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Autism Severity Aggregates with Family Psychiatric History in a Community-Based Autism Sample

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Scientific Abstract

The purpose of this study was to examine family psychiatric history in individuals with Autism Spectrum Disorder (ASD) and its association with clinical presentation. Participants were 798 individuals with a clinical diagnosis of ASD, confirmed by the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), enrolled in Rhode Island Consortium for Autism Research

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and Treatment (RI-CART), a statewide research registry. Prior research suggests a specific behavioral phenotype in individuals with ASD who have family members with psychiatric diagnoses, including higher IQ and less severe language impairment. However, studies have not specifically investigated autism severity. We hypothesized that increased psychiatric family history would be associated with increased autism severity symptoms. Results show a strong association of increased burden of first-degree family psychiatric history with higher autism symptom severity as measured by Social Responsiveness Scale, Second Edition (SRS-2), but not with ADOS-2 severity scores, IQ, or adaptive functioning. These findings support the importance of investigating the contribution of psychiatric family history towards clinical ASD presentation.

Lay Summary

This study explored how family psychiatric history is related to clinical presentation of Autism Spectrum Disorder (ASD). Higher amounts of first-degree family psychiatric history was associated with higher autism symptom severity as measured by the Social Responsiveness Scale, Second Edition (SRS-2). The contribution of psychiatric family history requires ongoing investigation.

Keywords

autism spectrum disorder; disease severity; family medical history; population study; registry

Introduction

The rate of psychiatric diagnoses in family members of individuals with Autism Spectrum Disorder (ASD) is elevated as compared to the general population (Fairthorne, Jacoby, Bourke, de Klerk, & Leonard, 2016; Xie et al., 2019). Depression is one of the most common disorders in individuals with ASD and their family members (Bolton, Pickles, Murphy, & Rutter, 1998; Cohen & Tsiouris, 2006; Ghaziuddin, Weidmer-Mikhail, & Ghaziuddin, 1998; Lever & Geurts, 2016; Micali, Chakrabarti, & Fombonne, 2004). Other disorders found to be especially frequent in families of children with ASD include bipolar disorder, anxiety disorders, obsessive compulsive disorders, and social phobia (DeLong & Dwyer, 1988; Micali et al., 2004; Piven et al., 1991; Smalley, McCracken, & Tanguay, 1995). Research has supported that family psychiatric history is a factor contributing to ASD risk (Larsson et al., 2005; Xie et al., 2019), including a genetic study (Luhrs et al., 2017), leading to interest in whether this may represent a specific group of individuals with ASD with a distinctive phenotype.

In this line of research, higher IQ in ASD individuals has been found to be positively associated with family history of psychiatric disease (Ghaziuddin & Greden, 1998; Robinson et al., 2014; Smalley et al., 1995). In one study, recurrent maternal mood disorders were associated with higher adaptive functioning (Cohen & Tsiouris, 2006) and another (that restricted participant IQ to above 70) found family history accounted for variation in adaptive behavior scores (Mazefsky, Williams, & Minshew, 2008). Maternal anxiety or depression has also been found to be associated with child phenotype of milder language delay with dysregulatory symptoms (Wiggins et al., 2019).

Thus, non-ASD psychiatric diagnoses in family members appears to aggregate with higher levels of cognitive and adaptive functioning in individuals with ASD, and perhaps with other behavioral phenotypic differences. However, research to date has been inconsistent about additional parameters of a behavioral phenotype associated with psychiatric family history, although preliminary studies suggest family psychiatric history is associated with interfering behaviors in ASD. For example, maternal anxiety/depression was associated with child symptoms of dysregulation such as anxiety, aggression, and reactivity (Wiggins et al., 2019), and another study found in individuals with ASD and history of maternal recurrent depression, teachers reported a more internalizing style and parents reported more problem behaviors (Cohen & Tsiouris, 2006).

