

The Connective Tissue Autonomic Immune Cluster in ADHD An Emerging Research Domain

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Abstract

A convergent line of research across three independent clinical-academic groups proposes that attention-deficit/hyperactivity disorder (ADHD) co-occurs, at rates exceeding chance, with a cluster of physical conditions centered on joint hypermobility, autonomic dysregulation, and immune hypersensitivity. This paper reviews the current state of that proposal — what is statistically established, what is mechanistically hypothesized, and what remains untested — drawing on the independently developed frameworks of J.J. Sandra Kooij (Amsterdam UMC/PsyQ), James Kustow (UK Adult ADHD Network), and Jessica Eccles (Brighton and Sussex Medical School). We distinguish three evidence tiers: (1) replicated statistical association between ADHD and hypermobility measures; (2) neuroimaging and physiological correlates of that association; and (3) a still-untested causal mechanism linking connective tissue structure to neuropsychiatric symptom expression via blood-brain barrier permeability and neuroinflammation. We conclude that the field has matured beyond a single-author hypothesis into an active, multi-site research domain, while the central causal chain remains, by the originating authors' own characterization, a research agenda rather than an established finding.

1. Introduction

ADHD is classified in DSM-5 as a neurodevelopmental disorder, with a well-established genetic and neurotransmitter-based etiology (Demontis et al., 2019). Over the past five years, three independent clinical research groups in the Netherlands and the United Kingdom have separately converged on the observation that adults with ADHD show a markedly elevated prevalence of joint hypermobility, autonomic dysfunction (particularly orthostatic intolerance), and immune/inflammatory conditions, relative to the general population. This paper synthesizes that convergence, examines its evidentiary basis, and identifies the boundary between what has been measured and what is proposed as explanation.

2. The Three Independent Frameworks

2.1 Kooij (Amsterdam UMC / PsyQ / Parnassia Group)

Kooij's framework, presented in her valedictory lecture "ADHD, bindweefsel en inflammatie" (Amsterdam UMC, 12 February 2026) and in an earlier peer-reviewed commentary (Kooij, 2025, *World Psychiatry*), proposes a four-stage model: (1) weak/hypermobile connective tissue → (2) increased permeability of vascular walls and the blood-brain barrier → (3) facilitated neuroinflammation via mast cell activation and cytokine signaling → (4) an ADHD-like or ADHD-exacerbating neuropsychiatric phenotype. Kooij frames this explicitly as a hypothesis under active

investigation, not an established mechanism: "*Er zijn steeds meer aanwijzingen dat ADHD een systeemziekte is... via hypermobiliteit en inflammatie kan mogelijk veel multimorbiditeit verklaard worden*" [there are increasing indications that ADHD is a systemic disease... hypermobility and inflammation may possibly explain much of the multimorbidity] (Kooij, 2026).

2.2 Kustow (UK Adult ADHD Network / The Grove Practice)

Kustow's "Somatic Super Syndrome" (3S) model, developed independently over approximately 15 years of clinical observation and formalized in a 2025 European Psychiatry conference presentation, names three interconnected systems rather than four: connective tissue dysregulation (hEDS/HSD), dysautonomia (particularly POTS), and immune hypersensitivity (MCAD, autoimmunity, allergy). Notably, Kustow does not list the brain/CNS as a fourth component of the system itself; in his model, neuropsychiatric symptoms are the *output* of the three-system interaction rather than a fourth node within it. Kustow also identifies as having hypermobility syndrome himself, a biographical detail that parallels Kooij's account of personal clinical discovery.

2.3 Eccles (Brighton and Sussex Medical School)

Eccles's body of work is methodologically distinct from both Kooij and Kustow in that it includes direct neuroimaging evidence rather than relying solely on epidemiological association or clinical pattern recognition. Her key finding — from the first neuroimaging study of hypermobility — identified altered neural reactivity in threat- and interoception-processing regions (amygdala, insula, anterior/posterior cingulate) in individuals with hypermobility and anxiety (Csecs et al., 2021). Eccles's framework foregrounds *interoception* — the neural processing of internal bodily signals — as the candidate mechanistic bridge between peripheral connective tissue variance and centrally-mediated psychiatric symptoms, a more specific and more directly testable mechanism than Kooij's barrier-permeability/inflammation chain. Eccles has also conducted an RCT-level intervention (the ADAPT trial) targeting this mechanism directly.

