Psychological functioning, brain morphology, and functional neuroimaging in Klinefelter syndrome

Anne Skakkebæk1,2 | Claus H. Gravholt2,3 | Simon Chang2,4 | Philip J. Moore5 | Mikkel Wallentin6,7

Abstract

Klinefelter syndrome (KS; 47,XXY) impacts neurodevelopment and is associated with an increased risk of cognitive, psychological and social impairments, although significant heterogeneity in the neurodevelopmental profile is seen. KS is characterized by a specific cognitive profile with predominantly verbal deficits, preserved function in non-verbal and visuo-spatial domains, executive dysfunction and social impairments, and by an increased vulnerability toward psychiatric disorders. The neurobiological underpinnings of the observed neuropsychological profile have not been established. A distinct pattern of both global and regional brain volumetric differences has been demonstrated in addition to preliminary findings of functional brain alterations related to auditory, motor, language and social processing. When present, the combination of cognitive, psychological and social challenges has the potential to negatively affect quality of life. This review intends to provide information and insight to the neuropsychological outcome and brain correlates of KS. Possible clinical intervention and future directions of research will be discussed.

Keywords

brain morphology, cognition, Klinefelter syndrome, neuropsychology, sex chromosomes

INTRODUCTION

With a prevalence ranging from 85 to 250 per 100,000 liveborn males, Klinefelter syndrome (KS; 47,XXY) is the most prevalent sex chromosome disorder in males (Gravholt et al., 2018). The classic phenotypic traits include hypergonadotropic hypogonadism, small testes and infertility (Klinefelter, Reifenstein, & Albright, 1942). In addition, an increased morbidity for a broad range of disorders have been documented (Bojesen, Juul, Birkebaek, & Gravholt, 2004, 2006; Swerdlow, Higgins, Schoemaker, Wright, & Jacobs, 2005). It has also become evident that KS impacts neurodevelopment and is associated with a high risk of cognitive, psychological and social impairments, although significant heterogeneity in the neurodevelopmental profile is seen. Characteristic of KS is a specific cognitive profile with predominantly verbal deficits, preserved function in non-verbal and visuo-spatial domains, difficulties with motor functioning, executive dysfunction and social impairments. The neurological etiology of the observed neuropsychological profile is still not clear. A distinct pattern of both global and regional brain volumetric differences has been repeatedly observed (Table 1). A number of different functional brain activations related to...
auditory, motor, language and social processing have also been suggested (Brandenburg-Goddard, Van Rijn, Rombouts, Veer, & Swaab, 2014; Van Rijn et al., 2008, 2012; Wallentin et al., 2016). The combination of these cognitive, psychological and social challenges adversely affects virtually every aspect of living with KS. By summarizing and analyzing the prevalence and relationship between psychological functioning, brain morphology and neurological assessment, this review intends to provide the newest information and insight to improve life outcome for persons with KS. Possible clinical intervention and future directions of research will be discussed.

The PubMed database were search using the Keyword "Klinefelter syndrome" as the Medical Subject Heading (MeSH) term. Article relevant to this review were obtained. Selected publications were included at the authors' discretion.

2 | PSYCHOLOGICAL FUNCTIONING

Many of the neurocognitive deficits associated with KS arise in early childhood and continue into adulthood, although there is significant variability in the severity of these deficits. Furthermore, it is estimated that only 25–40% of individuals with KS are ever diagnosed (Abramsky & Chapple, 1997; Bojesen, Juul, & Gravholt, 2003; Herlihy, Halliday, Cok, & McLachlan, 2011), and thus the current literature may be based on studies of a sub-sample of individuals with KS, which may not be representative of the whole KS population and may perhaps represent KS males with more significant deficits as these are more likely to be diagnosed.

