VULNERABILITY FOR AUTISTIC TRAITS IN BOYS WITH KLINEFELTER SYNDROME (47, XXY):

THE ROLE OF EXECUTIVE FUNCTIONING AND THEORY OF MIND

Vulnerability for autistic traits in boys with Klinefelter syndrome (47, XXY):
The role of executive functioning and Theory of Mind

Andrea Spruijt
University of Leiden
Faculty of Social and Behavioral Sciences
Under supervision of Dr. S. van Rijn

Abstract

One of the dysfunctions associated with Klinefelter syndrome (KS) (47,XXY) are difficulties in social functioning, which may arise as a consequence of executive functioning (EF) and Theory of Mind (ToM) deficits. In this study, the influence of EF on ToM skills in KS boys was examined, as well as how these skills relate to autistic features. ASD traits were assessed with the parent-report Autism-Spectrum Quotient. ToM skills were measured with the Social Cognitive Skills Test. EF skills were measured with the Clinical Evaluation of Language Fundamentals and Amsterdam Neuropsychological Tasks. 28 KS boys (Mage=13.2, *SD*=3.0) participated in this study, along with 45 ASD boys (Mage=11.9, *SD*=2.0) and 46 boys from the general population (Mage=12.2, *SD*=2.9) as control groups. KS boys showed substantially elevated levels of ASD traits compared to the general population, but lower levels than ASD boys. In addition, difficulties regarding ToM and cognitive flexibility were more prominent in KS boys than in ASD boys compared to the general population. ToM task performance could partly be explained by spatial WM and attention switching (as autistic trait) could partly be explained by ToM skills in KS boys. The current study highlights the importance of attention modulation skills and ToM skills in social functioning of individuals with KS, providing promising insights regarding prevention and intervention. Future studies should focus on the effectiveness of enhancing EF skills in KS boys and the role of the X chromosome in vulnerability for autistic traits.

Introduction

Upon studying neurodevelopmental dysfunctions associated with specific genetic syndromes, much knowledge can be gained about neurodevelopmental pathways in behavioral and cognitive disorders in the general population (Reiss et al., 2000). Furthermore, gaining insight in the aetiological mechanisms of these dysfunctions provides a powerful tool for diagnosing, preventing and treating individuals with specific genetic syndromes (Van Rijn & Swaab, 2011). One of the genetic syndromes that have been studied in order to investigate the human gene-brain-behavior linkages is Klinefelter syndrome (47, XXY), characterized by the presence of an additional X chromosome in boys and men. This genetic syndrome is considered to be one of specific interest, as the X chromosome contains a considerable amount of genes involved in neural development (Van Rijn & Swaab, 2011).

One of the dysfunctions associated with Klinefelter syndrome are the difficulties these individuals experience in social functioning (Geschwind et al., 2000). In males with Klinefelter syndrome, specific social functioning profiles have been found (Visootsak & Graham, 2009). For instance, males with Klinefelter syndrome have been described to have a high rate of early language delays, which may lead to deficits in social interactions (Ross et al., 2008; Leggett et al., 2010). In addition, males with Klinefelter syndrome may come to face with low self-esteem due to their physical stigma and vulnerability to bullying, which may contribute to impairments in social interactions (Visootsak et al., 2001). Furthermore, problems with emotional development seem to be of interest with regard to social functioning in these individuals, whereas both delayed emotional development and misperception of emotion recognition have been described (Robinson et al., 1979; Van Rijn et al., 2006). These specific deficits may result in the socially inappropriate behavior as well as the anti-social behavior that has been described in individuals with Klinefelter syndrome (Gotz et al., 1999; Ratcliffe, 1999).

Furthermore, these difficulties in social functioning might put Klinefelter men at risk of developing psychiatric disorders such as autism. Autism is a heterogeneous syndrome defined by impairments in three core domains: social interaction, language and range of interests (Bruining et al., 2010). Indeed, increased levels of autism traits have repeatedly been found in individuals with Klinefelter syndrome and consequently a vulnerability to autism spectrum disorder has been reported (Tartaglia et al., 2010; Van Rijn et al., 2008; Visootsak & Graham, 2009; Bishop et al., 2011; Van Rijn & Swaab, 2011; Cordeiro et al., 2012). These findings raise the question whether this autistic phenotype in Klinefelter men can be explained by similar underlying neurodevelopmental pathways as identified in the

overall autism spectrum disorder population, in the light of prevention and intervention of social functioning difficulties.

One of these aetiological mechanisms of social behavioral functioning that have been suggested in individuals with Klinefelter syndrome are difficulties with social cognitive processing. For instance, MRI studies have shown structural abnormalities in brain regions associated with social cognition and emotion, such as volume reductions in the insula, amygdala, anterior cingulate and superior temporal gyrus (Shen et al., 2004; Van Rijn et al., 2005). Interestingly, autism spectrum disorder has repeatedly been associated with social cognitive processing dysfunctions, along with structural abnormalities in brain regions associated with social cognitive processing such as the amygdala (Henderson et al., 2009; Schultz, 2005). These findings might indicate similar underlying mechanisms of social behavioral functioning in the autism spectrum population and the Klinefelter population.

