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# Cognitive mechanisms underlying disorganization of thought in a genetic syndrome (47,XXY)

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ABSTRACT

Because of the risk for development of psychopathology such as psychotic symptoms, it has been suggested that studying men with the XXY karyotype may help in the search for underlying cognitive, neural and genetic mechanisms. The aim of this study was to identify cognitive mechanisms that may contribute to disorganization of thought in XXY men.

A group of 24 XXY men and two non-clinical control groups ($N = 20$, $N = 18$) participated in the study. The level of disorganization of thought was measured using the Schizotypal Personality Questionnaire. We assessed IQ, lateralization of verbal information processing and executive functions including inhibition and mental flexibility.

XXY men with high levels of disorganization showed more severe impairments in mental flexibility and inhibition as compared to non-clinical controls and other XXY men. This subgroup also showed a stronger reduction in lateralization of verbal information processing. IQ measures did not differentiate XXY men with high versus low levels of disorganization.

These findings indicate that executive impairments in the domains of inhibition and mental flexibility might play a role in the increased vulnerability for disorganized thought in the XXY group. Reduced lateralization of verbal information processing points to non-optimal cerebral specialization in the XXY group, especially in XXY men with high levels of disorganization. This fits with deficits in brain functions most vulnerable to such maturational disruptions, i.e. executive dysfunctions. Our findings are in line with those reported for schizophrenia patients with thought disorder. We speculate that the underlying mechanisms of thought disorder probably are *deficit* specific rather than *disorder* specific.

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## 1. Introduction

Approximately 1 in 650 boys are born with the XXY chromosomal pattern, also known as Klinefelter syndrome (Bojesen et al., 2003). The presence of an additional X chromosome has been associated with effects on development. It is often found that XXY boys and men have specific cognitive difficulties in the face of relatively spared general intelligence (Geschwind et al., 2000). Recently, more attention has been focused on the mental consequences of this X chromosomal aneuploidy, driven by reports of vulnerability for schizophrenia-like symptoms and traits in men with XXY. The XXY chromosomal pattern has been associated with an increased risk (hazard ratio 4.7) for being hospitalized with a psychotic disorder (Bojesen et al., 2006) and the XXY pattern is found to be more prevalent among patients with schizophrenia as compared to the prevalence in the general population (DeLisi et al., 1994). With regard to the nature of psychotic symptoms, DeLisi et al. (2005) reported auditory hallucinations in 4 out of 11 XXY men. Furthermore, Boks et al. (2007) used the SCID to assess psychopathology in

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31 XXY men. Of these, 6 men showed psychotic symptoms, ranging from ideas of reference, paranoid delusions to visual and auditory hallucinations (among other psychotic symptoms). In a study on schizotypal traits and clinical schizophrenia symptoms in XXY adults, scores were significantly increased across all domains of the schizophrenia spectrum (van Rijn et al., 2006). Because of the risk for development of psychopathology, it has been suggested that studying XXY men may help in the search for underlying cognitive, neural and genetic mechanisms (DeLisi et al., 2005).

Previous findings with XXY adults have shown that although increased levels of schizotypal traits can be found across all domains (positive, negative, disorganization), the level of disorganization of thought and speech appears most strongly elevated (van Rijn et al., 2006). The aim of this study was to identify neuropsychological mechanisms that may contribute to disorganized thought.

It has been proposed that the pattern of cognitive strengths and weaknesses in Klinefelter syndrome may be the result of non-optimal specialization of the brain, such as reduced left–right lateralization of brain functions (Geschwind et al., 1998). Cerebral specialization, as reflected in hemispheric lateralization, results from differential rates of maturation of the two hemispheres driven by a variety of genetic, prenatal and perinatal environmental influences (Hellige, 2001). There is evidence to suggest that not only the pattern of cognitive strengths and weaknesses, but also the presence of psychopathology may be related to non-optimal specialization in the brain. In a recent functional neuroimaging study, reduced language lateralization was highly correlated with the degree of disorganized thought in adults with XXY (van Rijn et al., 2008a).

