Molecular Human Reproduction, Vol.16, No.6 pp. 418–424, 2010
Advanced Access publication on March 26, 2010 doi:10.1093/molehr/gaq022

MHR Basic science of reproductive medicine

NEW RESEARCH HORIZON ***Review***

Clinical and therapeutic aspects of Klinefelter's syndrome: sexual function

L. Vignozzi[1], G. Corona[1,2], G. Forti[3], E.A. Jannini[4], and M. Maggi[1,5,*]

[1]Sexual Medicine and Andrology Unit, Endocrinology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy [2]Endocrinology Unit, Maggiore-Bellaria Hospital, Bologne, Italy [3]Endocrinology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy [4]Course of Endocrinology and Medical Sexology, Department of Experimental Medicine, University of L'Aquila, L'Aquila, Italy [5]Centro Interuniversitario in Andrologia Sperimentale, University of Florence, Italy

*Correspondence address. E-mail: m.maggi@dfc.unifi.it

Submitted on December 15, 2009; resubmitted on March 5, 2010; accepted on March 9, 2010

ABSTRACT: Klinefelter's syndrome (KS) is the most common sex chromosomal aberration among men, with estimated prevalence of about 1 in 500 newborn males. The classical phenotype of KS is widely recognized, but many affected subjects present only very mild signs. While the association between KS and infertility has been well documented, few studies have investigated sexual function in the KS patients. In the present paper we reviewed studies addressed to emotional processing and sexual function in KS. We searched the following databases Medline, Pubmed, Embase, for Klinefelter's syndrome, sexuality. We focus on the peculiar contribution of genetic and hormonal background, which characterizes sexual dysfunction in KS. Abnormal structure and function of the emotional brain circuits have been described in KS. These alterations were less pronounced when the patients underwent to testosterone replacement therapy suggesting that they were mediated by testosterone deficiency. Accordingly, clinical studies indicate that sexual dysfunctions, eventually present in KS, are not specifically associated with the syndrome but are related to the underlying hypogonadism. In conclusion, androgen deficiency more than chromosomal abnormality is the major pathogenic factor of sexual dysfunction in KS.

Key words: endocrinology

Introduction

In 1942, Harry Klinefelter and colleagues described a male syndrome characterized by tall stature with eunochoidal body proportions, small testes, azospermia, gynecomastia and increased urinary excretion of FSH (Klinefelter *et al*., 1942) Fifteen years later, it was reported (Bradbury and Bunge, 1956; Hoffenberg *et al*., 1956; Plunkett and Barr, 1956; Riis *et al*., 1956) that patients with Klinefelter's syndrome (KS) had sex chromatin material in epithelial cells similar to normal females and then in 1959, Jacobs and Strong (1959) found that a chromatin-positive patient with KS had a 47,XXY karyotype.

The XXY karyotype occurs in 1 in 500 live male births and is the most common type of human chromosome anomaly (Smyth and Bremner, 1998). Unlike chromosomal abnormalities on autosomes, the 47,XXY karyotype leads to a relatively mild clinical presentation. This mildness is probably due to inactivation of most genes on the supernumerary X chromosome (Heard *et al*., 1997). However, there are genes that lie in the pseudo-autosomal region on the X chromosome that have homologues on the Y chromosome (Jegalian and Page, 1998), and tend to escape the silencing during the supernumerary X chromosome inactivation process (Carrel *et al*., 1999; Sudbrak *et al*., 2001). Nowadays, it is well recognized that Klinefelter's original description of the syndrome is too limiting, because it represents a broad spectrum of phenotypes, professions, incomes and socio-economic statuses (Lanfranco *et al*., 2004).

It has been recently reported that, in adulthood, most men with KS will visit their physicians because of (i) infertility and/or (ii) sexual dysfunction (Paduch *et al*., 2008). The issue related to infertility in KS have been significantly improved during the last 10 years by the advent of combined testicular sperm extraction, TESE (Devroey, 1998) and assisted reproductive technologies (ART) (Romundstad *et al*., 2008). This topic has been extensively covered by several recent reviews (Paduch *et al*., 2008; Wikström and Dunkel, 2008; Paduch *et al*., 2009). In contrast, the issue related to KS sexual function and dysfunction is less studied. In this review we provide an overview of available research studies investigating the pathogenesis of sexual function and dysfunction in KS.