Clarifying the association between family history and ASD phenotypes would have implications for research investigating patterns of heritability in ASD. Few studies have examined the association of family psychiatric history with autism severity measures. One study found parental depression but not anxiety was related to higher repetitive behavior scores using the parent interview tool Autism Diagnostic Interview-Revised (ADI-R) (Wallace, Anderson, & Dubrow, 2008). Another found that family psychiatric history of depression, social dysfunction, and shyness was not correlated with severity measures derived from observational or caregiver interview of ASD symptoms (Mazefsky, Williams, et al., 2008). In a study of infants at risk for ASD, increased amounts of psychiatric family history were associated with increased elevated items and total score on the POEMS (Parent Observation of Early Markers Scale), which assesses core symptoms and problem behaviors related to ASD (Feldman, 2019). To our knowledge, no studies have investigated autism severity as measured by the Social Responsiveness Scale, Second Edition (SRS-2) (Constantino, 2012) or the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) Autism Severity Score (Lord, 2012).

Given prior research that found individuals with family psychiatric history had more interfering behaviors, or higher ASD screening scores, we hypothesized that autism severity, as measured by caregiver report (SRS-2) and clinical exam (ADOS-2), would be higher for individuals with higher rates of psychopathology in first- and second-degree relatives. Using a large and heterogeneous study sample, we tested the degree to which severity of autism symptoms is related to the presence of psychiatric conditions in first- and second-degree family members. Understanding this covariation can have implications for the field's understanding of potentially shared etiologies and may translate to the knowledge base from which individualized treatments can be developed. We also hypothesized higher IQ and adaptive functioning would be associated with higher amounts of family psychiatric history which is supported by prior literature. In addition to these questions, we report the frequencies of these familial psychiatric disorders of individuals with ASD from a statewide patient registry.

Methods

Participants were drawn from the Rhode Island Consortium for Autism Research and Treatment (RI-CART) patient registry. Study procedures were approved by institutional review boards at all relevant institutions and conformed to recognized standards for studies

involving human subjects. RI-CART participants were based primarily in Rhode Island and neighboring geographic areas of Massachusetts. Full methodology of this consortium has been detailed previously (McCormick et al., 2020) including details about enrollment procedures and measures. This study was conducted with approval from the ethics review committee at Bradley Hospital/Lifespan Corporation. Assessments were typically conducted in a single visit and included a demographics questionnaire; an individual and family medical, neuropsychiatric, and developmental history; the Vineland Adaptive Behavior Scales, Second Edition or Third edition (VABS-II or Vineland-3) (S. S. Sparrow, Balla, D.A., & Cicchetti, D. V., 2005; S. S. Sparrow, Cicchetti, D.V., and Saulnier, C.A., 2016); the SRS-2; Kaufman Brief Intelligence Test Second Edition (KBIT-2) (Kaufman, 2004); and the ADOS-2 which was administered by a research-reliable ADOS-2 assessor. The SRS-2 is a caregiver completed questionnaire that assesses deficits in social behavior associated with ASD (Constantino, 2012). The ADOS-2 yields a calibrated severity score to describe autism symptom severity across age and language levels (Gotham, Pickles, & Lord, 2009; Lord, 2012). Caregivers completed a survey form to provide family history of neurodevelopmental and psychiatric disorders for both first-degree (biological parents and siblings) and second-degree relatives (biologic maternal and paternal aunts, uncles, and grandparents) of the participant. The form asked for caregivers to report the presence or absence of 19 disorders or conditions in family members.

