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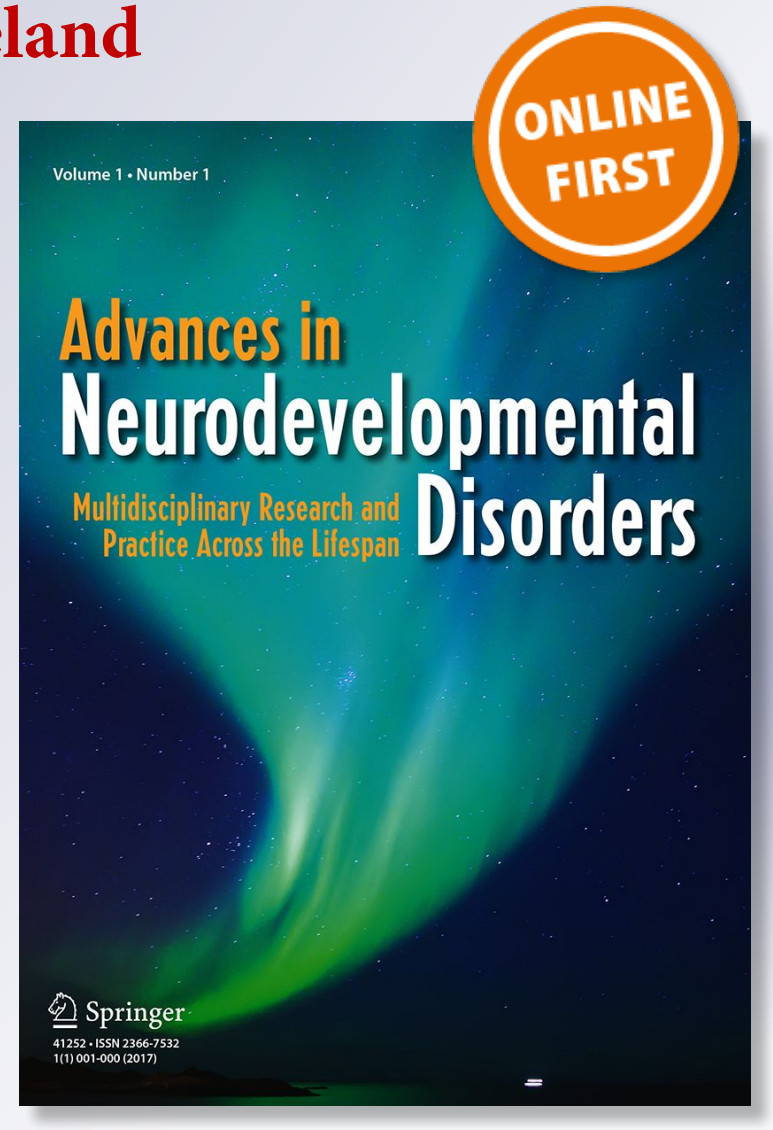

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ORIGINAL PAPER

Behavioral Inhibition in Boys with Sex Chromosome Aneuploidies Compared to a Clinical Sample

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Abstract Sex chromosome aneuploidies (SCA) in boys involve physiological, cognitive, and socioemotional challenges. Internalizing problems in boys with SCA are underexamined. We examined behavioral inhibition (BI) in boys with SCA, compared to a clinical sample. BI is a temperamental style characterized by shyness, withdrawal, and cautiousness, and represents increased risk for internalizing problems. Parents (76% mothers) completed the Behavioral Inhibition Questionnaire (BIQ; Bishop et al. 2003), which comprises total BI and BI in six specific domains. Parents of 25 boys with SCA participated (boys' *M* age = 11.7 years, SD = 4.5, range 2–18 years), including boys with karyotypes 47,XXY, 47,XYY, 48,XXYY, and 48,XXXY. We compared their BI to 100 boys referred to mental health clinics and treated for anxiety (*M* age = 11.7 years, SD = 2.3, range 7–17 years), and to norms from 307 Australian boys aged >5 years. Total BI in boys with SCA was at the same level as clinic-referred boys (effect size difference $d = 0.02$), and higher than norms ($d = 0.81$). Boys with SCA were significantly more inhibited in physical situations than clinic-referred boys ($p = .007$; $d = 0.71$). Differences were small to negligible for BI domains involving peer, unfamiliar adults, and performance situations (all $d \leq 0.34$). In conclusion, boys with SCA seem to be as behaviorally inhibited as boys treated for anxiety problems in mental health clinics. Inhibition in physical domains may be a particular challenge for boys with SCA.

