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Behavioral Inflexibility Across Two Neurogenetic Conditions: Down Syndrome & Fragile X Syndrome

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Abstract

Behavioral inflexibility (BI) has been highlighted to occur across genetic and neurodevelopmental disorders. This study characterized BI in two common neurogenetic conditions: Fragile X Syndrome (FXS) and Down Syndrome (DS). Caregivers of children with FXS (N = 56; with ASD = 28; FXS only = 28) and DS (N = 146) completed the Behavioral Inflexibility Scale (BIS) via an online survey. Total BIS scores were higher in FXS+ASD than both FXS only and DS (p <.001). Most endorsed items were similar across the three groups, but scores were higher in the FXS+ASD group. In all groups, BI associated with other clinical variables (receptive behaviors, anxiety, social communication). The current data suggest that BI is variable across neurogenetic conditions and higher in individuals with comorbid ASD.

Introduction

Across a number of genetic and neurodevelopmental disorders, inflexibility has been reported by parents and observed behaviorally (Didden et al., 2008; Green et al., 2007; Haig & Woodcock, 2017; Lecavalier et al., 2020; Peters-Scheffer et al., 2008; Sethi et al., 2018). Behavioral inflexibility (BI) is defined as rigid and inflexible patterns of behavior that contrast with the need to be flexible, open to change, and amenable during situations that are unpredictable and require more adaptive responding (Lecavalier et al., 2020). BI has been highlighted as particularly salient in ASD (Lecavalier et al., 2020; Peters-Scheffer, Didden, Sigafoos, Green, & Korzilius, 2013).

One of the core diagnostic domains of ASD is the presence of restricted and repetitive behaviors (RRBs), which includes the presence of inflexible and rigid behaviors and routines (American Psychological

Association, 2013) and inflexibility has long been considered a defining feature of ASD. BI, together with insistence on sameness and resistance to change have consistently been found to *isolate* together across measures and age ranges (Bishop, Richler, & Lord, 2006; Cuccaro et al., 2003; Lam, Bodfish, & Piven, 2008). Within ASD, BI is associated with deficits in several different areas of functioning, including cognition (Miller, Ragozzino, Cook, Sweeney, & Mosconi, 2015; Uddin et al., 2015), language (Muskett, Perkins, Clegg, & Body, 2010), social function (Christ, Holt, White, & Green, 2007), and mealtime behaviors and eating (Johnson et al., 2014). Inflexibility is also positively associated with increased severity of co-occurring psychiatric conditions, such as anxiety (Boulter, Freeston, South, & Rodgers, 2014.; Rodgers, Glod, Connolly, & McConachie, 2012; Wigham, Rodgers, South, McConachie, & Freeston, 2015) and depression (Gotham, Bishop, Brunwasser, & Lord, 2014). In contrast to ASD, less is known about the manifestation of BI in neurogenetic conditions, including those that are frequently diagnosed with comorbid ASD. The goal of this study is to describe the presence and presentation of BI in two neurogenetic conditions: Fragile X Syndrome (FXS) and Down syndrome (DS).

Behavioral Inflexibility in Neurodevelopment and Genetic Disorders

FXS is one of the most common inherited causes of intellectual disability and ASD, caused by mutations in the FMR1 gene and affects about 1 in 4,000 boys and 1 in 8,000 girls (Saul & Tarleton, 1993). Approximately half of individuals with FXS also have a diagnosis of ASD (Abbeduto, McDuffie, & Thurman, 2014; Budimirovic & Kaufmann, 2011; Demark, Feldman, & Holden, 2003). DS is a neurogenetic disorder and cause of intellectual disability that can result from an extra copy of chromosome 21 (trisomy 21) and occurs in 1 in 824 live births. Individuals with DS have historically been used as comparison groups to those with ASD (Bentenuto, De Falco, & Venuti, 2016; Seltzer, Abbeduto, Krauss, Greenberg, & Swe, 2004). However, a recent meta-analysis suggested that individuals with DS have increased prevalence of ASD, with comorbid rates estimated at 16% higher than the general population, but lower than individuals with FXS (Richards, Jones, Groves, Moss, & Oliver, 2015).

