Brain-based sex differences in autism spectrum disorder across the lifespan: A systematic review of structural MRI, fMRI, and DTI findings

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ABSTRACT

Females with autism spectrum disorder (ASD) have been long overlooked in neuroscience research, but emerging evidence suggests they show distinct phenotypic trajectories and age-related brain differences. Sex-related biological factors (e.g., hormones, genes) may play a role in ASD etiology and have been shown to influence neurodevelopmental trajectories. Thus, a lifespan approach is warranted to understand brain-based sex differences in ASD. This systematic review on MRI-based sex differences in ASD was conducted to elucidate variations across the lifespan and inform biomarker discovery of ASD in females We identified articles through two database searches. Fifty studies met criteria and underwent integrative review. We found that regions expressing replicable sex-by-diagnosis differences across studies overlapped with regions showing sex differences in neurotypical cohorts. Furthermore, studies investigating age-related brain differences across a broad age-span suggest distinct neurodevelopmental patterns in females with ASD. Qualitative comparison across youth and adult studies also supported this hypothesis. However, many studies collapsed across age, which may mask differences. Furthermore, accumulating evidence supports the female protective effect in ASD, although only one study examined brain circuits implicated in "protection." When synthesized with the broader literature, brain-based sex differences in ASD may come from various sources, including genetic and endocrine processes involved in brain "masculinization" and "feminization" across early development, puberty, and other lifespan windows of hormonal transition. Furthermore, sex-related biology may interact with peripheral processes, in particular the stress axis and brain arousal system, to produce distinct neurodevelopmental patterns in males and females with ASD. Future research on neuroimaging-based sex differences in ASD would benefit from a lifespan approach in well-controlled and multivariate studies. Possible relationships between behavior, sex hormones, and brain development in ASD remain largely unexamined.

1. Introduction

1.1. Neurobiological sex differences in ASD

There is a male preponderance of autism spectrum disorder (ASD) and related neurodevelopmental diagnoses like attention deficit hyperactivity disorder and intellectual disability (Werling and Geschwind, 2013). The current estimated sex assigned at birth (subsequently referred to as 'sex') ratio for ASD is 3:1 males to females (Loomes et al., 2017). When stratifying across phenotypes, the sex ratio of ASD without intellectual disability is 16:1; however, the sex ratio of ASD with moderate-to-severe intellectual disability it is 1.5:1 (Werling and Geschwind, 2013). These observations have led to hypotheses regarding

how sex-related biology may influence ASD risk. One such hypothesis, the female protective effect, proposes that aspects of female biology may be protective against genetic mutations or environmental stressors linked to ASD (Werling and Geschwind, 2013). This hypothesis is supported by accumulating evidence showing that females with ASD carry a greater genetic mutational burden than males (Ferri et al., 2018). Alternatively, other hypotheses highlight the possibility that aspects of male biology lead to greater vulnerability in ASD (Ferri et al., 2018). In the hopes of shedding light on sex-dependent vulnerability/protection in ASD, models have attempted to characterize ASD from a sex-related perspective. For example, the Extreme Male Brain model suggests that ASD symptoms represent an extreme end of the male phenotype (Baron-Cohen, 2002), while the Gender Incoherence model suggests that the

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ASD phenotype in females is more "masculinized" but in males it is more "feminized" (Bejerot et al., 2012). These models may not be mutually exclusive, and it is plausible that both "masculine" and "feminine" biological processes interact with ASD risk genes and environmental factors to influence the ASD brain mosaic across the lifespan in distinct ways for males and females (Eliot et al., 2021; Joel et al., 2015).

Since ASD is conceptualized as a neurodevelopmental disorder with a male bias, some etiological hypotheses have focused on dysregulation of processes involved in early sexual differentiation. The neuroscience of sex differences highlights prenatal development as a critical window for male vs. female brain organization (see McCarthy et al., 2017 for review). Rodent models show that sex differences in brain anatomy emerge during prenatal development and continue into the early postnatal period. In males, gonadal steroidogenesis drives brain masculinization via an increase in androgens and estrogens. The absence of such processes, combined with a later critical window for elevated estrogen exposure, results in female brain organization. Sex steroids modulate brain masculinization predominantly via processes of silencing or expressing genes associated with synaptic functioning and transcriptional regulation. One hypothesis to account for the male bias in ASD purports that high levels of fetal testosterone are associated with ASD and an ASD-like phenotype (Baron-Cohen et al., 2015, 2011), and this has recently been extended to elevated estrogens (Baron-Cohen et al., 2020). Although there is some compelling evidence for the fetal steroidogenic activity contributing to ASD risk, this is likely not happening in the absence of genetic factors.

To date, the study of ASD-associated genes has identified de novo mutations across hundreds of genes (Ferri et al., 2018; Satterstrom et al., 2020). While most of these genes are not sex-specific in and of themselves, they are broadly associated with processes also known to be modulated by sex steroids. Thus, promising emerging lines of research are examining the influence of sex hormones on genetic expression in pathways associated with autism risk genes (Crider et al., 2014; Nguyen et al., 2010). However, sex steroids can exert an influence on molecular, transcriptional, and epigenetic processes in the brain across the lifespan (McCarthy, 2016; McCarthy et al., 2017). For example, in contrast to sex-related prenatal programming of brain organization, puberty and adult hormonal transitions are viewed under the umbrella of activational processes. During these periods, the changing hormonal milieu engages and refines sex-dependent brain circuits important for reproductive and/or maternal behavior (McCarthy, 2016). In keeping with this conceptualization, the "two-hit" model of ASD suggests that genetic or environmental prenatal disruptions result in a neural system that shows altered sensitivity to activational processes during puberty, resulting in a second biological "hit" of ASD (Picci and Scherf, 2015). However, no studies to date have investigated the influence of hormones on adolescent ASD symptoms or co-morbid condition progression in ASD. These observations highlight the importance of considering major developmental and adult hormonal transitions (e.g., puberty, menopause) when characterizing brain-based sex differences in ASD.

Identifying mechanisms underlying the sex bias in ASD holds great clinical translational significance. By characterizing sex-related biological factors that increase ASD risk, treatments may be developed targeting specific systems underlying protection or vulnerability. Importantly, considering ASD risk only during early neurodevelopment may be a limited view. If gene-by-hormone interactions play a role in ASD risk, then early developmental and adult periods of hormonal transition may open new windows of decline or improvement in ASD-associated behaviors. Emerging phenotypic evidence in ASD provides some support for this view, highlighting sex-dependent trajectories across adolescence (Wagner et al., 2019). Using a longitudinal co-twin design, females with ASD showed a peak in maternally-reported ASD symptom severity during early adolescence and declines thereafter (Fig. 1a); however, males with ASD and unaffected male and female siblings showed modest linear increases in autistic traits from childhood into early adulthood. Little is known about sex differences in behavioral trajectories during adulthood in ASD. To address this, we combined data from our lab and the National Institute for Mental Health (NIMH) Data Archive (NDA). We identified cross-sectional evidence of greater age-related symptom variability during adulthood specific to females with ASD (Fig. 1b, see Supplementary Methods section S1 and Supplementary Tables 1 and 2 for details). Notably, for middle-age women with ASD, the lowest reported symptoms are observed just preceding the average age of menopause (~51 years), then symptoms increase as age increases. These findings provide further support for the need to investigate neurobiological sex differences in ASD across the lifespan.

Efforts in transcriptional genomics show promise to answer questions about gene expression in the brain across sexes, disorders, and developmental stages associated with hormonal transitions (Hernandez et al., 2021). Such research may eventually provide insights into sex-specific mechanisms driving ASD risk across the lifespan (Kissel and Werling, 2021). However, transcriptomics is a developing field and relies on brain donation. To date, high resolution characterizations of gene expression in the brain are limited to a handful of mostly male, neurotypical (NT) adults (Hawrylycz et al., 2012). Alternatively, MRI offers an in-vivo, non-invasive approach to characterizing sex differences in brain
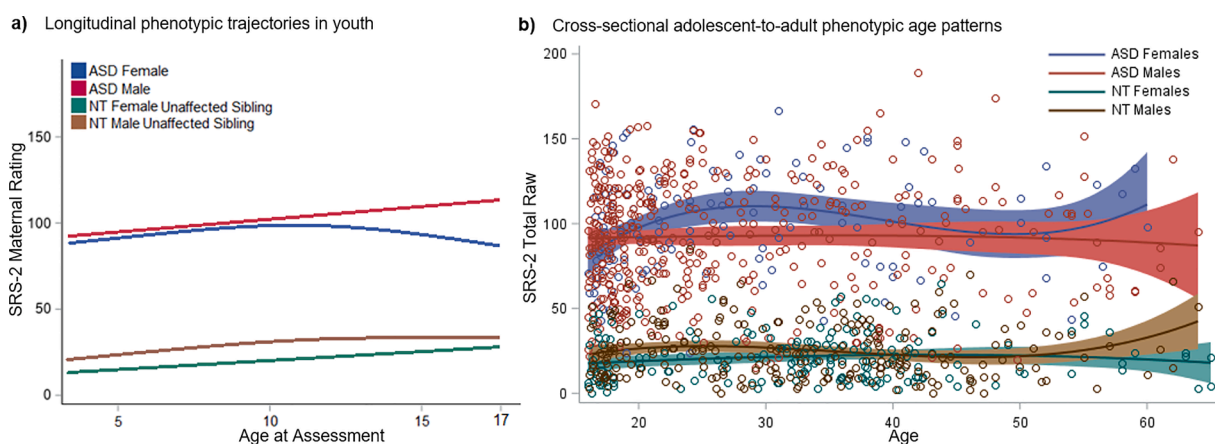

Fig. 1. A) Graphic approximation of Wagner et al. (2019) estimated longitudinal trajectories for maternal Social Responsiveness Scale – 2nd Edition (SRS-2) ratings from childhood through adolescence, highlighting distinct pubertal symptom trajectories in females with ASD. B) Scatterplot with cubic fit lines (best-fitting age model) and 95% confidence intervals for cross-sectional age-related SRS-2 ratings, highlighting distinct age patterns in females with ASD (age cubed-by-sex-by-diagnosis effect: $F = 5.64$, $p = .02$) and suggesting increasing symptom severity after the average menopausal age. Data includes NIMH NDA and data from our lab for participants ages 16–65, extending findings from Wagner et al. (2019) which sampled through 17 years of age for females with ASD. Please refer to Supplementary Methods S1 for methodological details and Supplementary Tables S1 and S2 for model fit and regression results.

anatomy, connectivity, and function across development. Findings from human neuroimaging studies may eventually be integrated with transcriptomic atlases (Arnatkevičiūtė et al., 2019; Fornito et al., 2019) as well as other genetic, histological, and animal studies to better understand sex differences in the etiology and progression of ASD across the lifespan. Furthermore, MRI also shows utility for biomarker discovery with potential translational value for predicting diagnosis, prognosis, and informing treatment development (Ecker et al., 2015).

1.2. Sex-related biology shapes the brain across development

Prenatal sex programming in the brain sets the stage for pubertal and adult hormones to activate and refine circuits implicated in "sex-typical" socio-emotional, cognitive, and mating behavior (McCarthy et al., 2017). Major disruptions to prenatal sex programming results in opposite gender features. For example, excessive exposure to prenatal androgens results in "masculinization" of biological females (e.g., congenital adrenal hyperplasia) while an absence of exposure to androgens results in "feminization" of biological males (complete androgen insensitivity syndrome), potentially affecting all aspects of sex-related development including the brain, physical features, and behavior/cognition (Auyeung et al., 2013; Bakker, 2018). Similarly, higher levels of fetal testosterone have been linked to more masculine brain and behavioral features as well as higher levels of ASD traits (Auyeung et al., 2013; Ferri et al., 2018). For example, in NT boys, fetal testosterone predicted gray matter (GM) volumes in a pattern reflecting more extreme "masculinization," including positive associations in regions linked to mental state inference (e.g., right temporo-parietal junction) and negative associations in regions linked to language and emotional processing (e.g., planum temporale and posterolateral orbitofrontal cortex; Lombardo et al., 2012). The consequences of disruptions to prenatal sex programming are not limited to early development. For example, animal models highlight that disruptions to prenatal sex programming reduce sensitivity to pubertal activational hormones (Götz and Dörner, 1976). Thus, a characterization of brain-based sex differences in ASD is needed across the lifespan, in particular for both early development and critical windows of hormonal transition.

In NT development, cellular processes of synaptic growth, pruning, and myelination occur across childhood and into adulthood with corresponding changes in brain anatomy, function, and connectivity, in particular during puberty (Kaczkurkin et al., 2019; Stiles and Jernigan, 2010). Measures of cortical thickness (CT), volume (CV), and surface area (SA) peak during early adolescence and then decline, with evidence suggesting an earlier peak for females (Kaczkurkin et al., 2019). In general, age-related patterns of regional GM volumes are more linear in males and curvilinear in females (Group, 2012). Measures of GM density have shown the most sensitivity to sex differential patterns of age-related variability, in particular in parietal, frontal, occipital, cerebellar, and striatal regions (Gennatas et al., 2017). With respect to brain function, older age is associated with reduced regional cerebral blood flow (rCBF) across adolescent development, especially to regions of the default mode, ventral attention, and fronto-parietal network (Satterthwaite et al., 2014). Higher rCBF during childhood may reflect glucose metabolism needs to support the developing brain (Goyal et al., 2014). From childhood to early adulthood, males show linear age-related patterns reflecting reduced rCBF as a function of age. In contrast, females show u-shaped age patterns in prefrontal, temporal, parietal, and insular cortices as well as the hippocampus and thalamus such that rCBF decreases as a function of age into mid-adolescence and thereafter increases (Satterthwaite et al., 2014). In contrast to GM, white matter (WM) development and myelination persists into the late 30s (Grydeland et al., 2013), with declining structural integrity thereafter (Lebel et al., 2010). Studies generally show greater WM integrity in male vs. female youth, although findings are mixed (Kaczkurkin et al., 2019). The mixed evidence in youth may be linked to sex differences in pubertal WM development (Kaczkurkin et al., 2019). How ASD interacts with sex

differences in patterns of age-related variability in MRI-based measures is underexplored, although emerging fMRI evidence suggests sex-by-diagnosis dependent patterns (Henry et al., 2018; Kozhemiako et al., 2020, 2019).

Both sex-hormone independent and dependent processes play a role in developmental brain changes (Juraska and Willing, 2017). Furthermore, characterizing the specific influence of circulating sex hormones on brain development is complicated by interconnected synthesis and signaling dynamics of sex steroids in the brain. For example, testosterone can be aromatized to estradiol (Lephart, 1996), androgen receptors can cross-activate nearby estrogen receptors (Peters et al., 2009), and androgen receptors can inhibit estrogen receptors in the context of receptor co-expression on a given cell (Garcia and Rochefort, 1979). Furthermore, measuring changes in hormone serum levels longitudinally, especially estrogens, is confounded by circadian and cyclical changes associated with menstruation. Animal studies allow for more controlled experimental manipulations of pubertal hormones. Evidence suggests pubertal brain changes are more dramatic in female rodents and ovarian hormones play a greater role than gonadal hormones in males (Juraska and Willing, 2017). In humans, structural brain differences linked to windows of ovarian hormone transitions (e.g., puberty, menstruation, pregnancy, menopause) include regions associated with the limbic, ventral attention, default mode, visual, and cerebellar networks as well as WM tracts such as the superior longitudinal fasciculus, cingulum, splenium of the corpus callosum, and fornix (Rehbein et al., 2020). However, evidence also suggests a role for androgens in brain development across sexes, which have been linked to pubertal changes in structures associated with fronto-parietal, limbic, ventral attention, default mode, and visual networks as well as WM integrity in the thalamus, precentral gyrus, genu of the corpus callosum, superior and anterior corona radiata, and superior frontal WM tracts (Vijayakumar et al., 2018). To date, the study of sex steroid influence on developmental brain differences in ASD remains unexplored (Lai et al., 2017; Picci and Scherf, 2015).

