

CHAPTER 8

EFFECTS OF AN EXTRA X CHROMOSOME ON LANGUAGE LATERALIZATION: AN FMRI STUDY WITH KLINEFELTER (XXY) MEN

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Abstract

De novo occurring genetic variations provide an opportunity to study the effects of genes on structure and function of the brain. In this regard, Klinefelter syndrome, characterized by a XXY chromosomal pattern, is of significant interest. Although general intelligence is average in XXY men, prominent effects of the extra X chromosome on cognition are observed in the language domain. One possible neural mechanism underlying these language deficits is reduced hemispheric specialization for language. However, there has been no study of brain activity patterns underlying language processing in XXY men. Also, the consequences for mental functioning in XXY men are as yet unresolved. The clinical relevance of exploring mental consequences in Klinefelter syndrome is illustrated by the finding that Klinefelter men manifest symptoms that are seen in schizophrenia. A possible commonality between these disorders is that both are characterized by language deficits.

We used functional Magnetic Resonance Imaging (fMRI) to reveal the effects of an extra X chromosome on language lateralization. This technique allows us to identify functional asymmetries in specific brain regions as well as to determine whether reduced lateralization, if found, is secondary to decreased function of the left- or increased activity in the right hemisphere. We explored the relation between loss of language lateralization and mental functioning in these men, with special interest in clinical phenomena of disorganization of thought and language.

Hemispheric dominance for language was assessed in 15 XXY men and 14 control men using fMRI. In each hemisphere, activity in five different language regions was analyzed: Broca's area, superior temporal gyrus, middle temporal gyrus, angular gyrus and supramarginal gyrus. Psychopathology was measured using the Positive and Negative Syndromes Scale for measuring schizophrenia symptoms and a schizotypal personality questionnaire.

Compared to controls, the XXY group showed reduced hemispheric specialization for language. This was due to increased activity in the language areas of the right hemisphere rather than reduced activity in the left hemisphere. Decreased functional asymmetry was most prominent in the superior temporal gyrus and correlated with symptoms of disorganization.

These findings may suggest that a genetic mechanism involving the X chromosome contributes to hemispheric specialization for language, since loss of language lateralization, most prominent in the superior temporal gyrus, was observed in this X chromosomal disorder. Moreover, loss in hemispheric specialization for language processing may have important consequences for mental functioning, as it was associated with dysfunctions in organization of thought and language.

Introduction

The study of *de novo* occurring genetic variations that are associated with neural, cognitive and behavioral abnormalities may increase our understanding of complex gene-brain-behavior relations. In this regard, Klinefelter syndrome, which is defined by the presence of an additional X chromosome in men, is of significant interest. Although general intelligence is average in XXY men, prominent effects of the extra X chromosome on cognition have been observed, particularly in the language domain (D. H. Geschwind et al., 2000a). The reported verbal disabilities include impairments in both language production and perception and indicate compromised language functions that are typically associated with the left hemisphere (Samango-Sprouse, 2001). For example, Klinefelter boys or men have difficulty understanding words, finding words and to verbally express their thoughts, all resulting in a verbal IQ that is lower than their performance IQ. As language is a crucial part of social communication, it has been proposed that these language impairments may contribute to the observed difficulties in social functioning in Klinefelter men (Samango-Sprouse, 2001; van Rijn et al., 2006b).

Although language impairments in Klinefelter syndrome are well-documented, underlying neurocognitive mechanisms are not well understood (D. H. Geschwind et al., 2000a). One possible neural mechanism involved in the verbal disabilities in Klinefelter syndrome may be abnormal hemispheric involvement in language processing. Although the left hemisphere is dominant for processing verbal information in right-handed individuals from the general population, there are indications that this dominance is diminished in XXY men. First, decreased language lateralization has been shown in a study of 32 XXY boys using a dichotic listening paradigm (Netley & Rovet, 1984). Second, in a more recent SPECT study, resting state blood flow patterns were more symmetrical in nine XXY men as compared to nine healthy controls (Itti et al., 2003). In that study, increased right temporal lobe blood flow was related to verbal impairments as measured with neuropsychological tasks assessed in the same week as the SPECT-session. Although these studies provide some indication that loss of hemispheric asymmetry in the processing of language may be a characteristic of the XXY phenotype, it is unclear whether the decreased language lateralization is secondary to decreased function of the left or increased activity in the right hemisphere. Moreover, it remains unresolved which specific language regions within the hemispheres are more bilaterally involved in processing language in XXY men.

Another reason for studying language lateralization in Klinefelter syndrome is that the consequences for behavioral and psychological or mental functioning in XXY men are as yet unresolved. The importance of considering this issue is illustrated by reports of reduced hemispheric specialization for language in patients with schizophrenia. In these patients, loss of language lateralization is thought to be related to language impairments as well as clinical symptoms associated with language, such as auditory hallucinations ('voices') or disorganization of language and thought (Kircher et al., 2002; I. E. Sommer et al., 2001b). Indeed, Klinefelter men manifest symptoms that are also observed in schizophrenia patients (van Rijn et al., in press), including disorganization and thought disorder. Moreover, the frequency of the XXY chromosomal pattern has been reported to be increased in patients with schizophrenia as compared to the general population (L.E. DeLisi et al., 1994).