2.1 | Intellectual function

The majority of boys and men with KS have IQ scores within the normal to low-normal range, with only few exhibiting mild intellectual disabilities (1.2%) (Leggett, Jacobs, Nation, Scerif, & Bishop, 2010; Simpson et al., 2003). Full-scale IQ follows a normal distribution in KS (Boada, Janusz, Hutaff-Lee, & Tartaglia, 2009), but with a mean score about 10 points below the mean of the general population (Bender, Puck, Salbenblatt, & Robinson, 1986; Ratcliffe, Butler, & Jones, 1990; Skakkebaek et al., 2015), with a weighted average full-scale IQ of 93 (Skakkebaek et al., 2015). Generally, boys and men with KS also have lower IQ compared to their siblings (Bender, Linden, & Harmon, 2001a). Lower verbal IQ (VIQ) is the main driver of the lower full-scale IQ, as VIQ is typically more affected than performance IQ (PIQ; nonverbal IQ). However, the difference between VIQ and PIQ can be small and there is evidence that the differences between VIQ and PIQ may vary with age. More pronounced differences are seen in childhood (Bender, Linden, & Robinson, 1989; Boone et al., 2001; Pennington, Bender, Puck, Salbenblatt, & Robinson, 1982; Samango-Sprouse, 2001) and have been suggested to be due to deficits in vocabulary, which are present in early childhood (Bender et al., 1989), whereas the decreasing differences between VIQ and PIQ in adolescence/adulthood may be due to a combination of psychological factors, such as increased psychological distress and hormonal dysfunction with hypogonadism (Gravholt et al., 2018). A recently published study demonstrated that 43% of the variance in VIQ and 45% of the variance in PIQ seen in patients with KS was explained by parental education (20%), prenatal/postnatal diagnosis (13%) and testosterone treatment (10–13%), with higher parental

### TABLE 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Measure</th>
<th>Age (SD)</th>
<th>n</th>
<th>Volume mm³ (SD)</th>
<th>Age (SD)</th>
<th>n</th>
<th>Volume cm³ (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warwick et al., 1999</td>
<td>Total brain volume</td>
<td>21.8 (4.2)</td>
<td>10</td>
<td>1,296.1 (87.8)</td>
<td>21.5 (1.3)</td>
<td>25</td>
<td>1,438.0 (85.3)</td>
</tr>
<tr>
<td>Patwardhan, Eliez, Bender, Linden, &amp; Reiss, 2000; Patwardhan et al., 2002</td>
<td>Gray + white matter vol.</td>
<td>27.3 (2.99)</td>
<td>10</td>
<td>1,220.5 (128.9)</td>
<td>26.81 (3.28)</td>
<td>10</td>
<td>1,267.1 (111)</td>
</tr>
<tr>
<td>DeLisi et al., 2005 Rezaie et al., 2009</td>
<td>Intracranial vol</td>
<td>34.6 (12)</td>
<td>11</td>
<td>1,472.97 (135.11)</td>
<td>36.5 (13)</td>
<td>11</td>
<td>1,593.65 (137.5)</td>
</tr>
<tr>
<td>Itti et al., 2006</td>
<td>Total brain volume</td>
<td>35.8 (11.8)</td>
<td>18</td>
<td>1,411.7 (95.1)</td>
<td>32.3 (11.3)</td>
<td>20</td>
<td>1,502.1 (158.8)</td>
</tr>
<tr>
<td>Bryant et al., 2011</td>
<td>Gray + white matter vol.</td>
<td>9.69 (1.70)</td>
<td>31</td>
<td>1,202.88 (110)</td>
<td>10.99 (1.72)</td>
<td>36</td>
<td>1,250.57 (95)</td>
</tr>
<tr>
<td>Lentin, Kasahara, Arver, &amp; Savic, 2013</td>
<td>Gray + white matter vol.</td>
<td>35.0 (6.8)</td>
<td>33</td>
<td>1,183.8 (112.6)</td>
<td>39.1 (10.5)</td>
<td>41</td>
<td>1,286.0 (111.2)</td>
</tr>
<tr>
<td>Shen et al., 2004 Giedd et al., 2007</td>
<td>Total cerebral volume</td>
<td>12.8 (5)</td>
<td>42</td>
<td>1,066.6 (119)</td>
<td>12.7 (5)</td>
<td>87</td>
<td>1,145.8 (103)</td>
</tr>
<tr>
<td>Raznahan et al., 2016 Nadig et al., 2018 Mankiw et al., 2017 Reardon et al., 2016</td>
<td>Total brain volume</td>
<td>12.8 (4.9)</td>
<td>58</td>
<td>1,290 (152.3)</td>
<td>12.8 (5.68)</td>
<td>89</td>
<td>1,393 (169)</td>
</tr>
<tr>
<td>Skakkebaek, Wallentin, &amp; Gravholt, 2015</td>
<td>Gray + white matter vol.</td>
<td>36.8 (10.5)</td>
<td>65</td>
<td>1,251.2 (88.8)</td>
<td>36.8 (10.3)</td>
<td>65</td>
<td>1,305.1 (110)</td>
</tr>
</tbody>
</table>

Note: A number of studies report on the same or subsets of the same dataset. Both age groups and methods for obtaining these measures vary and the numbers are thus difficult to compare directly. But all studies report smaller brain size for 47,XXY compared to 46,XY.
education, prenatal diagnosis and testosterone treatment associated with higher IQ scores (Samango-Sprouse et al., 2018). Testosterone treatment in this study, however, was not randomized, which may have biased the results regarding this effect. The only randomized study on children did not support any effect of testosterone on cognitive functions (Ross et al., 2017). The 20% variance in VIQ and PIQ explained by parental education in KS boys is similar to what is seen in the general population (Alati et al., 2008).

