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Review

Imaging Sex/Gender and Autism in the Brain: Etiological Implications

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The male preponderance in autism prevalence has brought together the disparate topics of sex/gender and autism research. Two directions of neuroimaging studies on the relationships between sex/gender and autism may inform male-specific risk mechanisms and female-specific protective mechanisms of autism. First, we review how sex/gender moderates autism-related brain changes and how this informs general models of autism etiology. Better-powered human neuroimaging studies suggest that the brain characteristics of autism are qualitatively, rather than simply quantitatively, different between males and females. However, age and comorbidities might substantially moderate the pattern of differences. Second, we review how the relationship between autism-related brain changes (separately in males and females) and normative brain sex/gender differences informs specific etiological–developmental mechanisms. Both human and animal studies converge to indicate that the brain characteristics of autism are partly associated with normative brain sex/gender differences, suggesting convergence or overlap between the mechanisms leading to and modifying the development of autism and the mechanisms underlying sex differentiation and/or gender socialization. Future animal work needs to investigate sex differences in rodent mutants modeling autism-relevant genes and environmental exposures. Future human work needs to address the substantial phenotypic and etiological heterogeneity of autism and to focus on longitudinal neuroimaging studies (from early development) on the developmental trajectories of sex/gender-differential neural characteristics of autism. Combining animal and human work links up the causal chain from etiological

SIGNIFICANCE

The male preponderance in autism prevalence has brought together research topics about sex/gender and autism. We review two directions of brain imaging studies on the relationships between sex/gender and autism, to inform male-specific risk mechanisms and female-specific protective mechanisms of autism. First, human neuroimaging studies suggest that the brain characteristics of autism are qualitatively, rather than simply quantitatively, different between males and females. Second, both human and animal studies converge to indicate that the brain characteristics of autism are partly associated with typical brain sex/gender differences, suggesting converging or overlapping underlying mechanisms. Sex and gender play critical roles in autism etiologies.

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factors, brain and physical development, to phenotypes. These together help delineate the different roles of sex and gender in relation to risk vs. protective mechanisms.

Key words: autism; sex; gender; brain; neuroimaging; animal model; etiology

INTRODUCTION

Autism spectrum disorder/condition (henceforth, "autism") is a behaviorally defined, early-onset neurodevelopmental syndrome marked by difficulties in social communication and social interaction (including difficulties with social-emotional reciprocity, nonverbal communication, and relationships) alongside difficulties in behavioral flexibility (including stereotyped/repetitive behaviors, insistence on sameness, unusually narrow interests, or atypical sensory reactivity) (APA, 2013; Lai et al., 2014). Autism has substantial genetic etiologies (Geschwind and State, 2015; Sanders et al., 2015; Lombardo et al., 2016b) and involves atypical brain development (Ecker et al., 2015; Sanders, 2015). However, discrete brain bases of autism have not been unequivocally identified across individuals (Anagnostou and Taylor, 2011; Haar et al., 2016). There is high heterogeneity across different levels of the biology of autism, involving over 800 genes (Sanders, 2015), and different forms of gene-environment factors likely interplay (Mandy and Lai, 2016). The identification of common brain developmental pathways is a focus of current neuroscientific research on autism.

Recent population studies of autism suggest a prevalence of around 0.76% to 2.6% (Kim et al., 2011; Mattila et al., 2011; Baxter et al., 2015; Idring et al., 2015; Brugha et al., 2016); for example, the latest surveillance of clinical diagnoses in the United States shows a rate of 1.46% (Christensen et al., 2016). Autism has long been reported as more common in males, with a sex/gender ratio of between 4:1 and 5:1 (mostly from clinic-based samples) (Fombonne et al., 2011; Christensen et al., 2016), yet many recent large-scale, population-based epidemiological studies that involve active case ascertainment show a male preponderance between 2:1 and 3:1 (Kim et al., 2011; Mattila et al., 2011; Idring et al., 2012; Jensen et al., 2014; Baxter et al., 2015). This slightly lowered sex/gender ratio may reflect better recognition of females in recent years (Jensen et al., 2014). Our understanding of autism has historically been male biased because of disproportionately small numbers of females being recruited into research studies. For example, the male:female ratio was traditionally around 8:1 in brain volumetric studies (Via et al., 2011) and 15:1 in task functional magnetic resonance imaging (fMRI) studies (Philip et al., 2012). Fortunately, in recent years, owing to more females being identified and participating in research studies, and because of research efforts merging multisite data, females are increasingly better represented in autism research (Watkins et al., 2014). This provides improved statistical power to address different empirical and theoretical questions about the relationships between sex/gender and autism (Lai et al., 2015).

In this article we use the term "sex/gender," acknowledging that "sex" refers to biology and "gender" refers to sociocultural aspects (as based on the World Health Organization definition, http://apps.who.int/gender/whatisgender/en/), whilst also acknowledging that in many scenarios the effects of the two cannot be unequivocally separated (Rippon et al., 2014). Delineating direct effects of sex from effects of biological and environmental variables correlated with sex, and from effects of components of gender, is difficult in humans. It can only be clarified by comprehensive research designs measuring (or manipulating) sex variables across levels, and gender variables across domains, and testing for their main effects, interaction effects, and mediation effects (Joel and McCarthy, 2016). As most research reviewed here (and neuropsychiatric research in general) does not test for the separate effects of sex vs. gender, findings should be treated as reflective of the effects of either or both—hence, the use of the term "sex/gender" (Springer et al., 2012).

The male preponderance in early-onset neurodevelopmental conditions and female preponderance in adolescent-onset emotional disorders may have etiological implications (Rutter et al., 2003; Zahn-Waxler et al., 2008). The male bias in autism prevalence has led to a link between the research on sex/gender and on autism. For example, it has been hypothesized that the male preponderance reflects male-specific vulnerability and female-specific protection (Wing, 1981; Tsai and Beisler, 1983), implicating specific etiological factors associated with sex and gender (Baron-Cohen et al., 2011; Werling and Geschwind, 2013; Schaafsma and Pfaff, 2014). Other research has compared behavioral or neurobiological characteristics between males and females with autism and speculated about etiological implications accordingly (with or without considering possible underlying on-average sex or gender differences that are present in human beings) (Bloss and Courchesne, 2007; Van Wijngaarden-Cremers et al., 2014; Supekar and Menon, 2015). The complex relationships between sex/gender and autism can be delineated into four different levels of inquiry to facilitate the interpretation of findings: Level 1, nosological and diagnostic challenges; Level 2, sex/gender-independent and sex/gender-dependent characteristics; Level 3, general models of etiology: liability and threshold; and Level 4, specific etiological–developmental mechanisms (Lai et al., 2015).

