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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Chapter 6

Summary and general discussion

Advanced social skills are necessary to successfully navigate the complexities of interpersonal communication. For example, skills as seemingly trivial as being able to engage in 'small talk' during social functions enhance social cohesiveness (Coupland, 2003), the forming of bonds with other people. There is great individual variability in social skills, and certain developmental conditions impair social functioning to a degree that necessitates intervention. Autism spectrum disorder (ASD) is the most well-known example of a disorder that involves social dysfunction. However, certain genetic conditions may also lead to social dysfunction. Klinefelter syndrome (47,XXY) is a genetic condition that occurs only in males. It is characterized by the presence of an extra X chromosome, and is associated with varying degrees of cognitive, social, and behavioral problems (Boada, Janusz, Hutaff-Lee, & Tartaglia, 2009; Visootsak & Graham, 2009). Males with 47,XXY are at increased risk of developing symptoms of psychosis, bipolar disorder, attention-deficit/hyperactivity disorder, and autism (Cederlof et al., 2014). Studying the neural phenotype of 47,XXY may provide essential information regarding mechanisms underlying the broad range of cognitive, social and behavioral problems associated with this condition. All neuroimaging studies to date focused on adult males with 47,XXY. However, studying children and adolescents with this condition may aid in determining the neural phenotype early in life.

From a gene-brain-behavior perspective, it is possible that the additional X chromosome that is present in 47,XXY leads to overexpression of X-linked genes. This overexpression may lead to dysregulation of genetic mechanisms. Many X-linked genes are involved in brain development, which indicates that an additional X chromosome may substantially influence the structural and functional architecture of the brain. Moreover, brain development appears to be modulated by the actual number of X chromosomes, specifically in regions responsible for adaptive social functioning (Raznahan et al., 2014; Vawter, Harvey, & DeLisi, 2007). These deviations in neural makeup may negatively impact cognitive development. Because of this impact on how incoming information is processed, cognitive impairments may lead to problems in the processing of, and reaction to, information from the environment. This means that disturbances in typical genetic mechanisms, through neural and cognitive pathways, may lead to problems in observable behavior. As ASD is diagnosed based on behavioral symptoms, individuals receiving this diagnosis may suffer from social problems as a result of many different underlying genetic and neural dysfunctions. In contrast, genetic conditions are characterized by a relatively homogeneous endophenotype, with substantial variation in behavioral outcomes. Therefore, studying genetic conditions such as 47,XXY may also help uncover different pathways to social dysfunction that are more difficult to uncover by studying idiopathic ASD, because of the variability in (endo)phenotypes (Mottron, Belleville, Rouleau, & Collignon, 2014; Muhle,

Trentacoste, & Rapin, 2004). Indeed, recent studies suggest there may be subtle differences between individuals with idiopathic ASD, and individuals with ASD associated with 47,XXY, in the expression of these symptoms and the underlying cognitive mechanisms (Bruining et al., 2010; Van Rijn et al., 2014; Van Rijn, Stockmann, Van Buggenhout, Van Ravenswaaij-Arts, & Swaab, 2014). Therefore, this thesis was aimed at assessing if individuals with 47,XXY and autistic symptomatology also differ from individuals with idiopathic ASD in the neural mechanisms underlying their cognitive and behavioral symptoms.

In the present thesis we used MRI to exploratively assess gray matter volume, white matter integrity, task-related brain activation, and intrinsic functional brain connectivity in individuals with 47,XXY compared with typical development, to gain insight into the mechanisms that contribute to cognitive and behavioral impairments specific to 47,XXY. In addition, we assessed similarities and differences in neural pathways to social dysfunction. As most neuroimaging studies to date focused on adult males with 47,XXY, and only a handful of pediatric neuroimaging studies have been performed, our samples consisted of boys between the ages of nine and eighteen. This made it possible to determine the neural phenotype early in life, which would open the door to early interventions when circumstances are more optimal in terms of neural plasticity.

