Advances in research on the neurological and neuropsychiatric phenotype of Klinefelter syndrome

Ivanka Savic

Purpose of review
Klinefelter syndrome, 47,XXY is the most common chromosomal aberration among men. It represents a naturally occurring human model for studies of both X-chromosome gene expression and potential androgen effects on brain development and function. The aim of this review is to combine available brain imaging and behavioral data to provide an overview of what we have learned about the neural underpinnings of cognitive, emotional and behavioral dysunctions in Klinefelter syndrome.

Recent findings
The behavioral phenotype of 47,XXY is characterized by language, executive and psychomotor dysfunction, as well as socioemotional impairment. The prevalence of schizophrenia, attention deficit hyperactivity disorder, autism spectrum disorders and affective regulation problems is increased. Neuroimaging studies of children and adults with Klinefelter syndrome syndrome show characteristic structural changes from typical individuals. There are increases in the grey matter volume of the sensorimotor and parietooccipital regions, as well as significant reductions in amygdala, hippocampal, insular, temporal and inferior-frontal grey matter volumes. Widespread white matter abnormalities have been revealed, with reductions in some areas (including anterior cingulate, bilaterally) but increases in others (such as left parietal lobe). Mechanisms underlying these developmental anomalies could include imbalance in gene dosage relative to typical men or women, as well as the potential consequence of endocrinological deficits.

Summary
Studies of Klinefelter syndrome could generate important information about the impact of anomalies in sex chromosome gene regulation on the development of cerebral grey and white matter and, ultimately, on human behavior.

Keywords
brain, MRI, neuropsychology, sex chromosome, XXY

INTRODUCTION

Many neuropsychiatric disorders show an uneven sex distribution in their prevalence. There are also sex-specific differences in symptoms, age at onset and treatment response [1■]. The origins of sexual dimorphism in psychiatric phenomena are largely unknown. One possible mechanism could be that normal sex differences in cerebral anatomy, connectivity and function render men and women susceptible to different aspects of psychopathology. Such anatomical and functional differences are ultimately linked to the role of sex-chromosome genes, which may be direct or indirect. Insights into the potential impact of anomalous sex chromosome gene expression on cerebral sex dimorphism in humans can be studied in the sex chromosome aneuploidies, so-called experiments of nature [2–4].

Klinefelter syndrome (47,XXY) is the most common form of sex chromosome aneuploidy, which occurs in one in 650 men. About 10% of identified cases are diagnosed in the prenatal period by amniocentesis. Most remain undiagnosed, but others may be picked up postnatally because of developmental delay, hypogonadism, gynecomastia or infertility. A few are identified because of associated behavioral

Department of Clinical Neuroscience, Karolinska Institute, Solna, Stockholm, Sweden

Correspondence to Ivanka Savic, Department of Clinical Neuroscience, Stockholm Brain Institute, Karolinska Institutet, Retziusväg 8, 171 77 Solna, Stockholm, Sweden. Tel: +46 8 51776761; fax: +46 8 660 15 01; e-mail: ivanka.savic-berglund@ki.se

or psychiatric disorders [5]. Klinefelter syndrome was originally described by Dr Klinefelter in 1942, and is characterized by a variety of physical and psychological features. A 'prototypical' physical phenotype includes tall stature, hypogonadism and fertility problems. Testosterone levels are normal or subnormal until puberty when, relative to the surge in normal males, they are substantially reduced [6,7], requiring pharmacological supplementation.

Many Klinefelter syndrome men are not significantly affected by their condition. On the other hand, for some the presence of the extra X chromosome is associated with cognitive, psychosocial, motor and language deficits. Because Klinefelter syndrome individuals show cognitive deficits even before puberty, at a time when testosterone levels are near normal [8], it is unlikely that the profile results from androgenic insufficiency affecting neural development. However, there are anecdotal studies that testosterone supplementation leads to better grey matter preservation in the superior temporal gyrus [9].