Sexual differentiation and behaviour is a multi-step process, which begins early in fetal life, according to the sex difference of the chromosomes established at conception (*chromosomal sex*). In fact, chromosomal sex determines gonadal production of androgens and the Mullerian inhibiting hormone (*gonadal sex*), which finally dictate the appearance of external and internal genitalia (*anatomic* or *phenotypic sex*). Sex differences between male and female brain organization and cognitive process occur either under the control of a complex series of genetic (*sex determining region Y*, SRY; silencing of

X chromosome; several epigenetic events), but also hormonal (gonadal steroid hormones and their receptors) events. SRY is the testis-determining gene, which causes the embryonic undifferentiated gonad to develop into a testis rather than an ovary (Goodfellow and Lovell-Badge, 1993). This event represents the primary developmental decision that will determine whether an individual will be and behave as a male or a female. Indeed the embryonic testis secretes sex steroids, particularly the surge of testosterone during the early period of development (an epoch of extreme sensitivity to the environment) that enters the brain causing a masculine pattern of brain development and behaviour. Sexual behaviour is controlled by a set of brain regions that do not operate independently, but function in a background in which genetic and hormonal factors are crucial (Pfaus, 2009). Hence, in order to answer the question of which is the main determinant of sexual dysfunctions, eventually present in KS subjects, we focused on the potential contribution of the peculiar genetic and hormonal background, which characterizes the syndrome.

Methods

A systematic search was performed using Medline up to February 2010. In an effort to identify the studies evaluating sexual function in KS the search term 'Klinefelter's syndrome' was combined consecutively with the following terms: 'erectile dysfunction', 'impotence', 'sexual functioning', 'ejaculation' 'premature and delayed ejaculation' and 'desire'. The search was limited to English-language papers.

Emotional brain in KS patients

Sexual behaviour is controlled by a set of complex neuroanatomical and neurochemical pathways, which are commonly referred to as the emotional brain. Summarizing the set of brain regions that are critically linked to emotion is plagued by the fact that none of these regions are 'purely affective', but deeply involved in numerous functions (Duncan and Barrett, 2007). Nevertheless some subcortical regions (namely the amygdala, the nucleus accumbens and the hypothalamus), and the major prefrontal cortex subregions (namely orbitofrontal cortex, the anterior cyngulate cortex and the ventromedial prefrontal cortex) have been depicted as 'core' emotional territories (Pessoa, 2008). Among these, the amygdala occupies a very geometric centre and is deemed to be a highly connected hub. In particular, amygdala projections broadcast important regulatory signals widely to the prefrontal cortex and the hypothalamus (Alheid, 2003; Swanson, 2003). Amygdala activation has been evidenced in rodents (Minerbo *et al*., 1994; Pfaus and Heeb 1997) and cats (Holmes and Egan, 1973), during mating behaviour. More recently research in humans has found amygdala activation in response to sexual stimuli using functional magnetic resonance imaging (MRI) (Karama *et al*., 2002; Holstege and Georgiadis, 2003; Baird *et al*., 2004; Ferretti *et al*., 2005; Ponseti *et al*., 2006; Childress *et al*., 2008), supporting a role for the amygdala in the processing of the emotional significance of stimuli that can trigger conscious desire. Amygdala neurons fire in response to novel rewards in the environment and the released dopamine turns attention and behaviour towards the rewarding situation, thus imbuing the stimulus with motivational 'valence' (Murray, 2007). Interestingly, the amygdala, and more extensively the whole brain reward circuitry (including also the prefrontal cortex, temporal regions, insula, striatum/pallidum), activates also during sexual cues presented outside awareness, suggesting that the ancient limbic reward circuitry can strike up a rapid and outside awareness prelude to passion (Childress *et al*., 2008).

Previous studies in rats (Cooke *et al*., 2000), sheep (Romeo and Sisk, 2001), primates (Pellis and Iwaniuk, 2002) and humans (Baird *et al*., 2004) have demonstrated a positive correlation between amygdala volume and sexual functioning.

Interestingly, a volume reduction in left temporal gray matter (Patwardhan *et al*., 2000; Itti *et al*., 2006), and a specific amygdala reduction (Patwardhan *et al*., 2002,) were demonstrated in adult KS patients in MRI studies based on manual delineation of regions of interest. In a larger structural MRI study, using automated method for voxel/regional parcellation and volumetric analyses, Shen *et al*. (2004) observed pronounced gray matter density reductions of the right amygdala, left insula and cingulated gyrus in 34 KS patients compared with 62 healthy matched controls. A decreased cortical thickness in the temporal regions has been reported to be present also in child KS patients (Rose *et al*., 2004; Giedd *et al*., 2007). Taken together, findings from MRI studies show structural abnormalities of brain regions that form part of a neural network subserving social cognition and emotion (Aleman *et al*., 2008).