Based on studies indicating non-optimal specialization of the brain in Klinefelter syndrome, we investigated specific neuropsychological functions that are generally thought to be most affected by non-optimal maturation. As the prefrontal 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 or genetic abnormalities (Anderson, 2001; Zelazo and Muller, 2002). In complex and dynamic environments, executive functions allow us to flexibly shift our mind set in response to changing demands, inhibit inappropriate or irrelevant thoughts and actions, and organize our thoughts and actions in a goal-directed way (Anderson, 2001). Deficits in cognitive inhibition and mental flexibility (set-shifting) may result in deregulation of thought and hence constitute potential cognitive mechanisms underlying symptoms of disorganization in XXY.

The phenotype of Klinefelter syndrome seems to show variability and although the risk for psychotic traits is increased, not all XXY men display severe psychopathology (Bojesen et al., 2006; Boks et al., 2007; DeLisi et al., 2005). Therefore, it may be possible to identify subtypes in the XXY population, which may help to gain insight in pathways to different phenotypical outcomes in Klinefelter syndrome. Knowledge of subtypes in phenotypical expression may not only be used to identify the underlying mechanisms contributing to increased risk for psychopathology, but also to guide the search for contributing genetic factors in future studies.

In sum, in the present study we tested the hypothesis that in contrast to XXY men with relatively low levels of disorganization, XXY men with high levels of disorganization have deficits in executive functioning, i.e. inhibition and mental flexibility, along with reduced lateralization of information processing.

## 2. Materials and methods

### 2.1. Subjects

24 XXY men participated in the study. The present study was part of a large study on cognition and psychopathology in Klinefelter syndrome at our department. Information regarding recruitment, in/exclusion criteria and diagnosis have been described in earlier reports (for example, van Rijn et al., 2006, 2008a). There was an overlap between the present subsample XXY men and the population XXY men reported on in these earlier studies: there was 79% overlap with the study on schizophrenia spectrum psychopathology (van Rijn et al., 2006) and 33% overlap with the study on the fMRI language lateralization and disorganized traits (van Rijn et al., 2008a). In this study, twenty-one men in the XXY group used testosterone supplements. Comorbid psychopathology was screened for using the Mini International Neuropsychiatric Interview-Plus (MINI-plus, Sheehan et al., 1994). The MINI-plus has been designed as a brief structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. It has good psychometric properties, i.e. good reliability and validity, and can be used to screen for subthreshold psychotic disorders. Life-time diagnoses in the XXY group are presented as online supplementary material. Because the present study was part of a larger study in which several non-clinical control groups have been included, there was one control group (control group I) for the lateralization task en another (control group II) for the executive tasks. The control groups were recruited using advertisements in local newspapers. Screening with MINI-plus showed that none of the control subjects met criteria for a psychiatric disorder. There were no significant group differences in age and mean level of education between clinical and control groups, see Table 1.

Left handedness was an exclusion criterion and all participants were right-handed. The research was approved by the ethical committee of the University Medical Center Utrecht and was in accordance with the declaration of Helsinki.

### 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. The MINI-plus was also administered at the department of Psychiatry, and the interview was conducted by a trained and qualified clinical rater.

### 2.3. Handedness

Handedness was measured using the Edinburgh Handedness Inventory (Oldfield, 1971). Handedness scores can range from −24 indicating complete left handedness, to +24 indicating complete right handedness.

**Table 1**
Characteristics (means, SD's) of the subgroups and statistical results of between group comparisons.

| | XXY− (N = 12) | XXY+ (N = 12) | Control I (N = 18) | Control II (N = 20) | p−value | Post-hoc tests |
|---|---|---|---|---|---|---|
| Handedness | 20.5 (4.3) | 19.4 (5.7) | 22.1 (2.3) | 20.1 (4.3) | 0.21 | n.s. |
| Age | 43.3 (6.1) | 38.8 (11.6) | 40.1 (13.8) | 35.7 (8.5) | 0.25 | n.s. |
| Raven APM | 9.6 (2.0) | 10.0 (1.6) | 10.1 (1.7) | 9.6 (1.5) | 0.18 | n.s. |
| NART | 41.8 (4.9) | 40.5 (5.3) | 43.5 (2.7) | 43.8 (4.6) | 0.78 | n.s. |
| Level of education | 8.9 (2.1) | 8.3 (2.5) | 9.8 (0.9) | 9.1 (1.8) | 0.14 | n.s. |
| SPQ disorganization | 5.4 (3.1) | 12.4 (2.9) | 3.1 (3.7) | 2.2 (2.4) | <0.001 | XXY+ > controls* XXY+ > XXY−* XXY− > controls* |

(Raven APM: Raven Advanced Progressive Matrices, NART: National Adult Reading Test, n.s.: not significant, *$p<0.01$).