In individuals with autism spectrum disorder, one of the key social cognitive impairments is the inability to attribute beliefs, feelings, desires and intentions to self and to others, known as Theory of Mind (ToM) (Premack & Woodruff, 1978). Logically, these skills are essential for social interactions and are thus considered as one of the underlying mechanisms of difficulties in social functioning in the autism spectrum population. A vast amount of research encourages this notion, claiming the relative specificity and uniqueness of Theory of Mind deficits in the autism spectrum population (e.g. Baron-Cohen, 1989). Nonetheless, while research has repeatedly linked autism spectrum disorder with problems considering Theory of Mind, there is an extensive lack of knowledge considering the characteristics of Theory of Mind within the Klinefelter population (Yirmiya et al., 1998).

However, in all studies that have been conducted, some children with autism spectrum disorder are able to pass Theory of Mind tasks, while children with different disorders fail to complete these tasks (Joseph & Tager-Flusberg, 2004). These findings challenge the specificity and uniqueness of Theory of Mind deficits in the autism spectrum population and consequently raise the question why some children are able to complete Theory of Mind tasks, despite of their autistic traits and hence social difficulties (assumed Theory of Mind impairments). One explanation for these surprising findings appears to be the difference in approach of autistic and non-autistic children when addressing Theory of Mind tasks. While the performance of non-autistic children primarily reflects intuitive social insights into people, autistic children appear to approach the tasks more as logical-reasoning problems and thus tend to rely more on non-social cognitive processes instead of social insight (Joseph & Tager-Flusberg, 2004). More specifically, executive functions appear to be of account when considering Theory of Mind task performance, whereas these functions

have been found to be significantly related to performance on these tasks in both typically developing children and children with autism spectrum disorder (Joseph & Tager-Flusberg, 2004; Pellicano, 2007; Fisher & Happé, 2005). Consequently, executive functions can be considered crucial for social interpretation and processing of social information. In addition, whereas executive functioning and Theory of Mind skills have been found to be significantly inversely related to social problems in children with behavioral problems, it can be hypothesized that executive functioning and Theory of Mind skills are indicators of metacognitive deficits that underlie social problems in individuals with autism spectrum disorder (Fahie & Symons, 2003). Since executive functions have been found to be trainable in children as young as four years of age, this hypothesis provides promising insights considering prevention and intervention of social functioning difficulties in the autism spectrum population (Diamond & Lee, 2011). Consequently, insights in executive functions and Theory of Mind skills may also be of specific interest in the Klinefelter population, especially when considering prevention and intervention of social functioning difficulties.

In line with this statement, it has been suggested that individuals with autism spectrum disorder indeed experience difficulties in executive functions, in addition to the previously described difficulties considering Theory of Mind. This would indicate that executive functions might be an underlying mechanism of the difficulties in social functioning in this population, whereas the strategy to rely on non-social cognitive processes (executive functions) instead of social insight will prove to be insufficient. However, studies aimed at investigating the relationship between autism spectrum disorder and executive functions have thus far provided the research field with inconclusive results. For instance, Williams and colleagues (2005) stated that working memory is a good predictor of Theory of Mind skills in children with autism spectrum disorder. Happé and colleagues (2006) stated that these working memory problems diminish over time, whereas several other studies concluded that working memory capacity increases, but not sufficiently (Amberry, 2006; Hill & Bird, 2006; Luna et al., 2007). Similar inconsistent results were found considering inhibition problems and cognitive inflexibility in children with autism spectrum disorder. Christ and colleagues (2007) found impaired performance of children with autism spectrum disorder on inhibitory tasks, while Sinzig and colleagues (2008) did not replicate these findings. Furthermore, Geurts and colleagues (2009) concluded that no consistent evidence for cognitive flexibilty deficits could be identified in this population, while others tend to disagree (Christ et al., 2007; Sinzig et al., 2008).

In contrast with the extensive research conducted upon executive functioning in individuals with autism spectrum disorder, studies on this topic are sparse in individuals with

Klinefelter syndrome; especially in school-aged children. Despite the sparsity of studies, contradictory findings can be identified in this population as well. For instance, Temple and Sanfilippo (2003) reported deficits on verbal inhibition, while Ross and colleagues (2008) found no differences from controls on verbal inhibition tasks. In addition, Lee and colleagues (2011) reported lower overall executive functioning in children with Klinefelter syndrome, but stated that performance did not differ significantly as a function of task, such as working memory. In contrast, Fales and colleagues (2003) concluded that verbal working memory is indeed impaired in individuals with Klinefelter syndrome. Nonetheless, whereas previous studies have shown more significant executive functioning difficulties upon tasks with pronounced verbal demands, it seems crucial to include non-verbal tasks before drawing conclusions (DeLisi et al., 2005; Fales et al., 2003; Boone et al., 2000). These findings raise more questions than answers, calling for extensive research on this topic.

Whereas the physical features of males with Klinefelter syndrome is often subtle and may only become apparent postpubertally, it is of the utmost importance that their social cognitive phenotype is identified in order to prompt chromosomal testing (Visootsak & Graham, 2009). More specifically, insights in the underlying neurodevelopmental mechanisms of social functioning in males with Klinefelter syndrome are crucial in light of prevention and intervention of social functioning difficulties in this population. The current study addresses these questions by examining the influence of executive functions on Theory of Mind skills in boys with Klinefelter syndrome. In addition, it will be examined how these skills relate to daily social functioning and, in particular, autistic features. Furthermore, severity of deficits in the Klinefelter population will be investigated by comparison with typically developing boys and with the autism spectrum disorder population. In order to do so, the following research questions will be explored.

Research question 1
To what extent do boys with Klinefelter syndrome exhibit autistic features compared to typically developing boys? If so, what is the degree of severity of autistic features compared to boys with autism spectrum disorder?