Recently it has been proposed that in 47, XXY men reduced activation in the amygdala is responsible for the less accurate perception of socio-emotional cues and impairment in emotional prosody in comparison to the general population (Van Rijn *et al*., 2006). Interestingly, amygdala, the central hub in the emotional brain, is recognized to be subject to a high degree of androgen-dependent plasticity, even in the adulthood (Cooke, 2006) as will be discussed below.

The reduced size of the amygdala (Patwardhan *et al*., 2002; Rose *et al*., 2004; Shen *et al*., 2004), as well as of the left temporal lobe (Patwardhan *et al*., 2000) in subjects with KS was found to be at least partly due to androgen deficiency, as it was less apparent in testosterone-replaced KS subjects (Patwardhan *et al*., 2000). In particular, in a small study involving 10 subjects with KS, variation in brain morphology associated with supernumerary X chromosome was not present in the subgroup of KS subjects that had received testosterone supplementation since puberty. This suggests that the human brain retains plasticity to be continually modified by externally supplemented hormones, such as testosterone. Indeed, androgen receptors are highly expressed in the male brain, and are particularly present in neurons constituting the neural rewarding circuits mediating sexual behaviours, such as the amygdala, the nucleus accumbens, the stria terminalis, the medial preoptic area and the ventromedial hypothalamus (see Phillips-Farfán and Fernández-Guasti, 2009 for review).

The 'morphogenic' and organizing action of testosterone on sexual dimorphic differentiation of the human fetal brain was first established by Phoenix *et al*. (1959). They demonstrated that female guinea pig exposed to testosterone during the fetal life permanently masculinized their sexual behaviour (Phoenix *et al*., 1959). It is now well known that exposure to testosterone during gestation induces masculinization of the brain (Arnold, 2009; Blaustein and McCarthy, 2009; Thornton *et al*., 2009; Schulz *et al*., 2009). Nevertheless, when prenatal testosterone was investigated in amniotic fluid, no significant difference was observed between XXY fetuses and XY controls, and both showed higher levels than the XX fetuses (Ratcliffe *et al*., 1994). Also in the neonatal period no indisputable hypoandrogenism was apparent in KS subjects because of studies reporting a normal (Ratcliffe, 1982; Aksglaede *et al*., 2007) or low (Lahlou *et al*., 2004; Ross *et al*., 2005) testosterone level.

Recently, Neufang *et al*. (2009) demonstrated that amygdala and hyppocampal volumes varied as a function of Tanner stages and were associated with circulating testosterone levels during male puberty. Indeed, during puberty, neural connections between amygdala and frontal areas are strengthened (Walker and Bollini, 2002) supporting a role for post-pubertal hormonal changes in the maturation and refinement of the limbic circuitry. Frontal brain activity increases during puberty (Casey *et al*., 2000; Rubia *et al*., 2000) and this is assumed to contribute to advances in cognitive processes (abstract reasoning skills and attentional capacities) that is a definite component of sexual maturation.

Similar organizational effects of testosterone have been demonstrated also in young adulthood (Witte et al., 2010). Neuroimaging studies have demonstrated that testosterone increases neural activity in the amygdala (Hermans et al., 2008; Derntl et al., 2009; van Wingen et al., 2009) and orbitofrontal cortex (Redouté et al., 2005; Hermans et al., 2008; van Wingen et al., 2009) in both sexes.

These data support the view that the crucial regions of the emotional brain are extremely sensitive to testosterone also during adulthood. In agreement, it has been demonstrated that testosterone level was positively associated with men's attention to socially relevant stimuli (Van Honk et al., 1999), and more recently with men's interest in sexual stimuli, evaluated both as self-regulated viewing times for pornographic images (Rupp and Wallen, 2007) and as reported attraction to femininity in women's faces (Welling et al., 2008). Taken together these data suggest that endogenous testosterone level may modulate men's interest in sexual stimuli. In adult males testosterone influenced reproduction and sexuality, whetting sexual desire but also regulating all the other steps of sexual response, namely sexual excitation and orgasm/ejaculation. Nowadays it is well known that one of the main physiological functions of testosterone is to tune up erection with sexual desire, finalizing erection to emotional processing (Corona et al., 2005; Vignozzi et al., 2005; Traish and Guay, 2006; Bhasin et al., 2007; Corona et al., 2009b).

