Sex Differences in the Brain: Implications for Explaining Autism

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Empathizing is the capacity to predict and to respond to the behavior of agents (usually people) by inferring their mental states and responding to these with an appropriate emotion. Systemizing is the capacity to predict and to respond to the behavior of nonagentive deterministic systems by analyzing input-operation-output relations and inferring the rules that govern such systems. At a population level, females are stronger empathizers and males are stronger systemizers. The "extreme male brain" theory posits that autism represents an extreme of the male pattern (impaired empathizing and enhanced systemizing). Here we suggest that specific aspects of autistic neuroanatomy may also be extremes of typical male neuroanatomy.

Leaving aside political correctness, there is compelling evidence for sexu8al dimorphism in the brain, cognition, and behavior (1). In this Viewpoint, we review the evidence at all three levels. Classic autism and Asperger syndrome (AS) are the two clearest subgroups on the autistic spectrum of conditions, and both affect males more often than females. We conjecture that understanding sex differences in the general population has implications for understanding the causes of autism-spectrum conditions.

The E-S Theory of Psychological Sex Differences

Although males and females do not differ in general intelligence, specific cognitive tasks reveal sex differences. Differences favoring males are seen on the mental rotation test (2), spatial navigation including map reading (3), targeting (4), and the embedded figures test (5), although there are conflicting studies regarding the latter (6). Males are also more likely to play with mechanical toys as children (7), and as adults, they score higher on engineering and physics problems (8). In contrast, females score higher on tests of emotion recognition (9), social sensitivity (10), and verbal fluency (11). They start to talk earlier than boys do (12) and are more likely to play with dolls as children (7). Effect sizes range from small (Cohen's $d = 0.2$ for emotion recognition) to large (Cohen's $d = 1.3$ to 1.9 for targeting), with a substantial degree of overlap between male and female distributions, even for

effects considered large by the conventions of psychology. All of these differences exist at the level of populations, not individuals; from such population differences, no inferences can or should be made about individuals.

Although these population differences partially arise from experiential factors, experiments in animals suggest a biological foundation. Male rats perform significantly better than females do on the radial arm and Morris water maze (*13*). This sex difference is eliminated by castrating males or by treating females with testosterone neonatally (*14*). Human males also commit fewer errors and require less time to complete a "virtual" maze (*15*). Young male vervet monkeys prefer to play with toy trucks, whereas young female vervets prefer dolls (*16*). This finding suggests that sex differences in toy preferences in children result, in part, from innate biological differences. Biological contributions to social interest are suggested by studies of human infants. When 1-day-old babies are presented with either a live face or a mechanical mobile, girls spend more time looking at the face, whereas boys prefer the mechanical object (*17*).

According to the empathizing-systemizing (E-S) theory of psychological sex differences, such differences reflect stronger systemizing in males and stronger empathizing in females (*18*). Systemizing is the drive to analyze a system in terms of the rules that govern the system, in order to predict the behavior of the system. Empathizing is the drive to identify another's mental states and to respond to these with an appropriate emotion, in order to predict and to respond to the behavior of another person. (Other people's emotional states and behavior cannot easily be predicted and responded to using systemizing strategies. Whereas a deterministic system given the same inputs always produces the same outputs, the input-output function of a person depends on subtle differences in current and past emotional context and is practically impossible to parameterize formally).

The E-S theory proposes that psychological sex differences are defined by the difference between the dimensions of empathizing (E) and systemizing (S), and it categorizes individual brain types as type S (S > E, more common in males), type E (E > S, more common in females), or type B (E = S, in those who are equally proficient at empathizing and at systemizing) (Fig. 1). Data from two questionnaires, the empathy quotient (EQ) and the systemizing quotient (SQ), reveal the existence of extreme types where S » E or E » S (Fig. 2), and SQ-EQ difference scores (Fig. 3) illustrate the differing profiles of the two sexes. Ongoing studies from our lab confirm the psychometric reliability and validity of these scales (*19*) and are evaluating how they correlate with performance tests (*20*).

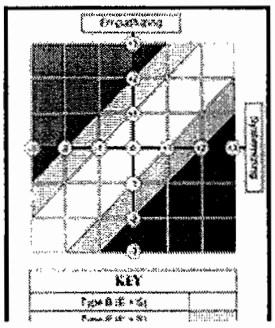

Fig. 1. The Empathizing-Systemizing model of sex differences at the psychological level.

