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## FRONTIER

- 681 Framework for internal sensation of pleasure using constraints from disparate findings in nucleus accumbens  
*Vadakkan KI*

## REVIEW

- 696 Metabolic disturbances associated with antipsychotic drug treatment in patients with schizophrenia: State-of-the-art and future perspectives  
*Chang SC, Goh KK, Lu ML*
- 711 Alternative models for transgenerational epigenetic inheritance: Molecular psychiatry beyond mice and man  
*Hime GR, Stonehouse SL, Pang TY*
- 736 Antipsychotics cardiotoxicity: What's known and what's next  
*Li XQ, Tang XR, Li LL*
- 754 Therapeutic role of yoga in neuropsychological disorders  
*Nourollahimoghdam E, Gorji S, Gorji A, Khaleghi Ghadiri M*
- 774 'Omics' of suicidal behaviour: A path to personalised psychiatry  
*Kouter K, Videtic Paska A*

## MINIREVIEWS

- 791 Environmental pollution with psychiatric drugs  
*Argaluz J, Domingo-Echaburu S, Orive G, Medrano J, Hernandez R, Lertxundi U*
- 805 Connecting brain and body: Transdiagnostic relevance of connective tissue variants to neuropsychiatric symptom expression  
*Sharp HEC, Critchley HD, Eccles JA*
- 821 Psychiatric sequelae in COVID-19 survivors: A narrative review  
*Putri C, Arisa J, Hananto JE, Hariyanto TI, Kurniawan A*
- 830 Metabotropic glutamate receptors and nitric oxide in dopaminergic neurotoxicity  
*Bashkatova V*

**ORIGINAL ARTICLE****Retrospective Cohort Study**

- 841** Factors causing a relapse of major depressive disorders following successful electroconvulsive therapy: A retrospective cohort study

*Kurimoto N, Inagaki T, Aoki T, Kadotani H, Kurimoto F, Kuriyama K, Yamada N, Ozeki Y*

**Retrospective Study**

- 854** Determinants of mechanical restraint in an acute psychiatric care unit

*El-Abidi K, Moreno-Poyato AR, Toll Privat A, Corcoles Martinez D, Aceña-Domínguez R, Pérez-Solà V, Mané A*

- 864** What factors explain anger and mental health during the COVID-19 pandemic? The case of Israeli society

*Braun-Lewensohn O, Abu-Kaf S, Kalagy T*

**SYSTEMATIC REVIEWS**

- 876** Measures of empathy in children and adolescents: A systematic review of questionnaires

*Sesso G, Brancati GE, Fantozzi P, Inguaggiato E, Milone A, Masi G*

- 897** Neurofeedback for insomnia: Current state of research

*Lambert-Beaudet F, Journault WG, Rudziavicius Provençal A, Bastien CH*

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## Connecting brain and body: Transdiagnostic relevance of connective tissue variants to neuropsychiatric symptom expression

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### Abstract

The mind is embodied; thoughts and feelings interact with states of physiological arousal and physical integrity of the body. In this context, there is mounting evidence for an association between psychiatric presentations and the expression variant connective tissue, commonly recognised as joint hypermobility. Joint hypermobility is common, frequently under-recognised, significantly impacts quality of life, and can exist in isolation or as the hallmark of hypermobility spectrum disorders (encompassing joint hypermobility syndrome and hypermobile Ehlers-Danlos syndrome). In this narrative review, we appraise the current evidence linking psychiatric disorders across the lifespan, beginning with the relatively well-established connection with anxiety, to hypermobility. We next consider emerging associations with affective illnesses, eating disorders, alongside less well researched links with personality disorders, substance misuse and psychosis. We then review related findings relevant to neurodevelopmental disorders and stress-sensitive medical conditions. With growing understanding of mind-body interactions, we discuss potential aetiopathogenetic contributions of dysautonomia, aberrant interoceptive processing, immune dysregulation and proprioceptive impairments in the context of psychosocial stressors and genetic predisposition. We examine clinical implications of these evolving findings, calling for increased awareness amongst healthcare professionals of the transdiagnostic nature of hypermobility and related disorders. A role for early screening and detection of hypermobility in those presenting with mental health and somatic symptoms is further highlighted, with a view to facilitate preventative approaches alongside longer-term holistic management strategies. Finally, suggestions are offered for directions of future scientific exploration which may be key to further delineating fundamental mind-body-brain interactions.

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**Core tip:** The association between vulnerability to psychological or psychiatric symptoms and hypermobile joints may initially appear counterintuitive to many clinicians. However, a relationship with anxiety is consistently confirmed across multiple studies worldwide. In this narrative review, we appraise increasing evidence linking neuropsychiatric presentations to hypermobility across the lifespan, including emerging links to neurodevelopmental disorders and stress-sensitive medical conditions. We discuss pertinent mechanistic insights in the context of growing understanding of mind-body interactions. We offer direction for future research and highlight implications for clinical practice, notably roles of timely screening and detection alongside longer-term holistic management strategies.