To assess hemispheric specialization for language in XXY men, we used functional Magnetic Resonance Imaging (fMRI). By using fMRI we are able to investigate lateralization of neural activity during language processing in XXY men. In addition, this technique allows us to identify specific language regions in which lateralization is diminished. Our second aim was to investigate the link between loss of language lateralization and mental functioning in these men, with special interest in those symptoms and personality traits pertaining to organization of thought and language, that are also seen in the schizophrenia spectrum.

Methods

Subjects

15 XXY men (mean age 36.9, SD 11.8) and 14 healthy control men (mean age 35.5, SD 9.5) participated in the fMRI study. XXY men were recruited from the Dutch Klinefelter Association, and were not selected for psychological, behavioral or cognitive abnormalities. Diagnosis of Klinefelter syndrome was confirmed by genetic analysis (i.e. karyotyping) using standard procedures. Of the XXY men, 14 were treated with testosterone supplements (mean age of treatment onset of 23.9, SD 7.1 years).

Controls were recruited using advertisements in local newspapers or were drawn from a database in our department. None of the control subjects had a history of psychiatric illness as confirmed with the Mini International Neuropsychiatric Interview plus (MINI) (Sheehan et al., 1998).

The primary language of all participants was Dutch. There were no significant

differences in age ($t(1,27)=-1.1$, $p=0.26$) or years of education between the groups (Klinefelter group 15.8 (SD 2.0), control group 15.4 (SD 1.8), $t(1,27)=0.41$, $p=0.68$). All participants were right-handed. Mean handedness score, as indicated by the Edinburgh Handedness Inventory (Oldfield, 1971), in the Klinefelter group (21.21, SD 3.1) did not significantly differ from that in controls (22.1, SD 2.1) ($t(1,27)=0.85$, $p=0.40$).

Exclusion criteria for both Klinefelter men and controls were neurological conditions or history of head injury with loss of consciousness, recent history of substance abuse and mental retardation. After complete description of the study to the subjects, written informed consent was obtained according to the declaration of Helsinki.

Schizophrenia psychopathology

Schizophrenia spectrum pathology was only measured in the Klinefelter group. Schizophrenia spectrum pathology in a larger population of Klinefelter men at our department as compared to healthy controls has been described elsewhere (van Rijn et al., in press). Schizotypal traits were measured using the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991). The SPQ is a self-report measure of schizotypal personality traits, which have shown to be normally distributed in the general population. It is regarded as an indicator of the genetic vulnerability to schizophrenia, since there is a gradient increase in schizotypal traits in relatives of schizophrenia patients that is in proportion to the risk for schizophrenia associated with the degree of kinship with the schizophrenic family member (Vollema et al., 2002). Factor analytical studies (Vollema & Hoijsink, 2000) have revealed three dimensions of schizotypy, being (a) *Positive schizotypy* (for example referential thinking and delusional atmosphere), (b) *Negative schizotypy* (for example constricted affect and social anxiety), and (c) *Disorganization* (odd speech and eccentric behavior).

A clinical measure of schizophrenia symptoms was also included. The Positive and Negative Syndromes Scale (PANSS) (Kay et al., 1987) is a widely used structured interview to assess symptom profiles in schizophrenia patients that are present in the week prior to the interview. The PANSS allows categorization of negative, positive, and general symptoms.

Language tasks

Language tasks were adopted from Ramsey et al. (2001). In the MRI scanner subjects completed three different tasks that have been shown to activate language areas in the brain, being a paced verb generation task, an antonym

generation task, and a semantic decision task. Difficulty of the tasks was set at a level that would allow Klinefelter men to perform comparable to healthy controls. All subjects practiced the tasks with a different set of stimuli before the scan session. In all tasks, a word was presented visually every 3 seconds and consisted of four to eight characters. Silent vocalization (i.e. without overt articulation) was used to avoid head motion. Each task was performed during 5 blocks of 29 s, alternated with rest periods of 29 s. A total of 360 functional scans were collected for each individual.

In the verb generation task, subjects were instructed to repeat a visually presented noun silently and subsequently silently vocalize an appropriate verb for the presented noun. In the antonym generation task, subjects had to think of a word that was of opposite meaning in response to the visually presented word. In the control condition for these tasks a number of dots, equal to the number of characters in the presented words, appeared on the screen. Finally, in the semantic decision task, subjects had to indicate, by pushing a button, whether the visually presented word was an animal. The control task also included button presses, which were cued by the presence of five dots (either three or five dots appeared). Performance was registered with a computer. Performance in the verb- and antonym generation tasks was assessed outside the scanner. Each task included 45 words, which were different from those presented during scanning, but presented with an identical interstimulus interval.