Cognitive inflexibility, including deficits in executive functioning, are well established in both FXS (Hooper et al., 2008, 2018; Kirk, Mazzocco, & Kover, 2005; Wilding, Cornish, & Munir, 2002) and DS (Daunhauer et al., 2014; Daunhauer, Gerlach-McDonald, Will, & Fidler, 2017; Rowe, Lavender, & Turk, 2006). Most of these studies have focused on specific domains of executive functioning rather than wider manifestations of inflexibility, such as insistence on sameness and difficulty with transitions.

While BI has not been extensively examined in neurogenetic syndromes, a number of studies have reported the presence of RRBs in both FXS and DS with research primarily focused on the topographies of behaviors and their frequency. Relatedly, the manifestation of RRBs appears to differ between the two conditions; individuals with FXS display more *higher-order* behaviors (e.g., insistence on sameness and adherence to routines; Moss, Oliver, Arron, Burbidge, & Berg, 2009; Moss, Oliver, Nelson, Richards, & Hall, 2013; Oakes et al., 2016), whereas in DS these behaviors manifest more commonly through *lower-order* behaviors (e.g., motor stereotypies; Evans & Gray, 2000b). Given the high rates of comorbid ASD diagnoses within FXS, it is unsurprising that these individuals also have high rates of RRBs. RRBs in FXS can manifest through repetitive questioning and preference for routines and rituals (Moskowitz, Will, Black, & Roberts, 2020; Moss et al., 2009, 2013; Oakes et al., 2016). Moss et al (2008) reported higher total and subscale scores from the Repetitive Behavior Questionnaire on compulsive behavior, insistence on sameness and repetitive speech in a sample of individuals with FXS. Using a semi-structured interview with parents, Woodcock et al. (2009) described child reactions to changes in routines, including repetitive questioning and emotional and negative reactivity. Recently, Moskowitz et al (2020) modelled the trajectories of RRBs in a large sample (N=153) of 1-18 year-olds with FXS and also found consistently high rates of *higher-order* RRBs over time compared to *lower-order* RRBs. These findings suggest that BI may also be problematic for individuals with FXS.

The presence and profile of RRBs in DS is somewhat less clear. Generally, rates of RRBs in DS are lower than individuals with ASD (Hamner et al., 2019), but higher than rates observed in typical development

(Evans, Kleinpeter, Slane, & Boomer, 2014b; Hepburn & Maclean, 2009). Rates of RRBs have been reported to reduce overtime in DS, albeit at a slower rate to typical development (Evans & Gray, 2000b; Evans et al., 2014b). While *lower order* behaviors are more commonly observed in DS (Hepburn & Maclean, 2009), *higher-order* behaviors such as unusual preoccupations, routines and rituals have also been reported (Glenn, Cunningham, Nananidou, Prasher, & Glenholmes, 2015). As with ASD, early RRBs in DS predict later maladaptive behavior and problem behavior (Evans, Kleinpeter, Slane, & Boomer, 2014a; Glenn et al., 2015).

Impact and Importance of Behavioral Inflexibility

BI is also observed in typical development, with routinized behaviors around bedtime routines, insistence that things are completed in a particular way and strong preferences for certain items or foods (Evans, Gray, & Leckman, 1999; Evans et al., 1997; Leonard, Goldberger, Rapoport, Cheslow, & Swedo, 1990; Zohar & Felz, 2001). The presence of inflexible behaviors in typical development supports the notion of this behavior occurring dimensionally in neurotypical development and across diagnostic groups, with inflexibility perhaps serving an important function in development and neurodiversity. The positive impact of inflexibility has been highlighted, particularly in supporting the reduction of anxiety in ASD, DS and typical development (Evans et al., 1999; Leonard et al., 1990; Uljarević & Evans, 2017).

However, the impact of BI on families has also been highlighted through in-depth parent report. Sethi et al (2018) reported the extent to which BI manifested across daily lives in families with a child with ASD, how pervasive its impact was on the family and child, how families needed to accommodate and plan for events and changes and the strategies they used, including preparation and avoidance. Positive impacts were also highlighted by families such as increased flexibility within the family, increased tolerance and using structure and predictability as a coping mechanism. This suggests that while BI may be a construct present across neurodevelopmental disorders, its behavioral expression and functional impact on families and children may differ.

