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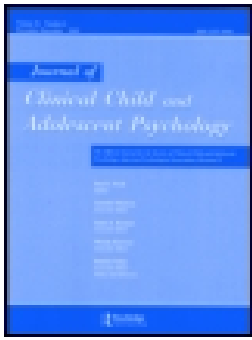
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Clinically Significant Anxiety in Children with Autism Spectrum Disorder and Varied Intellectual Functioning

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ABSTRACT

Objective: To evaluate how distinct presentations of anxiety symptoms and intellectual impairment influence the measurement and estimated rate of clinically significant anxiety in autism spectrum disorder (ASD).

Method: The sample included 75 children (ages 9–13 years) with ASD and varied IQ and 52 typically developing (TD) controls and parents. Parents completed anxiety symptom scales and a diagnostic interview, designed to (1) differentiate anxiety and ASD and (2) examine DSM-specified and unspecified (“distinct”) anxiety presentations in each child, including fears of change, special interests, idiosyncratic stimuli and social confusion rather than evaluation. Children completed standard intellectual and ASD diagnostic assessments.

Results: 69% of those with ASD had clinically-significant anxiety, including 21% DSM-specified anxiety disorders, 17% distinct anxiety, and 31% both. Only 8% of TD children had clinically-significant anxiety, all DSM-specified. DSM-specified anxiety disorders in children with ASD and intellectual impairment (IQ<70) were predominantly specific phobias. DSM-specified anxiety other than specific phobia was significantly less common in children with, versus without, intellectual impairment; this was not the case for distinct anxiety. The sensitivities of anxiety scales were moderate to poor, particularly in cases with intellectual impairment.

Conclusions: ASD is associated with more frequent and varied presentations of clinical anxiety, which may align with and differ from the specified anxiety disorders of the DSM. Standard parent report anxiety scales have reduced sensitivity to detect clinical anxiety in ASD, particularly in children with intellectual impairment.

“This summer [1937] we brought him to a playground slide and on the first afternoon when the other children were sliding on it he would not get about it, and when we put him up to slide down it he seemed horrorstruck. The next morning when nobody was present, however, he walked out, climbed the ladder, and slid down and he has slid on it frequently since, but slides only when no other child is present to join him in sliding.”

Case 1, “Donald”

“He frets when the bread is put in the oven to be made into toast, and is afraid it will get burned and be hurt. He is upset when the sun sets. He is upset because the moon does not always appear in the sky at night.”

Case 8, “Alfred”

Autistic Disturbances of Affective Contact by Leo Kanner, 1943

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects approximately 1–2% of children (Baio et al., 2018). Key features of the disorder, first

described by Kanner (1943), include deficits in social communication and reciprocity and restricted or repetitive interests and behaviors, which often have a preoccupying quality that may exacerbate social disadvantages. Anxiety and obsessive-compulsive symptoms have also long been observed in children with ASD, so much so that there has been debate regarding whether these symptoms should be considered core aspects of ASD rather than co-occurring disorders (Kerns & Kendall, 2012; Wood & Gadow, 2010). The present study investigated the premise that the behavioral overlap of anxiety and autism and, further, the distinct presentation of fears in autism complicate the assessment of these conditions and their empirical investigation.

The struggle to differentiate anxiety and ASD is observable in Kanner’s initial cases (Kanner, 1943). “Donald” is described as willing and able to play on a slide when alone, but “horrorstruck” by the presence of other children. His avoidance of children may reflect social disinterest,

consistent with ASD or, as Kanner suggests, a horror or fear of other children, more consistent with anxiety. This fear may be of negative evaluation (consistent with social anxiety disorder; SAD) or converge around other ASD-related challenges—for example, difficulties and subsequent anxiety around anticipating and interpreting social behavior. These latter fears could be conceptualized as secondary symptoms of ASD or instead as symptoms of an anxiety disorder, the presentation of which is distinct and shaped by the individual characteristics of children with ASD and their experiences. A similar conundrum is observable in the case of Alfred, who worries constantly (a symptom of generalized anxiety disorder; GAD), but whose worries are idiosyncratic and focused on changes, even those as quotidian as the setting of the sun and moon. Challenges also arise around the differentiation of sensory sensitivities and specific phobias of common (e.g., fear of loud sounds) and uncommon focus (e.g., fears of specific songs, toilets, beards), and around the classification of excessive fears that are circumscribed around a specialized or perseverative interest (Gjevik, Eldevik, Fjæran-Granum, & Sponheim, 2011; Kerns et al., 2014; Leyfer et al., 2006; Mayes et al., 2013). These fears also are closely aligned with ASD-related challenges—in this case, restricted and repetitive behaviors/interests (e.g., sensory differences, insistence on sameness, circumscribed interests) rather than social communication deficits. As such, they also appear to sit at the intersection of ASD and anxiety, raising questions for clinicians and researchers alike about how these symptoms should be characterized (Kerns & Kendall, 2012; Kerns et al., 2014).

Studies consistently suggest that children with ASD are more likely to develop problematic anxiety than other high-risk groups and experience poorer outcomes when co-occurring anxiety is present (Chiang & Gau, 2016; Eussen et al., 2013; Kerns et al., 2015; van Steensel, Bögels, & Dirksen, 2012). Findings are far less clear; however, about the proportion of children with ASD likely to develop clinically significant anxiety, which children are most at risk, and what the quality of their fears will be. One sign of this lack of clarity is that studies to date suggest that between 11–84% of children with ASD may experience clinically significant anxiety (Kerns & Kendall, 2012). Though studies of diagnosed anxiety disorders (rather than clinically significant symptoms) suggest a tighter range of 42–55%, which types of anxiety disorders are most common in ASD is unclear (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; Kerns et al., 2014; Gjevik et al., 2011; Leyfer et al., 2006; Muris, Steerneman, Merckelbach, Holdrinet, & Meesters, 1998; Simonoff et al., 2008). Specific phobia, GAD and SAD appear among the

most common. Obsessive compulsive disorder (OCD), which has been studied alongside the anxiety disorders, is also more common in some studies (Leyfer et al., 2006), but not all (de Bruin et al., 2007). However, specific estimates vary widely across studies, even when structured diagnostic interviews are used.

Kerns and Kendall (2012) suggest that this variability may be due, in part, to discrepancies in the differential diagnosis and operationalization of anxiety disorders, including distinct presentations of anxiety, operationalized as anxiety symptoms that are associated with distress and functional impairment, but which are qualitatively different from the specified anxiety disorders of the DSM. For example, though SAD has been reported to occur in close to 30% of children with ASD in some studies, rates are lower in studies in which fear of negative evaluation was required (8%; Kerns et al., 2014; Leyfer et al., 2006). In a sample of verbally-fluent children with ASD, Kerns et al. (2014) found that although 26% experienced clinically significant fears of social situations, only 17% met criteria for SAD. The remaining 9% had limited awareness of social evaluation and thus fell short of diagnostic criteria. As another example, Leyfer et al. (2006) observed that the rate of OCD in their sample (37%) would have been substantially lower – as has been the case in other studies (2–8.2%; de Bruin et al., 2007; Kerns et al., 2014; Simonoff et al., 2008) – if they had not allowed parents to make inferences about their children's internal states. Muris et al. (1998) also found that though the vast majority (72%) of children with ASD in their study displayed ritualistic behavior, few met diagnostic criteria for OCD due to their parent's inability to determine if these behaviors were distressing.

