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Vulnerability for autism traits in boys and men with an extra X chromosome (47,XXY): The mediating role of cognitive flexibility

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ABSTRACT

The XXY chromosomal pattern (Klinefelter syndrome, KS) has been associated with specific effects on physical, neurobiological, endocrinological and psychological development. This study was focused on the described risk for autism in KS, and the cognitive mechanisms that mediate this risk. Our aim was to assess whether autistic features in KS result from impairments in executive functioning, more specifically difficulties in cognitive flexibility.

In total, 71 boys and men with KS and 61 non-clinical controls participated in the study. Autistic features were assessed using the Autism-spectrum Quotient (AQ). Mental flexibility was measured using the Wisconsin Card Sorting Test (WCST).

The level of autism traits was significantly increased in the KS group, the effect size for total AQ score was 1.6. The KS group also showed significantly more difficulties in cognitive flexibility, as indicated by and increased number of perseverative (but not non-perseverative) errors in the WCST. This effect was independent of intellectual functioning, age or testosterone supplements. Within the KS group, the number of perseverative errors was significantly (positively) correlated with total AQ score.

Our findings suggest that KS can be associated with dysfunctions in mental flexibility, and that individuals with more mental flexibility problems also have more autism traits. This insight is relevant for diagnosis, prevention and treatment of severe problems in individuals with KS. Implications also extend beyond this specific syndrome. As executive dysfunctions in KS have also been linked to ADHD symptoms and thought disorder, this could be a shared mechanism contributing to overlap in symptoms and comorbidity between different psychiatric conditions.

1. Introduction

Boys and men with Klinefelter syndrome (KS) have two (or more) copies of the X chromosome instead of the usual one copy, leading to the 47,XXY chromosomal pattern. KS is the most common X chromosomal aneuploidy occurring in approximately 1 in 650 live born boys (Bojesen et al., 2003). The XXY chromosomal pattern has been associated with specific effects on physical, neurobiological, endocrinological and psychological development (Lanfranco et al., 2004). Even though behavioral outcome may be variable, group-wise analysis has indicated that on average, boys and men with KS have an increased vulnerability for problems in social adaptation. These social difficulties in KS may include social withdrawal, social anxiety, shyness, impulsivity, depressed adaptive skills, communication difficulties, unassertiveness, emotion regulation problems and difficulties in reading social signals (Boone et al., 2001; Geschwind and Dykens, 2004; Ratcliffe, 1999; Tartaglia et al., 2010; Van Rijn et al., 2006, 2008; Visootsak & Graham, 2009).

The severity of social and adaptive difficulties is illustrated by the reported increased levels of autism traits such as problems in areas of social skills, communication, attention switching and imagination, and increased attention to details, as has been measured with the Autism Spectrum Questionnaire in adults with XXY (van Rijn et al., 2008). Similarly, over 25% in the sample of boys studied by Tartaglia et al. (2010) had scores on the Social Responsiveness Scale (measuring autism traits) that were in the mild-to-moderate or severe range, although social awareness was relatively spared. In some cases, the autism traits reached a clinical

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threshold for diagnosis of ASD. Bruining et al. (2009) reported that 14 out of 51 boys with KS (27%) in their sample (a mixed group of referred cases and prenatal follow-up) met criteria for ASD, and Bishop et al. (2011) found that 2 out of 19 boys with KS (11%) in their prenatal follow-up sample met criteria for ASD. In the study by Tartaglia (a mixed group of referred cases and prenatal follow-up) 1 out of 20 boys (5%) met full criteria for ASD. These risks in the domain of social and adaptive behavior problems call for investigation of the underlying neurocognitive mechanisms in KS that help explain such vulnerabilities. Assessment of the cognitive abilities of individuals with KS is crucial in understanding why adaptation in social context may be a challenge and how we can provide support and influence these cognitive functions to improve outcome.

X chromosomal aneuploidies such as KS may help in gaining insight in the etiology of social adaptive problems and autistic symptoms, and may therefore also provide insights into mechanisms of neurodevelopment that extend beyond this specific syndrome. The fact that neurodevelopment and social skills are for a large part driven by genetic factors, possibly as high as 68% for social skills (Scourfield et al., 1999), warrants the study of social adaptive behavior in genetic conditions. Aneuploidies of the X chromosome are particularly interesting, considering the exceptional high density of genes on the X chromosome that are essential for neural development (Zechner et al., 2001). In order to gain more insight in the gene–brain–behavior relations in KS, it is important to dissect neurocognitive dysfunctions that mediate between the genetic level and the behavioral level (Zijlstra et al., 2010).

