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Autism spectrum disorder (ASD) symptom profiles of children with comorbid Down syndrome (DS) and ASD: A comparison with children with DS-only and ASD-only

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ABSTRACT

Background: Down syndrome (DS) is associated with increased rates of autism spectrum disorder (ASD), characterized by social−communicative impairments (SOC−COM) and repetitive behaviors and interests (RBI). However, little is known about the ASD symptom presentation in children with DS + ASD.

Aims: The current study sought to describe parent-report of SOC−COM and RBI symptoms on the Autism Diagnostic Interview -Revised (ADI-R) in children with DS (n = 22), DS + ASD (n = 11), and ASD (n = 66).

Method: SOC−COM and RBI scores from the ADI-R were compared across the groups whose autism status was ascertained using the Autism Diagnostic Observation Schedule.

Results: Differences in SOC−COM and RBI symptom severity was observed. The general pattern of findings was ASD > DS+ASD > DS. Dissimilar ASD symptom profiles were observed across groups. In ASD, SOC−COM scores were higher than RBI scores; in DS + ASD, similar SOC−COM and RBI scores were observed. Lastly, SOC−COM impairments were highly related to verbal cognition in youth with DS + ASD but not in those with DS or ASD.

Conclusions and Implications: These findings suggest that children with DS + ASD have a distinct profile of ASD symptoms that differs from peers with either disorder in isolation. Thus, care should be taken in evaluating and designing treatments for this group.

What this paper adds?

Few studies have examined the ASD symptom profile of youth with comorbid DS and ASD (DS + ASD). Of the limited research, no studies of DS + ASD examining ASD symptoms have used gold standard diagnostic measures to designate group membership. Consequently, the current study expands upon past research by examining ASD symptoms in children with DS + ASD, DS-only, and ASD-only who were diagnosed through direct assessment using the gold standard Autism Diagnostic Observation Schedule and whose ASD symptom severity was evaluated using the Autism Diagnostic Interview – Revised. Additionally, unlike prior research, this study considers the influence of verbal cognitive skills on children's ASD symptom severity. The current study's results indicated: (1) children with DS + ASD present with less severe

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social-communication impairments than peers with ASD, particularly when controlling for verbal cognitive abilities; (2) unlike peers with either condition in isolation, social-communication skills in DS + ASD were closely tied to verbal mental age; (3) even when verbal mental age was roughly equivalent, there was a trend for children with DS + ASD to have greater social-communication impairments than peers with DS, suggesting that lower verbal cognition alone cannot account for the ASD comorbidity. Given parent report of less severe social-communication impairments in youth with DS + ASD, comorbid ASD may be less likely to be detected early. However, the presence of comorbid ASD alongside severe verbal cognitive impairments indicates that this group is in great need of intensive services. Thus, efforts to identify these children early are of great importance.

1. Introduction

1.1. Background

There is a growing interest in the occurrence of comorbid autism spectrum disorder (ASD) in youth with genetic disorders characterized by intellectual disability (ID), such as Down Syndrome (DS). DS, the most common form of ID with a known genetic etiology, is characterized by a unique cognitive-behavioral phenotype (for a review, see Edgin, 2013) and traditionally, has been associated with friendly and affectionate personalities (Carr, 1994; Fidler, Most, Booth-LaForce, & Kelly, 2008). Despite this association, some youth with DS present with ASD, a disorder characterized by social and communicative impairments, and restricted, repetitive behaviors and interests (RBI), more frequently than typically-developing youth. Specifically, while 1.7 percent (i.e., 1 in 59; Center for Disease Control & Prevention, 2018) of typically-developing children are diagnosed with ASD, research suggests that between 16 and 42 percent (depending on the diagnostic measurements and criteria used) of children with DS meet criteria for a comorbid ASD diagnosis (DiGuiseppi et al., 2010; Oxelgren et al., 2017; Warner, Howlin, Salomone, Moss, & Charman, 2017). Even when the lowest prevalence rate is considered, there is consistent evidence that DS is associated with a significantly elevated risk of ASD relative to population estimates.

Past research examining those with dual diagnoses of DS and ASD (DS + ASD) suggests a unique cognitive-behavioral profile diverging from those with DS-only. For example, those with DS + ASD have a higher likelihood of greater cognitive impairment (DiGuiseppi et al., 2010) and developmental regression (Capone, Grados, Kaufmann, Bernad-Ripoli, & Jewell, 2005; Castillo et al., 2008) in comparison to those with DS-only. Children with DS + ASD also have greater withdrawal, aggression, anxiety, and poorer social cognition than peers with DS-only (Carter, Capone, Gray, Cox, & Kaufmann, 2007; Channell et al., 2015; Castillo et al., 2008; Dressler, Perelli, Bozza, & Bargagna, 2011; Magyar, Pandolfi, & Dill, 2012; Molloy et al., 2009; Warner, Moss, Smith, & Howlin, 2014;). Furthermore, children with the dual diagnosis have been found to have lower adaptive functioning levels (Dressler et al., 2011) and increased repetitive and stereotyped behaviors in comparison to those with DS-only (Carter et al., 2007; Hepburn & Maclean, 2009; Magyar et al., 2012). Research specifically examining ASD symptom severity using the Social Communication Questionnaire (SCQ) has found that children with DS + ASD and DS have comparable levels of nonverbal communication impairments. However, the comorbid group has significantly more impairments in Social and RBI domains than the DS-only group (Magyar et al., 2012). Given that children with DS + ASD have unique challenges in comparison to those with DS-only, youth with DS + ASD may require additional interventions that draw from the ASD intervention literature, in comparison to children with DS-only children.

