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Executive function in XXY: Comparison of performance-based measures and rating scales

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Abstract

Few studies have systematically assessed executive functioning (EF) skills in boys with XXY, and these are limited by small samples and restricted EF assessment. This study used a broader battery of performance-based measures as well as parent-rating scales of EF in 77 boys and adolescents with XXY (mean age = 12.5 years), recruited from a clinical trial and an outpatient clinic. Exploratory factor analyses were used to create EF domains from performance-based measures, and similar domains were measured using the Behavior Rating Inventory of Executive Function and Conners Parent-Rating Scales. The boys with XXY showed a distinct EF profile, with the greatest deficit in attention and more moderate deficits in working memory, switching, and planning/problem solving. Parent ratings showed similar challenges, as well as impaired inhibition. Independent sample *t*-tests showed no difference on performance measures between boys diagnosed or not diagnosed with attention-deficit/hyperactivity disorder (ADHD), although parents of boys diagnosed with ADHD reported more difficulties. There were no differences on performance-based tests between those diagnosed pre- and postnatally, although parents of postnatally diagnosed boys reported more metacognitive problems. Language deficits, cognition, and socio-economic status did not account for EF deficits.

KEYWORDS

executive function, Klinefelter syndrome, XXY

1 | INTRODUCTION

Males born with XXY have an additional X chromosome, and the effect of this additional genetic material on neurodevelopment and psychological functioning is an important area of study. The broad variability within the large population of males with XXY is described in almost all studies of neuropsychological functioning; however, results have shown a consistent profile of strengths and weaknesses that define the cognitive phenotype in XXY (Boada, Janusz, Hutaff-Lee, & Tartaglia, 2009, for review). Overall intellectual ability falls in the average range, but generally lower than sibling/control groups (Geschwind, Boone, Miller, & Swerdloff, 2000; Graham, Bashir, Stark, Silbert, & Walzer, 1988; Netley & Rovet, 1984; Pennington, Bender, Puck, Salbenblatt, & Robinson, 1982; Ratcliffe, Masera, Pan, & McKie, 1994; Rovet, Netley, Keenan, Bailey, & Stewart, 1996). Deficits are typically seen in verbal as opposed to nonverbal abilities, with documented difficulties in both expressive and receptive language skills (Bender et al., 1983; Bender, Linden, & Robinson, 1993; Boone et al., 2001; Geschwind et al., 2000; Graham et al., 1988; Robinson, Lubs, Nielsen, & Sorensen, 1979; Rovet et al., 1996). Language-based learning disabilities (e.g., dyslexia) are common, with some studies reporting that 50–75% of individuals with XXY will be identified with a reading disorder at some point in their development (Bender, Puck, Salbenblatt, & Robinson, 1986; Graham et al., 1988). Attention

problems are also commonly seen, with studies reporting 36 to 63% of their sample meeting criteria for attention-deficit/hyperactivity disorder (ADHD; Bruining, Swaab, Kas, & van Engelend, 2009; Tartaglia, Ayari, Hutaff-Lee, & Boada, 2012).

While deficits in executive functioning (EF) skills are often reported anecdotally in XXY, few empirical studies have been completed. EF is a cognitive domain that encompasses a set of interrelated, higher order processes that are responsible for purposeful, goal-directed behavior (Anderson, 2002). In typical populations, executive functions are good predictors of academic outcomes (Blair & Razza, 2007), and are not only important for complex cognitive tasks, such as sequencing steps in a task or generating new strategies to solve problems (Elliot, 2002), but are also involved in behavioral, emotional, and social functioning (Anderson, 2002). Components of the executive system are typically conceptualized to include working memory, initiation, judgment, planning, organization, and decision-making. The regulation of behavioral and emotional functioning, including response inhibition and self-monitoring, is also considered part of the EF construct (Gioia, Isquith, Retzlaff, & Espy, 2002). The domain of attention is closely linked with executive functions, with some models of EF including attentional control (Anderson, 2002), and EF deficits in children with ADHD have been well-described (Mahone & Denckla, 2017; Roth & Saykin, 2004).

In adults with XXY, studies have fairly consistently demonstrated deficits in EF, with only two studies not finding impairments (Bender, Linden, & Harman, 2001; Wallentin et al., 2016). Deficits in cognitive flexibility, planning, inhibition, and working memory are seen across studies (Boone et al., 2001; DeLisi et al., 2005; Fales, Knowlton, Holyoak, & Geschwind, 2003; Kompus et al., 2011; Skakkebaek et al., 2014; van Rijn, Aleman, DeSonneville, & Swaab, 2009). Given known impairments in language skills in individuals with XXY, Fales et al. (2003) compared performance on verbal and nonverbal EF measures, with greater impairment seen on a verbal working memory task than a nonverbal reasoning task. Boone et al. (2001) also found a relationship between language-mediated EF tasks and broader verbal skills.

In contrast, findings of studies investigating EF in children with XXY are less consistent. Bender et al. (1993) conducted one of the first studies of EF in adolescents with XXY. EF was assessed with the Wisconsin Card Sorting Test, an untimed measure of abstract reasoning, and the Trail Making Test, a timed measure of cognitive flexibility, working memory, and attention. No deficits were noted on the Wisconsin Card Sorting test. While low scores were documented on the Trail Making Test, the authors suggested that this may reflect poor processing speed rather than an EF deficit. Temple and Sanfilippo (2003) administered a relatively extensive EF battery to three boys with XXY. They did not identify deficits on the Trail Making Test or the Wisconsin Card Sorting Test, and performance on other EF measures, including the Tower of London, Verbal Fluency, and Rey Figure, was also average. While a deficit in inhibition on the Stroop Test was noted across their three subjects, Ross et al. (2008); Ross, Zeger, Kushner, Zinn, and Roeltgen (2009) did not identify deficits in inhibition on a Stroop-type task in their larger samples of children and adolescents with XXY.