Keywords Behavioral inhibition · Temperament · Sex chromosome aneuploidies · Klinefelter syndrome · Anxiety

Introduction

Behavioral inhibition (BI) is a temperamental pattern of behavioral and emotional responses, such as a tendency to react with fear, withdrawal, and cautiousness when exposed to new and unfamiliar situations, people, objects, or places (Kagan et al. 1984). BI is considered a moderately stable trait based on longitudinal studies following children from toddlerhood to later childhood (Degnan and Fox 2007; Hirshfeld et al. 1992; Kagan et al. 1987; Muris et al. 2011). This temperamental trait has been linked to later onset internalizing problems, such as social anxiety disorder (Clauss and Blackford 2012; Hayward et al. 1998; Schwartz et al. 1999) and depression (Hayward et al. 1998; Karevold et al. 2011; Kerr et al. 1997). It has been suggested that since inhibited children are less confident and assertive, they may tend to interpret ambiguous social situations negatively and experience more social rejection (Fox and Pine 2012; Schwartz et al. 1999). High BI may also involve fewer opportunities to interact with peers, impacting development of social competence (Garcia Coll et al. 1984; Kagan et al. 1984).

The above cited studies have focused on normally developing children. However, less is known about BI in children with increased risk of developmental problems, such as boys with sex chromosome aneuploidies (SCA), i.e., additional X

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and/or Y chromosomes. SCA are the most common chromosome aneuploidies in humans, with an estimated prevalence rate of 1:400 (Linden et al. 1995). Among boys, the most prevalent SCA karyotype (i.e., sex chromosome manifestation) is Klinefelter syndrome (47,XXY; prevalence 1:500), followed by 47,XYY (estimated prevalence 1:1000), and rarer karyotypes including 48,XXYY (estimated prevalence 1:18,000 to 1:40,000) and 48,XXXY (estimated prevalence 1:50,000; Bojesen et al. 2003). SCA in boys are associated with different physiological, cognitive, and socioemotional challenges (Cordeiro et al. 2012; Gravholt 2013; Ross et al. 2012; Tartaglia et al. 2011). In terms of cognitive abilities among boys with karyotypes 47,XXY and 47,XYY, full-scale IQ scores are generally within the normal range, with considerable individual variation (Leggett et al. 2010). Mean IQ tends to be lower and in the borderline to mild mental retardation range for tetrasomy conditions (Gravholt 2013). In terms of socioemotional problems, increased levels of anxiety, depression, attention deficit hyperactivity disorder symptoms, and behavior problems have been found in studies of boys with SCA (Ross et al. 2012; Tartaglia et al. 2012; Turriff et al. 2011).

A few studies have examined aspects of temperament in children with SCA. Boys with SCA have generally been described as more timid, less confident, and as having more problems relating to peers than controls (Bancroft et al. 1982; Bender et al. 1995; Cordeiro et al. 2012). A temperamental style close to BI was described as typical among 108 American boys with SCA aged 4 to 15 years (Ross et al. 2012). In this study, boys with 47,XXY and 47,XYY were rated significantly more anxious-shy by their parents compared to controls. Based on a parent-rated measure of child behavior in the domains of social awareness, social cognition, social communication, social motivation, and autistic mannerisms, Cordeiro et al. (2012) identified severe difficulties in social responsiveness in 20% of 102 boys with 47,XXY, 50% of 40 boys with 47,XYY, and 44% of 32 boys with 48,XXYY, compared to 7% of boys in a normative sample.

The social functioning of boys with SCA can be characterized by shyness, withdrawal, and anxiousness, and difficulties with social responsiveness have been found across karyotypes (e.g., Bancroft et al. 1982; Cordeiro et al. 2012; Ross et al. 2012). High BI may be particularly problematic for boys, due to social expectations that boys should be more assertive, active, physical, and risk-willing than girls. In a longitudinal study of temperament in children, Karevold et al. (2011) found a gender interaction effect in the association between parent-reported shyness and internalizing problems in children, where activity level served as a protective factor for boys, but not for girls. To further understand the range of challenges experienced by many boys with SCA, more research of their basic temperamental traits is warranted.

In the current study, we examined the temperamental style of BI among boys with SCA. Beyond getting knowledge of the levels of BI among boys with SCA, we compared this sample to a clinical sample of boys referred to community mental health services and treated for anxiety problems, as well as to norms. The norm group included a sample of 307 normally developing Australian children (Bishop et al. 2003). We addressed the following research questions: (1) To what degree do boys with SCA display BI, and in which domains? (2) How does BI in boys with SCA compare to a clinical sample and to norms? We expect boys with SCA will have elevated BI scores relative to norms. We made no specific assumption about how the SCA sample and clinic-referred boys will compare, due to a lack of previous studies.