Research question 2
To what extent do boys with Klinefelter syndrome experience problems with Theory of Mind compared to typically developing boys? If so, what is the degree of severity of Theory of Mind problems compared to boys with autism spectrum disorder?

Research question 3
To what extent do boys with Klinefelter syndrome experience problems with executive functioning compared to typically developing boys? If so, what is the degree of severity of executive functioning problems compared to boys with autism spectrum disorder?

Research question 4
To what extent can Theory of Mind skills be explained by executive functioning in boys with Klinefelter syndrome?

Research question 5
To what extent can autistic features be explained by executive functioning and Theory of Mind skills in boys with Klinefelter syndrome?

Methods

Design

The study sample consisted of 119 participants between 8 and 19 years of age (*M*=12.3, *SD*=2.6*)*. In total, 28 boys with Klinefelter syndrome were studied (Mean age=13.2, *SD*=3.0), along with 45 boys with autism spectrum disorder (Mean age=11.9, *SD*=2.0) and 46 control boys (Mean age 12.2, *SD*=2.9). Participants with Klinefelter syndrome were recruited through paediatricians, endocrinologists, the Dutch Klinefelter Association or via active follow-up after prenatal diagnosis with the help of clinical genetics departments. Participants with autism spectrum disorder were recruited through the Dutch Autism Centre and the Ambulatorium of Leiden University. Controls from the general population were recruited through Dutch primary schools, after-school day care and Dutch secondary schools. None of the control subjects had a history of psychiatric illness. Exclusion criteria for all participants were neurological conditions or history of head injury with loss of consciousness and intellectual disability.

After complete description of the study to the subjects, written informed consent was obtained. Participants were individually administered a battery of neuropsychological tests including tests to assess working memory, inhibition, cognitive flexibility and Theory of Mind skills. The present study was part of a larger study, indicating that not all neuropsychological tests administered will be discussed. Parents of the participants were requested to complete several questionnaires concerning their child.

Measures

Intellectual ability

In order to obtain an estimate of intellectual ability of all participants, the subtests 'Block design' (estimator performance IQ) and 'Vocabulary' (estimator verbal IQ) of the Dutch

version of the WISC-III for children (Kort et al., 2005) and WAIS-III for adults (Wechsler, 2005) were administered. Performance intelligence addresses various visuospatial abilities, whereas verbal intelligence addresses verbal skills. During the subtest 'Block design' participants were asked to analyze and synthesize an abstract design and reproduce that design from colored plastic blocks. During the subtest 'Vocabulary' participants were asked to orally explain the meaning of several words. Scores obtained on these subtests were used to calculate an estimate of total intellectual ability, using the algorithm 2.9*(standard score Block design + standard score Vocabulary) + 42.

Executive Functions

Verbal working memory was assessed using the subtest 'Digit span' of the Dutch version of the Clinical Evaluation of Language Fundamentals IV (CELF-IV, Kort et al., 2008). Participants were presented with several digits in random order by the examiner, after which they were asked to recite the digits correctly by recalling them in the same order. On the second part of this subtest the participants had to remember the order in which digits were presented, but had to recite them in reverse order. Whereas the first part of this subtask is considered to measure short term memory and the second part to measure working memory, the number correct responses on part 2 (backwards) was used for working memory analyses.

Spatial working memory was assessed using the subtask 'Spatial temporal span' (STS) of the Amsterdam Neuropsychological Tasks (ANT); a computer-aided assessment battery of response time tasks that allows for the systematic evaluation of information processing capacities (De Sonneville, 1999). The reliability and internal consistency of the subtasks of the ANT are satisfactory (De Sonneville, 2005). Participants were presented with nine squares on the computer screen, of which several squares were pointed out in random order by the computer program, starting with 2 squares and increasing stepwise up to 9 squares. During part 1, participants were asked to click the squares in the same order as they were pointed out. On the second part of this subtask, participants had to remember the order in which the squares were pointed out, but had to click them in reverse order. Both parts are aborted when both trials with the same amount of squares are incorrect and contain a maximum of 16 trials. Whereas the first part of this subtask is considered to measure short term memory and the second part to measure working memory, the amount of correct responses on part 2 (backwards) was used for working memory analyses.

Inhibition was assessed using the subtask 'GoNogo' GNG) of the Amsterdam Neuropsychological Tasks (ANT). During this task, participants were presented with one square at a time on the computer screen and were asked to click when presented with a square with an opening (Go-stimulus) and not to click when presented with a closed square

(NoGo-stimulus). Of both stimuli, an equal amount of 24 targets was presented. For analyses, percentage false alarms was used to represent inhibition.

Inhibition and cognitive flexibility were assessed using the subtask 'Shifting Set Visual (SSVIS) of the Amsterdam Neuropsychological Tasks (ANT). During this task, participants were presented with a horizontal bar, consisting of ten squares, which is permanently presented in the center of the screen. In each trial, a colored square moves across the bar in a randomly varied direction. The task consists of three parts, each requiring different responses. Part 1 (40 trials) requires spatially compatible responses: participants are instructed to copy the direction of the movement of a green-colored square. Part 2 (40 trials) requires spatially incompatible responses: participants are instructed to mirror the direction of the movement of a red-colored square and should thus inhibit spatially compatible responses. In part 3 (80 trials) the color of the moving square randomly alternates between green en red, hereby making both the direction of the movements and the color changes unpredictable. When the color of the square is green after a movement, a spatially compatible response is required and when the color of the square is red after a movement, a spatially incompatible response is required, thus reflecting the cognitive ability to mentally switch between two competing and unpredictable response sets. For analyses, the amount of errors on part 2 was used to represent inhibition and the amount of errors on part 3 was used to represent cognitive flexibility.