Scans

Scanning technique was adopted from Ramsey et al. (2001). Functional scans were acquired with a Phillips ACS-NT 1.5-T clinical scanner, using the blood-oxygen-level dependent sensitive, navigated 3D PRESTO pulse sequence (N.F. Ramsey et al., 1998), with the following parameter settings: TE/TR 35/24 ms, flip angle 9°, FOV 225x180x77 mm³, matrix 64x52x26, voxel size 4 mm isotropic, scan time per volume 2.4 s. Following the fMRI procedure, an anatomical scan was acquired.

fMRI analysis

Functional MRI data preprocessing and analysis was done using SPM2 (Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk).

Brain activity maps were obtained by analyzing the fMRI scans during all three tasks conjointly. It has previously been shown that such an analysis improves reliability of the subsequently computed laterality index, as compared to that obtained with individual task analysis (N. F. Ramsey et al., 2001). The rationale for conjoint analysis is that it improves sensitivity for brain activity that is present in all tasks, while reducing contribution of activity that is specific for individual language tasks.

All functional scans were registered to the last volume of the last block and coregistered to the anatomical scan. Next, all functional images were registered to an MNI standard brain, to enable group-wise comparisons. For each subject, a statistical map (i.e. T-map) was obtained from a general linear model regression analysis using a factor matrix that contained one factor modeling task activation for all three tasks combined. Eight discrete cosine functions were included to correct for low-frequency drifts.

Significant activation was then determined in each voxel by applying a threshold. The threshold corresponded to a p value of 0.001, uncorrected for multiple comparisons, and amounted to a T-value of 3.12. This relatively low threshold was applied to reduce the chance of a type II error (i.e. the failure to find a difference while there is a true difference between the conditions). Also, by setting the threshold at this T-value, one increases the likelihood that active voxels are present in both the left and the right hemisphere in each individual, allowing calculation of a more reliable laterality index.

Regions of interest

A map including five regions of interest (ROI), based on nine Brodmann areas (BA), was created using the WFU Pickatlas tool for SPM (Maldjian et al., 2003). This map was dilated with one voxel isotropic and coregistered with the T-maps. The advantage of using Brodmann areas is that volumes of the ROI's are of equal size across the hemispheres and across the groups. The following ROI's were created for the hemispheres separately: Broca's area and the homotopical region in the right hemisphere (BA 44, 45), superior temporal gyrus (BA 22, 38, 41, 42), middle temporal gyrus (BA 21), angular gyrus (BA 39) and supramarginal gyrus (BA 40).

Lateralization index

For each individual, the number of voxels above a threshold of $T=3.12$ ($p < 0.001$, uncorrected for multiple comparisons) was counted for all ROI's separately. A lateralization index for each ROI and all ROI's combined was calculated using the following algorithm:

$$\frac{\text{Active voxels left} - \text{active voxels right}}{\text{Total active voxels}}$$

The index ranges from -1 (complete right hemispheric dominance) to $+1$ (complete left hemispheric dominance). The advantage of using this index over absolute values is that this measure reflects hemispheric dominance within an individual, and is relative to overall brain activity in each individual. Individual lateralization indices for each language region, and all regions combined, were entered in an ANOVA.

Language lateralization

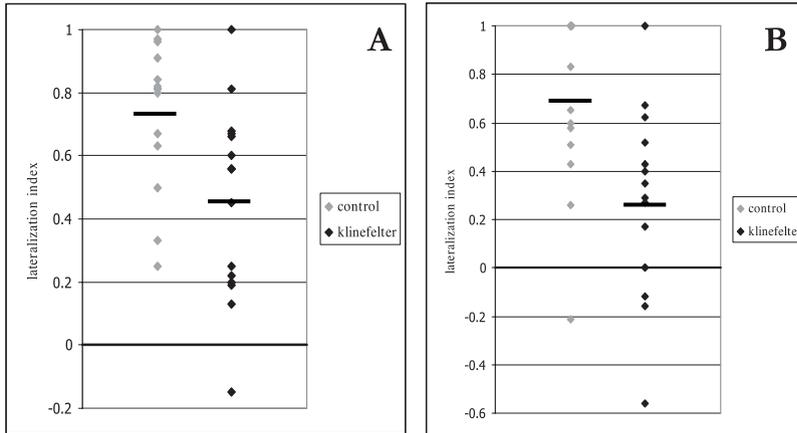
The mean lateralization index (for all language regions included) in the XXY group was 0.45 (SD 0.30), which was significantly lower than the index of 0.74 (SD 0.23) in the control group, $F(1,27)=7.6$, $p=.01$. See figure 1 for the distribution of lateralization indices in the groups. The lower lateralization index in the XXY group was due to increased language related activity in the right hemisphere as compared to controls ($F(1,27)=6.0$, $p=.02$), rather than group-differences in left hemispheric language-related activity ($F(1,27)=1.7$, $p=.20$).

More specifically, the mean lateralization index in the Superior Temporal Gyrus (STG, Brodmann area 22, 38, 41, 42) was significantly lower in XXY men (0.27, SD 0.39) as compared to controls (0.69, SD 0.36), $F(1,27)=8.2$, $p=.008$. See table 1 for the lateralization indices for each language region and figure 2 for activation patterns in a typical XXY subject and a typical control subject.