Testosterone replacement therapy (TRT) has been described to significantly improve cognitive function in the general population (Janowsky et al., 1994; Janowsky et al., 2000; Cherrier et al., 2001; Cherrier et al., 2002; Cherrier et al., 2005; Cherrier, 2009), and also in the depressed men (Vogel et al., 1985; Seidman and Rabkin, 1998; Seidman et al., 2001; Pope et al., 2003). More recently, also the negative symptoms in male schizophrenic patients have been correlated with serum testosterone level (Shirayama et al., 2002; Goyal et al., 2004; Akhondzadeh et al., 2006) and short-term testosterone treatment has been suggested as a therapeutic option in male schizophrenics (Ko et al., 2008).

In summary, all these studies indicate that testosterone exerts a morphogenetic and trophic effect on a well-mapped set of brain regions dedicated to emotional processing and sexual behaviour. This testosterone-dependent morphologic plasticity that have traditionally been thought to characterize fetal and neonatal life, might be operative also in adulthood, as demonstrated in the study of KS patients.

KS and sexual dysfunction

It is generally reported that in KS low libido and erectile dysfunction are present (Sørensen et al., 1979; Raboch et al., 2003; Paduch et al., 2008), however only few studies have specifically investigated this point (Wu et al., 1982; Yoshida et al., 1997, Corona et al., 2009a,). The findings are summarized in Table I.

Yoshida et al. (Yoshida et al., 1997) compared the sexual features of 40 KS patients to 40 non-azospermic infertile 46,XY patients by using a non-validated questionnaire on sexual function. Among their sample, 90% of KS patients showed normal and 10% a slightly decreased sexual desire, while 97.5% had a normal erection during the whole duration of intercourse, while the remaining demonstrated a normal erection with shrinkage after entering into the vagina. Orgasm was normal in 80% of KS patients, while it was slightly decreased in about 17%, and significantly decreased in about 2%. However, there was not a significant difference in the frequency of sexual function disturbances between the patients with KS and the control group. On the contrary, the mean frequency of intercourse in KS patients was significantly higher than in the control group. Another study compared coital activity in groups of married men with KS and in men with a varicocele investigated for marital infertility. Frequency of intercourse in both groups did not significantly differ (Raboch, et al., 2003.) One of the main limitations of these studies is that both have been performed in a population sample of subjects amongst whom the chief complaint was of infertility and not sexual dysfunction.

Corona et al. (2009a) analysed the prevalence and the specific sexual correlates of KS in a consecutive series of male adult patients attending an Outpatient Clinic for sexual problems. Interestingly, among a consecutive series of 1386 patients, a relatively higher prevalence (1.7%) of KS than that reported in the general population (Lanfranco et al., 2004), was observed (Corona et al., 2009a). This indicates that sexual dysfunction is a common feature of KS and that clinical settings for the treatment of sexual problems are a convenient site for the diagnosis of KS. In this population, as expected, KS was associated with lower level of education, a more frequent history of cryptorchidism, poorer pubertal progression, a less often performed military service, elevated triglycerides and a higher risk of gynecomastia (Corona et al., 2009a). When sexual parameters were evaluated, 22.7% of KS patients reported severe erectile dysfunction (an erection not sufficient for penetration in more than 75% of cases), 60.9% hypoactive sexual desire (HSD), 9.5% premature ejaculation and 9.5% delayed ejaculation. However, adjusting for age, in a multiple logistic regression model, only a higher risk for HSD continued to be observed in KS subjects (Corona et al., 2009a). The frequency of sexual intercourse and masturbation was not significantly different, whilst a higher risk of reduced ejaculate volume, and a later referral to an andrology service were observed in KS patients when compared with the control (Corona et al., 2009a). In addition, KS showed, even after adjustment for age, a higher prevalence of overt primary hypogonadism. When KS patients were compared with testosterone matched control subjects, all the above-mentioned sexual and non-sexual problems were no longer associated with the syndrome, and only the typical features of KS (namely gynecomastia, tall stature, higher frequency of cryptorchidism, history of poorer pubertal progression, lower level of education) retained association with the syndrome (Corona et al., 2009a). In conclusion this case–control study indicates that HSD, eventually present in the KS subjects, is more related to the testosterone deficiency than to the genetic abnormality. Accordingly, in a small placebo control study on the effect of TRT in subjects with KS it has been reported that an increase in sexual interest was observed during TRT (Wu et al., 1982).

