PS-08 Neurodiversity through the lens of sex

To accurately comprehend how biological sex interacts with neurodevelopmental variation, it is necessary to construct an analytical framework that rigidly separates three interacting layers of human development. The first layer is physiology, comprising the measurable biological substrates of genetics, epigenetics, and endocrinology. The second layer is behaviour, comprising the statistical averages and overlapping distributions of cognitive and social traits. The third layer is culture, comprising the variable environments, socialization pressures, and diagnostic paradigms that interpret and categorize human action. The interaction among chromosomal sex, gonadal hormones, and neurological development produces distinct cognitive profiles and psychiatric vulnerabilities. However, historical and methodological biases have routinely conflated culturally mediated symptom presentation with innate biological divergence.

This comprehensive report examines how sex interacts with neurodiversity—specifically Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), dyslexia, and schizophrenia. It systematically evaluates leading theories regarding the male preponderance in early-onset neurodevelopmental conditions, the empirical status of the extreme male brain and prenatal testosterone hypotheses, and the physiological protective factors delaying psychiatric onset in females. The analysis distinguishes rigorously between what is known about statistical averages and what can be reliably predicted about individuals, forming a foundation for understanding how men and women can best live and organize together.

Layer 1: Physiology and the Biological Substrate

The foundational layer of sex differences in neurodevelopment rests upon the unalterable biological realities of genetics and endocrinology. These measurable physiological mechanisms provide the specific biological vulnerability or resilience upon which neurodivergence develops.

X-Chromosome Inactivation, Imprinting, and Dosage Compensation

The mammalian mechanism of dosage compensation, known as X-chromosome inactivation (XCI), traditionally functions to silence one X chromosome in female (XX) somatic cells, theoretically equalizing gene dosage with males (XY). However, genomic analyses demonstrate that approximately 15% to 30% of human X-linked genes escape this inactivation, leading to biallelic expression and a fundamental dosage difference between males and females[1].

Research by Tukiainen, Disteche, and colleagues has demonstrated that inactive X (Xi) expression levels act as a highly robust linear predictor of female-male expression differences across tissues, meaning that female cells operate in a fundamentally different transcriptional environment than male cells[1]. This escape from XCI heavily influences immune response, neurodevelopment, and vulnerability to X-linked mutations, offering females a broader genetic buffering capacity against deleterious variants[2].

Furthermore, genomic imprinting on the X chromosome plays a critical and sexually dimorphic role in socio-cognitive development. In a landmark 1997 paper published in *Nature*, Skuse et al.

analyzed females with Turner syndrome (45,X)—a chromosomal condition resulting in a single X chromosome. By comparing females who inherited their single X chromosome from their mother (X^m) against those who inherited it from their father (X^p), the researchers observed a profound phenotypic divergence. The X^m females exhibited significant deficits in social cognition, impaired visuospatial perceptual skills, and a higher vulnerability to autistic traits compared to X^p females[4]. Because typical males (46,XY) inherit their single X chromosome exclusively from their mothers, they operate with an X^m profile. Skuse et al. concluded that there is a paternally expressed, imprinted X-linked gene that facilitates social cognition and protects against socio-communicative deficits[4]. The inherent absence of this X^p gene in typical males establishes a baseline physiological vulnerability in the domain of social cognition, laying the biological groundwork for the male preponderance in autism.

The Female Protective Effect (FPE) and Polygenic Liability

The consistently higher prevalence of neurodevelopmental conditions in males has led to the formalization of the Female Protective Effect (FPE) hypothesis. The FPE posits a liability-threshold model wherein females require a significantly higher burden of genetic mutations or environmental insults to exhibit the same degree of phenotypic severity as males. Wigdor et al., publishing in *Cell Genomics* (2022), provided definitive large-scale genetic evidence for this model by analyzing both rare de novo variants and common polygenic risk scores (PRS). Utilizing the Danish iPSYCH resource, the researchers conducted epidemiological analyses demonstrating that siblings of female ASD cases (n = 1,707) had significantly higher rates of clinical ASD than siblings of male ASD cases (n = 6,270; $p < 1.0 \times 10^{-10}$)[7]. Because siblings share approximately 50% of their segregating alleles, the higher recurrence rate in families with an autistic female implies that the female proband inherited a massive dose of familial genetic risk—a dose so high that it inevitably spilled over to her siblings. Furthermore, analyzing the Simons Simplex and SPARK collections, Wigdor et al. found that mothers of ASD cases (n = 7,436) carried significantly more polygenic risk for ASD than fathers of ASD cases (n = 5,926; 0.08 PRS standard deviations; $p = 7.0 \times 10^{-7}$)[7].