In order to quantify burden of co-occurring conditions, a series of composite summary variables representing the total number of types psychiatric and neurodevelopmental disorders present in at least one first- or second-degree relative was created. The following conditions were grouped as neurodevelopmental disorders: ASD, Attention-deficit/hyperactivity Disorder (ADHD), Developmental Delay, ID, Speech/Language Delay, Learning disability, and Motor/Coordination Delay, thus allowing for maximum of 7 as a score of neurodevelopmental disorders. The following conditions were grouped as Psychiatric disorders: depression, anxiety, Obsessive-Compulsive Disorder (OCD), Conduct Disorder (CD), Oppositional Defiant Disorder (ODD), personality/mood disorder, Bipolar Disorder, Schizophrenia, Posttraumatic Stress Disorder (PTSD), Eating Disorder, alcoholism, and drug addiction, thus allowing for a maximum of 12 as a score of psychiatric disorders. The composite variable represented the total number of disorders present in first- or second-degree relatives, not the total number of individuals afflicted. Specifically, if the proband had a father with depression, a brother with depression and a mother with anxiety, the composite score for first degree psychiatric history for that participant would equal two; that is the sum of one for the presence of depression and one for the presence of anxiety. This methodology was selected for the purpose of representing a genetic history based on information we had available in our cohort, and is a simple and widely used method of measuring familial risk (Ali et al., 2021). In our descriptive report of percentage of specific disorders in first- or second- degree relatives, these percentages were calculated using the information of whether caregivers reported the presence or absence of the specific disorder.

The full RI-CART registry consists of 1,819 participants. Participants had varying diagnostic indicators, including an ASD group with a community diagnosis of ASD and a positive (above threshold) ADOS-2 result, an ASD-Inclusive group that had a community diagnosis *or* a positive ADOS, and a smaller number of individuals referred to the study but without

either diagnostic indicator [21]. Participants were selected for this analysis if they met the following inclusion criteria: a caregiver-reported community diagnosis of ASD and a positive (above threshold score) ADOS-2 result, resulting in a sample size of 858. Thus, participants were excluded if they did not have both a community diagnosis and an elevated ADOS-2 result (961/1819). Of the remaining 858 participants, 60 caregivers did not respond to the family history questions. RI-CART participants who were excluded due to missing family history data (n = 60) did not differ from included participants (n = 798) on sex, race, ethnicity, income, or maternal education (respectively, p = 0.296, 0.158, 0.715, 0.650, 0.729). Those with missing family history were on average slightly older in age (mean = 16.2, SD = 13.6) than those without missing data (mean = 12.4 yo, SD = 8.15) (p = < 0.001). This difference was driven by a higher percentage of people over 21 (16% vs. 6%), which likely is due to adults who may not have had access to caregivers to accurately report information, thus omitting it. Sample characteristics for 798 participants are detailed in Table 1, and of these remaining 798 participants, 699 had available SRS-2 scores and 728 had available ADOS-2 severity Scores.

Statistical analyses included linear regressions and post-hoc t-tests were run using IBM SPSS Statistics Software (v.23). Two separate linear regressions were used to evaluate the relationship of ASD severity and family history of psychiatric disorders. These models only differed in use of measure of autism severity (SRS-2 and ADOS severity score). Biological sex was included as a covariate in these analyses. Due to information available, we were unable to control for family size or age of family members. Because age of participants could potentially have been related to the likelihood of diagnoses becoming evident in families, we ran a post-hoc analysis including age of enrollment that did not impact significance of model or change our findings. Additional linear regression analyses were run to explore the relationship between family psychiatric history and adaptive skills and IQ.

Results

Linear regression was used to evaluate the relationship of ASD severity and family history of psychiatric disorders. The first model, detailed in Table 2, included first- and second-degree family history of psychiatric disorders and neurodevelopmental disorders, sex, and ADOS-2 severity score. Autism severity measured with the ADOS-2 calibrated severity score was not significantly related to any of the predicting variables, with post-hoc test power of 0.215. The second model, detailed in Table 3, included the same variables as the first but with our second ASD severity measure of interest- the SRS-2 total score (instead of ADOS-2 severity score); this second model was significant ($F(5, 693) = 8.236$, $p < 0.001$, $R_2 = 0.056$, $R_{2Adjusted} = 0.049$). A significant relationship was found between SRS-2 total scores and the burden of family history of psychiatric conditions in first-degree relatives ($\beta = 0.170$, $t(698) = 4.244$, $p < .001$). Second-degree family history of psychiatric conditions and family history of neurodevelopmental disorders were not associated with either SRS-2 total scores or ADOS-2 severity scores. Follow up analyses were conducted to evaluate whether age at time of enrollment impacted models. This variable, when added to both above linear regressions did not significantly alter results nor was a significant predictor of outcomes. Post-hoc analyses were conducted in order to explore which specific family psychiatric