The cognitive and behavioral features that typify Klinefelter syndrome are potentially attributable to two types of genetic mechanism. First, there could be excessive expression of genes that lie in the pseudoautosomal regions of the X chromosome. These genes have homologues on the Y chromosome, therefore in Klinefelter syndrome there are effectively three copies; note that genes in this region are not subject to X inactivation although other regions of the X chromosome will be subject to X inactivation, as in normal females. Second, there is evidence that up to 15% of other genes on the 'inactivated' X chromosome usually escape inactivation in normal females. They could therefore be expressed in excess in Klinefelter syndrome relative to typical men, but may not be expressed to the same extent as in typical 46,XX women [10]. It is certainly intriguing that the typical cognitive characteristics of Klinefelter syndrome complement the corresponding cognitive profile of women with 45,X monosomy (Turner's syndrome) [11,12]. In the former condition, visuospatial skills are largely preserved but verbal skills are selectively impaired, but in Turner syndrome the opposite profile is usually seen. These observations raise questions about whether sex chromosomes play a critical role in the development and functioning of the human brain, and whether their dysregulation is therefore responsible for the cognitive, social, emotional and behavioral characteristics of sex chromosome aneuploidies.

Recent neuroimaging studies, which will be cited in this review, provide some interesting information on this yet rather speculative issue. Longitudinal data from magnetic resonance investigations of the developing brain have shown that boys and adults with Klinefelter syndrome have consistent changes in grey matter and white matter volume, structural volumes and white matter organization. Overall, these changes consist of significant increases in sensory–motor and parietooccipital grey matter, as well as significant reductions in the volume of the insula as well as the temporal lobe, the inferior-frontal cortex as well as the amygdala, hippocampus, caudate and cerebellum [2–4,8,9,13–18,19∎].

Diffusion tensor imaging (DTI) has revealed reductions in white matter within the left posterior internal capsule, bilateral anterior cingulate and the left arcuate bundle [17]. Some structural changes, such as the grey matter reductions in the amygdala and the superior temporal gyrus (STG), and increases in grey matter volume of the precentral and parietal regions, are complementary to those detected in Turner syndrome [20–22,23∎].

Our group recently finished a voxel-based morphometry study that compared men with Klinefelter syndrome and matched female and male controls, taking into account sex hormone levels and the digit ratio (a proxy for the androgen receptor-mediated action of fetal testosterone). We made this correction in an effort to discern between possible cerebral effects of X chromosome dosage, sex chromosome dosage and sex hormone levels [24]. We found that the reduced grey matter volumes of the amygdala, superior temporal cortex and insula and the increased grey matter in the parietal lobe of men with Klinefelter syndrome were linked primarily to the sex chromosome number. There was only a minor influence of testosterone deficiency. On the other hand, elevated grey matter volume in the motor cortex was related to the X chromosome number.

I will now attempt to relate the major characteristics of the cognitive phenotype of Klinefelter syndrome to these cerebral abnormalities, and speculate upon the actions of sex-chromosome anomalies on brain function.

LANGUAGE FUNCTIONS

Language difficulties represent the most common disability of children with Klinefelter syndrome, and have been identified in 70–80% of cases [25,26]. Impaired auditory processing and poor auditory memory appear to underlie many of the linguistic problems seen in this condition. Typically, affected children have difficulties with articulation, phonemic processing and word retrieval, in addition to

more generally delayed expressive language and verbal fluency skills [27,28].

People with Klinefelter syndrome also have difficulties in the more complex aspects of both impressive and expressive language, such as the recovery of words and verbal conceptual reasoning skills [25,29]. Problems with language limit the individual's capacity to communicate, and hence reduce social adaptation [30]. It is possible that such deficits partly explain the increased vulnerability to psychiatric disorders in men with Klinefelter syndrome.

Possible structural correlates of the vulnerability to psychiatric disorders of men with Klinefelter syndrome could be the grey matter deficits in the superior temporal gyrus and the inferior frontal gyrus, and the white matter anomalies found in the left arcuate bundle [17] (see below, and also Fig. 1).

The volume of grey matter in the superior temporal gyrus of women with X monosomy is increased [3,4], suggesting that the corresponding reduction in the volume of this region in Klinefelter syndrome men (compared with male and female controls) could be related to anomalous X-linked gene expression [24].