The literature is also equivocal on which children with ASD are most likely to develop clinically significant anxiety and this may also be explained, in part, by how anxiety symptoms are operationalized and assessed. For example, whereas some studies suggest that higher IQ is associated with greater anxiety symptoms (Mayes, Calhoun, Murray, & Zahid, 2011; Sukhodolsky et al., 2008), this finding has not been universal and a meta-analysis concluded that lower mean IQ was associated with greater anxiety in ASD (van Steensel, Bögels, & Perrin, 2011). Kerns and Kendall (2012) proposed that cognitive ability may be more predictive of anxiety quality than quantity. Specifically, they hypothesized that clinically significant anxiety may be equally prevalent in children with ASD with and without intellectual impairment when varied forms of anxiety are

considered, including those that are more behavioral (e.g. phobic avoidance) or distinct in quality (e.g., idiosyncratic fears, social fears without fears of evaluation). A test of this hypothesis in a sample of children with ASD and varied IQ has yet to be conducted and motivated the present study.

Finally, the vast majority of studies of anxiety in ASD have relied on parent report measures of anxiety rather than semi-structured interviews. The ability of these brief assays to differentiate ASD and anxiety symptoms and capture distinct presentations of anxiety in ASD may be limited given that most measures were developed and validated for children without ASD. Moreover, brief questionnaires do not allow for clinical clarification or judgment. Several reviews have noted that studies using questionnaires tend to yield lower estimates of anxiety in ASD than those using interviews, though this again may vary based on the form of anxiety being measured (Kerns & Kendall, 2012; van Steensel et al., 2011). For example, estimates of social anxiety appear higher in questionnaire versus interview studies, potentially due to poor differentiation in questionnaires of social difficulties due to anxiety versus other deficits in ASD. It is also notable that many commonly used anxiety scales were not designed for youth with intellectual disability. The detection of anxiety in children with ASD and lower cognitive abilities may thus be particularly poor when relying on this method of measurement. Consistent with these hypotheses, some studies suggest that the latent structure of anxiety as assessed by parent questionnaires is distinct in children with versus without ASD, particularly amongst children with ASD and co-occurring intellectual disability (Dovgan, Mazurek, & Hansen, 2019; White et al., 2015). Studies also suggest that agreement between questionnaires and interviews may be reduced, even in more cognitively-able children with ASD (Kerns et al., 2015). How these brief assays perform relative to a semi-structured interview in a more cognitively representative sample of children with ASD would add to this literature.

The primary aims of this study were to (1) compare the quality and quantity of clinically significant anxiety (both DSM-specified and distinct) in children with ASD versus typically-developing controls (TD) using a semi-structured interview adapted for ASD; (2) assess for differences in the quantity and quality of anxiety symptoms of children with ASD without versus with intellectual impairment (defined as $IQ < 70$); and (3) compare the results of the adapted interview to brief assays of anxiety.

Methods

Participants

Participants included 127 primary caregivers and their children (ages 9–13 years) – 75 with a diagnosis of ASD and 52 age-matched typically developing controls (TD). All were recruited as part of the Autism Phenome Project, an ongoing longitudinal research study focused on neurological and behavioral development in ASD. ASD participants and TD controls were recruited through the UC Davis MIND Institute subject database and through advertisements at regional schools, Parent Teacher Associations and pediatrician's offices. From 2006–2012, 404 children with ASD or TD were enrolled at ages 2–3.5 years of age for a comprehensive battery including behavioral, medical, and biological assessments. To be eligible, children were required to have no significant motor delays, vision or hearing problems, be ambulatory and to have one biological parent who spoke English and was willing to participate. All children in the ASD group were required to (a) meet the ASD cutoff score on the Autism Diagnostic Observation Schedule, Generic (ADOS-G) and (b) to meet the Autism Diagnostic Interview-Revised (ADI-R) full criteria for autism or (c) to meet on either the ADI-R Social or Communication Domains and to fall within 2 points of the other domain per Collaborative Programs of Excellence in Autism (CPEA) guidelines. Participants were excluded from TD if they showed verbal or performance reasoning deficits of > 2 SDs from the mean. In addition, the TD controls were screened and excluded for ASD with the Social Communication Questionnaire–Lifetime Edition (scores > 11).

Participants who met eligibility criteria and successfully completed both behavioral and neuroimaging protocols at T1 ($n = 277$) were followed for up to 3 additional time points through early and middle childhood; participants who missed a time point continued to be invited to subsequent time points (Time 2, $n = 211$; Time 3 $n = 183$; Time 4, $n = 132$ with recruitment ongoing). The subset of 127 children in this study were those who had successfully completed a diagnostic anxiety assessment at Time 4 ($N = 132$), which occurred between ages 9–13 years. A diagnostic anxiety assessment was not conducted prior to this time point, given research suggesting that the onset of most anxiety disorders occurs in middle childhood or later (Beesdo, Knappe, & Pine, 2009). Five children were excluded due to changes in diagnosis between initial enrollment and middle childhood (2 enrolled as TD and later received an ASD diagnosis; 3 enrolled as ASD but no longer met ADOS criteria in middle childhood).

Measures

Cognitive Ability

Intellectual functioning was assessed primarily via the Differential Abilities Scale, Second Edition, School Age or Early Years Batteries (DAS-II; Elliot, 2007). The DAS-II is a comprehensive assessment of intellectual abilities appropriate for children ages 5 and older. Participants unable to complete the DAS-II School Year protocols, were instead administered the DAS-II Early Year battery. The DAS-II General Conceptual Ability (GCA) index was used as an estimate of full-scale IQ. Children with $GCA < 70$ were considered to have intellectual impairment.

Autism Spectrum Disorder

ASD status and severity was re-assessed at Time 4 via the Autism Diagnostic Observation Schedule–Second Edition (ADOS-2; Lord et al., 2012), a semi-structured behavioral observation of social and communication deficits indicative of ASD. In addition to a diagnostic cutoff of ASD, the ADOS-2 yields a Calibrated Severity Score (CSS) that allows comparison of ASD severity across individuals with varied functional and verbal abilities (Gotham, Pickles, & Lord, 2009). ASD-status was also confirmed at study entry via the ADI-R (Lord, Rutter, & Le Couteur, 1994), a structured parent interview of ASD with inter-rater reliability and validity (Rutter, Bailey, & Lord, 2003). Interviewers were trained to research reliability standards on both the ADI-R and ADOS-2.

Anxiety

The Anxiety Disorders Interview Schedule–IV–Parent Interview (ADIS–P; Albano & Silverman, 1996) is a semi-structured interview conducted with parents to assess the presence of childhood anxiety disorders with strong inter-rater and test-retest reliability (Lyneham, Abbott, & Rapee, 2007; Silverman, Saavedra, & Pina, 2001). In this study, we used the ADIS–P modules for OCD, separation, social, and generalized anxiety disorders, and specific phobia. Each module receives a clinical severity rating (CSR), from 0 (no interference) to 8 (severe interference), with 4 representing the cutoff for significant interference, and—when all other criteria are met—diagnosis. Importantly, the reformation of anxiety disorders from DSM–IV to DSM–5 was focused on the re-organization of chapter structures rather than changes to diagnostic criteria. As such, the ADIS–IV–P assesses all DSM–5 diagnostic criteria for specific phobia, social, separation and generalized anxiety as well as OCD, though OCD is now listed under a separate chapter in DSM–5 (Kupfer, 2015). Though both parent and child interviews are typically preferred, studies on

the ADIS in children with ASD suggest that parent and child agreement is limited and clinicians often base diagnostic impressions on parent reports (Storch et al., 2012). Given this, and the limited verbal abilities of some participants, this study used only the ADIS–P.