Theory of Mind

Theory of Mind skills were measured using the Social Cognitive Skills Task (SCVT; Manen et al., 2010). The SCVT is an individually administered paper and pencil task that assesses the extent and any deficits in social cognitive functioning using seven comics relating to social situations in which a child is confronted with a problem. Per comic, participants were presented with eight questions by the examiner, corresponding with the eight subscales of the SCVT. These subscales are obtained by summing the corresponding questions per comic and cover skills associated with social cognitive functioning: identifying, discriminating, differentiating, comparing, perspective taking, relating, coordinating and discounting. The Dutch Commission Test Issues (COTAN) has evaluated the SCVT as sufficiently reliable (2009). Higher scores on the SCVT indicate higher levels of social cognitive skills.

Autistic traits

Autistic traits were measured using the Autism-spectrum Quotient (AQ; Baron-Cohen et al., 2001). The AQ is a questionnaire that assesses the degree to which an individual might have features of the autistic phenotype. In the present study the parental report version for

children was administered, consisting of fifty questions. The internal consistency and test-retest reliability of the AQ are satisfactory (Hoekstra et al., 2008). Five subscales cover personality traits associated with the autistic phenotype: social skills, communication, imagination, attention to detail and attention switching. Higher scores on the AQ indicate higher levels of autism traits.

Statistical analyses

Data were analyzed using SPSS for Mac (version 19.0; SPSS Inc., Chicago, IL, USA). The background variables ('Estimate of intellectual ability', 'Estimate of performance intelligence', 'Estimate of verbal intelligence' and 'Age') were analyzed using ANOVA. Two MANCOVA's, one for autistic traits and one for Theory of Mind skills were performed. Each had group (XXY, controls and ASD) as fixed factor, age and estimate of verbal intelligence as covariates and AQ subscales (5) or SCVT subscales (8) as dependent variables. A MANCOVA was performed to assess group differences on executive functions with group (XXY, controls and ASD) as fixed factor, age and estimate of verbal intelligence as covariates and Digit span, STS, GNG, and SSVIS scores as dependent variables. ANOVA's were used for all post hoc analyses of group effects. Level of significance was set at p=.05, two tailed. Effect sizes were calculated using Cohen's *d,* representing the difference between two means expressed in standard deviations (mean of the pooled standard deviations in the two groups).

Regression analyses were conducted with SCVT total score as dependent variable and executive functions (Digit span, STS, GNG, and SSVIS scores), age and estimate of verbal intelligence as independent variables, examining the XXY sample. Furthermore, regression analyses were conducted with all AQ subscales (5) as dependent variables and executive functions (Digit span, STS, GNG, and SSVIS scores), SCVT total score, age and estimate of verbal intelligence as independent variables, examining the XXY sample. Level of significance was set at p=.05.

Results

Preliminary data analysis

Outliers were identified using boxplots, after which outliers considerably influencing skewness and kurtosis (resulting in values higher than 3) were excluded from further analyses containing these variables. Boys with an estimate of intellectual ability below 60 were excluded from further analyses to maintain the exclusion criterium of intellectual disability. In total, 1 participant from the control group, 4 participants from the XXY group and 1 participant from the ASD group were excluded. To test for differences on the background variables 'Estimate of intellectual ability', 'Estimate of performance intelligence',

'Estimate of verbal intelligence' and 'Age' between the XXY, ASD and control group, ANOVA's and ANCOVA's were computed. Estimate of verbal intelligence differed between all groups, with exception of the ASD and control group ($F(2,113)=10.27$, $p<.001$), whereas estimate of performance intelligence did not ($F(2,113)=2.70$, $p=.07$). Estimate of intellectual ability differed between all groups, with exception of the ASD and control group ($F(2,166)=29.36$, $p < .001$), but this was no longer the case after controlling for estimate of verbal intelligence and age ($F(2,110)=2.43$, $p=.09$). Estimate of verbal intelligence and age will be taken into account during further analyses. Means and standard deviations are displayed in table 1.

Table 1
Mean intelligence score estimates in the XXY, ASD and control groups

	XXY	Control	ASD
Intellectual ability	81.8 (13.3)	101.3 (13.3)	99.5 (17.3)
Verbal intelligence	27.5 (10.4)	38.1 (8.3)	37.5 (11.4)
Performance intelligence	42.6 (10.8)	45.7 (12.1)	49.5 (13.2)

Autistic traits

For autistic traits, a multivariate effect of group was found ($F(10,186)=9.35$, $p<.001$). Univariate results indicated significant group effects at all individual subscales ($p<.05$). To assess specific group by group comparisons, post hoc ANOVA's were used. This revealed that the XXY group had significantly higher scores than the control group on the following subscales: 'Social skills' ($p<.05$, $d=1.1$), 'Attention switching' ($p<.01$, $d=1.1$) and 'Communication' ($p<.01$, $d=1.3$). In the XXY group, scores on these same subscales were significantly lower than in the ASD group ($p<.001$). The ASD group had significantly higher scores than the control group on all subscales ($p<.001$), with exception of the subscale 'Attention to details'. For means and standard deviations, see Figure 1. Covariates were non-significant and are not displayed ($p>.05$).