diagnoses were related to participant SRS-2 score. We ran a series of *t*-tests and applied Bonferroni correction for multiple comparisons. Results revealed that SRS-2 total scores were higher in individuals with a first-degree family history of depression (mean = 78.0, SD = 9.6) vs those with no family history of depression (mean = 74.6, SD = 10.5; $t = -4.396$, $p < 0.003$). While all other individual family psychiatric disorders also had higher SRS-2 total scores, none of the disorders other than depression survived correction of significance for multiple comparisons.

Adaptive functioning and IQ were also investigated using linear regression models. The model including overall scores on the Vineland Scales (N = 595, mean = 67.4, SD = 17.6) was significant (F(5,589) = 2.47, $p = 0.32$, $R_2 = 0.02$, $R_{2Adjusted} = 0.01$) although only the second-degree psychiatric family history variable was significantly associated with ($p = 0.002$) higher adaptive behavior scores. KBIT-2 scores were available for a subsample (N = 222, mean = 85.1, SD = 27.96). Linear regression was used to test whether IQ was associated with family history of psychiatric disorders, and sex and neurodevelopmental conditions were included in this model as well. The model was significant ($F(5, 216) = 2.460$, $p = 0.034$, $R_2 = 0.054$, $R_{2Adjusted} = 0.032$), with only family history of psychiatric conditions in second-degree relatives ($\beta = 0.155$, $t(221) = 2.086$, $p = 0.038$) being associated with higher KBIT-2 scores.

Given access to an effective sample size of 798 participants with complete family history information, this analysis also yields descriptive data about the rates of family psychiatric illness in clinical samples of individuals with ASD. The majority (66.8%) of these participants reported at least one first-degree relative with a psychiatric disorder and 65.9% reported at least one second-degree relative with the same. For the neurodevelopmental history portion, 53.9% reported having at least one first-degree relative with a neurodevelopmental disorder and 30.3% with at least one second-degree relative with the same. Figure 1 details percentages of participants reporting total number of different types of psychiatric and neurodevelopmental disorders in first-degree relatives.

The most common psychiatric disorders reported were overwhelmingly affective disorders, with 50.8% endorsing at least one first-degree relative with anxiety and 46.0% with at least one first-degree relative with depression. Other frequent psychiatric disorders in first-degree relatives of the group were PTSD (15.4%), OCD (13.7%), and bipolar disorder (12.4%). The most common neurodevelopmental disorders present in first-degree relatives were ADHD (31.5%), Speech/Language delay (22.3%), and Learning disability (17.5%). 16.9% of the sample reported a first-degree family history of ASD, and 4% reported a second-degree family history of ASD. For detailed information about first- and second-degree relatives, see Figure 2 for distribution of amount of neurodevelopmental disorders and Figure 3 for psychiatric disorders reported.

Discussion

In this study we examined the relationship between family psychiatric history and measures of participant autism severity, adaptive functioning, and IQ. The primary finding from this analysis revealed that family psychiatric history, as measured by the number of reported

family members with mental health diagnoses, was associated with higher levels of caregiver reported ASD symptoms and behaviors as measured by the SRS-2. Follow up analysis indicated that family history of depression may have driven this finding. Burden of second-degree family psychiatric history was associated with IQ, although psychiatric family history was not associated with ADOS-2 severity scores or adaptive behavior scores. We believe the null finding in regards to the ADOS-2 severity score was underpowered due to restricted range of severity scores of our sample (4-10). As expected, neurodevelopmental history did not impact clinical presentation. As descriptive findings, we presented frequencies of psychiatric disorders in first- and second-degree relatives as reported by caregivers of individuals with ASD, with the majority of participants reporting a first-degree relative with anxiety and almost half reporting a first-degree relative with depression.

