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Rigid-compulsive behaviors are associated with mixed bowel symptoms in Autism Spectrum Disorder

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Abstract

Based on clinical experience, we hypothesized that rigid-compulsive behaviors are associated with severe constipation and co-occurring diarrhea or underwear staining in children with autism spectrum disorder. Using data from the Autism Treatment Network, we evaluated the association between these gastrointestinal (GI) symptoms and measures of rigid compulsive behavior in children ages 2-17. Following statistical correction, four of five primary measures were significantly associated with constipation and diarrhea or underwear staining, including parental report of repetitive behavior, parental report of compulsive behavior, clinician diagnosis of OCD, and report of rituals observed on the Autism Diagnostic Observation Schedule. This association could point to a causal connection between these symptoms or to a common biological pathway that impacts both gut and brain.

Autism spectrum disorder (ASD) is defined by impaired social communication and repetitive and restricted patterns of behavior (Frances et al. 2000). ASD is common, with the prevalence most recently reported as 1/88 in the United States (Baio 2012). Although the 'negative symptoms' of ASD, including lack of social and communication behaviors, often receive more attention, the 'positive symptoms' of repetitive and compulsive behaviors can cause significant distress for individuals and their families (Gabriels et al. 2005). Leo Kanner's initial description of 'infantile autism' noted that changes in routine or attempts to manipulate rigid behaviors resulted in significant distress (1968).

Gastrointestinal symptoms are frequent in children with ASD, but the relationship between ASD and GI symptoms is unclear. A population-based case-control study found no significant difference in the overall incidence of gastrointestinal symptoms in ASD but did find increased incidence of constipation (33.9% vs. 17.6%) and food selectivity (24.5% vs. 16.1 %) (Ibrahim et al. 2009). A case-control study in an epidemiologic sample found no

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difference in the incidence of gastrointestinal symptoms in children with ASD but did not delineate specific GI symptoms (Black et al. 2002). Other studies indicate that altered stool patterns, including constipation, in children with ASD and GI symptoms are not associated with differences in dietary intake or composition (Gorrindo et al. 2006). A retrospective study in the Autism Genetic Resource Exchange (AGRE) reported enrichment of the ASD-associated *MET* gene variant in children with both ASD and gastrointestinal symptoms, who constituted 41% of the sample (Campbell et al. 2009; Wang et al. 2011). Published case series also report high prevalence of GI symptoms in ASD (Molloy, Manning-Courtney 2003; Valcianti-McDermott et al. 2006) but without population-based controls.

There is limited information in the literature regarding what behavioral symptoms may be associated with specific GI symptoms in ASD. Gorrindo and colleagues examined GI symptoms in children with ASD, finding that 85% of referred children were diagnosed as having functional constipation by a pediatric gastroenterologist. In this population, functional constipation was associated with lack of expressive language (adjusted odds ratio 11.98) (2012). Valcianti-McDermott and colleagues found that a history of language regression was associated with abnormal stooling patterns in children with ASD (2008). Mazurek and colleagues reported increased anxiety and decreased social responsiveness in patients with ASD and GI symptoms including include constipation, abdominal pain, bloating and/or nausea (2013). Other studies have reported associations between general GI symptoms and behavioral symptoms of ASD including sleep disturbance, food selectivity, irritability, social withdrawal and anxiety (Maenner et al. 2012, Nikolov et al. 2009) but did not look for associations with specific GI symptoms.

Our clinical experience suggests a possible association between rigid-compulsive behaviors and GI symptoms. The Treatment Resistant Autism Consultation Clinic at Vanderbilt focuses on patients with severe rigid-compulsive symptoms. Clinically, this subpopulation has a high incidence of severe constipation with co-occurring intermittent diarrhea or underwear staining, which is often described clinically as fecal incontinence or encopresis. Fecal incontinence in children is often associated with fecal retention (Brazzelli et al. 2011, Hyman et al. 2006, Rasquin et al. 2006, Di Lorenzo 2006). One study in children with ASD demonstrated that soiling was radiographically associated with constipation (Afzal et al. 2003). For these reasons, in our study, we considered diarrhea or underwear staining that occur in the context of constipation to be indicative of severe constipation with liquid stool escaping past a large bolus of stool partially obstructing the colon.