Successful social functioning requires individuals to adjust their behavior frequently in order to meet changing demands in the environment. Adapting to the environment is particularly required in social interactions, which are dynamic in nature. Social interaction refers to 'a dynamic, changing sequence of social actions between individuals who modify their actions and reactions according to the actions by their interaction partner(s)' (Beauchamp and Anderson, 2010). Such complex behaviors heavily rely on an intact system of cognitive functions, and related underlying neural circuitries, which are crucial for processing the high load of information and rapid organization of behavioral responses. One of the neurocognitive functions crucial to social adaptation is executive functioning (EF), which is dependent on frontal lobe integrity (Stuss, 2011). Executive functions are heavily relied on in novel or unfamiliar circumstances, where no previously established routines for responding exist, as opposed to execution of routine, well-learned behaviors. Executive dysfunctions therefore may lead to dysregulation of thought, emotion and behavior, including inappropriate, inflexible or non-adaptive social behavior (Beauchamp and Anderson, 2010). Several components of executive functions can be distinguished, such as organized search, strategic planning, inhibition, focused and sustained attention, monitoring, holding a mental representation "on-line" in working memory and flexibility of thought and action (Anderson, 2001). One component of EF that is of particular interest in relation to social adaptation, is cognitive flexibility (also termed attentional flexibility, mental flexibility, attention switching or set-shifting). Cognitive flexibility involves disengaging attention away from one source and then moving and reengaging it to another (Posner and Petersen, 1990). It allows individuals to consider behavioral alternatives, generate a diversity of ideas and respond to new or changing situations. Poor cognitive flexibility is illustrated by difficulties in regulation and modulation of behavior, perseverative or rigid behavior in situations that are complex or novel like social situations. Indeed, poor mental flexibility is a widely acknowledged feature of individuals with ASD, and may contribute to social adaptive problems that are core to the disorder (Hill, 2004).

Considering the importance of cognitive flexibility for social adaptation, our aim was to 1) assess cognitive flexibility skills in individuals with KS and 2) assess whether more cognitive flexibility problems are related to more problems in social adaptation and higher levels of autistic traits. Only recently studies have begun to systematically evaluate whether and how cognitive problems in KS are related to the behavioral phenotype. Addressing the relation between neurocognition and behavior in KS may prove to be an avenue leading to insight into at risk developmental pathways and targets for prevention and treatment. In addition, by studying KS we may increase our understanding of the neurobiological and neurocognitive factors that convey risk for problems in social adaptive behavior.

2. Methods and materials

2.1. Subjects

In total, 71 subjects with Klinefelter syndrome (28 boys and 41 adults, mean age 28.9, SD 16.6) and 61 non-clinical controls (25 boys and 36 adults, mean age 27.5, SD 15.8) participated in the study. Adults with KS were recruited from a) endocrinology clinics and b) the Dutch Klinefelter Association. All adults were postnatally diagnosed. Children with Klinefelter were recruited through a) pediatricians, b) endocrinologists, c) the Dutch Klinefelter association and d) active follow up after prenatal diagnosis with help of clinical genetics departments. Subjects in groups a, b, and c were considered 'referred' cases and constituted 46% of the total KS group. Subjects in group d were considered 'prenatal follow-up' cases and constituted 54% of the total KS group. These two different recruitment strategies allowed us to assess if our findings were affected by recruitment bias (at least in the group of children).

Diagnosis of Klinefelter syndrome was confirmed by standard karyotyping. In the KS group 58% used testosterone supplements, with a mean age of start of treatment at 25.3 years (SD 8.5). Controls from the general population were recruited using advertisements or had participated in earlier studies from our department in which they consented to registration of contact details for future studies. None of the control subjects had a history of psychiatric illness or head injury with loss of consciousness.

Inclusion criteria for both Klinefelter men and controls were Dutch as the primary language and age between 6 and 60 years. Exclusion criteria for both Klinefelter men and controls were a recent history of substance abuse, intellectual disability and neurological conditions. Neurological conditions included structural brain damage due to prenatal/birth complications, traumatic injury, tumors, stroke or infections, as well as neurological syndromes or diseases affecting the central nervous system. A diagnosis of hypotonia, which is common in KS, did not lead to exclusion. After complete description of the study to the subjects (>12 years) and their parents (<18 years), written informed consent was obtained according to the declaration of Helsinki. The study was approved by the Ethical Committee of the University Medical Center Utrecht.

2.2. Procedure

The tests were performed in a fixed order and administered by neuropsychologists at the department of Psychiatry of the University Medical Center Utrecht. Participants completed the tests in a quiet room without distractions. Intellectual functioning was assessed in order to evaluate executive functioning against the background of level of general intellectual functioning.

2.3. Intellectual functioning

Participants in the KS group completed all subtests of the Dutch adaptations of the WAIS-III (Wechsler Adult Intelligence Scales, Wechsler, 1997, 2005) and WISC-III (Wechsler Intelligence Scales for Children, Kort et al., 2005; Wechsler, 1991). Participants in the control group completed only two subtests, Block design and Vocabulary, i.e. V-BD short form. The V-BD short form was used to estimate full scale IQ (FSIQ) according to the algorithm (2.9*(sum of normed scores) + 42) (Campbell, 1998). The V-BD short form correlates high with the WISC-III full scale IQ ($r = 0.88$) (HerreraGraf et al., 1996) and the V-BD short form has been found valid for the estimation of intelligence, with a good reliability ($r = 0.91$) and validity (0.82) (Campbell, 1998).