However, other studies have found more significant EF impairments in boys with XXY. Problems with organization on the Rey-Osterrieth Complex Figure were identified by Ross et al. (2009). van Rijn and Swaab (2015) used a computerized measure to assess EF and found deficits in inhibition, cognitive flexibility, sustained attention, and visual working memory. Lee et al. (2011) used scores from different measures of flexibility, working memory, and planning to create an EF composite. Their sample consisted of children, adolescents, and young adults with XXY, and scores on this composite factor were significantly lower than a typically developing control group and a control group matched by verbal abilities.

Despite the known association between ADHD and executive dysfunction in the general population (Barkley, 1997), only one study (Lee et al., 2011) investigated the relationship between ADHD and EF in boys with XXY. In this study, individuals with both XXY and ADHD had more impaired EF performance than individuals with XXY without ADHD and typically developing peers.

In the studies reviewed, the methods used to measure EF were relatively narrow in scope, with most studies only including a limited number of performance-based tests. There is a significant body of literature (Anderson, 2002; Isquith, Roth, & Gioia, 2013) suggesting that performance-based measures of EF alone may not adequately identify EF deficits. Many studies in the general population have found little correlation between performance on EF tests and "real life" EF behavior (Sbordone & Guilmette, 1999), bringing into question the ecological validity of such tests. To address this concern, behavioral rating scales have been developed that allow a parent, teacher, or other adult informant to rate an individual's EF skills in everyday home or school settings. Only two studies used parent-rating scales to assess EF boys with XXY (Lee et al., 2015; van Rijn & Swaab, 2015), and both identified deficits across multiple domains, including inhibition, shifting, working memory, planning, and monitoring.

This study sought to build upon the existing literature in several ways. First, this study expands the previous literature by describing the EF skills of a large sample of boys with XXY by using multiple performance-based measures and parent-rating scales to assess EF. Rather than using single test scores, EF domains were derived via factor analysis. This is a more robust way of deriving data, as it reduces multiple scores into one, single factor, limiting the error associated with multiple analyses. Furthermore, using a statistical method to determine factors provides an objective way of determining which tests are measuring the same aspects of EF, allowing for more homogenous constructs. This study also sought to expand upon previous findings of differences between boys with XXY and ADHD by assessing performance on both test performance and rating scales. The difference between boys diagnosed prenatally and postnatally was also explored, as previous studies have found better outcome for prenatally diagnosed children (Robinson, Bender, & Linden, 1992; Ross et al., 2012; Tartaglia et al., 2012). Finally, given the typical neuropsychological profile associated with XXY, the study also sought to understand whether language deficits or broad cognitive deficits account for or contribute to EF deficits.

2 | METHODS

2.1 | Participants

Participants were children and adolescents, between the ages of 8 and 18, with a molecularly confirmed diagnosis of XXY. Participants were recruited from two sources: a placebo-controlled clinical trial studying the effects of exogenous testosterone on a variety of outcomes in XXY (n = 42) (NCT01585831; COMIRB 11-0874) and an outpatient clinic that treats children and adolescents with a diagnosis of sex chromosome aneuploidy (n = 35) (COMIRB 08-0513; Tartaglia et al., 2015). The Colorado Multiple Institutional Review Board approved these studies. For those participants seen for clinical care, the research consent includes the permission for use of clinical data to be used for research purposes. The parents of all participants signed informed consent and participants provided assent. Chart review was conducted to determine timing of diagnosis (prenatal or postnatal) and ADHD status. ADHD diagnostic category was assigned based on either: (a) a previous clinical ADHD diagnosis upon presentation to our site confirmed by clinical history and records review, or (b) results of direct neuropsychological assessment by our clinicians comprised of clinical history of symptoms and the neuropsychological measures and rating scales described below. Seven participants with a Full-Scale IQ below 70 were excluded from the study, leaving 77 participants for analysis.

2.2 | Measures

All participants completed a larger neuropsychological assessment battery as part of their research or clinical evaluation, of which the following EF measures were a part. Assessments were conducted by a neuropsychologist or trained research assistant and completed in one testing session lasting 3 to 4 hours with short breaks throughout. Parents completed rating scales during this assessment time. For 75% of the sample, the child's mother completed the rating scales. For participants recruited from the clinical trial, data from the baseline (pretreatment) neuropsychological evaluation was used.

2.2.1 | Child measures

The Wechsler Scales of Intelligence was used to measure intellectual functioning. Participants completed the Wechsler Intelligence Scale for Children-Fourth Edition (n = 60; WISC-IV; Wechsler, 2003), the Wechsler Intelligence Scale for Children-Fifth Edition (n = 12; WISC-V; Wechsler, 2014), the Wechsler Adult Intelligence Scale-Third Edition (n = 2; WAIS-III; Wechsler, 1997) or the Wechsler Adult Intelligence Scale-Fourth Edition (n = 1; WAIS-IV; Wechsler, 2008) depending on their age at evaluation and study or clinical protocol. The General Ability Index (GAI) was chosen as the primary measure of overall intellectual functioning, as the subtests that compose the GAI are consistent across different Wechsler measures.

The Delis Kaplan Executive Function System (DKEFS; Delis, Kaplan, & Kramer, 2001) is a set of tests measuring key components of executive function in individuals 8 years and older. Four subtests that measure cognitive flexibility, concept formation, response inhibition, and reasoning were chosen for inclusion in the study: Verbal Fluency, Color-Word Interference, Sorting, and 20 Questions. For Verbal Fluency, the participant must generate words to semantic and phonemic prompts, as well as switch between providing words for two different categories. The Color-Word Interference subtest is a version of the Stroop task. The participant is asked to name colors, read color words, and then name the color of the ink that a word is written in (for example, the word "red" would be written in blue ink). For the Sorting subtest, the participant must sort cards into two group based on verbal or visual concepts such as size or color. For the 20 Questions subtest, the participant must ask yes/no questions to determine which picture the examiner has chosen from an array.

The Spatial Span subtest, Wechsler Nonverbal Scale of Ability (Wechsler & Naglieri, 2006) is a short-term visual working memory test wherein the subject must tap the same sequence of blocks presented to them by the examiner.

The Tower of London: Drexel Second Edition (TOL-DX; Culbertson & Zillmer, 2005) is a test of executive functions emphasizing problem solving, planning, impulse control, rule governed behavior, and self-monitoring. For this measure, the subject must copy a bead design made by the examiner following a specific set of rules.