Thus, to begin to evaluate this possibility, it is important to compare ASD symptom profiles and severity of youth with DS + ASD to those with idiopathic ASD and to those with DS-only. Although this research area is growing, studies comparing the three groups have yielded mixed findings. For example, one study reported that children with ASD have greater difficulty relating to others, responding to emotion, and imitating others than children with DS + ASD (Dressler et al., 2011). In a study that used the SCQ to examine symptom profiles for children with DS + ASD and those with idiopathic ASD, the DS + ASD group had significantly lower scores (i.e., fewer symptoms) on the Social, Communication, and RBI domains and fewer emotional and peer-related problems than their peers with ASD-only (Warner et al., 2017). In the only study to date to examine youth with DS, DS + ASD, and idiopathic ASD, the SCQ revealed that the DS group had significantly fewer symptoms on all three symptom domain scales (i.e., Social, Communication, and RBI) than the DS + ASD and idiopathic ASD groups (Moss, Richards, Nelson, & Oliver, 2013). However, in contrast to Warner's et al. (2017) findings, the DS + ASD and ASD groups did not significantly differ on any domain.

Enriching our understanding of the symptom profile associated with DS + ASD is pertinent for improving clinical care of this population. First, this research may help clinicians better identify ASD symptoms in youth with DS at a younger age. Given that research has demonstrated that early diagnosis of ASD is associated with an increased success rate of intervention (for review, see Koegel, Koegel, Ashbaugh, & Bradshaw, 2014), early diagnosis of ASD in youth with DS is critical. Yet children with DS are less likely to be diagnosed with ASD as early as children without DS (for review see Reilly, 2009). Recognizing ASD symptoms early in children with DS may be difficult due to the limited understanding of the comorbid DS + ASD behavioral presentation, and due to the fact that developmental regression in those with DS + ASD occurs later than it does for those with ASD-only (Castillo et al., 2008). Therefore, improving clinician and caregiver's understanding of behavioral profiles of comorbid DS and ASD could lead to earlier recognition of ASD traits in this population, and ultimately lead to earlier access to intervention to improve cognitive and behavioral outcomes.

In addition, a better understanding of the traits associated with the comorbid diagnosis may contribute to improved outcomes for caregivers of children with DS + ASD. Research indicates that parents of youth with DS + ASD report heightened stress and feelings of isolation when their child displays behavior atypical of their genetic syndrome (Blacher, Kraemer, & Howell, 2010; Hepburn, Philofsky, Fidler, & Rogers, 2008). Providing caregivers with psychoeducation about symptoms related to a dual diagnosis could increase their ability to appropriately respond to, instruct, and support their child with DS + ASD, and ultimately create stronger parent-child relations (Suma, Adamson, Bakeman, Robins, & Abrams, 2016; Baird et al., 2001).

Lastly, understanding the symptom profiles of children with DS + ASD can contribute to the field's understanding of ASD. Because past research has suggested independent genetic underpinnings of the social, communication, and RBI symptoms associated with ASD (Ronald et al., 2006; For review see Happé & Ronald, 2008), providing descriptions of ASD symptom presentations and severity in those with a known genetic etiology, such as DS, may shed light on the genetic risk factors for different aspects of the ASD behavioral phenotype.

In summary, understanding the symptom profiles associated with comorbid DS + ASD is pertinent to support children's development, parent-child relations, and to provide greater understanding of ASD. However, very few studies have examined this comorbid group in comparison to both children with isolated DS and those with isolated ASD. Moreover, no studies to date have described the social-behavioral phenotype of youth with DS + ASD who were diagnosed using gold-standard diagnostic tools such as the Autism Diagnostic Observation Schedule (ADOS) or the Autism Diagnostic Interview-Revised (ADI-R). Rather, existing studies have used psychiatric interview and observation or diagnostic screeners to assign diagnoses. Utilizing diagnostic screeners may result in false positive diagnoses, as some items on these scales may be elevated due to ID rather than ASD symptomatology specifically (DiGuiseppi et al., 2010). Accurate identification of youth with DS + ASD is necessary to appropriately examine the symptom profiles of this group. Thus, the current study aims to fill this gap in the literature by describing ASD symptom profiles in children with DS + ASD, DS, and ASD, whose ASD diagnosis, or lack thereof, was determined using a gold-standard diagnostic tool, the ADOS.

2. Methods

2.1. Participants

DS and DS + ASD participants: Participants with DS were a subset of individuals previously enrolled in studies from two universities (for more information, see DiGuiseppi et al., 2010). Participants were eligible if they were born between January 1, 1996 to December 21, 2003 and had a caregiver who spoke English or Spanish fluently. These participants were originally recruited from a statewide registry of birth defects, which included families' contact information and most recent mailing address. Additionally, individuals were recruited through a parent organization which advertised the study via newsletters, mailings to group members, and at community events, such as workshops for parents.

For the purposes of the current study, children were included if they had complete data on the targeted ADI-R algorithm items (see below), had a diagnostic classification from the ADOS, and had complete data on the language subscales of the Mullen Scales of Early Learning. To be included in the DS-only group, the participant must have been free of an ASD diagnosis on the ADOS. This criterion resulted in the selection of 22 participants with DS. To be included in the DS + ASD group, the participant must have received an ASD diagnosis on the ADOS. This criterion resulted in 11 participants in the DS + ASD group. See Table 1 for descriptive information about these two groups.

2.1.1. ASD participants

Participants with a primary diagnosis of ASD were drawn from the National Database on Autism Research (NDAR) and were carefully matched to the DS participants using a 2:1 ratio. Participants were matched groupwise to the DS groups on sex, chronological age, and verbal mental age (an average of the MSEL Expressive and Receptive Language raw scores). The ASD group included 66 participants, 44 of whom were matched to the 22 DS-only participants, and 22 of whom were matched to the 11 DS + ASD participants. See Table 1 for descriptive information about this group.

Table 1
Descriptive data of participants.