2.4. Cognitive flexibility

Cognitive flexibility was assessed using the Wisconsin Card Sorting Test (WCST). This test is based on a rule learning paradigm, of which the card sorting principles are not revealed to the subject, but instead must be inferred from the feedback provided. After a subject scored ten consecutive cards correctly, the sorting principle was altered without warning. This procedure continues until the subject successfully completed six sorting categories (color, form, number, color, form, number), or until all 128 cards had been placed.

In order to ensure unequivocal theoretical interpretation that supports the characterization of the involvement of fundamental EF processes, cognitive flexibility was measured using the perseveration score (persisting current behavior despite a history of negative feedback), operationalized by the contrast between the number of perseveration errors (i.e. number errors in which the subject continued sorting by the previous correct category despite negative feedback) and the number of non-perseveration errors (Lezak et al., 2004).

Summary scores of the WCST are the total number of items administered (which refers to the number of items needed to complete the test) and the number of categories completed (which refers to the number of categories, i.e. each sequence of ten correct responses to a specific criteria sorting category, completed during the test).

2.5. Autism traits

The Autism-spectrum Quotient (AQ) (Baron-Cohen et al., 2001) is a questionnaire that assesses the degree to which any individual adult of normal intelligence might have features of the core autistic phenotype. For adults and adolescents there is a self-administered version, and for children there is parental report version. Although it is primarily developed and used as a dimensional measure, it has good test–retest reliability and good discriminative validity for Asperger syndrome at a cut-off score of 26 in a clinical population (16). Also, it has good discriminative validity for high functioning autism/Asperger syndrome in the general population using a cut-off score of 32 (15). Scores on the AQ have shown to be normally distributed in the general population. Five subscales cover personality traits associated with the autism spectrum; social skills, communication, imagination, attention to detail, and attention switching. Higher scores on the AQ indicate higher levels of autism traits.

2.6. Statistical analyses

Group differences in IQ and level of autistic traits were analyzed using ANOVA with the fixed factors 'group' (control versus Klinefelter) and 'age' (child <18 years, adult >18 years), and the IQ scores or total AQ score as the dependent variables. Group differences in scores on the WCST were analyzed using MANCOVA, with the fixed factors 'group' (control versus Klinefelter or prenatal follow up versus referred) and 'age' (child <18 years, adult >18 years), and the WCST parameters as the dependent variables (number of categories completed, total number of items, failure to maintain set, number of perseverative errors and number of non-perseverative errors), and FSIQ as a covariate. Repeated measures analyses with the within-subject factor 'error type' (perseverative errors, non-perseverative errors), the between-subjects factor 'group' (control, Klinefelter) and the covariate FSIQ, was used to test for interactions. In order to assess possible effects of testosterone supplements on performance in the WCST and level of autistic traits in the Klinefelter group, ANOVA was used comparing KS individuals with (+) and without (−) testosterone supplements. For correlational analysis Spearman's rho was used. Level of significance was set at 0.05, two-tailed.

3. Results

3.1. Intellectual functioning

In order to compare IQ scores between the groups, the estimated FSIQ was used as this was available for both groups. ANOVA with the factors 'group' and 'age' showed a significant main effect of group on estimated IQ ($F(1,126) = 50.9$, $p < 0.001$). Also, there was a significant main effect of age ($F(1,126) = 6.9$, $p = 0.009$), with higher FSIQ scores (irrespective of group membership) in adults as compared to children. However, there was no significant group by age interaction ($F(1,126) = 2.8$, $p = 0.10$). In other words, estimated FSIQ was lower in the KS group as a whole (87.2, SD 13.8) as compared to the control group (103.0, SD 12.8). Data from the complete Wechsler scales in the KS group revealed a FSIQ of 86.8 (SD 13.8), a PIQ of 90.9 (14.5) and a VIQ of 85.6 (13.9). The mean difference between VIQ and PIQ was 5.3 (SD 11.6).

3.2. Mental flexibility

On multivariate level, MANCOVA showed no significant main effect of FSIQ on performance in the WCST, $F(6,124) = 1.4$, $p = 0.20$. In support of our hypothesis, a significant main effect of group on performance in the WCST was present, $F(5,125) = 2.1$, $p = 0.03$. The tests of specific between subject effects showed that, central to our aim, the mean number of perseverative errors was higher in the KS group as compared to the control group, $F(1,128) = 5.4$, $p = 0.02$. As a consequence, the mean number of items (cards) in the KS group was higher as compared to the control group, $F(1,129) = 6.8$, $p = 0.01$. Group comparisons on other WCST parameters were not significant. Data are presented in Table 1.

Comparison of performance in the prenatal follow-up group versus the referred group did not produce significant main multivariate effects. Results did show a main multivariate effect of age

Table 1
Means and standard deviations for WCST parameters in the Klinefelter group and control group.

	Klinefelter (mean, SD)	Control (mean, SD)	*p* values	Effect size (Cohen's *d*)
Categories completed	4.7 (1.9)	4.9 (1.8)	0.62	0.10
Total number of items	105.4 (23.0)	93.5 (23.4)	0.01*	0.51
Perseverative errors	18.6 (13.1)	12.6 (13.2)	0.02*	0.46
Non-perseverative errors	14.4 (12.3)	15.1 (13.2)	0.75	0.05

*Significant at $p < 0.05$.

