S.I.: ASD IN ADULTHOOD: COMORBIDITY AND INTERVENTION



ASD Traits and Co-occurring Psychopathology: The Moderating Role of Gender

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Abstract The higher prevalence of autism spectrum disorder (ASD) in males, relative to that seen in females, is a well-replicated phenomenon. A growing body of research has suggested that there may be gender differences in core ASD deficits and patterns of psychiatric comorbidity among adolescents and adults with ASD. The present study sought to determine if association between psychiatric diagnoses and ASD traits differed by gender in a young adult analogue sample. Participants (n = 84) were university students, scoring either above or below a pre-determined cut-off of ASD traits. Using a structured psychiatric screening interview, ASD traits were found to more strongly predict exceeding screening threshold for mood disorders in females than in males. Future directions and clinical implications are discussed.

Keywords Gender · Autism · Comorbidity · Mood

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Introduction

Autism spectrum disorder (ASD) is diagnosed far more commonly in males, with a male to female diagnosis ratio of 5:1 (US CDC 2012). Further, in the non-ASD population, higher levels of ASD traits (in non-diagnosed adults) are found among males, as compared to females (e.g., Austin 2005; Baron-Cohen et al. 2001). The majority of research has included predominantly male samples, and there have been few studies comparing females with ASD to either males with the disorder or to non-ASD females (Thompson et al. 2003; Watkins et al. 2014).

Although dominated by biogenetic theories (e.g., Baron-Cohen et al. 2005; Ingudomnukul et al. 2007), research aimed at elucidating the underlying reasons for the gender difference in ASD prevalence has begun to investigate developmental and sociocultural influences that may differentially impact the manifestation of ASD symptoms among males and females with ASD, including the impact of differing patterns of psychiatric comorbidity (e.g., Goldman 2013; Kreiser and White 2014; Trubanova et al. 2014). Additionally, studies utilizing samples that may be less biased by clinical ascertainment (e.g., screening of high risk populations) have found a lower gender ratio in prevalence (i.e., higher rate of ASD diagnosis among females) as compared to national prevalence estimates (Baird et al. 2006; Kim et al. 2012; Zwaigenbaum et al. 2012), perhaps suggestive of the impact of biases in patterns of referral and diagnosis on the rate of diagnosis of ASD in females. A metaanalysis of the extant literature indicates that females with ASD demonstrate similar levels of social and communication deficits and less restricted and repetitive behaviors than males with the disorder; however, the authors caution that the lack of significant gender difference in social communication deficits may be an artifact of sample ascertainment



biases (i.e., underrepresentation of high functioning females; Van Wijngaarden-Cremers et al. 2013).

The prevalence of certain types of psychiatric comorbidity, including attention deficit hyperactivity disorder (ADHD), various anxiety disorders, and unipolar depression is higher among individuals with ASD as compared to estimated prevalence from population-based and non-ASD clinical studies (e.g., Gadow et al. 2005; Leyfer et al. 2006; Mazefsky et al. 2012; Simonoff et al. 2008, 2012; van Steensel et al. 2011). Several studies examining psychiatric comorbidity among children and adolescents with ASD have found that females with ASD have higher levels of internalizing problems and lower levels of externalizing behaviors as compared to males with the disorder. Solomon et al. (2012), in a sample of children and adolescents with ASD, found that adolescent females had significantly more anxiety, depression, and somatic symptoms than age-matched males with ASD and age-matched non-ASD females. None of the males with ASD or non-ASD females in the sample fell within the clinical range on a self-report measure of depression, whereas 26 % of females with ASD in the sample surpassed the clinical threshold. Likewise, May et al. (2013) found higher levels of social anxiety symptoms in school-age females with ASD as compared to males with ASD, consistent with gender differences found in the non-ASD comparison group (May et al. 2013). In both clinical and population-derived samples of children with ASD, higher levels of externalizing behaviors and aggression have been found in males as compared to females (Giarelli et al. 2010; Mandy et al. 2011; May et al. 2013).