1.3. Neuroimaging of sex differences in ASD

Various MRI techniques have been applied to characterize brain-based sex differences in ASD with primary modalities including structural MRI (sMRI), functional MRI (fMRI), and diffusion tensor imaging (DTI). sMRI techniques exploit the differences in T1 relaxation times between GM, WM, and cerebrospinal fluid to produce high-resolution (~1mm^3) anatomical images from which tissue measurements can be derived (Symms et al., 2004). Segmentations are then performed on T1-weighted sMRI via manual, intensity-, atlas-, or surface-based methods, or hybrid segmentation methods (Despotović et al., 2015). A common intensity-based segmentation is voxel-based morphometry (VBM) to determine local tissue density and regional volume of a certain tissue concentration (GM or WM; Friston and Ashburner, 2020). Common surface-based methods generate measures of CT, CV, SA, curvature, and cortical folding (i.e. gyrification); and quantification of subcortical volume and shape (Fischl, 2012; Schaer et al., 2012).

The most common fMRI techniques exploit the paramagnetic effect of deoxygenated hemoglobin on T2*-weighted sequences, which is known as the blood oxygenation-level dependent (BOLD) signal (Stippich and Blatow, 2007). BOLD is a delayed (~6 s) proxy of neuronal activity that is measured across the whole brain approximately every 1–3 s at ~ 3 m^3 resolution over the course of ~ 4–10 min (Kim and Ogawa, 2012). This technique was first applied in task-based studies, where the BOLD response is correlated with the onset of a task to make inferences about psychological processes (Gitelman et al., 2003). More recently, resting state fMRI (rs-fMRI) was developed to measure brain function in the absence of task demands. Functional connectivity (FC) analyses are applied to rs-fMRI data to investigate functional brain networks (Whitfield-Gabrieli and Nieto-Castanon, 2012). A number of analytical approaches have been developed including seed-based FC

(correlations in voxel time courses with a region of interest [ROI]), voxel-to-voxel FC (e.g., intrinsic connectivity, independent component analysis; ICA), and graph theoretical metrics describing brain network properties (e.g., efficiency, integration, segregation).

Diffusion-weighted imaging measures the tissue water diffusion rate, which can be modeled based on the degree of anisotropy and structural orientation to produce diffusion tensor imaging (DTI; Soares et al., 2013). DTI is mainly used to make inferences about structural WM connectivity. Common diffusional metrics include fractional anisotropy (FA; the directional preference of diffusion), mean diffusivity (MD; average diffusion rate), axial diffusivity (AD; diffusion rate along the main axis) and radial diffusivity (RD; diffusion rate in the transverse direction; Soares et al., 2013). Although DTI metrics are sensitive to microstructural architecture, exactly what each metric is measuring is still being elucidated. Some potential neurobiological links are demyelination associations with MD/FA and edema associations with RD (Soares et al., 2013).

MRI techniques have generally been applied in unimodal studies to assess sex, diagnosis, or interaction effects in ASD, often considering age as a covariate of non-interest. In part, this is due to an important effort to improve neuroimaging reproducibility by leveraging large group-wise samples, mitigating phenomena like artificial effect size inflation in the context of small-sample mass-univariate procedures (Reddan et al., 2017). However, this approach of collapsing across important sources of heterogeneity may mask true differences (Lombardo et al., 2019). There is also a general sex bias toward males in neuroimaging samples, further reducing power to interrogate questions about sex- and diagnosis-dependent age patterns. For example, in one of the largest recent mega-analyses aggregating sMRI data across many sites ($n = 3222$), the ratio of males to females with ASD was 6:1 (van Rooij et al., 2018). This discrepancy is double the estimated 3:1 sex ratio in ASD (Loomes et al., 2017). In spite of these challenges, emerging neuroimaging research in ASD highlights the need for a lifespan approach. For example, in a recent rs-fMRI study, Kozhemiako and colleagues (2020) found no brain differences in FC that were unique to females with ASD when collapsing across age. However, when probing further in their child-to-adult cross-sectional sample, they found that females with ASD showed age-related FC patterns across diffuse brain networks that were distinct from males with ASD and NT males and females.

In summary, increasing evidence suggests developmental stage (e.g., childhood, puberty, adulthood, menopause) and sex are important sources of heterogeneity that remain under-examined in ASD. In order to contextualize brain differences observed in females with ASD with consideration for major developmental hormonal transitions and compel further research on the topic, we conducted this systematic review to: 1) integrate the literature on neuroimaging-based sex differences in ASD from a developmental lens and 2) identify promising future directions for biomarker discovery of ASD in females.

2. Systematic review methods

We conducted a systematic search procedure according to PRISMA guidelines (Moher et al., 2009) using PubMed (January 2020) and MEDLINE (May 2020) databases of published, peer-reviewed studies. Search terms targeted articles investigating brain-based sex differences in ASD via MRI, including sMRI, rs-fMRI, task-based fMRI, and DTI studies. Additional articles were identified via Google Scholar alerts and review of key article bibliographies. Only one study was identified investigating sex differences in ASD using arterial spin labeling MRI (Peterson et al., 2019). Due to insufficient quantity of studies using this modality for integrative review, this study was excluded from summary tables; however, findings are considered in the Results section. Please refer to Supplementary Methods section S2 for details regarding search methodology, study inclusion criteria, and quality assessment procedures. In brief, peer-reviewed studies were included if they examined regional brain-based sex differences in ASD vs. NT groups using

validated MRI-based analytical methods with a minimum group-wise sample of $n = 10$. The first author conducted quality assessment review for all studies meeting inclusion criteria, and no studies were excluded although limitations are discussed in the qualitative review.

The database searches yielded a total of 844 articles. An additional 30 articles were identified via bibliographies of key articles and Google Scholar alerts after the database search was completed. After duplicate removal, 610 articles remained. Of these 610 articles, abstracts were screened and 421 met criteria for full-text eligibility assessment. In total, 50 articles met criteria for inclusion. Reasons for exclusion during full-text review were: 1) sample size included fewer than $n = 10$ per sex-by-diagnosis group ($n = 202$), 2) MRI-based sex differences were not investigated and/or reported ($n = 97$), 3) the study did not include both ASD and NT males and females ($n = 54$), 3) the study's focus was to test novel MRI-based analytical methods ($n = 6$), 4) the study did not investigate MRI-based measures ($n = 4$), or 5) the study was over 10 years old ($n = 2$; summarized in Fig. 2; however, findings from Schumann et al., (2009) are discussed in Results due to relevance). For a detailed, modality-specific overview of studies meeting criteria for inclusion, please refer to Supplementary Methods section S3. In general, regional effects were summarized in the Results section from a network perspective, using the Yeo et al. 7-network parcellation by (Yeo et al., 2011).

3. Results

3.1. Overview

Across studies included in this review, sMRI was the most well-represented modality. With respect to sex ratios, sample sizes were generally not balanced, with ASD male:female ratios ranging from 1:1 (Andrews et al., 2017; Beacher et al., 2012a; Bosco et al., 2019; Ecker et al., 2017; Giuliano et al., 2018; Irimia et al., 2018; Lai et al., 2013; Retico et al., 2016a; Schaer et al., 2015) to 6:1 (van Rooij et al., 2018). Amongst the matched samples, the largest sample of females with ASD was $n = 55$ (Irimia et al., 2018). Across studies, the largest samples of females with ASD came from three large-scale, multi-site analyses (e.g., $n = 274$ for Postema et al., 2019; $n = 224$ for van Rooij et al., 2018; $n = 129$ for Bedford et al., 2019). Of these studies, the ASD male:female ratio was 5.5:1, 6:1, and 2.8:1, respectively. In terms of age distributions, six studies examined early childhood development (≤ 7 years; Bosco et al., 2019; Giuliano et al., 2018; Nordahl et al., 2020; Reinhardt et al., 2019; Retico et al., 2016a; Schumann et al., 2010), six examined broader youth cohorts (e.g., age ≤ 23 years; Cauvet et al., 2019; Di & Biswal, 2016; Irimia et al., 2018; Supekar & Menon, 2015; Sussman et al., 2015; Westeinde et al., 2019), six examined broad youth to adult samples (Bedford et al., 2019; Postema et al., 2019; Richards et al., 2020; Schaer et al., 2015; van Rooij et al., 2018; Zhang et al., 2018), and four investigated adults only (Andrews et al., 2017; Beacher et al., 2012a; Ecker et al., 2017; Lai et al., 2013; Laidi et al., 2017). In general, samples including adults with ASD showed diminishing representation over age 35.

The second most-represented modality in this review was rs-fMRI. Sex distributions were largely unbalanced, with male:female ASD ratios ranging from 1:1 to 7:1. Among the neuroimaging approaches, rs-fMRI studies included two of the largest matched sex, age, and IQ-matched samples, including $n = 104$ (Kozhemiako et al., 2019) and $n = 92$ females with ASD (Kozhemiako et al., 2020). Across rs-fMRI studies, the largest overall sample comprised $n = 1587$ (Henry et al., 2018); however, the male to female ASD ratio was 5:1 ($n = 118$ females with ASD). Regarding age, one study focused on early childhood development (Lee et al., 2020), two examined a child to adolescent sample (Hernandez et al., 2020; Lawrence et al., 2020a); eight examined a broad youth to adult range (Alaerts et al., 2016; Henry et al., 2018; Holiga et al., 2019; Kozhemiako et al., 2020, 2019; Oldehinkel et al., 2019; Smith et al., 2019; Yang and Lee, 2018; Ypma et al., 2016), and
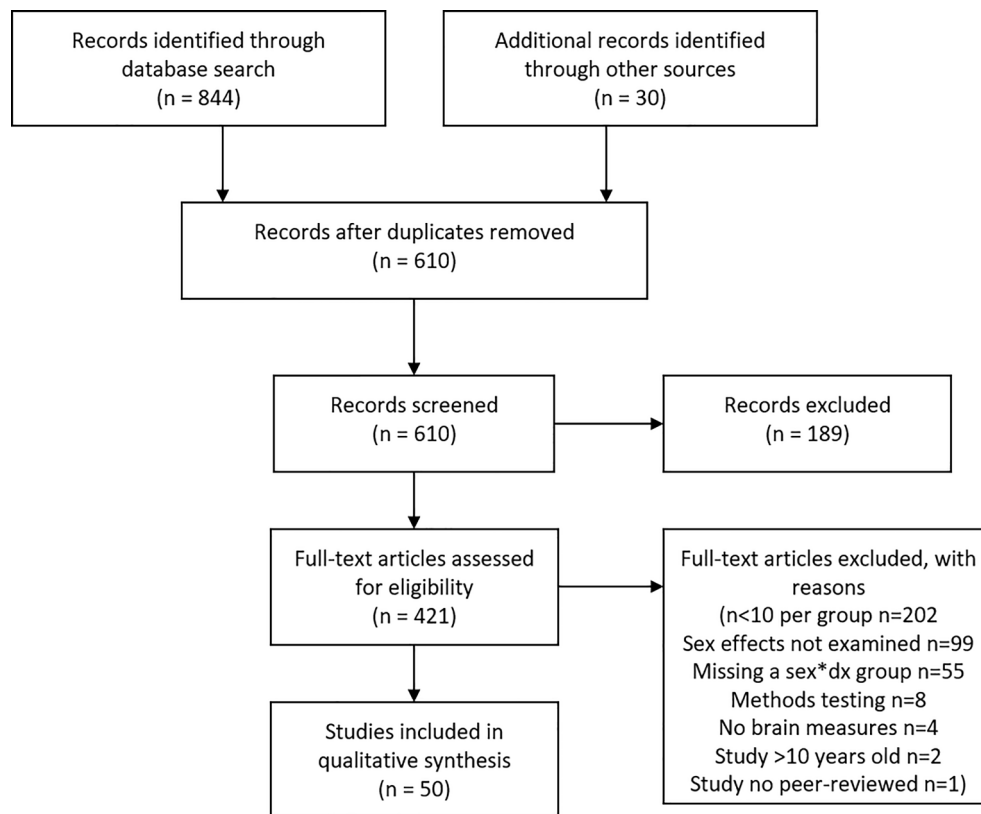
Fig. 2. PRISMA flow-chart indicating articles filtered during identification, screening, eligibility, and inclusion assessment.

one examined adults only (Guo et al., 2019). Similar to sMRI, for rs-fMRI, lifespan representation diminished after age 35, especially for females with ASD. Henry and colleagues (2018) highlight in their study that diminishing representation of older females likely attenuated sex-by-diagnosis differences with respect to age effects.

Of the seven task-based studies included in this review, all studies contained balanced samples with two exceptions (3:1 male:female ASD ratio; Bjornsdotter, Wang, Pelphrey, & Kaiser, 2016; Moessnang et al., 2020). The largest samples were from Moessnang et al. (2020; *n* = 394, *n* = 54 females with ASD), Lawrence et al. (2020b; *n* = 154, *n* = 39 females with ASD), and Lai and colleagues (2019; *n* = 119, *n* = 28 females with ASD). All other studies used smaller group-wise samples of *n* ≤ 16 (Beacher et al., 2012b; Bjornsdotter et al., 2016; Kirkovski et al., 2016; Schneider et al., 2013). Unlike other modalities, the majority of studies investigated adults with the exception of Lawrence et al. (2020b) who examined a child-to-adolescent sample and Moessnang et al. (2020) and Bjornsdotter et al. (2016) who examined child-to-adult samples.

Only seven studies used DTI to investigate sex differences in ASD. Male:female ratios varied from 1:1 (Beacher et al., 2012a; Irimia et al., 2017; Kirkovski et al., 2015) to 5:1 (Nordahl et al., 2015). While Zees-traten et al. (2017) used the largest overall DTI sample in this review (*n* = 213, *n* = 37 females with ASD), Irimia and colleagues' (2017) study contained the largest age, IQ, and sex-matched sample (*n* = 193, *n* = 55 females with ASD). Amongst DTI studies, two examined early childhood development (Andrews et al., 2019; Nordahl et al., 2015), two examined broader youth cohorts (Irimia et al., 2017; Lei et al., 2019), and three examined adult-only samples (Beacher et al., 2012a; Kirkovski et al., 2015; Zeestraten et al., 2017).

3.2. Most Sex-by-Diagnosis effects in regions showing NT sex differences

Among the whole-brain approaches investigating sex-by-diagnosis differences, most effects fell within structures that also show NT sex differences, including limbic, default mode, ventral attention, cerebellar, and visual regions (Bakker, 2018; Rehbein et al., 2020; Tan et al., 2020; Vijayakumar et al., 2018). For example, sex-by-diagnosis effects in morphometry studies generally fell within regions associated with the limbic, default mode, visual, as well as somatomotor (especially auditory/language regions) networks (see table 1 for a summary of sMRI study results; Cauvet et al., 2019; Ecker et al., 2017; Irimia et al., 2018, 2017; Postema et al., 2019; Schaer et al., 2015). Effect directions were not always reported (Irimia et al., 2018, 2017), but generally showed atypically lower CT, CV, or SA in females with ASD while males with ASD showed trends toward higher values compared to NT counterparts (Cauvet et al., 2019; Ecker et al., 2017). However, there is some evidence to suggest age-dependency of regional sex-by-diagnosis effects (see section 3.2).

The predominant sex-by-diagnosis effects in rs-fMRI studies were associated with limbic, default mode, ventral attention, and cerebellar connections (see table 2 for a summary of rs-fMRI study results; Alaerts et al., 2016; Lawrence et al., 2020a; Lee et al., 2020; Smith et al., 2019; Yang and Lee, 2018; Ypma et al., 2016). However, several of these studies used hypothesis-driven approaches, which were biased toward default mode seeds. Furthermore, the direction of sex-by-diagnosis effects was largely inconsistent across studies, which was likely impacted by methodological differences (e.g., age range studied, seed selection, etc.). Given findings of sex-by-diagnosis differences in patterns of regional age-related FC variability (Kozhemiako et al., 2020, 2019), development is likely an important consideration for interpretation of effect directions.

Task-based studies predominantly investigated social processes, implicating limbic and default mode regions in sex-by-diagnosis effects (see table 3 for a summary of task-based fMRI study results; Bjornsdotter et al., 2016; Kirkovski et al., 2016; Lai et al., 2019b; Schneider et al., 2013). Effect directions for social tasks generally reflected patterns of hyper- or typical activation in females with ASD and hypo-activation in males with ASD (Bjornsdotter et al., 2016; Kirkovski et al., 2016; Lai et al., 2019b; Lawrence et al., 2020b), with the exception of two studies

Table 1
Overview of sex differences findings from sMRI studies.