Given the heterogeneous presentation of ASD, identifying clinically meaningful behavioral phenotypes has long been a priority in the field. Our results could support such a phenotype with genetic underpinnings, which warrants further investigation. A subtype of ASD related to family psychiatric disorders would represent a meaningful way to homogenize an ASD population during studies, particularly within genetics, imaging, or outcome/treatment studies to optimize applicability of results. Conceptually, it has been speculated that individuals with family members who have mood or anxiety disorders are less likely to have Intellectual Disability (ID), perhaps due to greater etiological heterogeneity (i.e. ASD in those with ID more likely to be influenced by other genetic/environmental etiology factors unrelated to mood disorders) (Smalley et al., 1995). Relevant to this argument is a recent finding by Xie et al. (2020) that heritability estimates for ASD are higher in individuals without ID than those with ID. Our secondary findings are related to the reported frequencies of familial psychiatric and neurodevelopmental disorders in our participants. Our sample reported what seems to be a remarkably high amount of anxiety and depression, despite literature often finding families under-report psychiatric history (Hardt & Franke, 2007; Weissman et al., 2000). And although not directly comparable, these numbers appear to be higher than we would expect compared to a general population. Lifetime prevalence of a Major Depressive Episode in the US has been reported as 16.6% and Generalized Anxiety Disorder as 4.3% (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). Studies in the US have also reported lifetime prevalence of any type of anxiety disorder as 28.8%, and any mood disorder as 20.8% (Kessler et al., 2005). It is noteworthy that studies looking specifically at families of children with ASD have found higher prevalence than controls, and they estimate that the lifetime prevalence of parental mood disorders is 40.3%, and in siblings it is 32.4% (Smalley et al., 1995) which is more consistent with our findings. Another later study also looking at 17 families of probands with ASD found that the presence of at least one first degree family member with a mood disorder was 71% and with an anxiety disorder was 29% (Mazefsky, Folstein, & Lainhart, 2008). Prior literature has theorized that increased family psychiatric disorders may lead to a detection bias of ASD, representing increased access to mental health care leading to increased chance of ASD diagnosis in a child (Daniels et al., 2008), or families with children with ASD may be more likely to report family psychiatric disorders (which has not to our knowledge been investigated in the literature).

Given the limitations of our data we were not able to specifically look at either of these possibilities. The way our data set was recorded we also were unable to determine which caregiver/parent completed the form which potentially could have influenced family history variables if there was a recall bias based on status of caregiver (mother/father/other). However overall our data does support established research demonstrating high prevalence of familial depressive or anxiety disorders in individuals with ASD. Two research strategies could be employed in future work to address some of these limitations. First, longitudinal studies could investigate the presence of psychiatric disorders in families prospectively. Second, targeted comparison groups that include patients with non-ASD developmental disabilities could help to tease apart variation that is specific to ASD.

Other limitations of this study include that family history was obtained through participant or caregiver report, rather than a more sophisticated diagnostic process or external verification. Family history may also be influenced by variables family size, age of family member, and disease prevalence. Due to the nature of our data we were not able to account for these variables, which is why we utilized a dichotomous score rather than a more complex method. Current literature continues to support practical use of dichotomous scores in this manner (Ali et al., 2021), and we acknowledge it is unknown whether these factors relate to autism severity. Unlike prior studies our sample was broader across age, ability range, and types of family history assessed. This can be considered both a strength and weakness and may be a reason for our lack of replicating findings in regard to adaptive functioning and IQ. Recruitment was specifically broad and community based, and our experience and prior data demonstrated a full range of severity in our sample, especially children and adolescents (McCormick et al., 2020). Complexities related to guardianship and informed consent in adults may have impacted the recruitment in older individuals, potentially biasing that portion of the sample away from the most severely affected individuals (e.g., those in group home or other institutional settings). Additionally, as we restricted our sample to those with both a positive ADOS-2 result and community diagnosis, it is possible we excluded individuals with less severe or less prototypical symptoms of ASD, although it is unclear how either of these recruitment biases would affect this study. Furthermore, based on timing of recruitment, IQ scores were only available for a subset of our population.