This polygenic data corroborates earlier foundational work regarding rare structural variants. Jacquemont et al. (2014) in the *American Journal of Human Genetics* demonstrated that females diagnosed with ASD carry a significantly higher burden of rare de novo copy number variants (CNVs) and single nucleotide variants compared to males with ASD[8]. Specifically, the median number of genes per CNV identified in autistic females ranges from 10 to 15, compared to only 2 to 3 in autistic males[10]. This robustly replicated finding indicates that female neurophysiology possesses an inherent buffering capacity. It requires a profound, systemic disruption of integral biological pathways to breach the diagnostic threshold for autism or intellectual disability in a female, whereas male neurodevelopment can be derailed by significantly smaller genetic perturbations[10].

The Prenatal Hormone Milieu: Testosterone and Oestrogen

The organizational-activational hypothesis of brain development dictates that prenatal gonadal hormones permanently organize neural architecture, which is later activated by pubertal hormones. Baron-Cohen and colleagues have extensively investigated whether elevated prenatal testosterone (pT) serves as the primary physiological mechanism driving autistic neurodevelopment. Early longitudinal studies utilizing amniotic fluid extracted during routine second-trimester amniocentesis found positive correlations between amniotic pT and later parent-reported autistic traits—such as restricted interests and reduced eye contact—in typically developing children[12].

In 2015 and 2019, Baron-Cohen et al. published paradigm-shifting findings in *Molecular Psychiatry* by leveraging the massive Danish Historic Birth Cohort. Analyzing amniotic fluid from 128 boys later diagnosed with ASD and 217 matched controls (2015), they found elevated levels of a generalized steroidogenic factor[14]. In their 2019 follow-up, they expanded the analysis to investigate foetal oestrogens, recognizing that testosterone is aromatized into oestrogen in the brain. They observed that all four forms of foetal oestrogen—oestradiol, oestriol, oestrone, and oestrone sulphate—were significantly elevated in 98 male foetuses who later developed autism compared to 177 controls[14]. The inclusion of oestrogens expanded the narrow "foetal testosterone theory" into a broader "prenatal sex steroid theory" of autism, suggesting that early steroidogenic dysregulation is a core feature of the autistic biological substrate[12].

However, the empirical status of the pT hypothesis remains highly contested, with leading critics pointing to severe replication failures and methodological limitations. A 2021 study by Dooley et al. in *Psychoneuroendocrinology* assessed pT levels in 97 adolescents via amniotic fluid and found absolutely no statistical evidence for a direct association between pT and autistic traits beyond childhood (males, females, or full sample)[12]. This suggests that earlier findings linking pT to autistic traits may reflect transient developmental phenomena rather than permanent organizational shifts. Furthermore, foundational claims relying on proxy markers of pT, such as the 2D:4D digit ratio (the ratio of the index to ring finger length), have collapsed under rigorous scrutiny. Richards et al. reanalyzed amniotic testosterone and oestradiol against digit ratios at a 4.5-year follow-up and found highly erratic correlations with large confidence intervals, entirely failing to replicate earlier claims (e.g., Lutchmaya et al., 2004)[18]. The consensus dictates that while prenatal steroid dysregulation is a replicated phenomenon in clinical ASD cohorts, its direct, dose-dependent causal role in generating the broader autistic cognitive phenotype remains an open and highly controversial question.

Layer 2: Behaviour, Statistical Averages, and the Brain Mosaic

The transition from cellular physiology to macro-neuroanatomy and behaviour introduces a fierce debate regarding the existence of a "male brain" and a "female brain." Because behaviour and brain morphometry exist on statistical continuums with massive overlapping distributions, interpreting this data requires distinguishing strictly between population averages and individual prediction.