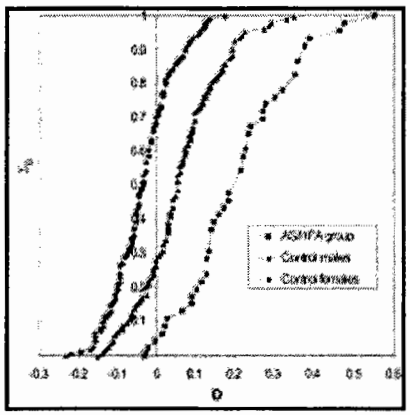

Fig. 2. Cumulative distribution function (Σ_D) of difference scores (D). This graph shows that the values of D between EQ and SQ significantly differentiate the three populations [males, females, and individuals with a diagnosis of AS/high-functioning autism (HFA)] (*82*).

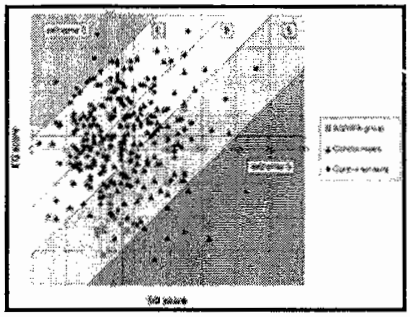

Fig. 3. SQ scores versus EQ scores for all participants, with the boundaries for the different brain types (*82*).

Sex Differences in Brain Structure

Although there is a great deal of individual variance in human brain morphometry (*21*), it is known that the cerebrum as a whole is about 9% larger in men and is also larger in boys (*21*), a difference that is driven more by white matter than by gray (*22*, *23*). Despite the larger total volume of white matter in men [and despite the conflicting studies of sex differences in specific corpus callosum measures (*24*)], three-dimensional (3D) morphometry suggests that the ratio of corpus callosum to total cerebral volume is actually smaller in men (*22*). This is consistent with the findings that increased brain size predicts decreased interhemispheric connectivity (*25*) and that larger brains come with proportionately smaller corpora callosa in humans (*26*) and other species (*27*). Reports of anatomically localized cerebral sexual dimorphism are less consistent (*28*), but the male amygdala undergoes an extended period of growth during childhood (*29*); it is larger in boys (*30*) and may remain larger in men (*28*). These anatomical differences likely result from differences in microarchitecture. There are more neurons in the male cerebral cortex (*31*), and in general, these neurons are more densely packed (*32*), albeit with some regional exceptions (*33*).

Overall, greater numbers and denser packing of neurons, together with more intrahemispheric white matter projecting from these neurons, indirectly suggest a pattern of increased local connectivity and decreased interhemispheric (or long-range) connectivity in the male brain. Physiological observations,

though sparse, seem consistent with this picture; language-related activation in female brains is more bilateral, suggesting greater interhemispheric connectivity (*34*, *35*), and the single study of gamma-band magneto-encephalography (MEG) reports increased phase locking between frontal and parietal sites in women during cognitive performance, again suggesting greater long-range connectivity (*36*).

The EMB Theory of Autism at the Psychological Level

An extension of the E-S theory of typical sex differences is the "extreme male brain" (EMB) theory (*37*). This theory proposes that individuals on the autistic spectrum are characterized by impairments in empathizing alongside intact or even superior systemizing. Adults with AS are more likely to have a brain of extreme type S (Fig. 2) and are distinguished by their high SQ-EQ difference scores (Fig. 3) (*38*). Table 1 gives the frequencies of all E-S brain types in the general population and in people with AS.

Table 1. Classifications of brain type based upon percentiles (*82*).

Brain type	**Extreme E**	**E**	**B**	**S**	**Extreme S**
Brain sex	Extreme female	Female	Balanced	Male	Extreme male
Defining characteristic	$S \ll E$	$S < E$	$S \approx E$	$S > E$	$S \gg E$
Percentile (per)	per < 2.5	2.5 ≤ per < 35	35 ≤ per < 65	65 ≤ per < 97.5	per ≥ 97.5
Female %	4.3	44.2	35.0	16.5	
Male %		16.7	23.7	53.5	6.1
AS/HFA %			12.8	40.4	46.8

Reduced empathy in people with AS is evident in their lower scores on emotion-recognition tests (*39*), the EQ (*40*), the friendship and relationship quotient (*41*), and tests of social sensitivity such as the "faux pas" test (*10*). Intact or even superior systemizing is seen in their higher scores on the SQ (*42*), tests of folk physics (*43*), and the embedded figures test (*44*) (although it is unclear if the latter is really a test of systemizing or simply a test of good attention to detail). It is also seen in their strong obsessions, or areas of narrow interest, which tend to focus on systems (*45*).

