A review of neurocognitive functioning and risk for psychopathology in sex chromosome trisomy (47,XXY, 47,XXX, 47,XYY)

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Purpose of review
About one in 650–1000 children is born with an extra X or Y chromosome, referred to as sex chromosome trisomies (SCTs). Studying SCTs may uncover unique insights in neurodevelopmental pathways underlying the risk for neurobehavioral problems and psychopathology. There is also a clinical need for more knowledge about the phenotype of SCT with the recent introduction of noninvasive prenatal screening.

Recent findings
The reviewed studies illustrate an increased vulnerability for psychopathology such as (symptoms of) autism spectrum disorder, attention-deficit/hyperactivity disorder, anxiety, depression and, to a lesser degree, psychotic disorders. Although traditionally the primary focus has been on language and learning problems, recent research suggests that impairments in executive functioning, social cognition and emotion regulation may also be key factors underlying the risk for neurobehavioral problems.

Summary
The research field of SCT is in need of a more longitudinal perspective to identify early markers of 'at risk' development, and to assess the effectiveness of early interventions. Neurocognitive markers that signal compromised neurodevelopment may prove to be helpful in this. Variability in the SCT phenotype provides a unique opportunity to identify not only genetic but also environmental factors that shape neurodevelopmental outcome, calling for studies focused on understanding individual differences.

Keywords
behavior, cognition, Klinefelter syndrome, trisomy X, XYY

INTRODUCTION

About one in 650–1000 children is born with an extra X or Y chromosome, resulting in the 47,XXY, 47,XXX or 47,XYY chromosomal pattern. The most common cause is nondisjunction of the X or Y chromosome during early cell division, most often during meiosis. Knowledge about the neurocognitive and behavioral phenotypes remains rather limited, which is somewhat surprising considering the disproportionate amount of genes on the X chromosomes that have been linked to brain functioning [1].

However, in the last two decades, sex chromosome variations have received increased attention, in part driven by an increasing awareness that studying gene–brain–behavior pathways in these genetic conditions may uncover new insights in mechanisms of developmental risk that may lead to psychopathology. It has been argued that this 'behavioral neurogenetics approach' [2] may provide a powerful tool that can complement the study of behaviorally defined populations. As sex chromosome trisomies (SCTs) can already be identified as early as prenatally, this offers the opportunity to prospectively study early neurodevelopmental markers of individual differences in outcome in terms of neurobehavioral symptoms and risk for psychopathology. There is also an increasing clinical need for knowledge about SCT. The number of children prenatally diagnosed with SCT is expected to increase with availability of the noninvasive prenatal screening test [3], which calls for more knowledge about the phenotype of SCT to be able to

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Curr Opin Psychiatry 2019, 32:79–84
DOI:10.1097/YCO.0000000000000471

KEY POINTS

- A subgroup of individuals with SCT is at increased risk for neurobehavioral problems and psychopathology.
- Neurocognitive factors that may drive this increased risk include impairments in language, executive functioning, social cognition and emotion regulation.
- Insight in these underlying cognitive mechanisms provides opportunities for improving diagnostic screening, and subsequent close monitoring of vulnerable children with SCT, in order to positively influence developmental outcome through early support and tailored intervention.
- As SCT can be identified already prenatally, studying SCT can help in identifying early markers of 'at-risk' developmental pathways in childhood.
- Variability in the phenotype in SCT may help in identifying risk and protective factors that shape developmental outcome of children, focusing not only on genetic factors but also on environmental factors.

monitor child development, and provide clinical care and early support or intervention if needed.

This need for knowledge may be most pressing for the neurobehavioral domain: so far, the majority of research studies (about 75%) have focused on the somatic/medical phenotype, with only 25% of the studies focusing on the neurobehavioral phenotype [4]. In addition to characterizing the variety and severity of behavioral problems that may be seen in SCT, it is also of great importance to have a better understanding of the mechanisms underlying the behavioral phenotype. Similar behavioral problems may arise from different underlying information processing dysfunctions in the brain. Knowledge about these cognitive dysfunctions that are core to behavioral problems in SCT is crucial for disentangling etiological pathways, and is also essential for identifying the nature of developmental vulnerability, as well as the identification of specific targets for intervention, enabling more tailored mental healthcare.

