X marks the spot: Structural and functional brain mapping in a genetically defined group at high risk of autism symptoms (47,XXY), and a comparison with idiopathic autism spectrum disorder

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Citation

Cover Page

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Title: X marks the spot : structural and functional brain mapping in a genetically defined group at high risk of autism symptoms (47,XXY), and a comparison with idiopathic autism spectrum disorder
Issue Date: 2015-11-11

Chapter 1

General introduction

Social behavior

Human beings are inherently social creatures. Although all primate brains are unusually large for body size as a result of the interaction between genetic mutations and the demands of living in complex social systems (Dunbar, 2009), our social interactions are infinitely more intricate. However, certain developmental conditions prevent individuals from adequately mastering social skills. This can lead to problems in adequately recognizing and interpreting social cues. Social skills develop gradually throughout childhood under the influence of both individual characteristics, and environmental factors. Social functioning involves cognitive abilities necessary to process social cues, communicative skills to successfully navigate social interactions, and the ability to use these skills across many domains in order to adapt to the social environment (e.g. at home, at work, or at social events) (Beauchamp & Anderson, 2010). Impairments in these skills significantly impact the ability to navigate our relatively fast-paced, complex social world, which is why it is important to investigate possible causes of impairments in social development. An example of a developmental disorder that has social dysfunction as its core feature, is autism spectrum disorder (ASD). The core symptoms of ASD include clinically significant deficits in social communication and interaction, and restricted, repetitive behavioral patterns. The individual manifestations of these deficits vary greatly, depending on the severity of the disorder, developmental level, and age (A.P.A., 2013). Full diagnostic criteria for autism spectrum disorder according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (A.P.A., 2013) are cited in Box I.

Box I. DSM-5 diagnostic criteria for autism spectrum disorder

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Autism spectrum disorder

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history:
  1. Deficits in social-emotional reciprocity;
  2. Deficits in nonverbal communicative behaviors used for social interaction;
  3. Deficits in developing, maintaining, and understanding relationships.
B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history:
  1. Stereotyped or repetitive motor movements, use of objects, or speech;
  2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior;
  3. Highly restricted, fixated interests that are abnormal in intensity or focus;
  4. Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment.
C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay.

Research on impaired social development has mainly focused on ASD, as social dysfunction is the main characteristic of this condition. These types of studies are very useful and important for gaining insight into the mechanisms behind problematic social development, but new perspectives may provide new insights. Studying genetic conditions may also help uncover different pathways to social dysfunction that are more difficult to uncover by studying idiopathic ASD. ASD is behaviorally defined, and may therefore include a wide variety of underlying mechanisms leading to social dysfunction (Mottron, Belleville, Rouleau, & Collignon, 2014; Muhle, Trentacoste, & Rapin, 2004). For this reason it may be useful to study populations defined by a genetic condition that often leads to social problems, and in some cases autistic symptomatology. Studies focused on sex chromosome aneuploidies such as Klinefelter syndrome may aid in determining developmental risks for social dysfunction. Social development is often compromised in 47,XXY. Their genetic profile is known and they have a relatively homogeneous endophenotype. This is of considerable benefit when looking for (neuro)biological markers of social dysfunction, because it allows for investigation of the relationship between genetic, neural,

cognitive, and behavioral outcomes. Therefore, by studying this population, gene-brain-behavior pathways to social dysfunction may be delineated.

Klinefelter syndrome

Typically, human cells contain 23 pairs of chromosomes. 22 of those pairs are autosomes, existing in both males and females, while the last pair consists of sex chromosomes that determine the sex of an individual. This means that in typical male development, a 46,XY karyotype is present. In 1942 Harry Klinefelter described a syndrome in males, characterized by gynecomastia (i.e. enlarged breast tissue), and a specific type of hypogonadism (i.e. diminished functionality of the gonads) (Klinefelter, Reifenstein, & Albright, 1942). In 1959 it was found that these individuals had an extra X chromosome, leading to the 47,XXY karyotype (Jacobs & Strong, 1959). This syndrome was coined Klinefelter syndrome. The prevalence of this condition is about 1 in 650 newborns (Bojesen, Juul, & Gravholt, 2003), and over the years research has shed light on its physical, behavioral, and cognitive ramifications.