3. Evidence Tiers

Tier 1 — Replicated statistical association (established)

Finding	Source	Measure
ADHD associated with hypermobility, OR 6.9 (symptomatic) vs. 4.7 (non-specified)	Case-control study, ScienceDirect 2021	Beighton score, DSM-5 ADHD
RR 5.6 (ADHD) / 7.4 (autism) in EDS vs. sibling controls	Cederlöf et al., 2016	Sibling-controlled
50% of adults with neurodevelopmental conditions (ADHD/autism/tics) show	Csecs et al., 2022	OR 4.51 vs. UK general
34/35 physical conditions elevated in ADHD vs. controls	Du Rietz et al., 2021 (Swedish Registry, n≈4)	Within-individual,
48% hypermobility, 82% dysautonomia, 97% ≥1 inflammatory symptom (n=4,111 women)	de Jong & van Anandel, ADHD & Women's Health Survey	Self-report survey

This tier is robust: multiple independent cohorts, consistent direction of effect, replication across countries (Sweden, UK, Netherlands).

Tier 2 — Physiological/neural correlates (emerging, single-group)

Eccles's neuroimaging findings (Section 2.3) constitute the only direct CNS-level evidence in this literature. They establish that hypermobility correlates with altered activity in specific, theoretically motivated brain regions — but do not, on their own, establish a causal direction or rule out shared upstream genetic confounding.

Tier 3 — Proposed causal mechanism (hypothesis, not yet tested end-to-end)

No published study has measured, within a single cohort, the full proposed chain: connective tissue quality → blood-brain barrier permeability → neuroinflammatory markers → ADHD symptom severity. The components are each measured separately, in separate studies, and assembled post hoc into a narrative chain by Kooij, Kustow, and Eccles. The COVID-19 medication-response finding (Merzon et al., 2020 — OR 1.68 untreated vs. 0.85 treated) is frequently cited as indirect support for an anti-inflammatory mechanism of ADHD medication, but is a single, non-replicated, pandemic-era cohort finding and does not itself test the connective tissue hypothesis.

4. What Remains Open

1. **Mechanism specificity:** Eccles's interoception model and Kooij's barrier-permeability/inflammation model are not mutually exclusive but are not yet shown to be the same mechanism operating at different levels of description, or two distinct, competing mechanisms.
2. **Direction of causation:** shared genetic liability (e.g., overlapping polygenic risk for ADHD and for connective tissue disorders) remains a plausible alternative to a direct causal chain from tissue to brain.
3. **Electromagnetic/biophysical properties of collagen:** no study identified in this review has measured piezoelectric or dielectric properties of collagen in EDS/hypermobility cohorts, despite long-standing evidence (outside this literature) that collagen is piezoelectric. This represents a genuine, unexplored gap between the structural/mechanical framing used by Kooij and Kustow and a biophysical framing that has not been brought into this specific research domain.
4. **Clinical translation:** symptomatic treatments (antihistamines, compression garments, low-dose naltrexone) are in use, but no disease-modifying treatment targeting the proposed shared mechanism has been validated in RCTs, with the partial exception of Eccles's ADAPT trial, which targets anxiety via interoception rather than the inflammatory chain.

5. Conclusion

What began as a single clinician's (Kooij's) post-hoc pattern recognition has, independently, also been arrived at by Kustow and given experimental grounding by Eccles. This convergence across three independent groups, using different methods (epidemiology, clinical pattern recognition, neuroimaging), strengthens confidence that the underlying statistical association (Tier 1) is real and not an artifact of any single group's methodology. It does not yet establish the proposed causal mechanism (Tier 3), which all three originating authors continue to characterize, in their own words, as a hypothesis requiring further research rather than a settled finding.

Annotated Reference List

Cederlöf, M., Larsson, H., Lichtenstein, P., Almqvist, C., Serlachius, E., & Ludvigsson, J. F. (2016). Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or hypermobility syndrome and their siblings. *BMC Psychiatry*, *16*, 207. Sibling-controlled design strengthens causal inference relative to simple case-control comparison by partially controlling for shared genetic/familial confounding. Reports RR 5.6 for ADHD and RR 7.4 for autism in EDS relative to siblings. This is the single strongest piece of Tier 1 evidence cited across all three frameworks.