Author	Sample Size Females		Males			Demographics Age			IQ			Methods: Sex Differences Analyses Sex-by-Diagnosis Effects Model	Tested?	Find-ings?	Age tested?	Cover-age?	DVs	Summary
	ASD	NT	ASD	NT	n	x̄	σ	Range	x̄	σ	Range							
Whole-brain Studies																		
Schumann 2010	9	12	32	32	85	4	0.2	1–5	86	17	NR	GLM	no, sex-split	n/a	yes – long.	GM & global WM	lobular & total vol.	In a preschool-aged sample, girls with ASD showed more atypical trajectories of brain development than boys.
Retico 2016	38	38	38	38	152	4	1	2–7	72	23	30–113	SVM, SVR	no, sex-split	n/a	no	GM only	VBM	↑ regional volumes in preschool-aged ASD, greater spatial extent in ASD-F than ASD-M
Supekar 2015	25	19	25	19	88	10	0	7–13	105	5	78–142	MVPASVR	no, dx-split	n/a	no	GM only	VBM	Multivariate, but not univariate, approach shows widespread sex differences in youth with ASD
Sussman 2015	11	22	61	116	210	NR		4–18	108	15	NR	GLM	yes	yes	yes	full	CT, CV, SA, subcort. vol.	Sex-by-diagnosis effects in youth for cerebellar & hippocampal volumes
Di 2016	36	54	182	172	444	13	3	<20	107	15	≥70	GLM	yes	no	yes - post hoc	GM/WM only	40 ICs	ITG/MTG sulcus source signal suggests age-dependent sex and diagnosis differences
Irimia 2018	55	41	55	43	194	13	3	NR	104	17	NR	SVM	yes	yes	no	GM only	CT, CV, SA, curvature, CD	SVM diagnostic classifiers on sex-balanced sample show post-hoc sex-by-diagnosis effects; different DVs show greater regional sensitivity to interaction effects
Postema 2019	274	429	1504	1400	3607	13[a]	NR	2–64	108	17	31–149	GLM	yes	yes	no	GM & subcort.	Homotopic assym. (CT, SA, vol.)	Heterogeneous youth-to-adult mega-analysis showing sex-by-diagnosis effects only in rostral ACC, predicting diagnosis in males but not females
van Rooij 2018	224	393	1347	1258	3222	16	9	2–64	101	20	65–149	GLM	yes	none	yes	GM & subcort.	CT, SA, subcort. vol.	Heterogeneous youth-to-adult mega-analysis showing no sex-by-diagnosis or age-by-sex-by-diagnosis effects
Cauvet 2019	11	20	17	26	74	16	3	9–24	97	16	62–142	co-twin	yes, post-hoc	yes	no	No TP, OFC, cereb-ellum	CV, CT, SA	In co-twin design, ↓ CV/SA predicts ↑ ASD traits in female youth across various regions; 2 regions predict ASD traits in males
Westeinde 2020[b]	12	30	20	40	102	16	4	11–24	98[c]	16	62 – 142[c]	co-twin	yes, post-hoc	yes	no	33 RRBI-linked regions	CT, CV, SA	In co-twin design (ASD subset), ↑ regional CT predicts ↑ RRBI traits in female but not male youth
Bedford 2019	129	355	362	481	1327	17	10	2–65	111	NR	49–149	GLM	no	none	no	GM only	CT, CV, SA	Youth-to-adult, sex-split mega-analysis shows more pervasive patterns of CT abnormality in females than males with ASD; Effect direction is similar but size ↑
Schaer 2015	53	51	53	53	210	17	8	5–56	107	14	NR	GLM	yes	yes	no	GM only	CV/CT/LGI	Only local gyrification of vmPFC/OFC shows sex-by-diagnosis effects in this older youth/adult sample
Andrews 2017	49	47	49	51	196	27	7	18–52	115	11	84–137	GLM	yes	no	no	GM/WM boundary	GM/WM constrast	No sex-by-diagnosis effects found, although diagnosis and sex main

(continued on next page)

Table 1 (*continued*)

Author		Sample Size Females		Males			Demographics Age			IQ			Methods: Sex Differences Analyses Sex-by-Diagnosis Effects						Summary
		ASD	NT	ASD	NT	n	x̄	σ	Range	x̄	σ	Range	Model	Tested?	Findings?	Age tested?	Cover-age?	DVs	
																			effects show reduced GM/WM contrast in adults with ASD & in NT/ASD women
Ecker 2017		49	47	49	51	196	28	7	18–52	117	10	84–136	GLM	yes	yes	no	GM only	CT	Sex-by-diagnosis effects of ↓ ventral temporal-occipital CT in women with ASD (inverse for men); greater spatial extent of diagnosis differences in women
Lai 2013		30	30	30	30	120	28	7	18–49	117	12	NR	GLM	yes	yes	no	GM/WM only	VBM	Sex-by-diagnosis effects for WM but not GM affecting several tracts with different regional effect patterns
Beacher 2012		13	15	15	15	58	31	8	≥18	33[d]	7[d]	NR	GLM	yes	yes	no	GM/WM only	VBM	Sex-by-diagnosis effect in inferior parietal cortex with ↓ volume predicting diagnosis in males
ROI-based Studies																			
Nordahl 2020		91	57	209	63	420	3	1	2–5	75	19	22–137	GLM	no	n/a	no	amyg-dala	vol.	↑ R amygdala vol., ↑ internalizing in young girls with ASD (not boys)
Reinhardt 2019	T1	63	50	137	59	309	3	1	2–4	84	18	NR	GLM	yes	none	yes – long.	hippo.	vol.	↑ R hippo. vol. growth, ↑ adaptive scores in young boys with ASD (girls = inverse trend)
	T3	13	17	43	23	96	5	0	NR	97	23								
Guiliano 2018		20	20	20	20	80	4	1	2–6	73	12	31–123	GLM	no, sex-split	n/a	yes - post hoc	CC & sub-regions	vol.	↑ CC volume in young boys with ASD (not girls)
Bosco 2018		38	38	38	38	152	4	1	2–7	72	23	30–113	GLM	no, sex-split	n/a	no	brain-stem	vol.	↑ brainstem volume young boys with ASD (not girls)
Zhang 2018		50	80	351	378	859	15	NR	7–27	107	NR	70–130	GLM	yes	none	yes	sub-cort. & global vol.	vol.	Uncorrected age-by-sex-by-diagnosis effects for total GM/WM, putamen, & hippocampal vol.
Richards 2020		55	92	382	419	948	16	6	6–35	109	13	79–138	GLM	yes (post-hoc)	yes	no	hippo., amyg-dala	shape/ vol. asymm.	Hippo. asymmetry ↑ in youth males with ASD but not females
Laidi 2017		17	27	117	133	294	28	10	18–64	104	16	≥70	GLM	yes	no	no	cerebellum	vol.	No sex-by-diagnosis for cerebellar regional vol. in adults.

[a]only median age reported; [b]study included in whole-brain section since 33 widespread cortical ROIs linked to ASD RRBI traits were examined; [d]escriptives reported for whole psychiatric sample, not ASD-subset only; [i]ntellectual functioning measured using the National Adult Reading Test; *autism spectrum disorder (ASD); neurotypical (NT); dependent variables (DVs); support vector machine (SVM); support vector regression (SVR); gray matter (GM); voxel-based morphometry (VBM); multivariate voxel pattern analysis (MVPA); not reported (NR); general linear model (GLM); longitudinal (long); cortical thickness (CT); cortical volume (CV); surface area (SA); subcortical volume (subcort. vol.); white matter (WM); independent components (ICs) inferior temporal gyrus (ITG); middle temporal gyrus (MTG); connectivity density (CD); temporal pole (TP); orbital frontal cortex (OFC); restricted/repetitive behaviors/interests (RRBI); local gyrification (LGI); ventromedial prefrontal cortex (vmPFC); right (R); corpus callosum (CC); hippocampus (hippo.); asymmetry (asymm.)

Table 2
Overview of sex differences findings from rs-fMRI studies.

Author	Sample Size Females ASD	NT	Males ASD	NT	n	Demographics Age x̄	σ	Range	IQ x̄	σ	Range	Methods: Sex Differences Analyses Model	Tested?	Find-ings?	Age tested?	Cover-age?	DVs	Summary
Whole-brain Studies																		
Kozhemiako 2019	104	107	115	114	440	13	4	6–26	109	16	NR	PLS	yes	no	yes	no cerebellum	VMHC & sub-sampled age-curvature	No sex-by-diagnosis effects for VMHC collapsing across age, but pervasive for VMHC age curvature. Most variance explained by 1) unique effects in NT females, 2) diagnosis differences, 3) sex differences in ASD.
Kozemhiako 2020	92	92	102	104	390	13	4	6–26	108	16	NR	PLS	yes	no	yes	no sub-cort.	ReHo & sub-sampled age-slope	Sex-by-diagnosis effects not observed for ReHo collapsing across age, but pervasive for ReHo age slopes. Most variance explained by 1) unique effects in ASD females, 2) unique effects in ASD males, 3) unique effects in NT males.
Henry 2018	118	261	591	617	1587	15	NR	5–64	110	NR	NR	Meta	yes	no	yes	no cerebellum	Modularity & global efficiency	Heterogeneous youth-to-adult *meta*-analysis with trending sex-by-diagnosis effects for modularity & global efficiency age patterns (sig. excluding age > 33, due to lack of older adult sampling).
Oldehinkel 2019	71	77	194	136	478	17	5	7–30	106	15	>70	GLM	no	n/a	no	whole-brain, 20 network	ICA	In sex-split analysis, magnitude of diagnosis effects in females were ~ 2x 1) greater for lower cerebellar-subcortical & higher cerebellar-temporo-parietal FC in ASD & were 2) smaller for lower sensorimotor-medial motor network FC in ASD.
Guo 2019	31	32	30	33	126	28	7	≥18	116	13	>70	GLM	yes	no	yes	whole-brain, 7 network	SMP & trad-itional	No sex-by-diagnosis effects for SMP or traditional graph

(continued on next page)

Table 2 (*continued*)

Author		Sample Size				Demographics							Methods: Sex Differences Analyses						
		Females		Males			Age			IQ					Sex-by-Diagnosis Effects				
		ASD	NT	ASD	NT	n	x̄	σ	Range	x̄	σ	Range	Model	Tested?	Find-ings?	Age tested?	Cover-age?	DVs	Summary
																		graph theory	theory. However, a trending age-by-sex-by-diagnosis effect was observed for global SMP ($p = .13$).
Hol-iga 2019[a]	AIMS	60	68	142	124	394	17	5	child - adult	107	14	≥70	GLM	yes	no	yes - post-hoc	cortical DC ↑/↓ in ASD masks	shifts from out to in DC mask	No sex-by-diagnosis effects for discovery or replication cohorts.
	ABIDE I	31	63	268	313	675	18	8		109	14	≥70							
	ABIDE II	44	127	262	263	696	14	6		112	14	≥70							
	InFoR	8	6	26	19	59	30	9	adult	106	18	≥70							
ROI-based Studies																			
Lee 2020		36	26	80	31	173	4	1	NR	79	19	NR	MDMR, GLM	yes	yes	yes	amyg-dala	MDMR, seed-to-voxel FC	The left amygdala connectome is more atypical in girls with ASD. GLM revealed sex-by-diagnosis effects of hyper-FC in ASD girls & hypo-FC in ASD boys for prefrontal regions (inverse for R PCC and L lingual gyrus).
Lawrence 2020		46	48	34	41	169	13	3	8–17	108	18	NR	GLM	yes	yes	no	SN/DMN/FPN mask	seed-to-voxel & ROI-to-ROI FC	Sex-by-diagnosis effects show 1) ↑ positive FC between SN & FPN/DMN in ASD vs. NT boy, 2) ↑ positive FC between DMN & FPN in ASD vs. NT girls 3) & ↑ positive FC within SN & negative FC between SN/FPN in NT boys vs. girls (no ASD sex diff).
Hernandez 2020		50	52	37	34	173	14	2	8–17	106	NR	NR	GLM	yes	yes	no	NAc seed	seed-to-voxel FC for NAc	Sex-by-diagnosis-by-risk load (OXTR alleles) effects in youth for L FP, caudate, & dmPFC (FC ↑ with ↑ risk in ASD females & NT males, but inverse pattern for ASD males & NT females). Inverse intx. pattern for L superior parietal cluster.
Alaerts 2016		42	75	42	75	234	14	4	7–30	107	13	NR	GLM	yes	yes	yes - post-hoc	pSTS, PCC; whole-	seed-to-voxel; all	Sex-by-diagnosis effects in youth/adults, such that ASD females show

Table 2 (*continued*)

Author		Sample Size Females ASD	NT	Males ASD	NT	n	Age x̄	σ	Range	IQ x̄	σ	Range	Model	Tested?	Find-ings?	Age tested?	Cover-age?	DVs	Summary
Yang 2018		24	24	24	24	96	14	5	NR	105	13	NR	GLM	yes	yes	no	brain atlas; mPFC, TPJ, precun.	ROI-to-ROI pairs; seed-to-voxel	patterns of hyper-FC & ASD males hypo-FC relative to NT counterparts. Sex-by-diagnosis effects generally showed hypo-FC in ASD girls & hyper-FC in ASD boys for TPJ/mPFC seeds with regions of the DMN. For the precuneus seed, hyper-FC in ASD girls and hypo-FC in ASD boys was observed with visual/DAN regions.
Ypma 2016	CFSA	16	20	35	20	91	15	2	12–18	108	13	65[b]	GLM	no, EMB con-trast	no	yes - post-hoc	DMN	DMN intra-FC (graph theory)	FC is lowest in ASD male youth, then ASD females, then NT males, & NT females with highest (effect size comparison).
	ABIDE I	55	89	408	428	980	16	7tpgoto"	6–58	108	14	107[b]							
Smith 2019		23	24	56	65	168	22	9	11–62	113	14	≥80	GLM	yes	yes	no	cereb-ellum	IC; seed-based post-hoc	Trending sex-by-diagnosis effects in STG & cerebellum (whole-brain). Small-volume correction in cerebellum showed 2 clusters with hyper-FC in ASD females & hypo-FC in ASD males vs. NT.

[a]not whole-brain, but degree centrality increase/decrease masks from EU-AIMS discovery cohort spanned much of the cortex; [b]IQ range reported as point differences between minimum to maximum; *autism spectrum disorder (ASD); neurotypical (NT); dependent variables (DVs); not reported (NR); partial least squares (PLS); voxel-mirrored homotopic connectivity (VMHC); general linear model (GLM); semi-metric edge percentage (SMP); degree centrality (DC); functional connectivity (FC); regional homogeneity (ReHo); independent components analysis (ICA); multivariate distance matrix (MDMR); left (L); salience network (SN); default mode network (DMN); fronto-parietal network (FPN); nucleus accumbens (NAc); frontal pole (FP); dorsomedial prefrontal cortex (dmPFC); posterior superior temporal sulcus (pSTS); posterior cingulate cortex (PCC); region of interest (ROI); medial prefrontal cortex (mPFC); right (R); temporo-parietal junction (TPJ); Extreme Male Brain (EMB); intrinsic connectivity (IC); superior temporal gyrus (STG)

that found either inverse patterns (Schneider et al., 2013) or no differences (Moessnang et al., 2020). In contrast, a study utilizing a visuospatial task showed sex-by-diagnosis effects trending toward hyperactivation in males with ASD and hypo-activation in females in regions of the visual and dorsal attention networks (Beacher et al., 2012b). Although not the focus of this review, we identified one study that used arterial spin labeling to examine sex differences in regional cerebral blood flow (rCBF) in ASD in a youth-to-adult sample (Peterson et al., 2019). Intriguingly, this study found patterns of sex-by-diagnosis differences, despite a small female sample and collapsing across a broad age range (6–61) in their analysis. Specifically, atypically reduced rCBF in regions associated with the limbic network was found in females with ASD with inverse patterns in males.

The least investigated MRI-based features were WM microstructure. However, a few studies found sex-by-diagnosis effects across tracts implicated in NT sex differences (Ritchie et al., 2018). While there is some convergence of regions implicated in sex-by-diagnosis effects across studies, the direction of sex differences and measures showing sensitivity vary as a function of age (see section 3.2). Projection and commissural tracts tended to show sex-by-diagnosis effects across developmental cohorts examined, in particular the internal capsule and corpus callosum (see table 4 for a review of DTI study results; Andrews et al., 2019; Beacher et al., 2012a; Lei et al., 2019; Nordahl et al., 2015). Older youth and adult studies showed more pervasive interaction effects beyond just commissural and projection tracts, including the cingulum, arcuate fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, and inferior fronto-occipital fasciculus (Beacher et al., 2012a; Irimia et al., 2017; Lei et al., 2019; Zeestraten et al., 2017).