The Test of Variables of Attention (TOVA; Greenberg, 1991) is a computer administered continuous performance test that measures attention and inhibitory control. The participant must press a button for a target stimulus and inhibit pressing a button for distractor stimuli.

2.2.2 | Parent measures

The Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) is a parent-completed questionnaire assessing executive function behaviors in the home environment. The subscales of the BRIEF assess two major domains of EF-behavior regulation and metacognitive skills. Subscales comprising the Behavior Regulation factor include Inhibit, Shift, and Emotional Control. Subscales comprising the Metacognitive factor include Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor.

The Conners' Parent-Rating Scales (Conners, 1997) is a parent-completed questionnaire assessing symptoms of inattention, distractibility, impulsivity, and hyperactivity.

2.3 | Data analyses

All analyses were performed using SPSS-26. Descriptive statistics were used to characterize the sample in terms of demographics, overall IQ, pre- versus postnatal diagnosis of XXY, and parental years of education. Principal axis exploratory factor analyses (EFAs) were performed in order to derive executive function composites from the

various tests that were administered. Variables with scaled or standard scores were transformed to *z*-scores, and then means were computed based on the EFA results to create EF subdomain composites. The *z*-score transformation was performed using the population mean and *SD* for each test/subtest in order to maintain each participant's standing relative to the normative group (Culbertson & Zillmer, 2005; Delis et al., 2001; Greenberg, 1991; Wechsler, 1997; Wechsler, 2003; Wechsler, 2008; Wechsler, 2014; Wechsler & Naglieri, 2006). The parent-rating scale scaled/standard scores (i.e., for attention, inhibition, behavior regulation, and metacognitive skills) were similarly transformed to *z*-scores, for ease of comparison (Conners, 1997; Gioia et al., 2000). Correlations were computed to show the association between performance-based EF tests and parent ratings. Effect sizes for performance-based domains and parent-rating scales were computed using Cohen's *d*. Independent samples *t*-tests were used to compare EF means on performance-based tests and parent-rating measures between those prenatally diagnosed versus postnatally diagnosed and those with and without a clinical diagnosis of ADHD. Lastly, each EF domain was regressed on to verbal IQ, nonverbal IQ, and parental years of education, in order to understand the extent to which the latter variables explained unique variance in each EF domain. An alpha of 0.05 was used for all analyses.

3 | RESULTS

Demographic characteristics of the sample are summarized in Table 1. Comparison of the research and clinically ascertained subgroups showed that they did not differ significantly in terms of age, GAI, rates of pre- versus postnatal diagnosis, parental education, race, or ethnicity, so the characteristics of the sample as a whole are provided. Mean age for the entire sample was 12.49 years. Twenty-six percentage of the sample was non-Caucasian, and 15.6% of the sample identified as being of Hispanic or Latino descent. The educational level of parents was relatively high, with 62% of participants' mothers and 58% of participants' fathers having obtained a bachelor's degree or higher. The latter, in addition to the exclusion of children with IQ's less than 70, likely raised the mean GAI of our sample slightly (i.e., 95.6), relative to previously studied cohorts. With regard to timing of diagnosis, 49.3% of participants were diagnosed prenatally.

Sixty-five percent (50/70) of participants had an ADHD diagnosis. Of those with ADHD, in 46% (23/50) the diagnosis was a new diagnosis based on current assessment, while in the remaining 54% (27/50) ADHD had been diagnosed by previous outside clinical assessments and confirmed at the current evaluation. Of those with ADHD, 60% (30/50) met criteria for ADHD-Predominantly Inattentive subtype and 40% (20/50) for ADHD-Combined subtype. Review of ADHD medication treatments showed that 56% (28/50) were on ADHD medications at the time of evaluation (stimulants alone n = 21, nonstimulants alone n = 4; combination of stimulant and nonstimulant n = 3). For those with a new diagnosis of ADHD not on medications, recommendations for treatment including a combination of behavioral and educational supports as well as medication options were provided by the team (psychology, neuropsychology, and developmental pediatrics). Given that individual participants were not assessed both on and off medication treatment, comparisons between treated and untreated groups were not felt to be informative.

TABLE 1 Demographic characteristics

	Mean (*SD*) or *N* (%)
Sample size	77
Age (years)	12.49 (2.0)
General Ability Index	95.6 (13.4)
Prenatal diagnosis	37 (49.3%)
Maternal education	
Partial high school	1 (1.3%)
High school or equivalent (GED)	4 (5.2%)
Some college/vocational training	20 (26.0%)
Bachelor's degree	24 (31.2%)
Graduate training (MA/MS/MD/PHD)	23 (29.8%)
Unknown	5 (6.5%)
Paternal education	
Partial high school	0 (0%)
High school or equivalent (GED)	10 (13.0%)
Some college/vocational training	16 (20.7%)
Bachelor's degree	21 (27.3%)
Graduate training (MA/MS/MD/PHD)	24 (31.2%)
Unknown	6 (7.8%)
Race	
Caucasian	57 (74.0%)
Black/African American	3 (3.9%)
Asian	1 (1.3%)
Native Hawaiian/Pacific islander	0 (0.0%)
American Indian/Alaska native	0 (0.0%)
Other race	1 (1.3%)
More than one race	5 (6.5%)
Unknown/not reported	10 (13.0)
Ethnicity	15.6% Hispanic or Latino

3.1 | Exploratory factor analyses

Each of the executive function tests administered yields various scores. In order to reduce the number of variables included in statistical analyses, and create more robust, reliable, and homogeneous indices of EF subdomains, selected variables from the EF tests were subjected to principal axis EFA with oblimin rotation. Preliminary selection of summary variables from each EF test was based on a conceptual understanding of the constructs that each test was designed to measure, as provided in the test manuals. Based on prior literature describing EF subdomains (Miyake & Friedman, 2012), we targeted the following five constructs to measure with our test battery: attention, inhibition, working memory, shifting, and planning/problem

solving. We also acknowledge that attention is not always considered a higher order executive process, but since it is often a foundational element in the ability to perform higher order functions, and since children with XXY often have significant attentional deficits, it was included as a factor in this article. A total of 15 variables purportedly measuring these five constructs were selected. EFAs were then used to verify that our selected variables loaded onto factors that could be described as measuring these five constructs.