Here, a compact review is provided of risk for psychopathology and neurocognitive vulnerabilities that may underlie this increased risk in individuals with SCT. Recent developments in this field are highlighted, and directions for future research are provided.

AUTISM SPECTRUM DISORDER SYMPTOMS

A systematic review has established a worldwide prevalence rate of autism spectrum disorder (ASD) of 0.6% in the general population [5]. Levels of autism symptoms and risk for ASD have shown to be significantly higher in SCT as compared to the general population. To illustrate, on average, 25% children with XXY (ranging from 12 to 47%) have autism symptoms in the mild/moderate-to-severe range [6–9]. When considering diagnostic classification of ASD, on average 18% of the children meet full ASD criteria, with a range of 10–27% [7,10,11]. When looking at the history of clinical diagnoses based on screening of medical files or parental report, this percentage is somewhat lower at 7% (ranging from 5 to 11%) [6,9,12]. Increased levels of ASD symptoms have also been found in adults with XXY, with 6.5% scoring above clinical cutoff [13]. This fits with a screening of hospital discharges in 860 adults with XXY, showing that ASD was diagnosed 6.2 times more often as compared to men with XY [14].

Also, for individuals with XXX, significantly increased rates of ASD diagnoses or clinically significant ASD symptoms have been observed, with an average rate of 15% of the children (ranging from 10.8 to 20%) [7,15].

In individuals with XYY, a clinical diagnostic classification of ASD has been found in on average 30% of the children (ranging from 19 to 43%) [9,10,12,16,17]. Studies using dimensional measures have shown that 35% of the boys have ASD symptoms in the mild–moderate range, and another 50% in the severe range [9].

ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS

A meta-analysis of worldwide attention deficit hyperactivity disorder (ADHD) prevalence in children found an overall estimate of 7.2% [18]. As compared to the general population, significantly higher levels of ADHD symptoms as well as increased risk for ADHD have been reported for SCT. Using dimensional measures, clinical levels of ADHD symptoms have been found in on average 35% of the children with XXY (with a range of 27–42%) [9,19,20], with inattentive symptoms more predominant than hyperactive/impulsive symptoms [20]. When considering full diagnostic classification of ADHD (either direct assessment or clinical history), on average 43% of the children and adolescents (with a range of 34–63%) meet diagnostic and statistical manual of mental disorders (DSM) criteria for ADHD [6,9,11,21]. In adults with XXY, ADHD was diagnosed 5.6 times more often according to a screening of hospital discharges in 860 adults with XXY as compared to 86 000 men with XY [14].

A review on XXX has reported an estimated 25–35% of the individuals with XXX having ADHD

[19,22]. Somewhat higher rates have also been reported with on average 49% (ranging from 46.7 to 52%) having attention symptoms in the clinical range [20,23], which is in line with a recent study reporting 48.9% of the girls with XXX having a diagnosis of ADHD [15].

For XYY, dimensional measures have shown that on average 69% of the XYY boys (ranging from 62 to 76%) had clinical levels of ADHD symptoms [9,20]. An average of 36% of boys with XYY (ranging from 11 to 52%) met full diagnostic criteria for ADHD, either based on clinical evaluation or history of psychiatric diagnoses [9,16,17].

PSYCHOTIC SYMPTOMS

On the basis of meta-analysis, the median global prevalence of psychotic disorders in the general population has been estimated at 0.46% [24]. A screening of hospital discharges in 860 adults with XXY revealed that psychotic disorders (schizophrenia or bipolar disorder) were diagnosed 7.4 times more often as compared to men with the typical XY pattern [14]. Clinical assessment studies have shown that 12% of the children with XXY [11] and 6.5% of the adults with XXY [25] meet DSM criteria for a psychotic disorder. In those with XXX, bipolar or psychotic disorders have been observed in 13.3% [15]. In individuals with XYY, psychiatric screening revealed a rate of 8% for bipolar disorder [17].

When considering dimensional measures, significantly higher rates of thought problems in SCT have been found in comparison to the general population: 37.8% of the children with XXY or XXY [19] and 30% of the individuals with XXX [23].