No studies have directly examined differences in rates of specific co-occurring psychiatric disorders by gender among adults with ASD; however, given that certain types of anxiety disorders (e.g., panic disorder, social anxiety disorder) and depression tend to emerge later in adolescence or in early adulthood in non-ASD populations (as reviewed in Kessler et al. 2007), gender differences in psychiatric comorbidity of adults with ASD is of particular interest. The goal of the present study was to better understand the relationship between ASD traits and psychiatric symptoms in young females, utilizing a brief clinician-administered screening interview. An analogue approach was used to maximize statistical power to detect gender differences, in order to inform subsequent research with clinical samples. The primary aim of the present study was to determine if gender moderates the relationship between self-reported ASD traits and the presence of certain types of psychiatric disorders (e.g., anxiety disorders, mood disorders, substance use disorders), which have been found to most commonly emerge in late adolescence and early adulthood among individuals without ASD (Substance Abuse and Mental Health Services Administration 2012).

Based upon the strong relationship found between ASD traits and symptoms of a variety of disorders (e.g., Cath et al. 2008; White et al. 2011), it was hypothesized that ASD traits would predict exceeding screening threshold for more psychiatric disorders (Hypothesis 1). It was also hypothesized that gender would moderate the relationship between ASD traits and number of psychiatric disorders that exceed screening threshold (Hypothesis 2). Specifically, a stronger relationship between ASD traits and number disorders exceeding screening threshold for females was expected. It was also hypothesized that ASD traits would be associated with exceeding screening threshold for internalizing disorders (i.e., anxiety and mood disorders) for females to a greater extent than males (Hypothesis 3).

Methods

There were two phases of the study, both of which were approved by the institution's human subjects research board. Phase I involved the completion of an online survey consisting of questions related to demographics and ASD traits. To avoid potential sampling and response bias, the survey was advertised as a questionnaire about personality and social concerns in college, rather than as an assessment of ASD characteristics.

Phase II involved an in lab session, including a brief structured psychiatric interview. Participants were enrolled into the study by groups to aid in recruiting individuals across the continuum of ASD traits, and to attempt to match males and females on type of major (e.g., STEM vs non-STEM); however, the intent of the study was to utilize a continuous approach to examining ASD traits, as this approach is more reflective of the dimensional versus categorical structure of ASD traits, and given statistical limitations with artificially dichotomizing variables (i.e., restriction of range, loss of power) (MacCallum et al. 2002). Participants were selected by separately rank ordering males and females, based on their ASD trait score (highest to lowest), and invited into the "high" ASD trait group by working down the rank ordered lists for each gender and invited into the "low" ASD trait group by utilizing a random number generator with remaining participants (after the "high" group was filled), matching on gender and type of major (Science, Technology, Engineering, Math (STEM) vs non-STEM).

Participants

Participants were undergraduate students at a public university that emphasizes training in science and technology who responded to campus-wide postings for the study.



Participants received extra credit for courses or, if not eligible for course credit, they were offered a small honorarium. A priori power analyses indicated that a sample size of 63-77 would achieve adequate power (power of 0.70 or 0.80) to detect a medium main effect. The average effect size in tests of moderation is 0.009 (Aguinis et al. 2001), and Kenny (2011) has suggested realistic effect sizes for small, medium, and large moderation effects to be 0.005, 0.01, and 0.025, respectively. Given the generally small effect sizes obtained when examining moderation (Frazier et al. 2004), and the preliminary nature of this study, an alpha of 0.1 was utilized for the interaction effect. The sample included a total of 84 participants drawn using the procedures previously described from the Phase I sample (n = 1039). Phase II participants were primarily Caucasian (77.6 %), STEM majors (63.5 %) and in their first through fourth year of college (92.9 %) (mean age = 19.95, SD = 1.50). The number of males (n = 39) and females (n = 45) was approximately even. Forty-one of Phase II participants (18 males and 23 females) exceeded the threshold on a measure of ASD traits, indicative of a high level of traits associated with the broader autism phenotype (for individuals who do not exceed the clinical threshold for ASD).