Even though our *N* of 77 is relatively large for this patient population, it was not sufficiently large from a statistical point of view to include all the relevant variables into one EFA. It is typical to have at least 10 participants per variable in an EFA, and our preliminary variable list included a total of 15 variables. An EFA that included all the variables was attempted, but did not reach a stable solution, most likely due to reduced sample size. Therefore, separate EFAs were conducted, testing different sets of variables based on initial hypothesized subdomain groupings. Two variables that cross loaded at greater than 0.30 were excluded. Table 2 shows results from two EFAs, one with six variables selected from subtests measuring attention, working memory, and switching, and one with seven variables selected from subtests measuring inhibition and planning/problem solving. The number of factors extracted in each EFA was determined by the number of hypothesized domains that the variables were predicted to measure (i.e., three for the first EFA and two for the second EFA). The total variance explained in the first EFA was 78%, while the total variance explained in the second EFA was 58%. All eigenvalues were above 1.0. In order to protect against the possibility that the factor solutions were somehow arbitrarily based on the specific variable sets included in each, additional EFAs were conducted that mixed and matched variable sets, with results being very similar to those shown in Table 2. Finally, an oblimin rotation was chosen for these EFAs because, as subdomains of a larger construct, they are not predicted to be totally independent from one another. This is consistent with results from prior studies of EF (Miyake & Friedman, 2012).

The Attention domain was composed of two variables from the TOVA, indexing omission errors and *d′* prime (i.e., ability to discriminate targets from nontargets). The Working Memory Index from the Wechsler Scale and the spatial span task from the WNV combined to create the Working Memory domain. The scores from the switching conditions of the Design Fluency and Verbal Fluency subtests from the DKEFS loaded on the Switching domain. The Inhibition domain was indexed by a combination of four variables: Set Loss scores from Design Fluency and Verbal Fluency subtests of the DKEFS and two variables from Condition 3: Inhibition portion of the Color-Word Interference (i.e., Stroop) subtest, also from the DKEFS. All four of these variables capture a participant's inability to inhibit a prepotent response, their lack of efficiency in doing so, or their inability to inhibit responses that violated one of the rules of the task. Finally, the Planning/Problem Solving domain was composed of variables from the Tower of London-DX, and 20 Questions and Sorting subtests from the DKEFS. These three variables indexed a participant's ability to plan moves to achieve a goal efficiently, be strategic in their approach to playing a version of a 20-Questions game, and their ability to generate novel ways of sorting cards that could be grouped based on a variety of characteristics. The results of the EFAs were used to guide creation of composites for each of the EF subdomains. The variables loading on each domain were unit-weight averaged for each participant to create a composite score. These composites were used in all subsequent analyses.

TABLE 2 Executive functioning (EF) variables and factor loadings from exploratory factor analyses

	Attention	Working memory	Switching	Inhibition	Plan/problem solving
Exploratory factor analysis #1					
Omissions Half 1 (TOVA)	0.83				
D-prime Half 1 (TOVA)	0.90				
WMI (WISC/WAIS)		0.95			
Spatial Span Total (WNV)		0.34			
DF Condition 3 score (DKEFS)			0.85		
VF Condition 3 Switching score (DKEFS)			0.44		
Exploratory factor analysis #2					
CWI Condition 3 (DKEFS)				0.35	
CWI Total Errors (DKEFS)				0.49	
DF Set Loss Errors (DKEFS)				0.77	
VF Set Loss Errors (DKEFS)				0.30	
20 Quest. Weighted Achievement (DKEFS)					0.42
Sorting Free Description (DKEFS)					0.76
Tower of London Total Moves (TOL-DX)					0.49

Note: Factor loadings less than 0.30 are omitted for clarity.

Abbreviations: CWI, Color-Word Interference subtest; DF, Design Fluency subtest; DKEFS, Delis Kaplan Executive Function System; TOL-DS, Tower of London-Drexel, 2nd edition; TOVA, Test of Variables of Attention; WISC/WAIS, Wechsler Series Intelligence Test; WM, Working Memory; WNV, Wechsler Nonverbal Ability Test.

Regarding the parent-rating scales, the Inattention and Hyperactivity/Impulsivity subscales from the Conners Parent-Rating Scale were used in order to have analogous scales to the Attention and Inhibition domains based on cognitive measures. From the BRIEF, the Behavior Regulation (BRI) and Metacognitive (MCI) Indices were used as measures of executive control processes. The BRI includes subscales measuring inhibition, shifting, and emotional regulation while the MCI includes subscales measuring initiation, working memory, planning/organization, and task monitoring.

Correlations between performance-based domains and parent-rating scales are presented in Table 3. Among the performance-based domains, Attention is not correlated with any of the other EF domains. Inhibition correlates significantly with Working Memory and Switching, but not Planning/Problem Solving. Lastly, Working Memory, Switching, and Planning/Problem Solving are all significantly intercorrelated. Among the parent-rating scales, all the domains are significantly intercorrelated. There are some significant correlations between performance-based EF domains and parent-rating scales (see highlighted box, Table 3). The Conners Hyperactivity/Impulsivity scale is significantly correlated with Working Memory, Switching, and Planning/Problem Solving. The BRIEF BRI is significantly correlated with all the performance-based domains, but the BRIEF MCI is only significantly correlated with Switching. Lastly, the Conners Inattention scale is not correlated with any of the performance-based domains. While significant statistically, the correlations between performance-based domains and parent-rating scales are modest, generally in the .25–.33 range.