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## INTRODUCTION

There is a rapidly growing body of evidence showing a curious excess of psychiatric burden among individuals with joint hypermobility. Common constitutional variants of connective tissue often present as joint hypermobility, reflecting increased laxity of ligaments and extended movement of joints beyond typically 'normal' limits (otherwise described as joint hyperlaxity, being double-jointed)[1]. Internationally, joint hypermobility is found in up to 20% of the general population, and is influenced by age, sex and ethnicity; hypermobility is more frequent in children, with higher prevalence in women, and Asian and African populations[2]. Hypermobility is also highly heritable, and has been proposed to be an autosomal dominant trait with incomplete penetrance, variable expressivity and influenced by sex[3]. The epidemiological characterisation is influenced by clinical definitions and assessment tools; the 9-point Beighton score is used most frequently to assess hypermobility in both clinical and research settings, although other methods include the Hospital del Mar criteria [4], and self-administered hypermobility questionnaires.

Hypermobility is a descriptive term and might exist as an asymptomatic and isolated feature. However, neuropsychiatric symptoms are among extra-articular manifestations that frequently accompany more widespread musculoskeletal symptoms that typically co-occur with hypermobility. In these cases, hypermobility appears as one feature of a multisystemic disorder[3]. This complexity is reflected in the current debate concerning terminology and classification: A consensus group in 2017 introduced the concept of hypermobility spectrum disorders (HSD); encompassing a continuum including hypermobile Ehlers-Danlos syndrome' (hEDS, previously EDS-HT), joint hypermobility syndrome [JHS, previously diagnosed according to the Brighton Criteria - Revised (1998)][5] and symptomatic hypermobility not fulfilling stricter criteria for other associated syndromes[6]. Diagnostic classification remains a contentious area, particularly since reliable genetic tests or physiological markers for HSD are presently lacking, so diagnosis relies solely on clinical criteria[6]. Hypermobility may also signal the presence of other heritable disorders of connective tissue including Marfan syndrome, osteogenesis imperfecta and Ehlers-Danlos syndromes which have a more clearly defined genetic basis[7]. Here, we review literature across a broad terminology referring to joint hypermobility and related syndromes.

Joint hypermobility is frequently under-recognised[3] and has a significant impact on quality of life across all age-groups[8,9]. Anxiety symptoms and disorders have a well-established link with hypermobility, yet growing evidence also now points

towards associations across psychiatric diagnoses, notably with affective illnesses, increasingly with neurodevelopmental disorders and with stress-sensitive medical conditions, including fibromyalgia, myelo-encephalomyelitis/chronic fatigue syndrome (ME/CFS) and irritable bowel syndrome (IBS). Awareness of these relationships are important to enhance understanding of early risk factors to allow screening and timely intervention for vulnerable individuals. The value of such a strategy is illustrated by a recent longitudinal study, which demonstrated that hypermobile children at age 14 years were more likely to suffer from anxiety and depression by age 18 years[10]. Increasing clinicians' awareness of the multisystemic features associated with hypermobility, especially psychiatric morbidity, will enable appropriate detection, diagnosis, and preventative intervention and can shape the implementation of effective longer-term holistic management strategies.

This paper presents a comprehensive narrative review of existent clinical knowledge and empirical evidence regarding the association of hypermobility with psychopathology. We also present a broad perspective on this expression of body-brain-mind interactions, including current mechanistic understanding, and we highlight implications for clinical practice and directions of future research.

## LITERATURE SEARCH

This is a narrative review based on a comprehensive search of online databases (including MEDLINE, Embase and PsychInfo). Search terms included were 'hypermobility' and 'joint laxity' combined with each diagnostic category. This search comprised studies published from 1980 to 2021. Reference lists of identified papers were further scrutinised for additional relevant articles.

## RESULTS

### **Anxiety**

The expression of anxiety in the context of joint hypermobility was first recognised in the late 1980s. Subsequent research has repeatedly demonstrated this association, which has been the subject of several substantive reviews (for example[11]). Anxiety disorders are the most prevalent set of psychiatric illnesses<sup>[12]</sup>, and hypermobility is most strongly linked to the expression of panic disorder and agoraphobia[13]. Moreover, state anxiety is a transdiagnostic symptom that is pervasive across distinct psychiatric disorders; even in non-clinical populations, hypermobility predicts elevated levels of trait and state anxiety, without necessarily reaching formal thresholds for anxiety disorder[14]. This pattern has been observed in the elderly[15] and in children, including both clinical[16,17] and non-clinical cohorts[18].

### **Affective disorders**

Hypermobility is becoming a recognised vulnerability factor for affective disorders, particularly depression, especially if comorbid anxiety is present[19,20]. Patients with clinically significant hypermobility (*i.e.*, HSD/hEDS) demonstrate higher rates of depressive disorders (for example[21]), recently summarised in a meta-analysis[13] although there are some inconsistencies within the literature[22]. A population-wide study, using Swedish national registries, observed a heightened risk of depression and increased rates of attempted suicide among hypermobile (EDS and HSD) individuals and their siblings[23]. Hypermobility is also associated with elevated self-report depressive symptoms in non-clinical populations[24]. There are a number of reasons why hypermobility may be linked to depression, and in many cases it is unclear whether studies have effectively controlled for anxiety, which could act as an explanatory mediator between hypermobility and depression, since these two conditions are highly comorbid. Other potential mediating factors common to both HSD/hEDS and depression include chronic pain, fatigue or impaired sleep[25].