COGNITIVE FUNCTIONS

Cognition is defined as the mental process by which knowledge is acquired, and includes perception, intuition and reasoning. There is significant variability in the cognitive abilities of children and adults with Klinefelter syndrome. On an average, patients

with Klinefelter syndrome are not intellectually disabled. They display, however, an imbalance between verbal intelligent quotient (IQ) and performance IQ, with consistently better visuospatial than verbal skills. As already noted, in women with X monosomy verbal IQ is usually superior to performance IQ [31].

Men with Klinefelter syndrome also have impaired executive functions, with particularly severe deficits in the inhibitory component [32]. In a study of dichotic listening (a speech sound task, wherein the main instruction was to focus one's attention on stimuli presented to either the right or the left ear), we recently found that Klinefelter syndrome men's attentional orientation was intact. Despite this observation, they had a selective deficit in inhibitory executive functions compared with both male and female controls [33■].

Unpublished follow-up analyses with DTI suggest that the observed reduction in inhibitory output to the contralateral hemisphere is related to reduced corpus callosum volume.

EMOTIONAL AND PSYCHOSOCIAL FUNCTIONS

Men with Klinefelter syndrome seem to be more sensitive, anxious and insecure, and show a higher incidence of anxious–depressive disorders than men in the general population [30]. They are reported to experience increased levels of emotional arousal yet they also have difficulties in expressing their emotions. Impairments in decoding facial expressions of emotion, specifically anger [11,34],
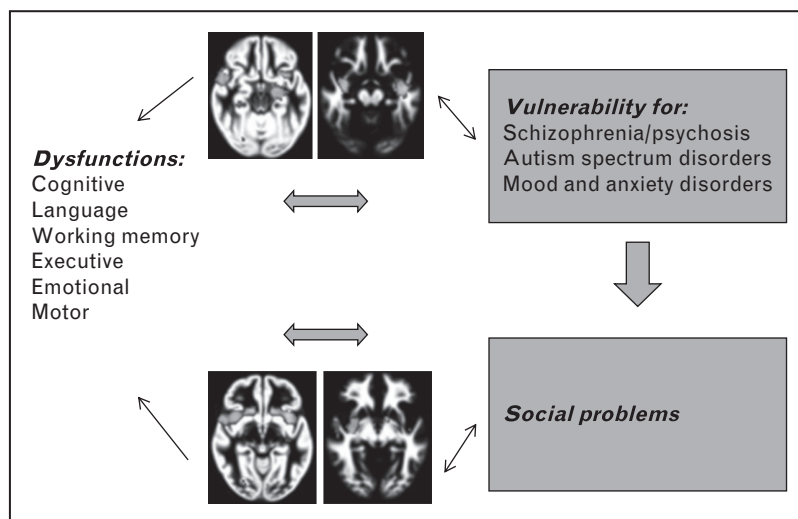

FIGURE 1. The psychoneurological phenotype of Klinefelter syndrome and its structural underpinnings. Grey clusters on the MRI images of the Montreal Neurological Institute atlas brain illustrate the major reductions in the grey matter and white matter in Klinefelter syndrome males in relation to both male and female controls investigated in a recent study from our group.

and difficulties in interpreting affective tone of voice (independent of the associated language dysfunction), are common [35]. Men with Klinefelter syndrome therefore have an altered perception of emotional stimuli, as well as impaired interpretation and labeling of such stimuli. In addition to problems with communication and imagination, they have increased attention to detail, at the expense of seeing 'the bigger picture' [8]. This combination of inaccurate perception of social–emotional cues, disability to describe own emotions and impaired language processing is very similar to autistic traits. Not surprisingly, Bruining *et al.* [36] found that 27% of the boys with Klinefelter syndrome in their study group met criteria for autism spectrum disorders.

Interestingly, several of the brain structures that appear to have an abnormal structure in Klinefelter syndrome (the amygdala, the STG, the caudate and putamen) constitute important relays in the network processing the perceptive component of social cognitive functions [37]. Klinefelter syndrome males have reductions in amygdala volume [2,3,18], in the grey matter volume in the orbitofrontal cortex, and in the uncinate fascicle [24], see also Fig. 1. These structural characteristics could provide a neural basis for the Klinefelter syndrome-associated altered perception of emotional stimuli, as well as for the impaired interpretation and labeling of such stimuli.