($F(4,122) = 2.7$, $p = 0.03$), with better performance (irrespective of group membership) in adults than in children. However, there was no significant main multivariate interaction effect between 'age' and 'group', meaning that mental flexibility was equally affected in children and adults with KS. In order to further explore possible age effects, correlational analysis was used. This showed no significant correlation between age and number of perseverative errors, $r = 0.13$, $p = 0.26$.

Further analysis of the error types in the WCST using repeated measures analysis showed a significant interaction between group and error type (perseverative errors, non-perseverative errors), $F(1,129) = 5.3$, $p = 0.02$ (see Fig. 1). In other words, the KS group showed specific problems in mental flexibility (expressed in perseverative errors), independent of overall performance on the WCST and independent of (estimated) intellectual functioning.

In order to assess possible effects of testosterone supplements on performance in the WCST, a within-group analysis was performed, i.e. comparing KS individuals with (+) and without (−) testosterone supplements. ANOVA showed no significant effects of testosterone supplements on 'number of categories completed' ($F(1,69) = 3.0$, $p = 0.08$), 'total number of items' ($F(1,69) = 0.5$, $p = 0.47$), 'perseverative errors'($F(1,69) = 0.2$, $p = 0.63$) and 'non-perseverative errors' ($F(1,69) = 2.3$, $p = 0.13$) (Table 2).

3.3. Autism traits

ANOVA showed a significant main effect of 'group', $F(1,128) = 77.5$, $p < 0.001$. Mean total AQ score was significantly higher in the KS group (23.4, SD 6.5) as compared to controls (13.3, SD 5.9). There was no significant main effect of age ($F(1,128) = 1.7$, $p = 0.18$) and no significant group by age interaction ($F(1,128) = 0.6$, $p = 0.42$).

The effect size for total AQ score was 1.6, which is a large effect size. Based on total AQ score, 39.4% of the boys and men with KS scored above cut-off for Asperger in a clinical population (>26), and 8.5% scored above the cut-off for high functioning autism/Asperger

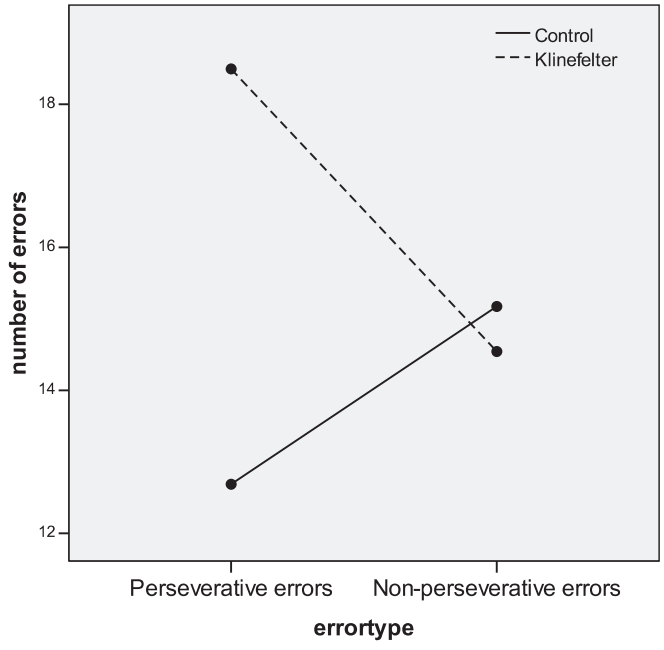

Fig. 1. A significant group by error type interaction (covaried for intellectual functioning) was found, indicating that on average, the Klinefelter group showed a disproportional amount of perseverative errors.

Table 2
Means and standard deviations for WCST parameters in those with (+) and without (−) testosterone supplements in the Klinefelter group.

	Testosterone+ ($n = 42$)	Testosterone− ($n = 29$)	Statistics
Categories completed	103.0 (24.4)	112.5 (19.5)	$F(1,69) = 3.0$, $p = 0.08$
Total number of items	4.7 (1.6)	4.4 (1.9)	$F(1,69) = 0.5$, $p = 0.47$
Perseverative errors	19.9 (16.5)	18.3 (11.9)	$F(1,69) = 0.2$, $p = 0.63$
Non-perseverative errors	14.4 (13.4)	19.2 (12.0)	$F(1,69) = 2.3$, $p = 0.13$

syndrome in the general population (>32). For information with regard to specific autism traits in children and adults with KS, we like to refer to previous studies from our group (Bruining et al., 2010; van Rijn et al., 2008).

In order to assess possible effects of testosterone supplements on level of autistic traits, a within-group analysis was performed, i.e. comparing KS individuals with (+) and without (−) testosterone supplements. ANOVA showed no significant effect of testosterone supplements on total AQ score, $F(1,69) = 0.03$, $p = 0.85$.