Analysis of the button presses during scanning indicated that performance in the semantic decision task was not significantly different between Klinefelter men and controls ($t(1,27)=-0.38$, $p=0.71$). Mean percentages correct were 90.6 (SD 8.8) and 89.3 (SD 8.4) respectively. Also, we observed no significant group differences in mean correct responses in the antonym-generation task (control group 42.1 (SD 3.4), Klinefelter group 41.2 (SD 3.8), $t(1,24)=0.52$, $p=0.61$) and verb-generation task (control group 40.4 (SD 3.2), Klinefelter group 34.6 (SD 9.0), $t(1,24)=1.8$, $p=0.08$) outside the scanner. Language lateralization in the XXY group did not correlate with handedness or age at which testosterone supplementation was started.

Figure 1

Distribution (and mean) of individual lateralization indices in the XXY and control group. Data are presented for all language regions combined (A) and for the superior temporal gyrus (STG) separately (B). In plot B, 7 controls have a lateralization index of 1.0.

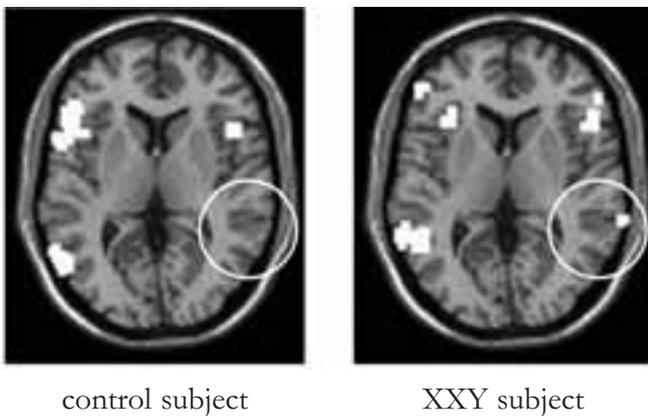
Figuur 1**Table 1**

Mean lateralization indices for each language region in XXY men and controls. (n.s.= not significant)

Language region (Brodmann area)	Lateralization index control group (mean, SD)	Lateralization index XXY group (mean, SD)	P-values
All language regions included	0.74 (0.23)	0.45 (0.30)	0.01
Superior temporal gyrus (22, 38, 41, 42)	0.69 (0.36)	0.27 (0.39)	0.008
Middle temporal gyrus ((21)	0.71 (0.42)	0.42 (0.39)	n.s.
Angular gyrus (39)	0.70 (0.55)	0.52 (0.45)	n.s.
Supramarginal gyrus (40)	0.68 (0.49)	0.38 (0.55)	n.s.
Broca (44, 45)	0.73 (0.30)	0.61 (0.35)	n.s.

Figure 2

Examples of brain activity patterns during language processing in a control subject (with an overall lateralization index of 0.82) and an XXY subject (with an overall lateralization index of 0.45), that illustrate the following findings in XXY men as compared to controls; *a*) more bilateral activity, *b*) more activity in the right hemisphere, rather than less activity in the left hemisphere and *c*) more bilateral activity only in the superior temporal gyrus (STG) (see circle). The slices are transaxial ($z=6$) through Broca's area and the STG in MNI space and show voxels (in white) with a T value above threshold in language regions.

Psychopathology

In the Klinefelter group mean total score on the Schizotypal Personality Questionnaire was 46.0 (SD 37.3), with a mean score of 14.0 (SD 14.0) for the positive dimension, 20.0 (SD 17.3) for the negative dimension and 12.0 (SD 7.2) for the disorganized dimension. Mean total score on the Positive and Negative Syndromes Scale (PANSS) was 46.5 (SD 9.7), with a mean score of 12.0 (SD 4.8) for the positive dimension, 10.3 (SD 2.9) for the negative dimension and 23.0 (SD 4.0) for the general symptoms dimension. For more details on schizophrenia spectrum pathology in a larger population of Klinefelter men at our department (of which the present is a subsample) as compared to healthy controls, see (van Rijn et al., in press).

Language lateralization and psychopathology

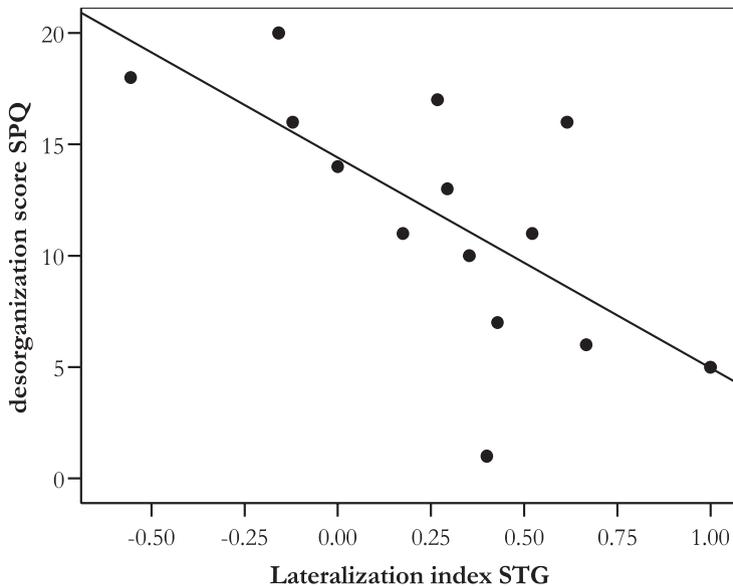
Within the Klinefelter group, the relation between language lateralization and psychopathology was assessed (N=14). Only the overall lateralization index and the lateralization index for the STG were analyzed, since only these were

significantly different between XXY men and controls. In both cases, the index was correlated with six measures of psychopathology (the positive, negative and general dimensions of the PANSS and the positive, negative and disorganized dimensions of the SPQ). After correction for multiple comparisons (Bonferroni), the p-level for significance was 0.008.