MOTOR FUNCTIONS

Boys with Klinefelter syndrome have problems with motor development [38]. They show difficulties in jumping and hopping, in bilateral coordination, and upper limb speed. Slow fine motor movements, reduced strength and running speed have also been observed [39,40]. Similar motor impairment has been detected also in XYY boys [39], suggesting the cause could result from the impact of sex-chromosome trisomy (e.g. overexpression of pseudoautosomal genes that have homologues on the X and Y chromosomes). On the contrary, there are similar motor problems associated with X monosomy in which such genes would be underexpressed. For example, poor sensory–motor integration has been described among women with Turner syndrome [38]. In general, the cerebral underpinnings of motor dysfunction that are found in association with sex chromosome aneuploidies have been little investigated. It would be necessary to undertake comparative studies of the identical motor task in both X-monosomic (45,X) females and Klinefelter syndrome (47,XXY) males in order to address outstanding questions about the role of sex chromosome-linked genetic dosage effects.

PSYCHIATRIC VULNERABILITY

Men with Klinefelter syndrome have an increased prevalence of psychiatric disturbances, ranging from attention deficit disorder in childhood to schizophrenia and severe affective disorders during adulthood [17,36,41]. 47,XXY aneuploidy is found in about 0.8–1% of men hospitalized for schizophrenia, representing a four-fold to five-fold excess over the incidence at birth of Klinefelter syndrome [42]. According to a recent study by Bruining *et al.* [36], 8% of the clinically identified Klinefelter syndrome population meet criteria for a psychotic disorder, 45% have isolated psychotic symptoms, and 24% meet criteria for depressive disorder. However, it must be emphasized that the proportion of men with Klinefelter syndrome in the general population who have been clinically identified is very small, and so these figures are likely to represent a biased sample.

In an extensive survey including 310 individuals with self-reported Klinefelter syndrome, clinically significant levels of depressive symptoms were detected in about 70% of participants, according to a Center for Epidemiologic Studies Depression Scale [43]. Structural brain differences in Klinefelter syndrome that could be associated with this increased risk of psychopathology could include a combination of amygdala, insular and STG volume reduction, and disorganization of the temporo-frontal white matter connections [17]. Of particular interest here is the grey matter volume reduction in the posterior portion of the STG, because this region includes the planum temporale, a structure implicated in language processing and thought disorder in schizophrenia [44].

Another possible biological mechanism could be a reduced hemispheric specialization for language processing, which according to some authors predisposes to disorders with dysfunctional thought processing. Van Rijn *et al.* [8] explored the relation between mental functioning and language lateralization, focusing on disorganization of thought in Klinefelter syndrome. They employed a psychiatric interview, including a measure of schizotypy [8]. They also conducted functional MRI studies, using three language tasks (a verb generation task, an antonym generation task and a semantic decision task). Compared with controls, the Klinefelter syndrome patients showed reduced hemispheric specialization for language, with decreased functional asymmetry in the STG and the supramarginal gyrus (part of Wernicke's area). Reduced lateralization in the STG correlated significantly with the disorganization of language processing [8]. These findings indicate that reduced hemispheric specialization for language processing

in the STG may be associated with disorganization of thought and language. Similar dysfunction is seen in the schizophrenia spectrum. Whether the reduced hemispheric asymmetry in Klinefelter syndrome is due to the extra X chromosome, the low testosterone levels during puberty or both is currently unknown and needs further investigation.

CONCLUSION

The presence of an extra X chromosome in Klinefelter syndrome is associated with the abnormal development of both grey and white matter in the frontal and temporal lobes. We speculate that these structural changes, in comparison with typical 46,XY males, provide a structural basis for the specific cognitive deficits observed in Klinefelter syndrome males.

Comparative neuropsychological and MRI studies of sex chromosome aneuploidies, examining patients with an excess or deficiency of X-linked or Y-linked genetic material, could provide insight into how the sex chromosomes influence the development of the 'social brain'. In this review of the neurobiological, cognitive and emotional consequences of the aneuploidy associated with Klinefelter syndrome, clues may be found that could eventually shed light on sex differences in vulnerability to neuropsychiatric disorders.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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