Main findings

As described in **chapter 2**, we assessed gray matter volume of brain regions important for social information processing in boys with 47,XXY compared with typically developing boys, and boys with idiopathic ASD. Boys with 47,XXY were found to have significantly less gray matter in the right superior temporal gyrus (STG) than typically developing boys. Additionally, they have significant gray matter volume reductions in the left and right insular cortex, and the left orbitofrontal cortex (OFC), compared with both typically developing boys, and boys with ASD. In **chapter 3** we report results from diffusion tensor imaging analysis, focused on white matter microstructure. We found reduced white matter/axonal integrity in the corpus callosum in boys with 47,XXY compared with typically developing boys, as well as reduced axonal integrity in the right inferior fronto-occipital fasciculus compared with boys with ASD. However, we found reduced radial diffusivity, indicating *enhanced* myelination, in boys with 47,XXY compared with typically developing boys in the left anterior corona radiata and sagittal striatum. **Chapter 4** contains results from a task-related fMRI study focused on social-cognitive information processing. Facial affect recognition is associated with similar neural activation patterns in all three groups. However, boys with 47,XXY were found to have increased activation during facial affect labeling in the right middle frontal gyrus (including Broca's area) compared with both typically developing boys, and boys with ASD. Boys with ASD on the other hand, showed increased activation in a different brain

region, i.e. the right amygdala. In **chapter 5** we describe results from resting state functional MRI analysis, i.e. intrinsic functional brain connectivity. Boys with 47,XXY were found to have increased intrinsic functional brain connectivity in the right precuneus/cingulate gyrus and frontoparietal network relative to typically developing boys. Relative to boys with ASD however, they showed decreased intrinsic functional brain connectivity between the left precentral gyrus/middle frontal gyrus and auditory network.

Deviating neural mechanisms involved in higher order cognitive functions in 47,XXY

It is widely accepted that the frontal lobes play an essential role in higher order processes responsible for conscious reasoning, and purposeful, goal-directed problem-solving (Ardila, 2008). The increased activation in middle frontal regions during social-cognitive information processing that was found in boys with 47,XXY (**chapter 4**), implies they may rely more on reasoning (i.e. higher order cognitive functions) instead of 'social intuition' when engaging in social decision making. However, task demands in our study were intentionally kept to a minimum, because we wanted to exclude brain activation related to task complexity in favor of activation related purely to social-cognitive information processing. As higher order cognitive deficits have been reported in 47,XXY (Boada et al., 2009; Boone et al., 2001; Lee et al., 2011; Van Rijn & Swaab, in press), it is possible this higher-order reasoning approach to social-cognitive information processing will prove ineffective with increasing task demands. Although speculative, this may be one of the reasons individuals with 47,XXY experience difficulties in identifying and interpreting facial expressions (Van Rijn et al., 2014).

Deviating neural mechanisms involved in social information processing difficulties in 47,XXY

Many brain regions are known to be involved in the neural network for social information processing. For example, the OFC is important for emotion regulation, decision-making and social information processing, including the recognition of mental states (i.e. theory of mind), and the processing of facial expressions (Baron-Cohen et al., 1994; Golkar et al., 2012; Noonan, Sallet, Rudebeck, Buckley, & Rushworth, 2010; Rolls, 2004; Rolls & Grabenhorst, 2008). Inferences about cognitive and behavioral dysfunctions based on structural brain deviations must be done with caution. However, it is possible that the reduced OFC volume that was found is one of the anatomical roots of social and cognitive problems associated with 47,XXY, such as deficits in theory of mind and facial affect processing (Van Rijn, Swaab, Aleman, & Kahn, 2006). The OFC is anatomically connected with a region adjacent to the frontal lobes, the insular cortex (Jakab, Molnar, Bogner, Beres, & Berenyi, 2012). The bilateral insular cortices are also significantly smaller in boys with 47,XXY, a finding that

is in line with research in adult males with 47,XXY (Bryant et al., 2011; Shen et al., 2004; Skakkebaek et al., 2013). This region is associated with emotion regulation, recognition of, and responses to, emotional stimuli and in particular internal emotional states, as well as social decision making processes (Adolphs, 2003; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). Males with 47,XXY show decreased neural activation in the insular cortex when asked to make social judgments (Van Rijn et al., 2012). Our findings suggest the socio-emotional impairments found in 47,XXY might be mediated by bilateral reductions in insular cortex volume in 47,XXY that are already present in childhood, and may possibly impact the brain function in this region as well. Other studies have shown that individuals with 47,XXY have trouble identifying and verbalizing internal emotional states, they are more easily emotionally aroused in terms of psychophysiological responses, and their emotional states exert more influence on their decision making processes (Van Rijn, Barendse, Van Goozen, & Swaab, 2014; Van Rijn et al., 2006). Our MRI findings imply that abnormalities in the OFC and insular cortices may be part of the mechanism underlying these deficits in emotion regulation in 47,XXY.