### 2.2 | Psychiatric disorders and personality

An increased risk of a wide range of psychiatric disorders is seen KS (Boks et al., 2007; Bruining, Swaab, Kas, & Van, 2009; Tartaglia, Ayari, Hutaff-Lee, & Boada, 2012), with one study reporting a more than three times greater risk of being hospitalized with a psychiatric disorder compared to the general population (Bojesen et al., 2006). Generalized anxiety is seen in approximately 12–18% of males with KS (Bruining et al., 2009; Tartaglia, Cordeiro, Howell, Wilson, & Janusz, 2010), whereas depression is seen in the 14–24% (Boks et al., 2007; Bruining et al., 2009; Tartaglia et al., 2010) with up to 70% reporting depressive symptoms (Turriff, Levy, & Biesecker, 2011).

Individuals with KS have generally been described as passive, unassertive, lacking initiative and socially withdrawn, but having high emotional arousal and difficulty approaching new events and mastering challenges (Bender, Linden, & Robinson, 1993; Leonard, 1990; Nielsen & Pelsen, 1987; Ratcliffe, 1999; Van Rijn, Swaab, Aleman, & Kahn, 2006; Walzer et al., 1978; Walzer, Bashir, & Graham, 1986), consistent with the findings of higher level of neuroticism and lower levels of extraversion, openness and conscientiousness in KS males (Skakkebaek et al., 2018). Personality traits such as neuroticism (defined as negative emotional arousal, emotional instability, negativity, lack of self-control, poor ability to manage psychological stress), extraversion and conscientiousness have been linked to an individual's vulnerability to psychiatric morbidity in the general population (Klein, Kotov, & Bufferd, 2011; Klein, Wonderlich, & Shea, 1993; Kotov, Gamez, Schmidt, & Watson, 2010; Krueger & Tackett, 2003), but also in KS, where neuroticism has been indicated to play a significant role in the development of both depression and anxiety. It has been proposed that neuroticism may be useful as a clinical marker to identify KS individuals at high risk for developing anxiety and depression (Skakkebaek et al., 2018). Clinical measures of personality, however, are not routinely administered to KS males. Interestingly, neuroticism has been found to show plasticity through training (Drake, Morris, & Davis, 2018), and interventions leading to decreased neuroticism levels may have practical implications improving the mental health and outcomes of individuals with KS.

### 2.3 | Executive functioning and attention-deficit/ hyperactivity disorder

Executive functions reflect higher order cognitive control processes that enables adaptive goal-directed behavior, including planning, organization, decision-making, flexibility, sustained attention, inhibition and problem solving (Lezak, Howieson, & Loring, 2004). Although the literature on executive functioning among KS patients is sparse, there are indications that executive functioning deficits can be observed in males with KS, although most of the evidence comes from studies on adults with KS (Bender et al., 1993; Bruining et al., 2009; Fales et al., 2003; Kompus et al., 2011; Ross et al., 2008; Temple & Sanfilippo, 2003; Van Rijn, Aleman, De Sonneville, & Swaab, 2009; Van Rijn & Swaab, 2015). Difficulties in cognitive domains such as attention, inhibition, working memory and cognitive flexibility have been reported, but these results are not consistent (Bender et al., 1993; Bruining et al., 2009; Fales et al., 2003; Kompus et al., 2011; Ross et al., 2008; Temple & Sanfilippo, 2003; Van Rijn et al., 2009; Van Rijn & Swaab, 2015). A link between verbal deficits and executive dysfunction in KS has been proposed with executive dysfunctions being secondary to the language deficits (Rovet, Netley, Keenan, Bailey, & Stewart, 1996). In support of this hypothesis, two studies found no deficits on non-verbal executive function task, while deficits on verbal tasks were identified (Bender, Linden, & Harmon, 2001b; Fales et al., 2003). However, Boone et al. (2001) reported deficits in both nonverbal and verbal executive function performance among adults with KS. Thus, there is no unequivocal evidence that language deficits underlie the deficits in executive functions, rather verbal and nonverbal deficits are seen across different cognitive domains including executive function. In addition, impaired executive function has been linked to emotion dysregulation among KS men, with lower cognitive flexibility and attention being associated with poor emotion regulation (Van Rijn & Swaab, 2020). Adverse life events also affect executive functions more severely in KS than in controls, resulting in decreased mental flexibility, inhibition in addition to impaired social cognition (Van Rijn, Barneveld, Descheemaeker, Giltay, & Swaab, 2018).