ANXIETY/DEPRESSION SYMPTOMS

Meta-analysis has shown global prevalence rates of 7.3% for anxiety disorders [26] and 12.9% for depression [27] in the general population. Data suggest that rates may be higher in SCT, although direct comparisons with control groups are lacking, except for two more recent studies using dimensional measures in SCT groups versus control groups, which showed mixed results [19,23]. In individuals with XXY, the average reported rate of depressive disorders is 26.9% (ranging from 12 to 68%) [6,11,25,28,29]. Clinically significant anxiety symptoms have been observed in on average 20.5% of the children with XXY (ranging from 14 to 27%) [6,19]. The reported rates of depression in XXX range from 17.8 [15] to 54% [28]. Anxiety disorders have been found in 19.5% [15] and clinical levels of anxiety-depression symptoms in 27–30% of the individuals with XXX [19,23]. As for XYY, a reported 13% had a depressive disorder and 26% had an anxiety disorder [17].

NEUROCOGNITIVE VULNERABILITY

Although IQ is typically at the borderline or lower end of the normal range [30], and intellectual disability is not common, the majority of children with SCT have specific cognitive impairments to some degree. Although the majority of studies have traditionally primarily focused on describing academic achievement and global intellectual levels, in recent years more and more studies have relied on comprehensive performance-based assessment of multiple and specific cognitive domains, as outlined below.

LANGUAGE

One of the best described and most recognized domains of cognitive vulnerability is language dysfunction. To illustrate, about 70–80% of children with 47,XXY have language difficulties that are typically present already from a young age [31]. This finding has been quite robust, being shown in numerous and unbiased samples [30,31]. Compromised language development is not only characteristic for boys with XXY, but also for boys with XYY and girls with XXX, although the degree of impairment may vary somewhat depending on the karyotype [32]. Difficulties include both receptive and expressive language skills (with the latter typically somewhat more affected), as well as difficulties in communication and language pragmatics [12,33]. Although the majority of studies have focused on school-aged children, more recent neuropsychological studies (of children with XXY and XXX) have started to investigate language development in children as young as 18–24 months, describing smaller vocabulary size and difficulties in lexical skills and emergent syntactic abilities [34▪,35].

With regard to the association between language dysfunction and psychopathology, two studies have shown that more compromised language functioning is directly associated with higher levels of autism symptoms in children, adolescents and adults with XXY [8,36].

EXECUTIVE FUNCTIONING

Executive functions are considered essential for flexible adaptive functioning in complex situations that have a high load of information, for inhibition of irrelevant actions and thoughts, for dealing with changing environmental demands and for organization of actions and thoughts in a goal-directed way. Although some of the early studies on

executive function emphasized primarily working memory impairments in SCT [37], there is now increasing evidence for significant difficulties (as compared to the general population) in a range of executive function functions including inhibition, mental flexibility, strategic planning, fluency, working memory and sustained attention regulation, with medium-to-large effect sizes [19,21,38,39]. Although the majority of studies have focused on XXY and XXX, executive function problems have also been found in boys with XYY, with somewhat more compromised scores as compared to XXY [32]. In a study including both boys with XXY and girls with XXX, rates of 16–37% of the children with clinically impaired executive dysfunction were found [19]. A very recent international investigation of boys with XXY showed rates of 23–57% of the children having executive function dysfunctions within the clinically impaired range [40▪]. Vulnerability in executive function also seems to translate to daily life difficulties in executive function as observed by parents [19,41]. Executive function problems may show variability across age [41,42], are observed in both boys with XXY and girls with XXX [19,41] and may be more pronounced in the context of early life stressors [43].

In terms of the role of executive function difficulties in behavioral symptoms and risk for psychopathology in SCT, there is evidence showing that compromised executive functioning is significantly associated with increased externalizing behavior problems [19], increased social difficulties and ASD symptoms [39,44], increased psychotic symptoms such as disorganized thought [45] and increased symptoms of ADHD [21].