The Autism Spectrum Addendum (ASA; Kerns, Renno, Kendall, Wood, & Storch, 2017) is a series of prompts and guidelines that are woven into the ADIS protocol to tailor the instrument for children with ASD. The ADIS/ASA gathers additional information about the child’s developmental level, social functioning and motivation, experiences and environment, sensory sensitivities and preservative cognitive style. This information is used to guide differential diagnosis of symptoms and estimations of the impairment due to anxiety as opposed to other difficulties (e.g., communication challenges, ASD-related social deficits). For example, guidelines for the differentiation of social avoidance due to anxiety versus ASD-related deficits in social motivation are provided. Guidelines for differentiating ASD-related perseveration or repetitive thinking from worry, and specific phobias from sensory sensitivities are also included. A copy of the manual and standards for research use and training can be obtained from the first author.

The ASA also allows interviewers to assess for “distinct” manifestations of anxiety that commonly arise in ASD, but do not match the anxiety disorders specified by the DSM. A CSR from 0 to 8 is assigned with 4 marking the cutoff for symptoms that cause interference and are considered “clinically significant” (herein referred to as “clinical”). Distinct anxiety types include “idiosyncratic fears” (e.g. fears of toilets, specific sounds, glasses, beards), “other social fears” which include social fears related to social confusion rather than fear of negative evaluation, “special interest fears” (i.e. excessive worry or anxiety related to perseverative interests), “fears of change” (i.e., children with anxious anticipation of and distress following changes or novelty) or “negative reactions to change” (i.e., children with distress following change, but who do not have anticipatory fears), and “ambiguous compulsive symptoms” which capture compulsions or rituals that were associated with negative rather than positive affect, but which could not be clearly identified as being used to “prevent or neutralize” distress consistent with DSM–IV and DSM–5 OCD criteria. Negative reactions to change are not conceptualized as symptoms of anxiety given the lack of an anticipatory component, but are frequently endorsed and thus measured to provide a more complete picture of this difficulty. Interfering symptoms in this domain are measured apart from the DSM–

specified and distinct anxiety symptoms as it is unclear if they reflect true anxiety or rather broad difficulties with emotion regulation or flexibility.

Studies of this tailored diagnostic approach support the convergent and discriminant validity of the measure and indicate strong inter-rater reliability of CSRs ($ICC = .85-.99$) and diagnoses (Cohen's $K = .67-.90$) and 2-week retest reliability of CSRs ($.77-1.00$) and diagnoses (100% exact agreement) amongst trained evaluators (Kerns et al., 2014, 2017). All interviewers were trained to criterion for this study. Specifically, training included readings and didactic training on the ADIS/ASA and differential diagnosis of anxiety and ASD, observation and dual coding of ADIS/ASA administrations by a reliable interviewer and administration under the supervision of a reliable interviewer. To be considered reliable, all interviewers were required to independently agree on all diagnoses and assigned CSRs within one point of the assigned CSRs of a reliable trainer (the first author). In addition, continued reliability was ensured via weekly meetings of the evaluators and training in which cases were reviewed and discussed.

The Child Behavior Checklist/6–18 years (CBCL; Achenbach & Ruffle, 2000) is a standardized parent-report questionnaire of positive and problematic behaviors in children with established psychometric properties (Achenbach & Ruffle, 2000). The CBCL includes both Syndrome Scales, which are referred to as empirically-based scales and capture clusters of different types of problem behaviors derived by factor analysis, and DSM-oriented Scales, which were constructed based on expert clinician determinations of problem behaviors best characterizing different DSM disorders. Given our focus on the DSM-derived anxiety, we elected to examine the DSM-oriented Anxiety Problems Scale. Our focus was on individuals with *T-Scores* of 65 or greater indicating an elevated risk for anxiety disorder. Though the psychometric properties of the CBCL syndrome scales have been mixed (Medeiros, Mazurek, & Kanne, 2017; Pandolfi, Magyar, & Dill, 2012), a recent study of 93 well-characterized youth with ASD and varied intellectual functioning found that the DSM Anxiety Problems scale had high internal consistency ($.81$) and correlated $r = .66$ with the severity of anxiety as assessed by a semi-structured diagnostic interview (Magyar & Pandolfi, 2017). Internal consistency of the Anxiety Problems scale was $\alpha = .71$ in both the ASD and TD groups ($\alpha = .74$ overall).

Multidimensional Anxiety Scale for Children, Parent Report (MASC-P; March, Parker, Sullivan, Stallings, & Conners, 1997) is a 39-item standardized parent-report questionnaire of child anxiety symptoms that yields a total anxiety symptom score that includes items related to harm avoidance, physical

symptoms, social anxiety and separation anxiety. It demonstrates strong internal consistency, retest stability, and a reliable 4-factor structure, convergent validity and clinical sensitivity in research in children without ASD with a *T-Score* of 65 or greater indicating clinically significant symptoms. There is some support for internal consistency ($.92$) and discriminant validity of the MASC in cognitively-able, anxiety treatment-seeking samples of children with ASD (Renno & Wood, 2013; White, Schry, & Maddox, 2012), but White et al. (2015) found metric invariance when comparing the factor structure of the MASC in cognitively-able anxious children with versus without ASD. Studies of the MASC in children with ASD and low IQ are lacking.

Screen for Child Anxiety and Related Emotional Disorders, Parent Report (SCARED-P; Birmaher et al., 1999) is a 41-item parent-report questionnaire of child anxiety symptoms that yields a total anxiety score that includes items related to somatic symptoms, generalized anxiety, separation anxiety, social phobia, and school phobia. In studies of outpatient psychiatric samples, the SCARED has demonstrated good convergent and divergent validity, sensitivity ($.71$) and specificity ($.67$). A total cutoff of 25 is considered optimal for detecting clinically significant anxiety (Birmaher et al., 1999). Stern, Gadgil, Blakeley-Smith, Reaven, and Hepburn (2014) also found acceptable internal consistency ($.92$), sensitivity ($.71$) and specificity ($.67$) and partial support for the factor structure of the SCARED in cognitively-able children with ASD seeking anxiety treatment.

Procedure

Participants, both those with ASD and TD children, who provided informed consent, and who participated and successfully completed the early phases of the APP were asked to return for a battery of behavioral measures, including the ADOS-2, DAS-II, ADIS/ASA, CBCL, MASC-P, and SCARED, when they reached 9–13 years of age (Time 4). Diagnostic assessment of anxiety disorders was conducted only at this middle childhood timepoint given that anxiety disorders typically begin to emerge at this age (Beesdo et al., 2009) and given cross-sectional research suggesting an uptick in anxiety symptoms during this period in children with ASD (Davis et al., 2011). The behavioral battery was completed in multiple, 3 to 4-hour sessions arranged to accommodate families' schedules. All interviewers were doctoral level psychologists or students who were trained to criterion on the ADI-R, ADOS2 and ADIS/ASA.

