

# DOCUMENT SUMMARY

This review article by Mottron et al. proposes the "enhanced plasticity hypothesis" to explain the significant male-to-female sex ratio bias in autism. The authors argue that males have a lower threshold for a "plastic reaction" in perceptual brain regions following a genetic or environmental trigger, making them more susceptible to developing an autistic neurotype. The paper provides extensive evidence from genetics, brain imaging, and animal models to support the concept of a "female protective effect," where females require a greater genetic load to be diagnosed. This framework is crucial for Enliten as it offers a scientific, non-pathologizing explanation for why autistic females are often missed by standard diagnostics and why their presentation may differ from males, validating the need for more nuanced, individualized assessment methods like the Enliten Interview.

## FILENAME

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## METADATA

- **Primary Category:** NEURODIVERSITY
- **Document Type:** research\_article
- **Relevance:** Core
- **Key Topics:** sex differences, autism, brain plasticity, female protective effect, genetics, Enhanced Perceptual Functioning (EPF), Trigger-Threshold-Target (TTT) model
- **Tags:** #sex\_differences, #autism, #brain\_plasticity, #female\_protective\_effect, #EPF, #TTT\_model, #genetics, #neurodiversity, #assessment\_bias, #late\_diagnosis

## CRITICAL QUOTES FOR ENLITENS

"Boys have a 4 to 7 higher-fold risk of developing autism than girls."

"The 'protective effect' observed in females with respect to the autism spectrum (AS) remains largely unexplained."

"We focus on sex differences in plasticity at the synaptic and regional level and hypothesize that these differences influence the threshold for the development of plastic reactions in specific brain areas involved in perception and language."

"Autism involves cognitive hyper-functioning and cortical reallocations , which have not yet been mechanistically related to sex."

"The sex ratio bias in autism may arise because males have a lower threshold than females for the development of this plastic reaction following a genetic or environmental event."

"A study of more than 9,000 dizygotic twins from population-based cohorts showed that siblings of autistic females exhibit significantly more autistic traits than siblings of autistic males , suggesting that female patients carry a higher 'genetic load' than male patients."

"The AS sex ratio cannot be explained by a genetic mechanism resulting from severe loss of function mutations found in AS individuals with a low IQ, but rather by factors present in AS individuals without ID, in whom severe loss of function mutations have not been found and SIS and PP are consistently reported."

"Sexual divergence of developmental trajectories also suggests that the plastic reaction happens in different regions in boys and girls, resulting in a different autistic phenotype in men and women. This explains why males and females may be diagnosed according to different symptoms and/or using different weights attributed to the three diagnostic areas."

## KEY STATISTICS & EVIDENCE

- **Sex Ratio:** Boys have a 4 to 7 times higher risk of developing autism than girls.
- **Prevalence of Talents:** In one study of 254 autistic individuals, the prevalence of special isolated skills (SIS) was 62.5%. In a smaller group from the same study, the prevalence of perceptual peaks (PP) was 58%, compared to 13% in controls.
- **Genetic Load in Females:**
  - Siblings of autistic females show significantly more autistic traits than siblings of autistic males, suggesting females carry a higher "genetic load".
  - Studies show that de novo copy number variants (CNVs) are more common in autistic females than males and disrupt more genes in females.
  - In a large CNV analysis, autistic females were twice as likely to have exonic deletions involving FMRP targets than autistic males.
  - In an independent cohort of 762 families, females had three times more deleterious autosomal CNVs and many more unique deleterious single-nucleotide variants (SNV) than males. The effect of these SNVs was also substantially more severe in autistic females.
- **RRBI Differences:** A meta-analysis concluded that while males and females had similar communication and social symptoms, girls showed fewer repetitive, restricted behaviors and interests (RRBI) than boys.

## THEORETICAL FRAMEWORKS

**The Enhanced Plasticity Hypothesis** This paper's central hypothesis proposes that the sex ratio bias in autism stems from differences in brain plasticity.

- **Core Tenet:** Males have a lower threshold than females for developing an "enhanced plastic reaction" in response to a genetic or environmental event. This plastic reaction targets specific brain areas, particularly those involved in perception and language, leading to the development of an autistic cognitive style.

- **Mechanism:** Interactions between genetic sex and hormones may result in higher synaptic and regional plasticity in perceptual brain areas in males compared to females. This increased plasticity makes them more susceptible to the cortical reallocations that characterize autism.
- **Contrast with Extreme Male Brain (EMB) Theory:** While the EMB theory attributes the sex ratio to autism being an "extreme" form of the typical male brain, the enhanced plasticity hypothesis focuses on the dynamic process of brain development and reorganization. It accounts for genetic findings not related to hormones and provides a mechanism for how different phenotypes can emerge in males and females.

**Trigger-Threshold-Target (TTT) Model** This model, introduced in a previous paper by the authors and applied here, links genetics, plasticity, and the cognitive profile of autism.

- **Trigger:** Genetic mutations (e.g., in genes related to synaptic function) or environmental insults act as the trigger.
- **Threshold:** Individuals have a certain threshold for initiating a plastic reaction. This threshold is hypothesized to be lower in males than in females. Similar mutations can lead to different phenotypes depending on this threshold.
- **Target:** The plastic reaction targets the most variable and plastic brain regions, which are often the sexually dimorphic perceptual and multimodal association cortices. This reallocation of brain resources leads to the pattern of cognitive strengths (e.g., Enhanced Perceptual Functioning) and challenges seen in autism.

**Enhanced Perceptual Functioning (EPF) and Regional Plasticity** The paper builds on the EPF model by connecting it to observable brain changes.

- **Regional Plasticity (Cortical Reallocation):** This is defined as the "experience-dependent dedication of a cerebral region to a cognitive function that does not typically map to this region in the general population".
- **EPF as a Result of Plasticity:** The EPF model posits that autistic cognitive strengths (like superior perceptual performance) result from strong encoding mechanisms, enhanced perceptual expertise, and a greater role for perception in overall cognition. The TTT model proposes that this is the direct result of an enhanced plastic reaction targeting perceptual brain regions.
- **Evidence:** Autistic individuals show higher activity in temporal, occipital, and parietal regions during visual tasks, and these areas of enhancement overlap with regions known to be highly variable and sexually dimorphic in the general population.

## POPULATION-SPECIFIC FINDINGS

**The Female Protective Effect and Phenotype** The paper provides a comprehensive biological explanation for why females are diagnosed with autism less frequently and may present differently.

- **Higher Mutational Burden:** Multiple large-scale genetic studies confirm that autistic females carry a significantly higher "genetic load" than autistic males. This includes more frequent and more severe *de novo* CNVs and SNVs. This suggests that females are protected and require a more significant genetic event to develop a recognizable autistic phenotype.

- **Different Phenotypes:** The model predicts that because the plastic reaction targets different brain regions in males and females (due to baseline sex differences in development), the resulting autistic phenotype will also differ.
- **RRBI Differences:** The most consistently reported phenotypic difference is that autistic girls show fewer repetitive, restricted behaviors and interests (RRBI) than boys.
- **Compensatory Strategies:** The observation that phenotypic differences are most often reported in adolescents and adults with typical intelligence suggests that "compensatory social communication strategies develop over time, especially in girls". This can mask the underlying neurotype and lead to missed or late diagnoses.
- **High-IQ vs. Low-IQ Autism:** The sex ratio imbalance is strongest in high-functioning autism. Autistic females and males with low IQ have a similarly high incidence of severe, likely gene-disruptive mutations. In contrast, such mutations are rare in high-functioning autistic males, suggesting the sex bias is driven by factors present in individuals without intellectual disability.