We want to highlight that while traditionally SRS-2 is used as a measure of autism severity, we question whether this should be a direct interpretation given the context of our findings. Instead of representing more core ASD symptoms, higher SRS-2 scores may be serving as a proxy measure for psychiatric co-occurring conditions in the participants themselves i.e. higher rates of maladaptive behavior due to unrecognized mood/psychiatric co-occurring conditions in these individuals. Although we had reported psychiatric diagnoses, we did not directly measure level of mental health impairment in our participants, including no measures of emotion dysregulation, maladaptive, or challenging behaviors. As we were unable to further test this hypothesis we hope this can be investigated in future studies. The lack of an association between family history and ADOS-2 severity scores may be consistent with this interpretation, although this null finding may also have been influenced by the small effective range of scores of the ADOS-2 calibrated severity scores. We also did not collect additional measures to account for family or parental stress/conflict which may be

related to our findings (Benson, 2006; Fairthorne et al., 2016; B. Ingersoll, Meyer, & Becker, 2011). Current literature clearly supports that having a child with ASD confers additional parental stress and is associated with depression and anxiety symptoms (Phetrasuwan & Shandor Miles, 2009; Wang et al., 2013; Weitlauf, Vehorn, Taylor, & Warren, 2014; Yirmiya & Shaked, 2005), however these studies have been limited by small sample sizes and self-report (Cohrs & Leslie, 2017), and depression/stress have not been shown to be clearly associated with greater ASD severity (Benson, 2006; Falk, Norris, & Quinn, 2014; Brooke Ingersoll & Hambrick, 2011). Based on this complex body of literature, and the lack of direct mental health assessment of the parents in our database, we cannot rule out the possibility that parental depression is associated with greater ASD severity due to increased parenting stress. However, prior findings reduce the likelihood that that is an artifact of our results.

In conclusion, our study supports the existence of a behavioral phenotype with higher SRS-2 scores in the context of higher amounts of reported family psychiatric history. Few prior studies have investigated the association of family psychiatric history and ASD measures specifically. Despite methodological limitations, our study and findings complement prior studies that (by other measures) suggest that when psychiatric disorders (particularly affective disorders) aggregate within a family, it impacts the presentation of ASD through increased interfering behaviors. Additionally we used our data to replicate prior studies that found IQ/adaptive functioning to be associated with more family psychiatric history, and found that second-degree relatives was associated with IQ and adaptive functioning. These findings indicate a need to rigorously investigate the role of psychiatric family history and ASD phenotypes, particularly with the potential for investigating shared biologic mechanisms that would provide a meaningful way to stratify a heterogeneous population to create an impactful study group in ASD research.

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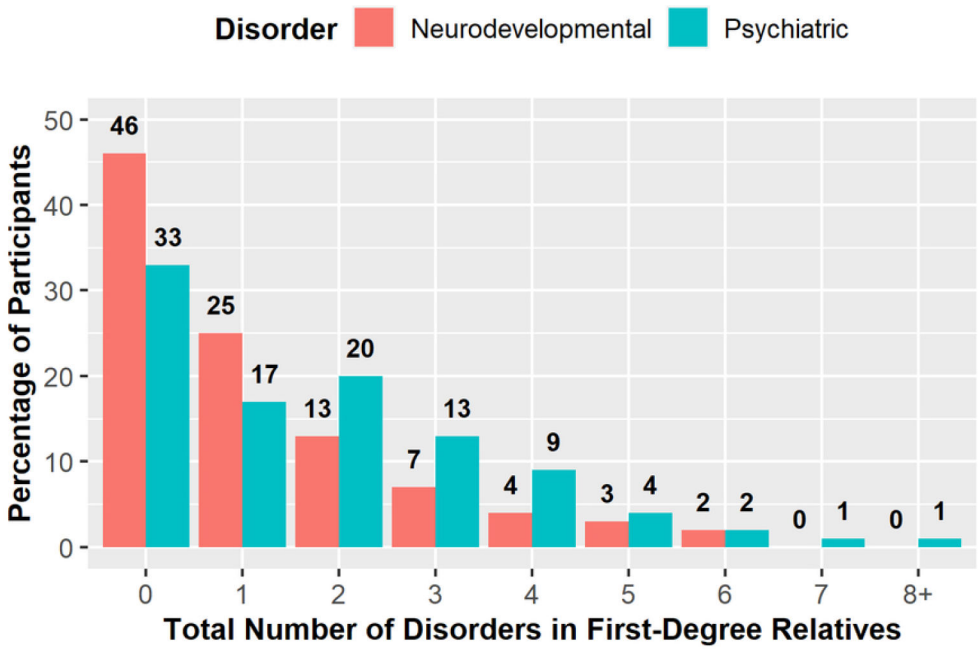

