What is the significance of recognizing Connective Tissue Variation as a transdiagnostic phenotype in Neurodevelopmental and Psychiatric Disorders?

Recognizing **connective tissue variation** as a **transdiagnostic phenotype** can improve stratification, mechanism-building, and early risk detection across psychiatric and neurodevelopmental disorders.

Recognizing connective tissue variation as a transdiagnostic phenotype is significant because it reframes joint hypermobility and related connective-tissue differences as a measurable cross-disorder marker rather than an isolated musculoskeletal finding (Sharp et al., 2021). This matters in a field where categorical diagnoses often miss shared biology, comorbidity, and within-disorder heterogeneity across neurodevelopmental and psychiatric conditions (Michelini et al., 2024; Mulders et al., 2022; Baker et al., 2018).

Conceptual Significance

A transdiagnostic phenotype is valuable when it captures liability that cuts across disorders, and multiple papers show that psychiatric and neurodevelopmental conditions share neural, genetic, and phenotypic structure beyond diagnostic boundaries (Park et al., 2022; Hettwer et al., 2022; Michelini et al., 2024; Apperly et al., 2024). Connective tissue variation fits that logic because hypermobility is heritable, not state-dependent, biologically plausible, and easily testable, which are features expected of an endophenotype (Sharp et al., 2021; Eccles et al., 2022).

The importance is not that connective tissue variation replaces diagnosis, but that it may define a clinically meaningful subgroup within and across diagnoses (Sharp et al., 2021; Hettwer et al., 2022). That subgrouping could help explain why the same person shows mixed neurodevelopmental, affective, anxiety, sensory, autonomic, and somatic features that categorical systems separate too sharply (Sharp et al., 2021; Michelini et al., 2024).

Why It Matters Clinically

- **Screening becomes earlier** because hypermobility in adolescence showed longitudinal association with later depression, and symptomatic hypermobility was associated with depression and anxiety at age 18 (Eccles et al., 2022).
- It supports a **biopsychosocial model** linking physical and mental health, rather than treating psychiatric symptoms as detached from bodily physiology (Sharp et al., 2021; Eccles et al., 2022; Sharp et al., 2021).
- It can flag **target symptom clusters** such as anxiety, sensory hypersensitivity, and related somatic burden across diagnoses (Sharp et al., 2021).
- It may improve **personalized assessment** in multisystem conditions such as autism by widening evaluation beyond purely neurofunctional symptoms (Zoccante et al., 2022).

Mechanistic Relevance

Several candidate mechanisms make connective tissue variation scientifically useful rather than merely descriptive. Proposed links include dysautonomia, altered interoception, immune dysregulation, and proprioceptive impairment, all of which can influence psychiatric symptom expression (Sharp et al., 2021; Eccles et al., 2022). In adolescents, resting heart rate partly mediated the association between hypermobility and later depression, supporting autonomic involvement (Eccles et al., 2022).

The idea also aligns with broader transdiagnostic neuroscience showing that shared disorder effects often map onto common connectivity and cortical-organization patterns rather than disorder-specific lesions alone (Park et al., 2022; Hettwer et al., 2022; Baker et al., 2018; Li et al., 2020). Across neurodevelopmental conditions, shared abnormalities have been tied to deep regulatory and cortical executive-perceptual systems, synaptic development, cytoskeletal remodeling, and related gene programs, which makes a body-wide connective phenotype conceptually compatible with multiscale shared vulnerability models (Diao et al., 2026; Michelini et al., 2024).

Shared transdiagnostic brain phenotypes have been identified in white matter, functional connectomes, and cortical organization from childhood through adulthood, and several are heritable or predictive of later disorder burden (Alnæs et al., 2018; Xiao et al., 2021). That broader literature strengthens the significance of connective tissue variation because it suggests that a simple peripheral phenotype could index deeper cross-disorder biology that standard diagnosis misses (Mulders et al., 2022; Michelini et al., 2024).

Evidence and Limits

What recognition adds	Supporting evidence
Cross-disorder marker of vulnerability	Hypermobility is proposed as an endophenotype and phenotypic subgroup across psychiatric disorders (Sharp et al., 2021)
Earlier risk identification	Adolescent hypermobility predicted later depression, with autonomic mediation in males (Eccles et al., 2022)
Mechanism-focused research	ECM, Tenascin-XB, CNS expression, and autonomic or immune pathways offer testable links (Sharp et al., 2021)
Better phenotyping than categories alone	Transdiagnostic models better capture co-occurrence, heterogeneity, and prediction than diagnostic labels alone (Michelini et al., 2024; Apperly et al., 2024)
Major caveat	Evidence is still incomplete on causal genes, longitudinal pathways, and which hypermobile individuals develop psychopathology (Sharp et al., 2021)

FIGURE 1 How recognizing connective tissue variation as a transdiagnostic phenotype changes interpretation of risk, mechanism, and clinical phenotyping.

The main significance of recognizing connective tissue variation as a transdiagnostic phenotype is that it offers a **measurable bridge between body and brain** that can organize heterogeneity, generate testable mechanisms, and support earlier, more holistic detection of risk across neurodevelopmental and psychiatric disorders (Sharp et al., 2021; Michelini et al., 2024). The evidence is promising but not complete: connective tissue variation appears useful as a cross-disorder marker, while its causal pathways and disorder specificity still need stronger longitudinal and mechanistic study (Sharp et al., 2021; Eccles et al., 2022; Michelini et al., 2024).

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