The Brain Mosaic Debate vs. Multivariate Predictive Accuracy

In 2015, Daphna Joel et al. published a highly influential paper in *PNAS* titled "Sex beyond the genitalia: The human brain mosaic." Analyzing structural MRI data from over 1,400 human brains utilizing voxel-based morphometry (VBM), Joel and colleagues assessed gray matter, white matter, and connectomic data. They argued that while group-level sex differences exist in specific brain regions, internal consistency is exceptionally rare. Defining an "internally consistent" brain as one possessing exclusively male-end or exclusively female-end features across all measured regions, they found that only 0% to 8% of individuals met this criterion. Instead, human brains are highly heterogeneous "mosaics" of male-leaning, female-leaning, and intermediate features[19]. Joel concluded that human brains do not belong to two distinct categories, rendering the concept of a strictly "male brain" or "female brain" biologically meaningless[19].

This framework was immediately and heavily critiqued by computational biologists and evolutionary psychologists. In 2016, Chekroud et al., Del Giudice et al., and Rosenblatt published independent rebuttals in *PNAS*. They argued that Joel's univariate analytical approach—assessing one brain region at a time—mathematically guaranteed a mosaic outcome, failing to capture the covariation of traits. When employing multivariate, machine-learning algorithms (e.g., penalized logistic regression, linear Support Vector Machines), the critics demonstrated massive biological divergence. Chekroud et al. achieved a 93% accuracy rate ($p < 10^{-16}$) in predicting an individual's sex category based purely on brain structure within a sample of 1,166 individuals[22]. Del Giudice et al. demonstrated through systematic simulations that Joel's methodology of defining "internal consistency" was so extreme that it systematically failed to detect large, consistent differences even when run on data distinguishing completely distinct biological species[23].

This academic debate perfectly illustrates the vital distinction between individuals and averages. Joel is correct that an individual's brain is a heterogeneous mosaic when viewed trait-by-trait, making it impossible to confidently reverse-engineer an individual's sex by looking at a single slice of neuroanatomy. Conversely, the critics are correct that on a multidimensional, statistical level, male and female brains occupy entirely distinct mathematical spaces[26]. This physiological overlap combined with multivariate statistical divergence perfectly sets the stage for understanding sex differences in cognitive behaviour.

The Empathizing-Systemizing (E-S) Theory and the Extreme Male Brain

The "Extreme Male Brain" (EMB) theory, an extension of the Empathizing-Systemizing (E-S) theory proposed by Simon Baron-Cohen, attempts to map these multivariate sex differences onto cognitive architecture. The E-S theory posits that typical females, on average, are biologically predisposed to be stronger empathizers (Type E: driven to identify mental states and respond with appropriate emotion), while typical males are stronger systemizers (Type S: driven to analyze, construct, and predict rule-based systems)[11]. The EMB theory suggests that autistic individuals exhibit an extreme Type S profile, representing a "masculinized" shift in

cognition regardless of their biological sex[27].
In 2018, Greenberg, Warrier, Allison, and Baron-Cohen published a massive empirical test of these theories in *PNAS*, leveraging a discovery dataset of 671,606 individuals (including 36,648 autistic individuals). The study confirmed the E-S predictions with unprecedented statistical power. Typical females scored significantly higher on the Empathy Quotient (EQ; Cohen's $d = 0.39$, $p < 2.2 \times 10^{-16}$), while typical males scored higher on the Systemizing Quotient (SQ; Cohen's $d = 0.31$) and Autism Spectrum Quotient (AQ; Cohen's $d = 0.18$)[27]. Autistic individuals exhibited the predicted "masculinized" profile: autistic females scored significantly lower on the EQ and higher on the SQ than typical females[27]. The researchers calculated a D-score (the standardized difference between EQ and SQ) and found that D-scores accounted for 19 times more of the variance in autistic traits (43%) than all other demographic variables combined, including sex[27].
Critiques of the EMB: The E-S theory and the EMB hypothesis have faced stringent methodological criticism. Ridley (2019) published a devastating theoretical review arguing that the questionnaires (AQ, EQ, SQ) are inherently circular. Because the psychometric instruments were developed by observing predominantly male autistic traits (e.g., restricted interests in mechanical systems, mathematics, or physics), they naturally detect males at higher rates[30]. The tests define autism through a lens of highly systematized, technical thinking and externalizing social deficits. Therefore, the finding that "autism is an extreme form of the male brain" is effectively a self-fulfilling artifact of how the testing instruments were engineered[30]. If a female's "restricted interest" is operationalized as a hyper-fixation on social dynamics, psychology, literature, or specific celebrities, her systemizing behaviour remains entirely invisible to the psychometric tools, exposing a massive cultural bias in behavioural measurement.