The STG has been implicated in the processing of facial information, such as facial expressions and gaze directions. Impairments in the processing of facial expressions have been reported in children and adults with 47,XXY, and eye tracking suggests they are less focused on other people's eyes (Van Rijn et al., 2014; Van Rijn et al., 2014; Van Rijn et al., 2006; Van Rijn et al., 2012). Hypothetically, these impairments might be mediated by the reduced gray matter volume in the STG that was found in our sample. The increased functional connectivity at rest between the frontoparietal network and the right precuneus/cingulate gyrus, might imply more global deviations in brain function. The precuneus is thought to be involved in emotional awareness (Van der Velde et al., 2013), and the cingulate gyrus is a central part of the limbic system, otherwise known as our 'emotional epicenter' (Kotter & Meyer, 1992). Increased intrinsic functional brain connectivity between these areas and the frontoparietal network, which is primarily associated with language functions (Smith et al., 2009), may imply a compensatory mechanism for the connection between language and emotion. Hypothetically, this compensatory mechanism could consist of processes similar to neural compensation. This is a term used to describe brain activation in individuals with brain pathology, in regions not used by individuals with intact brains, intended to (subconsciously) increase cognitive performance (Stern, 2009). Based on our findings, we hypothesize that in 47,XXY this compensatory mechanism may be inadequate, resulting in a problematic connection between language and emotion. This may (partially) explain the language and emotion processing deficits, such as alexithymia and problems with emotion labeling, that are among the most often reported domains of impairment in 47,XXY (Boada et al., 2009; Boone et al., 2001; Van Rijn et al., 2006).

Deviating neural mechanisms involved in language processing difficulties in 47,XXY

The increased intrinsic functional brain connectivity between the frontoparietal (language) network and the precuneus/cingulate gyrus, may reflect an ineffective neural compensatory mechanism for the connection between language and emotion. Research in typically developing individuals suggests language skills influence emotion processing abilities (Cutting & Dunn, 1999; Jablonka, Ginsburg, & Dor, 2012; Lindquist, Barrett, Bliss-Moreau, & Russell, 2006). Based on these studies, we suggest that in 47,XXY impaired language skills may contribute to impaired emotion processing. In our fMRI study focused on the neural mechanisms underlying facial affect labeling part of Broca's area, a region essential for language processing (Davis et al., 2008), showed increased activation in boys with 47,XXY during the labeling of prototypical facial expressions of emotions. This finding gives additional support for the hypothesis of a dysfunctional neural mechanism underlying problems in the connection between language and emotion processing. Broca's area is usually active in the left hemisphere, as this is the hemisphere that is most often dominant for language. In our fMRI study the increased activation was located in Broca's area in the right hemisphere. This is in line with an earlier fMRI study in adult males with 47,XXY that reported increased activation in language-related areas in the right hemisphere during a language processing task, suggesting individuals with 47,XXY may have reduced hemispheric specialization for language (Van Rijn et al., 2008).

Although our finding of reduced white matter integrity in the corpus callosum in 47,XXY does not equal actual damage to these fiber tracts, it does imply reduced efficiency of neural connections. In typically developing individuals the corpus callosum is involved in language functions (Bloom & Hynd, 2005; Van der Knaap & Van der Ham, 2011). Lesions in the corpus callosum have been associated with alexithymia, a term used to describe deficits in the ability to identify and verbalize one's emotional state, indicating problems in both language and emotion processing (Sifneos, 1973). Increased rates of alexithymia have been reported in 47,XXY (Van Rijn et al., 2006). Diminished integrity of fiber tracts in the corpus callosum may therefore be another part of the mechanism underlying this deficient connection between language and emotion in 47,XXY.