3.2 | EF deficits in boys with XXY

Administration of a broad set of executive function tests followed by derivation of domains representing five EF subdomains allowed us to see if children with XXY have a specific EF profile. EF subdomain composite scores, each denoting the average of *z*-scores from tests loading onto each domain, are provided in Table 4. Since different EF tests used in this study had their own normative samples, it is not possible to be completely certain that the population mean for the composite score is 0 (as it is for each subtest that went into a composite). Therefore, one-sample *t*-tests were not conducted. Effect sizes (Cohen's *d*) are reported, however, as an approximation of the magnitude of the deficit, assuming the various normative samples are comparable and approximate a population sample. Results indicate a large effect size for the Attention domain, and moderate effect sizes for Working Memory, Switching, and Planning/Problem Solving. The effect size for the Inhibition domain was negligible. The effect sizes were large for Conners Inattention, BRIEF BRI, and BRIEF MCI, while the Conners Hyperactivity/Impulsivity scale has a medium effect size.

Statistical significance is not the same as clinical significance. While some mean *z*-scores were below −1.0, some were only a third to a half *SD* below the mean (i.e., Working Memory, Switching, and Planning/Problem Solving). Therefore, it is useful to also know how many children in the sample exhibited a clinically significant deficit in each EF domain. Using a −1.0 *SD* as a cutoff, 49% of the sample showed a deficit on the Inattention domain, while 34% showed a deficit on the Working Memory and Switching domains. Twenty-two percent of the sample showed a deficit on the Planning/Problem Solving domain. These are all above 16%, which is the expected percentile for a *z*-score of −1.0. Furthermore, 82% of the sample had a deficit in at least one performance-based EF domain. On the parent-rating scales, 63% of the sample scored below −1.0 *SD* on Conners Inattention, 39% had a deficit on Conners Hyperactivity/Impulsivity, 64% had a deficit on the BRIEF BRI, and 78% had a deficit on the BRIEF MCI. Finally, 75% of the sample had a deficit on at least one EF parent-rating scale using the −1.0 *SD* cutoff. Imposing a stricter clinical cutoff that typically identifies the bottom 7% of a normal distribution (i.e., −1.5 *SD*), 54% still met criteria for a deficit in at least one performance-based EF subdomain, while 65% met criteria for a deficit on at least one parent-rating scale domain.

TABLE 3 Correlations among performance-based EF factors and parent-rating EF scales

	Attention factor	Inhibition factor	Working memory factor	Switch factor	Plan/probability solving factor	Conners inattention	Conners Hyp/imp.	BRIEF BRI
Attention factor	1.00							
Inhibition factor	0.13	1.00						
Working Memory factor	0.01	0.36**	1.00					
Switching factor	0.05	0.42***	0.43***	1.00				
Planning/Problem Solving factor	0.01	0.08	0.32**	0.32**	1.00			
Conners Inattention	**0.18**	**0.14**	**0.17**	**0.22**	**0.11**	1.00		
Conners Hyp./imp.	**0.11**	**0.18**	**0.28***	**0.29***	**0.26***	0.49***	1.00	
BRIEF BRI	**0.29***	**0.25***	**0.25***	**0.25***	**0.25***	0.59***	0.70***	1.00
BRIEF MCI	**0.07**	**0.23**	**0.20**	**0.33****	**0.02**	0.82***	0.38**	0.53***

Note: Significant correlations between performance-based EF domains and parent rating scales are marked in bold.
Abbreviations: BRI, Behavior Regulation Index; BRIEF, Behavior Rating Inventory of Executive Function; MCI, Metacognitive Index
*$p < .05$.
**$p < .01$.
***$p < .001$.

TABLE 4 Sample means, *SD*s, and effect sizes of executive function subdomains

Type of measure	EF factor or rating scale	*N*	Mean*	*SD*	Cohen's *d*
Performance-based	Attention	74	−1.33	1.32	−1.01
	Inhibition	70	−0.07	0.55	−0.13
	Working Memory	75	−0.57	0.89	−0.64
	Switching	70	−0.41	0.81	−0.51
	Planning/Problem Solving	73	−0.34	0.81	−0.42
Parent rating	Conners Inattention	67	−1.19	0.97	−1.23
	Conners Hyperactivity/Impulsivity	67	−0.70	1.01	−0.69
	BRIEF Behavioral Regulation Index	69	−1.32	1.25	−1.06
	BRIEF Metacognitive Index	69	−1.61	0.99	−1.63

Note: Means are the averages of the *z*-scores of the tests within each subdomain. Original *z*-scores for each test reflect standing relative to population mean of 0.

TABLE 5 Means, *SD*s, *p*-values, and effect sizes of executive function factors by time of diagnosis

	Prenatal diagnosis *N* = 37		Postnatal diagnosis *N* = 38		
	Mean	*SD*	Mean	*SD*	*p*-value
Attention	−1.17	1.27	−1.36	1.32	.53
Inhibition	0.00	0.62	−0.14	0.48	.28
Working Memory	−0.46	0.82	−0.64	0.96	.39
Switching	−0.33	0.84	−0.46	0.79	.52
Planning/Problem Solving	−0.35	0.83	−0.30	0.82	.79
Conners Inattention	−0.98	1.04	−1.43	0.82	.06
Conners Hyperactivity/Impulsivity	−0.76	0.99	−0.63	1.05	.59
BRIEF Behavioral Regulation Index	−1.23	1.20	−1.41	1.31	.54
BRIEF Metacognitive Index	−1.36	1.00	−1.87	0.92	.03

Note: Means are the *z*-score averages for the tests within each subdomain. Original *z*-scores for each test reflect standing relative to population mean of 0.

3.3 | EF differences between prenatally and postnatally diagnosed children

In the current sample, 37 children were prenatally diagnosed, 38 were postnatally diagnosed, and 2 did not have data on this variable. Independent sample *t*-tests showed a significant difference between pre- and postnatally diagnosed children on the BRIEF MCI scale, and a trend on the Conners Inattention Scale. No other domains or scales were significantly different (Table 5). On these two rating scales, the postnatally diagnosed children had more significant deficits compared to the prenatally diagnosed children. There was not a statistically significant difference between the proportion of clinical ADHD diagnoses in the prenatal versus postnatal subgroups (χ^2 (1.75) = 0.11, p = .74).