3.4. Relation between mental flexibility and autism traits

In order to assess the relation between problems in mental flexibility and autism traits in KS, the number of perseverative errors was correlated with total AQ score in the Klinefelter group. This analysis showed a significant correlation ($r = 0.25$, $p = 0.039$), with more perseverative errors (i.e. more mental flexibility problems) associated with higher levels of autism traits. None of the other WCST parameters showed significant correlations with total AQ score. Also, the number of perseverative errors was not significantly correlated with age, FSIQ, VIQ or PIQ. All correlations (but using estimated FSIQ scores) were separately run for the control group, with no significant results.

The relationship between autism traits and mental flexibility problems was also investigated using a categorical approach that is more closely linked to clinical practice. When the KS group was subdivided in those with a total AQ score below (KS−, $n = 43$) and above (KS+, $n = 28$) the cut-off for Asperger syndrome (>26), ANOVA showed significantly more perseverative errors in those above the cut-off (23.6, SD 16.5) as compared to those below the cut-off (16.4, SD 12.8) ($F(1,69) = 4.2$, $p = 0.04$). See Fig. 2.

4. Discussion

The present study has shown impaired executive functioning in the domain of reduced mental flexibility, in boys and men with KS as compared to nonclinical controls. The effect size was medium, indicating that KS can be associated with a considerable increased vulnerability for problems in mental flexibility. Focusing on individual differences, we found that more problems with mental flexibility in the KS group were associated with higher levels of autism traits. Based on these findings, we speculate that deficient mental flexibility may be one of the factors mediating risk for autism traits.

Although from a neurodevelopmental perspective one would expect the cognitive and behavioral phenotype in KS to present differently in childhood versus adulthood, our study did not show age effects. Moreover, although it is not yet well explored in individuals with KS, there is evidence to suggest that cognitive phenotypes might be influenced by androgen replacement in individuals with sex chromosomal abnormalities (Patwardhan et al., 2000; Ross et al., 2003; Samango-Sprouse et al., 2011). However, our study did not show differences in executive functioning or autistic traits between those who were taking or not

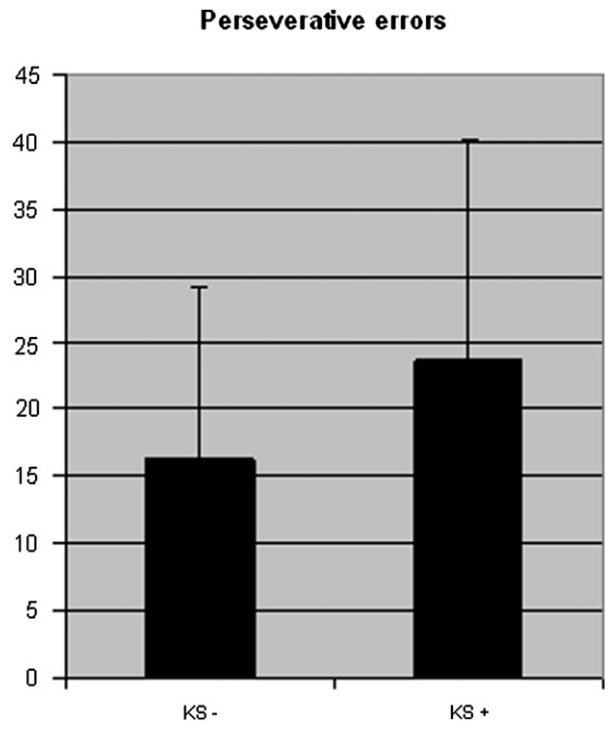

Fig. 2. The Klinefelter subgroup with high levels of autism traits (KS+) showed significantly more perseverative errors (mean, SD) in the WCST ($p < 0.001$), indicating more mental flexibility problems, as compared to the Klinefelter subgroup with lower levels of autism traits (KS−).

taking testosterone supplements. Finally, executive dysfunctioning in the KS group was found to be independent of intellectual functioning.

Although there is an increasing interest in the cognitive phenotype of individuals with KS, systematic studies on executive functioning are still fairly sparse. Focusing on mental flexibility there are a handful of studies. In their prospective follow-up study of children with X chromosome aneuploidies as compared to 25 nonclinical controls, Bender et al. (1993) assessed mental flexibility. In the 14 adolescents with XXY, performance on the Trail-making test, but not the Wisconsin Card Sorting Test (WCST), indicated reduced mental flexibility. Interestingly, the 11 girls with an extra X chromosome (XXX) also showed impaired mental flexibility based on performance on the Trail-making test as well as the WCST. Although speculative, similar deficits in XXY and XXX would fit with the idea that the extra X chromosome impacts brain development leading to deficient executive functioning. This hypothesis, however, requires further investigation.