The reduced gray matter volume in the STG that we found in boys with 47,XXY might contribute not only to the social problems associated with this condition, but also to the language impairments. Wernicke's area and Heschl's gyri are responsible for speech and auditory processing, respectively (Da Costa et al., 2011; Wise et al., 2001). They are part of the Wernicke-Geschwind model of language processing and located in the STG, making the STG a key structure in this model. The Wernicke-Geschwind model of language processing consists of

Broca's area, Wernicke's area, the superior temporal sulcus, inferior parietal lobule, middle temporal gyrus, and the arcuate fasciculus connecting these areas (Dick, Bernal, & Tremblay, 2014). Although this classic model has been deemed overly simplistic, it still serves as the basis from which language processing in the brain is studied. More importantly, most contemporary models of language processing also involve superior temporal areas (Dick et al., 2014). The reduced hemispheric specialization for language in the STG reported by Van Rijn et al. (2008) might be a functional consequence of anatomical deviations in STG development in 47,XXY. Additionally, the involvement of the corpus callosum in language processing is hypothesized to involve facilitation of interhemispheric communication between the left and right plana temporale, which include the STG (Bloom & Hynd, 2005; Van der Knaap & Van der Ham, 2011). Altogether, these findings suggest abnormal frontoparietal connectivity, abnormalities in Broca's area, gray matter volume deviations in the STG and reduced integrity of the corpus callosum may be part of the anatomical mechanism underlying language impairments in 47,XXY.

Enhanced myelination in 47,XXY

The finding of reduced radial diffusivity in the left anterior corona radiata and sagittal striatum in boys with 47,XXY may have important implications. Reduced radial diffusivity is associated with enhanced myelination of white matter (Alexander, Lee, Lazar, & Field, 2007), which enables neurons to transmit information faster and thus enhances neural communication. Clinical conditions that influence brain structure and function are usually associated with reduced myelin integrity. In our sample of boys with 47,XXY this effect appears to be reversed. Although speculative, we offer two possible explanations for this unexpected finding. The first concerns the use of steroid hormones. Individuals with 47,XXY often receive supplemental testosterone treatment to ameliorate some of the symptoms associated with this condition (e.g. decreased growth of facial and pubic hair). These hormones are known to enhance myelination in the human brain (Peper, Van den Heuvel, Mandl, Hulshoff Pol, & Van Honk, 2011). In our sample four participants received supplemental testosterone treatment at the time of the study, while five did not. If our finding of enhanced myelination is indeed a consequence of testosterone treatment, it could be an important protective factor that could potentially enhance neural communication in 47,XXY. As an already relatively small sample size prevented us from splitting our 47,XXY group into those who received testosterone treatment and those who did not, this hypothesis calls for future studies assessing the impact of hormone treatment on myelination. A second possible explanation for the enhanced myelination in 47,XXY comes from the finding that the gene for the myelin proteolipid protein lies on the X chromosome (Willard & Riordan, 1985). It is suggested that the pattern of gene inactivation is one of the mechanisms through which the extra X chromosome impacts phenotypic development in 47,XXY (Skakkebaek et al., 2014). Hypothetically,

the extra X that is present in this condition could influence functioning of the myelin proteolipid protein. Previous studies (Hodes 2000) suggest that additional copies of this protein may lead to severe somatic conditions. It is therefore unlikely that the enhanced myelination is a result of this gene simply escaping gene inactivation. However, studies in mice indicate that this gene may partially escape inactivation, which could hypothetically lead to overexpression. These results demonstrate the value of interdisciplinary research (e.g. neuroscience and clinical genetics) to further explore the possible effect of the additional X chromosome on the functioning of this protein. However, these explanations are very speculative at this point. More research is necessary to determine the exact origin of enhanced myelination in 47,XXY.

47,XXY versus idiopathic ASD

With the exception of reduced gray matter volume in the bilateral insular cortices in 47,XXY, all differences in brain structure and function between our 47,XXY and ASD groups pertain to the frontal lobes. Anatomically, boys with 47,XXY have reduced gray matter volume in the left OFC compared with boys with ASD, as well as reduced axonal integrity in the right inferior fronto-occipital fasciculus, a fiber bundle connecting the frontal lobe with the temporal and occipital lobes (Martino, Vergani, Robles, & Duffau, 2010). Functionally, boys with 47,XXY show decreased intrinsic functional brain connectivity between the auditory resting state network and the left precentral gyrus/middle frontal gyrus compared with boys with ASD. During social-cognitive information processing, boys with 47,XXY show increased brain activation in the right middle frontal gyrus compared with boys with ASD.