3.4 | Differences in EF deficits in boys with and without ADHD

In the current sample, 50 children either had a clinical diagnosis of ADHD prior to being tested or were given a diagnosis of ADHD following their evaluation. Twenty-five children did not have a diagnosis of ADHD, nor did they meet clinical criteria for a diagnosis at time of testing. Figure 1 provides results of independent sample *t*-tests showing significant differences on EF domains and scales between these two subgroups. Only the Conners Inattention and BRIEF MCI scales showed a statistically significant difference, with the ADHD subgroup consistently having worse scores. A trend in the same direction was seen for the BRIEF BRI scale. None of the performance-based domains showed a significant difference, and neither did Conners Hyperactivity/Impulsivity. The direction of effect for the nonsignificant domains and scales, however, was generally consistent, with the ADHD diagnosed children having slightly worse scores (with the only exception being Switching).

3.5 | Contribution of verbal IQ, nonverbal IQ, and parent education to EF subdomains

Children with XXY have known deficits in speech and language skills, and a high percentage of them also have specific learning disabilities, especially dyslexia (specific reading disability). As reported earlier, children with XXY also have slightly lower cognitive skills than the general population. In order to understand the effect of language and more general cognitive differences on EF, correlations were computed between VIQ and NVIQ and all of the EF domains and scales. Additionally, mean parental years of education, as a marker for SES, was

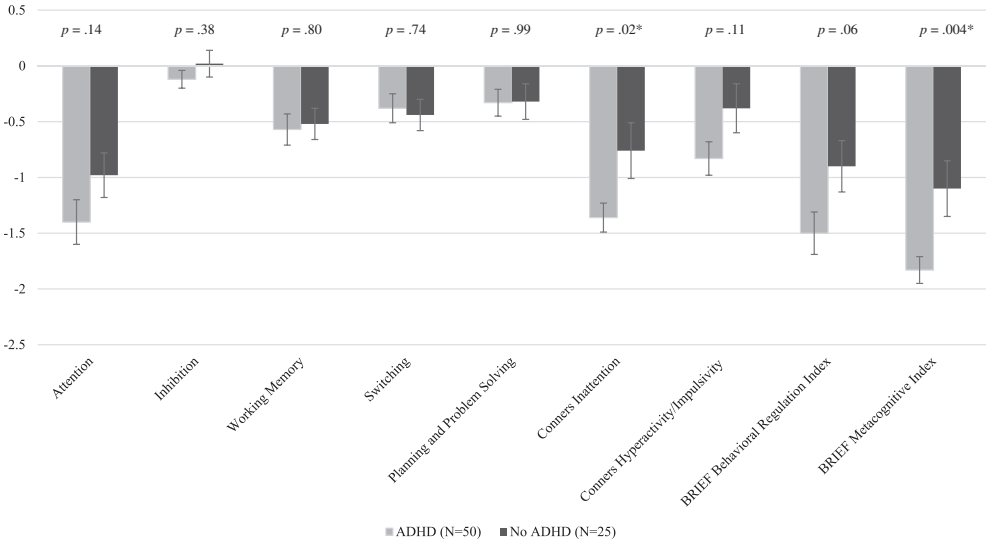

FIGURE 1 Executive function composite *z*-scores by ADHD diagnosis

TABLE 6 Correlations among executive functioning factors and scales and covariates

Executive functioning factors	Verbal IQ	Nonverbal IQ estimate	Parental years of education
Attention	0.08	0.14	0.06
Inhibition	0.20	0.23	0.15
Working Memory	0.48***	0.50***	0.34**
Switching	0.29*	0.51***	0.26*
Planning/Problem Solving	0.43***	0.57***	0.26*
Conners Inattention	0.30*	0.07	0.14
Conners Hyperactivity/Impulsivity	0.29*	0.19	0.14
BRIEF Behavioral Regulation Index	0.39***	0.27*	0.19
BRIEF Metacognitive Index	0.24	0.14	0.12

Note: Parental years of education = mean of mother and father years of education.
*$p < .05$.
**$p < .01$.
***$p < .001$.

also included. Nonverbal IQ is computed slightly differently depending on the version of the WISC/WAIS administered. However, the Block Design and Matrix Reasoning subtests are consistent across all versions. Therefore, a NVIQ estimate was computed for this study by taking the mean of these two subtests. This is consistent with the method used on the Wechsler Abbreviated Scale of Intelligence-II (WASI-II). In contrast, VIQ is computed in the same manner across the WISC/WAIS versions used, so the actual VIQ index score was used. The resulting correlations are shown in Table 6. Verbal IQ was significantly correlated with the Working Memory, Switching and Planning/Problem Solving EF domains, but not Attention and Inhibition. VIQ was significantly correlated with all of the parent-rating scales except BRIEF MCI. The nonverbal IQ estimate was correlated with the same three EF domains, but only with the BRIEF BRI parent-rating scale. Finally, mean parent years of education was only correlated significantly with the Working Memory, Switching, and Planning/Problem Solving EF domains, but none of the parent-rating scales.

Multiple regression analyses (method enter) were conducted to assess the amount of variance in each EF domain and parent-rating scale that was predicted by the linear combination of VIQ, NVIQ, and parental education. The resulting R^2 was not statistically significant when predicting Attention, Inhibition, Conners Inattention, Conners Hyperactivity/Impulsivity and BRIEF MCI. For these five regressions, the total amount of variance explained ranged between 6 and 11%. Significant multiple regressions were obtained when predicting Working Memory ($p < .001$), Switching ($p < .001$), Planning/Problem Solving ($p < .001$), and BRIEF BRI ($p < .05$), with the amount of variance explained (i.e., R^2) ranging from 16% for BRI to 34% for Planning/Problem Solving. Variance explained for Working Memory and Switching was 31 and 25%, respectively. Even in the multiple regressions that were significant, it should be noted there is still at least 66–84% of the variance in EF that is not explained by VIQ, NVIQ, or parent years of education. In terms of the significance of individual predictors of EF domains and parent-rating scales, NVIQ was the only

variable contributing significant unique predictive variance for Working Memory, Switching, and Planning/Problem Solving, while VIQ was the only variable contributing significant unique predictive variance for the BRIEF BRI. Parental years of education were not a unique significant predictor for any of the EF domains or parent-rating scales.