KS, metabolic syndrome and sexual dysfunction

Metabolic syndrome (MetS), diabetes and cardiovascular disease (CV) are often associated with KS (Swerdlow et al., 2001; Lanfranco et al., 2004; Bojesen et al., 2006; Ishikawa et al., 2008; Andersen et al., 2008; Høst et al., 2010). The association between hypogonadism, MetS and CV has also been emerging both in subjects with and without sexual dysfunction (see Corona et al., 2009b for review). In addition, prospective studies have clearly demonstrated that low T at baseline could predict the development of diabetes mellitus and MetS and vice versa (see Corona et al., 2009b for review). Although additional data are worthwhile, most cross-sectional studies have reported a direct correlation between testosterone concentrations and more favourable CV risk factor profiles, including higher high density lipids, lower triglyceride concentration, blood glucose, blood pressure and body mass index (see Corona et al., 2009b for review). In addition, both clinical and animal evidence shows that T exerts a favourable effect upon vascular reactivity, inflammation, cytokine production and adhesion molecule expressions, as well as on serum lipid concentration and haemostatic factors (see Corona et al., 2009b for review). The presence of hypogonadism in subjects with sexual dysfunction can further worsen the problem adding typical symptoms such as HSD and mood disturbances. Waist circumference and hypertriglyceridemia have been considered the most important MetS determinants of hypogonadism in subjects with sexual dysfunction (Corona et al.,

Table I Summary of the studies evaluating sexual function in patients with Klinefelter's syndrome (KS).

	Wu *et al.*, 1982	Yoshida *et al.*, 1997	Corona *et al.*, 2009a, b
Type of study	Double-blind placebo-controlled interventional study with oral TU	Observational cross-sectional study	Observational cross-sectional study
Population studied			
Main problem for medical consultation	Infertility/sexual dysfunction	Infertility	Sexual dysfunction
Number of KS [mean age ± SD]	4 [35.3 ± 8.5]	40 [32.2 ± 4.0]	23 [40.6 ± 12.3]
Number of controls [mean age ± SD]	0	55 [33.5 ± 4.2]	1356 [51.7 ± 13.0]
Sexual function in KS			
Sexual desire	Frequency of sexual thoughts/week; 2.5 ± 0.4	Normal 90%; slightly decrease 10%	Normal 39.1%; slightly decrease 26.1%; moderate or severe decrease 34.8%
Erectile dysfunction	25%	2.5%	Severe erectile dysfunction in 22.7%
Premature ejaculation	NA	NA	9.5%
Delayed ejaculation	NA	NA	9.5%
Perceived ejaculation volume reduction	NA	42.5%	Slightly reduction 28.6%: moderate or severe reduction 33.3%
Frequency of intercourse	4.5 ± 1.4 intercourse/week	4.4 ± 2.8 intercourse/month	Sexual intercourse/month: no = 22.2%; 1–2 = 27.8%; 3–7 = 50%; >7 = 0%
Frequency of masturbation	NA	NA	Masturbation/month: no = 44.4%; 1–2 = 38.9%; 3–7 = 11.1%; >7 = 5.6%
Guiltiness with masturbation	NA	NA	53.3%

NA, not available; TU, testosterone undecanoate; SD, standard deviation.

2009b). As stated above, KS patients demonstrated a higher prevalence of erectile dysfunction (Yoshida *et al.*, 1997; Corona *et al.*, 2009a) and hypertriglyceridaemia (Corona *et al.*, 2009a) when compared with patients without KS. Although the cross-sectional data available at the moment cannot allow any final conclusions to be drawn, our study suggests that KS-associated hypogonadism might play a major role in the pathogenic mechanism underlying KS-associated sexual dysfunction and MetS. In fact, the association between hypertriglyceridaemia and sexual dysfunction disappeared after adjustment for testosterone levels (Corona *et al.*, 2009a). Further longitudinal studies are advisable in order to better clarify these points.

Conclusions

In conclusion, studies reviewed strongly suggest that sexual features present in KS are not specifically associated with the syndrome but are more probably related to underlying hypogonadism. Hypogonadism, more than chromosomal abnormality, could underlie alterations in the emotional brain observed in KS patients. Hypogonadism also underpins the higher risk of hypertriglyceridaemia and sexual dysfunction observed in KS.