### 2.4. Intellectual functioning

The Raven's Advanced Progressive Matrices (APM-short form) (Raven et al., 1993) and the National Adult Reading Test (NART) (Nelson, 1982; Schmand et al., 1991) were used to match the groups on (estimates of) intellectual functioning.

The Raven APM is commonly accepted as a measure of general intelligence and has been shown to correlate with a number of standardized intelligence tests (Lezak, 1995; Raven et al., 1993). Subjects are shown 12 pictures of matrices (i.e., related patterns), each of which is a figural design with a part removed. The subject must choose the correct missing part from eight options. The NART (Nelson, 1982; Schmand et al., 1991) provides an estimate of verbal IQ and is based on the high correlation between reading ability, specifically of irregular words, with intelligence in the normal population (Willshire et al., 1991). We used the Dutch version of the test, which is composed of a list of 50 irregular words (i.e., pronunciation does not follow the normal phonetic rules) printed in order of increasing difficulty. Subjects are required to read these words aloud.

In addition, for the XXY group an IQ profile was obtained using the Dutch adaptations of the Wechsler Adult Intelligence Scales (Wechsler, 1997) for which distributions of norms scores in the Netherlands are available. In addition to full-scale IQ, verbal IQ and performance IQ, the WAIS-III yields standard scores (mean = 100, S.D. = 15) on four Factor Indexes known as verbal comprehension index, perceptual organization index, working memory index and processing speed index.

### 2.5. Disorganization traits

The Schizotypal Personality Questionnaire (SPQ) was used to quantify disorganization traits (Raine, 1991). The SPQ is a 74-item self-report measure of schizotypal personality traits, which have shown to be normally distributed in the general population. As this is a self-report measure, scores reflect subjective experience of schizotypal traits. Factor analytical studies (Vollema and Hoijtink, 2000) have revealed three dimensions of schizotypy, being (a) *positive schizotypy* (b) *negative schizotypy* and (c) *disorganization*. A total of 19 items load on the factor disorganization, of which an example is 'I often ramble on too much when speaking'. Both the XXY group and the two control groups completed the questionnaire.

### 2.6. Lateralization of verbal information processing

Hemispheric dominance for processing verbal information was measured with an auditory–verbal dichotic listening task, designed by Bouma et al. (Bouma, 1998). Performance on this task has been shown to correlate with size of the corpus collosum (Gootjes et al., 2006). A right ear advantage that is found with this task arises from verbal information from the right ear reaching the dominant left hemisphere directly, allowing faster and more accurately processing of verbal information as compared to information from the left ear, which has to cross over to the language-dominant left hemisphere.

Different series of four digits were presented to the left and right ear simultaneously. Groups of four digits were semi-randomly selected out of the monosyllabic Dutch digits (1–6, 8, and 10–12), presented with an inter-stimulus-interval of 500 ms., using earphones. Subjects were asked to report the digits they had perceived, with free recall. The task included 20 trials, of which the first 2 were practice trials. For each ear the total number of correctly recalled digits was determined, based on the first four reported digits. Maximal score for each ear was 72. The lateralization index in the dichotic listening task was calculated using the following formula: (correct right ear − correct left ear)/total correct) × 100. The index ranges from −100, (suggesting complete right hemisphere dominance) to +100 (suggesting complete left hemisphere dominance).