It is clear how the EMB theory might characterize people with AS, but to what extent does the EMB theory apply to the whole autistic spectrum? People with classic autism have empathy deficits, or degrees of "mind blindness," in that they are delayed in developing a "theory of mind" in childhood and joint attention in infancy (*46*). It is less straightforward to test systemizing in someone with little language or with a below-average intelligence quotient (IQ). Nevertheless, characteristic behaviors

such as "insistence on sameness," repetitive behavior, obsessions with lawful systems (e.g., train timetables), islets of ability (e.g., calendrical calculation), precocious understanding of machines, and superior attention to the detection of change all involve a strong interest in rule-based prediction and therefore can be read as signs of hypersystemizing. It is unclear whether the risk of reduced IQ or language difficulties increases as systemizing becomes so strong that attention is narrowed to understanding just one unique system, making generalization of knowledge irrelevant (*47*). Of course, such symptoms may reflect other processes than systemizing, and competing hypotheses need to be tested.

The EMB Theory of Autism at the Neuroanatomical Level

Recent hypotheses concerning neural connectivity in the autistic brain postulate an exaggerated version of what may also be going on in the typical male brain: a skewed balance between local and long-range connectivity (*48*–*51*). Such a connectivity difference could give rise to a deficit in empathizing, because empathy activates brain regions that integrate information from multiple neural sources (*52*). In autism, furthermore, long-range connectivity during an empathizing task is abnormally low (*53*). This notion of skewed connectivity is also compatible with strong systemizing, because systemizing involves a narrow attentional focus to local information, in order to understand each part of a system. Imaging studies are needed to confirm this relationship.

Young children with autism tend to have larger-than-average heads. Magnetic resonance imaging morphometry confirms that these large heads contain abnormally large brains, an increase driven more by white matter than by gray (*54*). Although not yet confirmed by in vivo tract tracing, the anatomical distribution of this white-matter hyperplasia suggests it occurs more in short-distance tracts, whereas the internal capsule and corpus callosum are proportionately reduced (*55*–*57*). The development of the amygdala in autism likewise seems an extreme of typical male brain development. In children with autism between 18 and 35 months old, the amygdala is abnormally large, even when corrected for total brain volume (*58*). This enlargement persists through early childhood (*59*, *60*), exactly during the period of sex-differential amygdala growth in normal boys. By the time children with autism reach adolescence, the enlargement has disappeared (*60*); by early adulthood, the amygdala in autism is abnormally small (*61*, *62*).

Like an exaggeration of typical males, children with autism show enlargement of the cerebral cortex that stems more from white matter than from gray and may affect short-distance more than long-distance tracts. Again like an exaggeration of typical boys, children with autism also show greater growth of the amygdala. Future research will need to map all aspects of autistic neuroanatomy that are hypermasculinized, as well as consider how to explain those aspects that are not.

Prenatal Androgens Produce Sex Differences in Brain and Behavior

Which biological mechanisms shape the sex differences described above and may be pushing the autistic brain to develop beyond that of the typical male? In this section we review evidence for prenatal androgens as a key biological mechanism. Androgens, including testosterone produced by the testes in fetal and neonatal life, act on the brain to produce sex differences in neural structure and function. Testosterone is a small lipophilic molecule that easily passes through the blood-brain barrier and across cell membranes. The androgen receptor (AR) is a classic steroid receptor found in the cytoplasm. Once bound to testosterone (or its metabolite dihydrotestosterone), the AR enters the nucleus, where it binds DNA and affects transcription. Testosterone can also be aromatized to estradiol within the target cell, binding to the estrogen receptor (ER-α or ER-ß) and influencing transcription similarly. Testosterone affects neural development by averting programmed cell death, influencing neural connectivity, and altering neurochemical profiles (*14*). For example, testosterone and estradiol modulate serotonergic and γ-aminobutyric acid neurotransmission, and they increase the formation of dendritic spines in a process mediated by brain-derived neurotrophic factor (BDNF).