This is the first time brain structure and function in these populations were compared, and a detailed interpretation of the observation that the differences appear to center around the frontal lobes requires more research. However, these results do suggest that reduced intrinsic functional connectivity between different regions of the cortex is a feature that is not specific for idiopathic ASD (Di Martino et al., 2014), as our 47,XXY group showed even more decreased intrinsic functional connectivity. Hypoconnectivity of cortical regions may therefore be a feature that is shared by 47,XXY and ASD, suggesting it may have a crucial role in social dysfunction. It may therefore be deficit specific rather than disorder specific. Importantly though, when asked to label facial expressions, boys with 47,XXY have substantially increased activation in frontal regions compared with boys with ASD. This, once again, may imply a form of neural compensation in 47,XXY, that is different from idiopathic ASD. In our study boys with ASD also showed increased activation during facial expression labeling, but in a different brain region (i.e. middle frontal gyrus in 47,XXY versus amygdala in ASD). The amygdala is part of the social brain network and heavily involved in automatic screening of emotional relevance, including facial expressions, in typical development, which may imply that boys with idiopathic

ASD rely more on social intuition. The profound deficits in this domain associated with ASD, however, suggest that this form of neural compensation is ineffective. Behaviorally both groups may experience similar social problems, but our findings clearly point towards differences in underlying neural compensatory mechanisms. The bilateral reductions in insular cortex and OFC volume that were found in 47,XXY compared with typically developing boys, were also present in comparison with boys with idiopathic ASD. These brain areas are important for awareness of internal emotional states, as well as the regulation of these states. This may suggest that social dysfunction in individuals with 47,XXY is influenced more heavily by defective emotion regulation (i.e. difficulties with monitoring one's internal emotional state, and using it as a social compass) than it is in individuals with idiopathic ASD.

These findings imply distinct differences in neural structure and function between 47,XXY and ASD. In addition to differences in the cognitive and behavioral components of the gene-brain-behavior hypothesis of social dysfunction, the brain component appears to differ substantially as well. However, boys with 47,XXY could not be distinguished from boys with ASD in our sample based on behavioral measures of autism symptoms. There may therefore be a multitude of pathways to social dysfunction, including heterogeneity in underlying neural mechanisms. Knowledge regarding the exact nature of these differences aids in specifying the behavioral deficits and has important scientific and clinical implications, which we will turn to now.

Scientific and clinical implications

The current thesis marks the first time that the structural and functional architecture of the brain were assessed across multiple domains, using various MRI techniques in one sample of children/adolescents with 47,XXY. This was also the first time that brain structure and function of boys with 47,XXY, who are at increased risk of developing autism symptomatology, was compared to that of boys with idiopathic ASD. The results provide interesting and important directions for future research. The presence of an extra X chromosome in 47,XXY, and/or the hormonal consequences of this condition, appear to significantly impact brain development. Together, these factors may contribute to the increased risk of problems in 47,XXY in higher order cognitive functions, social emotional information processing, and language processing. These neural pathways to social dysfunction show specific differences from those in idiopathic ASD, especially in the domains of frontal functions and emotion regulation.

Future research in this area should focus on replication of our findings in larger samples with varying age ranges, and further specification of the exact gene-brain-behavior pathways in 47,XXY. MRI offers great potential for investigating these mechanisms, especially when combined with other neurobiological,

cognitive, and behavioral measures. The functional MRI task from our study for example, was focused on decoding facial expressions. Adding neurophysiological measures such as eye tracking, which is used to gather data regarding the focus of the participants' attention, makes it possible to determine if the increased frontal activation found in 47,XXY in our study is top-down (i.e. the incoming information is processed differently in the brain), or bottom-up (i.e. brain activation differs, because the incoming information is different, due to a deviating focus of attention). For example, eye tracking has shown that adult males with 47,XXY fixate less on the eye regions of faces than typically developing males when assessing facial expressions (Van Rijn, in press). These types of studies may be of tremendous benefit to the specification of the exact deviations in social-cognitive processing in 47,XXY.