### 2.7. Executive functioning

Inhibition and mental flexibility was measured using the Shifting Set Task of the Amsterdam Neuropsychological Tasks (ANT) program (De Sonneville, 1999). The ANT test battery has proven to be helpful in defining neurocognitive deficit profiles in different clinical and nonclinical populations (Rommelse et al., 2008; Serra et al., 2003) and several studies have demonstrated satisfactory psychometric properties of ANT paradigms (for a review, see De Sonneville, 2005). The Shifting Set Task assesses inhibition of prepotent responses as well as mental flexibility. This paradigm has successfully been used to demonstrate deficits in these executive functions in subjects with diseases that are known to be associated with impaired frontal functioning, such as phenylketonuria (Huijbregts et al., 2002). A coloured square moves randomly to the right and to the left on a horizontal

bar that is permanently present on the computer screen. Depending on the colour of the square after the jump, the subjects should copy the movement, i.e. press right (left) when the square jumped to the right (left), or is required to 'mirror' the movement, i.e. press left (right) at a right (left) movement. The task consists of three parts. In part 1 (40 trials, green squares) the subject is required to copy the movements (fixed copy condition). In part 2 (40 trials, red squares) only trials that call for 'mirror' responses are presented (fixed mirror condition), requiring the inhibition of prepotent responses. In part 3 (80 trials, red and green squares) the square may change colour upon each jump in a random fashion which forces the subject to switch between response sets, which requires mental flexibility. Performance in part 3 is registered separately for green squares (part 3A: variable copy condition) and red squares (part 3B: variable mirror condition). The dependent measures in this task are accuracy (i.e. percentage errors) and reaction times, with inhibition defined by the 'fixed mirror (part 2) minus fixed copy (part 1)' conditions and mental flexibility defined by the 'variable copy (part 3A) minus fixed copy (part 1)' conditions.

### 2.8. Statistical analyses

Data were analyzed using SPSS (Statistical Package for the Social Sciences) version 14.0. Group differences (XXY−, XXY+, control group I, control group II) in the level of education, age, SPQ scores, handedness score, NART and Raven APM scores were analysed using ANOVA. IQ scores in the XXY group were compared to Dutch norm scores and between group differences (XXY−, XXY+) in IQ were analyzed using ANOVA. Group differences on the ANT (XXY−, XXY+, control group II) were analysed using repeated measures analysis, with inhibition and flexibility as within-subject factors respectively, and post-hoc ANOVA's to test our hypotheses of specific group differences. Group differences (XXY−, XXY+, control group I) in the lateralization indices obtained with the dichotic listening paradigm were analyzed using ANOVA. This was followed by a repeated measures analysis to test for group (XXY−, XXY+, control group I) by condition (left ear, right ear) interactions. The level of significance was $p = 0.05$.

## 3. Results

### 3.1. Disorganization

ANOVA indicated that mean total score on the SPQ was significantly higher ($F(1,56) = 19.5$, $p<0.001$) in the XXY group (35.6, SD 19.4) as compared to controls (17.1, SD 12.5). The level of desorganization traits, the focus of the present study, was significantly higher ($F(1,56) = 37.6$, $p<0.001$) in the XXY group (8.9, SD 4.6) as compared to controls (2.6, SD 3.0). The effect size (Cohen's $d$) was 1.7, which is a large effect. For the distribution of disorganization scores see Fig. 1.

In order to identify a subgroup of men with highest levels of disorganization, a median split in the XXY group was applied, resulting in two subgroups of equal size that were differentiated by a cut-off score of 10 (see Fig. 1). This cut-off score corresponded to 5% of the highest scores in the control group. To compare, Rossi and Daneluzzo (2002), using the same questionnaire, have reported mean disorganization scores of 2.4 for controls, 3.8 for depression, 9.3 for bipolar disorder and 7.7 for schizophrenia. Hence, the subgroup of XXY above the cut-off score of 10 (and a mean score of 12.4) may be considered to have high levels of disorganized features. All means and standard deviations in the XXY subgroups and two control groups are presented in Table 1. There were significant group differences (XXY−, XXY+, control group I, control group II) in mean disorganization score, $F(3,54) = 29.8$, $p<0.001$. For LSD post hoc results see Table 1.