Given variable sample sizes across studies, it is plausible that some effects are the product of sampling bias or noise. In order to determine if effects may be reproducible, sex-by-diagnosis differences reported across studies were categorized based on anatomical proximity (see tables 5 and 6). Regions implicated in sex-by-diagnosis differences across two or more studies (within a single modality or cross-modally) were considered "replicable," regardless of inconsistent effect directions across age cohorts. The Automated Anatomical Labeling GM (Tzourio-Mazoyer et al., 2002) and Johns Hopkins University WM (Hua et al., 2008; Wakana et al., 2007) atlases were used for regional classification. GM regions implicated in two or more studies included the bilateral superior frontal gyrus, inferior parietal lobe, precuneus, posterior cingulate, superior and middle temporal gyri, hippocampi, cuneus; right ventromedial prefrontal cortex, parahippocampus, insula; and left precentral gyrus. Visual comparison of regions showing replicable sex-by-diagnosis effects across studies showed overlap with regions implicated in NT sex differences (Fig. 3; Liu et al., 2020). Predominantly regions having shown NT male > female bias toward volumetric enlargement overlapped with regions expressing replicable sex-by-diagnosis differences in this review. For WM effects, tracts showing replicable interaction effects included the bilateral cingulum, sagittal stratum (inferior fronto-occipital fasciculus/inferior longitudinal fasciculus), right superior longitudinal fasciculus, corona radiata (anterior, superior, and posterior portions), right extreme capsule/uncinate fasciculus, and the corpus callosum. Many of these tracts overlapped with those showing sex differences in a large-scale study of NT adult microstructural integrity (Fig. 4; Ritchie et al., 2018), both in tracts showing patterns of male > female and female > male bias in WM integrity. Specifically, overlapping tracts included the bilateral cingulum as well as the right superior longitudinal fasciculus and superior corona radiata, which have shown male > female bias in NT adults, and the left sagittal stratum, which has shown an inverse pattern (Ritchie et al., 2018). Together, these findings highlight that regions and tracts showing replicable sex-by-diagnosis effects across studies in this review overlap to some degree with regions showing NT sex differences.

Findings of "replicable" sex-by-diagnosis effects predominantly in regions associated with male > female volumetric bias provides evidence in line with the Gender Incoherence model of ASD (Bejerot et al.,

2012). Put more simply, sex-by-diagnosis effects indicate that an ASD diagnosis influences regional brain-based sex differences. Females with ASD may show patterns closer to NT males, while males with ASD may show patterns closer to NT females, predominantly in regions showing a bias toward enlargement in NT males. It should be noted that sex-related models of ASD may be individually incomplete. It is plausible that both "masculine" and "feminine" processes interact with ASD risk genes in both males and females, and the influence of sex-related processes may vary across the lifespan. Furthermore, these models are not mutually exclusive (e.g., Gender Incoherence may explain some brain patterns, while the Extreme Male Brain model may explain others) and they do not directly explain mechanisms of protection or vulnerability. Finally, growing evidence in NT populations argues against brain sexual dimorphism (Eliot et al., 2021; Joel et al., 2015), a premise of these models when applied to neurobiology, and suggests that each person's "brain mosaics" are the distinct combination of both masculine and feminine processes interacting with individual genetic and environmental factors. However, the Extreme Male Brain (Baron-Cohen, 2002) and Gender Incoherence (Bejerot et al., 2012) models of ASD are widely cited and may inform the search for neurobiological mechanisms underlying female protection/male vulnerability. Thus, while "masculinization" processes may play a role in ASD in females and "feminization" processes may play a role in ASD in males, the search for sex-related mechanisms of protection and vulnerability still warrants consideration of both feminine and masculine processes across males and females with ASD.

3.3. Evidence for developmental dependency of sex-by-diagnosis effect directions

3.3.1. Overview

Across modalities in this review, most studies collapsed across age resulting in a lack of developmental contextualization of findings, with a few notable exceptions (Henry et al., 2018; Kozhemiako et al., 2020, 2019; Zhang et al., 2018). If patterns of age-related variability differ by sex and diagnosis, collapsing across developmental stages in analyses (e. g., childhood, adolescence, adulthood) could mask group differences. For example, few-to-no regional sex-by-diagnosis effects were observed across several broad age-span, cross-sectional morphometric studies, despite large sample sizes (Bedford et al., 2019; Postema et al., 2019; Van Rooij et al., 2018). A similar absence of sex-by-diagnosis effects when collapsing across broad age spans was found for whole-brain rs-fMRI studies (Guo et al., 2019; Henry et al., 2018; Holiga et al., 2019; Kozhemiako et al., 2020, 2019; Smith et al., 2019). Similarly for task-based fMRI, studies collapsing across broad age-spans showed no sex-by-diagnosis differences (Moessnang et al., 2020), while more homogeneous age ranges on similar tasks revealed effects (Kirkovski et al., 2016). DTI studies used more homogeneous age cohorts with respect to developmental stage (e.g., preschool-age or adults), and, in keeping with our hypothesis, more consistently detected sex-by-diagnosis effects (Andrews et al., 2019; Beacher et al., 2012a; Irimia et al., 2017; Nordahl et al., 2015; Zeestraten et al., 2017). Since many studies collapsed across age in their analyses, comparing studies that investigated youth and adult cohorts hints at divergent patterns of sex-by-diagnosis effects across age cohorts. Furthermore, we will highlight a few studies that directly interrogated differing patterns of age-related variability across sex-by-diagnosis groups (Henry et al., 2018; Kozhemiako et al., 2020, 2019), albeit one morphometric study was exploratory in nature and thus did not correct for multiple comparisons (Zhang et al., 2018).

3.3.2. Gray matter structure

Only one sMRI study directly investigated differential effects of age across sex-by-diagnosis groups, examining total GM and subcortical volumes (Zhang et al., 2018). Total GM volume showed an age-by-sex-by-diagnosis effect, such that males with ASD showed patterns suggesting less dramatic age-related declines in GM volume relative to NT

Table 3
Overview of sex differences findings from task-based fMRI studies.

Author	Sample Size Females ASD	NT	Males ASD	NT	n	Age x̄	σ	Range	IQ x̄	σ	Range	Model	Tested?	Findings?	Age tested?	Task	Contrasts	Cover-age?	Summary
Whole-brain Studies																			
Lawrence 2020	39	33	43	39	154	13	3	8–17	108	19	NR	GLM	yes	no	yes - post-hoc	weather prediction task, social reward condition	correct social > incorrect social	whole-brain & nAcc	Pairwise comparisons show ↑ activation to social reward in ASD girls (but not boys) in regions of vlPFC, OFC, anterior insula, OFC. ↑ nAcc activity in ASD girls than ASD boys.
Moessnang 2020	54	66	151	123	394	18	5	7–31	108	13	76–148	GLM	yes	yes	yes - age split	moving shapes (random, goal-directed, mentalizing)	Parametric modulator for ↑ mentalizing	whole-brain & R pSTS dmPFC	In a child-to-adult sample, no sex-by-diagnosis effects found, even when split separately into youth & adult samples.
Kirkovski 2016	14	12	13	11	50	31	9	19–56	111	14	82–139	GLM	yes	yes	no	moving shapes	mentalizing > random/ baseline	whole-brain & mPFC R TPJ	No ROI-based sex-by-diagnosis effects, but whole-brain showed R pSTS ↓ activation during mentalizing in ASD men & ↑ in ASD women
Schneider 2013	13	13	15	15	56	31	9	18–55	112	9	HFA	GLM	no: sex-split	n/a	no	emotional self-related stories	emotion > neutral	whole-brain	Relative to same-sex NT, ↓ activation in ASD women in midbrain/amygdala & ↑ in ASD men in dmPFC during empathizing
ROI-based Studies																			
Bjorns-dotter 2016 disc	4	5	18	12	39	11	3	4–18	105	18	72–141	GLM	no: sex-split	n/a	no	biological motion	coherent > scrambled	disc. sample contrast mask	↓ mean activation in pSTS circuit in ASD boys but not ASD girls for biological motion viewing
Bjorns-dotter 2016 rep	10	5	27	12	54	11	3	5–20	96	19	41–137								
Lai 2019	28	29	29	33	119	28	7	18–45	116	12	75–137	GLM	yes	yes	no	reflective judgments (physical features, self, or queen)	self > other, mentalizing > physical	vmPFC R TPJ	Sex-by-diagnosis effects during self-reflection & mentalizing. Relative to same-sex NT, ↓ activity in ASD men (but not ASD women) in vmPFC & R TPJ.
Beacher 2012	14	16	15	16	61	32	8	adult	33	7	HFA	GLM	yes	yes	no	verbal fluency & mental rotation task	naming > control, mental rotation > control	con-dition effects mask	Sex-by-diagnosis effects for mental rotation. Relative to same-sex NT, ↓ activation in ASD women & ↑ for ASD men in L precuneus & MFG. Inverse pattern in L lingual & MOG.

*autism spectrum disorder (ASD); neurotypical (NT); dependent variables (DVs); general linear model (GLM); medial prefrontal cortex (mPFC); right (R); temporo-parietal junction (TPJ); posterior superior temporal sulcus (pSTS); high funcioning autism (HFA); dorsomedial prefrontal cortex (dmPFC); nucleus accumbens (nAcc); ventrolateral prefrontal cortex (vlPFC), orbitofrontal cortex (OFC); middle frontal gyrus (MFG); middle occipital gyrus (MOG); ventromedial prefrontal cortex (vmPFC)

Table 4
Overview of sex differences findings from DTI studies.

Author	Sample Size Females ASD	NT	Males ASD	NT	n	Demographics Age x̄	σ	Range	IQ x̄	σ	Range	Model	Methods for Sex-Differences Analyses / Sex-by-Diagnosis Effects Tested?	Findings?	Age tested?	Coverage?	DVs	Summary
Whole-brain Studies																		
Andrews 2019	42	26	85	42	195	3	0.5	2–4	79	18	23–129	GLM	yes	yes	yes	whole-brain TBSS	FA/MD/RD/AD	Sex-by-diagnosis effects for AD in clusters of CC & R CR/external capsule with ↓ WM integrity in girls with ASD but not boys with ASD.
Lei 2019	25	15	56	23	119	10	4	4–21	100	20	46–158	GLM	no, sex-split	n/a	no	whole-brain TBSS	FA primary; AD/RD/MD exploratory	↓ FA in youth females with ASD relative to same-sex NT in bilateral cingulum, IFOF, ILF, SLF, uncinate, ATR, CST and forceps major/minor. No differences in males with ASD.
Irimia 2017	55	40	55	43	193	13	4	7–18	100	28	57–149	Multi-var.	yes	yes	no	whole-brain for GM ROIs	connectivity density (CD)	Sex-by-diagnosis effects in youth for CD in lateral temporal, temporo-parietal, & posteromedial cortex. No group-wise post-hoc testing.
Kirkovski 2015	13	12	12	12	49	30	9	21–55	111	14	82–139	GLM	yes	none	no	whole-brain TBSS	FA/MD/AD/RD	No sex-by-diagnosis effects in this small sample.
ROI-based Studies																		
Nor-dahl 2015 T1	21	25	97	44	187	3	0.4	NR	81	18	NR	GLM	yes	yes	yes	CC total & sub-regions	FA/MD/RD/AD	Sex-by-diagnosis effects for CC mean MD/RD/AD with ↓ WM integrity specific to girls with ASD relative to same-sex NT. Effects may show CC sub-region dependency.
T2	15	15	76	30	136	4	0.5	NR	NR		NR							
T3	8	12	34	20	74	5	0.4	NR	NR		NR							
Zee-straten 2017	37	54	61	61	213	27	7	18–52	117	12	73–137	GLM	yes	yes	no	5 frontal & 2 non-frontal tracts	tract mean FA	Sex-by-diagnosis effects for mean FA of frontal-emanating tracts (bilateral anterior/long AF, cingulum, uncinate, IFOF with ↓ WM integrity in men with ASD but not women with ASD.
Beacher 2012	13	15	15	15	58	31	8	NR	33	7	NR	GLM	yes	yes	no	CC, cing., CST, SLF, CR, MCP	tract mean FA/MD	Sex-by-diagnosis effects for mean FA of CC-body, cingulum, CR, SLF.

*autism spectrum disorder (ASD); neurotypical (NT); dependent variables (DVs); general linear model (GLM); tract-based spatial statistics (TBSS); fractional anisotropy (FA); mean diffusivity (MD); radial diffusivity (RD); axial diffusivity (AD); corpus callosum (CC); corona radiata (CR); white matter (WM); inferior fronto-occipital fasciculus (IFOF); inferior longitudinal fasciculus (ILF); superior longitudinal fasciculus (SLF); anterior thalamic radiations (ATR); multivariate (multivar.); cortico-spinal tract (CST); gray matter (GM); not reported (NR); cingulum (cing.); middle cerebellar peduncle (MCP)

males (no difference between female groups). For subcortical volumes, an age-by-sex-by-diagnosis effect was found for hippocampal volumes, such that age-related variability in males with ASD suggested more rapid increases in hippocampal volumes relative to females with ASD, with no differences in age patterns in NT groups (Zhang et al., 2018). Age-dependent sex-by-diagnosis differences in ASD were also found in the striatum. Zhang and colleagues (2018) found a significant age-by-sex-by-diagnosis effect, suggesting atypically reduced right putamen volumes that are most pronounced in adulthood for females with ASD. Given that high levels of variability in subcortical volumes have been found for NT males (Wierenga et al., 2018), longitudinal studies may be particularly useful for characterizing sex differences in striatal structures in ASD.

Cross-study comparison of youth and adult cohorts suggests differential effects of age across sex-by-diagnosis groups for limbic and cerebellar structures (Cauvet et al., 2019; Ecker et al., 2017; Lai et al., 2013; Retico et al., 2016a; Schaer et al., 2015; Supekar and Menon, 2015; Sussman et al., 2015; Westeinde et al., 2019; Zhang et al., 2018). With respect to the parahippocampus, reduced CT has been linked to higher ASD traits specific to male youth with ASD (Cauvet et al., 2019). However, in adults, parahippocampal CT was atypically greater in males with ASD and atypically reduced in females with ASD (Ecker et al., 2017). With respect to the OFC, youth cohorts have shown an association between greater CT and higher ASD traits in females (Westeinde et al., 2019). On the other hand, adult cohorts show some evidence of atypically reduced volume in females with ASD (see split-half supplementary analyses; Lai et al., 2013). Although CT and GM volume are different metrics, they are related (i.e., CT $\times$ SA = CV) and the contrasting effects in youth vs. adults may indicate different developmental trajectories. Regional cerebellar volumes also suggest age-dependent sex-by-diagnosis effects. Specifically, female youth with ASD uniquely showed atypical smaller inferior cerebellar volumes (lobule 8; Sussman et al., 2015) and atypically enlarged crus 1 volumes (Retico et al., 2016b); inverse patterns were observed in adults in a split-half supplementary analysis (Lai et al., 2013). Together, these results highlight age as a potentially important variable when investigating GM structural sex differences in ASD, especially for limbic, cerebellar, and striatal regions.

a. fMRI

Two rs-fMRI studies investigated sex-by-diagnosis group differences in age-related FC variability, finding pervasive differences (Kozhemiako et al., 2020, 2019). These studies used a subsampling approach to estimate a distribution of age-trajectories across males and females with and without ASD, investigating both homotopic (Kozhemiako et al., 2019) and local FC profiles (Kozhemiako et al., 2020). Data-driven multivariate partial least squares was used to estimate group differences explaining maximal variance. For homotopic FC, latent variables revealed the following contrasts ordered according to variance explained: 1) NT females vs. other groups, 2) diagnosis differences, driven more by males, and 3) sex differences in ASD. Visual inspection suggests particular divergence of homotopic FC age patterns in females with ASD within regions associated with default mode and limbic networks. Specifically, females with ASD showed more u-shaped age patterns while other groups showed flatter or inverted u-shape. For local FC, most variance was explained by: 1) ASD females vs. other groups, 2) ASD males vs. other groups, and 3) NT males vs. other groups. Comparing linear age patterns, females with ASD showed weaker negative associations in the limbic and ventral attention networks, stronger negative associations in the default mode and fronto-parietal networks, and stronger positive associations in the visual network. Graph theoretical studies also provide evidence of distinct age-related FC patterns in females with ASD. For example, Henry and colleagues (2018) reported a marginal age-by-sex-by-diagnosis interaction for global modularity. Specifically, while NT females showed u-shaped curvature and NT males showed flatter trajectories, ASD groups showed

inverted u-shaped curvature. For global efficiency, patterns of age curvature differed across diagnostic groups such that ASD showed u-shaped curvature and NT groups showed the inverse (Henry et al., 2018). Of note, age-by-sex-by-diagnosis interactions became significant for both metrics when removing mid-to-older adults, a cohort that showed sparser sampling. In contrast to FC studies, no task-based fMRI studies investigated group differences in patterns of age-related variability. Furthermore, given the limited number of studies and varying methodology, it is not possible to extrapolate different age patterns through cross-study comparison of youth vs. adult cohorts.