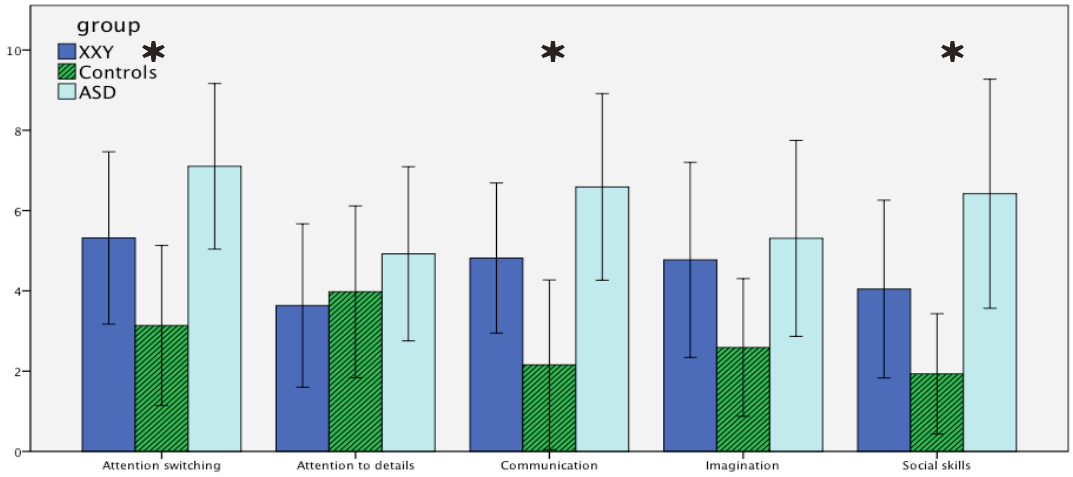

Figure 1. Means and SDs for subscales of the Autism Questionnaire in the XXY, ASD and control group. With regard to group differences, on three subscales (see *) the XXY group had significantly higher scores than the control group and lower scores than the ASD group.

Theory of Mind

For Theory of Mind skills, a multivariate effect of group was found ($F(16,192)=3.55$, $p<.001$). Univariate results indicated significant group effects on all individual subscales ($p<.05$) except for 'Discriminating' and 'Perspective taking'. To assess specific group by group comparisons, post hoc ANCOVA's were used. This revealed that the XXY group had significantly lower scores than the control group on the following subscales: 'Identifying' ($p<.03$, $d=.6$), 'Differentiating' ($p=.001$, $d=.9$), 'Comparing' ($p<.001$, $d=1.1$), 'Relating' ($p=.01$, $d=1.0$), 'Coordinating' ($p<.002$, $d=1.0$) and 'Discounting' ($p=.002$, $d=1.0$). In the XXY group, scores on the subscales 'Comparing' ($p<.001$, $d=1.1$), 'Relating' ($p<.03$, $d=1.2$) and 'Coordinating' ($p=.05$, $d=.8$) were significantly lower than in the ASD group ($p<.001$). The ASD group only showed significantly lower scores than the control group on the subscale 'Differentiating' ($p<.01$). For means and standard deviations, see Figure 2. Both covariates age ($p<.05$) and verbal intelligence ($p<.01$) were significant.

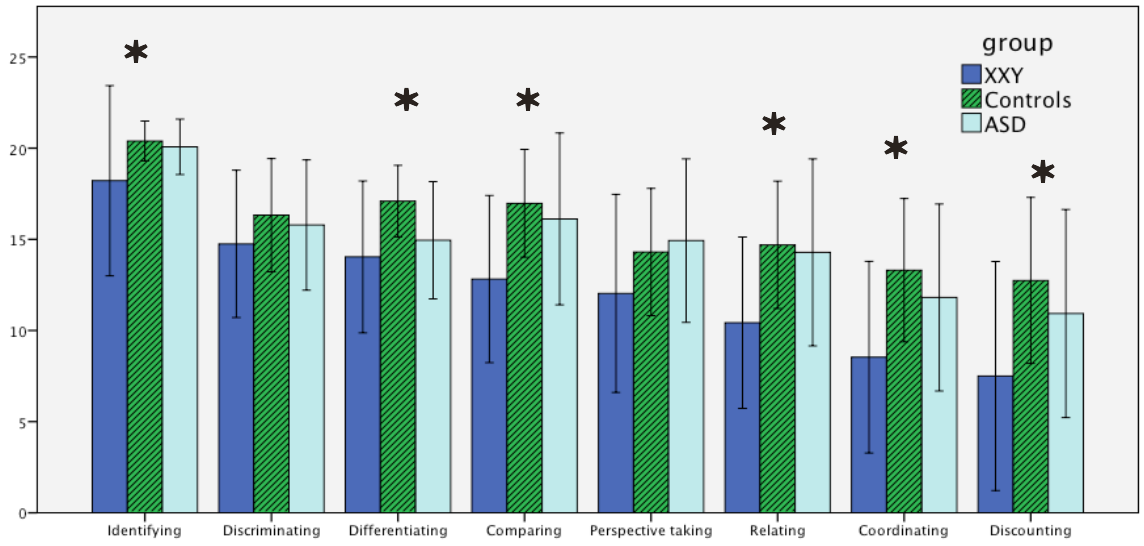

Figure 2. Means and SDs for subscales of the SCVT in the XXY, ASD and control group. With regard to group differences, on six subscales (see *) the XXY group had significantly lower scores than the control group.