Deficits in executive functions have been suggested to be part of the etiology of ADHD (Barkley, 1997). This is consistent with a higher prevalence of ADHD among males with KS aged 6–21 years (n = 57) (Tartaglia et al., 2010), with 36% meeting the diagnostic criteria for ADHD (DSM-IV) and with Ross et al. (2012) who reported that 42% of boys with KS (aged 4–15; n = 82) had significantly elevated symptoms of ADHD based on parents’ report of ADHD symptoms. An even higher prevalence was reported in the study by Bruining et al. (2009), who found that 63% of boys and adolescents with KS also had ADHD.

### 2.4 | Social skills and autism spectrum disorders

In addition to being withdrawn, boys and men with KS also exhibit significant deficits in social functioning. Two-thirds of boys with KS were reported to have poor social interaction and communication skills in one study, present in early childhood (Van Rijn et al., 2014), while other studies have reported social dysfunction in 42–47% of KS boys (Cordeiro, Tartaglia, Roeltgen, & Ross, 2012; Tartaglia et al., 2010). The underlying mechanism for these social impairments has been comprehensively investigated by Van Rijn (2015), Van Rijn et al. (2007),
Van Rijn, Barendse, van Goozen, and Swaab (2014), Van Rijn, Stockmann, van Ravenswaaij-Arts, and Swaab (2014). Van Rijn and Swaab (2015), and Van Rijn, de Sonneville, and Swaab (2018), who found that individuals with KS have difficulties in social cognitive functions related to perceiving, understanding and expressing social signals, with particular deficits in facial expression, affective tone of voice, reading social signals and theory of mind (ability to understand and interpret other people’s intentions and emotions). These social, cognitive and linguistic impairments combine to have profound, adverse effects on life adaptation and outcome in males with KS with consequences for both social-life and work-life (Bojesen, Stochholm, Juul, & Gravholt, 2011).

The percentage of boys and men with KS meeting the diagnostic criteria for autism spectrum disorder (ASD) appears to range from 5 to 27% (Bishop et al., 2011; Bruining et al., 2009; Ross et al., 2012; Tartaglia et al., 2010), significantly higher than in the general population. The studies by Cordeiro et al. (2012) and Tartaglia et al. (2010), however, also indicate that social deficits are common in KS males who do not fulfill the criteria for ASD.

### 2.5 | Language and academic achievements

General language impairments are present in the majority of boys and men with KS. Studies indicate that up to 80% of patients may experience difficulties in language skills (Bender et al., 1983; Leonard, 1990; Ratcliffe, 1982; Skakkebaek et al., 2013; Walzer, Graham, Bashir, & Silbert, 1982). These deficits often become apparent in childhood (Robinson, Lubs, Nielsen, & Sorensen, 1979), and typically persist into adolescence and adulthood (Mazzocco & Ross, 2007). The earliest signs of language deficits in boys with KS have been reported at the age of 2 years as delays in speech acquisition (Robinson et al., 1979). Significant deficits in both receptive language (comprehension of linguistic stimuli) and expressive language (production of linguistic content) have also been identified in boys and men with KS. Receptive language deficits among KS individuals include auditory discrimination and processing, semantic memory (Bender et al., 1983; Graham, Bashir, Stark, Silbert, & Walzer, 1988; Van Rijn & Swaab, 2015; Walzer, Bashir, & Silbert, 1990). Several components of expressive language are also affected in KS, including speech onset, articulation, word retrieval, verbal fluency and word formulation (Bender et al., 1989; Boone et al., 2001; Graham et al., 1988; Mazzocco & Ross, 2007; Rovet et al., 1996; Samango-Sprouse, 2001; Van Rijn & Swaab, 2015). Expressive language difficulties are particularly common among KS children (Boada et al., 2009), and these language difficulties are more pronounced when the task complexity increases, while KS children perform better in relation to relatively simple tasks (Geschwind, Boone, Miller, & Swerdlow, 2000; Graham et al., 1988; Mazzocco & Ross, 2007; Van Rijn & Swaab, 2015).