4 | DISCUSSION

The risk for EF deficits is known to be elevated in XXY, and findings in this study expand upon previous work to further delineate the EF profile associated with XXY. On performance-based measures, results showed that the domain of Attention was the greatest area of deficit, while the Inhibition domain was not an area of deficit. This is consistent with previous studies (Ross et al., 2008; Ross et al., 2009) which found greater problems with attention than inhibition on computerized attentional tasks. Working memory, switching, and planning/problem solving were also lower than average, with moderate effect sizes, supporting previous findings of EF deficits in boys with XXY (Lee et al., 2011; Ross et al., 2009; van Rijn & Swaab, 2015). At an individual level, 82% of the sample had a score one or more *SD*s below the mean in at least one EF domain. This indicates that these are still important domains to consider as areas of risk in XXY. EF deficits were not fully accounted for by language or cognitive deficits, or level of parent education.

Results are somewhat different for parent-report measures. In our sample, parent ratings showed greater deficits in initiation, working memory, planning, organizing, and monitoring than seen on performance-based tests, with larger effect sizes. While the greatest impairment was seen in attention on performance measures, metacognitive skills were the most impaired by parent report. This is not unexpected, as limited correlations between performance tests and rating scales have been reported in other medical and genetic disorders, including perinatal stroke (Krivitzky, Bosenbark, Ichord, Jastrzab, & Billinghurst, 2019), traumatic brain injury (Vriezen & Pigott, 2002), Neurofibromatosis Type 1 (Coutinho et al., 2017; Payne, Hyman, Shores, & North, 2011), epilepsy (MacAllister et al., 2012), early treated hydrocephalus (Anderson, Anderson, Northam, Jacobs, & Mikiewicz, 2002), phenylketonuria (PKU; Anderson et al., 2002), and focal frontal lesions (Anderson et al., 2002). Several hypotheses have been put forth to account for the limited correlation between performance-based and parent-report measures. It has been suggested that the manner of administration of traditional EF measures limits their ecological validity. Testing typically occurs in a quiet, structured, and supportive environment that does not allow for the novel and integrated problem solving required in real world situations (Stuss & Alexander, 2000; Turkstra, Coelho, & Ylvisaker, 2005). Another possibility is that these tests measure different aspects of the same construct (Ten Eycke & Dewey, 2016). For example, performance measures may assess the underlying, cognitive aspect of the skill, while parent-report measures may assess the behavioral manifestation of the skill and the child's ability apply those skills in home and school settings (Krivitzky et al., 2019). Given this, it is important to include both types of measures, allowing for a multi-level assessment that provides complementary information regarding EF skills (Isquith et al., 2013).

The relationship between intelligence and EF has long been considered (Ardila, Pineda, & Rosselli, 2000; Arffa, 2007; Mahone et al., 2002; Riccio, Hall, Morgan, & Hynd, 1994). In our sample, there were some correlations between VIQ and NVIQ with EF domains. However, the regression analyses showed that over two-thirds of the variance in EF was still unaccounted for, even when all three covariates (VIQ, NVIQ, and parental education) were entered together. Furthermore, the average IQ of our sample was in the average range, while EF skills were one to two *SD*s below the mean. This would suggest that overall intellectual ability cannot account for EF deficits seen in XXY, consistent with recent structural equation modeling results of EF in the general population (Friedman & Miyake, 2017).

Given the increased risk of ADHD associated with XXY (Bruining et al., 2009; Tartaglia et al., 2012), it is important to consider whether there are EF differences between those with and without ADHD. In our sample, there were no differences between XXY subgroups with and without ADHD on performance measures. This contrasts with studies of developmental ADHD, where children with ADHD show greater impairments on performance-based EF measures than children without ADHD (Krieger & Amador-Campos, 2018). This may suggest that EF deficits are part of the XXY phenotype and not solely related to an ADHD diagnosis. Indeed, 68% of the group *without* an ADHD diagnosis had at least one performance-based EF domain score that was more than one *SD* below the mean, while 60% had at least one EF parent-rating scale score that was more than one *SD* below the mean. In contrast to performance measures, group differences were seen on parent-rating scales, with parents of the ADHD group reporting more difficulties with attention and metacognitive skills. However, this is not unexpected, as rating forms include items consistent with the diagnostic criteria for ADHD.

Interestingly, the EF profile of boys with XXY seen in our sample is like that of children who have comorbid dyslexia and ADHD. In the latter group, it is also inattentive symptoms that are most prevalent, consistent with behavioral genetic studies that have shown that at least one genetic risk locus for dyslexia on chromosome 6p is pleiotropic for inattentive symptoms (Couto et al., 2009; Willcutt et al., 2002). Children with comorbid dyslexia and ADHD often have working memory difficulties (Tiffin-Richards, Hasselhorn, Woerner, Rothernberger, & Banaschewski, 2008), so the deficits seen in our sample of boys with XXY could have been influenced by comorbid dyslexia, which is highly prevalent in this population as well.

Consistent with previous studies indicating that postnatal diagnosis is associated with increased risk of cognitive difficulties (Ross et al., 2012; Tartaglia et al., 2012), greater problems with attention and metacognitive skills were reported by parents of children diagnosed postnatally than prenatally. However, this was not found for performance-based measures, which showed no difference between the groups. These findings may relate to differences in performance tests versus parent-rating scales or may indicate more similarities between these groups than previously identified. Future studies will be needed to replicate these findings.

This study contributes to the research in XXY in several ways. EF was investigated in one of the largest samples of only boys and adolescents with XXY, as compared to previous studies which used smaller and/or mixed diagnostic samples. Our sample is also one of the most racially and ethnically diverse XXY samples in the literature, with 71% identifying as Caucasian and 16% identifying as of Hispanic or Latino descent. This contrasts with other studies reporting 85 to 96% Caucasian and only 7 to 9% Hispanic or Latino (Lee et al., 2011; Ross et al., 2009; Tartaglia et al., 2012; Tartaglia, Cordeiro, Howell, Wilson, & Janusz, 2010). It is important to have an ethnically diverse sample in order to increase the generalizability of results to the XXY population as a whole, which mirrors the US census in its racial and ethnic diversity. The current study utilized a broad-based battery to assess EF and is the first study to include both performance-based and parent-report measures. Furthermore, EF domains were developed, providing a more robust and objective analysis of data. EF skills were explored in relation to ADHD diagnosis. These findings provide important, novel information regarding the EF phenotype in XXY.