Physical, cognitive, and behavioral consequences of Klinefelter syndrome

The physical phenotype of Klinefelter syndrome (47,XXY) is variable and often quite subtle. Gross facial or physical abnormalities are absent. Individuals with this condition typically have disproportionally long limbs, deviating distribution of body fat including gynecomastia, decreased growth of pubic and facial hair, hypogonadism, which may influence fertility, and deviations in testicular and penile development (Bojesen et al., 2003). Additionally, individuals with 47,XXY may have diminished muscle strength (Ross et al., 2008). Current treatment for the physical symptoms includes implementation of supplemental testosterone treatment at the beginning of puberty. This may contribute to, for example, improved muscle mass and increased growth of pubic and facial hair.

Behaviorally, 47,XXY is associated with impairments ranging from subtle to pronounced. Individuals with 47,XXY are at increased risk of developing internalizing behavioral problems, shyness and withdrawal (Tartaglia, Cordeiro, Howell, Wilson, & Janusz, 2010). Additional problems include hyperactivity, impulsivity, and an increased risk of a clinical diagnosis of attention-deficit/hyperactivity disorder (Bruining, Swaab, Kas, & Van Engeland, 2009; Cederlof et al., 2014; Tartaglia et al., 2010). Individuals with 47,XXY are also more vulnerable to psychotic-like symptoms, and they are at increased risk of developing psychotic disorders (Cederlof et al., 2014). Furthermore, within the study by Cederlof et al. (2014), 5-25% of males with 47,XXY were diagnosed with ASD. Even in the absence of a formal ASD diagnosis, prominent social behavioral difficulties may be present. Individuals with 47,XXY often display autistic symptomatology such as social anxiety, reduced assertiveness, impaired emotion regulation, and communicative difficulties (Bishop et al., 2011;

Cederlof et al., 2014; Cordeiro, Tartaglia, Roeltgen, & Ross, 2012; Tartaglia et al., 2010; Van Rijn et al., 2014).

47,XXY is associated with a wide range of cognitive problems. Typically, intellectual functioning is at the lower end of the normal range, and males with 47,XXY often have language and reading difficulties (Boada, Janusz, Hutaff-Lee, & Tartaglia, 2009). Additionally, executive dysfunction (i.e. problems with higher order processes responsible for purposeful, goal-directed problem-solving) has been reported in 47,XXY (Boada et al., 2009; Boone et al., 2001; Lee et al., 2011; Van Rijn & Swaab, in press). Lastly, social cognitive deficits may be present, particularly in the interpretation of facial expressions and tone of voice, identification and verbalization of emotions, and theory of mind (Van Rijn et al., 2007; Van Rijn, Stockmann, Van Buggenhout, Van Ravenswaaij-Arts, & Swaab, 2014; Van Rijn, Swaab, Aleman, & Kahn, 2006).