The linguistic difficulties seen in individuals with KS are also reflected in their academic performance. Domains such as reading, writing and word decoding are significantly affected (Pennington et al., 1982; Rovet et al., 1996), with 50–75% experiencing characteristics of dyslexia (Boone et al., 2001) and more than 50% receiving special education (Bender et al., 1986; Ratcliffe, 1999; Stewart, Bailey, Netley, Rovet, & Park, 1986; Walzer et al., 1982, 1986). These deficits, combined with increasing psychosocial challenges have significant socioeconomic implications for men with KS, whose educational levels and occupational prospects are diminished (Bojesen et al., 2011).

### 2.6 | The impact of testosterone therapy

Hypergonatropic hypogonadism is present in almost all men with KS and testosterone therapy is central in the care of KS (see the article by Chang et al. in this journal collection). The hypogonadism emerges around mid-puberty, but may be present earlier, even in the fetus with KS (Gravholt et al., 2018). A positive effect of testosterone therapy on cognitive and psychological outcome have been suggested by some studies (Mehta & Paduch, 2012; Patwardhan et al., 2000; Ross et al., 2017; Samango-Sprouse et al., 2013, 2015, 2018). However, only three of these studies are longitudinal studies (Ross et al., 2017; Samango-Sprouse et al., 2013, 2015), and furthermore, it is important to stress that appropriate control groups of placebo-treated KS have not been included in these studies. Two of these longitudinal studies found, that 3 months of testosterone therapy had a positive effect on KS patients’ cognitive function at Age 3 and 6 years and on social behavior function at Age 9 and 11 years, however, the indication for starting treatment with testosterone in those studies was small phallic (Samango-Sprouse et al., 2013, 2015), and not neurocognitive dysfunction. Thus, it must be emphasized that future studies should include a placebo treated control group. In the only randomized study to date, 2 years of testosterone therapy improved KS patients’ anxiety, depression and social skills, but no effects were found on cognitive functioning (Ross et al., 2017).

Interestingly, a recent published meta-analysis (Buskbjerg, Gravholt, Dalby, Amidri, & Zachariae, 2019) of 23 randomized controlled trials of the effect of testosterone supplementation on cognitive function in adult men without KS, did not find support of an beneficial effect of testosterone supplementation on cognitive functioning in men with testosterone levels within normal ranges and without any cognitive deficits, however they did find a smaller beneficial effect of testosterone supplementation when analyzing a subgroup of studies of men with various degrees of cognitive impairments. Their results also indicated that the effect of testosterone supplementation might depend on how testosterone is administered, with injection being superior to gel and cream. Unfortunately, none of the randomized controlled trials reported on the effect of testosterone treatment of outright hypogonadal men.

Future randomized controlled studies on cognitive, psychological and social outcomes among individuals with KS are needed to elucidate the beneficial effects of testosterone therapy.

### 3 | BRAIN MORPHOLOGY

The neuroanatomical underpinnings of the cognitive, psychological, social and behavioral phenotype seen in KS, have yet to be elucidated. Several
brain imaging studies have been conducted over the last 20 years to address this question, the results of which are examined below.

3.1 | Brain volume and cortical surface area

A search of the literature revealed 14 studies reporting measures of total brain volume in KS with a comparison to a male control group (Bryant et al., 2011; DeLisi et al., 2005; Giedd et al., 2007; Goddard, Swaab, Rombouts, & Van Rijn, 2016; Lentini et al., 2013; Mankiw et al., 2017; Nadig et al., 2018; Patwardhan et al., 2000, 2002; Raznahan et al., 2016; Reardon et al., 2016; Rezaie et al., 2009; Shen et al., 2004; Skakkebaek et al., 2013; Warwick et al., 1999). All studies reported KS to have on average smaller brain volume (Table 1; Figure 1). Some studies, however, were re-analyses of the same data or subsets of the same data, and a variety of different methods and measures were applied, making a direct comparison between studies difficult. We identified nine studies with independent data and in order to obtain method independent measures (i.e., independent of corrections for age, intracranial volume etc.) of size differences, we calculated the volume ratio between KS and male controls for these nine studies (Figure 1). A weighted average revealed that the brain volume of KS is 93.88% of control males’ volume ($t(8) = -9.8$, $p < .0001$). The study by Skakkebaek et al. (2013), including the largest cohort of KS males to date, indicated that this differential volume is observable both in gray and white matter, but not in CSF. Although the ages of study participants in Table 1 varied widely, brain-size differences between KS patients and controls did not vary with age, neither in Skakkebaek et al. (2013), or in the studies overall (Figure 2). Smaller brain volume also seems to be present in the absence of differences in head circumference in KS (Chang et al., 2015).