An increased risk of bipolar affective disorder (BPAD) is also reported in individuals with ESD/HSD (relative risk,  $RR = 2.7$ )[23]. In this study, no difference in rates of schizophrenia were observed between people with and without hypermobility. Similarly, hypermobility is over-represented in patients with BPAD diagnosis attending a psychiatric outpatient setting[26]. However, further detailed studies are lacking, and the potential mediating role of other conditions, such as attention deficit hyperactivity disorder (ADHD; see below), are as yet unexplored.

Thus the link between hypermobility and BPAD remains preliminary.

### **Eating disorders**

There are several case series and reports that describe the co-occurrence of EDS and eating disorders (reviewed in[27]). Elevated rates of hypermobility occur in both psychiatric outpatients with eating disorders[27] and in hospitalised in-patients with anorexia nervosa[28], who experienced excess gastrointestinal symptoms, orthostatic intolerance and fatigue (symptoms common to HSD/hEDS). A higher lifetime prevalence of eating disorder was also demonstrated in students with non-clinical hypermobility[29]. However, large and comprehensive epidemiological studies investigating this proposed link are lacking.

Mechanistically however, a proposed model of the relationship between eating disorders and HSD/hEDS recognises the contribution of both articular (such as temporo-mandibular disorders) and extra-articular features (including gastrointestinal problems, smell and taste abnormalities, dental problems, oral mucosal fragility) to difficult or painful eating, which reinforce dysregulated eating behaviour and associated weight loss[27,29]. Thus HSD/hEDS can plausibly contribute to, mask or even be misdiagnosed as an eating disorder.

### **Psychosis**

The link between hypermobility and schizophrenia-type psychosis remains much less apparent than that seen in relation to anxiety, affective and eating disorders. One case-control study reported similar prevalence of HSD/hEDS in patients with schizophrenia and controls[30], a finding that was confirmed in a population matched cohort study[23]. Even in psychiatric outpatients, schizophrenia was reported to be negatively associated with hypermobility[26]. Nevertheless, hypermobility is implicated as a clinical marker for co-morbid anxiety in schizophrenia: Patients with comorbid hypermobility and schizophrenia express elevated rates of panic/agoraphobia disorder, exacerbating positive psychotic symptoms[31].

### **Personality disorder**

Only one case-control study to date has investigated personality disorder in hypermobility, revealing elevated prevalence of personality disorder in JHS (RR = 5.8), especially of the obsessive-compulsive (anankastic) subtype[21]. It was speculated that that joint instability and associated imprecision of proprioception might underlie compensatory over-controlling behaviours (in the context of anxiety), and even that unrecognised JHS can contribute to perfectionism. However, rates of hypermobility were reported elsewhere to be no different in psychiatric outpatients with or without personality disorder[26]. While a number of possible putative mechanisms might link hypermobility to personality disorder (including anxious temperament and/or neurodevelopmental conditions including as ADHD), these findings should be interpreted cautiously, as there is an obvious need for large and well powered studies.

### **Addictions/substance misuse**

Studies investigating addiction and substance misuse in the context of hypermobility are sparse. Early findings of elevated hypermobility scores in female chronic alcoholic patients[32] have not been replicated since. One longitudinal study revealed significantly higher prevalence of at-risk drinkers and smokers in young females with hypermobility compared to controls[33]. It is possible that alcohol and tobacco use could be overused to cope with chronic pain and anxiety (or indeed to self-medicate against ADHD symptoms, see below) and further studies should evaluate and control for these variables.

### **Neurodevelopmental disorders**

In recent years, several authors have highlighted a relationship between hypermobility and neurodevelopmental disorders, notably autism (autistic spectrum disorders, ASD), ADHD and developmental coordination disorder (DCD)[34,35]. Interest in tic disorder (Tourette syndrome) and hypermobility is also growing. Hypermobility is frequently co-morbid with neurodevelopmental disorders and may contribute to the accompanying physical behavioural and cognitive symptoms that encompass motor difficulties, sleep and feeding problems, sensory hypersensitivities, behavioural hyperactivity, inattention, dysexecutive issues, speech and language problems and social deficits. Neurodevelopmental disorders most often present in school age children, and thus may precede or overshadow recognition of comorbid HSD/hEDS [35]. Nevertheless, these two clinical entities retain their association through into



adulthood[26,36]. Interestingly, however, subclinical expression of neurodevelopmental (ADHD, ASD or DCD) traits in the general population are not strongly associated with hypermobility, suggesting that the expression of this association is limited to clinical populations[37].