The gene-brain-behavior hypothesis of social dysfunction

From a gene-brain-behavior perspective, impairments in cognitive skills may lead to social behavioral problems. For 47,XXY, this gene-brain-behavior relationship could hypothetically be as depicted in Figure 1. X-linked genes are overexpressed as a result of the presence of an additional X chromosome. Certain genes on this additional X chromosome may escape the inactivation (lyonization) that occurs in normal development. Previous studies have shown that even in normal development, 8-15% of human genes consistently escape this inactivation process, while 10-13% escape X inactivation to a certain degree (Berletch et al., 2015). In the case of 47,XXY, genes that are of particular interest are the ones that not only escape inactivation, but also have a homologue on the Y chromosome, as this implies triple expression of these specific genes. This overexpression may lead to dysregulation of typical genetic mechanisms. Because many of the X-linked genes are present in brain tissue, dysregulation of these genes influences sexually dimorphic brain development, and thus disrupts typical development of the structural and functional architecture of the brain (Raznahan et al., 2014; Vawter, Harvey, & DeLisi, 2007). The presence of an additional X chromosome is associated with decreased volume of brain regions associated with social information processing (Raznahan et al., 2014). These deviations in neural architecture may contribute to dysfunctional development of cognitive skills. These cognitive dysfunctions, in turn, influence how effective incoming information is processed. Reduced effectiveness of information processing negatively influences how adequately individuals deal with, and respond to, information from their environment. The output of cognitive processing is a behavioral response. This means that the existence of cognitive dysfunction may contribute to the development of behavioral problems. Additionally, it means there may be various pathways to social dysfunction, which may show both overlap and differences between 47,XXY and idiopathic ASD.
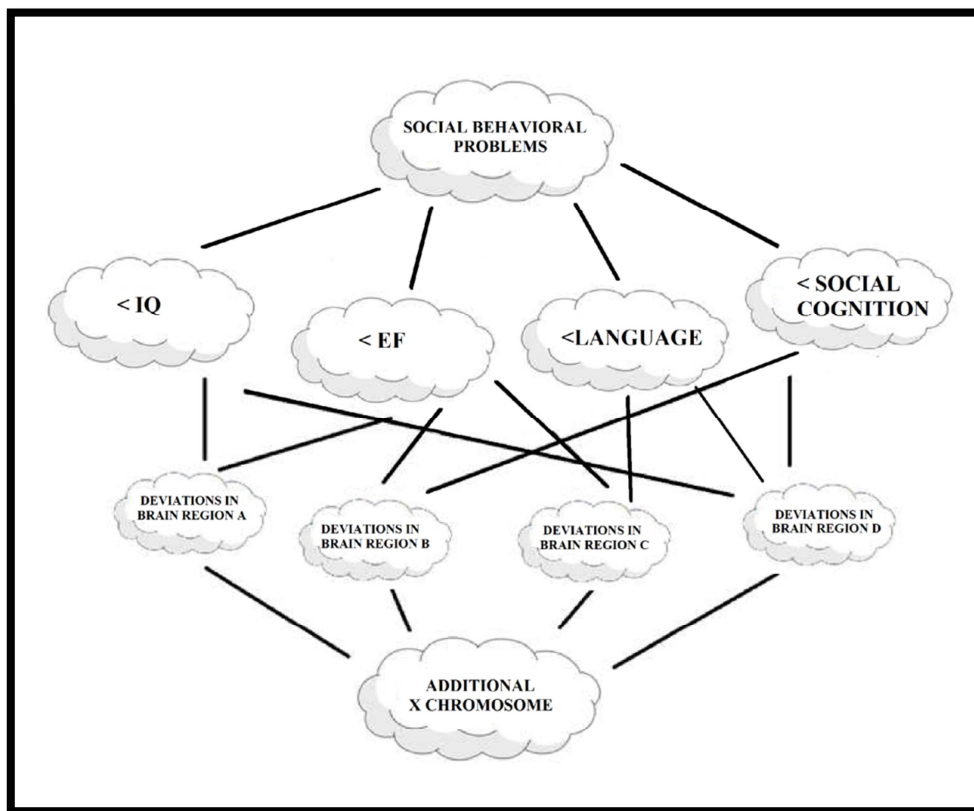
Figure 1. The gene-brain-behavior hypothesis of social dysfunction in 47,XXY

The neuroscience of 47,XXY

Although most aspects of the cognitive and behavioral phenotype associated with 47,XXY are relatively clearly delineated, less is known about the neural mechanisms underlying problems in these domains. Neural mechanisms are an important factor in the gene-brain-behavior hypothesis of social dysfunction in 47,XXY, as they represent the gateway through which genetic characteristics are expressed in behavior. This makes knowledge regarding these mechanisms essential for understanding the cognitive and behavioral issues associated with this condition. There are several ways of studying brain structure and function, but MRI allows for non-invasive, in vivo investigation of neural architecture. Structurally, gray matter and white matter can be investigated separately. For gray matter, voxel-based morphometry (VBM) offers the possibility of assessing differences in local gray matter volume, without a priori hypotheses regarding the exact location of potential differences (Good et al., 2001). For white matter, tract-based spatial statistics (TBSS) can be used to localize changes in the integrity of fiber tracts that connect different brain regions (Smith et al., 2006). Functionally, it is possible to investigate the activation of groups of neurons when an individual is performing a task (task-related brain activation), using

functional MRI (fMRI). It is also possible to assess neural activation patterns when an individual is at rest (intrinsic functional connectivity between brain regions), using resting state fMRI (RS-fMRI). RS-fMRI allows for the investigation of brain function independent of task execution and performance. This makes it particularly useful for investigation of the impact of an additional X chromosome on intrinsic functional brain connectivity. As cognitive skills are highly interrelated, it is likely impairments in one specific domain will influence performance (and neural activation patterns) in other domains. Using RS-fMRI, it is possible to assess differences and similarities in the architecture of functional networks across clinical conditions, irrespective of cognitive skills or group differences in task performance. This provides insight into deviations in intrinsic functional brain connectivity that may underlie some of these cognitive impairments. Using these different methodologies (VBM, TBSS, and (RS-)fMRI) in one sample provides essential information about brain structure and function. This may aid in further delineating the neural mechanisms underlying cognitive and behavioral problems associated with 47,XXY. This is especially important considering the vulnerability for autism symptoms in 47,XXY, which may arise as a consequence of different underlying neural abnormalities than in children with idiopathic ASD.