Current Study

Given that BI may negatively impact functioning in some children with ASD and thus potentially be considered a target for intervention, the Behavioral Inflexibility Scale (BIS) was previously developed as an outcome measure that can quantify the impact of inflexibility across a variety of aspects of daily living in ASD (Lecavalier et al., 2020). The BIS identified significant degrees of behavioral inflexibility in children with ASD both with and without a comorbid diagnosis of IDD. Based on this, we speculated that the BIS may also be useful for measuring the impact of inflexibility in other conditions associated with IDD. This could include a variety of neurogenetic conditions associated with IDD given that rigid and inflexible patterns of behavior have been reported to be part of the behavioral phenotype of several genetic conditions (Didden et al., 2008; Evans et al., 2014b; Hepburn & Maclean, 2009; Peters-Scheffer et al., 2013).

To date, the BIS has been examined in the context of ASD; further work is needed to determine if the BIS could be a useful instrument for measuring the impact of inflexibility in persons with IDD. The goal of this paper was to answer two research questions: (1) what is the profile of BI in two common neurogenetic conditions: FXS and DS; and (2) in these neurogenetic conditions, how does BI associate with RRBs, social communication and anxiety. We hypothesized that BI ratings would be higher for children with FXS, consistent with prior literature of higher rates of *higher-order* RRBs (Moskowitz et al., 2020; Moss et al., 2009) and highest ratings of BI in children with FXS+ASD. We also anticipated stronger correlations between BI and RRBs in FXS, given reports of increased RRBs in this population (Oakes et al., 2016; Reisinger, Shaffer, Tartaglia, Berry-Kravis, & Erickson, 2020). This study extends reports of higher rates of RRBs in neurogenetic conditions by specifically focusing on BI, which has known links to cognition, social function, language, and comorbid psychiatric conditions in ASD (Christ et al., 2007; Miller et al., 2015; Muskett et al., 2010; Wigham et al., 2015).

Methods

Participants Caregivers of children with a diagnosis of FXS or DS, ages 3 to 17 years, 11 months, were recruited via research registries (detailed below) to complete an online survey. Demographic characteristics of the caregivers and youth are presented in Table 1.

FXS Group. Caregivers of FXS children (*N* = 62) were recruited via the (blinded for review) FXS Research Registry. Individuals on the registry have a verified diagnosis of FXS and have agreed to be contacted for research opportunities. Of the 62 caregivers recruited, 56 had complete data across all measures. 50% of the children had a caregiver-reported co-occurring diagnosis of ASD (*N* = 28).

DS Group. Caregivers of DS children (N = 164) were recruited via DS Connect®; an NIH-funded and maintained registry of families with a child or adult diagnosed with DS who have agreed to be contacted for research opportunities. Families must complete a comprehensive health history questionnaire for inclusion in DS Connect®. Of the 164 caregivers recruited, 158 had complete data across all measures. 7.5% of children had a caregiver-reported co-occurring diagnosis of ASD. Due to the low number of participants with DS and co-occurring ASD (N=12), they were excluded from all subsequent analyses, resulting in a final N of 146.

Insert Table 1 here

Measures and Procedures. Staff from the respective recruitment registries contacted eligible families via email. Interested families followed a link to a secure website where they could create an online profile to complete the surveys. Caregivers completed a measure of BI, measures of ASD traits (social-communication and RRBs), a measure of anxiety and a demographic form. This study met ethical standards for human subjects research and was approved by the Institutional Review Board at (blinded for review).

Demographic Information. Caregivers completed a demographic form that provided information on caregiver and child demographics (sex, race, ethnicity, age). Caregivers were also asked to provide an estimate of their child's current IQ, ranging from below to above IQ (with an option for unknown). This information is included for reference only and not included in any analyses. Caregivers were also asked if their child had a co-occurring diagnosis such as ASD, intellectual disability, anxiety, depression or attention deficit/hyperactivity disorder. Demographic information is reported in Table 1.

Behavioral Inflexibility Scales (BIS). The BIS is a 38-item caregiver completed scale designed to measure BI in individuals with neurodevelopmental disorders, including ASD (Lecavalier et al., 2020). The development and validation of the BIS is outlined in detail by Lecavalier et al. (2020). The BIS was developed through an iterative process, including expert panel review, focus groups with stakeholders, cognitive interviews, and a large online survey with 943 parents of a child with ASD recruited via the Interactive Autism Network (https://iancommunity.org). The BIS provides a unidimensional set of 38 items that measure inflexibility on a 6-point scale from "Not at all a problem" to "Very severe or extreme problem." The most commonly endorsed items are reported in Table 2 and the BIS is available upon request from the first author. Raters assess behaviors over the past month. The BIS has a normative distribution in ASD, strong concurrent validity and good test-retest reliability (Lecavalier et al., 2020).