Layer 3: Culture, Diagnosis, and the Autistic Experience

Neurodivergent behaviour exists on a biological and statistical continuum, but the diagnostic boundaries that define it are culturally constructed. The interaction between shifting diagnostic criteria, societal gender expectations, and underlying neurobiology has historically obscured the true prevalence and presentation of female neurodivergence.

Prevalence Rates and the True Male-to-Female Ratio

For decades, the accepted male-to-female ratio in ASD was dogmatically estimated at 4:1 or 5:1, heavily skewing research, clinical models, and public perception toward male presentations[11]. In a pivotal 2017 systematic review and meta-analysis published in the *Journal of the American Academy of Child and Adolescent Psychiatry*, Loomes, Hull, and Mandy aggregated 54 studies encompassing 13,784,284 participants (53,712 with ASD). They determined that the true male-to-female odds ratio (MFOR) is not 4:1, but closer to 3:1 (MFOR = 3.25; 95% CI 2.93–3.62 in high-quality active screening studies)[34].
More recently, Loomes et al. (2024, *JAMA Psychiatry*) analysed updated global data and found

an overall M:F prevalence ratio of 2.89[32]. Crucially, prevalence ratios vary dramatically based on the presence of co-occurring intellectual disability. Among individuals with intellectual and language impairments, the sex ratio approaches 2:1, whereas in cohorts with average or above-average intelligence, the ratio historically expanded to 6:1 or even 10:1[10].
Recent longitudinal data from Sweden indicates a profound "female catch-up" effect. A 2024 registry study demonstrated that while the M:F ratio is heavily male-skewed in early childhood, it narrows significantly with age. By late adolescence and early adulthood (age 20), the cumulative incidence ratio approaches 1:1 in some active surveillance populations[37]. This indicates a profound diagnostic delay driven by cultural and clinical blind spots, not an innate biological absence of neurodivergence in females.

Context / Study Paradigm	Estimated M:F Ratio	Drivers of Variance	Primary Sources
Historical Clinical Average	4:1 to 5:1	Passive clinical referral; male-centric diagnostic tools (ADOS/ADI-R).	32
Loomes et al. (2017) Meta-analysis	~3:1	Adjusted for active ascertainment bias; massive sample size ($N =$ M).	34
ASD with Intellectual Disability	~2:1	Severe cognitive/motor phenotypes breach the female protective threshold early.	10
ASD without Intellectual Impairment	6:1 to 10:1	High cognitive capacity enables female camouflaging and diagnostic evasion.	39
Swedish Longitudinal	~1.2:1	Female catch-up effect; late	37

(Adulthood)		diagnoses following psychiatric decompensation.	

The Female Autism Phenotype and Camouflaging

Because "gold-standard" diagnostic instruments like the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) were validated on male-majority samples, autistic females without intellectual impairment are systematically missed[31]. Kentrou et al. (2019, 2021) have extensively documented this diagnostic delay. In a study of 1,211 autistic adults, 31.7% of autistic women received at least one erroneous psychiatric diagnosis (e.g., borderline personality disorder, anxiety, eating disorders) prior to their autism diagnosis, compared to only 16.7% of men[42]. Females frequently wait over a decade within the psychiatric system before their neurodivergence is accurately recognized.

The primary driver of this delay is **camouflaging** (or masking). Hull et al. (2019, *Journal of Autism and Developmental Disorders*) conceptualized camouflaging as the conscious or unconscious use of compensatory strategies to hide autistic traits and emulate neurotypical behaviour to avoid social exclusion[44]. Hull and colleagues developed the Camouflaging Autistic Traits Questionnaire (CAT-Q; $N = 832$), demonstrating robustly that autistic females score significantly higher on masking measures than both autistic males and non-autistic females[44]. Autistic girls often maintain closer physical proximity to peers, use more social words (e.g., discussing friendships) during clinical assessments, and engage in imaginative play, effectively disguising their core socio-communicative deficits from untrained clinicians[40].

