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Role of Parent-Reported Executive Functioning and Anxiety in Insistence on Sameness in Individuals with Germline *PTEN* Mutations

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Scientific Abstract

No studies to date have explored the correlates of insistence on sameness (IS) in individuals with germline pathogenic mutations in *PTEN*. This study aimed to characterize the relationship between IS and executive functioning (EF) and anxiety as well as with age, sex and Full-Scale IQ (FSIQ) among individuals with *PTEN* mutations. The sample included 38 individuals with *PTEN* mutation and ASD diagnosis (*PTEN*-ASD; $n = 38$; $M_{age} = 8.93$ years, $SD_{age} = 4.75$), 25 with

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ASD and macrocephaly but with no *PTEN* mutation (Macro-ASD; M_{age}= 11.99 years; SD_{age}= 5.15) and 23 with *PTEN* mutation without ASD (*PTEN*-no ASD; M_{age}= 8.94 years; SD_{age}= 4.85). The Repetitive Behavior Scale-Revised (RBS-R), the Child Behavior Checklist (CBCL), and the Behavior Rating Inventory of Executive Function (BRIEF) were used as measures of IS, anxiety, and Inhibitory Control, Set-shifting and Working Memory EF domains, respectively. FSIQ was also available. IS was significantly associated with FSIQ (r= −.36, p= .002), CBCL anxiety (r= .45, p< .001), BRIEF Inhibitory Control (r= .36, p= .002),Set-Shifting (r= .65, p< .001) and Working Memory (r= .27, p= .023) T scores. The final hierarchical regression model accounted for 44.2% of the variance in IS, with Set-Shifting as a unique independent predictor of IS score (t = 4.30, p< .001). This investigation furthers our understanding of IS by providing the first preliminary evidence for the EF—anxiety—IS interrelationship in individuals with *PTEN* mutations and with macrocephalic ASD.

Keywords

PTEN; Macrocephaly; Insistence on Sameness; Anxiety; Executive Functioning

Germline pathogenic mutations in *PTEN* are associated with a wide range of cognitive and neurodevelopmental clinical presentations (Frazier, 2019; Yehia, Keel, & Eng, 2020), with consistent evidence of universal macrocephaly, impaired executive functioning (EF) and elevated rates of autism spectrum disorder (ASD) (Frazier et al., 2015; Busch et al., 2019). In fact, pathogenic *PTEN* mutations are identified in approximately 2% of all ASD cases and 20% of macrocephalic individuals with ASD (Hansen-Kiss et al., 2017; Ciaccio et al., 2019). However, despite the established link between *PTEN* and ASD, the majority of previous research has focused on overly broad social-communication and restricted and repetitive (RRB) domains, both of which encompass a range of symptoms with diverse clinical correlates and suggested underlying mechanisms. Therefore, increased focus on narrowly defined symptom domains with distinct neurobiological underpinnings is necessary for advancing our understanding of specific clinical presentations and informing the development of individually tailored treatment and assessment strategies for this population. In this investigation, we focused on one such symptom domain—insistence on sameness (IS). When compared to other RRB domains, IS shows relative independence of IQ (Hus et al., 2007; Lam et al., 2008; South et al., 2005) and distinct genetic and neural underpinnings (Langen et al., 2010; Leekam et al., 2011). More specifically, IS has been linked to structural and functional atypicalities in caudate-dorsolateral prefrontal cortex associative/cognitive corticostriatal loop (Langen et al., 2010; Yerys, 2015). Additionally, previous studies showed familial aggregation of IS (Lam et al., 2008; Silverman et al., 2012; Szatmari et al., 2006; Uljarević et al., 2016) and 2q37.1-q37.3 (Cannon et al., 2010), 15q11-q13 (Shao et al., 2003), and 8p21.2–8p21.1 (Tao et al., 2016) genetic regions as harboring top signals for IS. Finally, IS occurs across a range of neurodevelopmental (NDD) and neuropsychiatric (NPD) disorders (Evans et al., 2017), including genetic syndromes (Leekam et al., 2011; Moss et al., 2009; Uljarević & Evans, 2017). Therefore, identifying mechanisms behind IS can inform the treatment approaches, regardless of the diagnostic status. Crucially, IS has been shown to negatively impact the functioning of affected individuals and their families, yet remains poorly characterized among individuals with *PTEN* mutations.