Recently, Lee et al. (2011) assessed executive functioning in 27 children and young adults with XXY as compared to 27 nonclinical controls. They found an overall impairment in executive functioning, among which reduced mental flexibility as measured with the Trail-making test. Effect sizes for mental flexibility were medium (0.40) to large (0.84), depending on whether the XXY group was compared to a verbally matched control group or a control group matched on socio-economic status (respectively). In a previous study from our department we also found evidence for impaired mental flexibility in 24 adults with XXY (all postnatally diagnosed) as compared to a nonclinical control group, using a set-shifting task from the ANT test battery (Van Rijn et al., 2009). Using the same paradigm, mental flexibility deficits were found in 44 boys with XXY (Swaab et al., in press), half of whom were actively followed up after prenatal diagnosis and half were referred cases that were postnatally diagnosed. In contrast, Ross et al. (2009) have not found impaired cognitive flexibility (as measured with the color-word inference test) in a sample of 62 boys aged 4 to 18 (no controls), who were referred to a pediatric endocrinology clinic after postnatal diagnosis of KS. Boone et al. (2001) also did not find cognitive flexibility problems, using the WCST, in 35 adults referred for endocrinological assessment and management of hypogonadism and/or infertility.

One factor that may help in understanding these contradictory findings may be that the individual differences in executive functioning problems are large within the KS population, with some largely unaffected and some severely affected, and hence are more difficult to systematically detect in groupwise comparisons, especially when group sizes are small. Variance in phenotypic outcome is to be expected with a genetic disorder such as KS. The extra X chromosome is only one of many genetic and environmental factors influencing neurodevelopment. Variance in phenotype may not be specific for KS, as large individual differences in executive functioning have also been noted for individuals with autism. Focusing on these individual differences is important, not only for the unraveling of neurodevelopmental factors (genetic, neurobiological, hormonal or environmental) that contribute to such deficits, but also for the understanding and prediction of at risk pathways, which is important for early diagnosis and preventive intervention.

Our findings suggest that, on average, KS can be associated with dysfunctions in mental flexibility, and that individuals with more mental flexibility problems also have more autism traits. Similarly, KS boys and men scoring above the cut-off score for Asperger on the Autism-spectrum Quotient had significantly more problems in mental flexibility as compared to those below the cut-off. Thus, mental flexibility problems may be one of the risk factors predisposing individuals with KS to autistic features. Interestingly, there is evidence to suggest that executive dysfunctions in KS may predispose to other types of psychopathology as well. Recently, Lee et al. (2011) assessed the relation between executive functioning and vulnerability for ADHD (Attention Deficit Hyperactivity Disorder) in boys and young adults with KS. The subgroup with levels of ADHD traits to a degree that diagnostic criteria were met could be dissociated from the subgroup without diagnosis of ADHD based on degree of executive functioning deficits. Hence, impaired executive functioning in KS may predispose to ADHD traits as well. Another line of research has shown that executive dysfunctioning in KS may be related to level of schizotypal traits (Van Rijn et al., 2009). Adults with high levels of schizotypal traits, more specifically disorganized schizotypy, were characterized by more problems in mental flexibility and inhibition as compared to those with low levels of schizotypy and non-clinical controls. In sum, deficits in executive functioning in KS may help explain increased social difficulties and may predispose to features from the autism, ADHD and schizotypal spectrum. It would be interesting to disentangle in future studies if there are specific executive dysfunctions that contribute to specific types of psychopathology within the KS population. It would be even more interesting to assess whether specific executive functions contribute to several types of psychopathology, indicating that this could be a shared mechanism contributing to overlap in symptoms and comorbidity between different psychiatric conditions. For example, there has recently been an increased interest in the overlap between autism and schizophrenia. Similarly, overlap between autism and ADHD has also been center of debate (Gargaro et al., 2011). Studying KS may prove to be an avenue of research that may create new insights in understanding such unique or shared pathways in the psychopathophysiology of various neurodevelopmental disorders.

Such unique or shared pathways may obviously not only include executive dysfunctioning, but also supporting underlying neural circuitries, particularly the frontal lobes. As the frontal regions in the brain are the last to reach maturity, skills mediated by these regions such as executive functions are considered to be most vulnerable for developmental disruptions including stress, trauma, hormonal or genetic abnormalities (Anderson, 2001; Zelazo and Muller, 2002). Indeed, executive functions are typically impaired in patients with acquired damage to the frontal lobes (Demakis, 2003) and found in several neurodevelopmental disorders that involve frontal lobe abnormalities, including ADHD, autism and schizophrenia (Eisenberg and Berman, 2010; Ozonoff and Jensen, 1999; Pennington and Ozonoff, 1996). Also in KS, frontal lobe abnormalities have been reported (Lenroot et al., 2009; Steinman et al., 2009). These studies have exclusively focused on anatomical characteristics however, so far there have been no functional neuroimaging studies on executive functioning in KS. We feel the evidence for executive dysfunctioning in KS not only warrants studies focusing on the impact on risk for psychopathology, but also calls for a search into the underlying neural mechanisms using functional neuroimaging studies.