	DS (n = 22)			DS + ASD (n = 11)			ASD (n = 66)			Stat. Sig.
	M	*SD*	*Range*	*M*	*SD*	*Range*	*M*	*SD*	*Range*	*F*
Age	58.5	14.33	37-91	57.73	16.40	37-84	50.74	14.10	30-99	F = 3.0, p = 0.06
Verbal MA	25.15	5.93	14.5-37	15.95	8.09	8.5-29.5	22.85	7.95	6.0-42.0	F = 5.5, p = 0.05$_a$
Verbal DQ	47.12	11.20	20.1-64.4	28.43	16.20	8.3-51.2	49.66	20.38	8.06-101.6	F = 6.3, p < 0.01$_a$
Nonverbal DQ	53.32	12.95	29.3-75.9	32.89	12.56	12.3-48.1	63.05	18.83	19.4-107.8	F = 15.49, p < 0.01$_a$
	N	%		N	%		N	%		χ^2
Sex: Female	7	31.8%		4	36.4%		22	50%		χ^2 = 0.7, p = 0.97
Race: WNH	19	86.4%		9	81.8%		28	63.6%		χ^2 = 4.85, p = 0.09

Note: a = DS > DS + ASD; ASD > DS + ASD; DS ˜ ASD.

2.2. Measures

2.2.1. Diagnostic

The Autism Diagnostic Observation Schedule (ADOS), used as the primary diagnostic tool for the study, is a performance-based observational assessment designed to evaluate social reciprocity, communication and language skills, and RBI related to ASD (Lord et al., 2000). Based on the participant's language and developmental levels, ADOS Modules 1 or 2 were administered to all participants included in the current study; Modules 3, 4, and 5 were not administered.

2.2.2. ASD-DS verbal mental age matching measure

The Mullen Scales of Early Learning (MSEL) is a developmental assessment tool used to evaluate infants and children between the ages of birth and 68 months (Mullen, 1984). For the purposes of the current study, an overall verbal score was determined by averaging participants' Expressive and Receptive Language subdomain raw scores. Additionally, MSEL scores were used to calculate verbal and nonverbal developmental quotients (DQ) for descriptive purposes. DQ scores were calculated by dividing the age equivalent domain score by the participant's chronological age and multiplying by 100. The Verbal DQ was the average DQ for the Expressive and Receptive Language subtests. The Nonverbal DQ was the average DQ for the Visual Reception and Fine Motor subtests.

2.2.3. Outcome measure

The Autism Diagnostic Interview - Revised (ADI-R) is a structured interview used as a diagnostic measure for ASD (Lord, Rutter, & Le Couteur, 1994; Rutter, Le Couteur, & Lord, 2003) which was used to evaluate symptom severity levels in the three diagnostic groups. (See procedures below for more details). This interview includes over 100 questions, and items focused on the three primary domains of ASD: (1) Social Reciprocity, (2) Communication and Language abilities, and (3) RBI. The ADI-R items are scored on the following scale: 0: "behavior of the type specified in the coding is not present"; 1: "behavior of the type specified is present in an abnormal form, but not sufficiently severe or frequent to meet the criteria for a 2″; 2: "definite abnormal behavior"; 3: "extreme severity of the specified behavior"; 7 for "definite abnormality in the general area of the coding, but not of the type specified"; 8 for "not applicable"; and 9 for "not known or not asked". Per the ADI-R algorithm instructions, responses of a 3 were recoded to 2, and responses of 7, 8, and 9 were recoded to 0 to create algorithm domain scores.

2.3. Procedures

2.3.1. Human subjects safety approvals

Data included in the current study on participants with DS and DS + ASD were collected under the approval of each university's Institutional Review Board (IRB). Data for participants with idiopathic ASD were obtained from NDAR and were collected under the approval of their respective institution's IRB. Senior author (NRL) and the respective university signed a Data Use Certification per NIH policy prior to accessing data. Consent was obtained for all participants in accordance with The Code of Ethics of the World Medical Association.

2.4. ASD diagnostic assignment

For the purposes of the current study, ASD diagnostic status for all participants (DS, DS + ASD, and ASD) was determined using the ADOS Total Score cutoff: Module 1 = 7; Module 2 = 8. Participants were originally classified as (1) Autistic Disorder (2) Autism Spectrum (3) Not Autism following the DSM-IV diagnostic classifications. These scores were reclassified to reflect the DSM-5 classifications as (1) Autism Spectrum Disorder or (2) Not Autism Spectrum Disorder. It is important to note that we elected to use the ADOS as the diagnostic classifier for the participants in the current study (as opposed to a clinical consensus diagnosis) as we wanted the method used to diagnose participants to be separate from the measure used to evaluate ASD symptom severity in the SOC − COM and RBI domains. Had we used clinical consensus (which includes evaluation of the ADOS, ADI-R, and expert clinical opinion), we would have conflated our diagnostic classifications with our outcome measures of interest: symptom severity in the SOC − COM and RBI domains as measured by parent interview on the ADI-R. Despite this decision to assign diagnoses based on the ADOS and not clinical consensus, it is important to note that with the exception of one participant in the DS-only group, there was convergence across methods – that is, participants' ADOS diagnosis scores matched their clinical diagnosis for the DS, DS + ASD, and ASD groups.

2.4.1. Data collection procedures

2.4.1.1. DS and DS + ASD groups. Youth in both DS groups completed the MSEL and ADOS during visits to the universities conducting the study, after appropriate consent procedures were completed. All ADOS ratings were completed by clinicians who had established research reliability on ADOS modules 1 and 2. Caregivers of participants completed the ADI-R with a trained, research-reliable clinician. All sessions were videotaped with permission, and 40% of these sessions were reviewed to assess administration and scoring. Clinicians maintained inter-observed reliability at 85% or higher for the ADOS and ADI (see DiGuiseppi et al., 2010 for further details). Data collection for the ASD group followed the original study's procedures.

2.4.1.2. ASD group. Youth with ASD were drawn from NDAR and matched on a 2-to-1 ratio for each participant with DS and DS + ASD. As mentioned above, to be included in the ASD group for the current study, the participant needed to meet criteria for ASD on the ADOS in order to have consistency in the methods of assigning ASD diagnoses among groups.