The overall lateralization index (including all language areas) did not correlate significantly with any psychopathology dimension, although the sumscore of all three dimensions of the PANSS did (spearman's $r=-.80$, $p=.001$). Functional lateralization in the STG, the specific language region in which lateralization was lower in XXY men as compared to controls, correlated significantly with the SPQ disorganization dimension (spearman's $r=-0.72$, $p=0.003$) (see Figure 3). The correlation was inverse, indicating that a decrease in lateralization in the STG was associated with more disorganization of thought and language.

Figure 3

Correlation between lateralization index for the superior temporal gyrus (STG) and score on the disorganization dimension of the Schizotypal Personality Questionnaire in the XXY group (spearman's $r=-0.72$, $p=.003$).



Discussion

Using functional Magnetic Resonance Imaging (fMRI) we were able to measure, for the first time, patterns of brain activity during language processing in 47,XXY men. By measuring the relative contribution of the right and left hemisphere in each individual it was shown that language activity in the brain was less lateralized in the XXY group as compared to healthy males. Loss of asymmetric processing of language was due to increased activity in the right hemisphere rather than reduced activity in the left hemisphere. Analysis of functional asymmetry within different language regions indicated that the superior temporal gyrus (STG) was the only region in which language was less lateralized in the XXY group. This regional loss of language laterality was highly correlated with the degree of disorganization in these subjects.

Reduced hemispheric specialization for language may contribute to the widely reported language deficits in XXY adults and children (Boone et al., 2001; D. H. Geschwind et al., 2000a; Money, 1993; Samango-Sprouse, 2001). These include disabilities in reading, articulation, phonemic processing, word finding, spelling, language expression, verbal memory, language comprehension and verbal fluency. The reported patterns of language impairments seem similar to those observed in developmental language disorders, for example dyslexia (D. H. Geschwind et al., 2000a). A proposed neurocognitive basis for the language profile in developmental language disorders is reduced hemispheric specialization for language in the brain. Findings of less cerebral asymmetry, both functional (Ors et al., 2005) and structural (Herbert et al., 2005), in developmental language disorders illustrate the contribution of cerebral lateralization to the development of language capabilities. Our fMRI study shows that specifically an increase in right hemispheric involvement in language may contribute to language impairments, which fits with findings from a SPECT-study (Itti et al., 2003) in which increased resting state blood flow in the STG in the right hemisphere was observed in nine XXY men. They observed that abnormal resting state activity in XXY men was correlated with verbal skills as assessed in a neuropsychological session.

The use of fMRI allowed us to identify specific areas in the brain underlying the loss of hemispheric specialization for language in Klinefelter syndrome. One of our key findings was that loss of functional asymmetry in the STG was the most prominent contributor to reduced language laterality. Our finding of functional abnormalities in the STG is consistent with studies reporting structural abnormalities in the temporal lobes in Klinefelter syndrome. An MRI study including 10 XXY men showed asymmetric reduction in volume of the

temporal lobes, with a smaller volume of the left temporal lobe in these men (Patwardhan et al., 2000). In a larger sample of 34 XXY men, Shen et al. (2004) found that more regions in the left, as compared to the right, temporal lobe were smaller in the XXY group in comparison to 62 healthy men. Two other studies have reported bilateral volume reductions of (regions in) the temporal lobe. DeLisi et al. (2005) observed smaller volumes of the STG bilaterally in 11 XXY men. Itti et al. (2006) measured smaller volumes of the temporal lobes bilaterally in 9 XXY men, but only volume reductions in the left hemisphere correlated with verbal skills.

Decreased functional and structural asymmetry of language area's in the brain in XXY men may be secondary to abnormal X chromosomal (in-)activation, since a pseudo-autosomal region on the X chromosome is thought to direct abnormal development of asymmetry in XXY men (D.H. Geschwind et al., 1998). Genes in the pseudo-autosomal region escape inactivation resulting in expression of both copies of the genes in XX women and XY men and all three copies in XXY men (i.e. overexpression). This dosage mechanism makes genes in this region prime candidates for abnormal brain development, including cerebral asymmetry, and cognition in XXY (D.H. Geschwind et al., 1998). For example, one candidate gene in the pseudo-autosomal (X-Y homologous) region that has been shown to escape inactivation resulting in expression of all three copies in Klinefelter syndrome is Protocadherin11XY (PCDH11XY), which is involved in axonal guidance in the brain (T. J. Crow, 2002; N. L. J. Ross et al., 2006).