Method

Participants

Participants included boys with SCA, clinic-referred boys without SCA, and norms. The SCA sample comprised 25 boys with karyotypes 47,XXY (n = 13), 47,XYY (n = 6), 48,XXYY (n = 3), or 48,XXXY (n = 3). The mean age of the SCA sample was 11.7 years (SD = 4.5, range 2 to 18 years). Socioeconomic status (SES) was estimated in accordance with guidelines from the Registrar General Social Class coding scheme, classifying parent occupational status into rank ordered socioeconomic status classes (Currie et al. 2008). For the SCA sample, 56% of families were categorized as high SES, 36% as medium, and 8% as low.

The clinical sample comprised all boys (N = 100; mean age = 11.7 years, SD = 2.3, range 7 to 17 years) from a clinical anxiety trial. SES was estimated to be high for 24%, medium for 44%, and low for 8% (Currie et al. 2008). SES was unknown for 24% of the families. The norm sample comprised 307 Australian normally developing boys aged 3 to 5 years with parent-reported BI scores (Bishop et al. 2003).

Procedures

We recruited the participants with SCA from two different settings. The database of Frambu resource center for rare disorders (Frambu), a national resource center for rare disorders in Norway, was used to recruit 18 participants. Frambu is a publicly funded but privately run specialist health institution serving all tiers of health providers in Norway with liaison services for rare genetic disorders. Families can self-refer and registration in the user database is voluntary. The response rate from the database was 47%. The remaining seven participants were recruited at the annual meeting of the Norwegian Klinefelter Syndrome Association. Information about the study was given at the meeting, and the attending families

were invited to take part. The number of attendants under 18 years was not registered, thus the response rate from this setting is unknown. In both settings, parents were given the questionnaire and a prepaid return envelope. Analyses are based on responses from 1 parent, 19 mothers (76%), and 6 fathers (24%).

Information about the karyotype details was parent-reported, and details were checked in medical records for the 18 participants from the health institution database. No discrepancies between parent report and medical records were found for karyotype. Access to medical records for the seven participants recruited from the user group meeting was not obtained.

The participants in the clinical sample were drawn from the Assessment and Treatment—Anxiety in Children and Adults study (ATACA). The study was a randomized controlled trial (RCT) of cognitive behavior therapy for anxiety disorders for which 221 children who were regular referrals to community child and adolescent mental health clinics in western Norway were assessed for eligibility. The clinics are part of the public health system in Norway. Referrals typically come from general practitioners and services are free of charge. Research participation is not required to access services.

Ethics We obtained informed consent from the parents of the participants in both samples. In ATACA, children over 11 years provided verbal assent. Children in the SCA sample did not provide assent, as no identifying information was collected. The regional boards for medical health research ethics in Norway (East and West) approved the SCA study and the ATACA study, respectively.

Measures

The Behavioral Inhibition Questionnaire (BIQ; Bishop et al. 2003) is a 30-item rating scale which measures BI in six domains. Higher scores represent higher levels of BI. Sixteen items are reversed to reduce the possible influence of response style. The six BI domains are unfamiliar situations (Unfamiliar; 8 items; e.g., *Approaches new situations or activities very hesitantly*); unfamiliar peers (Peers; 6 items; e.g., *Tends to watch other children*, *rather than join in their games*); unfamiliar adults (Adults; 4 items; e.g., *Is very quiet around new (adult) guests to our home*); separation situations (Separation; 4 items; e.g., *Gets upset at being left in new situations for the first time* (e.g., *kindergarten*, *preschool*, *childcare*); novel physical activities with a minor risk element (Physical; 4 items; e.g., *Is cautious in activities that involve physical challenge* (e.g., *climbing*, *jumping from heights*)); and performance situations (Performance; 4 items; e.g., *Is reluctant to perform in front of others*), as well as a BIQ total score. Parents were asked to rate frequencies of the behaviors in the six domains on a 7-point Likert scale from "almost never" to "almost always".

The BIQ has demonstrated good psychometric properties, with adequate internal consistency and test-retest reliability for mother and father ratings (Bishop et al. 2003¸ Kim et al. 2011). Confirmatory factor analysis has supported a six-factor structure corresponding to the six domains in the BI scale. The six factors also loaded onto a single higher-order general factor measuring overall BI. The BIQ has been proved reliable and valid not only for preschool children, but also for children aged up to 15 years (Broeren and Muris 2010).