2.5. Analytic method

2.5.1. Primary variables of interest

The primary variables of interest were derived from the ADI-R algorithm items in the Social, Communication, and RBI domains. Because items included in the ADI-R diagnostic algorithms vary based on chronological age and verbal abilities, a subset of ADI-R algorithm items shared by all participants in the current study regardless of age and verbal ability level was selected to create social-communication and RBI composites. These items were drawn from the following diagnostic algorithm: 2 years, 0 months to 3 years,

11 months, nonverbal items only. This specific item set was chosen over an examination of items that were drawn from each participant's age and verbal-ability appropriate algorithm, *because it allowed all participants to have data on all of the same items*. Having data on the same items across participants was a priority for the current project, as we were interested in the average "severity" rating of social-communication and RBI symptoms rather than whether a child met diagnostic criteria for ASD on the ADI-R. (The ADOS was the diagnostic measure for the current study). Thus, items belonging to the Social, Communication, and RBI domains for nonverbal participants on the 2 years, 0 months to 3 years, 11 months algorithm were the focus of the current study with two exceptions. ADI-R item 50, assessing direct gaze, was excluded, as it is coded as "0″ for those 5 years and older. Because the participants in the current study were both below and above the age of 5, this item was removed so as not to artificially lower social-communication composite scores for participants over age 5 who would automatically receive a 0 for this item regardless of parent report of direct gaze behaviors. Similarly, ADI-R item 39, addressing the skill of verbal rituals, was excluded. This item is automatically coded as "0″ for those with less than phrase speech (determined by item 30). Again, it was removed to reduce concerns about artificially lower RBI scores in those without phrase speech.

To be consistent with DSM-5 diagnostic criteria for ASD, items from the Social and Communication domains ("current" versions of items 31, 34, 35, 42, 43, 44, 45, 47, 48, 51, 52, 53, 54, 55, 56, 57, 59, 61, 62, 63; "ever" versions of items 33, 36, 37, 38, 58) were considered together and were averaged to form a Social-Communication (SOC-COM) composite score (i.e., a score that reflects the average rating of social-Communication items included on ADI algorithm for nonverbal children who were between 2 years, 0 months and 3 years and 11 months). Similarly, item scores from the RBI domain ("ever" versions of 39, 67, 68, 70, the higher score from items 69 and 71, and the higher score from items 77 and 78) were averaged to make an RBI composite score. Mean scores for the study-derived SOC-COM composite and RBI composite were evaluated in primary analyses (rather than using the sum) so that the average 'severity' of the Social-Communication and RBI composites could be compared directly on the same scale.

2.5.2. Analyses

Prior to conducting primary analyses, the distribution of scores on the ADI-R SOC-COM and RBI composites was evaluated. Because the data were not normally distributed, semi-parametric repeated measures ANOVA was utilized to compare SOC-COM and RBI scores as a function of diagnostic group. To account for differences in verbal mental age among the groups, a semi-parametric repeated measures ANCOVA with verbal mental age (VMA) as a covariate was also completed. These semi-parametric ANOVA/ANCOVA analyses were accomplished by utilizing permutation methods implemented in the "permuco" package in the R statistical language. These methods have been demonstrated in the literature to be robust to non-normal data (Frossard & Renaud, 2018).

In addition, the magnitude of group differences on the SOC-COM and RBI domains for each of the pairs of groups (DS vs. DS + ASD; DS vs. ASD; DS + ASD vs. ASD) was evaluated by calculating Cohen's *d* effect sizes (i.e., d = (Target group mean – Comparison group mean)/ Pooled standard deviation (Cohen, 1998)). A p value of ≤ .05 was used for all main analysis, and for tests of simple effects, Bonferroni corrected p-values were used to control for multiple comparisons.

3. Results

A 3 × 2 semi-parametric ANOVA with one between-subjects factor (Diagnostic Group: DS + ASD, DS-only, ASD) and one within-subjects factor (Algorithm domain composite score: SOC-COM, RBI) was conducted to examine differences among the three diagnostic groups on the two ADI-R domains. A main effect of diagnostic group was found ($F(2,96) = 60.21$, $p < 0.01$), such that the ASD group had higher scores (indicating greater impairment) than the DS + ASD group who in turn had higher scores than the DS-only group. A main effect of domain was also found ($F(1,96) = 4.07$, $p < .05$), such that the SOC-COM domain (M = 0.99) was significantly higher (denoting greater impairment) than the RBI domain (M = 0.85) when evaluated across groups. These main effects were qualified by a significant diagnostic group x domain interaction ($F(2,96) = 4.00$, $p < 0.05$; See Fig. 1).

To interpret this interaction, follow-up tests of simple effects (with Bonferroni correction for multiple comparisons) were conducted to examine between group differences. For SOC-COM, the DS-only group had significantly lower scores (i.e., less impairment) than both the ASD and DS + ASD groups ($ps < 0.01$), as expected. There was also a trend for the DS + ASD group to have lower SOC-COM scores than the ASD group, but this was not significant after correction for multiple comparisons (unadjusted $p = 0.032$). For RBI, both the DS and DS + ASD groups had significantly lower scores than the ASD group ($p < .01$); however, the two DS groups' scores did not differ from one another ($p = .12$). Despite failure of between group tests of simple effects to meet statistical significance in some cases, it is important to note that all pairwise, between-group comparisons were at least medium in effect and the general trend in findings was as follows: ASD > DS + ASD > DS (with higher scores indicating greater impairment) on both domains. Follow-up tests of simple effects to evaluate within-group differences in domain scores revealed the ASD group's SOC-COM domain score (M = 1.40) was significantly higher than the RBI domain score (M = 1.19, $p < 0.01$), whereas in the DS-only and DS + ASD groups, scores did not significantly differ across domains (i.e., SOC-COM ~ RBI; $ps > .10$). See Table 2 for test statistics and effect size results.