Support for X chromosomal effects on structural asymmetry of the superior temporal area in the brain is also provided by studies on brain volumes in individuals with Turner syndrome (46 XO, i.e. X monosomy). Decreased volume of the superior temporal sulcus in the left hemisphere as well as increased volume of the superior temporal gyrus in the right hemisphere (Kesler et al., 2003) have been observed in these subjects. In this study, increased right STG volume was related to lower verbal intelligence scores in Turner subjects (but not in controls). Involvement of the X chromosome in abnormal development of the STG, at least in Turner syndrome, was indicated by the observed imprinting effects. (Imprinting refers to differential expression of a gene depending on whether the gene is passed through from the mother or the father.) Only STG volumes in Turner subjects with the single X chromosome derived from the mother, and not those with an X chromosome from paternal origin, were different from controls. The findings that reduced asymmetry, either secondary to increased right hemisphere volume as in Turner syndrome

or decreased left hemisphere volume as in Klinefelter syndrome, can be accompanied by language dysfunctions, implies that reduced asymmetry may be a key abnormality in language processing deficits.

Decreased functional asymmetry in the STG in Klinefelter men correlated with the disorganization dimension of the schizotypy measure. Both items of this dimension, ‘odd speech’ (vague or over-inclusive) and ‘odd/eccentric behavior’, also separately correlated inversely with language lateralization in the STG. This is consistent with studies finding structural (Matsumoto et al., 2001; Menon et al., 1995; Rajarethinam et al., 2000; Rossi et al., 1994a; Shenton et al., 1992) and functional (Kircher et al., 2002) abnormalities of the STG to be related to disorganization symptoms such as thought disorder, in another disorder, i.e. schizophrenia. Specifically, in a functional MRI study with schizophrenia patients with formal thought disorder, higher levels of thought disorder were related to increased STG activity in the right hemisphere (Kircher et al., 2002). Interestingly, in schizophrenia, sex differences have been reported in the volume of the STG (Flaum et al., 1995; R.E. Gur et al., 2000). A genetic mechanism involving the sex chromosomes might explain this finding. An X-Y homologous, pseudo-autosomal genetic region directing development of asymmetry in the brain has been proposed (T.J. Crow, 2004) to underlie the observed sex differences in verbal abilities, handedness, relative rates of hemispheric growth and both ages of onset and prevalence of schizophrenia. The idea that reduced cerebral asymmetry and, more specifically, loss of language lateralization is one of the core developmental brain abnormalities underlying schizophrenia symptoms (Bhati, 2005; T.J. Crow, 2004) is supported by a range of language laterality studies in schizophrenia (Artiges et al., 2000; Dollfus et al., 2005; Kircher et al., 2002; I. Sommer et al., 2001a; Weiss et al., 2006). One of these studies not only assessed the degree of lateralization, but also examined whether this was secondary to increased right hemisphere activation or decreased left hemisphere activation (I. E. Sommer et al., 2001b). Similar to what we observed in the Klinefelter men, decreased lateralization of language in schizophrenia patients was due to increased activity in the right hemisphere, rather than decreased activity in the left hemisphere.

A proposed mechanism by which abnormal functional lateralization of the STG may contribute to disorganization and thought disorder, incorporates the differences in semantic processing between the left and right auditory association areas (including the STG). Semantic fields are groups of words and concepts that are closely related in meaning, often subsumed under a general term, forming a category (such as ‘animals’). In the left hemisphere, words are

associated with other words and concepts within small, focal semantic fields, whereas in the right hemisphere they are associated within large, diffuse semantic fields (Beeman & Chiarello, 1998). Therefore, the right hemisphere appears to be biased to aspects of language that require 'global' semantic processing, such as forming semantic relations that are only loosely coupled in meaning, generation of multiple meanings of words and the interpretation of whole sentences, stories or metaphors. In contrast, the left hemisphere seems to be biased to aspects of language that require 'local' semantic processing, such as single interpretations for each word. In the left hemisphere contextually inappropriate meanings of words are inhibited and one single meaning is selected. It is an imbalance in these complementary processes that is proposed to underlie disorganization symptoms and thought disorder (Kircher et al., 2002). An imbalance, created by 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, may explain the increased levels of disorganization in XXY men.

The degree to which functional asymmetries in the XXY brain represent the effects of testosterone- deficits or supplementation remains unclear. The relationship between testosterone levels and behavior is complex; timing of exposure, sensitivity to testosterone reflected in androgen receptor density and modulation by environmental factors are important determinants in the effects of testosterone (Craig et al., 2004). Furthermore, gonadal hormones may be one of many mechanisms by which sex chromosomes exert their influence on brain development. Recent animal studies have pointed to direct, non-hormonal, effects of sex-chromosomes on brain maturation (Dewing et al., 2003). In line with this, a recent longitudinal study dealing with the effects of testosterone treatment on language lateralization in transsexuals showed that language laterality is highly stable and not affected by hormonal interventions (I. E. C. Sommer et al., in prep).