Analytic Plan

The presence/absence of clinically significant symptoms (ADIS/ASA CSR ≥ 4) was calculated for each traditional and distinct anxiety module and children were categorized based on whether they met criteria for at least one DSM-specified anxiety disorder (including and excluding specific phobia), at least one clinically significant distinct anxiety, both or neither. Chi Square tests compared rates of clinically significant anxiety in TD versus ASD, as well in children with ASD by IQ ($<$ or ≥ 70). In the ASD sample, nonparametric correlations (*Spearman's ρ*) assessed the association of age and ADOS CSS with each participant's highest CSR in the DSM specified and distinct anxiety categories stratified by IQ group. An independent sample t-test compared the highest DSM and distinct CSR respectively by gender. Sensitivity, specificity, positive and negative predictive values with 95% confidence intervals were calculated for the SCARED, MASC and CBCL Anxiety subscale using the ADIS/ASA results as the gold standard. These metrics are presented using clinically significant anxiety of either type (DSM-specified or distinct), DSM-specified only and distinct only as the

criterion in the full sample, broken down by IQ, and for DSM-specified anxiety only in the higher IQ group.

Results

Sample Characteristics

Sample characteristics are included in Table 1. Age did not differ significantly in the TD v. ASD groups. Children with ASD were significantly more likely to be male (80%) than TD (62%), $X^2(1) = 5.2$, $p = .02$. Intellectual functioning was assessed in 93% ($n = 118$) of the sample and revealed broad range of cognitive functioning in the ASD group (IQ range: < 25 –170, $M [SD] = 77.39 [30.81]$) versus the TD groups (IQ range: 83–140, $M [SD] = 112.56 [13.62]$). Intellectual testing, though attempted, could not be completed in 8 youth in the ASD group with minimal to no communication skills. These youth were included in the intellectual impairment group. In addition, one youth who demonstrated average intellectual functioning at an earlier time point, (Full Scale IQ = 98 at 58 months) was categorized as being without intellectual impairment though he

Table 1. Sample demographic characteristics by diagnostic group ($N = 127$).

| | ASD ($n = 75$) | TD ($n = 52$) | | |
|---|---------------------|---------------------------|----------|----------|
| Age in Years, <i>mean (SD)</i> | 11.5 (1.0) | 11.6 (0.8) | | |
| Full Scale IQ ^{1,2} , <i>mean (SD)</i> | 77.4 (30.8) | 112.6 (13.6) ^a | | |
| Male, n (%) | 60 (80%) | 32 (62%) ^b | | |
| Race ³ , n (%) | | | | |
| White | 52 (71%) | 36 (72%) | | |
| Black | 5 (7%) | 0 (0%) | | |
| Asian | 5 (7%) | 4 (8%) | | |
| Mixed | 7 (10%) | 8 (16%) | | |
| Other | 3 (4%) | 2 (4%) | | |
| America Indian/Alaska Native | 1 (1%) | 0 (0%) | | |
| Hispanic ³ , n (%) | 17 (23%) | 13 (26%) | | |
| <30K | 12 (17%) | 7 (14%) | | |
| 30 to < 50K | 7 (10%) | 6 (12%) | | |
| 50k to < 75K | 13 (18%) | 8 (16%) | | |
| 75K to < 100K | 14 (20%) | 8 (16%) | | |
| 100K to <150K | 16 (23%) | 14 (28%) | | |
| 150K + | 9 (13%) | 7 (14%) | | |
| ADOS Severity Total, <i>mean (SD)</i> | 7.9 (1.6) | - | | |
| SCARED Parent Report Total, <i>mean (SD)</i> | 15.6 (11.6) | 10.4 (8.3) ^a | | |
| MASC Parent Report Total, <i>mean (SD)</i> | 54.3 (12.1) | 47.2 (9.0) ^a | | |
| CBCL DSM Anxiety Total, <i>mean (SD)</i> | 57.6 (7.6) | 52.7 (4.4) ^a | | |
| Level of Education ⁴ , n (%) | | | Mother | Father |
| No Formal School Completed | | | 1 (2%) | 0 (0%) |
| High School or Less | | | 3 (4%) | 11 (16%) |
| Some College | | | 12 (18%) | 11 (16%) |
| Technical or Associates Degree | | | 16 (24%) | 12 (18%) |
| Bachelor's Degree | | | 26 (38%) | 23 (34%) |
| Master's Degree | | | 8 (12%) | 7 (10%) |
| Doctorate | | | 2 (3%) | 4 (6%) |

Missing Data: ¹Based on Differential Abilities Scale-2, School-age or Early-years. ²Data missing for 9 ASD participants; ³Data missing for 2 ASD and 2 TD participants; ⁴Data missing for 7 ASD and 1 TD participant.

Significant Differences: ^a Different than ASD group, per independent samples t-test, at $p < .01$; ^b Different than ASD group, per chi-square analyses, at $p = .02$. All other ASD v TDC comparisons not significant.

Abbreviations: ADOS = Autism Diagnostic Observation Schedule; SCARED = Screen for Anxiety and Related Disorders, Parent Report, MASC = Multidimensional Anxiety Scale in Children, Parent Report, CBCL = Child Behavior Checklist.

was unable to complete IQ testing at the school-age follow-up due to severe disruptive behavior. Participants had a range of socioeconomic, educational levels, and racial and ethnic backgrounds, though over 70% were White/Caucasian and non-Hispanic in each group (see Table 1). There were no significant sociodemographic differences in the TD versus ASD groups.

There were no significant differences in Time 1 developmental quotients or ADOS CSS between the subset who completed the middle childhood battery and those who did not (n = 147); demographics were also similar between these groups (72% male, 54% non-Hispanic White/Caucasian, 80% male, 44% non-Hispanic White/Caucasian, respectively).

Rates of DSM-Specified Anxiety Disorders, OCD and Significant (CSR ≥ 4) Distinct Anxiety Symptoms in the ASD and TD Groups

Per the ADIS/ASA, children with ASD were significantly more likely to present with a DSM anxiety disorder than the TD group, $X^2(1) = 26.48, p < .001$. See Table 2. Within TD, 8% met criteria for a DSM anxiety disorder, including SAD (4%), Specific Phobia (4%), and Separation Anxiety Disorder (2%; with one child meeting criteria for multiple anxiety disorder types). No TD children displayed significant distinct anxiety per the ADIS/ASA; however, one child with a specific phobia diagnosis also had subclinical (CSR = 3) Fears of Change. Within ASD, 69% displayed clinically significant (CSR ≥ 4) anxiety symptoms, including 21% DSM anxiety disorders alone, 17% distinct anxiety alone, and 31%

with both DSM and distinct anxiety presentations (Figure 1a and b).