Although part of the diagnostic criteria for ASD, as noted, IS is not specific to this disorder but occurs across a range of NDD and NPD, albeit in a less severe form (Leekam et al., 2011). Importantly, IS is part of early normative development (Evans et al., 1997; Leekam et al., 2007) where, although never reaching the same degree of severity as in clinical conditions, it shows a steep increase from 15 to 24 months of age, plateaus between 36 and 48 months and gradually reduces to typically low levels by age of six (Uljarević et al., 2017a). During this developmental period, IS tends to become more intense at times of transition such as bedtime or going to nursery/kindergarten that are accompanied by normative fears (Evans et al., 1999). Reduction in IS and normative fears corresponds with the period when different EF facets including response inhibition and the ability to shift between mental sets and/or multiple tasks start to develop and mature (Zelazo et al., 2003).

Noted developmental trends of IS, fears and EF have led to suggestions that IS serve to control or constrain the environment, thus limiting unpredictability and reducing ensuing fears and anxiety during early development but tend to decrease as more mature and effective forms of self-regulation develop (Leekam et al., 2011; Uljarević et al., 2017b; Zohar & Felz, 2001). Conversely, in ASD where delays and impairments in EF are well-established (Hill, 2004), and the rate and severity of anxiety is high (South & Rodgers, 2017; Uljarević et al., 2016), IS persists and continues to serve a regulatory function. However, the inflexibility of IS behaviors might sustain and reinforce anxiety over time. Several indirect and direct lines of evidence support this theory. First, IS is stable and persistent in ASD and tends to be present across varying levels of cognitive functioning (Bishop et al., 2013; Esbensen et al., 2011; Uljarević et al., 2020). Second, both anxiety and EF deficits are highly prevalent in ASD (Hill, 2004; South & Rogers, 2017; Uljarević et al., 2019a; White et al., 2009). Third, more severe IS has been separately associated with anxiety (Lidstone et a., 2014; Rodgers et al., 2012) and poor EF (South et al., 2007), which, in turn, are inter-related (Hollocks et al., 2014). Finally, recent findings by our group provide evidence of the significant independent contribution of anxiety and EF in predicting more severe IS in ASD (Uljarević et al., 2017b).

EF deficits and anxiety are not specific to ASD, but rather, vary across a range of NDD and genetic syndromes (Otterman et al., 2019; Reardon et al., 2015). Therefore, it is likely that these factors would underpin IS regardless of the primary diagnosis. For instance, previous work has demonstrated the contribution of EF and anxiety to IS in both 22q11.2 Deletion Syndrome (DiGeorge Syndrome) (Uljarević et al., 2019b) and Down Syndrome (Uljarević & Evans, 2017). Anxiety is frequent in individuals with *PTEN* mutations (Yehia et al., 2020). Further, a majority of individuals with *PTEN* mutations present with frontal–subcortical dysfunction and a degree of EF deficits (Busch et al., 2013; 2019; Frazier et al., 2015). The only two studies that specifically explored RRB in individuals with *PTEN* mutations have reported similar RRB levels among *PTEN* with ASD and idiopathic ASD macrocephaly groups and significantly higher RRB in individuals with *PTEN* mutation without ASD diagnosis when compared to healthy controls (Busch et al., 2019). However, these studies did not consider more fine-grained domains such as IS. Here, we predicted that higher levels of IS would be associated with poorer EF abilities and higher severity of anxiety symptoms. EF is a complex, multifaceted domain encompassing multiple components including response inhibition control, set-shifting and working memory subdomains (Miyake &

Friedman, 2012), each of which has been theoretically linked to IS in ASD (Leekam et al., 2011). Although previous findings provide robust evidence for the link between general EF deficits and IS, findings in terms of which of the distinct EF subdomains show the strongest influence on IS have been less clear (Boyd et al., 2009; Faja & Darling, 2019; Mostert-Kerckhoffs et al., 2015; South et al., 2007; Yerys et al., 2009). Therefore, rather than focusing on the overall EF ability level, this study aimed to characterize the unique contribution of the response inhibition, set-shifting and working memory EF components in predicting the severity of IS. These relationships were explored across individuals with *PTEN* mutations with and without ASD and with ASD and macrocephaly but with no *PTEN* mutation (Macro-ASD). Macrocephaly has been suggested as a potential neurophenotype in ASD (Amaral et al., 2017) and idiopathic macrocephaly has been shown to have negative effects on processing speed and other EF-related domains (e.g., Biran-Gol et al., 2010; Muenchberger et al., 2006). Therefore, Macro-ASD group was included to eliminate potential confounding of macrocephaly on EF symptoms.