Measures

Broad Autism Phenotype Questionnaire (BAPQ; Hurley et al. 2007)

The BAPQ is a 36-item self-report questionnaire designed to assess ASD traits in individuals not exceeding the clinical threshold for ASD. The BAPQ is comprised of three theoretically based subscales thought to represent key components of ASD traits including: Aloof, Rigidity and Pragmatic Language. Internal consistency is quite good ($\alpha = .95$) and convergent validity has been established with direct clinical assessment of ASD traits (Hurley et al. 2007; Ingersoll et al. 2011; Wainer et al. 2011).

Mini International Neuropsychiatric Interview (MINI; Sheehan and Lecrubier 2006)

A brief, structured screening interview developed for the major disorders in the DSM-IV, the MINI was designed to be an efficient diagnostic screener for current psychiatric problems for use in research and clinical practice, but is not intended to be used for diagnostic purposes. The MINI has excellent inter-rate reliability (all kappa values above 0.75), test-retest reliability and good diagnostic concordance with the Structured Clinical Interview for DSM-IV (SCID) (Sheehan et al. 1998). In the present study, 10 of the 17 possible modules of the MINI, selected for general

frequency of occurrence, were examined: major depressive disorder, dysthymia, (hypo)manic episode, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder (OCD), alcohol abuse and dependence, non-alcohol psychoactive substance use disorders, and generalized anxiety disorder (GAD). Separate disorders on the MINI were converged into broader categories, based on type of problem. Three dependent, dichotomous (yes/no) variables were created: exceeding screening threshold for any DSM-IV anxiety disorder (i.e., panic disorder, agoraphobia, OCD, GAD, social phobia; n = 35 exceeded threshold), exceeding screening threshold for any substance use disorder (i.e., alcohol use disorder, substance use disorder; n = 21 exceeded threshold), and exceeding screening threshold for any mood disorder (i.e., major depressive disorder, dysthymia, bipolar disorder; n = 30 exceeded threshold). MINI administration training was provided to five graduate level clinical psychology students in during a 2-h long training session that reviewed information regarding the structured format of the MINI and administration rules, and each graduate research assistant was asked to practice the administration of two modules of the MINI with the principal investigator. Feedback was provided regarding administration, utilization of probing, and scoring.

Analyses

For hypotheses 1 and 2, a generalized linear model with ASD traits, gender, and the interaction between these variables as predictors of the number of diagnostic categories on the MINI exceeding screening threshold was used. ASD traits were mean centered. A poisson distribution and log lin link function were specified, given the ordinal nature of the dependent variable. For hypothesis 3, a series of logistic regressions with ASD traits, gender, and the interaction between these variables predicting exceeding screening threshold for each disorder group on the MINI were used. As mentioned, given our directional hypotheses, the generally small effect sizes obtained when examining moderation (Frazier et al. 2004), and the preliminary nature of this study, an *alpha* of 0.1 was utilized for the interaction effect.

Results

Participants exceeded screening threshold for a mean number of 1.31 disorders on the MINI (SD=1.57; range=0-6). Most (66 %) participants exceeded screening threshold for at least one disorder on the MINI (22.4 %)



exceeding screening threshold for one disorder, 10.6 % exceeding screening threshold for two disorders, 8.2 % exceeding screening threshold for three disorders, 10.6 % exceeding screening threshold for four disorders, 2.4 % exceeding screening threshold for five disorders, 1.2 % exceeding screening threshold for six disorders), which is similar to the rate (61 %) found in MINI validation studies (Sheehan et al. 1998). Table 1 shows the percentage of males and females exceeding screening threshold for each disorder.

As hypothesized, ASD traits predicted exceeding screening threshold for more disorders on the MINI (Wald Chi-square = 8.03, B = 0.04, p < .001). The interaction between ASD traits and gender in predicting number of disorders exceeding screening threshold was not significant (Wald Chi-square = 2.63, B = -0.01, p = .104). Given the generally small effect sizes obtained when examining moderation (Frazier et al. 2004), we also examined bivariate correlation strength across gender. There was a significant correlation of moderate strength between ASD traits and number of disorders exceeding screening threshold on the MINI for females (r = .46, p = .002), and a small non-significant correlation between ASD traits and number of disorders exceeding screening threshold on the MINI for males (r = .23, p = .16). A Fisher's r-toz transformation revealed that the strength of these relationships did not significantly differ (z = 1.16, p = .25).