**Autism:** Evidence for an overlap between hypermobility and autism is growing. Initially described in case reports (reviewed in[38]), excess hypermobility has since been demonstrated in children with ASD (average age 4 years) in a case-control study [39], although differences in passive muscular tonicity may be a confound[40]. At a population-level, elevated rates of ASD is apparent in individuals with EDS/JHS and their siblings[23]. Both ASD and HSD/hEDS are considered heritable spectrum disorders that appear in infancy and share clinical presentations that include motor and coordination difficulties, sensory hypersensitivity/hyperalgesia, autonomic dysfunction, proprioceptive impairments and sleep disorders[34]. This has led to the suggestion that EDS/HSD might be considered as a subtype of ASD[34].

Furthermore, there has been longstanding recognition of the positive association between ASD and heritable disorders of connective tissue including Marfan's syndrome[41] and osteogenesis imperfecta[42]. ASD is known to be associated with several genetic causes, the most common being Fragile X syndrome (caused by mutations in *FMR1* gene). Up to half of patients with Fragile X syndrome are hypermobile. Soft skin, scoliosis and flat feet are common, providing further evidence for variant of collagen or related connective tissue[43]. The gene *FMR1* negatively regulates protein translation, which theoretically could cause downstream effects on collagen formation[43]. More broadly, across monogenic genetic syndromes strongly associated with both ASD and hypermobility, and known genetic causes of EDS subtypes, analyses of gene interactions reveal extensive gene clustering that might represent a biological mechanisms for the observed clinical overlap[34].

**ADHD:** Increasing clinical awareness of the co-occurrence of ADHD and hypermobility was confirmed by two case-control studies[44,45] and a population based cohort study[23], which also demonstrated higher rates of ADHD in siblings of children with HSD/hEDS diagnosis. Co-occurrence of ADHD and HSD/hEDS is also seen in adults[36,46].

**DCD:** According to DSM-5[47], EDS/JHS is included both as a differential diagnosis and as a potential comorbidity of DCD (previously termed developmental dyspraxia) in acknowledgement of the functional and clinical similarities[48]. High rates of symptoms related to HSD/hEDS are found among patients with DCD diagnosis, including pain and autonomic dysfunction, and there are significant commonalities in their motor features[48].

In children with HSD/hEDS diagnoses, high rates of clumsiness, impaired coordination and dyspraxia are observed<sup>[49]</sup> and up to 55% meet DCD criteria[50,51]. Similarly, 46%-64% of children with DCD are hypermobile[52,53], the exact figure depending on appropriate use of age appropriate Beighton score cut-offs[51].

**Developmental tic disorder (Tourette syndrome):** Despite emergent evidence describing hypermobility in ASD, ADHD and DCD, data concerning neurodevelopmental tic disorders (such as Tourette's syndrome) are remarkably lacking. To our knowledge, no current data have assessed this relationship in children. The first work in adults found elevated prevalence (38%) of hypermobility amongst 24 adults with Tourette syndrome[36]. Interestingly, these individuals had a high comorbidity of obsessive-compulsive disorder diagnoses (37.5%), another condition which is yet to be investigated with respect to hypermobility.

### Stress medical sensitive conditions

**Fibromyalgia and ME/CFS:** Fibromyalgia and ME/CFS are both common overlapping disorders characterised by chronic pain, fatigue, sleep disturbance, cognitive complaints, gastrointestinal disturbance and affective problems.

There is further overlap of symptomatology and clinical findings with HSD/hEDS [54]. High rates of hypermobility are present in patients with fibromyalgia both as adults[55] and children[56], and in patients with ME/CFS, again both in adults[57] and children[58]. Hypermobility is specifically linked to the expression of pain and fatigue in these patients[59]. Conversely, the majority of EDS patients suffer from marked fatigue[60]. In fact, many patients with HSD/hEDS meet Fukada criteria for diagnosis of CFS[50], and hence it is argued that an assessment for hypermobility/variant connective tissues should be an integral part of a thorough evaluation of ME/CFS[61].

**IBS and functional gastrointestinal disorders:** Gastrointestinal symptoms (including nausea, abdominal pain, bloating, constipation and diarrhoea) are commonly experienced by patients with HSD/hEDS diagnosis[62]. Objectively, gastrointestinal dysmotility is observed[63] and is predicted by the symptoms and signs of dysautonomia, notably the occurrence of postural tachycardia syndrome (PoTS). Interestingly, psychiatric disorders, especially mood and somatoform disorders, occur at higher rates in patients with HSD/hEDS who experience gastrointestinal dysfunction and associated abdominal pain[64].

The prevalence of hypermobility appears to be greater in patients with IBS or gastrointestinal symptoms (especially functional dyspepsia) when compared to healthy controls[65]. This represents a subgroup (even variant phenotype) of patients who experience primary gastrointestinal problems with co-existing HSD/hEDS, who also demonstrate high comorbidity with chronic pain and fibromyalgia. These patients show increased somatisation score, urinary autonomic (symptom) score and reduced pain-related quality of life[66]. High rates of hypermobility are particularly observed in patients with constipation-predominant IBS[67], consistent with perturbation of colonic sensorimotor biomechanics consequent upon variant connective tissue.