Social-Communication Questionnaire (SCQ). Caregivers completed the SCQ (Rutter, Bailey, & Lord, 2003); a 40-item measure arranged onto three subscales: social interaction, communication, and stereotyped behaviors. The SCQ is based on the Autism Diagnostic Interview-Revised (Rutter, Le Couteur, & Lord, 2003) and asks caregivers to choice a dichotomous "yes"/"no" response for behaviors related to ASD symptomatology. The SCQ has strong discrimination between ASD and non-ASD cases (sensitivity 0.88, specificity 0.72; (Chandler et al., 2007)), though poorer discrimination below the age of four (Marvin, Marvin, Lipkin, & Law, 2017). The SCQ has been applied as a screener for ASD-traits in both DS (DiGuiseppi et al., 2010; Magyar, Pandolfi, & Dill, 2012) and FXS (Kidd et al., 2020). Studies have

suggested that a total score greater or equal to 12 can be ideal to maximize sensitivity (Norris and Lecavalier, 2010).

Repetitive Behavior Scales-Revised (RBS-R). The RBS-R (Bodfish, Symons, Parker, & Lewis, 2000) is a 43-item caregiver report questionnaire measuring a variety of repetitive behaviors. Items are rated on a four-point Likert-scale (0 = behavior does not occur through to 3 = behavior occurs and is a severe problem) and distributed along six subscales: Stereotyped Behavior, Self-Injurious Behavior, Compulsive Behavior, Ritualistic Behavior, Sameness Behavior, and Restricted Behavior. The RBS-R has good internal consistency (Lam & Aman, 2007) and reliability and validity (Bodfish, Symons, & Lewis, 1999). It has been widely used to capture repetitive behaviors in FXS (e.g. Oakes et al., 2016; Reisinger, Shaffer, Tartaglia, Berry-Kravis, & Erickson, 2020; Wolff et al., 2012) and extended to DS (Neil & Jones, 2016).

Parent Rated Anxiety Scale-Autism Spectrum Disorder (PRAS-ASD). The PRAS-ASD (Scahill et al., 2019) is a 25-item caregiver report questionnaire for measuring anxiety in youth with ASD ages 5 to 17. Like the BIS, the PRAS-ASD was developed via an iterative process with stakeholder focus groups and a large online survey (Bearss et al., 2016; Scahill et al., 2019) Parents rate their child's worries and anxiety-related behaviors on a scale from 0 to 3 (none to severe) over the past two weeks. The PRAS-ASD has good test-retest reliability and convergent validity with other pediatric anxiety measures (Scahill et al., 2019). It has not been used previously in individuals with FXS or DS. Cronbach's alpha for the PRAS-ASD indicates high internal consistency across both diagnostic groups (FXS alpha = 92; DS alpha = .91), consistent with previous findings in the ASD population (Scahill et al., 2019).

Analysis Plan.

To address our first research question (profiling BI across children with FXS and DS), we first measured the internal consistency of the BIS using Cronbach's alpha. We then separated our FXS group into those with a co-occurring diagnosis of ASD (FXS+ASD: n = 28) and those without a diagnosis of ASD (FXS

only: *n* = 28) and identified individual BIS items that were reported as the most problematic (i.e., the 10 items with the highest mean) for each group. We tested whether BIS total scores differed by age (continuous variable) and sex separately using a linear regression. We also tested whether total BIS scores varied as a function of diagnostic group using analysis of variance (ANOVA).

To address our second research question (associations between BI and other variables), we computed correlations between BIS total score and SCQ total score, RBS-R total score, RBS-R Insistence on Sameness (RBS-R IS) subscale score, and PRAS-ASD mean score. We tested whether these correlations were different from 0 using a t-test and corrected for multiple comparisons using the Bonferroni correction. Given that the PRAS-ASD was validated for 5 - 17 year-old's, we only examined associations with BIS scores for children in that age range (DS n = 146, FXS n = 28, FXS + ASD n = 28).