It should be noted that the present study has several limitations. This study did, unfortunately, not allow thorough investigation of the effect of testosterone deficiency or testosterone treatment on executive functioning. Longitudinal studies are needed in order to examine the impact of testosterone replacement therapy on cognition, including executive functioning, in KS. Such designs would also allow for further study of developmental effects in executive functioning problems, which is particularly interesting considering the ongoing development of the frontal cortex into early adulthood. Second, children and adults with KS were recruited using mixed strategies, as diagnosis resulted from prenatal screening as well as following developmental, endocrinological or infertility problems. This may have introduced bias in our findings. However, as also argued by Tartaglia et al. (2010), including only those diagnosed through prenatal screening may also result in a bias, as prenatal diagnosis may result in increased awareness and treatment of developmental problems, leading to improved outcomes. They concluded that this 'argues for inclusion of both prenatally and postnatally diagnosed participants to capture the complete spectrum of XXY.' In support of this, we would like to add that in our study the 'referred' group and the 'prenatal follow-up' group were similar in executive functioning skills. Hence, we feel that the observed group effects are not driven by a subgroup of more severely affected individuals.

All in all, the present findings stress the significance of studying executive functioning in KS, particularly in relation to vulnerability for social difficulties and related autistic features. Executive dysfunctioning may however convey risk for other types of psychopathology as well, including ADHD and schizotypy, which merely illustrates the impact and thus importance of executive functioning in individuals with KS. Obviously, investigation of such developmental risks is important for diagnosis, prevention and treatment of severe problems in individuals with KS. However, studying vulnerability for psychopathology and identifying cognitive mechanisms involved may also provide insights into mechanisms of neurodevelopment that extend beyond this specific genetic disorder.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Contributors

Sophie van Rijn participated in organizing, designing and executing the study, analyzing the data, writing all drafts of the manuscript, including the final version.

Marit Bierman participated in organizing and executing the study and writing/approval of the manuscript.

Hilgo Bruining participated in conceptualization and writing/approving of the manuscript.

Hanna Swaab participated in organizing, designing and executing the study, inclusion of participants and revising/approving the final version of the manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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References

Anderson V. Assessing executive functions in children: biological, psychological, and developmental considerations. Pediatric Rehabilitation 2001;4:119–36.
Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. Journal of Autism and Developmental Disorders 2001;31:5–17.
Beauchamp MH, Anderson V. SOCIAL: an integrative framework for the development of social skills. Psychological Bulletin 2010;136:39–64.
Bender BG, Linden MG, Robinson A. Neuropsychological impairment in 42 adolescents with sex-chromosome abnormalities. American Journal of Medical Genetics 1993;48:169–73.
Bishop DV, Jacobs PA, Lachlan K, Wellesley D, Barnicoat A, Boyd PA, et al. Autism, language and communication in children with sex chromosome trisomies. Archives of Disease in Childhood 2011;10:954–9.
Bojesen A, Juul S, Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. Journal of Clinical Endocrinology and Metabolism 2003;88:622–6.
Boone KB, Swerdloff RS, Miller BL, Geschwind DH, Razani J, Lee A, et al. Neuropsychological profiles of adults with Klinefelter syndrome. Journal of the International Neuropsychological Society 2001;7:446–56.
Bruining H, de Sonneville L, Swaab H, de Jonge M, Kas M, van Engeland H, et al. Dissecting the clinical heterogeneity of autism spectrum disorders through defined genotypes. PLoS One 2010;5:7.
Bruining H, Swaab H, Kas M, Van Engeland H. Psychiatric characteristics in a self-selected sample of boys with Klinefelter syndrome. Pediatrics 2009;123:e865–70.
Campbell JM. Internal and external validity of seven Wechsler Intelligence Scale for Children – third edition short forms in a sample of psychiatric inpatients. Psychological Assessment 1998;10:431–4.
Demakis GJ. A meta-analytic review of the sensitivity of the Wisconsin Card Sorting Test to frontal and lateralized frontal brain damage. Neuropsychology 2003;17:255–64.
Eisenberg DP, Berman KF. Executive function, neural circuitry, and genetic mechanisms in schizophrenia. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 2010;35:258–77.
Gargaro BA, Rinehart NJ, Bradshaw JL, Tonge BJ, Sheppard DM. Autism and ADHD: how far have we come in the comorbidity debate? Neuroscience & Biobehavioral Reviews 2011;35:1081–8.
Geschwind DH, Dykens E. Neurobehavioral and psychosocial issues in Klinefelter syndrome. Learning Disabilities Research & Practice 2004;19:166–73.
HerreraGraf M, Dipert ZJ, Hinton RN. Exploring the effective use of the vocabulary/block design short form with a special school population. Educational and Psychological Measurement 1996;56:522–8.
Hill EL. Evaluating the theory of executive dysfunction in autism. Developmental Review 2004;24:189–233.
Kort W, Schittekatte M, Dekker PH, Verhaeghe P, Compaan EL, Bosmans M, et al. WISC-III NL Wechsler intelligence for children (David Wechsler). 3rd ed. Amsterdam: Harcourt Test Publishers; 2005. Dutch version. Manual.
Lanfranco F, Kamischke A, Zitzmann M, Nieschlag PE. Klinefelter's syndrome. The Lancet 2004;364:273–83.
Lee NR, Wallace GL, Clasen LS, Lenroot RK, Blumenthal JD, White SL, et al. Executive function in young males with Klinefelter (XXY) syndrome with and without