Rates of different DSM anxiety disorders and clinically significant distinct anxiety in the ASD group are also presented in Table 2. At least one DSM anxiety disorder or OCD was present in 52% of the ASD group. DSM anxiety disorders included Specific Phobia (44%), Generalized Anxiety Disorder (15%), Separation Anxiety Disorder (7%), and SAD (7%; including fears of negative evaluation). Four percent met criteria for OCD. At least one clinically significant distinct anxiety was present in 48% of the ASD group. Distinct anxieties included Fears of Change (23%), Uncommon Phobias (15%), Other Social Fears (8%, e.g. social fears unrelated to negative evaluation), and Special Interest Fears (7%). In addition, 8% displayed Ambiguous Compulsive Behavior. Examples included requiring all the doors to be closed in the house and requesting that someone draw something repetitively in a specific way then cross it out while displaying distress. Clinically significant negative reactions to change – that is, difficulties coping with change *without* anticipatory fears or worries about change were also identified in 9% of children. Notably, 45% (n = 34) of children were described as having fears of or negative reactions to change by their parents, but only 32% of these were considered clinically significant.

For those with ASD and DSM anxiety disorders, 17% (n = 13) had more than one – all but one of whom had IQ > 70 – and 59% (n = 23) also had clinically significant distinct anxiety. For those with clinically significant distinct anxiety, 64% (n = 23) also had a DSM anxiety disorder.

Table 2. Rates of DSM anxiety disorders, OCD and clinically-significant (CSR>3) distinct anxiety in ASD and TD groups per the ADIS/ASA.

| | TD | ASD | | |
|---|--------|-----------------------|-------------------|-----------------------|
| | N = 52 | All IQ N = 75 | IQ < 70 N = 36 | IQ ≥ 70 N = 39 |
| <i>DSM Anxiety or OCD</i> | 4 (8%) | 39 (52%) ^a | 17 (47%) | 22 (56%) ^b |
| <i>DSM Anxiety (excluding phobia) & OCD</i> | 3 (6%) | 17 (23%) ^a | 3 (18%) | 14 (36%) ^c |
| Separation Anxiety Disorder | 0 (0%) | 5 (7%) | 2 (6%) | 3 (8%) |
| SAD | 2 (4%) | 5 (7%) | 0 (0%) | 5 (13%) |
| Specific Phobia | 2 (4%) | 33 (44%) | 15 (42%) | 18 (46%) |
| Generalized Anxiety Disorder | 1 (2%) | 11 (15%) | 0 (0%) | 11 (28%) |
| OCD | 0 (0%) | 3 (4%) | 1 (3%) | 2 (5%) |
| <i>Clinically Sig. Distinct Anxiety</i> | 0 (0%) | 36 (48%) | 17 (47%) | 19 (49%) ^b |
| Other Social Fear | 0 (0%) | 6 (8%) | 3 (7%) | 3 (8%) |
| Uncommon Phobias | 0 (0%) | 11 (15%) | 5 (14%) | 6 (15%) |
| Special Interest Fear | 0 (0%) | 5 (7%) | 1 (3%) | 4 (10%) |
| Fears of Change | 0 (0%) | 17 (23%) | 7 (19%) | 10 (26%) |
| Ambiguous OCD | 0 (0%) | 6 (8%) | 5 (14%) | 1 (3%) |
| <i>Other Difficulties</i> | | | | |
| Negative Reactions to Change | 0 (0%) | 7 (9%) | 3 (8%) | 4 (11%) |

OCD = Obsessive Compulsive Disorder. ^aSignificantly different than TDC at $p \leq .01$; ^bNot significantly different than IQ < 70 group. ^c Significantly different than IQ < 70 group at $p < .01$ Statistical comparisons not conducted for clinically significant distinct anxiety in TDC v. ASD group or individuals diagnoses given that some cells had zero cases.

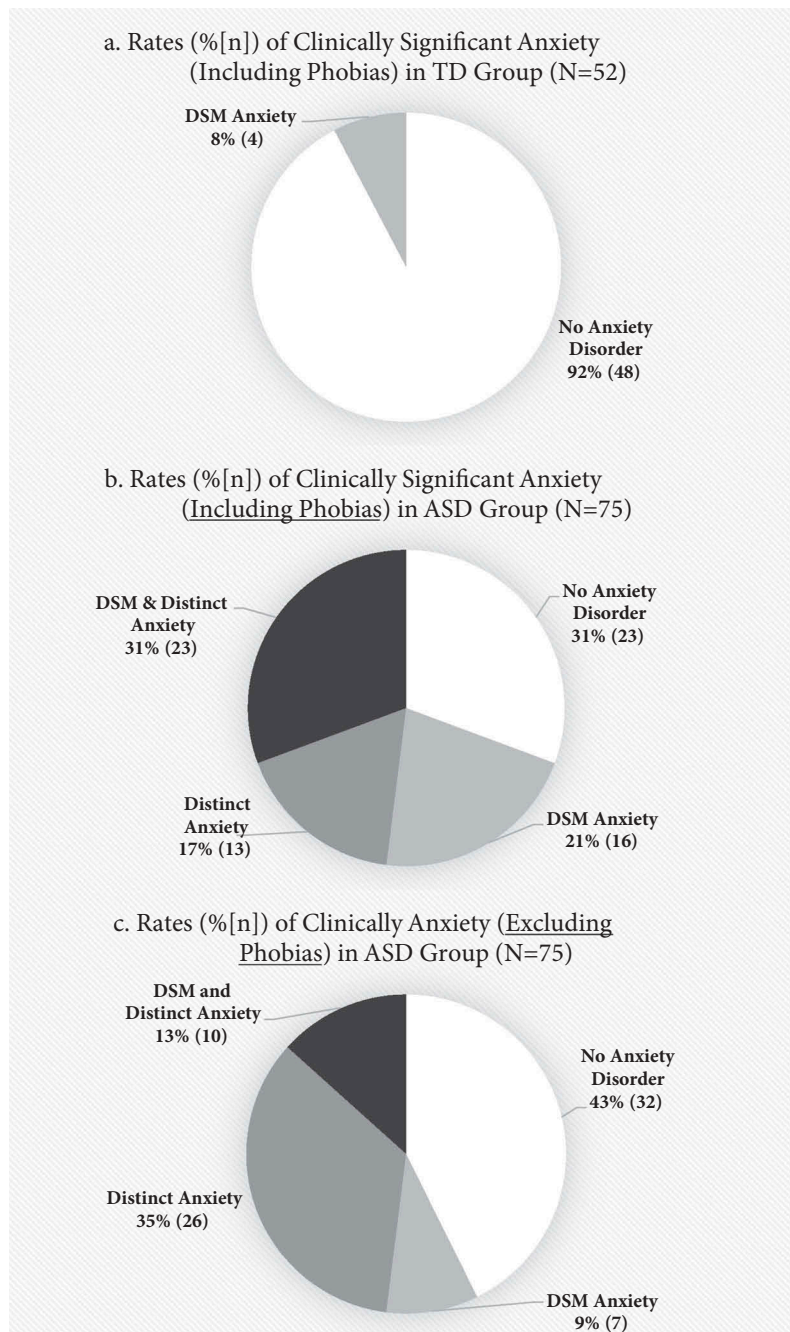


Figure 1. (a). Rates (%[n]) of clinically significant anxiety (including phobias) in TD group (N = 52). (b). Rates (%[n]) of clinically significant anxiety (including phobias) in ASD group (N = 75). (c). Rates (%[n]) of clinically anxiety (excluding phobias) in ASD group (N = 75).

TD = Typically Developing Children; ASD = Autism Spectrum Disorder.

All categories determined by Anxiety Disorders Interview Schedule/Autism Spectrum Addendum.