Methods

Participants

The sample comprised 86 individuals and included 38 individuals with *PTEN* mutation and ASD diagnosis (*PTEN*-ASD; $n = 38$; $M_{age} = 8.93$ years, $SD_{age} = 4.75$), 25 individuals with ASD and macrocephaly but with no *PTEN* mutation (Macro-ASD; $M_{age} = 11.99$ years; $SD_{age} = 5.15$) and 23 individuals with *PTEN* mutation without ASD diagnosis (*PTEN*-no ASD; $M_{age} = 8.94$ years; $SD_{age} = 4.85$). Participants were recruited across four sites (Cleveland Clinic, Stanford University Department of Psychiatry and Behavioral Sciences, University of California at Los Angeles and Boston Children's Hospital) as part of an ongoing, multicenter study designed to examine the natural history of germline heterozygous *PTEN* mutations (clinicaltrials.gov: NCT02461446). All participants underwent a screening assessment by a clinical psychologist with extensive expertise in ASD to ascertain whether they met DSM-5 ASD diagnostic criteria. The ASD diagnosis was confirmed using ADI-R and ADOS-2. This project was approved by the Institutional Review Boards across all four sites. Baseline descriptive statistics stratified by the group are presented in Table 1.

Measures

The Repetitive Behavior Scale-Revised (RBS-R; Bodfish et al., 2000).—The RBS-R is a 43-item parent-report scale designed to provide a comprehensive assessment of different types of RRB organized into 6 subscales. Each item is rated on a four-point Likert scale ranging from "behavior does not occur" to "behavior occurs and is a severe problem". Here we focused on the original Sameness subscale as a measure of IS. However, given that several RBS-R factor analyses (e. g. Bishop et al., 2013; Lam & Aman, 2007) have found that most of the items from the original Sameness and two items from the original Ritualistic scale load onto one single Ritualistic/Sameness factors, we have also re-run all the analyses using this factor.

The Child Behavior Checklist, Ages 1.5–5 and 6–18 (CBCL; Achenbach & Rescorla, 2000).—The CBCL is a parent-report instrument designed to assess behavior

and emotional problems in children and adolescents. Each item is rated on a three-point Liker scale ranging from “not true” to “very true or often true”. It provides eight empirically-based syndrome scales that are grouped into internalizing and externalizing problem domains. Here we focused on the anxiety domain using T scores.

The Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000).—The BRIEF is a parent-report instrument designed to assess different aspects of EF organized into eight subscales. Each item is rated on a three-point Likert scale ranging from “never” to “often”. Here we focused on the BRIEF Inhibitory Control, Set-Shifting and Working Memory T scores. Higher scores are indicative of more EF difficulties

Analysis Plan

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS v. 25.0, New York, NY). Diagnostic groups were compared on relevant variables using ANOVAs. All comparisons are supplemented with ω^2 and Cohen’s *d* effect sizes. Pearson *r* and point bi-serial correlations were used to explore the associations between RBS-R IS scale with variables of interest. Variables significantly associated with RBS-R IS score were then entered into a hierarchical regression model. All analyses were performed with bootstrapping using 5,000 resamples to provide more robust statistics and account for the potential skewness of the data (Efron & Tibshirani, 1993).