Results

Internal Consistency and Distribution of the BIS in FXS and DS: Cronbach's alpha indicates high internal consistency across both diagnostic groups (FXS alpha = 98; DS alpha = .97), which is consistent with previous findings in the ASD population (Lecavalier et al., 2020). Additionally, the Shapiro-Wilks test of normality suggests that the distribution of BIS total scores do not differ significantly from the normal distribution in the FXS group ($W = 0.97$, $p = 0.16$). The scores had minimal skew (skewness = 0.31) and were platykurtic (kurtosis = 2.44). However, in the DS group the scores do differ significantly from the normal distribution ($W = 0.92$, $p < .001$). The scores in this group were moderately positive skewed (skewness = 0.95) and leptokurtic (kurtosis = 3.45)

Most Endorsed Items in FXS and DS: Mean item scores for the top five endorsed items and total scores are presented in Table 2 by diagnostic group. The three groups shared one item that were considered to be the most problematic (Table 2). The FXS groups overlapped on three of the most endorsed items. The FXS

only and DS groups and the FXS+ASD and DS groups overlapped on two items. The item rated as most severe for the FXS groups was "my child gets stuck on particular activities or topics", whereas the item "my child can be hard to redirect from things he is doing" was rated most severe in DS.

Insert Table 2 here

Behavioral Inflexibility by Group and Demographic Variables: BIS total scores by diagnostic group are presented in the final row of Table 2. Children with FXS+ASD demonstrated greater inflexibility (*M* = 80.00, *SD* = 36.49) than both children with FXS only (*M* = 44.25, *SD* = 30.24) and children with DS (*M* = 42.60, *SD* = 31.10). Older children (*p* = .002, F[1, 197] = 10.08, β = 1.77) and males *(Cohen's d* = 0.42, *p* = .004, t[193.37] = 2.95) demonstrated the greatest inflexibility. After controlling for age and sex, children with FXS+ASD demonstrated greater inflexibility than children with DS and FXS only (p <.0001, t[194] = 4.128, B = 29.81). However, there were no statistically significant differences in behavioral inflexibility scores between children with FXS only versus children with DS (p =.82, t[194] = -0.22, B = -1.43), suggesting that the presence of ASD, not the diagnosis of FXS, differentiates the levels of BI observed in these neurogenetic disorders.

***Associations between BI, social communication, RRBs and anxiety*:** BI was highly related to both anxiety and RRBs in all groups with greater BI associated with heightened anxiety and more frequent/severe RRBs (Table 3; *p's* all <.01). In general, the highest magnitude of correlations between BI, anxiety and RRBs were found in the FXS only group, particularly for RRBs (Table 3; PRAS-ASD = .78; RBS-R = .88). BI was also highly correlated with the Insistence on Sameness Scale from the RBS-R in all groups (FXS+ASD = .79; FXS = .86; DS = .81). Higher BIS scores were associated with higher RBS-R-IS scores, suggesting overlap between insistence on sameness and BI. Social communication, as indexed by the SCQ, was also associated with BI in all groups (Table 3) and most strongly in the FXS only group (FXS+ASD = .69; FXS

= .79; DS = .61). Higher BIS scores were associated with higher SCQ scores, indicating more BI was accompanied by more social-communication impairments.

Insert Table 3 here

Discussion

In the present study, we extended previous work validating the BIS in ASD (Lecavalier et al., 2020) to two common neurogenetic conditions; FXS and DS. We proposed that BI would be a strong candidate for cross-syndrome clinical models. While BI manifested similarly across children with FXS and DS, there were differences in the distribution of BIS scores, most endorsed items, and in how problematic BI was rated by parents, particularly for children with FXS with a co-occurring diagnosis of ASD. In all groups, BI associated with other clinical variables (receptive behaviors, anxiety, social communication).

Overall, children with FXS+ASD had higher BI scores than children with FXS only and those with DS. Mean total BIS scores in the FXS+ASD group were comparable to the mean total BIS scores from the ASD group reported by Lecavalier et al (2020), who reported a mean total score of 83.9 (SD = 38.6). Both the FXS only and DS groups had similar mean total scores—scores that were nearly half the total score of the FXS+ASD males and the previous ASD sample (Lecavalier et al., 2020). While the 12 DS+ASD cases were removed from our main analysis, exploratory analysis revealed their total BIS score to be 91.40 (*SD* = 23.56) – higher than the FXS+ASD group and more than double the total score for the DS only group. Thus, it appears that the presence of ASD in addition to a neurogenetic disorder is the driver of higher BI ratings.