Given differences among the groups on verbal MA, and in particular, the fact that the DS + ASD group had the lowest verbal MA among the groups, three additional sets of analyses were undertaken. First, correlations were completed to examine relations between ADI domain (SOC-COM and RBI) scores and verbal MA among the three groups. Then a semi-parametric repeated measures ANCOVA was completed with verbal MA covaried. Finally, a subset of participants with DS, DS + ASD, and ASD matched on verbal MA were examined using non-parametric tests to compare differences in ADI-R symptom severity within a subgroup of participants with similar verbal ability levels.

Relations between verbal MA and the ADI-R domain scores are depicted in Fig. 2. As can be seen, the DS + ASD group had a notably strong correlation between their SOC-COM and Verbal MA scores (R = -0.86; i.e., lower verbal MA associated with higher

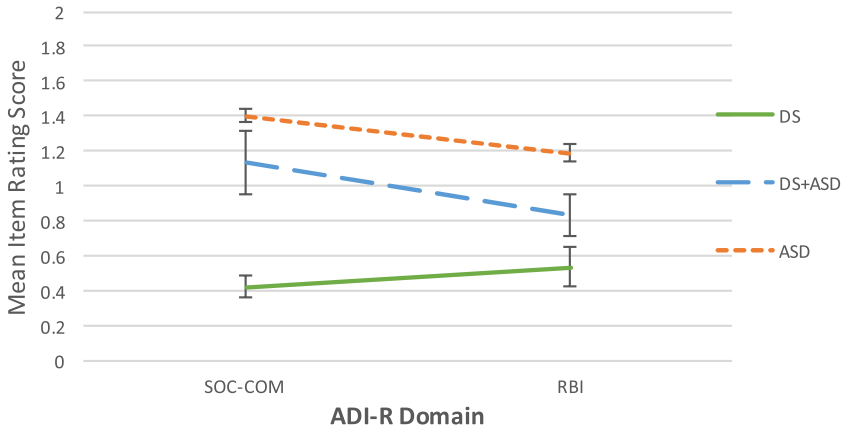

Fig. 1. Mean scores for Social-Communication (SOC-COM) ADI-R algorithm items (sections A & B) and Restricted, Repetitive, and Stereotyped Behaviors and Interest (RBI) ADI-R algorithm items (section C) as a function of group. See Table 2 and text for details about between- and within-group comparisons with and without verbal MA as a covariate.
Note: Higher scores denote greater impairment

Table 2
Mean Domain Scores by Diagnostic Group and Comparison of Domain Scores Between Groups.

		DS	DS + ASD	ASD	Pairwise Comparisons	*d*	Unadjusted	VMA covaried
Soc-Com	*M (SD)*	0.42 (0.30)	1.14 (0.58)	1.40 (0.34)	*DS vs. DS + ASD*	−1.54	$p < 0.01$*	$p = 0.52$
	Range	0.05-1.21	0.37-1.89	0.63-1.95	*DS vs. ASD*	−3.08	$p < 0.01$*	$p < 0.01$*
					DS + ASD vs. ASD	−0.56	$p = 0.03$	$p < 0.01$*
RBI	*M (SD)*	0.54 (0.55)	0.84 (0.40)	1.19 (0.38)	*DS vs. DS + ASD*	−0.62	$p = 0.12$	$p = 0.83$
	Range	0-2.00	0.40-1.60	0.60-2.00	*DS vs. ASD*	−1.38	$p < 0.01$*	$p < 0.01$*
					DS + ASD vs. ASD	−0.91	$p = 0.01$*	$p = 0.15$

Note: Higher scores denote greater impairment.
* Survives Bonferoni correction for multiple comparisons.

impairment), unlike the DS group (R = -0.42) and ASD group (R = -0.43). In contrast, when examining the association between RBI and Verbal MA scores, the association was not significant for any diagnostic group (DS R = 0.14; DS + ASD R = -0.19; ASD R = -0.01).

Given the strong relationship between verbal MA and SOC-COM in the DS + ASD group alongside group differences in verbal MA, a 3 × 2 semi-parametric ANCOVA with one between-subjects factor (Diagnostic Group: DS + ASD, DS-only, ASD) and one within-subjects factor (Algorithm domain composite score: SOC-COM, RBI) was conducted with verbal MA as a covariate. Again, a main effect for diagnostic group was found ($F(2,95) = 62.19$, $p < 0.01$), such that the ASD group had higher scores (indicating greater impairment) than the DS + ASD group and DS group, who did not differ. Similarly, a main effect for domain was found ($F(1,96) = 4.07$, $p < .05$), such that the SOC-COM domain was significantly higher than the RBI domain across groups. Again, these main effects were qualified by a significant diagnostic group by domain interaction ($F(2,96) = 4.00$, $p < 0.05$).

Follow-up tests of simple effects with verbal MA covaried were completed in order to interpret this interaction. First, consistent with the findings described above without verbal MA as a covariate, the DS-only group had significantly lower scores than the ASD group on both domains ($ps < 0.01$) as expected. In contrast to the findings above without verbal MA as a covariate, the DS + ASD and DS groups did not differ on either domain ($ps > .5$) when verbal MA was covaried. Lastly, the DS + ASD group did not differ from the ASD group on the RBI domain (inconsistent with the findings without verbal MA covaried), but had significantly lower scores than the ASD group on the SOC-COM domain ($p < 0.01$; this differs some from the trend toward group differences when verbal MA was not covaried). Tests of simple effects to evaluate within-group differences in domain scores were largely similar to those described above without verbal MA covaried. Specifically, in the ASD group, the SOC-COM domain score was significantly higher than the RBI domain score ($p < 0.01$), whereas in the DS-only and DS + ASD groups, scores did not significantly differ across domains (i.e., SOC-COM ~ RBI; $ps > .05$). See Table 2.