Finally, it can be speculated that TRT could produce an improvement of KS-associated increased risk of MetS and CV, besides the improvement of sexual function. However, further intervention studies are needed to confirm this hypothesis.

In agreement with this view, early recognition and TRT have been reported not only to significantly improve bone mineral density, body fat mass, strength, goal-directed thinking and self-esteem, but also sexual dysfunction (Myhre *et al.*, 1970; Beker, 1972; Skakkebaek *et al.*, 1981; Nielsen *et al.*, 1988; Kubler *et al.*, 1992; Zitzmann *et al.*, 2002; Nieschlag and Behre, 2004; Zitzmann and Nieschlag 2004).

We therefore propose that TRT should start as soon as possible in order to revert hypogonadism-related signs and symptoms (including sexual dysfunction) and to avoid the unwanted consequences of androgen deficiency.

References

Akhondzadeh S, Rezaei F, Larijani B, Nejatisafa AA, Kashani L, Abbasi SH. Correlation between testosterone, gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. *Schizophr Res* 2006;**84**:405–410.

Aksglaede L, Petersen JH, Main KM, Skakkebaek NE, Juul A. High normal testosterone levels in infants with non-mosaic Klinefelter's syndrome. *Eur J Endocrinol* 2007;**157**:345–350.

Aleman A, Swart M, van Rijn S. Brain imaging, genetics and emotion. *Biol Psychol* 2008;**79**:58–69.

Alheid GF. Extended amygdala and basal forebrain. *Ann N Y Acad Sci* 2003; **985**:185–205.

Andersen NH, Bojesen A, Kristensen K, Birkebaek NH, Fedder J, Bennet P, Christiansen JS, Gravholt CH. Left ventricular dysfunction in Klinefelter syndrome is associated to insulin resistance, abdominal adiposity and hypogonadism. *Clin Endocrinology* 2008;**69**:785–791.

Arnold AP. The organizational-activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues. *Horm Behav* 2009;**55**:570–578.

Baird AD, Wilson SJ, Bladin PF, Saling MM, Reutens DC. The amygdala and sexual drive: insights from temporal lobe epilepsy surgery. *Ann Neurol* 2004;**55**:87–96.

Beker KL. Clinical and therapeutic experiences with Klinefelter's syndrome. *Fert Steril* 1972;**23**:568–578.

Bhasin S, Enzlin P, Coviello A, Basson R. Sexual dysfunction in men and women with endocrine disorders. *Lancet* 2007;**369**:597–611.

Blaustein JD, McCarthy MM. Phoenix, Goy, Gerall, and Young, Endocrinology, 1959: 50 years young and going strong. *Endocrinology* 2009;**150**:2501–2506.

Bojesen A, Kristensen K, Birkebaek NH, Fedder J, Mosekilde L, Bennett P, Laurberg P, Frystyk J, Flyvbjerg A, Christiansen JS *et al.* The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes Care* 2006;**29**: 1591–1598.

Bradbury JT, Bunge RG. Newer concepts of the Klinefelter syndrome. *J Urol* 1956;**76**:758–765.

Carrel L, Cottle AA, Goglin KC, Willard HF. A first-generation X-inactivation profile of the human X chromosome. *Proc Natl Acad Sci USA* 1999;**96**:14440–14444.

Casey BJ, Giedd JN, Thomas KM. Structural and functional brain development and its relation to cognitive development. *Biol Psychol* 2000;**54**:241–257.

Cherrier MM. Testosterone effects on cognition in health and disease. *Front Horm Res* 2009;**37**:150–162.

Cherrier MM, Asthana S, Plymate S, Baker L, Matsumoto AM, Peskind E, Raskind MA, Brodkin K, Bremner W, Petrova A *et al.* Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology* 2001;**57**:80–88.

Cherrier MM, Anawalt BD, Herbst KL, Amory JK, Craft S, Matsumoto AM, Bremner WJ. Cognitive effects of short-term manipulation of serum sex steroids in healthy young men. *J Clin Endocrinol Metab* 2002;**87**: 3090–3096.

Cherrier MM, Matsumoto AM, Amory JK, Ahmed S, Bremner W, Peskind ER, Raskind MA, Johnson M, Craft S. The role of aromatization in testosterone supplementation: effects on cognition in older men. *Neurology* 2005;**64**:290–296.