comorbid attention-deficit/hyperactivity disorder. Journal of the International Neuropsychological Society 2011;17:522–30.
Lenroot RK, Lee NR, Giedd JN. Effects of sex chromosome aneuploidies on brain development: evidence from neuroimaging studies. Developmental Disabilities Research Reviews 2009;15:318–27.
Lezak M, Howieson DB, Loring DW. Neuropsychological assessment. 4th ed. New York: Oxford University Press; 2004.
Ozonoff S, Jensen J. Brief report: specific executive function profiles in three neurodevelopmental disorders. Journal of Autism and Developmental Disorders 1999;29:171–7.
Patwardhan AJ, Eliez S, Bender B, Linden MG, Reiss AL. Brain morphology in Klinefelter syndrome: extra X chromosome and testosterone supplementation. Neurology 2000;54:2218–23.
Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. Journal of Child Psychology and Psychiatry and Allied Disciplines 1996;37:51–87.
Posner MI, Petersen SE. The attention system of the human brain. Annual Review of Neuroscience 1990;13:25–42.
Ratcliffe S. Long-term outcome in children of sex chromosome abnormalities. Archives of Disease in Childhood 1999;80:192–5.
Ross JL, Roeltgen D, Stefanatos GA, Feuillan P, Kushner H, Bondy C, et al. Androgen-responsive aspects of cognition in girls with Turner syndrome. Journal of Clinical Endocrinology and Metabolism 2003;88:292–6.
Ross JL, Zeger MPD, Kushner H, Zinn AR, Roeltgen DP. An extra X or Y chromosome: contrasting the cognitive and motor phenotypes in childhood in boys with 47, XYY syndrome or 47, XXY Klinefelter syndrome. Developmental Disabilities Research Reviews 2009;15:309–17.
Samango-Sprouse CA, Gropman AL, Sadeghin T, Kingery M, Lutz-Armstrong M, Rogol AD. Effects of short-course androgen therapy on the neurodevelopmental profile of infants and children with 49, XXXXY syndrome. Acta Paediatrica 2011;100:861–5.
Scourfield J, Martin N, Lewis G, McGuffin P. Heritability of social cognitive skills in children and adolescents. British Journal of Psychiatry 1999;175:559–64.
Steinman K, Ross J, Lai S, Reiss A, Hoeft F. Structural and functional neuroimaging in Klinefelter (47, XXY) syndrome: a review of the literature and preliminary results from a functional magnetic resonance imaging study of language. Developmental Disabilities Research Reviews 2009;15:295–308.
Stuss DT. Functions of the frontal lobes: relation to executive functions. Journal of the International Neuropsychological Society 2011;17:759–65.
Swaab H, Bruining H, Bierman M, Van Rijn S, van Engeland H, & De Sonneville L. Executive function deficits in Klinefelter boys, explaining high risk for developmental psychopathology? in press.
Tartaglia N, Cordeiro L, Howell S, Wilson R, Janusz J. The spectrum of the behavioral phenotype in boys and adolescents 47, XXY (Klinefelter syndrome). Pediatric Endocrinology Reviews 2010;8(Suppl. 1):151–9.
Van Rijn S, Aleman A, De Sonneville L, Swaab H. Cognitive mechanisms underlying disorganization of thought in a genetic syndrome (47, XXY). Schizophrenia Research 2009;112:91–8.
Van Rijn S, Swaab H, Aleman A, Kahn RS. X Chromosomal effects on social cognitive processing and emotion regulation: a study with Klinefelter men (47, XXY). Schizophrenia Research 2006;84:194–203.
van Rijn S, Swaab H, Aleman A, Kahn RS. Social behavior and autism traits in a sex chromosomal disorder: Klinefelter (47XXY) syndrome. Journal of Autism and Developmental Disorders 2008;38:1634–41.
Visootsak J, Graham Jr JM. Social function in multiple X and Y chromosome disorders: XXY, XYY, XXYY, XXXY. Developmental Disabilities Research Reviews 2009;15:328–32.
Wechsler D. Wechsler intelligence scale for children-third edition (WISC III). San Antonio, TX, USA: The Psychological Corporation; 1991.
Wechsler D. Wechsler adult intelligence scale-third edition (WAIS-III). San Antonio, TX, USA: The Psychological Corporation; 1997.
Wechsler D. WAIS-III NL. Wechsler adult intelligence scale WAIS-III. 3rd ed. Amsterdam: Harcourt Test Publishers; 2005. Dutch version. Manual.
Zechner U, Wilda M, Kehrer-Sawatzki H, Vogel W, Fundele R, Hameister H. A high density of X-linked genes for general cognitive ability: a run-away process shaping human evolution? Trends in Genetics 2001;17:697–701.
Zelazo PD, Muller U. Executive function in typical and atypical development. In: Goswami U, editor. Handbook of childhood cognitive development. Oxford: Blackwell; 2002.
Zijlstra R, Bierman M, Swaab H, Van Rijn S. Role of the X chromosome in social behavioural dysfunction and autism-like behaviour. European Psychiatric Review 2010;3:47–50.