In sum, the present study provides evidence for a loss of language lateralization, most prominent in the superior temporal gyrus, in XXY men. Moreover, we found that the loss in hemispheric specialization for language processing may have important consequences for mental functioning, as it was associated with dysfunctions in organization of thought and language. This suggests that a genetic mechanism involving the X chromosome is involved in the development of hemispheric specialization for language. Although speculative, such a mechanism may involve genes that are overexpressed as a result of escaping inactivation. Alternatively, it might be an epi-genetic

mechanism, involving an environmentally (i.e. non-genetic) induced change in gene function, or epi-static, involving suppression of expression of other genes. Future genetic studies with XXY men may provide insight into the mechanisms by which genes on the X chromosome direct development of functional asymmetry in the brain.

References

- Artiges E, Martinot J-L, Verdys M, Attar-Levy D, Mazoyer B, Tzourio N, et al. Altered hemispheric functional dominance during word generation in negative schizophrenia. *Schizophrenia Bulletin* 2000; 26: 709-721.
- Beeman MJ, Chiarello C. Complementary right- and left-hemisphere language comprehension. *Current Directions in Psychological Science* 1998; 7: 2-8.
- Bhati MT. The brain, language, and schizophrenia. *Current Psychiatry Reports* 2005; 7: 297-303.
- 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: Jins* 2001; 7: 446-56.
- Craig IW, Harper E, Loat CS. The genetic basis for sex differences in human behaviour: Role of the sex chromosomes. *Annals of Human Genetics* 2004; 68: 269-284.
- Crow TJ. Handedness, language lateralisation and anatomical asymmetry: relevance of protocadherin XY to hominid speciation and the aetiology of psychosis - Point of view. *British Journal of Psychiatry* 2002; 181: 295-297.
- Crow TJ. Cerebral asymmetry and the lateralization of language: Core deficits in schizophrenia as pointers to the gene. *Current Opinion in Psychiatry* 2004; 17: 97-106.
- DeLisi LE, Friedrich U, Wahlstrom J, Boccio_Smith A, Forsman A, Eklund K, et al. Schizophrenia and sex chromosome anomalies. *Schizophrenia Bulletin* 1994; 20: 495-505.
- DeLisi LE, Maurizio AM, Svetina C, Ardekani B, Szulc K, Nierenberg J, et al. Klinefelter's syndrome (XXY) as a genetic model for psychotic disorders. *Am J Med Genet B Neuropsychiatr Genet* 2005; 135: 15-23.
- Dewing P, Shi T, Horvath S, Vilain E. Sexually dimorphic gene expression in mouse brain precedes gonadal differentiation. *Molecular Brain Research* 2003; 118: 82-90.
- Dollfus S, Razafimandimby A, Delamillieure P, Brazo P, Joliot M, Mazoyer B, et al. Atypical hemispheric specialization for language in right-handed schizophrenia patients. *Biological Psychiatry* 2005; 57: 1020-1028.
- Flaum M, Swayze II VW, O'Leary DS, Yuh WTC, Ehrhardt JC, Arndt SV, et al. Effects of diagnosis, laterality, and gender on brain morphology in schizophrenia. *American Journal of Psychiatry* 1995; 152: 704-714.

- Geschwind DH, Boone KB, Miller BL, Swerdloff RS. Neurobehavioral phenotype of Klinefelter syndrome. *Mental Retardation and Developmental Disabilities Research Reviews* 2000; 6: 107-16.
- Geschwind DH, Gregg J, Boone K, Karrim J, Pawlikowska-Haddal A, Rao E, et al. Klinefelter's syndrome as a model of anomalous cerebral laterality: testing gene dosage in the X chromosome pseudoautosomal region using a DNA microarray. *Developmental Genetics* 1998; 23: 215-29.
- Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI, et al. Temporolimbic volume reductions in schizophrenia. *Archives of General Psychiatry* 2000; 57: 769-75.
- Herbert MR, Ziegler DA, Deutsch CK, O'Brien LM, Kennedy DN, Filipek PA, et al. Brain asymmetries in autism and developmental language disorder: A nested whole-brain analysis. *Brain* 2005; 128: 213-226.
- Itti E, Gaw Gonzalo IT, Boone KB, Geschwind DH, Berman N, Pawlikowska-Haddal A, et al. Functional neuroimaging provides evidence of anomalous cerebral laterality in adults with Klinefelter's syndrome. *Ann Neurol* 2003; 54: 669-73.
- Itti E, Gaw Gonzalo IT, Pawlikowska-Haddal A, Boone KB, Mlikotic A, Itti L, et al. The structural brain correlates of cognitive deficits in adults with Klinefelter's syndrome. *Journal of Clinical Endocrinology and Metabolism* 2006; 91: 1423-1427.
- Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome rating Scale (PANSS) for Schizophrenia. *Schizophrenia Bulletin* 1987; 13: 261-276.
- Kesler SR, Blasey CM, Brown WE, Yankowitz J, Zeng SM, Bender BG, et al. Effects of X-monosomy and X-linked imprinting on superior temporal gyrus morphology in Turner syndrome. *Biological Psychiatry* 2003; 54: 636-646.
- Kircher TTJ, Liddle PF, Brammer MJ, Williams SCR, Murray RM, McGuire PK. Reversed lateralization of temporal activation during speech production in thought disordered patients with schizophrenia. *Psychological Medicine* 2002; 32: 439-449.
- Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003; 19: 1233-9.