Childress AR, Ehrman RN, Wang Z, Li Y, Sciortino N, Hakun J, Jens W, Suh J, Listerud J, Marquez K *et al.* Prelude to passion: limbic activation by "unseen" drug and sexual cues. *PLoS One* 2008;**3**:1506–1510.

Cooke BM. Steroid-dependent plasticity in the medial amygdala. *Neuroscience* 2006;**138**:997–1005.

Cooke BM, Chowanadisai W, Breedlove SM. Post-weaning social isolation of male rats reduces the volume of the medial amygdala and leads to deficits in adult sexual behavior. *Behav Brain Res* 2000;**117**:107–113.

Corona G, Petrone L, Mannucci E, Ricca V, Balercia G, Giommi R, Forti G, Maggi M. The impotent couple: low desire. *Int J Androl* 2005;**28**:46–52.

Corona G, Petrone L, Paggi F, Lotti F, Boddi V, Fisher A, Vignozzi L, Balercia G, Sforza A, Forti G *et al.* Sexual dysfunction in subjects with Klinefelter's syndrome. *Int J Androl* 2009a;**32**:1–8.

Corona G, Mannucci E, Forti G, Maggi M. Hypogonadism, ED, metabolic sindrome and obesity: a pathological link supporting cardiovascular diseases. *Int J Androl* 2009b;**32**:587–598.

Derntl B, Windischberger C, Robinson S, Kryspin-Exner I, Gur RC, Moser E, Habel U. Amygdala activity to fear and anger in healthy young males is associated with testosterone. *Psychoneuroendocrinology* 2009;**34**:687–693.

Devroey P. Testicular sperm extraction and intracytoplasmic sperm injection. *Hum Reprod* 1998;**13**:2045–2046.

Duncan S, Barrett LF. Affect is a form of cognition: a neurobiological analysis. *Cogn Emot* 2007;**21**:1184–1211.

Ferretti A, Caulo M, Del Gratta C, Di Matteo R, Merla A, Montorsi F, Pizzella V, Pompa P, Rigatti P, Rossini PM *et al.* Dynamics of male sexual arousal: distinct components of brain activation revealed by fMRI. *Neuroimage* 2005;**26**:1086–1096.

Giedd JN, Clasen LS, Wallace GL, Lenroot RK, Lerch JP, Wells EM, Blumenthal JD, Nelson JE, Tossell JW, Stayer C *et al.* XXY (Klinefelter syndrome): a pediatric quantitative brain magnetic resonance imaging case-control study. *Pediatrics* 2007;**119**:232–240.

Goodfellow PN, Lovell-Badge R. SRY and sex determination in mammals. *Annu Rev Genet* 1993;**27**:71–92.

Goyal RO, Sagar R, Ammini AC, Khurana ML, Alias AG. Negative correlation between negative symptoms of schizophrenia and testosterone levels. *Ann N Y Acad Sci* 2004;**1032**:291–294.

Heard E, Clerc P, Avner P. X-chromosome inactivation in mammals. *Annu Rev Genet* 1997;**31**:571–610.

Hermans EJ, Ramsey NF, van Honk J. Exogenous testosterone enhances responsiveness to social threat in the neural circuitry of social aggression in humans. *Biol Psychiatry* 2008;**63**:263–270.

Hoffenberg R, Jackson WP, Shapiro BG, Uys CJ. Primary male hypogonadism with female nuclear sex. *Lancet* 1956;**271**: 857–859.

Holmes JE, Egan K. Electrical activity of the cat amygdala during sexual behavior. *Physiol Behav* 1973;**10**:863–867.

Holstege G, Georgiadis JR. Neurobiology of cat and human sexual behaviour. *Int Rev Neurobiol* 2003;**56**:213–225.

Høst C, Bojesen A, Frystyk J, Flyvbjerg A, Christiansen JS, Gravholt CH. Effect of sex hormone treatment on circulating adiponectin and subforms in Turner and Klinefelter syndrome. *Eur J Clin Invest.* 2010; **40**:211–219.

Ishikawa T, Yamaguchi K, Kondo Y, Takenaka A, Fujisawa M. Metabolic syndrome in men with Klinefelter's syndrome. *Urology* 2008; **71**:1109–1113.