To our knowledge, no previous study has examined the co-occurrence of rigid-compulsive behaviors with constipation within the ASD population. Interestingly, in an analysis of the Epidemiologic Catchment Area study (North et al. 1995), North and colleagues found an association between constipation and lifetime diagnosis of obsessive-compulsive disorder (OCD) in women but not in men. A small case-control study in a primary care population found an association between irritable bowel syndrome with constipation and OCD symptoms (Masand et al. 2006) Given the dearth of literature in this area specific to the ASD population, we aimed to use the large Autism Treatment Network database to evaluate the hypothesis that children with ASD and constipation with diarrhea or underwear staining are more likely to have repetitive or OCD-like behavior.

METHODS

Participants

Participants in this study were selected from the Autism Treatment Network (ATN), a network of 17 medical centers in the United States and Canada. All ATN participants have clinical DSM-IV diagnoses of Autistic Disorder, Asperger's Disorder or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS), as well as Autism Diagnostic Observation Schedule (ADOS) scores consistent with Autism Spectrum Disorder ("What is the ATN" 2012).

Measures

All measures in this study were collected from the ATN database. Upon the initial visit to an ATN clinician, parents fill out several forms. The Parent Baseline Assessment includes questions about the child's age, gender (male or female), race (White/Caucasian or non-White/Caucasian), and ethnicity (Hispanic/Latino or non-Hispanic/Latino) (Supplement 1). The Developmental and Medical History form asks questions about the child's development, previous psychiatric and previous medical diagnoses (Supplement 2). The GI symptom questionnaire asks parents to indicate by checking yes or no whether certain GI symptoms, including constipation, diarrhea, reflux and underwear staining, are currently a problem or have been a problem in the last three months (Supplement 3). At follow-up appointments, parents fill out the Parent Concerns questionnaire within the Parent Diagnosis and Treatment Form (Supplement 4), where they indicate behaviors that they have noticed to be problematic within the last month and indicate by checkbox if they are "mild", "moderate" or "severe".

After referral to the ATN, most children (94% in our study) receive an evaluation by an ATN clinician with the ADOS Autism Diagnostic and Observational Schedule (ADOS) for an ASD diagnosis. Clinicians also complete an initial screening for psychiatric illness with a DSM-IV-guided symptom checklist (Supplement 5) that is also completed at each subsequent visit. They note whether specific symptoms are present or not present in the child at that point in time based on observation and discussion of the child with the ATN team, medical records, and interview with the parent. At each follow-up appointment clinicians update the DSM-IV checklist and complete a Diagnosis and Treatment form where they check medical and behavioral symptoms present in the last three months and then more specifically within the last week by indicating "yes" or "no" (Supplement 6). The Diagnosis and Treatment form also asks clinicians to indicate what medications the child is taking at that time. If a clinician suspects a child needs referral to a specialist for a particular diagnosis that is found during the visit, the clinician completes a Targeted Referral Form (Supplement 7), which is entered into the database as well.

Most participants in our sample (78%) received cognitive testing to allow an estimate of IQ, most commonly including the Bayley Scales of Infant and Toddler Development, the Leiter International Performance Scale-Revised Edition, Mullen Scales of Early Learning, or the Abbreviated Battery from the Stanford Binet Intelligence Scale, Version 5 (25-28).

GI Symptoms

The GI symptom checklist was used to determine presence of constipation, diarrhea, reflux or underwear staining. Additionally, the Diagnosis and Treatment checklist was used to screen for presence of constipation and the Targeted Referral Form was used to identify children referred to a GI specialist for constipation.

Within the ATN database, 5076 out of 5693 children had sufficient data collected from the above measures to place them within five categories representing the independent variable: Group 0 (Control) - no Gastrointestinal Symptoms; Group 1 (Constipation and Diarrhea or Underwear Staining) – Constipation and either diarrhea or underwear staining symptoms; Group 2 (Constipation without Diarrhea or Underwear Staining) – Constipation symptoms without diarrhea or underwear staining symptoms; Group 3 (Reflux) – Reflux symptoms and not constipation, diarrhea or underwear staining symptoms; Group 4 (Diarrhea) – Diarrhea and not constipation. Report of one of the above symptoms on any of the questionnaires qualified that subject for placement in a symptom group regardless of whether that symptom was reported as present or absent on another symptom questionnaire.