Cross-study comparison of youth vs. adult cohorts is challenging for rs-fMRI studies due to their high-dimensional nature (Alaerts et al., 2016; Lawrence et al., 2020a; Yang and Lee, 2018). Even studies utilizing comparable age cohorts (mean age: 14, broad youth-to-adult range) and similar default mode network seeds showed inconsistent results (Alaerts et al., 2016; Yang and Lee, 2018). This may be partially influenced by slight differences in seed choice. For example, Alaerts and colleagues (2016) examined FC of bilateral posterior superior temporal sulcus and posterior cingulate cortex seeds, finding hyper-FC in females with ASD and hypo-FC in males with ASD for subcortical and prefrontal connections. In contrast, Yang and colleagues (2018) investigated medial prefrontal, temporoparietal junction, and precuneus seeds, generally finding hypo-FC in females with ASD and hyper-FC in males with ASD. However, applying developmental contextualization may improve coherence. For example, findings from Kozhemiako et al. (2020) suggest females with ASD may show more rapid decreases in local FC in the default mode network from childhood to young adulthood compared to males with ASD and NT groups. Upon further inspection of the aforementioned discrepant rs-fMRI seed-based findings, many connections showing patterns of hypo-FC in females with ASD and hyper-FC in males with ASD were more "local" connections within the default mode network (e.g., medial prefrontal connections with dorsomedial prefrontal and mid-cingulate cortex; Yang and Lee, 2018). In contrast, effects showing hyper-FC in females with ASD and hypo-FC in males with ASD were generally more distant connections within the default mode or with other networks (Alaerts et al., 2016; Yang and Lee, 2018). Together, these findings highlight the importance of characterizing sex differences in trajectories of FC development, which may shed light on inconsistent patterns of sex-by-diagnosis effects for studies collapsing across age.

a. White matter

For investigations of WM microstructure, no studies directly interrogated differential effects of age across a broad range. Across studies, the direction of sex-by-diagnosis differences and the sensitivity of different diffusional metrics differed as a function of age cohort examined. In youth cohorts, findings suggest atypically reduced WM integrity specific to females with ASD, while adult studies suggest lower WM integrity specific to males with ASD. For example, preschool-aged children showed atypically higher AD in females with ASD (suggesting lower WM integrity) but not in males with ASD for the corpus callosum as well as the right corona radiata and external capsule (Andrews et al., 2019; Nordahl et al., 2015). In an older youth sample, analysis of diagnosis differences separately across male and female groups revealed that FA (but not MD/AD/RD) showed sensitivity to sex differential effects (Lei et al., 2019). Specifically, females with ASD showed atypically lower WM integrity across diffuse projection, commissural, and association tracts; diagnosis differences were not observed in males. In contrast to youth findings suggesting reduced WM integrity specific to females with ASD, adult studies showed the inverse. Specifically, atypically lower FA was found across diffuse tracts in males with ASD but not females (Beacher et al., 2012a; Zeestraten et al., 2017). Speculatively, inconsistent findings in youth vs. adult cohorts suggest sex differential trajectories of WM development in ASD. Consistent with this hypothesis, one cross-sectional sMRI study showed that age modulated the sex-by-

Table 5
Regional sex-by-diagnosis or equivalent effects from primary study analyses observed across methods and dependent metrics for cortical and subcortical GM regions (excludes age-by-sex-by-diagnosis interaction effects).

Study	Modality	Methods	Hypothesis agnostic?	Age	Region (seeds in italics[a])	Hemi.	Metrics	Females	Males
Cauvet 2019	sMRI	Co-twin	Yes	Youth	SFG	L	SAˆ	ASD < NT	ASD ~ NT
Alaerts 2016	rs-fMRI	Univariate	Yes	Broad	SFG - MTG	L - R	ROI-ROI FC	ASD > NT	ASD < NT
Alaerts 2016	rs-fMRI	Univariate	Yes	Broad	SFG - Precuneus	R - L	ROI-ROI FC	ASD > NT	ASD < NT
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*mPFC* - SFG	L	Seed-to-voxel FC	ASD ~ NT	ASD > NT
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*mPFC* - SFG	R	Seed-to-voxel FC	ASD < NT	ASD > NT
Lee 2020	rs-fMRI	Univariate	No - DMN seed	Preschool	*L Amygdala* - dmPFC	L	Seed-to-voxel FC	ASD > NT	ASD < NT
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*mPFC* - dmPFC	L	Seed-to-voxel FC	ASD > NT	ASD ~ NT
Alaerts 2016	rs-fMRI	Univariate	No - DMN seed	Broad	*PCC* - dmPFC	R/L	Seed-to-voxel FC	ASD > NT	ASD < NT
Beacher 2012	Task fMRI	Univariate	Yes	Adult	Premotor	L	Activation	ASD < NT	ASD ~ NT
Alaerts 2016	rs-fMRI	Univariate	Yes	Broad	MFG - ITG	L - L	ROI-ROI FC	ASD > NT	ASD < NT
Alaerts 2016	rs-fMRI	Univariate	No - DMN seed	Broad	*L STS* - MFG/SFG	R	Seed-to-voxel FC	ASD > NT	ASD < NT
Alaerts 2016	rs-fMRI	Univariate	No - DMN seed	Broad	*L STS* - Premotor/Precentral	L	Seed-to-voxel FC	ASD > NT	ASD < NT
Alaerts 2016	rs-fMRI	Univariate	No - DMN seed	Broad	*PCC* – Premotor/Precentral	L	Seed-to-voxel FC	ASD > NT	ASD < NT
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*L TPJ* - SMA	L	Seed-to-voxel FC	ASD < NT	ASD > NT
Alaerts 2016	rs-fMRI	Univariate	Yes	Broad	Frontal pole - STG	L - L	ROI-ROI FC	ASD < NT	ASD > NT
Lee 2020	rs-fMRI	Univariate	No - DMN seed	Preschool	*L Amygdala* - Anterior Prefrontal	L	Seed-to-voxel FC	ASD > NT	ASD ~ NT
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*Precuneus* - IFG (tri)	R	Seed-to-voxel FC	ASD < NT	ASD > NT
Irimia 2018	sMRI/DTI	Multivariate	Yes	Youth	Orbital IFG	L	CD	NR	NR
Lai 2019	Task fMRI	Univariate	No - DMN ROIs	Adult	vmPFC	R/L	Activation	ASD ~ NT	ASD < NT
Schaer 2015	sMRI	Univariate	Yes	Broad	vmPFC/OFC	R	LGI	ASD ~ NT	ASD < NT
Westeinde 2020	sMRI	Co-twin	No - RRBI ROIs	Youth	Orbital gyrus	R	CT/CTˆ	ASD > NT	ASD ~ NT
Irimia 2018	sMRI/DTI	Multivariate	Yes	Youth	Medial orbital sulcus	R	CT	NR	NR
Irimia 2018	sMRI/DTI	Multivariate	Yes	Youth	Straight Gyrus	Rˆ/L	CT/CV, CDˆ	NR	NR
Postema 2019	sMRI	Univariate	Yes	Broad	rACC	n/a	CT Assymmetry	ASD ~ NT	ASD < NT
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*mPFC* - MCC	L	Seed-to-voxel FC	ASD < NT	ASD > NT
Cauvet 2019	sMRI	Co-twin	Yes	Youth	Superior precentral sulcus	L	CV/SA	ASD < NT	ASD ~ NT
Cauvet 2019	sMRI	Co-twin	Yes	Youth	Subcentral gyrus/sulcus	R	SA	ASD < NT	ASD ~ NT
Alaerts 2016	rs-fMRI	Univariate	Yes	Broad	Postcentral - Vermis 8	L - L	ROI-ROI FC	ASD > NT	ASD < NT
Westeinde 2020	sMRI	Co-twin	No - RRBI ROIs	Youth	Intraparietal sulcus	R	CT	ASD > NT	ASD ~ NT
Beacher 2012	sMRI	Univariate	Yes	Adult	IPL/rolandic operculum	R	VBM	ASD ~ NT	ASD < NT
Beacher 2012	Task fMRI	Univariate	Yes	Adult	IPL	L/R	Activation	ASD < NT	ASD > NT
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*L TPJ* - IPL	L	Seed-to-voxel FC	ASD > NT	ASD < NT
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	SMG	R/L	CD	NR	NR
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*mPFC* - Angular	R	Seed-to-voxel FC	ASD < NT	ASD > NT
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	Angular gyrus	R/L	CD	NR	NR
Lai 2019	Task fMRI	Univariate	No - DMN ROIs	Adult	TPJ	R	Activation	ASD ~ NT	ASD < NT
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	Jensen's sulcus	R/L	CD	NR	NR
Lawrence 2020b	rs-fMRI	Univariate	No - DMN/SN/FPN	Youth	*Orbito-insular* - Precuneus/PPC	R - L	Seed-to-voxel FC	ASD ~ NT	ASD > NT
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	Precuneus	R/L	CD	NR	NR
Beacher 2012	Task fMRI	Univariate	Yes	Adult	Precuneus	L	Activation	ASD ~ NT	ASD > NT
Alaerts 2016	rs-fMRI	Univariate	Yes	Broad	Precuneus - Vermis 8	R - L	ROI-ROI FC	ASD > NT	ASD < NT
Alaerts 2016	rs-fMRI	Univariate	No - DMN seed	Broad	*L STS* - PCC/Paracentral	L	Seed-to-voxel FC	ASD > NT	ASD < NT
Lee 2020	rs-fMRI	Univariate	No - DMN seed	Preschool	*R Amygdala* - PCC	R	Seed-to-voxel FC	ASD < NT	ASD ~ NT
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*R TPJ* - PCC	L	Seed-to-voxel FC	ASD < NT	ASD > NT
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*mPFC* - PCC	L	Seed-to-voxel FC	ASD < NT	ASD > NT
Irimia 2018	sMRI/DTI	Multivariate	Yes	Youth	Isthmus cingulate	R/L	CV/SA	NR	NR
Cauvet 2019	sMRI	Co-twin	Yes	Youth	Subparietal sulcus	R	SAˆ	ASD < NT	ASD ~ NT
Cauvet 2019	sMRI	Co-twin	Yes	Youth	Pericallosal sulcus	R	SA	ASD < NT	ASD ~ NT
Irimia 2018	sMRI/DTI	Multivariate	Yes	Youth	Pericallosal sulcus	Lˆ	SA	NR	NR
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	Parieto-occipital sulcus	R/L	CD	NR	NR
Cauvet 2019	sMRI	Co-twin	Yes	Youth	STG	R/L	CV/SA	ASD < NT	ASD ~ NT
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	STG	R/L	CD	NR	NR
Irimia 2018	sMRI/DTI	Multivariate	Yes	Youth	STG	R	Curvature	NR	NR
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	STS	R/L	CD	NR	NR
Ecker 2017	sMRI	Univariate	Yes	Adult	MTG/STS	R	CT	ASD < NT	ASD > NT

Table 5 (*continued*)

Study	Modality	Methods	Hypothesis agnostic?	Age	Region (*seeds in italics*[a])	Hemi.	Metrics	Females	Males
Kirkovski 2016	Task fMRI	Univariate	No - DMN ROIs	Adult	pSTS	R	Activation	ASD > NT	ASD < NT
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	Planum polar	R/L	CD	NR	NR
Cauvet 2019	sMRI	Co-twin	Yes	Youth	MTG	L	CV/SA	ASD < NT	ASD ~ NT
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	MTG	R/L	CD	NR	NR
Ecker 2017	sMRI	Univariate	Yes	Adult	MTG/ITG, fusi., ling., parahippo.	L	CT	ASD < NT	ASD > NT
Beacher 2012	Task fMRI	Univariate	Yes	Adult	ITG	L	Activation	ASD ~ NT	ASD > NT
Ecker 2017	sMRI	Univariate	Yes	Adult	ITG, fusi., ling., parahippo., occ.	R	CT	ASD < NT	ASD > NT
Irimia 2018	sMRI/DTI	Multivariate	Yes	Youth	TP	R/L	Curvature/CT	NR	NR
Alaerts 2016	rs-fMRI	Univariate	Yes	Broad	TP - MFG	R - R	ROI-ROI FC	ASD > NT	ASD < NT
Cauvet 2019	sMRI	Co-twin	Yes	Youth	Parahippocampus	R	CT	ASD ~ NT	ASD ~ NT
Irimia 2018	sMRI/DTI	Multivariate	Yes	Youth	Parahippocampus	R/L^	CV	NR	NR
Sussman 2015	sMRI	Univariate	Yes	Youth	Hippocampus	R/L	Volume^	ASD < NT	ASD ~ NT
Alaerts 2016	rs-fMRI	Univariate	No - DMN seed	Broad	*R STS* - Hippo/thalamus	R/L	Seed-to-voxel FC	ASD > NT	ASD < NT
Alaerts 2016	rs-fMRI	Univariate	No - DMN seed	Broad	*L STS* - Hippo/fusiform/thalamus	L	Seed-to-voxel FC	ASD > NT	ASD < NT
Lee 2020	rs-fMRI	Univariate	No - DMN seed	Preschool	*L Amygdala* - lingual	L	Seed-to-voxel FC	ASD < NT	ASD > NT
Lee 2020	rs-fMRI	Multivariate	No - DMN seed	Youth	Amygdala	L	MDMR	n/a	n/a
Alaerts 2016	rs-fMRI	Univariate	No - DMN seed	Broad	*L STS* - Insula/putamen/thalamus	R	Seed-to-voxel FC	ASD > NT	ASD < NT
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	Short insular gyrus	R/L	CD	NR	NR
Cauvet 2019	sMRI	Co-twin	Yes	Youth	Anterior occipital sulcus	L	CV^	ASD ~ NT	ASD > NT
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*Precuneus* - SOG	R	Seed-to-voxel FC	ASD > NT	ASD ~ NT
Beacher 2012	Task fMRI	Univariate	Yes	Adult	MOG	R	Activation	ASD < NT	ASD > NT
Irimia 2018	sMRI/DTI	Multivariate	Yes	Youth	Occipital pole	R/L	SA	NR	NR
Yang 2018	rs-fMRI	Univariate	No - DMN seed	Broad	*Precuneus* - cuneus	L	Seed-to-voxel FC	ASD > NT	ASD < NT
Irimia 2018	sMRI/DTI	Multivariate	Yes	Youth	Cuneus	R	SA	NR	NR
Irimia 2017	DTI/sMRI	Multivariate	Yes	Youth	Cuneus	R/L	CD	NR	NR
Smith 2019	rs-fMRI	Univariate	No - Cerebell. ROI	Broad	Cerebellum crus II	L^	IC	ASD > NT	ASD < NT
Smith 2019	rs-fMRI	Univariate	No - Cerebellum ROI	Broad	Cerebellum lobule 8A/B	R^	IC	ASD > NT	ASD < NT
Sussman 2015	sMRI	Univariate	Yes	Youth	Cerebellum (inferior 8B)	R/L	Volume	ASD < NT	ASD ~ NT
Sussman 2015	sMRI	Univariate	Yes	Youth	Cerebellum (inferior 10)	R/L	Volume^	ASD ~ NT	ASD ~ NT

*hypothesis agnostic (hypoth. agnostic); default mode network (DMN); hemisphere (hemi); resting-state fMRI (rs-fMRI); dorsomedial prefrontal cortex (dmPFC); dorsal prefrontal cortex (DPFC); left (L); functional connectivity (FC); autism spectrum disorder (ASD); neurotypical (NT); medial prefrontal cortex (mPFC); posterior cingulate cortex (PCC); right (R); structural MRI (sMRI); surface area (SA); dorsolateral prefrontal cortex (dlPFC); superior frontal gyrus (SFG); temporo-parietal junction (TPJ); supplementary motor area (SMA); restricted/repetitive behaviors/interests (RRBI); diffusion tensor imaging (DTI); cortical thickness (CT); region of interest (ROI); middle temporal gyrus (MTG); middle frontal gyrus (MFG); inferior temporal gyrus (ITG); ventromedial prefrontal cortex (vmPFC); ventro-median prefrontal cortex (VMPFC); orbitofrontal cortex (OFC); local gyrification index (LGI); salience network (SN); fronto-parietal network (FPN); cortical volume (CV); connectivity density (CD); not reported (NR); ventrolateral prefrontal cortex (vlPFC/VLPFC); inferior frontal gyrus (IFG); rostral anterior cingulate (rACC); prefrontal cortex (PFC); superior temporal sulcus (STS); posterior STS (pSTS); fusi. (fusiform); ling. (lingual); parahippo. (parahippocampus); occ. (occipital cortex); temporal pole (TP); posterior parietal cortex (PPC); mid-cingulate cortex (MCC); hippo. (hippocampus); intrinsic connectivity (IC); inferior parietal lobule (IPL); voxel-based morphometry (VBM); supramarginal gyrus (SMG); dorsal attention network (DAN); superior occipital gyrus (SOG); middle occipital gyrus (MOG); superior temporal gyrus (STG); orbitofrontal gyrus (OFG); ^indicates a marginal sex-by-diagnosis effect; [a]italics indicates the region was selected as a hypothesis-driven seed in rs-fMRI seed-to-voxel analysis; [b]for seed-to-voxel analysis, DMN assignment is based off of the cluster/ROI rather than the study-selected seed; [c]regions falling outside the DMN are assigned a network based on visual inspection of spatial overlap with Yeo et al. (2011) 7-network parcellation for cortical regions and Ji et al. (2019) parcellation for subcortical regions.