Given the differences in findings depending on whether or not verbal MA was covaried, exploratory analyses were completed in which a subsample of participants with similar verbal MA levels from each group were compared (n = 9 per group). The DS subsample included 9 participants with the lowest verbal MA scores within the DS group while the DS + ASD subsample included the 9 participants with DS + ASD with the highest verbal MA scores. Then, an ASD subsample (n = 9) was selected with comparable verbal MA to the DS + ASD and DS groups. The groups did not significantly differ on verbal MA ($p = 0.82$). Because of the small sample sizes, we used nonparametric statistics to compare the groups. Using a Mann-Whitney U test, we found that in comparison to the DS group, the ASD group had significantly higher SOC-COM ($p < 0.01$) and RBI scores ($p = 0.01$). When comparing the ASD group to the DS + ASD group, there was a trend towards the ASD group having higher SOC − COM scores than the DS + ASD group ($p = 0.06$)

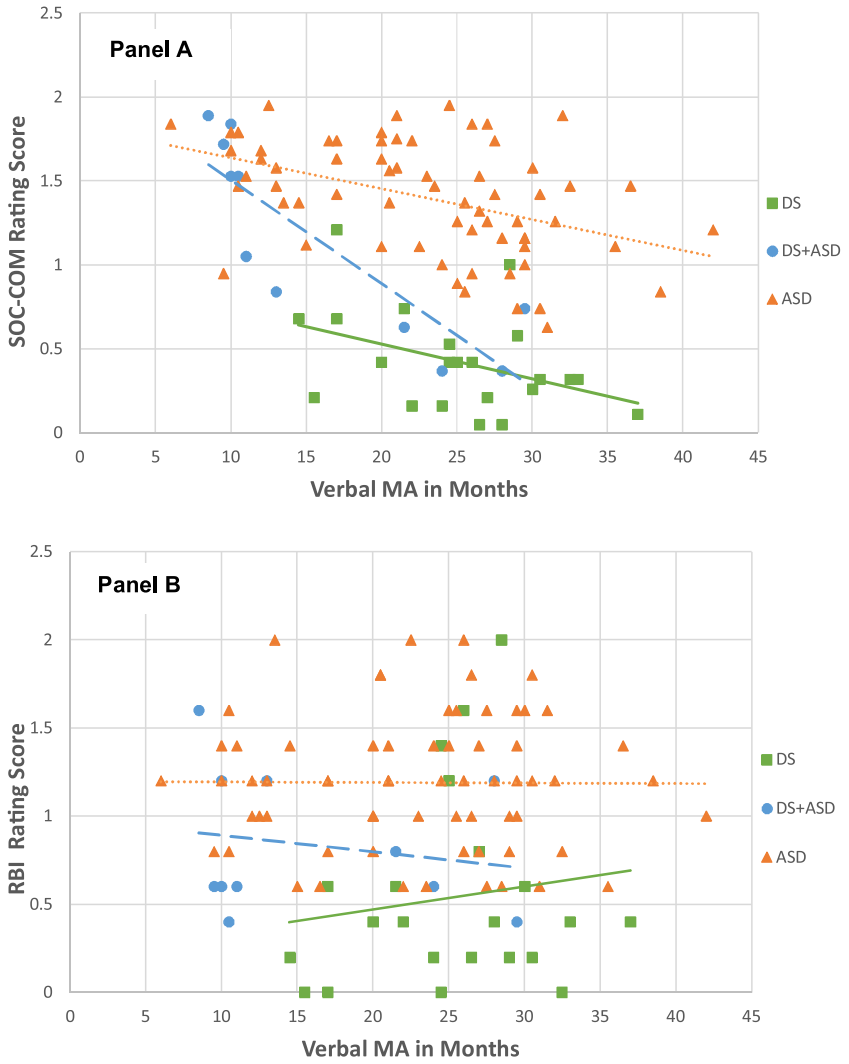

Fig. 2. Panel A Scatterplot of the relation between social communication (SOC-COM) and verbal MA as a function of diagnostic group; Panel B Scatterplot of the relation between restricted and repetitive behaviors and interests (RBI) and verbal MA as a function of diagnostic group. For both panels, the solid trend line represents the DS group, the dashed trend line represents the DS + ASD group, and the dotted trend line represents the ASD group.

supported by a large effect size. The ASD group had significantly higher scores on the RBI domain in comparison to the DS + ASD group ($p = 0.04$). In comparison to the DS group, there was a trend for the DS + ASD group to have higher scores on the SOC-COM domain ($p = 0.06$), supported by a large effect size. Additionally, the DS + ASD had significantly higher scores on the RBI domain ($p = 0.005$) in comparison to the DS group. See Table 3 for the results.

4. Discussion

4.1. Findings and interpretation

Little is known about the ASD symptom profile of youth with comorbid DS + ASD. The very small existing literature suggests that children with DS + ASD differ from children with DS on autism symptom measures and other aspects of psychosocial functioning, and studies comparing children with DS + ASD to those with ASD have yielded inconsistent findings. Consequently, researchers and clinicians have been unable to draw robust conclusions about shared and unique features of these conditions to inform clinical care. Moreover, no studies of which we are aware have examined all three groups using gold standard diagnostic measures to designate group membership and to examine symptom severity. Given the complexities in assigning diagnoses of ASD in youth with different genetic disorders associated intellectual disability (Hepburn & Moody, 2011) and the high degree of false positive results when screening ASD via questionnaires in DS (DiGuiseppi et al., 2010), the current study adds to the literature by describing ASD symptom

Table 3
Mean Verbal MA and Domain Scores by Diagnostic Subsamples (n = 9) and Comparison of Domain Scores Between Subsamples.