- Matsumoto H, Simmons A, Williams S, Hadjulis M, Pipe R, Murray R, et al. Superior temporal gyrus abnormalities in early-onset schizophrenia: Similarities and differences with adult-onset schizophrenia. *American Journal of Psychiatry* 2001; 158: 1299-1304.
- Menon RR, Barta PE, Aylward EH, Richards SS, Vaughn DD, Tien AY, et al. Posterior superior temporal gyrus in schizophrenia: grey matter changes and clinical correlates. *Schizophrenia Research* 1995; 16: 127-135.
- Money J. Specific neuro-cognitive impairments associated with Turner (45,X) and Klinefelter (47,XXY) syndromes: a review. *Social biology* 1993; 40: 147-151.
- Netley C, Rovet J. Hemispheric lateralization in 47,XXY Klinefelter's syndrome boys. *Brain Cogn* 1984; 3: 10-8.
- Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971; 9: 97-113.
- Ors M, Ryding E, Lindgren M, Gustafsson P, Blennow G, Roseñ I. Spect findings in children with specific language impairment. *Cortex* 2005; 41: 316-326.
- 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.
- Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. *Schizophrenia Bulletin* 1991; 17: 555-64.
- Rajarethinam RP, DeQuardo JR, Nalepa R, Tandon R. Superior temporal gyrus in schizophrenia: A volumetric magnetic resonance imaging study. *Schizophrenia Research* 2000; 41: 303-312.
- Ramsey NF, Sommer IE, Rutten GJ, Kahn RS. Combined analysis of language tasks in fMRI improves assessment of hemispheric dominance for language functions in individual subjects. *Neuroimage* 2001; 13: 719-33.
- Ramsey NF, Van Den Brink JS, Van Muiswinkel AMC, Folkers PJM, Moonen CTW, Jansma JM, et al. Phase navigator correction in 3D fMRI improves detection of brain activation: Quantitative assessment with a graded motor activation procedure. *NeuroImage* 1998; 8: 240-248.
- Ross NLJ, Wadekar R, Lopes A, Dagnall A, Close J, DeLisi LE, et al. Methylation of two Homo sapiens-specific X-Y homologous genes in Klinefelter's syndrome (XXY). *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics* 2006; 141: 544-548.

- Rossi A, Serio A, Stratta P, Petruzzi C, Schiazza G, Mancini F, et al. Planum temporale asymmetry and thought disorder in schizophrenia. *Schizophrenia Research* 1994; 12: 1-7.
- Samango-Sprouse C. Mental development in polysomy X Klinefelter syndrome (47,XXY; 48,XXXXY): Effects of incomplete X inactivation. *Seminars in Reproductive Medicine* 2001; 19: 193-202.
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry* 1998; 59 Suppl 20: 22-33;quiz 34-57.
- Shen D, Liu D, Liu H, Clasen L, Giedd J, Davatzikos C. Automated morphometric study of brain variation in XXY males. *NeuroImage* 2004; 23: 648-653.
- Shenton ME, Kikinis R, Jolesz FA, Pollak SD, LeMay M, Wible CG, et al. Abnormalities of the left temporal lobe and thought disorder in schizophrenia. A quantitative magnetic resonance imaging study. *The New England Journal of Medicine* 1992; 327: 604-12.
- Sommer I, Aleman A, Ramsey N, Bouma A, Kahn R. Handedness, language lateralisation and anatomical asymmetry in schizophrenia: Meta-analysis. *British Journal of Psychiatry* 2001a; 178: 344-351.
- Sommer IE, Ramsey NF, Kahn RS. Language lateralization in schizophrenia, an fMRI study. *Schizophr Res* 2001b; 52: 57-67.
- Sommer IEC, Cohen-Kettenis PT, Van Raalten T, van der Veer AJ, Gooren LJG, Kahn RS, et al. No effects of cross-sex hormones on cerebral lateralization: an fMRI study in transsexuals. in prep.
- van Rijn S, Aleman A, Swaab H, Kahn R. 47,XXY Karyotype and Schizophrenia Spectrum Pathology. *British Journal of Psychiatry* in press.
- 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). *Schizophr Res* 2006; 84: 194-203.
- Vollema MG, Hoijsink H. The multidimensionality of self-report schizotypy in a psychiatric population: an analysis using multidimensional Rasch models. *Schizophr Bull* 2000; 26: 565-75.
- Vollema MG, Sitskoorn MM, Appels MCM, Kahn RS. Does the Schizotypal Personality Questionnaire reflect the biological-genetic vulnerability to schizophrenia? *Schizophrenia Research* 2002; 54: 39-45.

Weiss EM, Hofer A, Golaszewski S, Siedentopf C, Felber S, Fleischhacker WW. Language lateralization in unmedicated patients during an acute episode of schizophrenia: A functional MRI study. *Psychiatry Research - Neuroimaging* 2006; 146: 185-190.