However, while in adults the association between hypermobility and functional gastrointestinal disorders appears relatively robust, in children there is increasing evidence that the prevalence of hypermobility is similar for children with IBS, functional abdominal pain or functional constipation, and for healthy controls[68-70]. Intriguingly, this suggests that, in hypermobile individuals, IBS and functional GI symptoms may develop later in life perhaps interacting with hormonal or other maturational changes that impact connective tissue compliance.

**Other associated stress-sensitive medical conditions:** There are reports demonstrating that HSD/hEDS is also associated with increased risk of migraine (in females)[71], and with chronic regional pain syndrome[72], chronic myofascial pelvic pain[73], and stress incontinence[74].

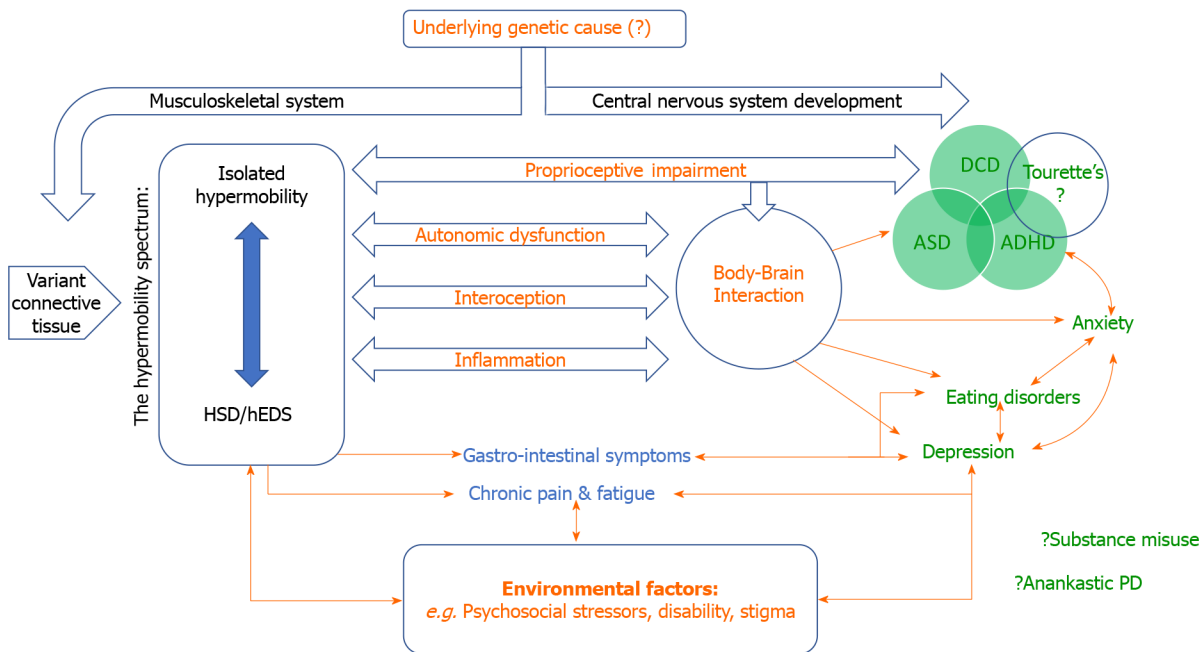
## DISCUSSION

The 'biopsychosocial approach' in psychiatry acknowledges the contribution of interconnected and interacting influences on the development and maintenance of psychiatric symptoms and diagnoses, including biological vulnerabilities, psychological factors and dynamic social context. The associations highlighted within this review, linking psychiatric symptoms and conditions to constitutional differences in connective tissue (apparent, in part, as joint hypermobility), likely depend on multiple mechanisms, which may differ between disorders. Hypothetically, joint hypermobility may represent a non-specific signature of a general mechanism linking variant connective tissue to psychological vulnerability, manifesting in a continuum across neurodevelopmental and psychiatric disorders. Alternatively, a pre-existing pathological process (as yet undiscovered) could predispose to both psychopathology and hypermobility in parallel *via* independent actions on the musculoskeletal and central nervous systems (Figure 1).

### Psychosocial factors

Through lived experience, the presence of hypermobility from early childhood may directly underpin the development of psychiatric disorders. Excluding neurodevelopmental conditions, this makes temporal sense: The presence and consequences of hypermobility in childhood precedes the typically later emergence of psychiatric disorders in adolescence and adulthood. When symptomatic from a young age, the daily challenges of living with physical risks and difficulties associated with HSD/hEDS (including chronic pain and disability, threat of injury secondary to connective tissue fragility, restriction of social and physical activities and associated stigma) contribute to psychiatric vulnerability, avoidant behaviours and the development of anxiety and depressive symptoms[75].