Results

Descriptives and detailed group comparisons across all measures are presented in Table 1. There were no sex, race or ethnicity differences among the three groups; however, there were significant differences in terms of age ($F = 3.45$, $p = .036$ $\omega^2 = .05$) with post-hoc comparisons showing that Macro-ASD subgroup was significantly older than *PTEN*-ASD ($p = .045$, $d = .62$). Significant group differences were also found for FSIQ ($F = 14.43$, $p < .001$, $\omega^2 = .27$) with post-hoc comparisons showing that *PTEN*-no ASD group had higher FSIQ scores than both Macro-ASD and *PTEN* ASD groups (both $p < .001$, *d* range: 1.17–1.61). Significant group differences were also found for BRIEF Inhibitory Control ($F = 6.47$, $p = .003$, $\omega^2 = .13$) and Set-Shifting ($F = 5.49$, $p = .006$, $\omega^2 = .11$) with post-hoc comparisons showing that *PTEN*-no ASD group endorsed significantly fewer Inhibitory Control difficulties than both Macro-ASD and *PTEN*-ASD groups and significantly fewer Set-Shifting difficulties than Macro-ASD group. Although the *PTEN*-no ASD group had lower CBCL Anxiety scores than the other two clinical groups, the difference did not reach statistical significance ($F = 1.64$, $p = .20$, $\omega^2 = .08$).

As shown in Table 2, RBS-R Sameness score was significantly associated with CBCL Anxiety ($r = .42$, $p < .001$) and the BRIEF Inhibitory Control ($r = .36$, $p = .002$), Set-Shifting ($r = .65$, $p < .001$) and Working Memory ($r = .27$, $p = .023$) T scores. This pattern remained largely unchanged after controlling for the effects of FSIQ. Importantly, Fisher r-to-z transformation showed that the relationship between key variables of interest was not significantly different between *PTEN*-ASD, Macro-ASD and *PTEN*-No ASD groups (Sameness—CBCL Anxiety $z \leq 1.45$, $p \geq .07$; Sameness—BRIEF Inhibitory Control: $z = 1.51$ and .25, $p \geq .07$; Sameness—BRIEF Set-Shifting: $z \leq 1.29$, $p \geq .10$; Sameness—

BRIEF Working Memory: $z \leq .93$, $p \geq .18$). The only exception was the Sameness—BRIEF Inhibitory Control association that was somewhat stronger in *PTEN*-No ASD than in *PTEN*-ASD group (z=1.85, p= .032). Before conducting regression, we looked for evidence of multicollinearity. The highest Variance Inflation Factor value in the regression model was 1.66, significantly lower than the suggested cut-offs of 5 (Sheather, 2009) or 10 (Kutner et al., 2004). Therefore, multicollinearity was not a concern. Table 3 summarizes the hierarchical regression. The first three steps with the diagnostic group (Step 1), FSIQ (Step 2) and CBCL Anxiety score accounted for 7.2%,8.9% and 7.7% of the variance, respectively. In the fourth step, BRIEF Inhibitory Control, Set-Shifting and Working Memory T scores accounted for an additional 21.9% of variance (ΔF= 6.31, p= .001). The final model accounted for 45.7% of variance (F= 6.59, p< .001) in IS, with BRIEF Set-Shifting T score as a unique independent predictor (t = 4.12, p< .001). Re-running the regression model using the Bishop et al. (2013) Ritualistic/Sameness score instead of the original Sameness score showed very similar results with the full model accounting for 42.1% of the variance (F= 5.71, p< .001) in IS, with BRIEF Set-Shifting T score as a unique independent predictor (t = 3.99, p< .001).

Discussion

The main aim of our study was to explore the correlates of insistence on sameness (IS) in individuals with germline pathogenic mutations in *PTEN*. Consistent with our predictions and previous literature in ASD (Uljarević et a., 2017; 2019) we found that IS was associated with higher levels of anxiety and greater difficulty across inhibitory control, set-shifting and working memory components of executive functioning across the clinical groups.

We first considered the relationship between IS and age and FSIQ. IS was originally conceptualized as a “higher-order” RRB domain by Prior & McMillan (1973) and later Turner (1999), who hypothesized that IS would be more prevalent in older individuals with higher IQ. However, subsequent findings have suggested that after early childhood, IS remains stable and relatively independent of IQ (Hus et al., 2007; Lam et al., 2008), which is consistent with our findings. Nevertheless, it is important to emphasize that longitudinal studies on the trajectory of IS (and other RRB domains) are lacking, and it will be necessary for future research to further explore the results reported here.