In the current study, the BIQ was rated retrospectively. Parents were asked to rate their children at preschool age, with the instruction "Please think back to how your son was in preschool (aged 3 to 5 years)". The BIQ total internal consistency was excellent for the SCA sample (α = .95) with subscale reliability as follows: Unfamiliar (α = .93); Separation (α = .92); Peers (α = .85); Adults (α = .79); Physical (α = .60); and Performance (α = .65). The BIQ total was excellent for the clinical sample (α = .96), with subscale reliability as follows: Unfamiliar (α = .92); Separation (α = .91); Adults (α = .90); Performance (α = .85); Physical (α = .82); and Peers (α = .79).

Data Analyses

We used SPSS version 22.0 for all analyses. *T*-tests were applied to compare mean scores between the SCA sample and the clinical sample. A Bonferroni-corrected significance level of $p < .008$ was applied to adjust for the number of tests (i.e., the six BI domains). We calculated between group effect sizes using Cohen's *d* ([mean group 1—mean group 2/pooled standard deviation] Cohen 1988), and interpreted the effect sizes using the following criteria: 0.10 to 0.29= small, 0.30 to 0.49= medium, and >0.50= large (Cohen 1992). Data on parent SES was missing for 24% of participants in the ATACA sample. As this was not a main variable, BI scores from these 24 participants were kept in all analyses. We included all participants with <20% missing items on the BI, resulting in no missing BI data in any of the samples. Given the small sample size of the SCA group, we did not distinguish karyotypes in the analyses.

Results

There was no significant mean age difference between the SCA sample (11.7 years) and the clinical sample (11.7 years; t = .094, p = .925). The difference in SES between the two samples was not significant (x^2 = 4.822; df = 2, p = .09). See Table 1 for mean BIQ scores for the SCA sample, the clinical sample, and norms, including between sample effect sizes.

The effect size differences between the SCA sample and norms were large for BIQ total, BIQ peers, BIQ physical, BIQ unfamiliar, BIQ performance, and medium for BIQ separation, with the SCA sample being more inhibited. There was

Table 1 Behavioral inhibition scores

BIQ scale	Clinical sample (n = 100) M (SD)	SCA vs. clinical d[a]	SCA sample (n = 25) M (SD)	SCA vs. norms d[a]	Norms[b] (n = 307) M (SD)
Total	117.5 (36.5)	0.02	118.1 (38.3)	0.81	89.7 (31.3)
Separation	17.4 (7.0)	0.33	15.1 (6.8)	0.47	12.0 (6.4)
Peers	24.1 (7.2)	0.01	24.1 (9.3)	0.58	19.0 (8.3)
Adult	15.8 (6.7)	0.34	13.6 (6.5)	0.01	13.6 (6.1)
Unfamiliar	32.0 (11.1)	0.02	32.2 (12.9)	0.84	23.0 (8.8)
Physical	12.1 (5.9)	0.71*	16.1 (5.4)	1.33	9.1 (5.1)
Performance	16.1 (5.8)	0.16	17.0 (5.5)	0.73	13.1 (5.3)

BIQ behavioral inhibition questionnaire, *SCA* sex chromosome aneuploidies, *M* mean, *SD* standard deviation

*Difference is significant with p = 0.007

[a] Effect size Cohen's d ([mean group 1—mean group 2/pooled standard deviation] Cohen 1988)

[b] Bishop et al. 2003

a negligible difference for BIQ adults. Significance levels of differences between the SCA sample and norms could not be calculated as we did not have access to raw data from the norm sample.

The differences between the SCA sample and the clinical sample were non-significant, with small to negligible effect size differences for BIQ total, BIQ peers, BIQ unfamiliar, and BIQ performance. A large effect size difference was found for BIQ physical, with the SCA sample being more inhibited than the clinical sample. This was the only significant difference between the SCA sample and the clinical sample (t = 2.972, df = 24, p = .007). Medium effect size differences were found on BIQ adults and BIQ separation, with the clinical sample being more inhibited than the SCA sample. However, these differences were not significant.

Discussion

We examined the temperamental trait BI in a sample of boys with SCA, and largely found support for our expectation that BI among these boys was higher than for norms. Previous studies of boys with SCA have shown increased risk of both physical and socioemotional challenges for these boys (Cordeiro et al. 2012; Gravholt 2013; Ross et al. 2012; Tartaglia et al. 2011). The finding that boys with SCA have high BI suggests they have difficulties in participating in important activities with peers in kindergarten, school, and leisure activities. This represents a developmental risk for boys with SCA, as peer relations represent an important arena for the development of emotional and behavioral adjustment (Rose and Rudolph 2006). The exception to the general pattern of elevated BI in boys with SCA concerned interaction with adults. Boys with SCA were rated as less inhibited in interaction with adults than boys in the clinical sample, and their scores were similar to norms. Boys with SCA have been described as having problems in relationships with peers (Bancroft et al. 1982), and in some cases, problems with social responsivity (Cordeiro et al. 2012). Because boys with SCA may experience problems relating with peers, they may be more oriented towards adults.