However, research on the structural and functional architecture of the brain in 47,XXY is limited. Only a handful of structural neuroimaging studies have been performed. These suggest that this condition is associated with gray matter volume reductions in the cerebellum, insular cortex, cingulate, inferior frontal lobe, caudate nucleus, amygdala, hippocampus, temporal pole, and superior temporal gyrus, as well as enlarged ventricles (Bryant et al., 2011; DeLisi et al., 2005; Giedd et al., 2007; Itti et al., 2006; Shen et al., 2004; Skakkebaek et al., 2013; Steinman, Ross, Lai, Reiss, & Hoeft, 2009). White matter integrity in 47,XXY has been investigated in only one study. The results from this study suggest reduced integrity of fiber tracts in the left posterior limb of the internal capsule, bilateral anterior cingulate, and left arcuate bundle (DeLisi et al., 2005). To date, only three functional magnetic resonance imaging (fMRI) studies have been conducted. All studies were focused on task-related brain activation, meaning intrinsic functional connectivity between brain regions (independent of task performance) has not yet been investigated. Current findings indicate the presence of functional abnormalities in the amygdala, insula, fusiform gyrus, and superior temporal sulcus, related to social information-processing (Van Rijn et al., 2012). Deviations in brain function in the left middle temporal gyrus, left inferior frontal gyrus, cerebellum, middle occipital gyrus, inferior occipital gyrus, inferior temporal gyrus, parahippocampal gyrus, fusiform gyrus, superior temporal gyrus and supramarginal gyrus have been associated with language processing in 47,XXY (Steinman et al., 2009; Van Rijn et al., 2008).

Rationale for the research questions in the present thesis

In order to increase our understanding of the cognitive impairments and social dysfunction associated with 47,XXY, it is of the utmost importance to gain insight into the neural mechanisms underlying these problems. They are an essential component of the gene-brain-behavior hypothesis of 47,XXY. This is not only to the benefit of science, as it aids in understanding the neurobiology of social dysfunction, but may also have important implications for the diagnosis and treatment of these social problems. In line with this aim, a number of important and distinct differences between social dysfunction in 47,XXY and idiopathic ASD have been reported. For example, males diagnosed with 47,XXY and ASD are generally more socially anxious than males with idiopathic ASD, and they show a specific cluster of ASD symptoms that differs from individuals with idiopathic ASD in the domains of communication and reciprocal social interaction (Bruining et al., 2010; Van Rijn et al., 2014). This means that the behavioral component of the gene-brain-behavior hypothesis of social dysfunction appears to be slightly different for 47,XXY than it is for idiopathic ASD. Additionally, while theory of mind deficits are associated with both conditions, these deficits seem to be driven by different disturbances in the underlying cognitive mechanisms. In 47,XXY they are suggested to be related to executive dysfunction, while being associated with language and face recognition impairments in ASD (Van Rijn, Stockmann, Van Buggenhout, Van Ravenswaaij-Arts & Swaab, 2014). These findings strongly suggest that the cognitive component of the gene-brain-behavior hypothesis of social dysfunction may also differ between these two populations. It is currently unclear if similarities and differences in the cognitive and behavioral characteristics of 47,XXY and idiopathic ASD also extend to the neural phenotypes of both conditions. There are no neuroimaging studies directly comparing these groups, meaning it is unknown whether or not the brain component of the gene-brain-behavior hypothesis of social dysfunction differs between individuals with 47,XXY and ASD, and individuals with idiopathic ASD. However, since both populations may experience severe social impairments that require treatment, it is essential to gain insight into various pathways to social dysfunction. If the neural pathways to problematic behaviors differ between these groups, it implies the mechanisms leading to social dysfunction in 47,XXY are different from idiopathic ASD. In other words, they 'think differently'. These differences may be a valid starting point for the development and selection of tailored mental health care strategies that aim to more effectively ameliorate severe social problems.