Executive functions

For executive functions, a multivariate effect of group was found ($F(10,164)=2.62$, $p<.01$). Univariate results indicated a significant group effect on the subtask SSVIS, reflecting 'Cognitive flexibility' ($p=.001$). To assess specific group by group comparisons, post hoc ANCOVA's were used. This revealed that the XXY group had significantly higher scores (indicating more errors) than the control group ($p=.002$, $d=1.1$) and the ASD group ($p=.003$, $d=1.0$). The ASD group did not differ significantly from the control group ($p>.05$). For means and standard deviations, see Figure 3. Covariate age was significant ($p<.01$), whereas verbal intelligence was not ($p>.05$).

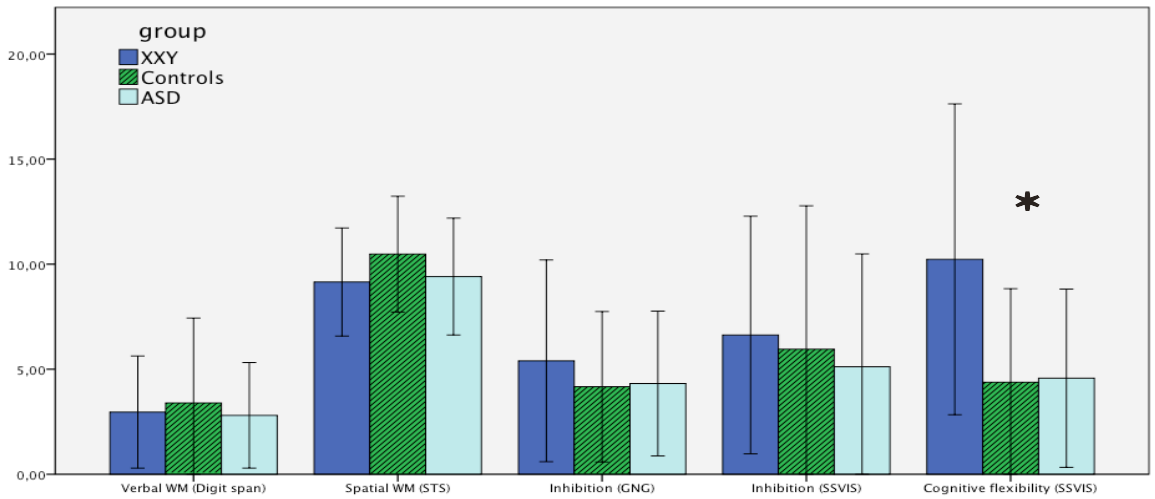

Figure 3. Means and SDs for Verbal WM (number correct Digit span), Spatial WM (number correct STS), Inhibition (% false alarms GNG), Inhibition (number errors SSVIS) and Cognitive flexibility (number errors SSVIS) in the XXY, ASD and control group. With regard to group differences, on one subscales (see *) the XXY group had significantly worse scores than the control group and ASD group.

Executive functions explaining Theory of Mind skills

Multiple regression analysis was used to examine the relation between executive functions and Theory of Mind skills in the XXY group, as displayed in table 2 (using the stepwise procedure). SCVT total score was used as dependent variable and EF subtasks, age and estimate of intellectual ability were used as independent variables. The results of the regression were significant (R^2=.59, F(2,19)=13.45, p<.001) and indicated the two predictors 'Spatial working memory' (STS) and 'Age', which explained 54.3 percent of the variance in SCVT scores. Results of this regression analysis are displayed in table 2. The remaining executive functions variables were not significantly associated with total SCVT score, nor was verbal intelligence (also see table 2).

Table 2
Results of the significant multiple regression analyses for the XXY group

Dependent variable	Independent variables	*t*	β	*p*	*B*	SE	N
SCVT	Age	3.54	.53	**<.01	4.77	1.35	22
	Spatial WM (STS)	2.98	.45	**<.01	4.81	1.62	
	Verbal WM (Digit span)	.49	.10	.63			
	Inhibition (GNG)	.83	.14	.42			
	Inhibition (SSVIS)	-.94	-.16	.36			
	Cognitive flexibility (SSVIS)	-.65	-.11	.52			
	Verbal intelligence	.65	.12	.53			
Attention switching (Subscale AQ)	SCVT	-2.68	-.55	*.02	-.05	.02	19
	Verbal WM (Digit span)	<-.01	<-.01	.99			
	Spatial WM (STS)	-.36	-.08	.72			
	Inhibition (GNG)	-.63	-.13	.54			
	Inhibition (SSVIS)	.49	.10	.63			
	Cognitive flexibility (SSVIS)	.69	.15	.50			
	Verbal intelligence	.11	.03	.91			
	Age	1.16	.30	.26			

Executive functions and Theory of Mind skills explaining autistic traits

Multiple regression analyses were used to examine the relation between executive functions, Theory of Mind skills and autistic traits in the XXY group (using the stepwise procedure). All subscales of the AQ (5) were used as dependent variables in separate analyses and SCVT total score, EF subtasks, age and estimate of verbal intelligence were used as independent variables. The results of one of the regression analyses were significant (R^2=.30, F(1,18)=7.17, p=.02) and indicated the independent variable 'SCVT' explained 26 percent of the variance in scores on the subscale 'Attention switching'. Results of this regression analysis are displayed in table 2. The AQ subscales 'Social skills' (R^2=.49, F(8,18)=1.21, p=.38), 'Attention to detail' (R^2=.35, F(8,18)=.67, p=.71), 'Communication' (R^2=.30, F(8,18)=.53, p=.81) and 'Imagination' (R^2=.65, F(8,18)=2.30, p=.11) could not be explained significantly by the independent variables.

Discussion

In this study, the influence of executive functions on Theory of Mind skills in boys with Klinefelter syndrome was examined, as well as how these skills relate to daily social functioning and in particular, autistic features.