Measures of Rigid-Compulsive behavior

We selected the five most specific measures of rigid-compulsive behavior for primary analysis, including notation of rituals on the ADOS, a “yes” answer to diagnosis or suspected diagnosis of OCD on the Developmental and Medical History form, any concerns for compulsive behaviors or repetitive behaviors on the Parental Concerns form including answers of “mild”, “moderate” and “severe”, and a “yes” checked for rigid or inflexible behaviors noted on the DSM-IV checklist.

Our eight secondary measures included indicators of repetitive but not necessarily compulsive behaviors, including mannerisms, repetitive behaviors, or verbal perseveration on the ADOS, or restricted interests or stereotypies on the DSM-IV checklist. We also included prescription of atypical antipsychotic medications or serotonin reuptake inhibitor or medications as they are sometimes used to treat rigid compulsive behaviors. We also included prescription of medications sometimes used to treat rigid compulsive behavior (serotonin reuptake inhibitors or antipsychotics) and family history of anxiety or OCD in a blood relative to include mother, father, grandparent, sibling, aunt, uncle or cousin noted on the Developmental and Medical History.

Exploratory Measures

To evaluate the specificity of relationships with rigid-compulsive behavior, we explored relationships between GI symptoms and hyperactivity / inattention symptoms on the Developmental and Medical History or Parent Concerns questionnaire as well as relationships between GI symptoms and seizure disorders reported on the diagnosis and treatment checklist.

Covariates

Covariates included age, gender, race and ethnicity, diagnosis, IQ, and verbal status (verbal vs. nonverbal) from the ADOS characterization.

Statistical Analysis

We identified our primary group for analysis as having constipation plus diarrhea or underwear staining. We used logistic regression, both with and without covariates, to compare these children (Group 1) against children with no GI symptoms (Group 0) for our primary analysis, but also compared Group 0 to the other GI symptom groups 2-4 to evaluate the specificity of any relationship observed between Group 1 and the dependent variables. The Bonferroni approach was used to correct for multiple comparisons. A p-value < 0.01 was considered as statistically significant for the analysis of primary variables and $p < 0.00385$ for the analysis of secondary variables. Other analyses were considered exploratory and are reported without statistical correction.

RESULTS

Children ranged in age from 2-17 years. In the primary analysis, 2957 children were in group 0 (no GI symptoms) and 806 were in group 1 (Constipation plus diarrhea or underwear staining) (Table 1). There were several quantitatively small but statistically significant demographic differences between these two groups. The children in group 0 were slightly more likely male (85.1% in group 0 vs 83.6% in group 1), less likely White/Caucasian (76.2% in group 0 vs. 81.5% in group 1), and slightly younger (mean age 5.86 years in group 0 vs. 5.91 years in group 1). IQ did not show statistically significant differences between the groups.

Demographic analysis was also performed on all five groups divided by specific GI symptoms. Overall, 43.5% of the 5076 ATN subjects had at least one GI symptom. Among the covariates, diagnosis, sex, age, race, and verbal status demonstrated statistically significant differences between the GI symptom groups. Diagnostic differences were small but significant (Supplemental table 1, $p = 0.0019$), with the PDD-NOS group least likely to have GI symptoms and the Asperger's group least likely to have diarrhea symptoms without constipation. Gender differences were greater with female participants showing an increase in overall GI symptoms that were largely accounted for by constipation symptoms without diarrhea or staining ($P < 0.0001$). Age, race and verbal status differences were also small but significant with younger children more likely to have diarrhea symptoms ($p < 0.001$), white participants more likely to have GI symptoms overall ($P = 0.0094$), and nonverbal patients more likely to have GI symptoms overall ($P = 0.0087$). Interestingly, differences in IQ were not statistically significant between GI symptom groups ($P = 0.07$).

Among the five primary measures of rigid-compulsive behavior in the total population, all measures demonstrated significant associations with constipation and diarrhea or underwear staining prior to adjustment for covariates. After adjustment for covariates, which resulted in a decrease in the overall sample size (Table 2), four of five measures remained significantly associated with constipation and diarrhea or soiling. These measures included both parental report and direct observation. Children with constipation and diarrhea or soiling were more likely to have a parental report of repetitive behavior on the Parental Concerns questionnaire (OR 1.61, 95% CI 1.31-1.99, $p < 0.0001$), compulsive behavior on the Parental Concerns questionnaire (OR 1.77, 95% CI 1.39-2.26, $p < 0.0001$), and OCD diagnosis per parental report on the Developmental and Medical History form (OR 1.91, 95%CI 1.31-2.77 $p =$