The current review aims to update evidence in relation to Level 2, in neuroimaging studies, and their relevance for etiological investigations at Levels 3 and 4. Previous Level 2 investigations have shown a variety of possible behavioral and cognitive sex/gender differences in autism (e.g., less intensity or a different quality of repetitive and stereotyped behavior in females, higher social motivation and camouflaging in females, or sex/gender differences in the profiles of executive,

visuospatial, or sensory processing [Kirkovski et al., 2013; Lai et al., 2015; Hull et al., 2016]). Eventually it will be important to link findings of behavioral phenotypic sex/gender differences with brain sex/gender differences in autism, yet studies thoroughly addressing this are still rare. Further investigations to clarify mechanistic relationships between behavior and brain are required to inform etiologies of autism in relation to sex/gender.

We also discuss the contribution of animal neuroimaging studies of sex differences and autism. The arrival of high-field magnets, specialized transmit/receive coils, powerful gradients, and tailored data processing algorithms has brought the wealth of human neuroimaging techniques to rodent models. The possibility of using brain imaging as an intermediate translation tool between human clinical studies and rodent molecular neuroscience is exciting. Much of our understanding of how biological sex shapes brain development comes from rodent studies. Early studies, for example, showed that prenatal injection of testosterone into female rodents was sufficient to masculinize brain networks and resulted in male-like sexual behaviors in adulthood (Phoenix, 2009). Advances in our abilities to manipulate the genome have brought mouse studies to the fore, providing insight into molecular mechanisms behind brain sex differences. These advances have been elegantly reviewed (McCarthy, 2010). As our understanding of the genetics of autism increases, so does the importance of animal models to understand the function and interactions of putative causative genes. Novel gene-editing techniques (Ran et al., 2013) pave the way for the rapid translation of clinical genetics findings to model systems. Whilst this body of research only covers a subset of autism, since so far only 15% to 30% of people with autism have an identified genetic mutation, it provides important clues about possible molecular mechanisms underlying distinct subtypes of autism (de la Torre-Ubieta et al., 2016).

CAN NEUROIMAGING STUDIES OF SEX/GENDER AND AUTISM INFORM THE ETIOLOGICAL MECHANISMS OF AUTISM? UNCOVERING RISK AND PROTECTIVE PROCESSES

Investigating how sex/gender manifests in the brain, how autism manifests in the brain, and how they moderate each other provides hypothesis testing for certain (but not all) etiological theories of autism. This assumes that brain changes substantially derive from the operation of etiological (risk and protective) mechanisms. There are two separate directions of investigation.

Note that from a statistical point of view, "risk" and "protective" are two sides of a coin (since the absence of a risk factor is protective, and lack of a protective factor increases risk) that is simply one variable that shifts an individual's underlying liability to autism. However, from a mechanistic point of view, "protective mechanisms" refer to processes that operate in the presence of "risk mechanisms," and they can be different mechanisms operating on the same pathophysiological pathways. We therefore use the two terms separately, to refer to actual mechanisms that play different roles in the emergence of autism.

Direction 1: Investigating How Sex/Gender Moderates Autism-Related Brain Changes, and How This Informs Hypothesis Testing of General Models of Autism Etiology

Most general etiological models of autism now include an explanation of why females are more protected from developing autism, and of the male bias in prevalence (Lai et al., 2015). This phenomenon has been referred to as the "female-protective effect." It might be helpful to distinguish "female-protective mechanisms" and "female-protective effects (female protection)," the latter simply restating the male preponderance in prevalence and the former focusing on candidate etiological factors.

In population genetics, the examination of the Carter effect (Carter, 1961) has often been taken as a test of whether there is a female-protective mechanism at play that reduces the risk of developing autism (but note that an absence of the Carter effect does not indicate an absence of female-protective mechanisms [Constantino, 2016]). That is, if a higher quantitative burden of genetic susceptibility is required to cross the threshold to be affected in females than in males, there should be a higher level of familial aggregation of autism or autistic-like traits amongst the relatives of females with autism (assuming there is a positive association between the genetic burden and behavioral characteristics). This has been confirmed in studies measuring autistic-like traits (Robinson et al., 2013) and when examining sibling recurrence rates of clinical autism diagnoses in multiplex families (Szatmari et al., 2012; Frazier et al., 2015; Werling and Geschwind, 2015). However, it is not confirmed in studies of clinical diagnoses of autism in population-based or high-risk "infant-sibling" samples (Constantino et al., 2010; Ozonoff et al., 2011; Grønborg et al., 2013; Sandin et al., 2014).

A critical issue here is that female-protective mechanisms that take effect in the presence of autism risks are most easily revealed by studying females who do *not* have autism—for example, by studying females who have an increased risk of developing autism but who do not go on to develop the full autism phenotype (e.g., using an infant-sibling design [Chawarska et al., 2016]). They can then be contrasted with those who do develop the full autism phenotype (i.e., who potentially have experienced less protection). Family-based genetic studies (Geschwind and State, 2015) or high-risk infant sibling designs (Jones et al., 2014; Szatmari et al., 2016) are first steps toward uncovering the exact protective mechanisms. With advances in genetics potentially allowing for meaningful quantification of etiological risks, one further way to reveal how protective mechanisms work is to compare individuals who have quantifiable, comparable levels of risks but who are categorically discordant in diagnostic

status, or, in a dimensional view, who show widely varied levels of autistic characteristics. Phenotypically, protective mechanisms may lead to an absence or a lower level of symptoms such that females do not reach a threshold for diagnosis, and that such milder levels might be more apparent in studies of the "broader autism phenotype" (Sucksmith et al., 2011; Piven et al., 2013).

If any candidate protective mechanisms are revealed in individuals who carry risks but do not develop autism, such mechanisms will then have to be ubiquitously present in the general population so that they can be confirmed (i.e., so they account for the sex/gender bias in prevalence).

In contrast, studies focusing on females with diagnosed autism (Turner et al., 2015) or on how males and females with autism differ from each other (Polyak et al., 2015) provide a direct examination of the risk mechanisms of autism and how sex/gender moderates the risk mechanisms. We therefore review neuroimaging studies on how sex/gender moderates autism-related brain changes (i.e., studies of sex/gender-independent and sex/gender-dependent brain characteristics of autism), and explain how different experimental designs are needed to study risk vs. protective mechanisms.

Human neuroimaging studies informing risk mechanisms. Providing that etiological risks affect neurobiology and brain development, and subsequently influence cognition and behaviors that define autism, neuroimaging techniques that can reveal the structural and functional characteristics of the brain can be used to test at the brain level whether there is evidence supporting or disproving the general etiological model of female protection. Specifically, comparing autism-related brain changes between males and females gives clues of whether there are *quantitative* and/or *qualitative* differences between sexes/genders. This, in combination with additional levels of etiological investigations, may inform sex/gender-differential mechanisms and "brain routes" to autism.