Smaller KS brain volume also reflected smaller cortical surface area (Raznahan et al., 2016), and both measures have been found to be related to the increased X chromosome dosage. Overall brain volume of KS males is thus similar to that of 46,XX women in the general population, while the brain volume of 47,XXX males, another sex chromosome aneuploidy with an extra Y chromosome, has been found to be similar to that of 46,XY males (Raznahan et al., 2016). Thus, it appears to be the addition of an X chromosome—rather than any added sex chromosome—that is responsible for the effect. This is supported by findings that further increasing the X chromosome dosage (e.g., 47,XXX or 49,XXXXY), causes further reduction in brain volume and surface area (Raznahan et al., 2016).

3.2 | Structural cortical asymmetry

It has been suggested that structural brain asymmetries could be tied to sex chromosomes (Crow, 1993; Wallentin, 2009, 2018, 2020), perhaps linking differences in brain structure to the differences observed in verbal abilities between KS and control males. Verbal abilities are thought to be left-lateralized in the brain, and a structural difference in lateralization may thus account for the observed functional difference. It has been hypothesized that the magnitude of the brain torque (i.e., a combination of rightward frontal and leftward occipital asymmetry) would be increased in KS as a function of sex chromosome dosage (Crow, 1993). However, this prediction was not supported by data (Rezaie et al., 2009), who found no differences in brain torque between KS and control males. Moreover, no significant overall hemisphere asymmetry difference between KS and controls has been observed either (Rezaie et al., 2009; Skakkebaek et al., 2013; Warwick et al., 1999).
3.3 | Localized structural differences

Local volumetric differences are primarily found in the ventral (e.g., medial temporal) and central (subcortical) parts of the brain (Bryant et al., 2011; DeLisi et al., 2005; Giedd et al., 2007; Goddard et al., 2016; Lentini et al., 2013; Mankiw et al., 2017; Nadig et al., 2018; Patwardhan et al., 2000, 2002; Raznahan et al., 2016; Reardon et al., 2016; Shen et al., 2004; Skakkebaek et al., 2013), and these local differences alone predict status (i.e., KS or male control) in 96.9% of cases (Skakkebaek et al., 2013). To date, however, there is no evidence to support a direct link between these volumetric differences and the cognitive profile of KS persons (Skakkebaek et al., 2013), nor have any structural differences between KS participants receiving testosterone treatment and those who do not been found (Skakkebaek et al., 2013). A major problem with investigating local structural differences in the face of a global size difference is how to correct for the latter. Often, total brain volume correction methods assume linear scaling, which can exaggerate sex-chromosome aneuploidy effects on subcortical anatomy, given that subcortical volumes are not linearly related to total brain volume among healthy humans (Reardon et al., 2016).

3.4 | Cerebellum

A few studies report decreased cerebellar volume among KS males (Lentini et al., 2013; Mankiw et al., 2017; Skakkebaek et al., 2013). A detailed study by Mankiw et al. (2017) found that the average cerebellar volume of 56 KS adolescents was 88.2% as large as male controls (93.7 cm³ and 106.2 cm³, respectively). This significant size bellar volume of 56 KS adolescents was 88.9% the size of controls', but not to striatum (92%) or thalamus (93%). However, this lack of significance in the Reardon et al. study may have been due to the low age (mean age 12 years) of the participants and smaller sample size (n = 38) relative to that of Skakkebaek et al. (2013) (n = 65, mean age 36 years), rather than a scaling issue. Future studies with larger samples and a broader range of ages could clarify the comparability of these findings.

3.5 | Limbic and paralimibic structures: Amygdala, hippocampus, insular cortex

Several studies have found smaller cortical volume in the medial temporal lobes in KS patients (Giedd et al., 2007; Lentini et al., 2013; Nadig et al., 2018; Patwardhan et al., 2002; Skakkebaek et al., 2013, 2015), as well as in the mouse XXY model (Raznahan et al., 2015). Nadig et al. (2018) found that the average amygdala volume of 56 KS adolescents was 88.2% as large as male controls (2.26 cm³ vs. 2.54 cm³, 89%), even after correcting for total brain size. Nadig et al. (2018) also found that KS males’ hippocampal volume of 4.32 cm³ was 94.5% the size of the volume for controls (4.57 cm³), although this difference was not significant when correcting for total brain volume. In addition, several studies have also reported smaller volume in the insular cortex of KS patients relative to male controls (Goddard et al., 2016; Lentini et al., 2013; Shen et al., 2004; Skakkebaek et al., 2013).