Overall, it was found that autistic traits were more prominent in the Klinefelter group than in the control group, which was in line with the hypothesis. Furthermore, as expected, autistic traits were most prominent in the autism spectrum disorder group. Scores on social skills, attention switching and communication were higher than in the Klinefelter group and in the control group. Scores in the Klinefelter group were overall in between those of the autism spectrum disorder group and the control group, with exception of attention to details. Interestingly, difficulties regarding Theory of Mind skills were most prominent in the Klinefelter group and not in the autism spectrum disorder group. The Klinefelter group had more difficulties in identifying, differentiating, comparing, relating, coordinating and discounting perspectives of others compared to the control group and showed more problems in comparing, relating and coordinating perspectives of others than the autism spectrum disorder group. Surprisingly, the autism spectrum disorder group hardly showed any Theory of Mind impairments compared to the control group, with exception of the skill differentiating between perspectives of others. Regarding executive functions, the Klinefelter group showed more problems with cognitive flexibility as compared to the control group and the autism spectrum disorder group. Again, the autism spectrum disorder group did not show executive functioning impairments compared to the control group. In the Klinefelter group, Theory of Mind task performance could partly be

explained by spatial working memory. Furthermore, Attention switching (as autistic trait) could partly be explained by Theory of Mind task performance in this group.

To rule out any effect of age and verbal intelligence, we covaried for age and estimate of verbal intelligence in all analyses. Hence, the differences in autistic traits, Theory of Mind skills and executive functions between the Klinefelter group, the autism spectrum disorder group and the control group are independent of age and verbal intelligence.

In line with previous studies, increased levels of autism traits were found in the Klinefelter group when compared to controls (Tartaglia et al., 2010; Van Rijn et al., 2008; Visootsak & Graham, 2009; Bishop et al., 2011; Van Rijn & Swaab, 2011; Cordeiro et al., 2012). Though levels of autistic traits were not higher across all dimensions of the autism phenotype such as described by van Rijn and colleagues (2008; 2011), autistic features were above general population levels regarding social skills, attention switching and communication. This is in line with previous studies, as especially communication and social skills deficits have repeatedly been linked to Klinefelter syndrome (Tartaglia et al., 2010; Visootsak & Graham, 2009; Bishop et al., 2011; Cordeiro et al., 2012). However, upon examination of the severity of these increased levels by comparison with the autism spectrum disorder group, the Klinefelter group tended to score lower on autistic traits. An explanation for these findings might be the so-called 'broad phenotype' of autism; a concept referring to the finding that relatives of people with autism often show mild autistic traits (Bishop et al., 2004). As autism spectrum disorder is a neurodevelopmental disorder with a considerable genetic component, genes are considered to play a crucial role in the risk of developing autistic traits (e.g. Rutter, 2000; Santangelo & Tsatsanis, 2005). For instance in monozygotic twins, the likelihood of autism is greatly increased when one of the twins has autism, along with increased susceptibility to other neurodevelopmental difficulties that affect social interaction (Folstein & Rutter, 1977; Bailey et al., 1995). Though this likelihood was considerably lower in dizygotic twins, some of the co-twins of the children with autism spectrum disorder displayed increased levels of autistic traits as well. These twin studies suggest a genetic origin of the autistic traits in relatives of people with autism. Since Klinefelter syndrome is a genetic syndrome, this genetic origin might also be of consequence regarding the autistic traits as identified in this group in the current study. However, it remains unclear whether the same genetic variants as identified in relatives can be considered explanatory for the autistic traits as displayed by individuals with Klinefelter syndrome. Nonetheless, it has been hypothesized that the X chromosome may be of consequence in the risk of developing autistic traits, since other X chromosomal disorders such as Turner syndrome (X0) have repeatedly been linked to an increased risk of developing

autism spectrum disorder (Mazzocco et al., 1998; McCauley & Sybert, 2006). Furthermore, the parent of origin of the extra X chromosome has been found to influence autistic traits in individuals with Klinefelter syndrome, emphasizing the possible role of the X chromosome in the risk of developing autistic traits (De Bruin et al., 2010). Notwithstanding the promising insights of these findings, extensive research is needed to understand the specific characteristics regarding the link between the X chromosome and the development of autistic traits.

Interestingly, the opposite was found for difficulties considering Theory of Mind skills, which were far more prominent in the Klinefelter group than in the autism spectrum disorder group. In fact, the autism spectrum disorder group hardly showed any difficulties regarding Theory of Mind compared to controls, with exception of the skill differentiating between perspectives of others. This finding was surprising, whereas deficits in Theory of Mind skills have repeatedly been linked to autism spectrum disorder and are considered as one of the underlying mechanisms of difficulties in social functioning in this population (e.g. Baron-Cohen, 1989). Consequently, one would expect more severe deficits in Theory of Mind skills than identified in the current study. Nonetheless, several studies have stated that some children with autism spectrum disorder are able to pass Theory of Mind tasks, while children with different disorders fail to complete these tasks (Joseph & Tager-Flusberg, 2004). Joseph and Tager-Flusberg (2004) state that this surprising performance might be due to the difference in approach of autistic and non-autistic children when addressing Theory of Mind tasks. While the performance of non-autistic children primarily reflects intuitive social insights into people, autistic children appear to approach the tasks more as logical-reasoning problems and thus tend to rely more on non-social cognitive processes such as executive functions instead of social insight. However, the Klinefelter group did show more difficulties considering Theory of Mind skills, which would indicate that these individuals either do not or cannot rely on non-social cognitive processes such as executive functions.