The Cost of Culture: Autistic Burnout and Suicidality

Camouflaging to survive within neurotypical culture exacts a catastrophic physiological and psychological toll. Raymaker et al. (2020, *Autism in Adulthood*) formally defined "autistic burnout" through community-based participatory research involving qualitative thematic analysis. Burnout is distinct from occupational burnout and clinical depression; it is characterized by (1) chronic, pervasive exhaustion not alleviated by ordinary sleep, (2) the loss of previously mastered skills (e.g., loss of executive function, selective mutism, inability to perform activities of daily living), and (3) a radically reduced tolerance to sensory stimuli[48]. Raymaker identified the primary causes as the cumulative load of life stressors, prolonged masking, and a severe mismatch between external expectations and internal abilities[49].

This relentless depletion directly correlates with severe psychiatric outcomes. Cassidy et al. (2014, 2018, *Lancet Psychiatry*) established that suicidality is alarmingly high in the autistic population. In a study of adults with Asperger's syndrome (autism without intellectual disability), 66% reported lifetime suicidal ideation (a fourfold increase over the general population), and 35% had planned or attempted suicide[52]. Autistic females, in particular, report significantly higher rates of suicidal ideation and suicidal self-harm compared to autistic males, likely mediated by the higher burden of camouflaging and diagnostic delay[54].

Premature mortality is a grim downstream consequence of this systemic failure. Hirvikoski et al.

(2016, *Lancet Psychiatry*) conducted a population-based matched case-cohort study of 27,122 autistic individuals in Sweden. They found that premature mortality was increased 2.56-fold globally. Strikingly, for autistic adults without intellectual disability, suicide was the leading cause of premature death, with the risk amplified nearly 9-fold compared to the neurotypical population[56].

Divergence Beyond Autism: ADHD, Dyslexia, and Schizophrenia

The interaction between biological sex and neurodevelopment extends beyond autism, revealing a unified pattern of ascertainment bias, physiological protection, and sexually dimorphic symptom presentation across multiple domains.

Attention-Deficit/Hyperactivity Disorder (ADHD)

Sex differences in ADHD closely parallel those in autism regarding both prevalence and clinical presentation. A 2015 meta-analysis by Arnett et al. confirmed that ADHD is diagnosed significantly more frequently in males, driven largely by males exhibiting higher rates of hyperactive, impulsive, and externalizing behaviours[59]. Because male symptoms are disruptive to classroom and family environments, they trigger clinical referrals. Conversely, females with ADHD tend to present with the inattentive subtype—characterized by internalizing symptoms, daydreaming, and cognitive disorganization. This leads to profound diagnostic delays and a high likelihood of being misdiagnosed with primary anxiety or depression in adolescence. Physiologically, dopamine dysregulation is central to ADHD. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) studies reveal altered striatal dopamine transporter (DAT) availability in ADHD populations[62]. Sex differences in dopamine receptor density and turnover—which are partially modulated by circulating oestradiol—influence both the clinical presentation of ADHD and the pharmacological response to stimulants like methylphenidate[62].

Dyslexia: The Ascertainment Bias

Although contemporary genomic datasets in this specific review focus predominantly on autism and psychiatric conditions, the broader epidemiological literature on dyslexia perfectly illustrates the cultural layer of diagnostic bias. Historically, the male-to-female ratio for reading disabilities was cited as 3:1 or even 4:1. However, foundational epidemiological studies (e.g., Shaywitz et al., 1990, *JAMA*) demonstrated that this ratio was heavily influenced by referral bias. When objective reading assessments are applied uniformly to entire populations rather than relying on teacher or parent referrals, the true physiological deficit ratio drops closer to 1.5:1 or 1.2:1. Boys with dyslexia frequently act out in frustration, drawing clinical attention through externalizing behaviour, whereas girls with dyslexia tend to sit quietly and deploy camouflaging strategies to hide their reading deficits. This mirrors the diagnostic evasion seen in autism and ADHD, demonstrating a unified theory of sex-biased neurodevelopmental ascertainment.

Schizophrenia: The Oestrogen Protection Hypothesis

Unlike ASD and ADHD, which present in early childhood, schizophrenia typically onsets in late

adolescence or early adulthood. While the overall lifetime prevalence of schizophrenia is relatively equal between the sexes, the clinical trajectory is profoundly sexually dimorphic. Men generally experience an earlier onset, more severe negative symptoms, and poorer long-term functional prognoses.