Table 6
Regional sex-by-diagnosis or equivalent effects observed across modalities investigating WM effects.

Study	Modality	Methods	Hypoth. agnostic?	Age	Region (seeds in italics)	Hemi.	Metrics	Females	Males
Zeestraten 2017	DTI	Univariate	No - Frontal tracts	Adult	AF (Anterior Seg.)	R/L	mean FA	ASD ~ NT	ASD < NT
Zeestraten 2017	DTI	Univariate	No - Frontal tracts	Adult	AF (Long Seg.)	L	mean FA	ASD ~ NT	ASD < NT
Zeestraten 2017	DTI	Univariate	No - Frontal tracts	Adult	AF (Posterior Seg.)	R^/L^	mean FA	ASD ~ NT	ASD < NT
Lai 2013	sMRI WM	Univariate	Yes	Adult	AF	R	VBM	ASD > NT	ASD ~ NT
Beacher 2012	DTI	Univariate	Yes	Adult	SLF (AF Long)	R^/L^	mean FA	ASD ~ NT	ASD~<NT
Beacher 2012	DTI	Univariate	Yes	Adult	Cingulum	R/L	mean FA	ASD ~ NT	ASD < NT
Zeestraten 2017	DTI	Univariate	No - Frontal tracts	Adult	Cingulum	R/L	mean FA	ASD ~ NT	ASD < NT
Lai 2013	sMRI WM	Univariate	Yes	Adult	Cingulum	R/L	VBM	ASD > NT	ASD ~ NT
Zeestraten 2017	DTI	Univariate	No - Frontal tracts	Adult	ILF	R^/L^	mean FA	ASD ~ NT	ASD < NT
Lai 2013	sMRI WM	Univariate	Yes	Adult	ILF	R/L	VBM	ASD > NT	ASD ~ NT
Beacher 2012	DTI	Univariate	Yes	Adult	CR	R/L	mean FA	ASD ~ NT	ASD < NT
Andrews 2019	DTI	Univariate	Yes	Preschool	CR	R	RD	ASD > NT	ASD < NT
Lai 2013	sMRI WM	Univariate	Yes	Adult	Internal capsule	R/L	VBM	ASD ~ NT	ASD > NT
Zeestraten 2017	DTI	Univariate	No - Frontal tracts	Adult	UF	R/L	mean FA	ASD ~ NT	ASD < NT
Andrews 2019	DTI	Univariate	Yes	Preschool	Anterior external capsule (UF/IFOF)	R	RD	ASD > NT	ASD < NT
Zeestraten 2017	DTI	Univariate	No - Frontal tracts	Adult	IFOF	R/L	mean FA	ASD ~ NT	ASD < NT
Lai 2013	sMRI WM	Univariate	Yes	Adult	CC - Splenium	R/L	VBM	ASD > NT	ASD ~ NT
Nordahl 2015	DTI	Univariate	No - CC ROI	Preschool	CC - Orbitofrontal	n/a	Cross-sectional area	ASD ~ NT	ASD < NT
Nordahl 2015	DTI	Univariate	No - CC ROI	Preschool	CC - Ant./Sup. Frontal	n/a	Cross-sectional area	ASD < NT	ASD ~ NT
Nordahl 2015	DTI	Univariate	No - CC ROI	Preschool	CC - Post. Parietal	n/a	Cross-sectional area	ASD < NT	ASD ~ NT
Nordahl 2015	DTI	Univariate	No - CC ROI	Preschool	CC	n/a	MD/RD/AD	ASD > NT	ASD ~ NT
Andrews 2019	DTI	Univariate	Yes	Preschool	CC	n/a	RD	ASD > NT	ASD < NT

*white matter (WM); hypoth. (hypothesis); default mode network (DMN); hemi. (hemisphere); diffusion tensor imaging (DTI); autism spectrum disorder (ASD); neurotypical (NT); arcuate fasciculus (AF); seg. (segment); right (R); left (L); structural MRI (sMRI); voxel-based morphometry (VBM); fractional anisotropy (FA); superior longitudinal fasciculus (SLF); inferior longitudinal fasciculus (ILF); corona radiata (CR); radial diffusivity (RD); uncinate fasciculus (UF); corpus callosum (CC); ant. (anterior); sup. (superior); post. (posterior); mean diffusivity (MD); axial diffusivity (AD); inferior fronto-occipital fasciculus (IFOF); ^indicates a marginal sex-by-diagnosis effect

diagnosis differences in WM volume (Zhang et al., 2018). Age-related variability in males with ASD suggested more dramatic increases in WM volume across development relative to females with ASD, while no age-by-diagnosis effects were observed for NT groups. However, the two DTI studies examining age effects focused on preschool-age development and showed similar trajectories across sex and diagnosis groups (Andrews et al., 2019; Nordahl et al., 2015). Thus, further studies examining differential age trajectories for WM microstructure are needed across broader age ranges, including adolescent development.

3.4. Studies show evidence in line with the female protective effect

Many studies in this review suggest more atypical brain structure and function in females with ASD. These findings were generally observed in studies examining diagnosis differences separately across males and females. Such investigations may be insightful for detecting diagnosis effects that differ in males and females with ASD, but do not reach threshold for interaction. Findings of more atypical brain features in females with ASD are compatible with the female protection hypothesis (Werling and Geschwind, 2013), which posits that females require more ASD-related pathology to reach diagnostic threshold. Importantly, more atypical brain features in females with ASD could reflect compensatory processes or be a byproduct of ASD pathology. One study in this review conducted a more direct interrogation of mechanisms underlying female protection in ASD by examining sex differences in associations between reward circuit FC and ASD genetic risk load as well as links with symptom severity (elaborated on below; Hernandez et al., 2020).

With respect to morphometric investigations, females with ASD have shown some evidence of greater ASD-related brain abnormality across development. In early development, girls with ASD show more widespread diagnosis effects for regional brain volumes (Retico et al., 2016a) and more atypical volumetric trajectories (Schumann et al., 2010). Similarly, ROI-based studies investigating amygdala volumes have shown that girls with ASD have a greater magnitude of volumetric enlargement relative to NT (Schumann et al., 2009), although not at sex-by-diagnosis thresholds (Nordahl et al., 2020). In older youth and adults, two co-twin morphometry studies found more widespread regional associations with ASD traits in females with ASD compared to males with ASD (Cauvet et al., 2019; Westeinde et al., 2019). In a well-powered study investigating a broad age range (median age: 14 years), females with ASD showed more pervasive ASD-related CT abnormalities with accompanying larger effect sizes than males (Bedford et al., 2019). Finally, adult females with ASD have shown more pervasive abnormalities of ventral temporo-occipital CT compared to males with ASD, despite comparable symptom severity and even after controlling for IQ (Ecker et al., 2017).

There is also some evidence of greater functional brain differences in females with ASD. In early development, an ROI-based study found more atypical left amygdala FC in females with ASD compared to males (Lee et al., 2020). In broad age-span samples, females with ASD have shown more pervasive atypical patterns of age variability in local FC (Kozhemiako et al., 2020). Similarly, females with ASD have shown larger effect sizes for atypically reduced intrinsic DMN FC compared to NT counterparts (Ypma et al., 2016), albeit males with ASD show the lowest levels across all groups. In contrast, other FC studies show similar diagnosis effects across males and females. For example, similar effect
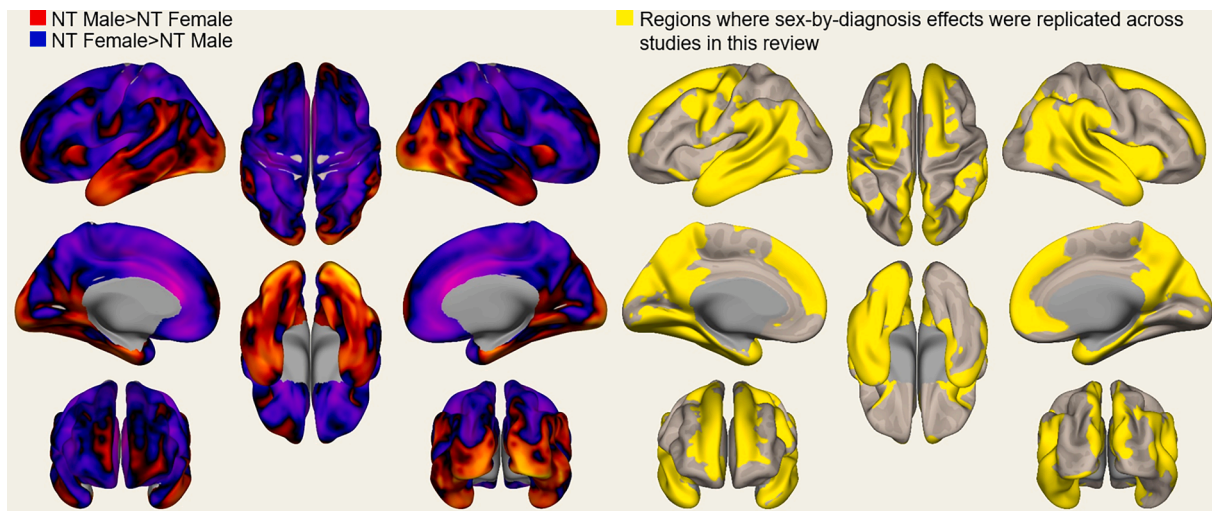
Fig. 3. In neurotypical adults, regions showing a reproducible male bias toward volumetric enlargement (Liu et al., 2020) overlap with regions showing replicable sex-by-diagnosis differences in this review. These observations suggest that processes involved in brain "masculinization" may substantially contribute to sex-by-diagnosis gray matter effects across studies. However, this does not preclude a role for "feminization" processes in brain-based sex differences in ASD, with evidence suggesting their role in female protection in ASD (see section 4.1 and 4.2). Left panel: Sex differences in gray matter volume in a large sample of neurotypical adults (figure generated using shared, uncorrected t-map from Liu et al., 2020: https://www.neurovault.org/images/303304/). Right panel: Regions implicated in significant gray matter sex-by-diagnosis differences (regardless of the effect direction) that were found across two or more studies. Mask was generated using WFU PickAtlas (Maldjian et al., 2003) in SPM-12, regions were marked using AAL (Tzourio-Mazoyer et al., 2002).

sizes were generally found for male vs. female diagnosis differences for within- and between-network FC (Oldehinkel et al., 2019). For task-based studies, two investigations analyzed diagnosis differences separately across males and females and found pervasive atypical activation specific to females with ASD for social tasks (Lawrence et al., 2020b; Schneider et al., 2013). These effects were localized to regions associated with the limbic and ventral attention networks.

Only one study of WM microstructure investigated diagnosis effects separately across groups. Despite comparable symptom severity across groups, this study revealed pervasive differences in WM microstructure suggesting reduced integrity specific to youth females with ASD compared to NT counterparts. No differences were observed between male groups. These findings were observed across association tracts (bilateral cingulum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus), projection tracts (bilateral anterior thalamic radiations and cortico-spinal tract), and commissural tracts (forceps major and minor). Together, findings across sMRI, fMRI, and DTI studies show evidence of more atypical brain structure and function in females with ASD vs. males with ASD when compared to NT counterparts.

Only one study directly investigated mechanisms underlying potential female protection, examining sex differential FC-genetic risk load (OXTR risk alleles) associations for reward circuitry as well as links with ASD symptom severity (Hernandez et al., 2020). They found that sex modulated associations between reward circuit FC and genetic risk only in ASD participants. Compared to males with ASD, females with ASD showed more positive associations between genetic risk and nucleus accumbens FC with striatal regions and the bilateral frontal poles. Furthermore, left frontal pole-nucleus accumbens FC was linked to reduced symptom severity in females with ASD. These findings directly parallel prior observations in NT males (Hernandez et al., 2017), potentially suggesting some patterns of "male-typical" reward circuitry engagement in females with ASD to compensate for social difficulties.

3.5. Dimensional vs. categorical measures may show distinct sensitivity

Categorical (i.e., ASD diagnosis vs. no ASD diagnosis) and dimensional (i.e., viewing autistic traits/symptoms continuously) approaches

may reveal distinct brain features of ASD (Andrews et al., 2020; Elton et al., 2016). Furthermore, given phenotypic heterogeneity within and across sexes in ASD, dimensional measures may show more sensitivity for detecting brain features related to core ASD traits. Importantly, given the focus of this review on characterizing sex differences across the lifespan, dimensional measures will be critical for biomarker discovery to predict sex differences in symptom course and risk trajectories. To highlight this, a recent longitudinal DTI study in ASD suggests that tracts showing categorical differences in developmental trajectories are distinct from those predicting symptom course (Andrews et al., 2020).

Many studies in this review conducted post-hoc examination of symptom associations for regions showing differences in their primary categorical analyses of sex-by-diagnosis effects. However, only a handful of studies examined both categorical and dimensional associations with brain features in their primary whole-brain analyses of sex differences in ASD (Bedford et al., 2016; Kozhemiako et al., 2020, 2019; Moessnang et al., 2020; Oldehinkel et al., 2019). In terms of morphometry, one study showed more widespread ASD-related effects in females using dimensional vs. categorical measures of symptom severity (Bedford et al., 2019). Specifically, females with ASD showed positive associations between CT and symptom severity in regions associated with default mode, ventral attention, and limbic networks; in contrast, case-control comparison revealed only sparse effects. In contrast, dimensional analyses in males largely mirrored categorical diagnosis findings. FC studies also show some evidence of distinct sensitivity of dimensional measures. For example, symptom severity was positively linked to higher local FC in the limbic and ventral attention networks across ASD and NT females, while categorical comparison revealed higher local FC in females only in the ventral attention network. For males with ASD, higher somatomotor FC was found in both categorical and dimensional analyses. Of note, limbic network FC was positively linked to Autism Diagnostic Observation Schedule – 2nd Edition scores in females with ASD across all three subscales (communication, social, and stereotyped behaviors/restricted interests) but to self-reported autistic trait levels in NT females, highlighting the influence of measurement technique/tool on findings. Other studies did not reveal sex-differential associations with symptom severity for measures of within- and between-network FC (Oldehinkel et al., 2019) or task-related activation during mentalizing

(Moessnang et al., 2020). Together, these studies show some evidence suggesting distinct sensitivity of dimensional measures for detecting structural and functional brain differences related to ASD in females.