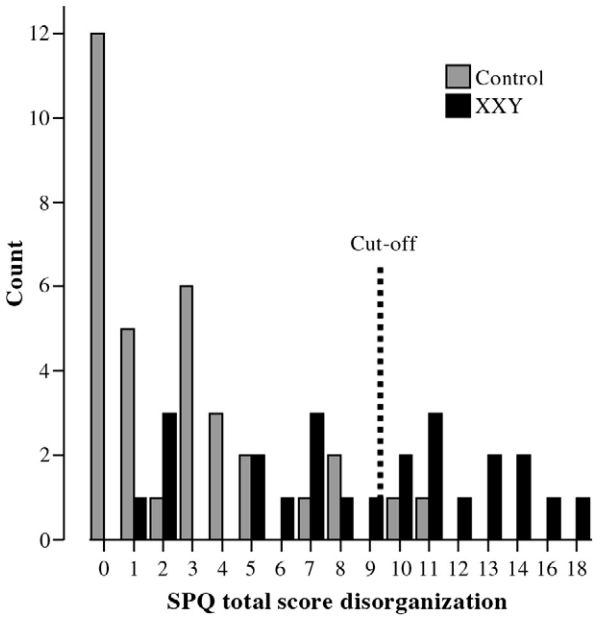


**Fig. 1.** Frequency distribution (count = number of subjects) of the SPQ disorganization scoreS in the XXY group and the control group. In order to identify a XXY subgroup with high levels of disorganization traits (XXY+), a median split was applied, resulting in a cut-off score of 10, i.e. above the 5% highest scores in the control group.

Considering all subsales of the SPQ, the XXY+ group also scored significantly higher than the XXY− group on 'unusual perceptual experiences' ($p = 0.014$) and 'referential ideas' ($p = 0.034$), besides the disorganized subscale 'odd speech' ($p<0.001$). For information regarding profiles of schizotypal traits in a larger sample XXY men, see van Rijn et al. (2006).

### 3.2. Handedness

ANOVA showed no significant group differences (XXY−, XXY+, control group I, control group II) in mean handedness scores, $F(3, 58) = 1.4$, $p = 0.24$. None of the LSD-post hoc tests were significant. Results are presented in Table 1.

### 3.3. Intellectual functioning

ANOVA showed no significant group differences (XXY−, XXY+, control group I, control group II) in mean NART scores or mean Raven APM scores, $F(3,58) = 1.5$, $p = 0.20$ and $F(3,58) = 0.50$, $p = 0.68$ respectively. Also, none of the LSD-post hoc tests were significant. Results are presented in Table 1.

**Table 2**
Mean WAIS-III scores in the XXY group as a whole and the XXY subgroups with disorganized traits below (XXY−) and above (XXY+) the cut-off.

| | XXY total | XXY− | XXY+ | XXY− versus XXY+ |
|---|---|---|---|---|
| Full scale IQ | 93.1 (10.3) | 92.4 (9.6) | 93.8 (11.7) | $F(1,22)=0.09$, $p=0.76$ |
| Verbal IQ | 92. 4 (11.8) | 92.4 (11.5) | 92.9 (13.0) | $F(1,22)=0.01$, $p=0.93$ |
| Performance IQ | 92.4 (19.4) | 86.8 (25.6) | 96.7 (11.4) | $F(1,22)=1.47$, $p=0.24$ |
| Verbal comprehension | 92.4 (12.0) | 91.3 (10.3) | 94.6 (13.27) | $F(1,22)=0.43$, $p=0.51$ |
| Perceptual organization | 98.8 (11.5) | 95.1 (7.6) | 101.6 (14.0) | $F(1,22)=1.83$, $p=0.19$ |
| Working memory | 98.9 (16.3) | 98.9 (17.1) | 98.4 (17.0) | $F(1,22)=0.01$, $p=0.94$ |
| Processing speed | 95.6 (9.6) | 97.5 (9.8) | 95.1 (8.9) | $F(1,22)=0.36$, $p=0.55$ |

Scores on the WAIS-III indicated that in the XXY group full scale IQ, verbal IQ performance IQ and all the index scores were within the normal range (at the lower end however) as compared to the distribution of norm scores. Most important, there were no significant differences in IQ scores between the XXY− group and XXY+ group. Results are presented in Table 2.

