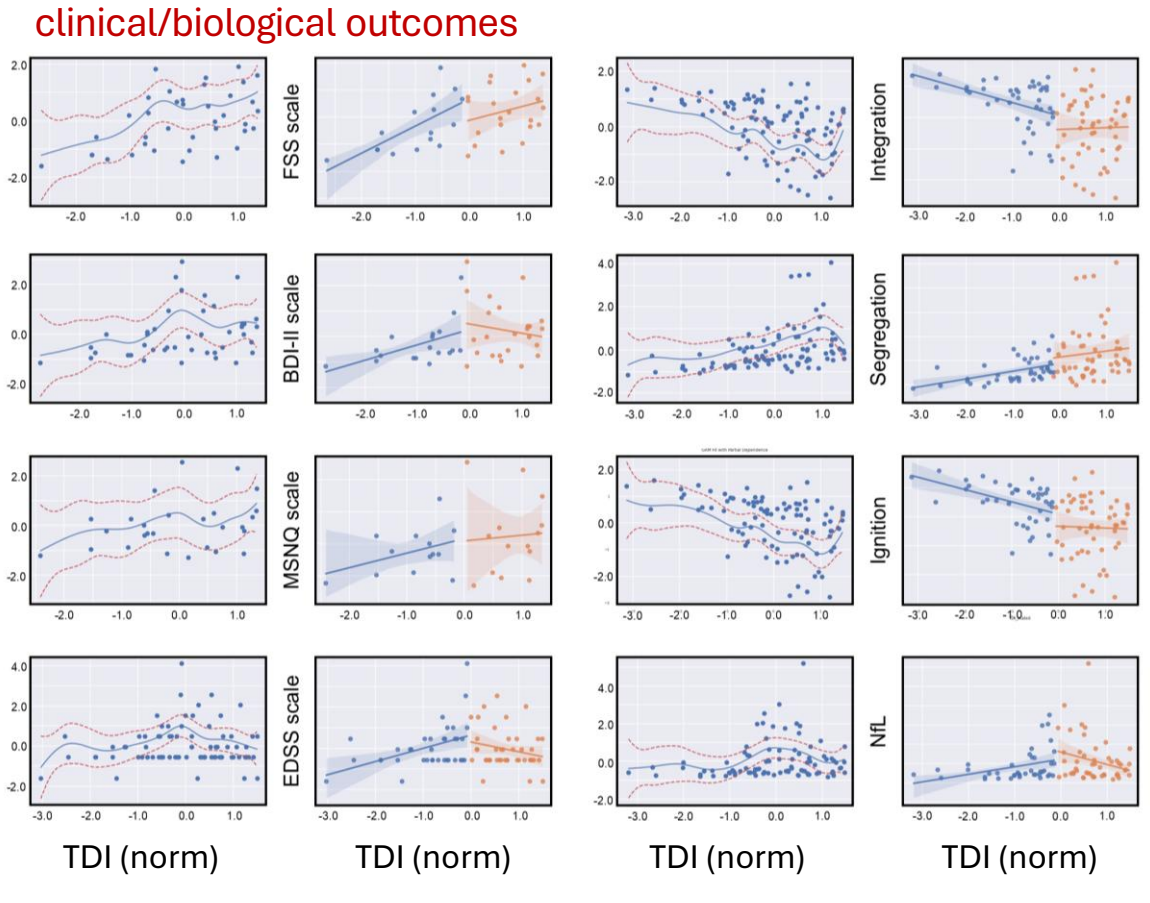
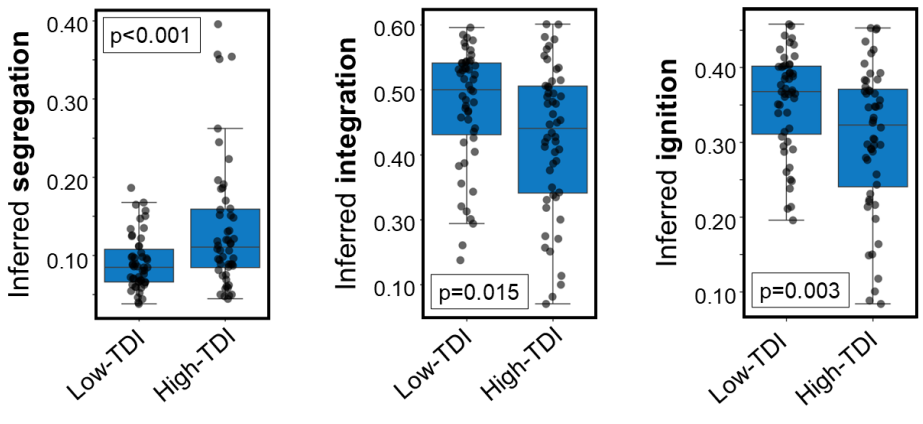


Fig. 3. TDI and global connectivity outcomes



DISCUSSION: The TDI provides a meaningful, integrative marker in MS, capturing subtle associations with fatigue, mood, and executive dysfunction beyond traditional lesion metrics. The nonlinear threshold effect suggests that once a critical level of disconnection is reached, its association with clinical and biological measures disappears, highlighting a possible saturation point in symptom expression linked with global connectivity alterations.