Indeed, upon examination of executive functioning skills, the Klinefelter group tended to show worse performance compared to the control group and the autism spectrum disorder group, when regarding cognitive flexibility. Despite the sparsity of studies on this topic, several support the claim of lower executive functioning skills in boys with Klinefelter syndrome (Temple & Sanfilippo, 2003; Lee et al., 2011; Fales et al., 2003). More specifically, Klinefelter syndrome has been associated with dysfunctions in cognitive flexibility, in which more difficulties with cognitive flexibility were associated with higher levels of autistic traits (Van Rijn et al., 2012). Consequently, these findings would be in line with the hypothesis that individuals in the autism spectrum disorder group are able to approach Theory of Mind tasks as a logical-reasoning problem relying on non-social

cognitive processes instead of social insight, while individuals in the Klinefelter group lack sufficient executive functioning skills to rely on this same strategy. It could thus be hypothesized that the worse performance of the individuals in the Klinefelter group on Theory of Mind tasks might be explained by their worse executive functioning skills, whereas they may neither be able to rely on social insight nor on non-social cognitive processes such as executive functions.

Interestingly, Theory of Mind task performance could indeed partly be explained by executive functioning skills in boys with Klinefelter syndrome. More specifically, spatial working memory partly explained the aforementioned worse Theory of Mind skills as displayed by the individuals with Klinefelter syndrome. In line with this finding, Ozonoff and McEvoy (1994) identified similar developmental trajectories of executive functions and Theory of Mind task performance, hypothesizing that these skills may be interdependent. In correspondence to this hypothesis, Gazzalay (2011) established the relationship between early attentional modulation and working memory, indicating an influence of early processing of relevant and irrelevant stimuli on subsequent working memory performance. Considering the aforementioned findings that especially cognitive flexibility appears to be impaired in the Klinefelter group, in combination with the role of working memory skills in Theory of Mind task performance, this finding suggests a link between attentional modulation and Theory of Mind skills. Furthermore, Joseph and Tager-Flusberg (2004) emphasize the distinction between higher level cognitive aspects of Theory of Mind and more fundamental attentional components of Theory of Mind, of which the latter may be more tightly liked to social interaction deficits. Thus, executive functioning skills and especially attention modulation skills may consequently be of the utmost importance in Theory of Mind task performance in boys with Klinefelter syndrome and may be directly related to social functioning.

Consistent with this statement, Theory of Mind task performance partly explained the occurrence of autistic features in boys with Klinefelter syndrome. Intriguingly, the only autistic features that could be explained by Theory of Mind skills in boys with Klinefelter syndrome are difficulties regarding attention-switching skills. These findings emphasize the importance of attention modulation skills in social functioning difficulties with regard to boys with Klinefelter syndrome. Moreover, these findings highlight the complex and dynamic relationships among attention modulation, Theory of Mind and social functioning in these individuals, calling for more extensive research on this topic.

A topic of interest might be whether individuals with Klinefelter syndrome indeed do not or cannot rely on non-social cognitive processes such as executive functions when facing

Theory of Mind tasks and whether enhancing executive functioning skills leads to increased Theory of Mind skills. Since training executive functioning skills has previously been successful in improving Theory of Mind task performance in children with autism spectrum disorder, interventions aimed at improving these skills may also prove to be effective in individuals with Klinefelter syndrome (Fisher & Happé, 2005). Attention modulation skills appear to be of specific interest, whereas these appear to be most impaired and seem to play an important role in Theory of Mind task performance. Furthermore, the autistic traits as identified in the Klinefelter group may suggest an X chromosomal influence on the risk of developing autistic traits and thus research on this topic may provide crucial knowledge on possibly one of the aetiological mechanisms of autism spectrum disorder. Genomic imprinting seems to be of specific interest, whereas the parental origin of the X chromosome has been found to influence autistic traits in Klinefelter syndrome and may thus provide important insights in the aetiological mechanisms of both autism spectrum disorder and the autistic phenotype in Klinefelter syndrome.

Limitations for this study are that the autism spectrum disorder group was merely used as a reference group to assess severity of traits in the Klinefelter group, hampering the possibility to draw firm conclusions on the relationships between executive functions, Theory of Mind skills and social functioning in this group. Furthermore, reaction times of the executive functioning tasks were not taken into account in this study, indicating that the differences in performance may be due to differences in the ability to swiftly respond by clicking. Nonetheless, the current study describes social cognitive deficits that may have important implications for social functioning in the Klinefelter population, especially when considering prevention and intervention.

The current study provides promising insights regarding prevention and intervention of social functioning difficulties in individuals with Klinefelter syndrome. Since executive functions have been found to be trainable in children as young as four years of age, interventions aimed at improving executive functioning skills in boys with Klinefelter syndrome at a young age might be an effective strategy to reduce social functioning difficulties (Diamond & Lee, 2011). Though autistic traits were found to be less severe than in the autism spectrum disorder group, the Klinefelter group showed significantly higher levels of autistic traits than controls, requesting intervention. Equally pressing are the findings that the Klinefelter group showed significantly worse executive functioning skills and Theory of Mind skills as compared to the control and autism spectrum disorder group, suggesting intervention aimed at improving these skills is in order. However, extensive research on this topic is crucial before firm conclusions can be drawn. Nonetheless, the

current study has highlighted the importance of attention modulation skills and Theory of Mind skills in social functioning of individuals with Klinefelter syndrome, providing an opportune starting point for further research.

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