There was a significant main effect of ASD traits (Wald Chi-square = 4.85, B = 0.09, p = .04) and a significant gender by ASD traits interaction in predicting exceeding screening threshold for mood disorders (Wald

Table 1 Number of participants exceeding screening threshold for disorders on the MINI and BAPQ scores by group (high vs low ASD traits) and gender (female n = 45; male n = 39)

	Males		Females	
	High $(n = 21)$	Low $(n = 18)$	High $(n = 21)$	Low $(n = 24)$
n (% of total	group)			
Anxiety disorder	12 (57 %)	4 (22 %)	10 (48 %)	11 (46 %)
Mood disorder	10 (48 %)	6 (33 %)	10 (48 %)	4 (17 %)
Substance use disorder	7 (33 %)	7 (39 %)	3 (14 %)	4 (17 %)
M(SD)				
BAPQ	3.6 (0.39)	2.5 (0.50)	3.5 (0.43)	2.3 (0.35)
Number of MINI disorders	1.67 (1.74)	.83 (1.10)	1.76 (1.97)	1.00 (1.19)

Scores > 3.15 on the BAPQ exceed the screening threshold for presence of broader autism phenotype

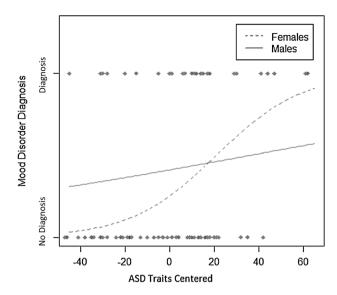


Fig. 1 Logistic curves plotted separately by gender for the relationship between BAPQ (mean centered) and mood disorder diagnosis status on MINI (exceeding vs not exceeding screening threshold for a mood disorder)

Chi-square = 3.07, B = -0.04, p = .08). For females, the relationship between ASD traits and exceeding screening threshold for mood disorders strengthened as ASD traits increased (Fig. 1). There were no significant main effects of ASD traits or gender differences in the relationship between ASD traits and exceeding screening threshold for anxiety disorders or substance use disorders (Table 2).

Discussion

This is the first study to demonstrate that ASD traits are related to increased likelihood of exceeding screening threshold for other psychiatric disorders, particularly mood disorder. Our findings are in line with previous studies documenting the strong correlation between ASD traits and symptoms of depression (e.g., Cath et al. 2008; Kanne et al. 2009; Rosbrook and Whittingham 2010), and with research that has documented increased prevalence of major depressive disorder among relatives of probands with ASD (e.g., Bolton et al. 1998; Piven and Palmer 1999). Gender did not significantly moderate the relationship between ASD traits and number of disorders exceeding screening threshold, regardless of type, exceeding threshold. Post hoc analyses, with G*Power, confirmed that we were underpowered to detect our small moderation effect (odds ratio = 1.01) (power = .12). However, gender did moderate the effect of ASD traits on likelihood of exceeding criteria for a mood disorder. ASD traits more strongly predicted mood disorder for females (at $\alpha = .10$; small



Table 2 Logistic regressions with BAPQ, gender, and interaction between BAPQ and gender predicting exceeding screening threshold for anxiety, substance use, and mood disorders (n = 84)

Variable	В	SE	Wald Chi-square
Anxiety disorders			
BAPQ	0.02	0.03	0.25
Gender	-0.02	0.48	0.00
$BAPQ \times gender$	0.01	0.02	0.21
Substance use disorde	rs		
BAPQ	-0.02	0.04	0.24
Gender	1.12	0.54	4.40*
BAPQ × gender	0.01	0.02	0.13
Mood disorders			
BAPQ	0.09	0.04	4.85*
Gender	0.73	0.52	1.98
$BAPQ \times gender$	-0.04	0.02	3.07 ^a
Gender	0.73	0.52	1.98

BAPQ was mean centered

effect based upon Cohen's (1988) guidelines). This finding is consistent with prior findings of higher levels of affective problems among females with ASD (e.g., Solomon et al. 2012), the higher rate of depression found in female as compared to male relatives of ASD probands (Bolton et al. 1998), and findings of relatively higher rates of depression among females as compared to males in the non-ASD literature (Kessler et al. 2003). Higher levels of depression among females with ASD may be reflective of shared vulnerability of ASD traits and affective problems, particularly in females (e.g., Bolton et al. 1998), or of unique gender based sociocultural processes (i.e., differential culturally based social demands, including differential peer expectations) that may lead to increased isolation and stress experienced by females with core social deficits.