Correspondingly, intense fear of pain and subsequent pain-avoidant strategies that limit movement (kinesiophobia) are common in HSD/hEDS[76]. These increase the likelihood of deconditioning and symptom progression, thereby furthering physical and psychological disability. In addition, problematic hypermobility is typically under-recognised and diagnostic delay is common[3]. Consequently, patients may experience frustration if their complaints are trivialised by healthcare professionals, adding to suffering and exclusion[75]. High anxiety and distress may drive



**Figure 1** Diagram illustrating possible pathways for the aetiopathogenesis of psychiatric disorders in joint hypermobility. Orange text: Putative mechanisms; Blue text: Symptoms related to Hypermobility Spectrum Disorders/hypermobile Ehlers-Danlos Syndrome; Green text: Psychiatric and neurodevelopmental disorders. ASD: Autism spectrum disorder; ADHD: Attention deficit hyperactivity disorder; DCD: Developmental coordination disorder; PD: Personality disorder.

maladaptive behaviours including tobacco/alcohol use and disordered eating[33], and the psychosocial complexity surrounding hypermobility is associated with poorer quality of life in both adults[8] and children[9]. In hEDS patients, the psychological expression of high anxiety interacts with more severe fatigue and depressive symptoms, pain catastrophising, somatosensory amplification, to predict poorer social functioning and worse general health[20].

The bidirectional interaction between pain and psychological ill-health is widely recognised; chronic pain influences psychiatric symptoms including depression and anxiety, while low mood and negative emotions increase and maintain the experience of pain[77]. In this context, psychiatric disorders in HSD/hEDS may be secondary to pain symptoms rather than a primary or parallel manifestation. Hypermobility is a risk factor for chronic widespread pain[78], and hypermobile individuals exhibit sensory hypersensitivity to nociceptive stimuli[79] and secondary central sensitisation [80]. In fact, the presence of pain, rather than the degree hypermobility, is associated with the expression of psychiatric symptoms in EDS patients[81]. Similarly, the experience of pain and gastrointestinal dysfunction, rather than connective tissue features *per se*, is associated with higher rates of psychiatric disorders (especially mood and somatoform conditions) in HSD/hEDS patients[64].

### Genetic factors

The relationship with pain is more nuanced; rates of psychiatric disorder are higher for HSD/hEDS than for other chronic pain conditions[13]. Thus, psychosocial theories fail to explain the full extent of all associations between hypermobility and psychopathological distress. This is particularly evident when considering neurodevelopmental disorders and in individuals with seemingly expressing sub-syndromic and isolated hypermobility. Instead, alternate theories propose that a common set of pathological mechanisms fundamentally predispose to the expression of both hypermobility and psychopathological symptoms (for example, as genetic pleiotropy).

There is interesting evidence from animals: Hypermobility is linked to exaggerated reactivity of behavioural/emotional arousal and excitability in dogs[82]. This finding suggests that the link between joint hypermobility and the affective control of bodily arousal is a universal transdiagnostic trait in mammals, influencing the expression of anxiety and behavioural responses. Moreover, such findings argue against conscious awareness and social implications of living with physical symptoms as a primary driver for the raised levels of psychopathology associated with hypermobility.

Genetic and/or early environmental influences are suggested by the increased risk of psychiatric disorders observed in the (unaffected) first-degree relatives of HSD/hEDS patients[23]. However, unlike other heritable disorders of connective tissue and EDS subtypes, genetic origins for HSD/hEDS remain poorly understood[3]. Previous identification of a genetic anomaly common to both anxiety and hypermobility, a duplication within chromosome 15, failed confirmation in subsequent studies[83]. A promising link has been noted between EDS and the gene *TNXB* (6p21.33), encoding the extracellular matrix glycoprotein *Tenascin-XB*, which is directly involved in connective tissue structure[84]. This molecule was recently identified as integral in enteric motor neurons and influencing nociceptive sensory neurons[85] and is expressed in the brain, suggesting further roles within the central nervous system. The extracellular matrix plays a critical role in both variant connective tissue and central nervous system development, and so alterations could predispose to abnormalities across central and peripheral systems[86].

### ***Autonomic dysregulation and interoception***

HSD/hEDS frequently co-occurs with autonomic dysfunction commonly experienced as symptoms of orthostatic intolerance and, in severe cases, PoTS[87]. The diagnosis of PoTS focuses on the characteristic elevation of heart rate during postural change and accompanying orthostatic intolerance[88]. The widespread presence of variant connective tissue is implicated as one potential physiological mechanism for the overlap between HSD/hEDS and dysautonomia. Within blood vessels, more compliant connective tissue may cause abnormal vascular reactivity, notably increased venous pooling on standing, which reduces venous return. Heart rate acceleration and a secondary hyperadrenergic state would thus result[87].

There is significant phenomenological overlap between symptoms of anxiety and panic and the symptoms of autonomic dysfunction in orthostatic intolerance and PoTS: Physical symptoms include palpitations, breathlessness and dizziness[88], and these themselves could trigger and amplify anxiety states or be misperceived or diagnosed as panic attacks. Enhanced bodily awareness (described below) may be both a consequence and maintaining factor for such experiences, since altered autonomic reactivity will influence emotional state and vulnerability to psychiatric disorders[89]. Autonomic dysfunction is also demonstrable in children with neurodevelopmental conditions linked to hypermobility, notably ASD[90] and ADHD[91]. Again, there is symptomatic overlap between PoTS and ASD in both affective symptoms and sensory sensitivities[34]. The causal relationship between altered autonomic function and neurodevelopmental phenotypes remains unclear but evidence for an interactive association continues to grow.