The finding that BI was greater in children with FXS+ASD aligns with reports of higher rates of RRBs, particularly for higher order behaviors, in this population (Moskowitz et al., 2020; Richards et al., 2015). BI was still rated as problematic and occurring for families with a child with DS and FXS only, however,

at a lower rate than both FXS+ASD and ASD (Lecavalier et al., 2020). Based on previous research, it could be that BI in children with DS and FXS falls somewhere on a continuum between neurotypical children and children with other neurodevelopmental/genetic conditions (Evans & Gray, 2000a; Evans et al., 2014a).

In both neurogenetic groups, the majority of most endorsed items overlapped. These included "my child gets stuck on particular activities or topics", "my child is reluctant to try new things", and "my child has difficulty transitioning between activities." However, the scores for these items were consistently higher in the FXS+ASD group.

Results suggest that older children demonstrate greater BI than their younger peers. This finding contrasts to the lack of association between BI and chronological age in the large ASD sample reported by Lecavalier et al., 2020 and suggests that there may be age-related changes in BI with regards to severity and presentation over the course of development that vary by neurogenetic condition and the presence/absence of ASD.

There were modest to strong associations between BI and social communication, RRBs and anxiety. In all groups, RRBs, rated via the RBS-R, were highly correlated with BI and modestly higher in the FXS only group, extending the findings of Lecavalier et al (2020), who reported a strong relationship between BI and RRBs in ASD. Strong associations were reported between the RBS-R IS scale and BI in all groups. Social communication, as indexed via the SCQ, associated with BI in all groups but most strongly in the FXS only group. Heightened anxiety was associated with greater BIS scores. A growing body of evidence indicates that anxiety leads to decreased cognitive flexibility (for a review, see Hartley & Phelps, 2012). It may be that BI is also increased in the presence of anxiety, particularly in neurogenetic syndromes.

The internal consistency of the BIS in these two neurogenetic conditions is similar to that of the previous ASD validation sample. However, there was evidence of non-normality in the DS group, potentially

indicating higher variance or skewed scores within this group compared to FXS and the previous ASD sample (Lecavalier et al., 2020).

Clinical Implications. Given the heightened rates of BI in male children with FXS+ASD, the BIS could be used to identify problem areas for children and families that could be targeted with intervention. It could utilized as a marker of change within intervention studies. Extending the BIS to other neurogenetic groups, such as Prader Willi Syndrome (PWS) and Angelman Syndrome, would be a logical future direction given reports of BI and RRBs in the consitions (Haig & Woodcock, 2017; Moss et al., 2009) and interventions focused on flexibility in PWS (Robb, Waller, Woodcock, & Woodcock, 2019).

Limitations. While comparable to or larger than other FXS samples (Roberts et al., 2009; Wolff et al., 2012), our FXS sample was smaller in size to our DS group. This sample also comprised of 50% with a co-occurring ASD diagnosis. We also only had a small sample of DS+ASD children (n = 12), therefore excluded these children from main analysis. No neurotypical control group or children with IDD without a known genetic condition were available for inclusion in our data set. Future research should include neurotypical controls to further tease apart the effects of neurogenetic conditions on BI severity and any age-related effects on BI.

While the inclusion of the PRAS-ASD to capture anxiety and its associations with BI in children with FXS and DS is novel, the lack of reliability and validity data for this measure in neurogenetic populations is a limitation. Given the difficulty of accessing large samples of both children with FXS and DS, gaining sufficient samples to assess reliability and validity would be a challenge. Further, modified versions of the SCQ have been proposed and tested for FXS that may serve as a better screener for ASD-traits than the version of the SCQ used within this study (Kidd et al., 2020).