Figure 1.

Total number of reported psychiatric and neurodevelopmental disorders in first-degree relatives by percentage of participants (n = 798).

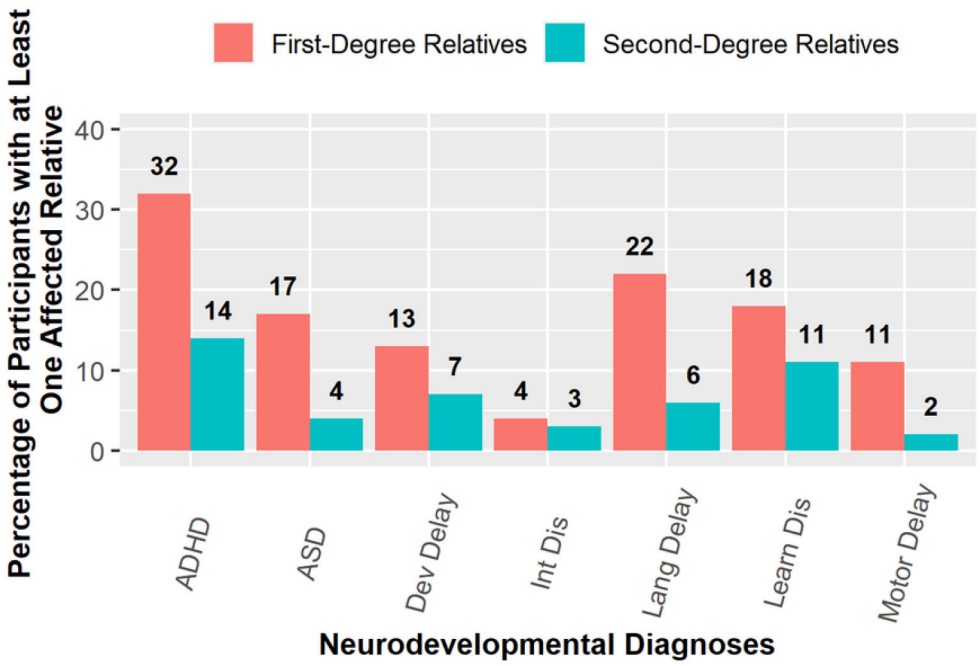

Figure 2.
Percentage of participants with at least one affected relative of specific neurodevelopmental disorders reported in first- or second-degree relatives (n = 798).