### 3.4. Lateralization of verbal information processing

ANOVA showed significant group differences (XXY+, XXY−, control group II) in the lateralization index ($F(2,39)=4.2$, $p=0.02$). Post-hoc tests revealed that the mean lateralization index in the XXY+ group (−3.8, SD 22.9) was lower as compared to the XXY− group (20.5, SD 34.8) ($p=0.05$) and the control group (27.8, SD 30.3) ($p=0.007$). A repeated measures analysis of the percentage identified digits also indicated significant between-group differences. A significant group (XXY+, XXY−, control group II) by condition (left ear, right ear) interaction was present ($F(2,39)=4.1$, $p=0.02$). Paired *t*-tests showed that significantly more digits from the right ear, as compared to the left, were reported in the control group ($t(1,17)=-3.8$, $p=0.001$) and the XXY− group ($t(1,11)=-2.3$, $p=0.03$). In contrast, the percentage identified digits was not different for the left ear and right ear in the XXY+ group ($t(1,11)=0.36$, $p=0.72$), as shown by a paired *t*-test. Thus, both the control group and the XXY− group showed a right ear (i.e. left hemisphere) dominance, but this was absent in the XXY+ group. ANOVA as well as repeated measures analysis indicated that the mean score in the XXY− group was not significantly different from the control group. Means and standard deviations are presented in Table 3.

No significant correlations were found between the lateralization index and the inhibition scores or the mental flexibility scores (accuracy and reaction times).

**Table 3**
Percentage correctly identified digits (mean, SD) presented to left ear (right hemisphere) the versus the right ear (left hemisphere) in the XXY subgroups and controls.

| | Left ear | Right ear |
|---|---|---|
| Control | 34.8 (15.0) | 61.8 (15.3) |
| XXY− | 37.2 (16.5) | 58.3 (15.3) |
| XXY+ | 46.1 (13.9) | 43.7 (15.0) |

The difference in scores between the left and the right ear reflects the degree of lateralization of verbal information processing, which was significantly lower in the XXY+ group as compared to the XXY− group and controls.

### 3.5. Executive functioning

#### 3.5.1. Inhibition

The XXY+ group, but not the XXY− group, showed significantly more difficulties with inhibiting prepotent responses as compared to controls. This was evident in a trend-significant group (XXY+, XXY−, control group I) by condition (copy, mirror) interaction ($F(2,41)=3.8$, $p=0.06$) in the repeated measures analysis. As our hypothesis was that, as compared to controls, only the XXY+ group would show deviate scores and not the XXY− group, separate ANOVA's were used. Indeed, as compared controls, the XXY+ group showed a stronger absolute increase in percentage errors as compared to controls ($F(1,43)=-7.6$, $p=0.04$), whereas the XXY− group did not significantly differ from controls ($F(1,43)=-1.4$, $p=0.67$). Scores are presented in Table 4. Calculation of effect sizes, i.e. Cohen's *d*, revealed a strong effect size (0.72) for the XXY+ group and, as predicted, a weak effect size for the XXY− group (0.24) as compared to controls. No significant group differences in reaction times were found. IQ scores did not significantly correlate with measures of inhibition.

#### 3.5.2. Mental flexibility

The XXY+ group, but not the XXY− group, showed more difficulties with mental flexibility as compared to controls. This was evident in a significant group (XXY+, XXY−, control

**Table 4**
The increase in percentage errors (mean, SD) in the mirror condition as compared to the copy condition of the Set Shifting Task (reflecting the degree of inhibition difficulties), was significantly higher in the XXY+ group compared to the XXY− group and controls.

| | Copy | Mirror |
|---|---|---|
| Control | 3.5 (4.4) | 5.8 (6.2) |
| XXY− | 4.0 (3.4) | 7.9 (6.1) |
| XXY+ | 2.5 (2.9) | 12.5 (15.8) |

**Table 5**
The increase in percentage errors (mean, SD) in the variable condition as compared to the fixed condition of the Set Shifting Task (reflecting the degree of difficulties in mental flexibility), was significantly higher in the XXY+ group compared to the XXY− group and controls.

| | Fixed | Variable |
|---|---|---|
| Control | 3.5 (4.4) | 1.9 (2.7) |
| XXY− | 4.0 (3.4) | 6.1 (6.4) |
| XXY+ | 2.5 (2.9) | 9.0 (8.2) |

group I) by condition (fixed copy, variable copy) interaction ($F(2, 41) = 5.3$, $p = 0.008$) in the repeated measures analysis, as well as a significant group difference in the absolute increase in percentage errors revealed by post hoc ANOVA tests (XXY+ versus controls: $p = 0.002$ and XXY− versus controls: $p = 0.14$) results are presented in Table 5. No significant group differences in reaction times were found. IQ scores did not significantly correlate with measures of mental flexibility.