3.6. The benefits of well-controlled designs and multivariate approaches

For morphometric studies, more pervasive sex-by-diagnosis effects have been observed across studies using well-controlled designs (e.g., co-twin; Cauvet et al., 2019; Westeinde et al., 2019) and multivariate approaches (Irimia et al., 2018, 2017), despite collapsing across age. Co-twin designs measure associations between ASD symptom severity and brain measures, thus controlling for heterogeneity that often confounds cross-sectional comparisons (e.g., age, sex, shared-environment and genetics). Furthermore, these studies examine dimensional (rather than categorical) associations with ASD, which may add to their distinct sensitivity. To date, two studies have used co-twin designs to interrogate sex differences in cortical morphometry, both showing pervasive associations with ASD traits in females but not males (Cauvet et al., 2019; Westeinde et al., 2019).

Similarly, multivariate approaches can improve statistical power in neuroimaging analyses by incorporating information about inter-regional covariance patterns and mitigating stringent correction associated with independent testing across voxels, vertices, or atlas regions (Habeck, 2010). For example, Irimia and colleagues (2018) used support vector machines to classify diagnosis differences on a high-dimensional feature set (whole-brain atlas maps for CV, CT, SA, curvature, and connectivity density) with balanced male-to-female representation. Using this approach, they found that many classifying features showed post-hoc sex-by-diagnosis interactions. Importantly, different metrics showed higher regional classifying performance than others (e.g., curvature interaction effects in the temporal pole were stronger than CT). It is plausible that the use of multivariate approaches with multiple morphometric features may further enhance sensitivity by identifying structural characteristics that are robust to developmental effects in broad youth-to-adult samples.

4. Discussion

The primary objectives of this review were to: 1) integrate the literature on neuroimaging-based sex differences in ASD from a developmental lens and 2) identify promising future directions for biomarker discovery of ASD in females. Across studies in this review, there was a general lack of developmental contextualization. However, this review highlights growing evidence suggesting developmentally distinct sex-by-diagnosis differences in brain structure and function; thus, collapsing across age may mask sex differences in ASD. Converging evidence across modalities shows a predominance of sex-by-diagnosis effects in regions that show sex differences in NT cohorts, including limbic, default mode, ventral attention, visual, and cerebellar regions. When examining replicable effects across studies, visual inspection of brain regions showing sex-by-diagnosis differences in ASD predominantly overlapped with regions showing a male > female GM volumetric bias in a study of adult NT sex differences (Liu et al., 2020). This observation provides evidence in line with the Gender Incoherence model of ASD (Bejerot et al., 2012), suggesting the brain mosaic of females with ASD may show some regional patterns more similar to NT males and the inverse for males with ASD. However, this does not preclude the role of "feminization" processes in females with ASD or "masculinization" processes in males with ASD in female protection/male vulnerability. Finally, a great deal of evidence in this review suggests that females with ASD show more atypical brain structure and function when compared to NT counterparts, in line with the female protective effect. However, only one study was found that examined brain circuits implicated in "protection" (Hernandez et al., 2020) by investigating sex differences in FC-genetic risk associations and relationships with ASD core symptoms. Finally, we highlight that studies

using dimensional measures of ASD and those using multivariate analysis approaches to investigate sex differences show distinct sensitivity and informativeness above and beyond categorical investigations.

4.1. An endocrine perspective on brain-based sex differences in ASD

Reproductive steroids can act on nearly every aspect of neuronal functioning, including synaptic wiring, excitability, gene transcription, intracellular regulation, neurotransmitter regulation, and even the formation of network-level circuits (Rubinow and Schmidt, 2019). Given that the vast majority of genetic polymorphisms implicated in ASD are associated with neuronal functioning (Ferri et al., 2018), it is unsurprising that circuits generally showing sex differences in NT also show sex-by-diagnosis differences in ASD. There is also accumulating evidence suggesting a hormonal influence on ASD. For example, higher rates of hormone dysfunction disorders are observed in ASD, including precocious puberty, dysmenorrhea, polycystic ovarian syndrome (Ferri et al., 2018), and premenstrual dysphoric disorder (Lever and Geurts, 2016). Thus, interpreting brain-based sex differences in ASD from an endocrine and genetic sex perspective may reveal new targets for future basic science and biomarker research. To date, most human research on the effects of sex steroids on the brain comes from sMRI studies (Bakker, 2018; Rehbein et al., 2020; Tan et al., 2020). Notably, evidence suggests that sex steroids influence brain structure in regions that often overlapped with those showing sex-by-diagnosis differences in this review (Tan et al., 2020). Specifically, a recent study in NT adults found that sex-steroid receptor allele efficiency influenced regional GM and WM volumes, predominantly within regions of the limbic, ventral attention, and default mode networks as well as across several projection and association WM tracts (Tan et al., 2020). The overlap between regions showing NT sex differences and regions expressing sex-by-diagnosis effects in this review may suggest an interaction between sex steroids and ASD-related genetics in brain development.

There is some evidence to suggest that regional brain volumes in ASD might be disproportionally affected by androgen exposure, in particular during early development. For example, it has been found that ventromedial prefrontal and dorsal anterior cingulate volumes are modulated by androgen receptor (AR) allele efficiency (Tan et al., 2020). In this review, females with ASD showed an association between higher ASD symptom severity and thicker ventromedial prefrontal and dorsal anterior cingulate cortices (Bedford et al., 2019). This association was not observed in males with ASD, perhaps reflecting a ceiling effect for androgen exposure. With respect to WM, AR allele efficiency in NT adults showed the strongest and most pervasive volumetric associations across sex steroid receptors, in particular for projection tracts (Tan et al., 2020). An early developmental study highlights atypically higher FA in ASD, both in females and males (Andrews et al., 2019), with the strongest diagnosis effects in a cluster overlapping with WM regions showing strong AR effects (left anterior corona radiata; Tan et al., 2020). However, older female youth with ASD showed reduced FA compared to NT counterparts across diffuse tracts (Lei et al., 2019), which may be attributable to inverse effects of estrogen receptor (ER) alpha on WM development (Tan et al., 2020). Furthermore, cross-sectional evidence suggests greater increases in total WM volume in males with ASD relative to females with ASD and NT groups (Zhang et al., 2018), which may reflect compounding effects of pubertal androgen exposure in males with ASD. Androgens may also influence NT sex differences in visuospatial task performance, with males generally showing an advantage, as well as underlying brain activation patterns (e.g., greater inferior parietal activation for mental rotation; Bakker, 2018). In line with this, adult men with ASD showed even greater activation than NT counterparts in the inferior parietal lobule for mental rotation (Beacher et al., 2012b). These findings align with evidence suggesting atypically high androgen exposure during early development across sexes in ASD, which may compound across development in males with ASD (Ferri et al., 2018).

Developmental effects of androgens and estrogens may help explain

discrepant sex-by-diagnosis effects observed across age cohorts in this review. Common to both AR and ER, volumes of the hypothalamus, temporal, insular, and rostral prefrontal cortex were sensitive to allele efficiency (Tan et al., 2020). Furthermore, AR vs. ER allele efficiency display inverse associations with regional volumes. Multivariate studies investigating adolescent sex differences in ASD found that many of these (or proximal) regions showed sex-by-diagnosis morphometric differences (Irimia et al., 2018, 2017). When the direction of sex-by-diagnosis effects were reported, adolescent/adult cohorts showed smaller middle temporal CV/SA/CT in females with ASD vs. NT females and inverse patterns in males (Cauvet et al., 2019; Ecker et al., 2017). This region is generally smaller in NT females than NT males (Ritchie et al., 2018; Tan et al., 2020), suggesting an exaggeration of regional sex differences. Speculatively, given higher levels of circulating androgens in males and estrogens in females across NT development, in particular during puberty (Sisk and Foster, 2004), this may suggest atypical levels or sensitivity in ASD. This is also supported by cross-sectional evidence suggesting attentuated declines in total GM volume from childhood to adulthood in males with ASD relative to NT males (Zhang et al., 2018). To date, no studies have investigated the role of androgen and estrogen exposure on brain development in ASD, although these findings suggest a possible sex, age, and diagnosis-dependent influence on the brain.

Specific to estrogen receptor beta (ERβ), normal variation in allele efficiency predicts regional brain volumes only in females (Tan et al., 2020). Regions uniquely associated with ERβ allele efficiency in NT women included the frontal poles, posterior cingulate and precuneus, right temporal and insular cortex, and regional striatal volumes (Tan et al., 2020). Greater reward circuit FC with the striatum and frontal pole showed positive associations with genetic risk in females with ASD, but negative associations in males with ASD. Furthermore, frontal pole and reward circuit FC in females with ASD was linked to reduced symptom severity (Hernandez et al., 2020). These findings suggest a

potentially protective role of ERβ in females with ASD.

In line with this observation, post-mortem tissue analysis has shown reduced ERβ, associated coactivators, and enzymes (aromatase) in the superior frontal gyrus of adolescent males with ASD (Crider et al., 2014). Another post-mortem study found that reduced aromatase in the prefrontal cortex was linked to lower levels of a protein byproduct of RORA (Nguyen et al., 2010), an ASD-risk gene that is modulated by sex hormones (Ferri et al., 2018). One potential mechanism of protection via ERβ is through synaptic plasticity, a hypothesis that is not new to the study of sex differences in ASD (Mottron et al., 2015). ERβ also plays a fundamental role in female pubertal development by activating kiss-peptins, which trigger hormonal transitions (Pineda et al., 2010). This may help explain distinct trajectories of pubertal symptom improvement in females with ASD (Wagner et al., 2019), especially given the importance of ERβ in the developmental tuning of cognitive-affective brain networks (Rubinow and Schmidt, 2019). Thus, ERβ may interact with ASD risk genes to produce sex differences in brain structure and function, potentially contributing to female protection given a greater abundance of estrogens. However, ERβ polymorphisms have also been linked to conditions that show higher co-morbidity in females with ASD (Weir et al., 2020; Westwood and Tchanturia, 2017), including cardiovascular disease (Ogawa et al., 2000; Rexrode et al., 2007), anorexia nervosa (Eastwood et al., 2002; Timko et al., 2019), and adolescent depression (Geng et al., 2007). This evidence suggests that, while ERβ may be protective in ASD, it may also be associated with risk for other co-morbid conditions. Finally, sex steroid polymorphisms, in particular ERβ, have been implicated in gender dysphoria (Fernández et al., 2018), a condition that shows high prevalence in ASD (Glidden et al., 2016). Importantly, other ovarian hormones including progesterone and GABA-mediating hormones (allopregnanolone and DHEAS) influence brain development in females and may play a role in female protection in ASD, but their effects on brain development remain less well-studied (Rehbein
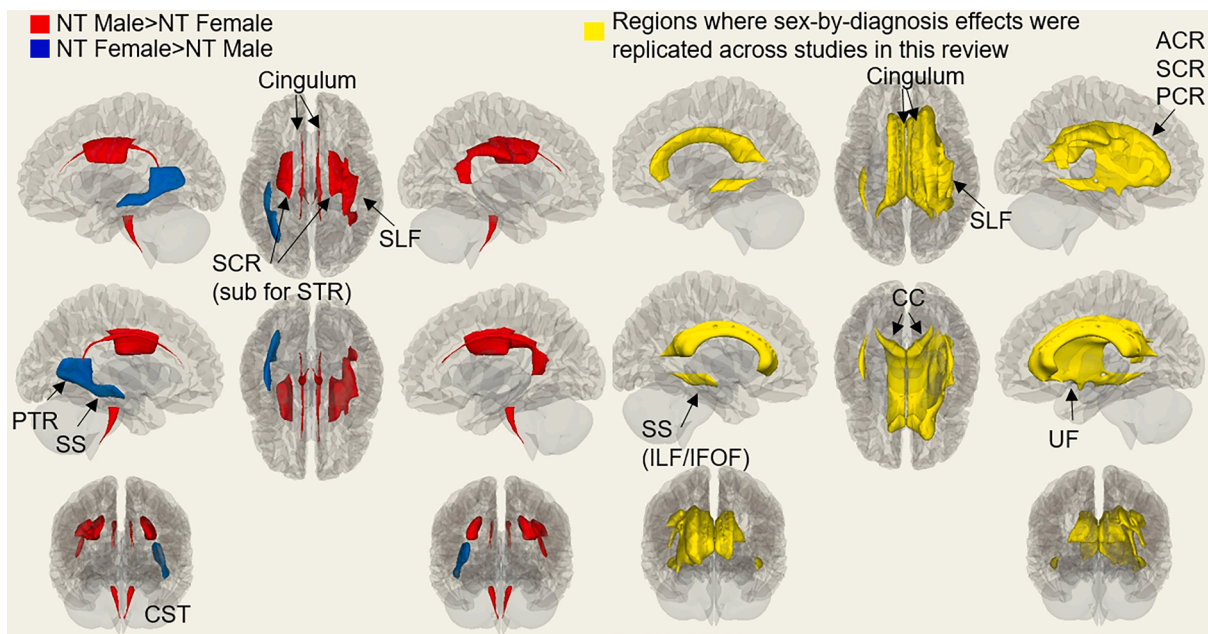

Fig. 4. In neurotypical adults, tracts that have shown both male > female and female > male microstructural integrity (Ritchie et al., 2018) overlapped with tracts implicated in sex-by-diagnosis differences in ASD across two or more studies. Specifically, tracts overlapping with those observed in neurotypical sex differences include the right superior longitudinal fasciculus, bilateral cingulum, and sagittal stratum (ILF/IFOF). Importantly, given the limited number of studies and potentially age-dependent sex-by-diagnosis differences, the direction of interaction effects were inconsistent across studies in this review. Left panel: Tracts having shown significant sex differences in FA in neurotypical adults when controlling for total brain volume (Ritchie et al., 2018). Right panel: Tracts showing sex-by-diagnosis effects across two or more studies in this review (either measured via volume or DTI microstructural metrics). Mask was generated using WFU Pick-Atlas (Maldjian et al., 2003) in SPM-12, tracts or their closest equivalent were marked using the JHU atlas (Hua et al., 2008; Wakana et al., 2007) *Abbreviations: Anterior/Superior/Posterior Corona Radiata (ACR/SCR/PCR), Superior Thalamic Radiations (STR), Superior Longitudinal Fasciculus (SLF), Posterior Thalamic Radiations (PTR), Sagittal Stratum (SS), Inferior Longitudinal Fasciculus (ILF), Inferior Fronto-Occipital Fasciculus (IFOF), Corticospinal Tract (CST), Uncinate Fasciculus (UF).

et al., 2020; Syan et al., 2017). Taken together, the role of ERβ and other ovarian hormones in ASD-related differences warrants further study.

4.2. A genetics perspective on brain-based sex differences in ASD

While certain aspects of sex-related brain differences appear to be linked to the sex-specific hormonal milieu, hormones do not act in isolation. Genetic processes likely play an important role ranging from sex chromosome-specific effects, sex chromosome gene-by-gene interactions, sex steroid-by-gene interactions, or other sexually dimorphic processes influencing gene transcription. A recent large-scale study revealed highly replicable sex differences in GM volume in NT adults (Liu et al., 2020). Visual inspection showed that regions with a male bias toward enlargement overlapped with regions expressing replicable sex-by-diagnosis effects across studies and modalities in this review (Fig. 2). Importantly, regions of GM volumetric enlargement in NT males showed higher expression of sex chromosome genes (both X- and Y-linked), in particular those implicated in axonal development, outgrowth, targeting, and dendritic spine/synapse regulation (Liu et al., 2020). Many of these cellular actions show dysfunction in ASD (Gilbert and Man, 2017). The higher incidence of ASD in chromosomal disorders highlights a potential role for sex chromosomes in ASD etiology (Tartaglia et al., 2017), although idiopathic cases of ASD suggest the role is small (Ferri et al., 2018), albeit potentially larger in females with ASD for X chromosomal mutations (due to higher mortality rates for males with a single X chromosome; Turner et al., 2019). Furthermore, regions showing volumetric enlargement in NT males showed higher expression of genes associated with signatures of deep-layer (5/6) cortical neurons (Liu et al., 2020), which project mostly to subcortical structures including the basal ganglia, thalamus, brainstem, and cortico-spinal tract (Brodmann, 2007). Aberrant cortico-subcortical connectivity and function have been found in ASD (Cerliani et al., 2015; Martino et al., 2011; Maximo and Kana, 2019; Woodward et al., 2017; Braden et al., 2017). There is some evidence of sex differences in cortico-subcortical FC patterns in ASD (Alaerts et al., 2016), including inverse links to ASD genetic risk in males vs. females (Hernandez et al., 2020). Finally, regions showing volumetric enlargement in NT men were associated with face processing (Liu et al., 2020), highlighting that these sexually dimorphic structures may play a phenotypically relevant role in ASD (Aoki et al., 2015; Nickl-Jockschat et al., 2015). Together, these observations indicate that genetic processes involved in brain "masculinization" may substantially contribute to sex-by-diagnosis effects found in this review. However, this does not preclude a role for "feminization" processes in brain-based sex differences in ASD, with emerging evidence suggesting their role in female protection in ASD (see section 4.1).