0.0007). Similarly, these children were more likely to have clinician report of rituals based upon direct observation during the ADOS (OR 1.53 times, 95% CI 1.11-2.10, $p = 0.0085$) compared to children without GI symptoms. Rigid/inflexible behaviors on the DSM-IV checklist were not significant after correction for covariates and multiple comparisons ($p = 0.0142$). Children with constipation only, without diarrhea or soiling, also demonstrated increased odds of having parental report of OCD on the Developmental and Medical History form with odds ratio 1.88 (95% CI 1.28-2.76 $p = 0.0012$). All other groups of GI symptoms did not show positive association with these measures of rigid-compulsive behavior.

Among the eight secondary measures of rigid-compulsive compulsive behavior, two showed a significant association with constipation and diarrhea or underwear staining in the total population before adjustment for covariates (Table 3), and both remained significant after correction for covariates. Children with constipation and diarrhea or underwear staining were more likely to have a family history of anxiety or OCD reported on the Developmental and Medical History form (OR 1.64 95% CI 1.32-2.03, $p < 0.0001$) and more likely to have received treatment with an atypical antipsychotic reported on the Diagnosis and Treatment form (OR 2.17 95% CI 1.58-3.00 $p < 0.0001$) than asymptomatic children. The other six secondary measures were not significantly associated with constipation and diarrhea or underwear staining. Similar to primary measures, children with GI symptoms outside of constipation and diarrhea or underwear staining did not demonstrate significant associations with any of the secondary measures of rigid-compulsive behavior. Additionally, presence of hyperactivity or inattention symptoms was not significantly associated with any constellation of GI symptom, nor was the presence of seizure disorder (Supplemental Table 2).

DISCUSSION

Consistent with our clinical observations, all five primary measures of rigid-compulsive behavior were significantly associated with constipation and diarrhea or underwear staining. Four of five of these measures remained significantly associated even after correcting for covariates, with odds ratios ranging from 1.53-1.91, despite the reduced sample size due to missing data for some individuals. Among secondary measures of rigid-compulsive behavior, only family history of OCD or anxiety and treatment with atypical antipsychotic medication were associated with constipation and diarrhea or underwear staining after correction for covariates; although a few other variables were nominally associated. We observed no significant association with measures of hyperactivity/inattention symptoms, suggesting specificity for the relationship between constipation and diarrhea or underwear staining and rigid-compulsive behavior.

The current study has several important limitations. While the ATN registry is large and provides opportunities to evaluate relationships between medical and behavioral data across domains, we were also constrained by the available data in the registry. Not all measures were present for all participants, creating variability in the composition of data available across measures. Further, the sample size decreased significantly when correcting for covariates. Measures of rigid and compulsive behavior were mostly based upon parental report, with clinician ratings only available from the DSM checklist or the standardized

interaction with the child during the ADOS. Measures of GI symptoms were also based upon parent report. Although parent-report by questionnaire and prospective GI clinician diagnosis were shown to be in good agreement in a recent cross-sectional study (Gorrindo et al. 2012), diagnosis by a gastroenterologist remains the gold standard. As a result, constipation and diarrhea or underwear staining was defined on the basis of a surrogate composite of parent reported symptoms. Of note, even if this surrogate measure is not specific for severe constipation and diarrhea or underwear staining, the data still indicate that patients with rigid-compulsive behaviors are at risk for these mixed bowel symptoms. Irritable bowel syndrome can include both constipation and diarrhea symptoms, but clinical diagnosis of irritable bowel syndrome was not available within the database. Finally, data on toilet training is not included within the ATN. Diarrhea or underwear staining is difficult to measure in children who struggle with toilet training, a common problem in ASD (Ando 1977).