## 4. Discussion

As expected, the XXY group reported increased levels of disorganized schizotypal traits, referring to deregulation of thought and speech. Central to our aim, XXY men with high levels of disorganization (XXY+) could be differentiated from the other XXY men (XXY−) and controls based on measures of cognitive inhibition and mental flexibility (set shifting), but not on intellectual functioning. As predicted, lateralization of information processing was reduced in the XXY group and differentiated XXY men with high levels of disorganization from other XXY men and controls.

Intelligence scores, i.e. total IQ, verbal IQ, performance IQ and the index scores, were not different between XXY+ and XXY− men. A lack of significant subgroup differences suggests that the subgroup with high levels of disorganization was not a generally more severely affected subpopulation of XXY men, which adds to the specificity of our findings in other cognitive domains. Although no group differences were found in general intelligence, significant differences were observed in other cognitive domains.

First, in the XXY group significant within-group differences were found in executive functioning, i.e. cognitive inhibition and mental flexibility. The XXY group as a whole displayed more problems in mental flexibility compared to controls. When considering the XXY subgroups separately, only the more severely disorganized XXY subgroup was characterized by impairments in mental flexibility, as compared to the other XXY men as well as controls. Moreover, although cognitive inhibition was not significantly impaired in the XXY group as a whole, the subgroup of XXY men with high levels of disorganization did show a significant deficit in cognitive inhibition, i.e. inhibition of prepotent responses, as compared to controls. In contrast, XXY men with disorganization scores below the cut-off could not be differentiated from controls. Other studies have reported mixed findings with regard to executive functioning in Klinefelter syndrome (Boone et al., 2001; Itti et al., 2006; Ross et al., 2008; Temple and Sanfilippo, 2003), which may be related to factors such as sample size, age and the use of verbal or visual tests.

Our findings are in line with the cognitive impairments found in schizophrenia patients with disorganized thought. A meta-analysis identified two cognitive mechanisms that are consistently associated with thought disorder: executive dysfunctioning, primarily inhibition, and impaired processing of semantic information (Kerns and Berenbaum, 2002). In line with these findings, executive dysfunction, especially the inability to inhibit prepotent responses, seems to be strongly related to higher levels of thought disorder in schizophrenia (Stirling et al., 2006). It may be relevant to note that also in people with autism spectrum disorders, aspects of disorganized thought such as loose associations are related to inhibition problems, i.e. a reduced ability to inhibit prepotent responses (Solomon et al., 2008). Interestingly, Klinefelter syndrome has been associated with increased vulnerability for schizophrenia spectrum pathology as well as autism spectrum pathology (Boks et al., 2007; Bruining et al., 2009; DeLisi et al., 2005; Jha et al., 2007; Merhar and Manning-Courtney, 2007; van Rijn et al., 2006, 2008b). Cognitive control functions such as inhibition and mental flexibility may be involved in guiding discourse, for example in selecting and maintaining a topic, suppressing irrelevant thoughts and speech during conversation, organizing and planning of thoughts and speech as well as the flexibility to adapt to new information i.e. the input of others in communication. We propose that these cognitive mechanisms might be deficit-specific, rather than disorder-specific.