	DS (= 9)				DS + ASD (n = 9)				ASD (n = 9)			
	M	SD	Md	IQR	M	SD	Md	IQR	M	SD	Md	IQR
VMA	19.56	3.69	20.00	16.3-23.0	17.5	8.19	13.00	10.3-26.0	18.94	8.05	17.00	11.8-28.3
Soc-Com	0.53	0.34	0.53	0.2-0.7	0.98	0.54	0.84	0.5-1.5	1.48	0.28	1.47	1.3-1.7
RBI	0.27	0.25	0.20	0.0-.5	0.78	0.34	0.60	0.5-1.2	1.11	0.23	1.20	0.9-1.3

Pairwise Test Results			
	DS v. ASD	DS v. DS + ASD	ASD v. DS + ASD
VMA	p = 0.63 (d = 0.10)	p = 0.40 (d = 0.32)	p = 0.59 (d = 0.18)
Soc-Com	p = 0.001 (d = 3.05)	p = 0.06 (d = 1.00)	p = 0.06 (d = 1.16)
RBI	p < 0.001 (d = 3.50)	p = 0.005 (d = 1.71)	p = 0.04 (d = 1.13)

profiles in youth with DS + ASD whose diagnoses were carefully ascertained via gold-standard, direct assessment using the ADOS (which incidentally converged with clinical diagnosis in 97% of cases within our DS sample, 100% for DS + ASD and ASD). Furthermore, the current research uses different measures to assign ASD diagnoses (ADOS) and to evaluate the severity of ASD symptoms (ADI-R). Moreover, unique to the current study, the influence of children's verbal cognitive skills on ADI ratings were examined by including participant's verbal mental age scores.

The results of the current investigation are summarized as follows. First, as expected, the youth with DS received lower ratings (indicating less impairment) than the ASD-only group on both the SOC-COM and RBI domains. These differences survived Bonferroni corrections for multiple comparisons and were also maintained when ANCOVA analyses were completed with verbal MA covaried. Second, our results indicated that youth with DS + ASD differ from both their peers with DS and their peers with idiopathic ASD in the severity of their ADI-R SOC-COM and RBI impairments. Specifically, for the DS + ASD vs ASD comparison, the DS + ASD group was found to have lower RBI ratings than the ASD group with and without verbal MA covaried (although this difference was not statistically significant when verbal MA was included in the model). For the SOC-COM domain, the DS + ASD group had lower scores than the ASD group with and without verbal MA covaried (although this group difference did not survive Bonferroni correction for multiple comparisons in our analyses without verbal MA covaried). Moreover, in follow-up analyses in which a small subsample of participants with ASD with similar verbal MA scores to the DS + ASD group were compared, the DS + ASD group had significantly lower RBI scores than the ASD group and a trend was observed in which the DS + ASD group presented with less significant impairments on the SOC−COM domain. When examining effect size data, medium to large effect sizes were found for differences between DS + ASD and ASD-only group, suggesting clinically meaningful differences that some of our analyses may have been underpowered to detect.

Lastly, turning to comparisons of the DS + ASD group and their peers with DS-only, children with DS + ASD demonstrated greater ASD symptomatology. However, depending upon the particular analysis, this may not have reached statistical significance, particularly in regards to analyses of RBI symptoms. When examining symptoms on the SOC-COM domain without verbal MA covaried, the DS + ASD group received significantly higher scores on this domain (indicating greater impairment). In contrast, when verbal MA was added as a covariate to analyses, the DS and DS + ASD groups did not differ on this domain. In follow-up analyses in which a small subsample of participants with DS with similar verbal MAs to the DS + ASD group were compared, we found significant differences in RBI ratings and a trend for differences on SOC-COM ratings ($p = .06$), with the DS + ASD group demonstrating greater impairments than peers with DS-only. However, large effect sizes were found for differences between DS + ASD and DS-only group, suggesting clinically meaningful differences for both SOC-COM and RBI domains.

In summary, the results of the current investigation largely indicate that the ASD symptom severity of children with DS + ASD differs from their peers with DS-only and ASD-only. Although some of these group differences were not significant due to issues of power and Bonferroni corrections, the findings of the ANCOVA, with verbal MA covaried, and the exploratory analyses of verbal MA matched groups, both continued to demonstrate the unique symptom profiles of each diagnostic group. These differences were further supported (exploratory analyses) by the large effect sizes yielded for each of the group comparisons. Thus, even when accounting for verbal cognitive impairment associated with the DS + ASD group, the three diagnostic groups differ in terms of ASD symptom severity.

Given differences in findings, particularly between the DS and DS + ASD groups when verbal MA was covaried, relations between verbal MA and the ADI-R symptoms domains were examined within each group. Verbal MA scores were highly correlated with SOC-COM impairments in the DS + ASD group, but only modestly correlated in the other two groups. (See Fig. 2). Thus, there appears to be a very close relation between verbal abilities and ASD symptoms in those with DS + ASD which is not as pronounced when either condition is considered in isolation.

One might interpret this finding as suggesting that those with DS + ASD represent a subset of youth with DS with more severe cognitive impairments that negatively impact their development in other domains, such as social communication skills. An alternative explanation is that impairments in core social relatedness skills in youth with DS + ASD impact this group's ability to learn effectively from their environment, resulting in lower verbal and general cognitive abilities for this group. Unfortunately, the nature

of this study does not allow us to further clarify these possibilities. However, we did complete follow-up analyses with a subsample of the DS and DS + ASD groups (n = 9 in each group) who were matched on verbal MA in order to determine if the differences between the DS and DS + ASD groups could be reduced to differences in verbal abilities alone. Exploratory, nonparametric analyses revealed a trend towards a significant group difference on SOC-COM, such that the DS + ASD group had higher scores on this domain, and a statistically significant difference on the RBI domain, with higher scores in the DS + ASD group. When examining effect sizes of this verbal MA matched subsample, large effect sizes for both the SOC-COM and RBI domains indicated clinically meaningful differences exist even when verbal MA is largely similar. Therefore, it appears that the presence of parent reported SOC-COM impairments in youth with DS + ASD cannot be explained by lower verbal MA in this group alone. However, these results should be interpreted with caution, as these subsamples were notably small and these analyses were exploratory.

Regardless of the cause of their social-communication deficits, it is important to note that youth with DS + ASD may be at a greater risk for poorer long-term outcomes, due to potentially lower social-communication in addition to lower verbal cognitive abilities in comparison to their counterparts with DS-only. Thus, identifying ASD comorbidity in youth with DS is pertinent to address this group's needs and to increase awareness that these children may need additional supports and possibly interventions than are used with youth with DS alone.