Seeman (2020) and Riecher-Rössler (2018, *Schizophrenia Bulletin*) have extensively documented the "oestrogen protection hypothesis." Oestrogens, particularly 17β-oestradiol, operate through three distinct receptor subtypes ($ER\alpha, ER\beta$, and GPER) to exert profound neuroprotective, anti-inflammatory, and psychoprotective effects across the central nervous system[65]. Crucially, oestradiol acts as an endogenous neuromodulator that dampens dopamine receptor sensitivity, effectively functioning as an intrinsic, naturally occurring atypical antipsychotic[64].

Because of this physiological protection, females experience a significantly later first-onset of schizophrenia. Furthermore, premenopausal women often experience symptom fluctuations tightly correlated with their menstrual cycle, with psychotic exacerbations occurring predictably during low-oestrogen phases[68].

The most striking clinical evidence for this hypothesis is the "second peak" of schizophrenia onset in women. While first-episode psychosis drops drastically for men after age 40, incidence rates for women spike during perimenopause and menopause[67]. As ovarian oestradiol production ceases, the neurological buffer is abruptly removed, leading either to late-onset schizophrenia or a severe, rapid deterioration in women with pre-existing, previously stable chronic schizophrenia[65].

This biological reality has led to the development of targeted hormonal augmentation therapies. Kulkarni et al. conducted multiple randomized, double-blind, placebo-controlled trials (RCTs) supplementing standard antipsychotics with raloxifene (a selective oestrogen receptor modulator) in menopausal women with schizophrenia. A meta-analysis of these RCTs (e.g., utilizing 120mg/day of raloxifene) demonstrated significant superiority over placebo in reducing total symptom severity (measured via PANSS), yielding a highly robust weighted effect size (Hedges' $g = 0.57$; $p < 0.001$)[70]. Despite this overwhelming evidence, current treatment guidelines are predominantly derived from male-centric clinical trials, resulting in postmenopausal women frequently being overmedicated with standard antipsychotics while being denied targeted, sex-specific endocrine support[64].

Synthesis

10-Line Summary of Robust Findings

1. The historical 4:1 male-to-female autism diagnostic ratio is deeply flawed; massive systematic reviews indicate a true biological prevalence ratio closer to 3:1, which narrows to 2:1 in populations with co-occurring intellectual disability.
2. Females possess a robust physiological "protective effect," requiring a significantly higher mutational load—measured via rare copy number variants and common polygenic risk scores—to cross the threshold into psychiatric diagnosis.
3. Approximately 15% to 30% of X-linked genes escape X-chromosome inactivation,

mediating measurable sex differences in immune function, neurodevelopment, and socio-cognitive vulnerabilities.
4. Large-scale psychometric data confirms that males, on average, score higher on systemizing, while females score higher on empathizing; autism represents a masculinized shift on these specific, though culturally mediated, metrics.
5. Autistic women without intellectual impairment engage in exhausting levels of camouflaging, successfully mimicking neurotypical behaviour to evade social exclusion, which drives severe diagnostic delays.
6. The psychological toll of chronic camouflaging directly results in "autistic burnout"—a debilitating state of exhaustion, skill regression, and sensory intolerance that is distinct from clinical depression.
7. Autistic adults without intellectual disability face an alarming 9-fold increased risk of premature mortality due to suicide, with females showing profound psychiatric vulnerability.
8. ADHD in females presents primarily as inattention rather than disruptive hyperactivity, delaying clinical identification and rendering females highly susceptible to misdiagnosis.
9. 17β-oestradiol acts as a potent endogenous neuroprotectant that dampens dopamine receptor sensitivity, fundamentally delaying the onset and reducing the severity of schizophrenia in premenopausal women.
10. The menopausal drop in oestradiol triggers a uniquely female "second peak" of schizophrenia onset and symptom exacerbation, which can be significantly ameliorated by adjunctive therapies like raloxifene (Hedges' $g = 0.57$).