For 29% (n = 22) of children with ASD, the only DSM-anxiety disorder diagnosed was a specific phobia. As such, rates of DSM anxiety disorders changed substantially when this presentation was excluded (Figure 1c): 57% presented with clinically significant anxiety, including only 9% DSM anxiety disorders alone, 35% distinct anxiety alone, and 13% with both (23% with DSM anxiety disorders and 48% with distinct anxiety disorder overall).

Intellectual Impairment and Clinically Significant Anxiety in ASD

Rates of DSM anxiety disorders and clinically significant distinct anxiety were compared in youth with ASD with and without intellectual impairment (GCA < 70 or GCA \geq 70 respectively, on DAS-II; Table 2). Rates of both DSM-anxiety disorders (47% v. 56%, ns) and

Table 3. Concordance of brief parent report measures with ADIS/ASA.

| ADIS/ASA Determination ¹ | | SCARED (N = 70) %(95% CI) | MASC (N = 71) %(95% CI) | CBCL Anxiety Subscale (n = 71) %(95% CI) |
|---|-------------|------------------------------|----------------------------|---|
| Any Clinically Significant Anxiety | Sensitivity | 29.2 (28.8, 29.6) | 31.3 (30.8, 31.7) | 24.5 (24.1, 24.9) |
| | Specificity | 90.9 (90.5, 91.3) | 91.3 (90.9, 91.7) | 95.5 (95.2, 95.7) |
| | PPV | 87.5 (87.0, 88.0) | 88.2 (87.7, 88.7) | 92.3 (91.8, 92.8) |
| | NPV | 37.0 (36.6, 37.4) | 38.9 (38.5, 39.3) | 36.2 (35.8, 36.6) |
| DSM Anxiety Disorder | Sensitivity | 31.4 (30.9, 31.9) | 37.1 (36.6, 37.7) | 30.6 (30.1, 31.1) |
| | Specificity | 85.7 (85.3, 86.1) | 94.1 (93.9, 94.4) | 94.3 (94.0, 94.5) |
| | PPV | 68.8 (68.0, 69.5) | 86.7 (86.2, 87.2) | 84.6 (84.0, 85.2) |
| Clinically Significant Distinct Anxiety | NPV | 55.6 (55.1, 56.0) | 59.3 (58.8, 59.7) | 56.9 (56.5, 57.3) |
| | Sensitivity | 29.4 (28.9, 29.9) | 26.4 (26.0, 26.9) | 20.6 (20.2, 21.0) |
| | Specificity | 83.3 (82.9, 83.7) | 88.9 (88.6, 89.2) | 83.8 (83.4, 84.2) |
| Any Clinically Significant Anxiety, IQ < 70, N = 33 | PPV | 62.5 (61.7, 63.3) | 69.2 (68.4, 70.0) | 53.8 (53.0, 54.7) |
| | NPV | 55.6 (55.1, 56.0) | 56.1 (55.7, 56.6) | 53.5 (53.1, 53.9) |
| | Sensitivity | 9.1 (8.7, 9.5) | 0.0 | 13.0 (12.6, 13.5) |
| | Specificity | 90.9 (90.4, 91.5) | 1.00 | 1.00 |
| Any Significant Anxiety, IQ ≥ 70, N = 38 | PPV | 66.7 (65.0, 68.4) | NaN ² | 1.00 |
| | NPV | 33.3 (32.8, 33.9) | 33.3 (32.8, 33.8) | 33.3 (32.8, 33.9) |
| | Sensitivity | 46.2 (40.9, 90.4) | 57.7 (57.1, 58.3) | 34.6 (34.0, 35.2) |
| | Specificity | 90.9 (90.4, 91.5) | 83.3 (82.7, 84.0) | 91.7 (91.2, 92.2) |
| DSM Anxiety Disorder, IQ ≥ 70, N = 38 | PPV | 92.3 (91.8, 92.8) | 88.2 (87.7, 88.7) | 90.0 (89.4, 90.6) |
| | NPV | 41.7 (41.0, 42.3) | 47.6 (46.9, 48.3) | 39.3 (38.7, 39.9) |
| | Sensitivity | 52.3 (51.7, 53.1) | 61.9 (61.2, 62.6) | 42.9 (42.2, 43.5) |
| | Specificity | 87.5 (87.0, 88.0) | 76.5 (75.8, 77.1) | 94.1 (93.8, 94.5) |
| | PPV | 84.6 (84.0, 85.2) | 76.5 (75.8, 77.1) | 90.0 (89.4, 90.6) |
| | NPV | 58.3 (57.7, 59.0) | 61.9 (61.2, 62.6) | 57.1 (56.6, 57.7) |

¹ADIS/ASA determinations were considered the gold standard in these analyses. ²NaN = Not a number; could not be calculated given that the MASC did not correctly identify any children in this subsample with clinically significant anxiety. ADIS/ASA = Anxiety Disorders Interview Schedule/Autism Spectrum Addendum; SCARED = Screen for Anxiety and Related Emotional Disorders, Parent Report; MASC = Multi-dimensional Anxiety Scale for Children, Parent Report; CBCL = Child Behavior Checklist, DSM Anxiety Problems Subscale.

distinct anxiety (47% v. 49%, *ns*) were not significantly different for children with or without intellectual impairment. However, the vast majority of DSM anxiety disorders in children with IQ < 70 were specific phobias, while DSM anxiety disorders (other than phobia) were significantly less common in children with (8%) versus without (36%) intellectual impairment ($X^2(1) = 8.11, p < .01$). That is, the similar rate of DSM anxiety in both low and high IQ groups appeared to be driven by a high rate of specific phobias, as opposed to other forms of DSM anxiety, in children with intellectual impairment. Specific phobia was diagnosed at similar rates in both groups (42% and 46%, respectively). Rates of other types of DSM anxiety disorder were too low in the intellectually impaired group for statistical comparison. There were no significant differences in specific distinct anxiety presentations by IQ status.

Child Characteristics Associated with Clinically Significant Anxiety in ASD

The highest CSR given for any DSM anxiety on the ADIS/ASA was significantly correlated with the highest CSR given for any distinct anxiety in children without (*Spearman's* $\rho = 0.39, p = .01$), but not with intellectual impairment (*Spearman's* $\rho = 0.02, ns$) in the ASD group. Neither DSM, nor distinct anxiety CSR were significantly correlated with ADOS severity or age in children with ASD, regardless of IQ status. Neither differed significantly by gender. A series of post-hoc,

one-way ANOVA suggested no significant differences in age, ASD severity (ADOS SA and RRB comparison scores), IQ or overall anxiety severity (top CSR on ADIS/ASA) for children with distinct alone, DSM-alone or mixed presentations of clinical anxiety; however, these groups were relatively small and thus there was limited power to detect differences.

Concordance of Clinical Interviews with Brief Parent Report Measures

We next calculated the sensitivity, specificity, PPV and NPV of the parent-report MASC total, SCARED total and CBCL DSM Anxiety Problem subscale total in detecting cases with clinically significant anxiety overall and by presentation (DSM v. distinct) based on the ADIS/ASA (see Table 3). Whereas specificity (76.5%–100% across measures) was strong, sensitivity (0%–61.9%) and NPV (33.3%–61.9%) were generally weak. PPV was mixed, appearing stronger for any significant anxiety (87.5%–92.3%) and DSM anxiety disorders (68.8%–86.7%) than for distinct anxiety (53.8%–69.2%).