Interoception refers to the afferent signalling to brain of changes in the internal physiological state of the body, and the perception of these changes. Interoceptive signals therefore represent the sensory limb of autonomic control loops (*e.g.*, the baroreflex), yet also reach perceptual awareness as physiological feelings including palpitations, nausea and arousal. In this way, interoceptive signals can guide motivation behaviour and are fundamental components of emotional feeling states. Central interoceptive representation and/or misinterpretation of dysregulated peripheral autonomic function may underpin the generation of a range of symptoms associated with hypermobility[92]. Dysregulated interoceptive processes are implicated in the expression of specific psychiatric symptoms, particularly anxiety[92]. Hypermobility individuals demonstrate enhanced subjective sensitivity to internal bodily sensations[93] and in more objective measures of detecting interoceptive signals. These differences are shown to mediate the relationship between state anxiety and hypermobility[94] and offer a potential treatment target for intervention.

Neuroimaging studies in hypermobile individuals reveal structural[93] and functional brain differences[94] notably within brain systems critical to emotional processing and anxiety[95], including regions such as insular cortex, that are also specifically implicated in interoceptive representation[94]. However, much of this work has been conducted in sub-clinical cohorts. While findings endorse a potential autonomic/interoceptive basis to vulnerability to anxiety and other neuropsychiatric symptoms, further work is needed to map these relationships in patients with psychiatric disorders in the context of hypermobility and to dissect levels of putative interoceptive dysfunction.

### ***Immune dysregulation***

Extensive bi-directional communication exists between the brain and the immune system and, increasingly, immune mechanisms are implicated in the pathogenesis of psychiatric disorders[96]. A specific association appears to exist between immune



system and hypermobility: Mast cell related disorders (giving allergy-like symptoms often across multiple organ systems) are commonly reported in patients with EDS/hEDS, highlighting a deep interrelationship between connective tissue and immune function occurring across genetic, molecular and physiological levels[97]. The concurrent expression of connective tissue impairments and immune dysfunction is speculated to influence vulnerability to psychiatric disorders. This may extend to neurodevelopmental disorders[34], as recent evidence highlights immune dysregulation in ASD[98].

### **Proprioceptive abnormalities**

Abnormal proprioception is observed in both hypermobility and neurodevelopmental disorders and may account for their association[38]. Symptoms of both are present from early in childhood and appear highly heritable. Impaired proprioception particularly affects the lower limbs of children and adults with HSD/hEDS[99] and often leads to issues with coordination, balance, clumsiness and motor problems. Poor proprioception may directly account for the relationship between hypermobility and DCD[100]. Moreover, it is speculated that maintaining motor competences despite impaired proprioceptive function may overload executive functions and compete for attentional resources. This may in turn reinforce inattention in ADHD[101], and could further impact the timely acquisition of social and communication skills, thereby exacerbating ASD traits[34].

### **Implications for practice**

We echo other authors calling for widened awareness of the diverse manifestations of hypermobility, particularly in psychiatry[34]. A recently proposed ‘neuroconnective phenotype’ model usefully describes the symptom profiles often expressed by people with hypermobility, including behavioural, psychopathological, somatic symptoms, somatosensory symptoms and somatic illness[11]. Considering the evidence presented here, we recommend vigilance for potentially overlooked mental health symptoms within the plethora of difficulties faced by patients living with HSD/hEDS. These should be part of a holistic clinical formulation that can enable appropriate psychoeducation, referral to mental health services, prompt diagnosis and access to optimal treatments.

Alongside this, we recommend screening for hypermobility, particularly in those presenting with neurodevelopmental disorders, but also in other mental health presentations, notably of panic and anxiety, in the context of physical symptoms, since articular and extra-articular features are often present[102] (Table 1). Simple screening using a 5-point questionnaire can detect hypermobility with high sensitivity and specificity[1] (Table 2). Early assessment can prompt referral to specialist services and thus reduce delayed or misdiagnosis of HSD/hEDS. It also widens opportunities for early intervention to prevent progression of psychological as well as physical symptoms throughout the lifespan.

Currently, there no specific guidelines for the psychological or pharmacological management of psychiatric conditions in patients with HSD/hEDS. Nevertheless, considering the complex difficulties faced by these patients, we recommend multidisciplinary management across mental and physical health professionals, including early involvement of physiotherapy to facilitate improvement of proprioception and bodily awareness[19].

### **Limitations**

One considerable limitation in evaluating the growing evidence base describing the association between joint hypermobility and psychiatric disorder is the variable use of assessment tools to measure hypermobility. Specific genetic tests or biomarkers do not exist. The use of assorted self-report questionnaires and distinct clinical assessment scales is liable to subjective interpretation and observer dependence, limiting reliability. Furthermore, the application of age-dependent cut-off scores remains controversial. Our review has considered articles covering the whole spectrum of hypermobility and related disorders yet highlights the need for further disentangling research.

Nevertheless, individuals with higher anxiety and more severe symptoms are more likely to seek medical attention, join patient support associations and participate in research studies, even among ‘non-clinical’ populations. Those recruited may be experiencing higher distress, and hence introduce sampling bias. Published studies may therefore overlook (and over-pathologise) the spectrum of hypermobility presentations.