Second, reduced lateralization of information processing was found in the XXY group, especially in those men with high levels of disorganization. Reduced lateralization of verbal information processing points to non-optimal cerebral specialization. This finding fits with deficits in brain functions most vulnerable to such maturational disruptions, i.e. executive dysfunctions. Our finding of an absence of a right ear (i.e. left hemisphere) dominance in the Klinefelter group as a whole is in line with other studies indicating reduced cerebral lateralization (Itti et al., 2003; van Rijn et al., 2008a) and diminished left hemisphere dominance (Geschwind et al., 1998; Netley and Rovet, 1984; Ross et al., 2008). Our findings also fit well with an earlier neuroimaging study showing that the level of disorganization of thought and speech is related to the degree of hemispheric lateralization of neural activation during language in XXY men (van Rijn et al., 2008a). Schizophrenia patients with thought disorder also display reduced cerebral asymmetry in language areas and reduced hemispheric lateralization of verbal information processing (Kircher et al., 2002; Rossi et al., 1994). Kircher et al. (2002) have proposed that an imbalance in the complementary language processes of the left and right hemisphere may underlie disorganization symptoms and thought disorder in schizophrenia patients. Increased right hemispheric activity leading to generation of distantly related meanings together with reduced left hemispheric activity resulting in loss of inhibition and selection of meaning, might contribute to disorganization of thought.

It should be noted that the present study has several limitations. First, the sample sizes in the subgroups were relatively small. Nonetheless, the high consistency of the subgroup findings across measures adds face validity in interpreting the results. Second, full IQ profiles were not obtained for the control group. However, the groups were well matched on estimates of intellectual functioning and level of education. In line with this, mean IQ scores in the two XXY subgroups (XXY− and XXY+) were not significantly different in the face of significant differences in executive functioning and lateralization of verbal information processing.

Third, we have focused on subclinical disorganized traits, rather than clinical symptoms of thought disorder. The SPQ is a self report measure and scores reflect subjective experiences of schizotypal traits. The findings of the present study encourage us to study disorganization more thoroughly in Klinefelter syndrome using clinical measures such as the Thought, Language, and Communication Scale developed by

Andreasen (1986). Furthermore, the subgroup of XXY men that showed significant impairments in executive functioning did not only show high levels of disorganization but also increased levels of unusual perceptual experiences and referential ideas. This suggests that reduced cognitive control might also contribute to other psychotic-like traits in men with Klinefelter syndrome. However, disentangling the cognitive mechanisms of specific psychotic traits is difficult, as many of these traits co-occur, both in men with XXY as well as individuals with schizophrenia. Finally, we were not able to assess the role of testosterone treatment on cognitive functioning. With regard to language lateralization, interesting findings have been reported in longitudinal studies with transsexuals, which show that cognitive hemispheric asymmetries and language laterality assessed with fMRI is highly stable and not affected by androgen supplements (Sommer et al., 2008; Wisniewski et al., 2005). Although there is not much known about the effects of testosterone therapy on executive functioning in Klinefelter syndrome, in girls with Turner syndrome androgen replacement therapy does not affect executive functioning (Ross et al., 2003). Future studies in XXY children might help resolve this issue, as such studies allows one a) to assess the effect of testosterone therapy on cognitive functioning in adolescence and b) to study cognitive functions such as executive functioning in preadolescent XXY boys before puberty related testosterone deficiencies become apparent and testosterone therapy is typically started (Salbenblatt et al., 1985; Wikström et al., 2006).

Studying Klinefelter syndrome may be relevant for the understanding of schizophrenia spectrum pathology. First, as our findings are in line with studies in schizophrenia, this study has shown that the observed deficits probably are *deficit* specific rather than *disorder* specific. Hence, executive dysfunction may represent a generic mechanism important for regulation of thought and speech in different populations. One of the advantages of studying Klinefelter syndrome is that a prenatal diagnosis allows one to investigate childhood developmental factors that convey or influence risk for psychosis. Studying executive functioning in future longitudinal and neuroimaging studies with XXY boys may help gain insight in the early predictors of risk for deregulation of thought and speech later in life. Finally, our findings may have clinical implications, as they may help in a) identifying mechanisms that may explain difficulties in communication in many XXY men, b) stressing the importance of subtyping in clinical populations, and c) identifying targets for treatment of disorganization in thought and speech in Klinefelter syndrome.

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**Contributors**

Sophie van Rijn participated in organising, designing and executing the study, analysing the data, writing the first draft of the manuscript as well as the final version. André Aleman participated in the design, interpretation and writing. Leo de Sonneville participated in analysing the data and writing. Hanna Swaab participated in conceptualization, design of the study, inclusion of patients, interpretation and writing. All authors contributed to and have approved the final manuscript.

**Conflicts of interest**

All authors declare that they have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2009.04.017.

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