If risk mechanisms leading to autism in males and females are mostly *quantitatively different*, one would expect the autism-related brain changes in females with autism to be more substantial than those in males with autism. This might be in terms of the size of the diagnostic effect in similar brain regions, or females might show additional brain changes beyond those seen in males (Lai et al., 2015). These quantitative differences may echo the findings that females require a greater dose of the risk factors (e.g., genetic mutations) to exhibit the autism phenotype (Sanders et al., 2011, 2015; De Rubeis et al., 2014; Iossifov et al., 2014; Jacquemont et al., 2014). Some small-sample studies in toddlers (with females with autism $n < 10$) indeed found that in terms of cerebral cortical lobar gray matter volume, girls with autism have more changes (i.e., larger effect size) than males with autism compared with same-sex/gender controls, respectively (Bloss and Courchesne, 2007; Schumann et al., 2010), yet for cerebellum volume the direction of change is opposite between boys and girls with autism (Bloss and Courchesne, 2007). An even smaller study (with $n = 7$ females with autism) did not find female toddlers with autism show more substantial autism-related brain changes than boys with autism (Sparks et al., 2002). However, a recent larger-scale source-based morphometry study analyzed a subsample (aged 6–20 years, matched on age but not IQ across groups) from the multicenter Autism Brain Imaging Data Exchange (ABIDE, http://fcon_1000.projects.nitrc.org/indi/abide/) initiative (with $n = 36$ females with autism) and found one gray matter volume source at bilateral inferior and middle temporal lobes showing significant effects of diagnosis and sex/gender. In particular, the overall effect sizes between individuals with autism and control subjects were slightly larger in females than in males, but such effect was mainly found between 12 and 14 years (Di and Biswal, 2016b). This finding supports quantitative differences, but only in a confined age range.

If brain-level evidence supporting the *quantitative sex/gender difference* hypothesis can be found in more large-scale studies, we should further examine whether the more substantial autism-related brain changes in females are related to why these females "cross the border" to show the clinical phenotype. Importantly, we need to test whether the association between etiological risks (e.g., pathogenic genetic mutations) and autism-related brain changes differs by sex/gender. The quantitative hypothesis predicts no sex/gender differences in the association pattern but only in the effect size of changes at both the brain and the etiological risk levels, whereas the qualitative hypothesis predicts different association patterns by sex/gender.

If risk mechanisms leading to autism in males and females are instead mostly *qualitatively different*, one would expect that males and females with autism differ in the kind of autism-related atypical patterns of brain activity or structure they show (Lai et al., 2015). This has been increasingly shown in larger-scale neuroimaging studies (with $n = 13$–53 females with autism) of brain anatomy (Nordahl et al., 2011, 2015; Beacher et al., 2012a; Lai et al., 2013b,; Schaer et al., 2015; Retico et al., 2016) and functional activation patterns (Beacher et al., 2012b; Schneider et al., 2013; Alaerts et al., 2016; Di and Biswal, 2016a; Kirkovski et al., 2016). Findings indicative of substantial sex/gender differences in autism are also found in other levels including cognition (Bolte et al., 2011; Lemon et al., 2011; Lai et al., 2012; Goddard et al., 2014; Kauschke et al., 2016; Lehnhardt et al., 2016), early physical growth trajectory (Suren et al., 2013; Campbell et al., 2014), anthropometry (Bejerot et al., 2012), childhood genome-wide gene expression (in transformed lymphoblastoid cell lines) (Tylee et al., 2016), and adulthood serum protein profiles (Schwarz et al., 2011; Kong et al., 2012; Ramsey et al., 2012; Steeb et al., 2014). All these imply that the biology of autism may be substantially different in males and females across developmental stages.

Nordahl and colleagues (2011) found that in preschoolers with autism, early overall brain volume overgrowth appears more evident in some boys (i.e., those who have developmental regression), but not in girls. They also differ in the size and structure of the corpus callosum, relative to same-sex/gender chronological age-

matched controls (Nordahl et al., 2015). Both boys and girls with autism have smaller callosal regions projecting to the superior frontal cortex. However, boys with autism have a smaller section linked to the orbitofrontal cortex, whilst girls with autism have a smaller section linked to the anterior frontal cortex. In addition, there are no alterations in callosal fiber microstructural properties in boys with autism relative to typically developing boys, whereas all diffusivity measures are increased in girls with autism relative to typically developing girls. Both male and female preschoolers with autism in this study were, however, developmentally delayed compared with controls. Therefore, it is difficult to rule out whether developmental level has a role in moderating the sex/gender-differential neuroanatomy.

In a separate cohort, Retico and colleagues (2016) measured regional gray matter volume and used a support vector machine-based analysis to generate prediction models to classify young children (2–7 years) with autism (with $n = 38$ females with autism) vs. chronological age- and developmental level (nonverbal IQ)-matched controls. In this well-matched sample, they found that the gray matter voxels most discriminative of autism vs. control differ substantially by sex/gender. Although both "discrimination maps" for boys and girls involve bilateral ventral precuneus and posterior cingulate cortex, the majority of discriminative voxels are distinct by sex/gender. Owing to the balanced match across groups, the sex/gender-differential neuroanatomy discovered here is quite unlikely to be confounded by factors associated with chronological age or developmental (IQ) level.

In adults, Beacher and colleagues (2012a) in a small-scale study (with $n = 13$ females with autism; autism groups showed lower estimated intelligence than control groups) found a range of sex/gender-dependent autism-related brain changes, evidenced by significant diagnosis-by-sex/gender interactions (in a two-factorial design) in total white matter volume, regional gray matter volume in the right parietal operculum, and fractional anisotropy in the body of the corpus callosum, cingulum, and corona radiata. Lai and colleagues (2013b) also used a two-factorial design in an independent, larger sample (with $n = 30$ females with autism; autism groups and control groups were matched on age and full-scale IQ) and found significant diagnosis-by-sex/gender interactions in terms of regional brain volumes. Most importantly, using spatial overlap analysis, they demonstrated that autism-related brain volumetric changes in women are distinct from those in men, across both gray and white matter. Finally, Schaer and colleagues (2015) analyzed a well-matched subsample from the ABIDE dataset with the largest sample of females with autism to date ($n = 53$), across a wide age range (8–39 years), with all groups matched on age and verbal and performance IQ. In a two-factorial design they found no main effects of diagnosis on cortical volume, thickness, or local gyrification. However, they found a significant diagnosis-by-sex/gender interaction in the ventromedial prefrontal and orbitofrontal cortices: males with autism showed decreased gyrification compared with typically developing males, whereas females with autism showed no such decrease (but instead a trend of increase) compared with typically developing females. It is worth noting that source-based morphometry on another sample from ABIDE with a different age range (6–20 years, matched on age but not IQ across groups) failed to find significant diagnosis-by-sex/gender interactions across all 20 gray matter and 20 white matter independent volume sources in the whole sample; a trend of interaction was, however, noted in a subgroup 12 to 14 years of age at the volume source showing significant main effects of both diagnosis and sex/gender in the whole sample (Di and Biswal, 2016b). Overall, these findings (which mainly or partly involve adolescent and adult samples) do not seem substantially confounded by intellectual level. However, they mainly come from studying individuals without concurrent intellectual disability. It is therefore unknown how intellectual functioning may further moderate teenage and adulthood sex/gender-differential neuroanatomy in autism when it comes to the subgroups with concurrent intellectual or severe communication disabilities.