3.6 | Subcortical structures: Striatum, pallidum, thalamus

Previous studies have found local volumetric differences between a KS group and controls in subcortical structures, including the striatum, pallidum and thalamus (Giedd et al., 2007; Lentini et al., 2013; Skakkebaek et al., 2013). Consistent with other studies, Reardon et al. (2016) found KS-related differences across subcortical structures when they applied linear scaling, but when they used allometric analysis to take the sublinear scaling into account, the differences between KS and control males were found to be limited to the pallidum (which was 88.9% the size of controls'), but not to striatum (92%) or thalamus (93%). This lack of significance in the Reardon et al. study may have been due to the low age (mean age 12 years) of the participants and smaller sample size (n = 38) relative to that of Skakkebaek et al. (2013) (n = 65, mean age 36 years), rather than a scaling issue. Future studies with larger samples and a broader range of ages could clarify the comparability of these findings.

3.7 | Hypothalamus and pituitary gland

The precise roles of the hypothalamus and the pituitary gland in KS-related conditions is not well understood and has not been directly investigated. In XXY mice increased hypothalamic volume has been found (Raznahan et al., 2015), whereas Lentini et al. (2013) found that hypothalamic and pituitary volumes in human KS males were smaller than those of male controls. Nonetheless, a wide range of previous studies demonstrate sex chromosome-related differentiation in the hypothalamus and pituitary gland.

One region of potential interest is the sexually dimorphic nucleus of the preoptic area (SDN-POA) in the hypothalamus. The SDN-POA displays volumetric sex differences in both animals and humans (Swaab & Hofman, 1988). The volume and cell number difference in the SDN-POA has appeared in humans at the age of 2–4 years of life (Swaab, 2003) and is influenced by postnatal levels of testosterone (Dohler et al., 1984; Panzica et al., 1987). Although this timespan may overlap to some degree with the onset of hypogonadism in KS, it is not presently known whether the region follows a normal developmental trajectory in children with KS. Most neuro-morphometric studies conducted on KS men have not been tailored to study small nuclei, such as the SDN-POA, and variability may be considerable, given that size in 46,XY men has also been observed to fluctuate with age (Swaab, 2003).

Whether structural effects of sex chromosome aneuploidy can be observed in the nuclei of the hypothalamus needs to be investigated. Electric stimulation of the preoptic area in monkeys has been found to elicit penile erection and ejaculation (Oomura, Yoshimatsu, & Aou, 1983; Robinson & Mishkin, 1966), and the median preoptic area is thought to be important for the recognition of sensory stimuli as appropriate sexual targets, and for the integration of this recognition with sexual motivation (Swaab, 2003). Along these lines, KS men report higher frequencies of orgasmic problems, lower intercourse
satisfaction, as well as erectile dysfunction, and delayed ejaculation (Skakkebaek, Moore, Chang, Fedder, & Gravholt, 2017). Further studies using updated volumetric techniques (Makris et al., 2013; Osada et al., 2017) are needed to elucidate this speculative link between these symptoms and hypothalamic structure and function.

The pituitary gland in humans similarly exhibits sex differentiation. Females have been found to have a larger pituitary than males, despite males having a larger total brain volume (Wong et al., 2014). Furthermore, testosterone and estradiol levels have been found to predict pituitary volume in a non-affected group of males, controlling for the effects of age and puberty stage (Wong et al., 2014). The functional relevance of pituitary volume is yet to be established, and the causal mechanisms are also unknown. Research would be needed to investigate whether there might be a feedback loop within the hypothalamic–pituitary–gonadal-axis where gonadal growth and testosterone release stimulates pituitary/hypothalamic development and vice versa. Such a feedback-loop could be the origin for both the hypogonadal effects observed in KS and a potential abnormal hypothalamic/pituitary structure and function.

4 | FUNCTIONAL NEUROIMAGING

The few functional neuroimaging studies of KS males in the literature include investigations of executive functioning and stimulus adaptation (Wallentin et al., 2016), language processing and lateralization (Van Rijn et al., 2008; Wallentin et al., 2016) and social cognition (Brandenburg-Goddard et al., 2014; Van Rijn et al., 2012).

4.1 | Perception and motor responses

In the most comprehensive functional neuroimaging study to date, Wallentin et al. (2016) included tests of both low-level perception, executive function and stimulus adaptation in a relatively large sample of adult KS (n = 49). Participants were shown words denoting color (red, green, yellow) in either the auditory or the visual modality and responded with a button-press.