5 | LIMITATIONS

It is important to acknowledge limitations of our study. This study did not include a control group for a direct comparison. While the normative samples of the EF tests used in this study were typically ascertained by the various authors so that they would be representative of the US census, we acknowledge that they come from different samples. Even though our sample was different from test normative expectations on certain measures, it is unclear whether our group would be different from a matched research sample and having a single control group against which to compare our sample would have been beneficial. As with any cross-sectional study in XXY, ascertainment bias and composition of the study sample must be considered. This sample came from a combination of patients who volunteered for a clinical research trial of testosterone treatment (with costs paid by research funds) and those who presented for evaluation in our interdisciplinary clinic (funded by public and private health insurance). The sample included a broad representation of patients from across the US (with 30–40% from Colorado), and were ascertained for a variety of reasons from the prenatal period to postnatal diagnoses due to physical findings at birth, developmental delays, behavioral/learning symptoms, or pubertal delays in adolescence. The SES level of our sample was relatively high and likely not representative of the XXY population as a whole. Indeed, our sample's overall cognitive ability was higher than might be expected, and their performance on most EF measures was clinically in the average range. To account for this, SES was used as covariate and was found to account for only 5% of the variance in EF performance. This suggests that SES did not significantly contribute to our sample's EF performance; however, it will be important for future studies to examine EF in samples with a wider range of SES and cognitive abilities. Conclusions drawn from these results must be considered with the composition of this broad and diverse study sample in mind. For a physician, therapist, psychologist, or educator evaluating a child or adolescent with XXY presenting with clinical concerns, the study sample is felt to be representative of the types of XXY patients seeking clinical evaluation, and results presented here generalizable to a diverse group of clinically identified individuals with XXY.

5.1 | Directions for future research

The current study used an exploratory sample. Future research will be needed to corroborate findings with a larger cohort. Future studies should consider using one or more control groups matched on characteristics known to affect EF including SES, ADHD, and LD status, medication status, and extent of special education support.

Future studies should consider EF functioning within the broader context of the development of EF skills over childhood and adolescence. Executive functions have a protracted development and the prefrontal regions associated with EF are the last to reach maturity (Anderson, 2001). Different aspects of EF develop at different rates and come “on-line” at different ages. For example, Welsh, Pennington, and Grossier (1991) found that planning and organization were first observed at age 6, impulse control, set maintenance, and hypothesis testing were seen by age 10, and verbal fluency, motor sequencing, and complex planning skills were developed by adolescence. The current study had a relatively large age span and it is possible, that with a larger sample size, different patterns of functioning may be seen across development. Lee et al.'s (2015) study found that parent-report EF skills were more impaired at older ages, suggesting that there may be differences in EF functioning of XXY individuals at different ages. Future research should compare EF performance between younger and older children/adolescents and adults, to determine whether EF development is similar to those without XXY and discern whether the EF profile is consistent over time.

While the relationship between EF and ADHD in boys with XXY was explored, this study did not consider the contribution of other diagnoses commonly seen in XXY that also have EF deficits including autism, language disorders, and dyslexia. Future studies should investigate the EF profile of children with XXY and other comorbid conditions to explore differences and similarities between the groups. Furthermore, future research should investigate the relationship between EF, academic outcome, and adaptive functioning in XXY.

Finally, future research should explore the effect of ADHD medications on EF performance. In children with developmental ADHD (without XXY), studies have shown improvement on parent-rating scales of EF (Yang et al., 2012), as well as on performance tests of working memory (Bedard, Martinussen, Ickowicz, & Tannock, 2004; Ince, Algedik, Demirdogen, Emul, & Demir, 2015; Rubio Morrell & Hernandez, 2019; Yang et al., 2012), cognitive flexibility (Ince et al., 2015; Yang et al., 2012), planning, decision-making, and inhibition (Rubio Morrell & Hernandez, 2019) following treatment with medication. Studies in XXY suggest that individuals with ADHD have a positive response to medication with regard to symptom reduction (Tartaglia et al., 2012), but no studies have investigated whether

medication improves performance on EF measures. Future research should longitudinally follow the same sample of children, with testing conducted pre-treatment and posttreatment to determine the specific domains that improve with medication treatment.

6 | CLINICAL CONCLUSIONS

While these results are interesting to analyze and consider within the context of EF and neuropsychological functioning, and lead to many important future research questions, they also highlight some clinical pearls that are important for consideration in clinical and education settings. These include:

- There is a wide range of EF skills in this cohort, with some children scoring in the average range. However, a significant majority of the sample (82%) scored one or more *SD*s below the mean in at least one performance-based EF domain, and 75% of the sample scored one *SD* or more below the mean on at least one EF parent-rating scale.
- Individuals with XXY are at risk for deficits in EF skills even when they have normal cognitive abilities (normal IQ scores).
- Attentional deficits were the most significant on both direct assessment and parent report, while inhibition/hyperactivity/impulsivity domains were the least impaired. Thus, further evaluation for attention deficits and ADHD-Inattentive subtype should be strongly considered in XXY even without symptoms of hyperactivity or impulsivity.
- Parent report of EF difficulties are often more significant than what is seen on direct neuropsychological assessment. This highlights the challenge of applying basic EF skills to more demanding academic and daily life contexts. It also highlights the importance of considering other comorbid risk factors in XXY that may contribute to overall functioning including language, learning, anxiety, and social difficulties.
- Given the presence of EF deficits in children with XXY who do not have a co-occurring diagnosis of ADHD, the latter subgroup may still benefit from evaluation of EF skills and supports for any identified EF deficits in home and educational settings.

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CONFLICT OF INTEREST

None.

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