In brief, most (but not all) larger-scale studies examining neuroanatomy in autism stratified by sex/gender converge to show overall sex/gender-differential brain structural characteristics. Nevertheless, studies so far frequently include participants spanning a wide age range, but do not have sufficient power to formally test for the moderating roles of age on sex/gender-differential neuroanatomy in autism. It has been shown that age substantially moderates autism-related brain anatomy particularly during the teenage years in males (Zielinski et al., 2014; Lin et al., 2015), but little is known for females. Descriptively, there seems to be substantial influence from age on how sex/gender moderates autism-related brain characteristics (Di and Biswal, 2016b), but a formal examination of age-moderating effects using well-powered large-scale datasets is still pending.

Using the ABIDE dataset but investigating the functional organization of the brain, Alaerts and colleagues (2016) analyzed an age-matched sample (with $n = 42$ females with autism, aged 7–30 years; on average, the autism groups scored 9–10 points less than the control groups on full-scale IQ) using seed-based (from posterior superior temporal sulcus and posterior cingulate cortex) and whole-brain functional connectivity analyses. They found that males with autism generally show hypoconnectivity, whereas females with autism generally show hyperconnectivity, relative to same-sex/gender controls. The authors did not find any region for which autism-related connectivity changes were in the same direction in males and females, corroborated by the presence of significant diagnosis-by-sex/gender interactions. These suggest a strong sex/gender-differential neural expression of autism in intrinsic functional organization of the resting-state brain network (Alaerts et al., 2016). A preliminary study also using the ABIDE dataset (with $n = 28$ females with autism, aged 6–20 years; the autism groups scored slightly lower than the control groups on full-scale IQ)

further identified diagnosis-by-sex/gender interactions on the connectivity between precuneus and medial cerebellum/dorsal frontal cortex (Di and Biswal, 2016a). Therefore, sex/gender-differential neural characteristics of autism also seem to present in the intrinsic functional organization of the brain, and it is too early to conclude how age or IQ moderates these findings.

Finally, in the task-evoked functional neuroimaging literature, three fMRI studies in adults using similar factorial designs to test for the moderating role of sex/gender in the neurobiology of autism all found substantial diagnosis-by-sex/gender interactions in regional activation patterns. Significant sex/gender-moderating roles on autism-related effects were evident during an emotion recognition and empathy task, showing decreased activation in women with autism relative to control women, but no differences between men with autism and control men, in the midbrain and left amygdala; however, age was not matched across all groups (Schneider et al., 2013). Similarly, during a mental rotation task, decreased activation in women with autism was seen in the temporo-parieto-occipital region relative to control women, and increased activation in the same region was seen in men with autism relative to control men; age was matched across groups, but on average the autism groups scored lower on estimated intelligence (Beacher et al., 2012b). Finally, during an automatic mental state attribution task, no difference between women with autism and control women was seen, but decreased activation in the right posterior superior temporal sulcus was found in men with autism relative to control men; age was, however, not matched across males and females, though it was matched across diagnostic groups (Kirkovski et al., 2016). How these moderating roles of sex/gender might be further influenced by age or intellectual level cannot be determined based on the studies so far.

In sum, when better-powered datasets are used, although it is not always clear if the main effects of diagnosis are present across males and females, across sample ages (from toddlers to adults), and across imaging modalities, there are almost always clear diagnosis-by-sex/gender interactions. However, studies do not consistently show the same pattern of interaction, or in the same brain regions. Despite high sample heterogeneity that likely gives rise to the lack of exact replication of regional findings (except that orbitofrontal cortex has been implicated by two studies [Nordahl et al., 2015; Schaer et al., 2015]), the consistent message from human neuroimaging studies so far is that the neural characteristics of autism are substantially qualitatively different between males and females. As these neuroimaging findings are derived not just from studies of older individuals but also toddlers, they could reflect sex-differential etiological mechanisms of autism that begin very early in life, even before the appearance of the autism phenotype. However, these neural findings could equally reflect sex/gender-differential consequences of living with autism, as most studies are conducted with adults. Prospective neuroimaging studies focusing on very young children before the onset of the full syndrome of autism are complementary to the existing literature and key to clarify the issues of nature vs. nurture.

Human neuroimaging studies informing protective mechanisms. Neuroimaging studies could also offer clues about the neural characteristics that reflect (female) protective mechanisms against autism. For example, it has been proposed that comparing brain activation patterns during biological motion processing between individuals with autism, their unaffected siblings (US), and controls (TD) reveals "compensatory activity" (i.e., the intersection of US–TD and US–autism differences, $US > TD \wedge US > autism$) (Kaiser et al., 2010). This pattern could otherwise indicate how protective mechanisms manifest in the brain. Taking this approach to investigate neural characteristics of females who carry risks of autism but who do not develop an autism phenotype (e.g., in an infant-sibling design [Szatmari et al., 2016]), and comparing with the pattern in males, may inform how female-protective mechanisms operate in the brain.

Animal neuroimaging studies. Human neuroimaging data show that autism-related brain changes likely differ between males and females. However, this needs to be interpreted in the context that neuroimaging studies in autism are plagued by heterogeneity, with few findings being reproducible (Anagnostou and Taylor, 2011). The reason for this has been ascribed to a mix of the autism phenotype in neuroanatomy being both subtle and prone to artifacts (in particular, in-scanner head motion) (Haar et al., 2016). An alternative hypothesis for the lack of consistency in anatomical studies of autism relates to etiological heterogeneity, with multiple genes implicated, each accounting for only a small proportion of the etiological variance, though they may converge on common pathways (Geschwind and State, 2015; Sanders, 2015). The combination of mouse models of genes (or environmental factors) implicated in autism with high-field mouse magnetic resonance imaging (MRI) has allowed that question to be answered directly.

A series of individual studies (Ellegood et al., 2010, 2012, 2013, 2014; Horev et al., 2011; Dodero et al., 2013; Portmann et al., 2014; Steadman et al., 2014; Pagani et al., 2016) as well as an omnibus investigation of 26 mouse models (Ellegood and Crawley, 2015; Ellegood et al., 2015) has lent credence to the role of heterogeneity from genetics to imaging outcomes. Many individual mutations are associated with striking patterns of neuroanatomical alterations, yet consistency across mutations is limited. There is evidence for subgroupings of autistic models based on their imaging outcomes (Ellegood et al., 2015), an effort that will have to be extended to more models and reconciled with human neuroimaging data.

The vast majority of these studies, as is common in basic research (Beery and Zucker, 2011), were conducted in male mice only. The male preponderance of autism makes the choice of males obvious if experiments are carried out in a single sex only, though it is clearly a missed opportunity that the research community must remedy going forward. Yet the existing mouse data do suggest

that one possible interpretation of the diagnosis-by-sex/gender interactions in the human neuroimaging data is that, whilst sample sizes are still relatively small, the mix of etiologies included among males and females in each sample might have differed enough to drive the apparent interaction.