The relationship between ASD traits and comorbidity and effect of gender may be particular to mood disturbance. This finding lends support to the notion that females with ASD may be at risk for specific types of comorbidity, as opposed to comorbidity that is not specified and reflective of more diffuse processes or "general distress".

The present study is distinguished from both the extant literature examining gender differences in individuals with ASD and research examining ASD traits in non-ASD samples, in that we used direct assessment (as opposed to the sole use of self- or parent-report) to determine presence of psychiatric disorders. Although an analogue sample was used, careful ascertainment procedures were utilized in order to recruit participants with a range of ASD feature severity, and a considerable portion of our sample included

individuals exceeding screening threshold on our measure of ASD traits (48.2 %).

Our ability to generalize our findings to other samples or clinical populations is limited, given the unique characteristics of our sample (i.e., college students at a science and technology focused university). Recent concerns of measurement non-equivalence of ASD traits when comparing non-clinical and clinical samples (Frazier et al. 2013) and the strong relationship and overlap between self-report measures of ASD traits and other forms of psychopathology (e.g., social anxiety in non-clinical samples; White et al. 2012), which may lead to artificially inflated scores on self-report measures of ASD traits, suggest caution in the generalization of these findings to males and females diagnosed with ASD.

Additionally, there are cautions in the interpretation of the relationship between ASD traits and psychiatric comorbidity in this sample, given our use of an interview that, although well-validated, is meant to be used for screening purposes. Although the brief clinical interview used has been found to have good diagnostic concordance with full-length diagnostic interviews, it is unclear how many of the participants exceeding screening threshold would indeed meet diagnostic criteria using more rigorous procedures. Additionally, although the MINI was administered by graduate student clinicians trained in both full and brief semi-structured clinical diagnostic interviews, the current study is limited in that reliability procedures were not utilized in order to establish rater agreement or consensus on diagnoses. It is also important to note that in our present study there was a higher than expected rate of participants exceeding screening threshold for bipolar mood disorder (22.6 %). It is possible that for some participants, elevated bipolar scores were indicative of more global emotion regulation difficulties (e.g., periods of irritability and anger, hyperactivity) and social difficulties and misunderstanding (e.g., ideas that others do not understand or agree with), perhaps experienced to a higher degree by participants with elevated ASD traits. As the MINI was validated for both males and females, there is no indication that it is functioning differentially for males and females in our sample. Finally, given the predominantly small moderation effects found in the psychological literature (Frazier et al. 2004), despite our use of a somewhat liberal alpha value to detect moderation effects and a priori power analysis for detecting a medium size effect, we were largely underpowered to detect clinically significant gender moderation in this sample.

Future research with large and well defined ASD samples is sorely needed in order to examine gender differences in risk for specific psychiatric disorders across the lifespan. Based upon current findings, there is a need to



^{*} p < .05

a p = .08

examine mood disturbance in adults with ASD, particularly adult females. Further, there is a need to attempt to disentangle comorbid conditions, as comorbidities may be reflective of differential underlying processes, as opposed to global heightened distress related to ASD symptoms.

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Author contributions NK conceived of the study, participated in its design and coordination, ran in lab sessions, performed statistical analyses, and drafted the manuscript; SWW participated in the design and interpretation of the data, and helped to edit the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest There are no conflicts of interest to report.

Informed Consent Informed consent was obtained from all participants included in the study.

Ethical Standard All procedures performed were approved by the institution's human subjects research board and in accordance with the national research committee and with the 1964 Helsinki and its later amendments or comparable ethical standards.

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