Our observations suggest an association between IS, anxiety and all facets of executive functioning across *PTEN*-ASD, *PTEN*-no ASD and Macro-ASD groups. These results are consistent with a range of studies across ASD, other NDD and genetic syndromes that reported positive associations between IS and anxiety (Rodgers et al., 2012; Uljarević & Evans, 2017) and EF deficits (Mostert-Kerckhoffs et al., 2015; South et al., 2007) and between EF and anxiety (Hollocks et al., 2014). For instance, higher levels of anxiety have been associated with more severe IS across a number of populations, including ASD (Lidstone et al., 2014), Down Syndrome (Uljarević & Evans, 2017), Williams-Beuren Syndrome (Rodgers et al., 2012) and normative development (Pietrefesa & Evans, 2007). Furthermore, individual differences in EF have been linked with anxiety symptoms across normative development (Hughes & Ensor, 2011), ASD (Wallace et al., 2016) and other NDD (Dajani et al., 2016). In addition, our results mirror previous findings from our

group that have demonstrated the relationship between EF and anxiety with IS in ASD (Uljarević et al., 2017b) and 22q11.2 deletion syndrome (Uljarević et al., 2019b). Crucially, although previous findings consistently demonstrated a relationship between IS and global EF deficits, the role of more fine-grained EF components was not well-characterized. Our findings suggest that although all three EF domains are related to IS, impairments in set-shifting play the most significant role.

Several study limitations are important to note. Although germline *PTEN* mutations have a relatively low prevalence, and all analyses were supplemented with effect sizes and robust bootstrapped confidence intervals, given the small sample size, our current data should nevertheless be treated as preliminary. This study was also limited by the cross-sectional design. Further, given the reliance on parent-report measures, observed associations between key variables of interest could have been inflated through common-method variance. Therefore, it will be necessary for future research to incorporate multimodal assessments into longitudinal designs in order to further characterize the complex interplay between executive functioning, anxiety and IS at different points of development and with this population.

Despite their clinical significance, interventions specifically focused on IS are currently lacking (Grahame et al., 2015). Our study further extends previous findings (e.g., Evans et al., 1999; Lidstone et al., 2014; Uljarević et al., 2017; Uljarević et al., 2019b) pointing out to impairments in EF and elevated levels of anxiety as key mechanisms behind IS, regardless of the primary diagnosis and/or diagnostic status. Crucially, in the intervention context, these findings point to both EF and anxiety as viable intervention targets in individuals with germline *PTEN* mutations, ASD and other NDD. Interventions based on modified cognitive behavior therapy (CBT) have been shown as effective in anxiety reduction in ASD (Weston et al., 2016) and as feasible and well-tolerated in individuals with intellectual disabilities (Unwin et al., 2016). More recent parent-led treatment programmes such as Coping with Uncertainty in Everyday Situations (CUES©; Rodgers et al., 2018) aimed at improving children's response and coping with uncertainty, have also been shown to be feasible and acceptable in ASD (Rodgers et al., 2018). There is evidence that a range of computerized and group-based interventions can be somewhat effective in improving EF across both community and clinical samples (Diamond & Lee, 2011). For instance, several randomized controlled trials have demonstrated improvements in EF in children with attention-deficit/hyperactivity disorder (Klingberg et al., 2005) and ASD (Kenworthy et al., 2014). Therefore, it will be important in future work to explore the effects of these types of interventions on IS in individuals with *PTEN* mutations.

In summary, this investigation provided the first preliminary evidence for the role of impaired EF and anxiety as potential mechanisms underlying IS in individuals with *PTEN* mutations and youth with ASD and macrocephaly. Despite the noted limitations, our pilot findings offer promising insights into designing interventions targeting IS and may suggest biomarkers during clinical trials for alleviating IS.

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Table 1.