Direction 2: Clarifying the Relationship Between Autism-Related Brain Changes (Separately in Males and Females) and Normative Sex/Gender Differences in the Brain May Inform Specific Etiological–Developmental Mechanisms

Female-specific protective mechanisms and male-specific risk mechanisms may both account for the male preponderance of and female protection against autism (Werling and Geschwind, 2013). Moving from general models of etiology (Level 3) to identify specific etiological–developmental mechanisms (Level 4) (Lai et al., 2015), one approach is to examine factors associated with normative/typical sex and gender differentiation to see if they also act as risk or protective mechanisms to the sex/gender-differential liability of autism. In other words, this involves clarifying the relationship between normative sex/gender differences and characteristics of autism. It is worth noting that these are not necessarily sex/gender-independent etiologies for autism.

Genetic and molecular bases. At the biological level, sex differentiation originates from the interplay of genetic variations, prenatal environments, and epigenetic effects (McCarthy, 2016), which are all candidate mechanisms for sex/gender-differential liability of autism (Baron-Cohen et al., 2011; Schaafsma and Pfaff, 2014; Lai et al., 2015). Brain gene expression studies show that sex-differentially expressed genes do not overlap with autism candidate genes (Ziats and Rennert, 2013), and there is no systematic sex-differential expression of autism risk genes (Werling et al., 2016). However, genes expressed at higher levels in males are significantly enriched for genes upregulated in expression in autistic brains (that highlight downstream or interacting pathways including astrocyte and microglia markers, but not autism risk genes themselves) (Werling et al., 2016). In addition, gene ontology enrichment analysis also indicates that male-biased transcriptional modules/pathways are also implicated by autism candidate genes (Ziats and Rennert, 2013). These findings imply that typical males sit closer to the liability threshold for developing autism based on naturally male-heightened gene expression patterns in the brain (e.g., those involving astrocyte and microglial functions), and typical females sit farther from the threshold owing to heightened expression of potentially "protective" genes (e.g., those involving neuronal and synaptic functions).

In terms of sex-related prenatal environment, males on average have higher levels of prenatal testosterone than females (Kuijper et al., 2013). Levels of prenatal testosterone start rising around week 8, and the surge finishes around week 24 (Hines, 2005). This prenatal surge is necessary for sexual differentiation of the male gonads. A Danish population-based epidemiological study of male children indicated that enhanced prenatal steroidogenic activity (across the delta-4 sex steroids from progesterone through to testosterone, as well as cortisol) is associated with a later diagnosis of autism (Baron-Cohen et al., 2015). A Swedish population-based epidemiological study showed that maternal polycystic ovary syndrome (PCOS, which is associated with a hyperandrogenic maternal environment) increases the odds of autism diagnosis in both male and female offspring, especially when presented with obesity (which indicates even more severe hyperandrogenemia) (Kosidou et al., 2016). These findings suggest the possibility that sex steroid–associated (downstream or upstream) mechanisms could be associated with risk mechanisms of and protective mechanisms against autism. How this operates to affect gene expression and neurodevelopment remains to be investigated. In animal models, sex differentiation of the brain involves immune mediators and microglia (Lenz and McCarthy, 2015; McCarthy et al., 2015), and prenatal steroid influences microglial activation during early brain development (Lenz et al., 2013). Neuroimaging in animal models is a promising way to disentangle specific brain changes reflective of the interactions amongst genetic predispositions (reflecting typical sex differentiation as well as autism risks), prenatal hormonal environment, and neuroimmune or other mediating processes.

Animal neuroimaging studies. There are large-effect macroscopic and mesoscopic sex differences in rodent neuroanatomy, exemplified by the increased size in males in the bed nucleus of the stria terminalis (BNST), the medial amygdala (MeA), and the medial preoptic area (MPOA). Structural MRI of the mouse brain clearly reveals these differences, and also points to lesser-known alterations in brain structure, including certain larger cerebral and cerebellar cortices in females (Spring et al., 2007; Corre et al., 2016). The estimated percent differences between males and females in these areas are consistently smaller with MRI than with histological techniques.

To what extent do typically sexually dimorphic brain regions and regions with large-effect on-average sex differences appear when examining the brain outcomes in mice modeling autism-related genetic mutations? The hypothalamus (which contains the MPOA) is one of the most affected brain regions, as shown in a study of 26 mouse lines related to autism (Ellegood et al., 2015), followed closely by the BNST. In that study, patterns of covariation of effect were also examined. This divided the brain into three such patterns, including one encompassing the BNST, hypothalamus, and amygdala—all sexually highly different regions. There is thus preliminary evidence that one brain module affected by autism-related genes overlaps with the main sexually dimorphic network (Ellegood et al., 2015).

The Four Core Genotype (FCG) model enables the separation of sex differences into those originating from sex steroids and those due to sex chromosomes. In this model, the testes-determining gene (*Sry*) is removed from

the Y chromosome and optionally reinserted onto an autosome, thus separating gonadal sex (where presence of *Sry* leads to male gonads) from XX and XY sex chromosome complements (De Vries et al., 2002). The FCG mouse model has been used, for example, to determine that juvenile social behavior is influenced by sex chromosomes (Cox and Rissman, 2011), as is white matter myelination (Moore et al., 2013). The use of the FCG model is discussed elsewhere (Arnold, 2009). Corre and colleagues (2016) used the FCG model to provide insights into the origins of neuroanatomical sex differences. The neuroimaging data replicated decades of research into the organizational effects of testosterone in determining sex differences in the BNST, MeA, and MPOA. In other words, the core module implicating brain differences in autism from the animal model clustering approach (Ellegood et al., 2015) may be influenced by the organizational effects of sex steroids. Multiple other areas of the brain, including the corpus callosum, sensorimotor cortex, and cerebellar cortex, show clear sex chromosome origins. Given the debate about possible overrepresentation of X chromosome genes in autism (Baron-Cohen et al., 2011; Pinto et al., 2014), any potential convergence of these brain areas with autism imaging findings should be followed up.

Sex chromosome aneuploidies (SCAs) provide further insight into the role of the sex chromosomes in brain development and, potentially, autism. Each of the common SCAs has a greater-than-expected autism comorbidity (Bruining et al., 2009; Baron-Cohen et al., 2011). In a recent series of studies on XO, XX, XY, and XXY mice, Raznahan and colleagues discovered a stepwise pattern of effect in the size of the BNST, MPOA, and MeA, with $XO < XX < XY < XXY$ (Raznahan et al., 2013, 2015). Other brain regions, in particular in cerebellum, pons, and cortex, showed the inverse. These mice, as in humans with these chromosomal anomalies, do not have completely normal gonadal function, so it is difficult to separate chromosomal dosage from gonadal steroid effects. Nevertheless, SCAs provide insights into how sex influences brain structure and function.