Turning to the existing literature, our findings are largely consistent with Warner et al. (2017) in which children with comorbid DS + ASD were found to have significantly fewer SOC-COM and RBI symptoms than those with ASD-only. In contrast, our findings differ from Moss' (2013) findings, which indicated that the DS + ASD group and idiopathic group did not differ on ASD symptom severity ratings. However, the current study, along with Warner's et al. (2017) study, accounted for verbal abilities when examining participants' symptom severity (i.e., Warner et al. (2017) matched on language level, measured by use of phrase speech). Therefore, accounting for verbal abilities of children with DS + ASD may reveal differences in ASD symptom severity for those with DS + ASD and children with ASD-only.

The results of the current investigation have implications for elucidating the differences in ASD symptom presentation in children with and without genetic disorders. First, in youth with DS + ASD, a close relationship between verbal cognitive abilities and SOC-COM symptoms was found that was not present in the ASD-only group, suggesting that different cognitive processes may be at play in the presentation of SOC-COM symptoms in these groups. Second, the profile of SOC-COM and RBI scores on the ADI-R varied as a function of group. While youth with ASD had greater impairments in the SOC-COM than the RBI domain on the ADI-R, similar degrees of impairment in these domains were found in the DS + ASD group. These findings bring to light the question of whether the etiological and neural underpinnings of ASD in those with and without discrete genetic syndromes is similar and whether research studies of children with a primary diagnosis of ASD should take care to examine results with and without youth with genetic syndromes included.

Before turning to the clinical implications of the current study, we will discuss our study's limitations. First, this study had a notably small sample size of children with DS + ASD. Due to the requirements of the study, including completing the gold-standard play-based assessment, the ADOS, and due to the rarity of the comorbid disorders, our sample included 11 children with DS + ASD. To account for this small sample size, we completed semi-parametric analyses, which provided a comprehensive examination of severity scores between groups. Additionally, we examined effect size data between groups on ADI-R subdomains as an additional means to understand the clinical significance of the group differences. Although we have taken measures to address our limited sample size, future research should examine these populations using a larger sample, perhaps by conducting a multi-site investigation. Studies with larger sample sizes could possibly detect more nuanced cognitive and behavioral differences between DS + ASD and their peers with either condition alone than we were able to detect with this small sample.

Furthermore, the current study provided an analysis of the ASD symptom severity using the parent-report measure, the ADI-R, among the three diagnostic groups whose ASD status was determined by using the ADOS. For the purposes of this study, we wanted to keep the diagnositic measurement separate from the measure used to evaluate ASD symptom severity, and thus, the ADOS was used to diagnosis ASD, rather than clinical consensus. While this may be viewed as a limitation, it is important to note that only one participant with DS received an ASD diagnosis on the ADOS without a converging clinical consensus diagnosis of ASD. Thus, results were likely to be very similar had clinical consensus diagnosis been used rather than ADOS diagnosis. Another possible limitation of the current research is that ASD severity assessment relied entirely on the parent's perspective. In some cases, these parent reports may not be truly reflective of a child's abilities. Specifically, a parent report may not provide as accurate of findings as a performance-based assessment. Although past studies have examined ADOS performance of children with DS (Hepburn et al., 2008; Starr, Berument, Tomlins, Papanikolaou, & Rutter, 2005), research has yet to examine those with DS + ASD in comparison to those with DS-only and ASD-only using a performance based measure. Examination of children with DS + ASD using a performance based measure could reveal significant differences that parent report may not be attuned to. Thus, this is also a direction for future research.

4.2. Clinical implications and conclusions

Acknowledging these limitations, the results of the current study have important clinical implications for the identification and treatment of children with DS + ASD. First, our results suggest that the presence of ASD symptoms in children with DS + ASD may be subtler and less readily recognized by parents than ASD symptoms in children with idiopathic ASD. The combination of (a) less severe ratings of SOC-COM and RBI symptoms in the DS + ASD vs. ASD-only group and (b) the relationship of verbal MA and SOC-COM symptoms in the DS + ASD group may contribute to the trend of ASD diagnoses being made less frequently and/or later in youth with DS + ASD (for review see Reilly, 2009). Given the importance of early intervention for maximizing developmental outcomes in youth with ASD (MacDonald, Parry-Cruwys, Dupere, & Ahearn, 2014; Orinstein et al., 2014), these findings underscore the importance of

incorporating standardized ASD screening for children with DS as routine care within the first years of life. Such screenings may help to identify children with DS + ASD who would otherwise remain unidentified and may result in an earlier age at diagnosis and more timely clinical interventions.

Furthermore, our findings highlighting group differences between those with DS + ASD and their counterparts with either diagnosis in isolation may be informative for the development of tailored interventions for children with DS + ASD. Although children with DS + ASD may benefit from interventions traditionally created for children with intellectual disability or DS, this group may also benefit from interventions developed for youth with idiopathic ASD as well. Research on children with a primary diagnosis of ASD has shown that early intervention prior to the age of three has a significantly positive impact on children's development. Specifically, interventions at this young age can reduce the severity of ASD symptoms (Dawson et al., 2010; Green et al., 2015). Consequently, tailored early intervention during early toddlerhood would likely be advantageous for children with DS + ASD, as well, to ultimately reduce symptom severity.

In addition to addressing ASD symptoms of those with DS + ASD, treatment for this comorbid group should also be reflective of the child's DS diagnosis. Specifically, intellectual impairment and speech and language deficits associated with DS may influence the efficacy and success of traditional intervention for ASD within this unique population. However, despite the volume of research supporting evidence based interventions for children with primary diagnoses of ASD, studies examining interventions for children with ASD and comorbid genetic disorders remain scant. Research examining social skills intervention created for adults with DS + ASD has yielded positive findings (Davis, Spriggs, Rodgers, & Campbell, 2017). However, research has yet to examine the efficacy of such interventions for children with DS + ASD. Consequently, future research should investigate the efficacy of current ASD interventions for children with DS + ASD, and examine possible adaptations to traditional ASD interventions for this population.

Declarations of interest

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