A recent review suggests that gene sets associated with glial and immune function, which show a male expression bias and are upregulated in ASD, may be candidates for female protection/male vulnerability in ASD (Kissel and Werling, 2021; Werling et al., 2020). Importantly, genes associated with glial function show higher expression in regions with a NT adult female > male bias in GM volume (Liu et al., 2020), and these brain regions were less commonly implicated in GM effects observed in this review. It should be noted that the majority of genomic results implicating glial and immune gene sets in the ASD sex bias come from the mid-fetal stage of development (Kissel and Werling, 2021). In contrast, neuroimaging studies of sex differences in ASD have exclusively examined post-natal stages of development. Evidence from this review highlights that developmental stage is a critical consideration when examining sex differences in ASD, and distinct neurobiological processes may contribute to female protection/male vulnerability at different stages of ASD neurodevelopment. Furthermore, genomic analyses of candidate genes for the sex bias in ASD have largely examined bulk tissue samples from the human prefrontal cortex (Kissel and Werling, 2021), but sampling other brain tissue, in particular structures implicated in sex-related brain differences (e.g., hypothalamic nuclei, bed nucleus of the stria terminalis), may yield novel

insights into genes implicated in female protection or male vulnerability. As future genomic studies examine other brain structures and developmental stages, overlapping patterns of sex differential gene expression and altered expression patterns in ASD may reveal new insights into mechanisms of protection or vulnerability in ASD (Kissel and Werling, 2021). Finally, it should be highlighted that the observation of replicable sex-by-diagnosis GM effects overlapping with regions showing a male > female GM volumetric bias is qualitative. Brain structures showing a female > male volumetric bias have also been implicated in sex-by-diagnosis effects in ASD (e.g., medial prefrontal cortex, precuneus, etc.) and may play a role in female protection. Future neuroimaging research may benefit from examining of specific behavioral traits implicated in female protection (e.g., compensatory social behaviors, social motivation, etc.) and their associated brain patterns across critical stages of neurodevelopment.

4.3. Age-dependent sex-by-diagnosis patterns and the arousal system

Sex steroids can alter sensitivity and resilience in response to stressors, either environmental or physiological, as well as interact with peripheral systems (e.g., stress, gut, immune) to impact brain function and symptom expression in psychopathology (Rubinow and Schmidt, 2019). In particular, interactions between stress/arousal response systems and sex steroids may play an important role in sex differences in ASD. Differences in the brain arousal system in ASD have received surprising limited attention, although accumulating evidence and theory points to its potential role in both ASD core symptoms and common comorbidities, including learning, attention, sensory and emotional processing, homeostatic regulation, sleep, and executive functioning (Bast et al., 2018; London, 2018). In general psychopathology, pubertal-onset disorders characterized by hyper-arousal and stress dysregulation show a female preponderance (e.g., anxiety, depression, post-traumatic stress disorder, insomnia; Bangasser et al., 2016; Hodes and Epperson, 2019; Timko et al., 2019; Wellman et al., 2018; J. Zhang et al., 2016a). Furthermore, many of these disorders show high co-morbidity with ASD (Haruvi-Lamdan et al., 2020; Lai et al., 2019a). Thus, understanding sex differences in the brain arousal system may help contextualize findings, especially given evidence that this system shows sex-dependent development.

The core brainstem nucleus associated with arousal is the locus coeruleus (LC), which regulates norepinephrine release to the limbic system (see Bangasser et al., 2016 for review and citations therein). In rodents, this region shows female-specific neurogenesis that persists through puberty, which may suggest a sex-specific role in pubertal development. Furthermore, estrogen regulates norepinephrine release and synthesis to LC projection regions and the LC is more sensitive to stress hormone exposure in females. Together, these findings highlight that the brain arousal system is modulated by sex hormones and development. From a network perspective, the LC shows FC to the inferior cerebellum and regions of the ventral attention, default mode, and medial visual networks (Mäki-Marttunen and Espeseth, 2021). Across modalities, sex-by-diagnosis differences in ASD were common across regions associated with the arousal network (see table 5 for a summary of regional sex-by-diagnosis effects). Furthermore, sex differences in the LC network have been shown in the parahippocampus, hippocampus, orbitofrontal cortex, midbrain, and middle temporal gyrus with higher FC in NT men than women (S. Zhang et al., 2016b). These regions show overlap with regions showing age-dependent morphometric sex-by-diagnosis effect patterns in youth vs. adults, specifically the parahippocampus (Cauvet et al., 2019; Ecker et al., 2017), hippocampus (Zhang et al., 2018), and orbitofrontal cortex (Lai et al., 2013; Westeinde et al., 2019). While functional evidence suggests pervasive sex-by-diagnosis differences in functional brain development in ASD (Kozhemiako et al., 2020), age-dependent structural sex-by-diagnosis effects may reflect more dramatic (e.g., pubertal) effects of development. Further research on sex differences in the arousal network

as well as the influence of stress on brain function and development in males and females with ASD is warranted.

4.4. Limitations and future directions

4.4.1. The daunting complexity of neurodevelopmental sex differences in ASD

Popular theories like the extreme male brain hypothesis posit that the ASD phenotype represents the extreme end of masculinization (Baron-Cohen, 2002), and thus neurobiological phenotypes would reflect hyper-masculinization. However, the Extreme Male Brain (Baron-Cohen, 2002) and Gender Incoherence model (Bejerot et al., 2012) overlook the potential complexity of gene-by-hormone interactions on early brain organization and development. Despite this, many neuro-imaging studies investigating sex differences in ASD focused on testing these hypotheses or synthesized findings from these perspectives, generally with mixed support for one or both theories (Beacher et al., 2012; Lai et al., 2013; Ecker et al., 2017; Ympa et al. 2016; Alaerts et al., 2016; Kozhemiako et al., 2019). However, there is accumulating evidence suggesting that aspects of atypical brain structure and function in ASD are sex-dependent and modulated by development. Put simply, in ASD, sex assigned at birth and its accompanying biology may differentially interact with ASD genetics, environmental factors, or prenatal disruptions to the hormonal milieu that have been associated with ASD. Furthermore, biological processes associated with reproduction influence the brain not only during early developmental organization, but also across the lifespan. Thus, viewing sex differences in ASD as static and phenotypic traits as being wired only during early development is likely a limited view. This is highlighted by new evidence suggesting a late-emerging ASD phenotype where symptoms do not begin to present until adolescence or adulthood (Riglin et al., 2021). A thorough characterization of neuroendophenotypes of ASD in males and females will require a lifespan approach, including examination of windows of hormonal transition, as well as a deeper consideration for lifespan phenotypic heterogeneity.

Emerging evidence suggests that brain differences in ASD vary as a function of sex, development, and symptom severity. However, other factors may interact with sex assigned at birth, including environment (e.g., diet, immune health, stress) and co-morbid conditions (e.g., intellectual disability, attentional impairments, etc.) to produce distinct brain and behavioral differences in ASD. The predominant case-control paradigm, where all individuals with ASD are considered statistically equivalent, remains the most common approach in neuroimaging studies. Addressing questions about ASD heterogeneity using stratified or dimensional models comes with challenges. Such investigations require both 1) large sample sizes (e.g., $n > 100$ per group) to mitigate sampling bias and small-sample effect size inflation and 2) rich feature sets that permit sample stratification and dimensional investigation across sources of heterogeneity (Lombardo et al., 2019). The few studies detecting differential effects of age across sex-by-diagnosis groups included groupwise samples of approximately $n = 100$ or more (Henry et al., 2018; Kozhemiako et al., 2020, 2019). Data for these studies were derived from shared data sources like ABIDE and ENIGMA. While these data sharing efforts permit larger sample investigations, they show a poverty of phenotypic data at the participant level. Emerging efforts like the EU-AIMS Longitudinal European Autism Project have been initiated to address this gap, but more are needed. In the meantime, approaches that examine dimensional brain-ASD associations (e.g., observational measures; self-report measures; specific ASD symptom measures including social communication, repetitive behaviors, sensory processing, etc.) and stratify across critical demographic or biological variables (e.g., sex, gender identity, developmental stage) may improve the detection of clinically relevant features of ASD neurobiology. Normative modeling approaches also show utility for contextualizing deviations from NT age- and sex-related brain patterns (Ecker et al., 2017; Tung et al., 2021). Furthermore, given sex differences in the female ASD

phenotype and ascertainment bias towards detecting ASD in males (Halladay et al., 2015), studies using biological measures of ASD severity (e.g., polygenic risk scores) alongside observational or self-report measures of ASD severity may be particularly insightful. Using smaller sample investigations with rich phenotypic data, these features may then be examined for clinical predictive utility, including prognosis, treatment response, and other functional outcome variables. Furthermore, sex-differential neurobiological features may inform basic science investigations to characterize etiological implications of sex differences in ASD.

4.5. Considering method sensitivity in study design

Certain statistical methods in this review stand out as being particularly useful for early-stage, exploratory characterizations of sex differences in ASD. For example, multivariate methods revealed more sex differential effects across studies in this review (Irimia et al., 2018, 2017; Kozhemiako et al., 2020, 2019; Supekar and Menon, 2015). Furthermore, the two co-twin designs included in this review revealed more pervasive sex-by-diagnosis effects, suggesting that uncontrolled factors like demographics, environment, and genetics may impact sensitivity. Future cross-sectional explorations of sex differences in ASD may benefit from applying multivariate statistical methods for high-dimensional, whole-brain analyses as well as well-controlled experimental designs (e.g., longitudinal, co-twin).

Different neuroimaging modalities and metrics may show greater sensitivity to sex and age-related differences in ASD. In the case of sMRI, there may be a complex relationship between brain region, age, sex, and morphometry. For example, Irimia and colleagues (2018) found that distinct structural metrics showed differing regional sensitivity to sex-by-diagnosis differences. Furthermore, development may confound sensitivity, especially in GM morphometry studies. This is highlighted by the absence of sex-by-diagnosis findings, despite large sample sizes, in heterogeneous and broad age-span samples (Postema et al., 2019; van Rooij et al., 2018). In NT groups, traditional morphometric indices (e.g., CT, CV, SA) have shown mixed regional sensitivity to age and sex effects (Gennatas et al., 2017). Alternate metrics like GM density have shown more global sensitivity to age, sex, and age-by-sex differences (Gennatas et al., 2017). Similarly, rCBF has shown promise as a biomarker of developmental sex differences in NT cohorts (Kaczkurkin et al., 2019; Satterthwaite et al., 2014). However, only one study to-date has used rCBF to investigate sex differences in ASD (Peterson et al., 2019). In particular given findings of poor reproducibility in rs-fMRI studies (King et al., 2019), further investigation of sex differences in brain function in ASD using rCBF is warranted. Finally, findings suggest age-dependent sensitivity of DTI metrics to sex-by-diagnosis differences, with AD showing sensitivity during early development and FA showing sensitivity in youth and adults. Alternate metrics like neurite density index have shown greater sensitivity to age-related WM differences in NT groups (Genc et al., 2017; Tamnes et al., 2018) and future investigations of sex differences in ASD may benefit from their use. In summary, while traditional neuroimaging measures may bear modest sensitivity to age- and sex- differences, emerging techniques show promise.

4.6. A focus on adult hormonal transition windows is needed

This review highlights cross-sectional evidence suggesting brain developmental trajectories differ according to sex and diagnosis. However, little is known about age-related patterns during adulthood. Both women and men experience decline in circulating hormones across the adult lifespan, but the mechanism, rate, and consequences are quite different, and how these transitions may interact with ASD is almost completely unknown. For men, andropause is a gradual decline in testosterone levels that affects aspects of health (Matsumoto, 2002). While andropause effects on cognitive function and the brain are not clear (Elbejjani et al., 2017; Irie et al., 2006), there is some evidence that

low levels of testosterone in late life contribute to Alzheimer's disease risk (Lv et al., 2016). Conversely, menopause is an abrupt decline of estrogens and progesterone due to loss of ovarian function at midlife (Greendale et al., 1999), which negatively affects cognition and increases Alzheimer's disease risk (Maki and Henderson, 2016; Mosconi et al., 2018). The most common brain finding following menopause is reduced hippocampal size, but the hormonal loss may also be related to shrinkage of orbitofrontal, inferior frontal, anterior cingulate, middle and superior temporal, and parietal cortices and functional differences in the hippocampus and regions of the prefrontal cortex (Frizell and Dumas, 2018; Rehbein et al., 2020). We present cross-sectional data suggesting that middle-age women with ASD show lowest symptoms just preceding the average age of menopause (~51 years), then symptoms increase as age increases (Fig. 1b). Conversely, men have a more stable age relationship with symptoms in mid-to-late life (Fib. 1b), which suggests the gradual loss of testosterone may not affect ASD symptoms. The abrupt loss of ovarian hormones may negatively impact the neurocircuitry underlying "protection" in women with ASD. Lastly, menopause can be associated with an onset of depressive symptoms, especially in women who previously had affective disorder diagnoses (Greendale et al., 1999), which poses a specific vulnerability for many women with ASD and co-morbid depression. Limited representation of middle age and elderly adults with ASD, in particular women, in research remains a shortcoming. Future longitudinal studies with larger samples will be required to achieve adequate statistical power for detecting sex-by-diagnosis differences in brain aging trajectories. Understanding the influence of hormonal change (e.g., menopause) on brain differences in mid-to-older adult women with ASD is also warranted.

4.7. Conclusions and future directions

There is a burgeoning literature on neuroimaging-based sex differences in ASD. Growing evidence suggests that patterns of sex differences in ASD are age-dependent. However, the majority of studies in this review used samples with broad age-spans and collapsed across age in their analyses, which may mask sex-by-diagnosis effects that vary developmentally. Sex-by-diagnosis effects across studies and modalities showed substantial spatial overlap with regions showing NT sex differences, in particular across limbic, default mode, ventral attention, visual, and cerebellar network regions (Bakker, 2018; Rehbein et al., 2020; Tan et al., 2020; Vijayakumar et al., 2018). This observation suggests that ASD-related genetics may interact with sex-related biology (e.g., genetic and endocrine processes) to produce distinct neurodevelopmental trajectories. In NT adults, regions showing a reproducible male bias toward volumetric enlargement (Liu et al., 2020) overlap with regions that showed replicable sex-by-diagnosis differences in this review (Fig. 2). Thus, processes involved in brain "masculinization" may substantially contribute to sex-by-diagnosis functional and structural GM differences across studies. However, this does not preclude a role for "feminization" processes in brain-based sex differences in ASD, with evidence implicating ERβ in female protection. Furthermore, interactions between sex and stress/arousal system function may influence ASD neurodevelopment, which is highlighted by the overlap between regional sex differences in the arousal network and regions showing age-dependent sex-by-diagnosis effects in this review. Behaviorally, the hypothesis that ASD risk genes interact with sex-related biology to produce distinct developmental trajectories is also supported by evidence of 1) distinct adolescent symptom improvement in females with ASD (Wagner et al., 2019) and 2) cross-sectional evidence of greater symptom variability across adulthood for females with ASD, including potential symptom exacerbation following menopausal (Fig. 1). Future research would benefit from a focus on lifespan trajectories, in particular across critical windows of hormonal transition. Relationships between ASD severity (e.g., behavioral or genetic risk scores) or symptom progression, sex hormones, and brain development remain largely

unknown. Finally, given the still limited scientific knowledge of brain-based sex differences in ASD, future large-sample exploratory studies are warranted focusing on methods that are optimally sensitive to sex, age, and diagnosis differences, including 1) high-dimensional, multivariate analytical methods, 2) well-controlled designs (e.g., co-twin, longitudinal), and 3) neuroimaging techniques that are sensitive to sex differences across development and aging.

CRediT authorship contribution statement

Melissa J.M. Walsh: Conceptualization, Data curation, Formal analysis, Project administration, Funding acquisition, Writing - original draft. **Gregory L. Wallace:** Conceptualization, Methodology, Writing - review & editing. **Stephen M. Gallegos:** Investigation. **B. Blair Braden:** Conceptualization, Investigation, Supervision, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102719.

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