Lastly, there has been an upsurge of interest in the role of the immune system in creating sex differences in the brain (Papenfuss and Whitacre, 2009; Schwarz and Bilbo, 2012; Lenz and McCarthy, 2015; McCarthy et al., 2015) and playing a role in autism (Ashwood et al., 2011; Eloi Akintude et al., 2013). A surprising and fascinating result from a combined mouse brain imaging and behavior study showed that the loss of functional T-cells (through the removal of the beta and gamma chains on the T-cell receptor) significantly altered sexual dimorphisms in brain structure and behavior (Rilett et al., 2015). Given the role of immune cells (and not just microglia) in determining sex-dependent behavioral outcomes (Sorge et al., 2015), this clearly is a scientific direction that warrants following closely in the future.

Normative sex/gender differences revealed by human neuroimaging studies. Neuroimaging studies investigating human brain development have found differences in developmental trajectories between males and females. Although brain size at birth does not differ, brain growth rates between birth and postnatal day 90 indicate nonlinear and region-specific expansions of the infant brain, with male brains growing faster than female brains (Holland et al., 2014). Later in development, males show consistently larger brain volumes than females (Ruigrok et al., 2014); however, these differences may be due to sex differences in body size (Peters, 1991; Peters et al., 1998). In humans, some but not all of these later sex differences in regional brain size are predicted in the same direction by variation in fetal testosterone exposure during midgestational fetal development, suggesting that there are early (fetal) organizational effects of testosterone on brain regions that later exhibit sex differences (Lombardo et al., 2012). It is also worth noting that pubertal hormonal processes may have additional activational and organizational impacts altering brain developmental trajectories (Sisk and Zehr, 2005; Schulz et al., 2009; Berenbaum and Beltz, 2011). The onset of puberty starts earlier in females than in males on average (Marshall and Tanner, 1969, 1970; Dorn et al., 2006; Susman et al., 2010). Peak gray matter volumes are on average measured earlier in females than in males (Giedd et al., 1999; Raznahan et al., 2014; Wierenga et al., 2014a). These differences in volume may be due to increases in cortical surface area rather than cortical thickness (Wierenga et al., 2014b). Pubertal stage also influences the developmental trajectory of subcortical structures differently in males and females (Goddings et al., 2014). In addition, sex/gender differences are found in white matter tract development during the pubertal period (Herting et al., 2012; Simmonds et al., 2014).

On-average typical sex/gender differences have also been reported in functional activation for tasks involving empathy (Schulte-Ruther et al., 2008), emotion (Sacher et al., 2013), language (Gauthier et al., 2009; Bitan et al., 2010), and visuospatial processing (Weiss et al., 2003; Hugdahl et al., 2006). More recently, studies have revealed sex/gender differences in intrinsic properties of the brain such as regional homogeneity (Dai et al., 2012), voxel-mirrored homotopic connectivity (Zuo et al., 2010), and local functional connectivity density (Tomasi and Volkow, 2012), amongst other characteristics of the intrinsic functional organization of the brain (Biswal et al., 2010; Tian et al., 2011; Wang et al., 2012; Satterthwaite et al., 2015).

Human neuroimaging studies informing risk mechanisms. As reviewed above, there exist on-average sex/gender differences (McCarthy, 2016) but not necessarily sexual dimorphism (McCarthy et al., 2012) in the human brain, for example, in terms of structural features (Giedd et al., 2012; Ingalhalikar et al., 2014; Ruigrok et al., 2014; Joel et al., 2015; Chekroud et al., 2016) and gene expression across development (Shi et al., 2016). Normative sex/gender differences found in the brain are likely partly transient and partly persistent, partly context dependent and partly context independent; and importantly, there is high regional specificity in terms of

mechanisms leading to "masculinization" vs. "feminization" (Joel and McCarthy, 2016). Assuming that human brain sex/gender differences are the product of both biological sex differentiation and gender socialization, and autism-related brain changes similarly are the product of autism risk mechanisms (that act against and overcome protective mechanisms), any above-chance commonality between human brain sex/gender differences and autism-related brain changes may reflect the fact that mechanisms contributing to normative sex/gender differences overlap partly with the etiologies of autism.

In search of risk mechanisms, there are two theoretical predictions linking on-average normative sex/gender differences to autism—namely, the "extreme-male-brain" (EMB) (Baron-Cohen, 2002) vs. the "gender-incoherence" (GI) (Bejerot et al., 2012) hypotheses. The EMB hypothesis stems from the findings that in specific cognitive and behavioral domains typically showing on-average male–female performance differences—namely, empathy and systemizing (i.e., the drive to analyze or construct systems)—individuals with autism (irrespective of sex/gender) tend to show a performance pattern shifted towards or beyond the typical male range (Baron-Cohen, 2002, 2005). The GI hypothesis stems from findings in anthropometry and endocrinology that on a normative male–female dimension, adult females with autism tend to shift away from the typical female range towards the typical male range, whereas adult males with autism tend to shift towards the typical female range (Bejerot et al., 2012). Both hypotheses, descriptively, would predict that autism-related brain changes in females are partly associated with neural masculinization, whereas the autism-related brain changes in males are predicted to be partly feminized by the GI hypothesis but "hypermasculinized" by the EMB hypothesis (Lai et al., 2013b). At the etiological and mechanistic levels it is, however, unclear if the EMB and GI hypotheses are mutually exclusive or simply that the underlying mechanisms have different effects in the two sexes/genders. For example, it has been argued that a hypermasculinized brain may not be the expected outcome of increased sex steroid action (McCarthy et al., 2015).

So far, two published studies have been particularly informative. Lai and colleagues (2013b) used whole-brain voxel-based morphometry to test the spatial overlap between normative sex/gender differences in regional brain volume and autism-related regional brain volume changes in adult males and females, respectively. They found that in both gray and white matter, the overall pattern of autism-related brain changes in females strongly and significantly resemble neural masculinization, whereas those in males show a weaker but still significant level of resemblance to feminization. Alaerts and colleagues (2016) performed resting-state functional connectivity analyses across the whole brain and showed that in the context of normative sex/gender differences in functional connectivity (i.e., higher overall connectivity in males than in females), females with autism tend to show a pattern of hyperconnectivity resembling a shift towards the level seen in typical males (i.e., masculinization), whereas males with autism tend to show a pattern of hypoconnectivity resembling a shift towards that of typical females (i.e., feminization). Both studies, though using different imaging modalities and testing individuals in different ages, converge to show that *at the whole-brain level*, females with autism seem to present an overall pattern of neural masculinization and males with autism likely show neural feminization, fitting the descriptive predictions from the GI hypothesis.

Whether this holds at a more *local level* remains unclear. For example, Ypma and colleagues (2016) specifically examined intra-default mode network resting-state functional connectivity and found that both males and females with autism showed hypoconnectivity compared with neurotypical males and females, in the context that neurotypical males showed lower connectivity than neurotypical females. This may be interpreted as reflecting masculinization in females with autism, but it does not support feminization in males with autism. Similarly, Di and Biswal (2016b), using source-based morphometry, found that in the only gray matter volume source (involving bilateral inferior and middle temporal regions) that showed significant main effects of both diagnosis (autism > control) and sex/gender (male > female), group difference patterns fit with the descriptive predictions of the EMB hypothesis. In a nutshell, neural masculinization in females with autism has been rather consistently found across global and local levels, whereas findings regarding males with autism tend to vary. More studies are required to delineate regional brain characteristics in relation to EMB, GI, or other hypotheses, and to identify how local findings correspond with overall patterns at the whole-brain level, as well as physical, cognitive/psychological, and other biological levels.