Neuroimaging is a sensitive tool to assess the architecture of, and cooperation between, neural networks in these conditions. However, to date, no comprehensive (f)MRI studies have been conducted, using different MRI techniques in one sample of individuals with 47,XXY. Additionally, there is a lack of studies focused on children/adolescents with this condition, with only

one published (preliminary) study to date (Steinman et al., 2009). This means it is currently unclear if deviations in neural structure and function develop early in life. This is an important factor to assess, as it aids in determining the appropriate moment for preventive and/or early interventions for behavioral issues. For this reason, the present thesis reports on studies using MRI to exploratively assess gray matter volume, white matter integrity, task-related brain activation, and intrinsic functional brain connectivity in children/adolescents with 47,XXY. Because of the reported social problems in this population, and the increased risk of developing ASD, imaging results from the 47,XXY sample were not only contrasted with typically developing boys, but also with a sample of boys with idiopathic ASD.

Outline of the present thesis

Participants and design
All studies in the present thesis included three samples of participants: one group consisted of boys with 47,XXY, one group consisted of boys with idiopathic ASD, and one group consisted of non-clinical, male controls. All participants were between the ages of nine and eighteen at the time of the studies. The 47,XXY group was recruited using various strategies, to avoid recruitment bias as much as possible. The sample consisted of boys who were actively followed up after prenatal diagnosis with the help of clinical genetics departments in the Netherlands and Belgium, as well as boys whose parents actively sought information about the condition of their child (recruited through support groups and calls for participants, with the help of the Dutch Klinefelter Association), and those who were seeking help for developmental problems (recruited through pediatricians, psychologists, psychiatrists and clinical genetics departments). A number of boys with 47,XXY received supplemental testosterone treatment at the time of the study. Detailed information regarding characteristics of the 47,XXY group is reported in the respective chapters.

The ASD group was recruited through the Center for Autism, a pediatric psychiatric outpatient department in the Netherlands. All boys with ASD were classified according to the DSM-IV criteria (A.P.A., 1994), using the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, & Le Couteur, 1994) parental questionnaires, parental interviews, developmental history and family history, information from primary physicians as well as elaborate expert clinical observations. All ASD diagnoses were reached through consensus among a multidisciplinary team of mental health professionals, including board-certified pediatric psychiatrists with experience in the field of autism. Non-clinical controls were recruited through schools in the western part of the Netherlands and screened for psychopathology. None scored in the clinical range (>70) on any of the scales of the Child Behaviour Checklist (CBCL) (Achenbach, 1991).

Inclusion criteria for all participants were Dutch as primary language, and an age between nine and eighteen years. Exclusion criteria were a recent history of substance abuse, intellectual disability (<60 IQ points), scan or motion artifacts (i.e. mean displacement >5 mm), as well as neurological conditions (e.g. structural brain damage due to prenatal/birth complications, tumors, strokes or diseases affecting the central nervous system). Details regarding the procedure for each study are provided in the respective chapters.

In **chapter two** we report on the volume of gray matter structures related to social information processing in all three samples, using voxel-based morphometry. Based on earlier findings, the brain regions of interest were the superior temporal cortex, amygdala, orbitofrontal cortex, insular cortex, and medial frontal cortex. In **chapter three** we evaluate white matter microstructure, using tract-based spatial statistics, to assess if deviations in brain structure also extend to white matter. Fractional anisotropy (an expression of the directionality of white matter tracts), radial diffusivity (an indication of myelination), axial diffusivity (an indication of axonal integrity), and mean diffusivity (the average diffusion of water within white matter tracts) were assessed. Taken together, these measures provide a quantification of white matter integrity. In **Chapter four** we focus on brain activation during two aspects of social-cognitive information processing: recognizing/matching facial expressions, and assigning a verbal label to facial expressions. Although both 47,XXY and ASD are associated with deficits in processing facial expressions this study used fMRI to specify this impairment, by assessing differences in neural activation patterns during these two different aspects of facial affect processing. In **chapter five** we assess intrinsic functional brain connectivity, using resting state fMRI. This allows for investigation of the presence of deviations in intrinsic functional brain connectivity that may underlie some of the cognitive and behavioral impairments associated with 47,XXY. In **chapter six** the main findings are summarized and integrated. The scientific and clinical implications of deviations in brain structure and function in 47,XXY, and differences in brain structure and function between 47,XXY and ASD, are discussed. Lastly, limitations and directions for future research are provided.

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