We had no a priori expectation of how BI in boys with SCA would compare to a clinical sample of boys referred to community mental health clinics and treated for anxiety problems, due to a lack of previous empirical studies. The only significant difference between these samples was on the BI physical domain, i.e., novel physical activities with a minor risk element. In fact, boys with SCA scored higher on physical BI both compared to the clinical sample and to norms. Thus, boys with SCA may have considerable problems participating in physical activities with peers, including physical activity in play. Boys with SCA often show delayed motor development, which is suggested to be due to hypotonia (i.e., low muscle tone), and hypermobility (i.e., flexible joints; Ross et al. 2008; Visootsak et al. 2001). Furthermore, many boys with SCA have impaired gross motor function and coordination, especially in running speed and agility (Ross et al. 2009). By mastering important skills like biking, skiing, and jumping later than their peers, these boys may experience lack of self-efficacy in physical situations from an early age. Experiencing shortcomings may result in withdrawal from physical activity, and thus reinforce motor delays. Physical play in childhood involves learning and practice of skills that are considered a necessary part of socialization. Whereas girls mainly establish and maintain social dominance verbally, boys tend to use physical skills and play to adjust peer group status (Eaton and Enns 1986; Pellegrini and Smith 1998). Being a physically inhibited and unassertive boy may influence social function, self-esteem, and relations to the peer group negatively. Activity level has been found to be a protective factor for internalizing problems among shy boys (Karevold et al. 2011).

BI is not always associated with dysfunction and distress. Evidence of BI as a protective factor comes from studies of externalizing problems. For example, ADHD has been argued to represent a deficit in BI (Barkley 1997). Kerns et al. (2001) studied children with ADHD and found that compared to healthy controls, children with ADHD scored significantly lower on BI. Boys with SCA have been reported to have a high prevalence of behavioral problems and ADHD symptoms, including impaired inhibitory executive functions and problems with impulse control (e.g., Kompus et al. 2011; Ross et al. 2007; Temple and Sanfilippo 2003). Furthermore, risk-taking is not uncommon among boys with SCA (Simpson et al. 2005). Thus, evidence suggests boys with SCA have a double disadvantage with increased risk of both internalizing and externalizing problems.

The current study has limitations. In terms of generalizability, the small size of the SCA sample limits generalizability and reduces statistical power. Four karyotypes are represented, and potential variations in BI between karyotypes could not be examined due to the small sample size. The SCA sample was recruited via a resource center and a user organization, and may as such not be generally representative of boys with SCA. Due to the wide age ranges, the SCA and clinical samples were rated retrospectively, whereas the children from the norm group were rated concurrently at ages 3 to 5 years. Although the BIQ is validated up to 15 years (Broeren and Muris 2010), there may have been recall bias in parent report. The use of a norm group from Australia raises the question of whether the cultural and sociodemographic differences may be a limitation. However, at the present, no normative sample in Norway has been rated on the BIQ. Finally, BI scores were parent-reported and may have limited overlap with the boys' own perception of their BI.

Future research using combined methods such of parent-reported retrospective rating and self-reported measures of BI could provide insight into the stability of BI in boys with SCA. The inclusion of observational data would further strengthen findings. Examining the relationship between physical activity and social problems in boys with SCA could help create guidelines for parents and health care professionals working with this group. Given the musculoskeletal pain and somatic complications that boys with SCA are at risk of developing, this is an important area for intervention. Future research need to address whether measures of BI is an adequate method for predicting which children are at risk of developing internalizing problems. Little is still known of why some high BI children develop internalizing problems and some do not. More knowledge of both biological and environmental factors influencing risks and resilience among boys with SCA is necessary to create preventative interventions.

Authors' Contributions KWF: Designed and executed the SCA study, contributed to design and execution of the clinical study, assisted with the data analyses, and wrote the paper. MSW: Conducted the data analyses, and collaborated in the writing. SS: Co-designed and executed the SCA study, assisted with data preparation, and collaborated in the writing. BSH: Co-designed and executed the clinical study, and collaborated in the writing. OEH: Designed and executed the clinical study (PI), and collaborated in the writing. GJW: Co-designed and executed the clinical study, and collaborated in the writing.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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