A few previous studies have also tested relationships between GI symptoms and other core or associated behavioral symptoms in ASD, with some differences from our findings that may relate in part to different ways of assessing and analyzing GI symptoms. In partial agreement with Gorrindo and colleagues, our results indicate that GI symptoms in general were more common in non-verbal patients; however constipation was not specifically associated with non-verbal status, as they found (2012). Their ascertainment of GI symptoms included a gastroenterologist diagnosis; whereas we had parent report of symptoms without a formal diagnosis. Additionally, our sample was considerably younger than theirs (5.9 +/- 3.4 in contrast to 10.8 +/- 3.7 years old), which could also explain different results, especially given the small but significant association of GI symptoms with younger age in their sample. In our sample, GI symptoms did not vary a great deal with age. In general GI symptoms tend to decrease significantly as children age, but symptoms still persist in many children. Valcienti-McDermott reported an association between language regression and report of GI symptoms in 8 year olds (2008), which may also be partially consistent with our findings without separation of language ability generally from language regression specifically. It is difficult to know why difficulties with language may be associated with report of GI symptoms. Children with less developed language ability may also have less developed ability to indicate their needs around toileting. A study by Mazurek and colleagues using the ATN database reported an association between anxiety and decreased social responsiveness with GI symptoms that strengthens with the number of GI symptoms reported but did not specifically investigate the relationship between restrictive-repetitive behaviors and GI symptoms (2013). Maenner and colleagues were the only previous group to consider a specific association between stereotypic or repetitive behaviors and GI symptoms in general. While they did not find any relationship, their study is difficult to compare with ours because they did not assess specific GI symptom domains (2012). Adams and colleagues also investigated the relationship between gastrointestinal symptoms and autism symptoms as measured by the six question Gastrointestinal Severity Index (6-GSI) and Autism Treatment Evaluation Checklist (ATEC) respectively (2011). They found that report of multiple symptoms on the 6-GSI correlated strongly with higher ATEC scores and possibly correlated with higher scores on ATEC subscales of speech/language/communication, sociability, and health/physical/behavior.

A number of plausible biological or behavioral factors could contribute to the associations found in this study and are worthy of future study. Common systems in the brain and bowel could mediate these symptoms. For example, the serotonin system has been implicated in autism (Veenstra-VanderWeele, Blakely 2012, Murphy et al. 2006, Mulder et al. 2004) and in gastrointestinal disorders and their treatment (Gershon 2013, Ruepert et al. 2011, Ford et al. 2009). In mouse models, genetic manipulation of key components of the serotonin system, including tryptophan hydroxylase and the serotonin transporter, affects both behavior and gut function (Chen et al. 2001, Gershon 2013, Murphy et al. 2008, Lesch et al. 2012). ASD genetic risk, including genes involved in both brain development and GI function, such as the *MET* receptor tyrosine kinase, also could contribute to convergent symptoms in subgroups of children with ASD (Campbell et al. 2009). From a behavioral perspective, rigid-compulsive symptoms could impact bowel habits. For instance, a child's resistance to change during toilet training could lead to a pattern of stool retention. Conceptually, discomfort from mixed bowel symptoms could also lead to exacerbation of rigid-compulsive symptoms. Future studies could use a combination of clinical symptoms and biomarkers to parse the heterogeneity seen in ASD.

To confirm a relationship between rigid-compulsive behavior and mixed bowel symptoms, a prospective, hypothesis-driven study design will need to include more precise criteria for rigid-compulsive behaviors, a more specific and directed evaluation for GI symptoms, as well as relevant biomarkers such as whole blood serotonin levels or genetic markers. More specific evaluation for GI symptoms would include evaluation by GI specialist and history directed at clarifying the roles of behavior and biology regarding etiology of constipation. Such a history would include details such as rituals around toileting, co-occurring psychosocial stressors, presence of primary vs. secondary encopresis, family history of GI illness, or other co-occurring psychiatric illness. Additionally, obtaining a family history of GI symptoms could be useful in establishing a genetic or familial component to bowel symptoms. If our data are replicated in a prospective follow-up study, further work should examine the directionality of the relationship between rigid-compulsive symptoms and severe constipation and diarrhea or underwear staining. For example, a treatment study could evaluate whether rigid-compulsive symptoms improve after treatment of constipation. Conversely, behavioral treatment of rigid-compulsive symptoms could have benefits extending to bowel symptoms.