Are there possible biological correlates of neural masculinization in females with autism? Studies examining hormonal regulation in females with autism may speak partly to this. Serum levels of testosterone, luteinizing hormone, and androstenedione have been found to be elevated in women with autism (Ruta et al., 2011; Schwarz et al., 2011). Women with autism also report a higher frequency of sex steroid hormone–associated conditions than women without autism, such as irregular menstrual cycles, dysmenorrhea, menorrhagia, delayed or early-onset puberty, hirsutism, or a diagnosis of PCOS (Ingudomnukul et al., 2007; Pohl et al., 2014). In a population-based registry study, females with autistic disorder showed increased incidence of histologically confirmed ovarian cancer, although the absolute number of incident cases was low (Chiang et al., 2015). In two separate studies on age of menarche, women with autism reported experiencing menarche later than women without autism (Knickmeyer et al., 2006), and heightened level of autistic traits at 2 years of age is associated with later menarche in a typical birth cohort (Whitehouse et al., 2011). However, menarche occurs towards the end of pubertal development (Marshall and Tanner, 1969), and the onset can be influenced by body mass index and stress. Nevertheless, all the reports above suggest that females with autism are more prone to experience physical (and

potentially mental) challenges associated with sex hormone regulation. For individuals with autism, steroid hormones during puberty may influence the brain at a different stage of development (i.e., reorganizational), potentially interacting differently with early or prenatal (i.e., organizational) neurodevelopment compared with that seen in neurotypical individuals (Picci and Scherf, 2015).

All these findings provide potential insights into specific etiological and developmental hypotheses of autism. Beyond the substantial evidence showing that neural representation of risk processes to autism may be qualitatively different by sex/gender (as reviewed in Direction 1), it is likely that this difference is partly underpinned by mechanisms associated with sex differentiation and/or gender socialization. However, findings so far are cross-sectional and derived from school-age children, adolescents, and adults, so it is difficult to clarify whether such sex/gender-differential neural masculinization/feminization is a product of biological sex differentiation mechanisms or experiential gender-related socialization processes, or both. To delineate these, we need to adopt similar research designs and hypothesis testing in early development, even before the onset of the full behavioral syndrome of autism.

Human neuroimaging studies informing protective mechanisms. The search for protective mechanisms needs to be based on studying individuals at high risk but who do not go on to develop autism. A substantial proportion of autism risk runs in common genetic variants that exist widely in the general population (Gaugler et al., 2014). Various types of inherited and de novo genetic risks of autism occur in the general population as well (Robinson et al., 2016). One approach, therefore, is to explore candidate protective mechanisms from known sex/gender differences in the general population. For example, male-biased brain gene expression is enriched with genes involved in neurodevelopmental, neurological, and psychiatric disorders, whereas female-biased brain gene expression does not show such a pattern (Shi et al., 2016). This indicates that the female protective effect of autism may be partly underpinned by female-differentially expressed genes in the brain. Structural brain sex/gender differences may also provide clues (Giedd et al., 2012; Ingalhalikar et al., 2014; Ruigrok et al., 2014; Joel et al., 2015; Chekroud et al., 2016). However, to qualify as a candidate characteristic involved in the protective mechanisms against autism, it has to present early in development, before the onset of early signs and/or a full syndrome of autism. The literature to date on normative brain sex/gender differences does not include large enough data on this early developmental period. Therefore, it cannot provide unequivocal or conclusive implications on how female protection presents itself in the brain early in development. Population-based pregnancy or birth cohort studies with a focus on the brain will be the "holy grail" to uncover the brain basis of female protection against autism.

Despite a lack of data early in development, the relationship between normative sex/gender differences and brain characteristics in autism does provide clues. For example, there are findings showing that in the general population, domains of autistic traits and cognitive features are more correlated in males but less correlated in females; based on this, it may be that females are more resilient to developing autism due to an underlying more *fractionable* neurocognitive architecture (i.e., having more redundancy in the presence of risk processes) (Lai et al., 2015). The brain structural bases for this might include heightened interhemispheric connectivity in females than males (Ingalhalikar et al., 2014), but there has not been direct evidence to link the causal chain.

In another example, studies have described on-average neurocognitive sex/gender differences in aspects of social cognition and social perception, including processes underlying empathy (Christov-Moore et al., 2014) or more specifically in constructs such as biological motion processing (Anderson et al., 2013). As individuals with autism are impaired in aspects of social cognition (such as cognitive empathy, also known as "theory of mind" or "mentalizing") and social perception (such as biological motion perception) (Pelphrey et al., 2011), the female advantage in the general population in these domains has been assumed to be part of the female-protective mechanisms of autism. The main difficulty in confirming such an inference is that most studies on social cognition and perception are based on findings from children and adults, long after the age of onset of autism, and therefore it is difficult to argue the protective role in etiology and early development. Furthermore, it is difficult to tease apart the role of gender socialization that may already be in place early in life (i.e., nurture effects) vs. biological sex differentiation (i.e., nature effects) and to delineate which plays a protective or instead a moderating role on how one presents social characteristics. Population-based pregnancy or birth cohort studies with a focus on early brain function and subsequent cognitive characteristics will be the key to uncovering female-protective mechanisms against autism.

Finally, if candidate female-protective mechanisms are revealed from population-level sex/gender differences in early development, we will have to confirm if they are specifically protective against autism by examining whether similar mechanisms operate in the presence of evidently enhanced risk of autism. This could be revealed from longitudinal studies focusing on early developmental trajectories, such as infant-sibling designs (Szatmari et al., 2016) in which heightened familial risks for autism are present, or studies on individuals carrying known large-effect genetic risk factors for autism (e.g., those having autism-related genetic disorders or pathogenic/"causal" mutations). Females who carry these enhanced risks but who do not develop autism-related characteristics or the full autism syndrome likely benefit from certain protective mechanisms specific to autism (Singer, 2015).

FUTURE DIRECTIONS

Neuroimaging has the potential to bridge human population studies and molecular neuroscience in understanding sex/gender effects on the brain and how they relate to the

emergence of autism. In the field of animal imaging, studies investigating sex differences in mouse mutants modeling autism-relevant genes and environmental exposures are still missing. Further, as we increase our understanding of how sex influences brain development, imaging the timing of emergence of sex differences and how they relate to the emergence of phenotypes in autism-related mouse models will be key. In addition, the main effort to date has been on imaging brain structure. Although this should continue, investigations of function, physiology, and quantitative MRI techniques can only increase our conceptualization of sex/gender differences in autism.