Child IQ and verbal IQ were significantly correlated with total scores on the SCARED, MASC and CBCL Anxiety Problems Subscale (Table 4). Sensitivity was poorest for detecting any significant anxiety in cases with intellectual impairment (0%–0.13); the majority of cases in this group were missed. When restricting the sample to children without intellectual impairment, specificity was maintained (83.3%–91.7%) and

Table 4. Pearson correlations (R[n]) between IQ, verbal IQ with brief measures of anxiety.

| | SCARED Total | MASC Total | CBCL Anxiety Problems Total |
|-----------|--------------|------------|-----------------------------|
| IQ | 0.48* (61) | 0.55* (62) | 0.38* (63) |
| Verbal IQ | 0.49* (56) | 0.50* (57) | 0.39* (58) |

* $p < .01$. Given some missing data, the sample size for each correlation is indicated as R(n).

sensitivity improved, but not to satisfactory levels (34.6%–57.7%). All measures were most sensitive in detecting DSM anxiety disorders in children without intellectual impairment (the group most similar to that for whom these measures were designed), yet sensitivity (42.9%–61.9%) and NPV (57.1%–61.9%) remained modest. Sensitivity for detecting children with DSM anxiety disorders other than simple, specific phobia was also modest (CBCL 38%; MASC 63%; SCARED 44%).

Discussion

The extent to which anxiety disorder estimates in children with ASD are biased by the inconsistent differentiation of anxiety and ASD symptoms is unclear (Kerns & Kendall, 2012). The present study used a rigorous, tailored examination of DSM-specified anxiety disorders and other “distinct” forms of problematic anxiety in a well-characterized, intellectually diverse sample to provide more precise and nuanced estimates of anxiety disorders in ASD and evaluate how anxiety presentation and intellectual impairment contribute to measurement bias. Youth were assessed in middle childhood, given research suggesting that anxiety disorders typically begin to emerge at this age (Beesdo et al., 2009).

Findings affirm that DSM-specified anxiety disorders are prevalent and significantly more common in ASD (52%) versus TD (8%), even when diagnostic criteria are strictly applied and care is taken to differentiate overlapping and ambiguous symptoms. This rate falls within the range reported in other studies of DSM-specified anxiety disorders in population-based (42%) and outpatient samples of children with ASD (55%; de Bruin et al., 2007; Simonoff et al., 2008) and strengthens these findings. Specifically, in contrast to prior work, the interview used in this study collected additional information regarding relevant features of ASD in order to minimize errors in differential diagnosis (e.g. overshadowing of anxiety by autism symptoms or over-attribution of autism-related deficits to anxiety) and provide refined estimates of clinical anxiety.

The presence of distinct or idiosyncratic fears in ASD has repeatedly been documented, but rarely systematically assessed (see Magiati, Ozsivadjian, & Kerns,

2017). Present findings align with a prior study (Kerns et al., 2014) in suggesting that almost 50% of children with ASD present with functionally impairing fears and worries that differ qualitatively from DSM-specified diagnoses, including excessive fears related to change (23%), idiosyncratic stimuli (e.g. toilets, songs; 15%), social confusion rather evaluation (8%), and special interests (7%). In addition, 8% of children presented with compulsive behaviors, which though negative in valence, did not clearly serve a neutralizing function (as is characteristic in OCD). Of those children with ASD and clinically significant anxiety, 69% had distinct symptoms. In addition, almost two-thirds of children with distinct anxiety also had DSM-specified anxiety disorders. This suggests that distinct and DSM presentations commonly co-occur in ASD, a consistent finding across studies (Kerns et al., 2014, 2017).

Findings are consistent with a recent study which found fears of uncertainty to be the most common expressions of anxiety in children with ASD (Keen, Adams, Simpson, Den Houting, & Roberts, 2019) and with a significant canon of work demonstrating a close relationship between anxiety and intolerance of uncertainty in ASD (Boulter, Freeston, South, & Rodgers, 2014; Chamberlain et al., 2013; Wigham, Rodgers, South, McConachie, & Freeston, 2015). In the present sample, fears or negative reactions to change were reported in 45% and deemed clinically significant in 32%; only specific phobias were more common (44%). The rate of additional uncommon phobias (e.g. fears of bubbles, songs; 15%) was also similar to that found in Kerns et al. (2014), but lower than the 41% reported by Mayes et al. (2013), who did not assess the severity of fears and conceptualized a broader range of fears as unusual (e.g. heights, weather, small spaces) in their estimate. Overall, findings indicate that reliance on DSM-specified anxiety disorders alone may result in substantial underestimation and incomplete characterization of impairing anxiety problems in children with ASD. The few studies to use anxiety measures, which are developed for children with ASD and also query about fears of uncertainty, sensory and non-evaluative social fears, are thus far consistent in suggesting that clinical anxiety occurs in closer to two-thirds of children with ASD (Den Houting, Adams, Roberts, & Keen, 2018; Kerns et al., 2014) as opposed to the range of 40–55% suggested by studies using un-adapted measures (de

Bruin et al., 2007; Gjevik et al., 2011; Simonoff et al., 2008; van Steensel et al., 2011).

Our TD comparison group provided two additional important findings: (1) clinically significant distinct anxiety was not reported in children without ASD (though subclinical fears of change were reported in 1 child), and (2) rates of DSM-anxiety disorders were in the expected range (8%) for this age group (Costello, Egger, & Angold, 2005). Fears and intolerance of uncertainty are well-documented in children with anxiety disorders and associated with worry and anxiety in nonclinical populations (Osmanoglu, Creswell, & Dodd, 2018). Though these fears are not unique to ASD, as noted above, they may be distinctly prominent and exaggerated (e.g. Donald's fear of the setting sun). Future comparisons with other, high risk groups that share some similarities with ASD, such as children with other developmental delays (e.g. Fragile X, Down's syndrome), attention-deficit hyperactivity disorder and specific language impairments may illuminate the extent to which children with ASD demonstrate a truly *unique* vulnerability and profile of anxiety.

The second aim of this study was to examine how intellectual impairment is related to the expression and detection of significant anxiety in ASD. The research literature has been inconclusive regarding the relationship of intellectual functioning to anxiety disorder risk in ASD. Consistent with the hypotheses of Kerns and Kendall (2012), the present results suggest a nuanced relationship between a child's developmental level and the quality, but not the quantity of anxiety symptoms in children with ASD. That is, for children with intellectual impairment (and thus lower mental age), the only DSM-anxiety diagnoses given were specific phobias (42%) and separation anxiety disorder (6%) – anxiety disorders which research suggests have the earliest age of onset in childhood (Beesdo et al., 2009). OCD was also diagnosed in 3% of these youth. By contrast, the full range of childhood DSM-anxiety disorders were seen in children with ASD and IQ>70. These findings suggest that positive associations between IQ and anxiety in ASD, as seen for all parent-report measures of anxiety in this study, may be misleading and result from a reduced sensitivity to detect the expression of anxiety in developmentally immature youth. Though there were no significant differences in the rates of DSM anxiety disorders or distinct anxiety by IQ status, DSM-anxiety disorders *other than* specific phobia were significantly less common in children with (18%) versus without (35.7%) intellectual impairment. Findings are consistent with prior research demonstrating a significant relationship between certain types of anxiety (e.g. GAD) and IQ in ASD, but not others (e.g.

phobia, avoidance; Sukhodolsky et al., 2008) and between greater language ability (often associated with IQ) and DSM-specified, but not distinct anxiety symptoms (Kerns et al., 2014).