Csecs, J. L. L., Iodice, V., Rae, C. L., Brooke, A., Simmons, R., Quadt, L., Savage, G. K., Dowell, N. G., Prowse, F., Themelis, K., Mathias, C. J., Critchley, H. D., & Eccles, J. A. (2022). Joint Hypermobility Links Neurodivergence to Dysautonomia and Pain. *Frontiers in Psychiatry*, *12*, 786916. Co-authored by Eccles; the source of the widely cited "50% of neurodivergent adults are hypermobile" finding that independently triggered both Kooij's and Kustow's clinical investigations. Functions as the connective node between all three frameworks in this review.

Csecs, J. L. L., Dowell, N. G., Savage, G. K., Iodice, V., Mathias, C. J., Critchley, H. D., & Eccles, J. A. (2021). Variant connective tissue (joint hypermobility) and dysautonomia are associated with multimorbidity at the intersection between physical and psychological health. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*. Eccles's group's foundational multimorbidity paper; one of the few sources in this literature with a clinical academic neuroimaging program behind it rather than survey/registry data alone.

Demontis, D., Walters, R. K., Martin, J., et al. (2019). Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics*, *51*, 63–75. Establishes the conventional genetic/neurotransmitter basis of ADHD against which the connective-tissue hypothesis is positioned as an additional, not replacement, explanatory layer. Cited by Kooij (2025) to clarify that her hypothesis does not displace established genetic etiology.

Du Rietz, E., Brikell, I., Butwicka, A., Leone, M., Chang, Z., Cortese, S., D'Onofrio, B. M., Hartman, C. A., Lichtenstein, P., Faraone, S. V., Kuja-Halkola, R., & Larsson, H. (2021). Mapping phenotypic and aetiological associations between ADHD and physical conditions in adulthood in Sweden: a genetically informed register study. *Lancet Psychiatry*, *8*(9), 774–783. The Swedish national registry study (n≈4 million) underlying the "34 of 35 conditions" finding central to Kooij's lecture. Genetically informed design (within-individual, full-sibling, half-sibling comparisons) allows partial decomposition of genetic vs. environmental contribution — among the most methodologically rigorous Tier 1 sources in this domain.

Eccles, J. A., et al. — Joint hypermobility and autonomic hyperreactivity research program, Brighton and Sussex Medical School (multiple publications, 2019–2025). Includes the first neuroimaging study of hypermobility, identifying altered amygdala/insula/cingulate reactivity in hypermobile individuals with anxiety. Provides the only Tier 2 (neural correlate) evidence in this review; introduces *interoception* as a more mechanistically specific candidate pathway than Kooij's barrier-permeability framing.

Kooij, J. J. S. (2025). New developments and potential future research directions in adult ADHD. *World Psychiatry*, *24*(3), 381–382. Kooij's own peer-reviewed (non-lecture) statement of the hypothesis, predating her valedictory lecture by several months. Establishes that the hypothesis entered formal peer review independently of the lecture's media attention, and explicitly frames it as provisional.

Kooij, J. J. S. (2026, February 12). *ADHD, bindweefsel en inflammatie* [Valedictory lecture]. Amsterdam UMC / Vrije Universiteit Amsterdam. Primary source for the four-component systemic model (connective tissue, vasculature/BBB, immune system, brain) discussed in this review. A valedictory lecture, not a peer-reviewed primary research output; functions here as a synthesis/agenda-setting document rather than as evidence in itself.

Kustow, J. (2025). *Hypermobility, immune dysfunction and dysautonomia cluster in ADHD. European Psychiatry, conference presentation, DOI: 10.1192/j.eurpsy.2025.189.* Source of the named "Somatic Super Syndrome" (3S) model. Independently developed from Kooij's framework via ~15 years of clinical observation; provides the most explicitly named and structurally distinct (3-component vs. Kooij's 4-component) version of the same underlying cluster.

Merzon, E., Manor, I., Rotem, A., Schneider, T., Vinker, S., Golan Cohen, A., Laudén, A., Weizman, A., & Green, I. (2021). *ADHD as a Risk Factor for Infection With Covid-19. Journal of Attention Disorders, 25(13), 1783–1790.* Source of the OR 1.68 (untreated) vs. 0.85 (treated) finding used by Kooij as indirect support for an anti-inflammatory mechanism of ADHD medication. A single pandemic-era cohort study; not replicated; tests medication-infection association, not the connective tissue hypothesis directly. Cited across this literature with more interpretive weight than its single-study status warrants.

Prepared as a literature synthesis, not a peer-reviewed primary research contribution. Tier classifications and the identification of open mechanistic gaps (Section 4) reflect editorial synthesis by the author of this review, not claims made by Kooij, Kustow, or Eccles themselves.