This study demonstrates an association between mixed bowel symptoms and rigid-compulsive behaviors in patients with ASD. Our results suggest that clinicians should screen for constipation and diarrhea or underwear staining symptoms in children with ASD who have prominent rigid-compulsive symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Relationship Between GI symptoms and diagnosis, demographic variables, verbal status, age and IQ

	Total N	No GI Symptoms	Constipation + Diarrhea or Staining	p-value
Diagnosis	3763	2957	806	0.89
Autism (%)		1960(66.2)	556(69.0)	
Asperger's (%)		259(8.8)	75(9.3)	
PDD-NOS (%)		738(24.9)	175(21.7)	
Ethnicity	3607	2844	763	0.82
Hispanic/Latino (%)		284(10.0)	71(9.3)	
Non-Hispanic/Latino (%)		2560(90.0)	692(90.7)	
Sex	3719	2934	785	<0.001
Male (%)		2498(85.1)	656(83.6)	
Female (%)		436(14.9)	129(16.4)	
Race	3719	2934	785	0.0013
Non White/Caucasian (%)		698(23.8)	145(18.5)	
White/Caucasian (%)		2236(76.2)	640(81.5)	
Verbal Status	3486	2739	747	0.22
Non-verbal (%)		640(23.4)	189(25.3)	
Verbal (%)		2099(76.6)	558(74.7)	
Age (Range 2-17 years)	3719	2934	785	<0.001
Mean(SD)		5.86(3.52)	5.91(3.40)	
IQ	2930	2314	616	0.63
Mean(SD)		75.82(23.69)	76.65(24.22)	

Chi-square used for categorical variables; unpaired t-test used for age and IQ

Table 2
Relationship Between GI symptoms and Primary Measures of Rigid-Compulsive Behavior

	<i>Unadjusted</i>			<i>Adjusted^a</i>		
	No GI Symptoms	Constipation + Diarrhea or Staining	OR	95% CI	P value	P value
ADOS Rituals	602	134	1.53*	1.14-2.06	0.005	0.009
DMH OCD	2098	701	2.1*	1.54-2.85	<0.001	<0.001
DSM Rigid-Inflexible	1036	249	1.34*	1.12-1.61	0.002	0.014
Par Compulsive	637	134	1.69*	1.36-2.10	<0.001	<0.001
Par Repetitive	932	191	1.66*	1.39-2.00	<0.001	<0.001

ADOS Rituals is the scoring of ritualistic behavior on the ADOS. DMH OCD is the designation of OCD on the Developmental and Medical History Form. DSM Rigid-Inflexible is the scoring of this symptom domain of ASD on the DSM checklist. Par Compulsive and Par Repetitive are based upon parent reports of these symptoms on the Parental Concerns questionnaire.

Logistic Regression,

^a Adjusted for diagnosis, race, sex, age, ethnicity, verbal status, IQ,

* Bonferroni corrected p-value < 0.05

Table 3
Relationship Between GI symptoms and Secondary Measures of Rigid-Compulsive Behavior

	Unadjusted			Adjusted ^a				
	No GI Symptoms	Constipation + Diarrhea or Staining	OR	95% CI	No GI Symptoms	Constipation + Diarrhea or Staining	OR	95% CI
ADOS Mannerism	1446	360	1.24	1.06-1.46	1175	289	1.24	1.02-1.50
ADOS Repetitive	324	81	1.16	0.89-1.51	263	62	1.16	0.89-1.65
DSM Stereotypies	807	198	1.24	1.02-1.50	686	176	1.19	0.96-1.49
ADOS Topic	708	171	1.20	0.99-1.45	589	145	1.15	0.91-1.42
DSM Restricted Interests	593	140	1.27	1.03-1.57	473	108	1.30	1.02-1.67
Treatment with AAP	2776	713	2.00 [*]	1.54-2.60	2085	534	2.17 [*]	1.58-3.00
Treatment with SSRI	2762	733	1.41	1.07-1.87	2059	545	1.45	1.03-2.05
Family History OCD/Anxiety	1390	341	1.68 [*]	1.41-2.06	1135	269	1.64 [*]	1.32-2.03

ADOS Mannerisms, Repetitive, and Topic are the scoring of mannerisms, repetitive motor behaviors, and excessive focus on a topic on the ADOS. DSM Stereotypies is the scoring of this symptom domain of ASD on the DSM checklist. Treatment with AAP or SSRI is treatment with atypical antipsychotic or serotonin reuptake inhibitor, respectively.
Family History of OCD / Anxiety is family history of either OCD or anxiety in a blood relative to include mother, father, grandparent, sibling, aunt, uncle or cousin recorded on the Developmental and Medical History form.

^a Adjusted for diagnosis, race, sex, age, ethnicity, verbal status, IQ

* Bonferroni corrected p-value < 0.01