This thesis also provides starting points for intervention research. The results suggest the existence of various pathways to social dysfunction, as demonstrated by the findings that were specific to boys with 47,XXY compared with those with idiopathic ASD. This could hypothetically mean these groups are differentially susceptible to treatment. Research on the development of tailored interventions for social dysfunction, intended to enhance treatment effect, may benefit from knowledge regarding differences in these neural mechanisms. A particularly relevant area of research in this respect, is real time fMRI neurofeedback. This technique is aimed at modifying behavior by modifying brain function. Real time information about changes in neural activation is provided to an individual during multiple training sessions, with the intention of facilitating self-regulation of this activation. The idea is that this will produce changes in brain function, which may in turn lead to changes in cognition and/or behavior (Stoeckel et al., 2014). More research is necessary to determine its effectiveness in influencing behavior by influencing brain activation. However, real time fMRI neurofeedback may potentially increase resilience in individuals at risk for social dysfunction, by correcting known dysfunctions in neural activation patterns before severe developmental problems become apparent. In 47,XXY, potential targets for treatment could for example be brain regions known to contribute to language and emotion processing in typical development, in an attempt to modify the current, ineffective, neural compensatory mechanism. Conversely, in individuals with formal diagnoses of psychiatric conditions such as ASD, real time fMRI neurofeedback may be used to directly target neural systems underlying social dysfunction in order to improve behavior (Stoeckel et al., 2014). The first studies focused on this potential next generation therapeutic tool have yielded positive results in individuals with contamination anxiety, not only in changing the functional architecture of the brain, but also in inducing behavioral changes that last for several days after the training session (Robineau et al., 2014; Scheinost et al., 2013). In the current thesis we identified differences in the specific neural systems contributing to social dysfunction. Our work could therefore be a valuable source of information, and will hopefully stimulate

research on real time fMRI neurofeedback for social dysfunction, by identifying potential targets for treatment.

From a clinical perspective, the current thesis may aid in creating awareness among clinicians of the existence of great individual variability, not only in behavioral symptoms of social dysfunction or autism, but also in the mechanisms underlying this dysfunction. This may impact the selection of mental health care strategies. For example, if individuals with 47,XXY indeed use a more rational approach (involving frontal lobe areas) during social-cognitive information processing, clinicians may be able to use this knowledge to determine how to best implement interventions in this population. For example, social skills training for 47,XXY could focus more on explanations of *why* certain behaviors are adaptive in social situations, and less on practicing social situations through role-play. In addition, the knowledge that emotion regulation impairments may be mediated by bilateral reductions in insular cortex volume specifically in 47,XXY, may aid in making clinicians aware of the possibility that the etiology of their emotion regulation problems differs from those with idiopathic ASD. This, in turn, may signify these individuals require a different type of treatment more focused on identifying and monitoring one's own internal emotional state. Lastly, our results suggest that deviating development of brain structure and function in 47,XXY is already present during childhood. This means that interventions aimed at preventing or ameliorating behavioral problems in individuals with 47,XXY, may be most effective when implemented prior to adolescence.

Limitations

Although all reported results from our study were significant and methodologically sound, there were some unavoidable limitations. Part of the (f)MRI data was of insufficient quality to include in analysis due to movement of the participants, or other artifacts. This resulted in relatively small sample sizes, which may have led to a lack of power to detect more subtle differences in neural structure and/or function, and prevented correlational analysis of cognitive and (f)MRI data. However, the (f)MRI data used in analysis was thoroughly evaluated and of good quality, making the reported results more reliable. In addition, boys with idiopathic ASD in our sample were, on average, relatively high functioning, a limitation inherent to imaging research due to the demands associated with participation (e.g. having to lie very still in a confined space). Lastly, autism spectrum symptoms in boys with 47,XXY were assessed using the Social Responsiveness Scale (Constantino & Gruber, 2005). Although this measure shows high correlations with the Autism Diagnostic Interview-Revised (Constantino et al., 2003; Lord, Rutter, & Le Couteur, 1994), no formal diagnostic assessment for ASD was conducted in our 47,XXY participants.

Concluding remarks

The current thesis provides insight into the neural mechanisms underlying cognitive and behavioral problems in 47,XXY, and differences in these mechanisms between individuals with 47,XXY (which is associated with an increased risk of autism spectrum symptomatology) and individuals with idiopathic ASD. Individuals with 47,XXY show characteristic deviations in brain structure and function associated with higher order cognitive functions, social emotional information processing, and language processing. Additionally, while boys with 47,XXY show considerable overlap with boys with idiopathic ASD in autism symptomatology, there are specific differences in the underlying neural mechanisms that revolve around the frontal lobes and insular cortices. Gene-brain-behavior relationships are extraordinarily complex, and disentangling individual aspects of these relationships will require a substantial amount of additional research. It is our hope that the hypotheses generated from our results will give direction to future studies within these populations.

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