**Table 1** Indications prompting screening for hypermobility spectrum disorders/hypermobile Ehlers-Danlos syndrome amongst patients presenting to mental health services (adapted from Ross and Grahame 2011[102])

	Extra-articular features	Articular features
In children and adolescents	Prolonged fatigue or tiring easily  Poor motor coordination or 'clumsiness' (such as poor ball catching and poor handwriting)  Chronic widespread pain or 'growing pains'  Delayed walking, with bottom shuffling instead of crawling	Joint dislocations/subluxations (including congenital hip dislocation)  Recurrent ankle sprains
In adults	Prolonged unexplained fatigue (including ME/CFS)  Chronic widespread pain, particularly if unresponsive to analgesia (including fibromyalgia)  Functional gastrointestinal disorders (such as IBS, functional dyspepsia, constipation)  Autonomic dysfunction (such as orthostatic intolerance or PoTS)  Progressive loss of mobility secondary to pain or pain-avoidance strategies  Laxity in supporting tissues (such as hernias, varicose veins, pelvic floor dysfunction)  Soft/hyperextensible skin, unexplained striae, easy bruising	Recurrent joint dislocations  Multiple soft tissue injuries/rheumatisms  Premature osteoarthritis  Persistent or recurrent joint pains

ME/CFS: Myelo-encephalomyelitis/chronic fatigue syndrome; IBS: Irritable bowels syndrome; PoTS: Postural tachycardia syndrome.

**Table 2** Five-point screening questionnaire for detecting hypermobility (from Hakim and Grahame 2003[1])

1 Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2 Can you now (or could you ever) bend your thumb to touch your forearm?
3 As a child, did you amuse your friends by contorting your body into strange shapes OR could you do the splits?
4 As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
5 Do you consider yourself 'double-jointed'?
Answering yes to two or more questions suggests hypermobility with sensitivity 80%-85% and specificity 80%-90%

### Future research

There is strong evidence linking the expression of mental health disorders to hypermobility as a signature of variant connective tissue. However, future research is needed to investigate the genetic, neural and psychophysiological mechanisms for such mind-body interactions. Longitudinal studies are needed to better identify which hypermobility individuals develop psychiatric symptoms or diagnoses to delineate contributions of precipitating, perpetuating, and preventative factors and map how these progress with time. Such fresh insights offer the potential for the implementation of early preventative strategies in at-risk individuals, minimising complications in later life.

We argue that variant connective tissue contributes to the pathogenesis of mental health disorders: This likely represents an 'endophenotype'; a measurable component along the pathway between phenotype and disease, an important emerging concept in neuropsychiatric research[103]. In this respect, hypermobility is clearly heritable, and presents with excess relative risk in relatives[23]. In addition, its role has biological plausibility, is not state dependent, and is easily testable. However, there remains much to understand, not least how hypermobility is connected with candidate genes. In this context, across psychiatric disorders the presence of hypermobility could represent a phenotypic subgroup of patients[103]. Hypermobility may also act as a clinical marker for specific target symptoms *e.g.*, anxiety[16], as demonstrated in hypermobile patients with schizophrenia[31] or for sensory hypersensitivities, *e.g.*, to olfactory stimuli in patients with panic disorder[104].

More research is also needed to determine if this patient subset responds differently to treatment, allowing for a 'personalised medicine' approach. For example, a dietary intervention (low FODMAP) for irritable bowel syndrome is reportedly more effective in hypermobile compared to non-hypermobile patients[105]. Dysfunctional coping strategies are associated with hypermobility[33], so psychological approaches addressing these could prove beneficial. Anecdotally, sensitivity to unwanted drug side-effects is high in this group. The first randomised controlled trial of a targeted non-pharmacological therapy for anxiety in the context of hypermobility is currently ongoing, comparing modified interoceptive training to standard supportive treatment in individuals with hypermobility and anxiety[106].

## CONCLUSION

In conclusion, alongside the well-known link between hypermobility and anxiety, recognition of which has expanded across age groups, there is growing evidence of associations with depression, eating disorders, neurodevelopmental conditions and stress-sensitive medical conditions. There remains a paucity of evidence for links with schizophrenia and addictions. We recommend clinicians across different specialities are aware of the transdiagnostic nature of HSD/hEDS, which may present with both primary and secondary difficulties in psychological and physical domains. In particular, professionals encountering patients with mental health difficulties should consider the prospect of underlying hypermobility as a potential influence on neuropsychiatric symptom progression in this subgroup of patients.

While hypermobility and psychopathological attributes are conventionally considered distinct, their association affirms the pervasive interplay of mind, brain and body. Perceptions, emotions, cognitions and behaviours are dynamically coupled to the state of the body through both unconscious and conscious mechanisms[89]. Further investigation of the psychophysiological, cellular, molecular and genetic underpinnings of the link between hypermobility and psychiatric disorders may provide clinically relevant insights to improve recognition, identify treatment targets, and plan holistic management strategies across the lifespan that combine both psychiatric and somatic approaches.

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