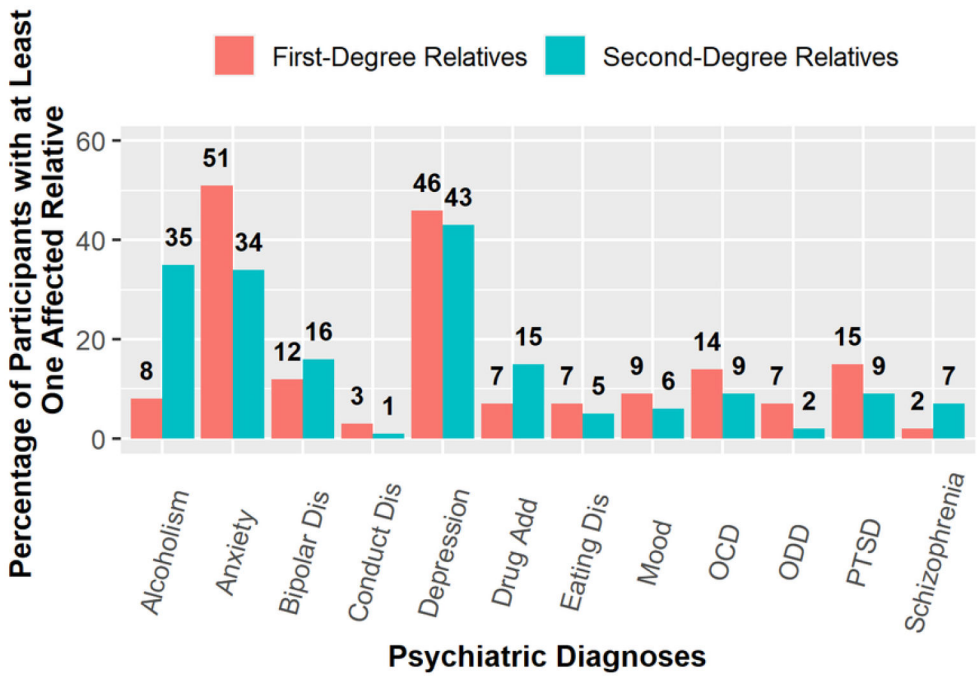

Figure 3.

Percentage of participants with at least one affected relative of specific psychiatric disorders reported in first- or second-degree relatives (n = 798).

Table 1.

Sample characteristics of 798 participants.

Age at enrollment In years	
Mean	12.4
Range	2.3-67.8
Biologic sex	
Male	80.6%
Female	19.4%
Race	
American Indian/Alaska Native	0.4%
Asian	1.4%
White	75.1%
Black or African American	4.3%
Other	2.3%
Multiracial	7.6%
Missing or preferred not to answer	9.0%
Household Income	
$0 to $14,999	8.2%
$15,000 to $29,999	14.2%
$30,000 to $49,999	14.0%
$50,000 to 99,999	26.9%
$100,000 to $149,999	14.9%
> $150,000	7.9%
Missing or Preferred not to answer	14%
ADOS-2 Severity Score	
Mean	7.3
Standard deviation	1.7
Range	4-10
Missing	8.8%
SRS-2 Score	
Mean	76.2
Standard deviation	10.3
Range	41-90
Missing	12.4%

Table 2.

Linear regression model with variables of first- and second-degree family psychiatric and neurodevelopmental histories, sex, and ADOS-2 severity score.

	df	Mean Square	F	R Square	Significance
Regression with ADOS severity score as dependent variable	(5, 722)	1.852	0.627	0.004	0.679

Predictor variables	β	*SE*	*P*
Number of first-degree neurodevelopmental disorders	−0.011	0.045	0.780
Number of first-degree psychiatric disorders	−0.029	0.036	0.481
Number of second-degree neurodevelopmental disorders	0.029	0.071	0.454
Number of second-degree psychiatric disorders	−0.050	0.036	0.213
Biologic sex	−0.039	0.161	0.810

Table 3.

Linear regression model with variables of first- and second-degree family psychiatric and neurodevelopmental histories, sex, and SRS-2 score.

	df	Mean Square	F	R Square	Significance
Regression with SRS as dependent variable	(5, 693)	825.824	8.236	0.056	**<.001**

Predictor variables	β	*SE*	*P*
Number of first-degree neurodevelopmental disorders	0.006	0.264	0.880
Number of first-degree psychiatric disorders	**0.170**	**0.216**	**<0.001**
Number of second-degree neurodevelopmental disorders	0.069	0.441	0.076
Number of second-degree psychiatric disorders	0.072	0.217	0.068
Biologic sex	0.069	0.941	0.062