Due to the remote nature of our study, we only asked parents for estimates of their child's current IQ and functioning level. Given the crude nature of this approach, the potential for parental inaccuracies and the number of missing or not known responses in the DS group, these variables were not included in our analysis. However, future research should include standardized assessments of IQ and language as these child characteristics may explain the relationships between BI and other areas of development. Further, the child's diagnosis of FXS and DS was not able to be formally verified. However, DS-Connect requires families to complete a comprehensive health history questionnaire for inclusion and the (blinded for review) FXS Research Registry requires laboratory confirmation of the child's FXS diagnosis to determine eligibility for inclusion. Parent report of ASD diagnosis was also used in the FXS group. We also relied upon parent-reported co-occurring ASD diagnoses in both groups.

Conclusions. BI is a construct common across multiple neurodevelopmental and neurogenetic disorders. The presentation and severity of BI varies slightly by the genetic etiology of children, with higher ratings of BI in children with FXS+ASD. Unlike children with ASD where ratings of BI were stable across biological sex and age, BI was rated as higher in males and increased with age. Given that BI is associated with negative clinical outcomes, future work should extend the BIS to other neurogenetic conditions, such as Dup15q, Angelman Syndrome, Prader Willi Syndrome and William's Syndrome.

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Table 1. Demographic Information by Diagnostic Group

	FXS+ASD (n = 28)	FXS only (n = 28)	Down syndrome (n = 146)	Test statistic	P-value
Average Child Age in Years*	12.90 (*sd* = 3.76)	11.20(*sd = 4.66)*	9.33 (*sd* = 3.96)	F = 10.25	< .001
Male Sex *,**	25 (89%)	17 (61%)	71 (49%)		< .001
Parent Race**	White (n = 27) Other (n = 1)	White (n = 25) Asian (n = 2) Other (n = 1)	White (n = 138) Black(n = 2) Other (n = 6)		.19
Parent Ethnicity**	Non-Hispanic (n = 24) Hispanic (n = 4)	Non-Hispanic (n = 28)	Non-Hispanic (n = 133) Hispanic (n = 13)		.12
Parent Estimate of Child IQ/functioning level*,**	Below average (n = 26) Unknown(n = 2)	Below average (n = 19) Average (n = 7) Unknown(n = 2)	Below average (n = 95) Average (n = 9) Above average (n = 1) Unknown (n = 41)		<.005

Note: sd = standard deviation, IQ = intelligence quotient
*Statistically significant differences across groups at the .01 level after correcting for multiple comparisons using Bonferroni's correction (.05 / 5 comparisons = .01)
**Due to small cell size, group differences were examined using Fisher's exact test

Table 2. Most Endorsed BIS Items by Diagnostic Group: Mean and Total Scores

Item	FXS+ASD		FXS only		DS	
My child resists having to change the way he usually does things	2.54	(1.26)	1.68	(1.06)	1.99	(1.16)
My child takes a long time to get comfortable in new situations	2.79	(1.29)	1.96	(1.10)	1.64	(1.23)
My child gets stuck on particular activities or topics	3.18	(1.25)	2.29	(1.46)	2.01	(1.32)
My child has trouble coming up with new ways of doing things "trouble even when the situation calls for it	2.71	(1.24)	1.64	(1.16)	1.65	(1.29)
My child has difficulty transitioning between activities	2.89	(1.29)	1.64	(1.16)	1.96	(1.33)
My child can be hard to redirect from things he is doing	3.00	(1.36)	1.86	(1.51)	2.08	(1.28)
My child is reluctant to try new things	3.04	(1.26)	1.75	(1.08)	1.35	(1.21)
Average BIS Total Score	80.00	(36.49)	44.25	(30.24)	42.60	(31.10)

SD reported in ( )
Shaded areas refer to most commonly endorsed items

Table 3. Correlations between BIS Total Scores and other constructs

	FXS+ASD	FXS only	DS
PRAS-ASD	0.67***	0.78***	0.60***
RBS-R Total	0.70***	0.88***	0.79***
RBS-R IS	0.79***	0.86***	0.81***
SCQ	0.69***	0.79***	0.61***

***Significant at the alpha = 0.017 level after correcting for multiple comparisons applying the Bonferroni correction for multiple comparisons (.05 / 3 comparisons = .017)

Note: Correlations between PRAS-ASD and BIS were run only for children ages 5 and older. Correlations were tested whether they are significantly different from 0 using a t-test. Also, we tested for differences between groups using a Fisher's exact test of the Z-transformed correlations (Diedenhofen & Musch, 2015). After correcting for multiple comparisons, no differences between groups were found.