Demographic Characteristics and Descriptives

	PTEN-ASD[a] N= 38	Macro-ASD[b] N= 25	*PTEN*-no ASD[c] N= 23	Statistics	Posthoc
CA (Mean (SD))	8.93 (4.75)	11.99 (5.15)	8.94 (4.85)	F= 3.45, p= .036 ω^2= .05	b>c
Sex (Number (%))				χ^2= 2.55, p = .28	NA
Male	30 (78.9)	21 (84)	15 (65.2)		
Female	8 (21.1)	4 (16)	8 (34.8)		
Race (Number (%))				NA	NA
White/Caucasian	30 (78.9)	14 (56)	12 (52.2)		
Black/African American	1 (2.6)	-	-		
Asian	-	5 (20)	3 (13)		
Multiracial	5 (13.2)	5 (2)	6 (26.1)		
Pacific Islander	-	1 (4)	-		
Unknown/Not Reported	2 (5.3)	-	2 (8.7)		
Ethnicity (Number [%])				NA	NA
Hispanic	6 (15.8)	2 (8)	1 (4.3)		
Not Hispanic	31 (81.6)	23 (92)	21 (91.4)		
Unknown/Not Reported	1 (2.6)		1 (4.3)		
FSIQ (Mean (SD)	66.32 (22.95)	74.30 (24.50)	99.14 (17.40)	F= 14.43, p< .001, ω^2= .27	c>a, b
Inhibitory Control [1]	62.55 (13.71)	66.04 (14.96)	51.37 (11.76)	F= 6.47, p= .003, ω^2= .13	c< a, b
Set-Shifting [1]	61.45 (12.82)	68.26 (12.11)	54.58 (15.45)	F= 5.49, p= .006, ω^2= .11	c< b
Working Memory [1]	70.57 (12.92)	69.35 (14.33)	60.74 (18.14)	F= 2.65, p= .078, ω^2= .04	NA
CBCL Anxiety [2]	60.16 (8.70)	60.35 (9.81)	56.35 (7.97)	F= 1.64, p= .20, ω^2= .08	NA

Note:

[a]: possible T-score range: ≤ 30–100

[b]: possible T-score range: ≤ 50–100

BRIEF: Behavior Rating Inventory of Executive Function; CA: Chronological Age; CBCL: Child Behavior Checklist; FSIQ: Full scale intelligence quotient.

Table 2.

Correlations Between Variables of Interest

	CA	FSIQ	Sex	CBCL Anxiety	Inhibitory Control	Set-shifting	Working Memory	RBS-R Sameness
CA	1	−.21	−.02	.17	.18	.17	.15	.08
FSIQ	−.21	1	.13	−.22	−.34**	−.38**	−.29*	−.36**
Sex	−.02	.13	1	−.02	−.15	−.15	−.13	−.14
CBCL Anxiety	.17	−.22	−.02	1	.40**	.53**	.42**	.42**
Inhibitory Control	.18	−.34**	−.15	.40**	1	.58**	.56**	.36**
Set-shifting	.17	−.38**	−.15	.53**	.58**	1	.49**	.65**
Working Memory	.15	−.29*	−.13	.42**	.56**	.49**	1	.27*
RBS-R Sameness	.08	−.36**	−.14	.42**	.36**	.65**	.27*	1

Note:

* $p < .05$

** $p < .01$

CA: Chronological Age; CBCL: Child Behavior Checklist; FSIQ: Full scale intelligence quotient.

Table 3.

Hierarchical regression with RBS-R Sameness Score as dependent variable

	R2Δ	R2Δ Change	B	SEB	β	t	BCa 95% CI
Step 1	.072*						
Diagnostic Group			−1.78	.75	−.27	−2.01	−3.12; −.28
Step 2	.161*	.089*					
Diagnostic Group			−.95	.91	−.16	−1.03	−2.49; .76
FSIQ			−.07	.03	−.32	−2.32	−.13; −.005
Step 3	.238*	.077*					
Diagnostic Group			−.72	.89	−.11	−.80	−2.33; .90
FSIQ			−.06	.03	−.27	−2.01	−.12; .00
CBCL Anxiety			.17	.07	.29	2.25	.04; .31
Step 4	.457**	.219**					
Diagnostic Group			.99	.72	.15	1.12	−.33; 2.09
FSIQ			−.03	.03	−.17	−1.37	−.10; .02
CBCL Anxiety			−.004	.09	−.007	−.05	−.14; .14
Inhibitory Control			.03	.06	.09	.61	−.11; .17
Set-shifting			.25	.05	.70	4.12	.15; .35
Working Memory			−.05	.04	−.17	−1.17	−.15; .03

Note:

* p< .05

** p< .01

CA: Chronological Age; CBCL: Child Behavior Checklist; FSIQ: Full scale intelligence quotient.