The relative predominance of specific phobia and distinct anxiety presentation in autistic children with v. without ID has substantial measurement implications. Most brief measures of anxiety in school-age youth inquire broadly about DSM anxiety disorders and thus may be less sensitive to this more constrained and distinctive presentation. Consistent with this hypothesis, all brief parent-report measures of anxiety included in this study had limited sensitivity to detect clinically significant anxiety in the ASD group, particularly amongst children with ID, for whom almost all cases were missed. Yet, this explanation is likely not sufficient as sensitivities for detecting cases with DSM anxiety disorders other than specific phobia in this study were also modest. By contrast, a prior study found that the CBCL anxiety problems subscale detected 83% of ASD cases with an anxiety diagnosis (Magyar & Pandolfi, 2017). As such, further research is needed to understand what may account for these discrepancies in the CBCL's detection of affective problems in ASD across studies (see also Medeiros et al., 2017; Pandolfi et al., 2012).

Whereas some studies suggest that the construct of anxiety may not be adequately captured by standard anxiety questionnaires (Dovgan, Mazurek, & Hansen, 2019; Jitlina et al., 2017; Kerns, Maddox, et al., 2015; White et al., 2015), others have reported adequate psychometric properties in ASD samples (Stern et al., 2014; van Steensel, Deutschman, & Bögels, 2013). Our findings suggest that these tools are likely most appropriate for detecting DSM anxiety in children with ASD and minimal intellectual impairments – a subgroup of children with ASD upon which most affirmative studies have focused. A recent study found that few children seeking cognitive-behavioral treatment (CBT) for anxiety presented with solely distinct symptoms; rather the majority had DSM-specified disorders, both with and without clinically significant distinct anxiety (Kerns et al., 2017). The focus on treating DSM-specified anxiety disorders in cognitively-able children in these studies may explain why measures like the SCARED and MASC have proven useful and sensitive to treatment (Reaven, Blakeley-Smith, Culhane-Shelburne, & Hepburn, 2012; Wood et al., 2015). Nonetheless, current findings suggest that these measures may fall short in detecting clinical anxiety amongst children with ASD who are not treatment seeking (i.e. relatively low risk samples) or who have co-occurring intellectual impairment. Moreover,

they suggest these measures may tell an incomplete story even about the anxiety of verbal children with ASD and DSM-specified anxiety, many of whom will also present with additional, distinctive fears and worries.

Limitations

Though the ADIS/ASA incorporates clinical judgment, clinicians were constrained in their judgments to information provided by the parent in this study. Self and teacher reports of internalizing symptoms, like anxiety, often differ in youth with (Blakeley-Smith, Reaven, Ridge, & Hepburn, 2012; Kaat & Lecavalier, 2015) and without ASD (Miller, Martinez, Shumka, & Baker, 2014), and these differences in perspective may provide important, complementary insights regarding the expression and pervasiveness of a child's symptoms (De Los Reyes & Kazdin, 2005). Future studies should examine differences in the prevalence of symptoms based on parent, child and composite (diagnoses endorsed by parent or child) reports and also what mental age and verbal abilities may be required for various child and parent report measures to be useful. Additional limitations include the small number of nonwhite and female children with ASD in this sample, which constrains the generalizability of our results to children with similar sociodemographic characteristics and may have prohibited detection of gender differences.

Clinical Implications and Future Directions

It has been hypothesized that anxiety in ASD may reflect an artifact of phenotypic overlap, or a distinct co-occurring condition, either similar (e.g. comorbidity) or varied in presentation from monomorbid anxiety (Kerns & Kendall, 2012; Wood & Gadow, 2010). Our results add to a wealth of studies indicating a prevalence of anxiety symptoms that can be reliably differentiated and appear to reflect a distinct construct from ASD and support the hypothesis that anxiety conditions manifest in both a traditional and distinct manner in ASD (Kerns & Kendall, 2012; Renno & Wood, 2013). Distinct anxiety, though thematically related to ASD symptoms (e.g., insistence on sameness, sensory difficulties), had a stronger relationship to DSM anxiety than ASD severity. Whereas distinct anxiety was *not* significantly associated with ASD severity (in children of either IQ group), it was associated with DSM anxiety in intellectually-able children

with ASD. DSM and distinct anxiety were not significantly associated in children with ASD and intellectual impairment, but this may be explained by the limited amount and variety of DSM anxiety in this group. Moreover, the base rates of significant distinct anxiety (6–23%) were not consistent with their being conceptualized as integral or inevitable consequences of ASD (Folstein, 2012). Kerns et al. (2014) also reported that significant DSM and distinct anxiety occur in a substantial subset, but not all, children with ASD and were more strongly related to one another than ASD severity. Finally, a growing number of researchers, content experts, parents and verbal individuals with ASD are advocating for the behaviors described here as “distinct anxiety” to be recognized as fears and worries (Magiati et al., 2017; Robertson et al., 2018) and distinct expressions of anxiety are increasingly being incorporated into adapted measures (Kerns et al., 2017; Rodgers et al., 2016; Scahill et al., 2019). In support of this movement, the present findings reiterate not only the fearful and anxious quality of these symptoms, but also their association with significant additional functional impairment for many children with ASD.

With regard to future directions, assessing a broader range of anxiety problems in ASD with greater accuracy may shed light on how anxiety relates to the phenotype and developmental trajectory (Baribeau et al., 2019) and outcomes of children with ASD (Kerns, Kendall, et al., 2015; Lecavalier et al., 2017; Pellecchia et al., 2016; van Steensel et al., 2012) and aid in the identification of anxiety biomarkers, such as physiological (Hollocks, Howlin, Papadopoulos, Khondoker, & Simonoff, 2014) and amygdala responses (Herrington et al., 2017), in ASD. Accurate assessment is also critical to ensure that the full range of children suffering from anxiety problems are identified and given access to appropriate interventions. An important next step to achieving this goal will be determining if distinct anxiety presentations require a tailored intervention approach (Wood et al., 2015) or a focus on potential transdiagnostic mechanisms like intolerance of uncertainty (Rodgers et al., 2017). Finally, to achieve more accurate diagnosis and treatment in community settings, it will be important to understand the extent to which ASD providers perceive anxiety disorders in their clients and how these perceptions are shaped by provider (e.g., discipline, experience), child (e.g., intellectual functioning, gender, expression of anxiety) and structural characteristics (e.g., the ability to assign an appropriate diagnostic code; Wainer et al., 2017).

Disclosure statement

Connor Kerns receives royalties for an edited book on anxiety and autism published by Academic Press. In addition, she has received honoraria and consulting fees for training others researchers on the Autism Spectrum Addendum. David Amaral is on the Scientific Advisory Board of Stemina Biomarkers Inc. and Axial Biotherapeutics and has consulted for Roche/Genetech and Labcorp.

Data availability

Data from the Autism Phenome Project cohort is deposited in NDAR according to NIH policy (nda.nih.gov).

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