List of Contested or Open Questions

Domain	Core Question	Current Status / Controversy
Prenatal Hormones	Are elevated foetal androgens a primary causal factor in human neurodevelopmental divergence?	Contested. While amniotic fluid studies show correlations in childhood, recent adolescent follow-ups fail to replicate these findings, and proxy markers (2D:4D ratios) have collapsed under rigorous scrutiny.
Cognitive Theory	Does the "Extreme Male Brain" accurately describe autism biology?	Contested. Critics argue that psychometric tools (e.g., AQ, SQ) are circularly engineered to detect

		socialization patterns specific to boys, rendering the theory a cultural artifact rather than a biological law.
Neuroanatomy	Should human brain structure be conceptualized as an overlapping "mosaic" or a dimorphic binary?	Highly Contested. Univariate analyses show near-total trait overlap (0–8% internal consistency), while multivariate machine-learning algorithms can predict biological sex from brain structure with >90% accuracy.
Pharmacology	How should psychiatric dosing be adjusted for sex?	Open. Given variations in dopamine receptor density, oestrogen modulation, and drug metabolism, it remains unclear how quickly psychiatry can pivot from male-default dosing algorithms to sex-stratified pharmacological guidelines.

5 to 10 Most Important Sources to Read in Full

Authors & Year	Publication	Title & Relevance	Sources
Loomes et al. (2017)	*Journal of the American Academy of Child & Adolescent Psychiatry*	*What Is the Male-to-Female Ratio in Autism Spectrum Disorder?* The definitive meta-analysis dismantling the 4:1	[34]

		ratio.	
Wigdor et al. (2022)	*Cell Genomics*	*The female protective effect against autism spectrum disorder.* Vital genetic evidence of female polygenic buffering.	[7]
Greenberg et al. (2018)	*PNAS*	*Testing the Empathizing–Systemizing theory of sex differences...* Massive psychometric test (n=671,606) of the EMB theory.	[27]
Joel et al. (2015)	*PNAS*	*Sex beyond the genitalia: The human brain mosaic.* The foundational paper arguing against dimorphic brain categories.	[20]
Hull et al. (2019)	*Journal of Autism and Developmental Disorders*	*Development and Validation of the Camouflaging Autistic Traits Questionnaire (CAT-Q).* Quantifies female masking.	[44]
Raymaker et al. (2020)	*Autism in Adulthood*	*"Having All of Your Internal Resources Exhausted...": Defining Autistic Burnout.* Crucial	[49]

		qualitative definition of burnout.	
Hirvikoski et al. (2016)	*The Lancet Psychiatry*	*Premature mortality in autism spectrum disorder.* The definitive population study on the 9-fold suicide risk in autism.	[56]
Seeman (2020)	*Journal of Psychiatry and Psychiatric Disorders*	*Estrogen and Schizophrenia.* Exhaustive review of the oestrogen protection hypothesis and female symptom trajectories.	[65]

Implications for Living Together

Note: Translating biological and statistical variance into social policy must be done cautiously to avoid the naturalistic fallacy—the assumption that which is biologically "natural" or statistically "average" is inherently morally "good," or that statistical averages dictate individual destiny.

For Couples and Families:

Partners and parents must recognize that internalizing behaviours—such as quiet inattention, daydreaming, or intense social exhaustion—are as valid a manifestation of neurodivergence as externalizing behaviours like hyperactivity or physical stereotypies. Families should actively look out for signs of "camouflaging" in daughters and partners, recognizing that a superficial veneer of social competence may be hiding catastrophic internal distress. Accommodating sensory boundaries and providing low-demand recovery time is vital to preventing autistic burnout within the home.

For Small Groups and Organizations:

Workplaces must move beyond the culturally dominant stereotype of the "male autistic savant." Recognizing neurodiversity means actively adjusting physical environments to mitigate sensory overload (e.g., harsh lighting, open-plan office noise) and valuing direct, systemizing communication styles alongside empathic, consensus-driven ones. Organizations must understand that the energy required to "mask" in a neurotypical corporate environment directly depletes an employee's executive function; therefore, flexible, outcome-based work environments inherently yield higher productivity and lower psychiatric attrition.

For Societies and Healthcare Systems:

Diagnostic criteria, clinical training, and pharmacological dosing must be aggressively updated to account for physiological sex. Continuing to base autism and ADHD diagnostics primarily on male behavioural expressions leaves a generation of females exposed to systemic misdiagnosis, polypharmacy, and an elevated risk of suicide. Furthermore, psychiatric systems must integrate endocrine awareness—such as anticipating extreme psychotic vulnerability during the menopausal transition—into standard care protocols. Ultimately, society must decouple human worth from the ability to seamlessly perform neurotypical sociability, replacing forced assimilation with structural accommodation.

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