SOCIAL COGNITION AND EMOTION

Social cognition refers to the ability to perceive, understand and express social signals, which is crucial for successful social adaptation. Emotions, if well regulated, also have an important role in social functioning by facilitating behaviors that are adaptive to the social environment [33]. In the last decade, several studies in individuals with XXY or XXX have revealed significant impairments in these areas as compared to the general population. These include difficulties in reading social signals from social gaze direction [46] or tone of voice [47] and difficulties in recognizing emotional expressions from faces [48,49▪,50], which may be more pronounced in the context of early life stressors [43]. A reported 16–43% of the children with XXY [40▪] and 33% of the adults with XXY [49▪] have facial affect recognition problems in the clinically impaired range. In addition to understanding facial expressions, research suggests that significantly more children with XXY or XXX have difficulties with theory of mind [48], referring to the attribution of mental states, intentions and emotions to others. A very recent study suggests that children and adults with XXY may have disproportionate difficulties when 'social load' of information increases, revealing difficulties in the higher order labeling and interpretation of social cues [49▪].

The processing of facial emotions has been studied in more detail using eyetracking. One of these studies showed that adults with XXY looked less to the eye region of faces and did not show the typical tendency to first fixate on the eyes when presented with a face [51]. Shorter looking times were associated with poorer social functioning. Another eyetracking study in adults with XXY showed decreased attention to the eyes of characters displaying emotions, but increased affective arousal in response to these emotions [52]. This hyperarousal fits with studies showing increase social anxiety in men with XXY [13] and children with XXY or XXX [7], as well as increased subjective emotional arousal in response to emotion-inducing events, and increased influence of emotions during strategic, goal-directed tasks in adults with XXY [50]. Such increased affective arousal levels may negatively affect social interactions, especially as difficulties in recognizing and labeling of own emotions have been found in adults with XXY [50], which likely hampers the implementation of emotion regulation strategies. Indeed, more problems in the regulation of emotions have been reported for children and adolescents with XXY or XXX [41].

CONCLUSION

The reviewed studies illustrate an increased risk for social, emotional and behavioral problems in individuals with SCT. Although traditionally the primary focus has been on language and learning problems, more recent research suggests that impairments in executive functioning, social cognition and emotion regulation may also be key factors underlying the risk for behavioral problems and psychopathology. Insight in these underlying cognitive mechanisms provides opportunities for improving diagnostic assessment, and subsequent close monitoring of vulnerable children with SCT, in order to positively influence developmental outcome through early support and tailored intervention. Early implementation of preventive interventions, delivered during key windows of opportunity when neurodevelopment is most sensitive for environmental influences, has the potential to optimize quality of life and reduce risk for mental health problems later in life [53].

Ascertainment and recruitment biases are always important factors in SCT research, and contribute to the variance in the described vulnerabilities and lack of representation for the full population. In interpreting study findings, it is important to distinguish cohorts recruited for research purposes versus those that represent clinical samples. Also, cohorts identified through postnatal identification likely overestimate severity of the SCT phenotype (because of preselection of more severe cases), whereas cohorts identified based on prenatal screening may underestimate severity of the phenotype (because of higher socioeconomic status and implementation of early support and intervention). Increased awareness of these biases and increasing attempts to investigate the impact of these biases in studies with mixed prenatal/postnatal samples are helpful in determining the full range of outcomes in SCT.

The research field of SCT is in need of a more longitudinal perspective to study the described neurocognitive and behavioral aspects of the phenotype of SCT already from an early age onward. SCT can already be diagnosed prenatally, providing the responsibility and at the same time unique opportunity to identify early markers of 'at risk' development. Neurocognitive assessments that signal compromised neurodevelopment may prove to be helpful in this.

Studying SCT may also help in generating specific genetic hypotheses. Although few studies so far have attempted to link specific genes on the X or Y chromosomes to the neurobehavioral phenotype, recent studies have yielded very promising results [54]. Nonetheless, it is important to acknowledge that it is not all about the genes, and that is only in interaction with the environment that the phenotype is shaped, contributing to variability in outcome in SCT. This calls for a more integrated perspective considering developmental vulnerabilities in children with this genetic syndrome in the context of environmental factors, which may also help in identifying protective factors that could be targeted to reduce developmental risk as much as possible. Focusing on subgroups and individual differences rather than relying on group averages may also help uncover key mechanisms that contribute to risk for specific and different types of psychopathology.

Acknowledgements

None.

Financial support and sponsorship

This work was supported by a personal grant (to S.v.R., grant number 016.165.397) from the Netherlands Organization for Scientific Research (NWO).

Conflicts of interest

There are no conflicts of interest.

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