In the field of human neuroimaging, the challenge of nonreplication and low statistical power (Button et al., 2013) needs to be resolved, potentially with several complementary approaches. One is to increase sample size by means of large-scale, multicenter prospective projects (Zwaigenbaum et al., 2011; Baribeau et al., 2015; Loth et al., 2016), or, less ideally, by data sharing and pooling across existing datasets (Halladay et al., 2015), such as the ABIDE initiative (Di Martino et al., 2014). Another approach has to deal with increasing the fidelity of acquired neuroimaging data since improvements in signal-to-noise ratio should lead to improved estimates of effect size and thus statistical power (Lombardo et al., 2016a). Yet another approach, more specific to the problem of heterogeneity in autism, is to stratify the autism population past the standard diagnostic label in a way that improves sensitivity to honing in on neurobiological mechanisms of interest, which may substantially differ across the many different subtypes of "autisms" (Coleman and Gillberg, 2012; Lai et al., 2013a; Lombardo et al., 2015). Once such stratification is implemented, it may then be easier to identify common and divergent findings of sex/gender-differential neural characteristics across subgroups. Subgroups that used to be difficult to include in neuroimaging studies (e.g., individuals with concurrent communicative or intellectual disability) can now be included, thanks to advanced data acquisition and analytic methods, such as sleep scans (Lombardo et al., 2015), decreased scanning time (e.g., using simultaneous multislice imaging [Barth et al., 2016]), prospective motion correction at imaging acquisition (Tisdall et al., 2012), and biophysically and statistically principled denoising techniques that leverage echo-time dependence in multiecho acquisitions (Kundu et al., 2012, 2013; Lombardo et al., 2016a). In either approach, to adequately address research questions about sex/gender and autism, it is important to include equal numbers of males and females in the study (Lai et al., 2015; Joel and McCarthy, 2016).

Another challenge is to further disentangle the relationship between sex/gender, autism, and other key factors contributing to the phenotypic heterogeneity of autism, such as intellectual and language capabilities, comorbidity pattern, age, and developmental trajectory. As autism is highly associated with co-occurring psychiatric, medical, and neurodevelopmental conditions (Gillberg, 2010; Lai et al., 2014), as a general principle, a less confounded examination of sex/gender differences in autism relies on having comparable distributions of common co-occurring conditions (or level of symptoms, traits, or abilities) across the male and female autism groups. Substantial variance in these distributions further provides opportunity to reveal how sex/gender interacts with co-occurring conditions when it comes to the association with neuroimaging measures (or other variables of interest). For example, females with autism have been found to be more likely to have concurrent intellectual disabilities and neurological conditions than their male counterparts (Bolton et al., 2011; Frazier et al., 2014). The generalizability of these clinical findings, however, can be challenged by potential nosological dilemma and diagnostic/ascertainment bias (Lai et al., 2015). Importantly, linking available sex/gender-differential neuroimaging findings to this phenotypic/clinical sex/gender difference is problematic as the former comes mainly from samples without significant intellectual or neurological disabilities. To move forward, for example, in understanding the role of intelligence, we need to test for sex/gender-differential characteristics across individuals with a wide range of (different subdomains of) intellectual abilities, by means of stratification by categorical IQ ranges and modeling different effects of IQ. This approach may uncover the relationships amongst sex/gender, autism, and neurophenotypic heterogeneity in an incremental manner.

In terms of an overarching research design, what is missing are longitudinal neuroimaging studies starting from early development, not only in individuals who later develop autism but also in those who carry heightened risks but who do not show atypical neurodevelopment or go on to develop autism. These will be key to revealing the developmental trajectories of sex/gender-differential neural characteristics of autism, to delineate different roles of sex vs. gender, and to clarify risk vs. protective mechanisms at play.

A further challenge is to link up the causal chain. Animal imaging studies take a bottom-up approach to identify common downstream effects of high-effect-size causal factors. It is uncertain how the findings can be generalized to humans, since highly penetrant genetic mutations and nongenetic (e.g., environment-related) risks only explain about half of the total liability to autism (Gaugler et al., 2014). Nevertheless, the hope lies in the findings that the heterogeneous genetic and environmental risks contributing to autism converge on key downstream pathophysiological mechanisms, including protein synthesis, transcriptional and epigenetic regulation (e.g., chromatin modification), synaptic development and signaling, and microglial and neuroimmune regulation (Geschwind and State, 2015; Sahin and Sur, 2015; Sanders, 2015; Lombardo et al., 2016b,c). Therefore, convergent animal imaging findings (Ellegood et al., 2015) may provide meso- and macroscopic-level brain markers corresponding to the converging molecular-level mechanisms. In the same vein, future human neuroimaging studies need to gather candidate (genetic and environmental) etiological information at an individual level to

facilitate causal investigation. A genetics-first approach, such as the Simons Variation in Individuals Project, which explores multilevel consequences of recurrent genetic variants that increase liability to autism (and other atypical neurodevelopmental conditions) such as deletion or duplication of chromosomal segment 16p11.2 (Simons VIP Consortium, 2012), is a useful initial step echoing the parallel animal imaging approach (Qureshi et al., 2014; Chang et al., 2016). Broadening this approach to study sex/gender-associated risk and protective mechanisms of autism requires sex/gender-normed quantification of atypical neurobiology and the multiple candidate etiological factors, and then the comparison of "brain-etiological factor" association patterns across sexes/genders will inform how sex/gender moderates the "neural routes to autism."

In the process linking up the causal chain, on the one hand we need to examine whether brain findings can be reasonably interpreted as caused by the interaction of candidate etiological factors and moderators, in the light of sex/gender differences. On the other hand, we need to test whether the brain findings can reasonably account for cognitive and behavioral characteristics of autism, again in the light of sex/gender differences. These require complex modeling, and there is a risk of making interpretations based on spurious correlations. For example, simply testing the correlation between measures in the brain showing sex/gender differences in autism and behavioral measures also showing sex/gender differences in autism risks finding spurious correlations that are difficult to interpret. As a general principle, testing relationships between etiologies, brain, cognition, and behavior stratified by sex or gender, then testing whether sex or gender moderates the relationships, is a clear first approach to disentangle the complexity (Bedford et al., 2016).

Uncovering the relationship between sex/gender and autism is a journey mapping risk and protective factors in human development. This applies not only to autism but also other atypical neurodevelopmental conditions that have a sex/gender-biased prevalence (Rutter et al., 2003; Zahn-Waxler et al., 2008) and potentially share similar risk and protective mechanisms (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Jacquemont et al., 2014; Taylor et al., 2016). A transdiagnostic approach (Baribeau et al., 2015; Ameis et al., 2016; McGrath et al., 2016; Sonuga-Barke et al., 2016) that further includes an angle focusing on sex/gender will be particularly illuminating. If we discover what protects females, we may better understand how to foster resiliency.

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CONFLICT OF INTEREST STATEMENT

None of the authors have potential or known conflicts of interest in relation to this work.

ROLE OF AUTHORS

Study concept and design: M-CL. Drafting of the manuscript: M-CL, JPL. Critical revision of the manuscript for important intellectual content: DLF, ANVR, AP, MVL, SB-C.

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