In the fetal primate brain, substantial AR binding is observed in the cerebral cortex, cerebellum, mediobasal hypothalamus, amygdala, corpus callosum, and cingulate cortex of both sexes. Detectable levels of enzymes that convert testosterone to its active metabolites are also found in these regions (*63*). ER-α is found in the hypothalamus and amygdala, with lower concentrations also in the cerebral cortex (*64*). ARs are present as early as the first trimester, with high expression in temporal cortex and other regions (*65*). AR binding in the developing cerebral cortex is higher in the right frontal lobe and the left temporal lobe in males, an asymmetry that is not present in females (*66*). Rats show a sexually dimorphic asymmetry in cortical thickness, dependent on testosterone and possibly related to receptor distribution. Although the literature on anatomical and functional asymmetries in humans is contentious, a number of researchers have suggested that the male brain is more strongly lateralized than the female brain (*67*). Although information on AR distribution in the human fetal brain is limited, AR distribution may be conserved across species. The single study of ER distribution in the human midgestational fetus shows ER-ß but no ER-α expression in cortex (*68*).

In humans, exposure to atypically high levels of prenatal androgens results in masculine behavior and ability patterns (*69*). For example, females with congenital adrenal hyperplasia (CAH), a genetic condition that elevates fetal testosterone (FT), show tomboy behavior (*70*). Normal interindividual variation in prenatal hormone levels, measured in amniotic fluid, correlates with later sex-typed behavior (*71*–*74*).

All the sexually dimorphic brain regions discussed previously are rich in ARs, and their development therefore may be rather directly affected by testosterone (*28*), either early in fetal life or later. This raises the following question: If autism is an extreme of the male brain, is this the result of elevated FT, abnormalities in ARs or the genes controlling FT, or sexually dimorphic gene expression unrelated to FT? Currently, there are six clues that FT may play a role in autism: (i) FT is associated with low ratios of second-to-fourth digit length (*75*), and a low digit-length ratio is in turn associated with autism-spectrum conditions (*76*). (ii) Girls with CAH manifest more autism-like traits than their unaffected sisters (*77*). (iii) Within normal development, FT is inversely correlated with behaviors

that, in the extreme, would count as diagnostic symptoms for autism. These are eye contact, vocabulary development, social functioning, and narrow interests (*72*–*74*). (iv) There is preliminary evidence of somatic hypermasculinization in autism, although a comprehensive study of this is needed (*78*). (v) There is precocious puberty in boys with autism. (vi) Serotonin levels (*50*) and BDNF levels are elevated in autism (*67*), and these are mediated by FT. A direct test of the FT hypothesis using amniocentesis is under way in our laboratory.

Further Work

Investigation of the EMB theory of autism demands more detailed normative data, especially in the areas of histology and physiology. Does network architecture differ between the sexes, and if so, in what ways? What can diffusion tensor imaging reveal about sex differences in white-matter topography? What will the application of new methods of functional connectivity analysis reveal about normal sex differences in functional imaging and quantitative electroencephalography (EEG) and MEG? Do males with more "female" E-S profiles have more "female" brain anatomies, and vice versa? And how do these differences in brain structure and dynamics change during development?

In parallel, the correlation between autism and exaggerated male brain characteristics can be explored by detailed anatomic study of regions that are known to be sexually dimorphic in the normal brain but that have not yet been investigated in the autistic brain, such as the interstitial nuclei of the anterior hypothalamus (*79*). In addition, it will be important to distinguish brain dimorphisms mediated by testosterone from those that arise more directly from genetic factors or those that depend on experience. Evidence for direct genetic effects on brain sexual dimorphism does exist. For example, mice in which chromosomal sex and gonadal sex do not correspond differ behaviorally in maze learning and neurochemically in vasopressin innervation of the lateral septum (*14*). Because 15% of X-chromosome genes escape X inactivation in humans (*80*), X-chromosome gene-dosage effects may play a role in such direct genetic effects. Neuroanatomical observations in populations with anomalous sex-chromosome variations may prove informative. In addition, it has been suggested that an imprinted X locus may explain sex differences in social and communicative skills and the male vulnerability to social and communicative impairments (*81*).

How the EMB theory applies to females with autism is also of interest. If a male brain is a risk factor for autism, this may explain the lower prevalence in females. If the EMB theory does apply to autism, might it apply more broadly to a range of neurodevelopmental conditions that affect males more than females? Lastly, even if the EMB theory can explain some core characteristics of autism, it will be important to establish which other comorbid characteristics require different explanations.

Conclusion

The EMB theory was first formulated by Hans Asperger as a clinical anecdote more than 60 years ago.

In the past decade, it has been reformulated to be psychologically testable. Using psychometric definitions of the typical male and female brain, we have observed that people with autism-spectrum conditions show an exaggeration of the male profile. Evidence reviewed above suggests this may also apply to aspects of autistic neuroanatomy. The challenge ahead will be to test this theory across the whole autistic spectrum.