KS males exhibited greater activation for auditory stimuli in primary auditory cortices, and for motor output in left primary motor cortex (which was relevant to right-hand button-presses in the task) (Figure 3). However, no activation difference was observed for visual stimuli, suggesting that this activation was not a response to all low-level signals, but rather to specific systems. The authors suggested that the increased activations may act as a compensatory mechanism, although they found no evidence for age or testosterone level modulations. Further studies are needed to assess the reliability of these findings, and to elucidate their potential causes.

4.2 | Higher order cognition and learning

The visual stimuli used by Wallentin et al. (2016) made up a simple Stroop paradigm (Stroop, 1935), in which participants were to report the color in which the word was written in and thus override their tendency to read the word. Furthermore, participants were asked not to respond to words written in yellow. This experiment thus tested participants’ executive function (Stroop and no-go tasks). The Stroop task is known to be correlated with activation in frontal brain regions involved in language processing and in verbal working memory (Huang, Su, & Ma, 2019; Novick, Trueswell, & Thompson, 2010; Wallentin, Gravholt, & Skakkebaek, 2015). KS participants displayed normal response time and Stroop effect, with no differential brain activity during this task compared to control men. In the same study, an adaptation contrast was added by making one of the color words occur more often than the other (randomized across participants). Both KS and control participants exhibited comparable decreases in brain activation (in left premotor, sensorimotor, and parietal regions) and response-time adaption to more frequent stimuli. KS and control participants thus seem to learn about the statistical structure of the
stimuli equally well, suggesting that the previously observed KS-related learning deficits (Walzer et al., 1986, 1990) are not attributable to a relative deficiency in adapting to statistical properties of the perceptual input, neither at the behavioral nor at the neural level.

4.3 | Language activation and lateralization

Given the language deficits observed in KS, it is important to test for differential brain activation associated with language stimuli (Van Rijn et al., 2008; Wallentin et al., 2016). Conflicting evidence has been observed with one study suggesting an altered language lateralization (Van Rijn et al., 2008), whereas another did not (Wallentin et al., 2016). It should be noted however, that the two studies differed greatly in design and analysis procedure. Additionally, KS men have been found to exhibit a significantly decreased response to written words in the visual word form area in the ventral part of the temporal lobe (Wallentin et al., 2016) (Figure 3). This area develops as a function of learning to read (Dehaene & Cohen, 2011; Wallentin, Michaelsen, Rynne, & Nielsen, 2014) and the effect may be related to the greater reading deficits observed in KS persons.

4.4 | Face processing

Following up on the known social deficits associated with KS, two studies have investigated sensitivity to facial expressions (Brandenburg-Goddard et al., 2014; Van Rijn et al., 2012). One of these studies found that KS men exhibited less activation than controls in the amygdala and fusiform face area (Van Rijn et al., 2012), while another study found a tendency for increased activation in the amygdala (Brandenburg-Goddard et al., 2014). The latter study also found that KS men relied more on prefrontal brain areas for processing of facial expressions (Bishop et al., 2011). At present, there is thus no consistent pattern in the studies of brain correlates of social functioning in KS.

5 | CONCLUSION

Psychological functioning is compromised in a large proportion of boys and men with KS. Educational, cognitive and behavioral interventions to address these challenges are needed. Furthermore, randomized and longitudinal studies on cognitive and psychological endpoints are important to systematically assess the potential psychological, social and behavioral benefits of testosterone therapy. The neuroanatomical and functional brain alteration seen in males with KS are most likely the result of both genetic and hormonal factors, however the neurobiological underpinnings of the cognitive, psychological, social and behavioral phenotype seen in KS have not been established, and should be further addressed in future studies. Here, we have introduced areas of uncertainty and suggested future avenues for research. Specifically, research focusing on studying the effect of testosterone supplementation should be conducted in a strict randomized placebo-controlled setting, in order to draw conclusions on the putative influence of testosterone on neurocognitive functioning. Furthermore, we suggest that studies of neurocognitive intervention schemes of both adolescents and adults with KS should be conducted, since research in other patient populations suggests that such interventions may improve for example executive functioning. Again, such studies should be appropriately placebo controlled. It is also clear that there are large gaps in our current knowledge of the natural history of neurocognitive functioning among males with KS, and most research to date has focused on children, adolescents and younger adults and not much is known about the aging male with KS. Large epidemiological or multicenter studies could help fill these gaps in knowledge and will be important to describe how neurocognitive functioning affects the occurrence of psychiatric disorders.

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