Itti E, Gaw Gonzalo IT, Pawlikowska-Haddal A, Boone KB, Mlikotic A, Itti L, Mishkin FS, Swerdloff RS. The structural brain correlates of cognitive deficits in adults with Klinefelter's syndrome. *J Clin Endocrinol Metab* 2006;**91**:1423–1427.

Jacobs PA, Strong JA. A case of human intersexuality having a possible XXY sex-determining mechanism. *Nature* 1959;**183**:302–303.

Janowsky JS, Oviatt SK, Orwoll ES. Testosterone influences spatial cognition in older men. 1994

Janowsky JS, Chavez B, Orwoll E. Sex steroids modify working memory. *J Cogn Neurosci* 2000;**12**:407–414.

Jegalian K, Page DC. A proposed path by which genes common to mammalian X and Y chromosomes evolve to become X inactivated. *Nature* 1998;**394**:776–780.

Karama S, Lecours AR, Leroux JM, Bourgouin P, Beaudoin G, Joubert S, Beauregard M. Areas of brain activation in males and females during viewing of erotic film excerpts. *Hum Brain Mapp* 2002;**16**:1–13.

Klinefelter HF, Reifenstein EC, Albright. Syndrome characterized by gynecomastia, aspermatogenesis without a-Leydigism and increased excretion of follicle-stimulating hormone. *J Clin Endocrinol Metab* 1942; **2**:615–624.

Ko YH, Lew YM, Jung SW, Joe SH, Lee CH, Jung HG, Lee MS. Short-term testosterone augmentation in male schizophrenics: a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2008; **28**:375–383.

Kubler A, Schulz G, Cordes U, Beyer J, Krause U. The influence of testosterone substitution on bone mineral density in patients with Klinefelter's syndrome. *Exp Clin Endocrinol* 1992;**100**: 129–132.

Lahlou N, Fennoy I, Carel JC, Roger M. Inhibin B and anti-Müllerian hormone, but not testosterone levels, are normal in infants with nonmosaic Klinefelter syndrome. *J Clin Endocrinol Metab* 2004;**89**:1864–1868.

Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. *Lancet* 2004;**364**:273–283.

Minerbo G, Albeck D, Goldberg E, Lindberg T, Nakari M, Martinez C, Garritano J, Smock T. Activity of peptidergic neurons in the amygdala during sexual behavior in the male rat. *Exp Brain Res* 1994;**97**:444–450.

Murray EA. The amygdala, reward and emotion. *Trends Cogn Sci* 2007; **11**:489–497.

Myhre SA, Rluvalcaba RHA, Johnson HR, Thuline HC, Kelley VC. The effect of testosterone in Klinefelter's syndrome. *J Pediatr* 1970;**76**:267–276.

Neufang S, Specht K, Hausmann M, Güntürkün O, Herpertz-Dahlmann B, Fink GR, Konrad K. Sex differences and the impact of steroid hormones on the developing human brain. *Cereb Cortex* 2009;**19**:464–473.

Nielsen J, Pelson B, Sorensen K. Follow-up of 30 Klinefelter males treated with testosterone. *Clin Genet* 1988;**33**:262–269.

Nieschlag E, Behre HM. Clinical uses of testosterone in hypogonadism and other conditions. In: Nieschlag E, Behre HM, Nieschlag S (eds). *Testosterone: Action, Deficiency, Substitution*, Vol. **2004**, 3rd edn. Cambridge: Cambridge University Press, 2004, 375–400.

Paduch DA, Fine RG, Bolyakov A, Kiper J. New concepts in Klinefelter syndrome. *Curr Opin Urol* 2008;**18**:621–627.

Paduch DA, Bolyakov A, Cohen P, Travis A. Reproduction in men with Klinefelter syndrome: the past, the present, and the future. *Sem Reprod Med* 2009;**27**:137–148.

Patwardhan AJ, Eliez S, Bender B, Linden MG, Reiss AL. Brain morphology in Klinefelter syndrome: extra X chromosome and testosterone supplementation. *Neurology* 2000;**54**:2218–2223.

Patwardhan AJ, Brown WE, Bender BG, Linden MG, Eliez S, Reiss AL. Reduced size of the amygdala in individuals with 47,XXY and 47,XXX karyotypes. *Am J Med Genet* 2002;**114**:93–98.

Pellis SM, Iwaniuk AN. Brain system size and adult-adult play in primates: a comparative analysis of the roles of the non-visual neocortex and the amygdala. *Behav Brain Res* 2002;**134**:31–39.

Pessoa L. On the relationship between emotion and cognition. *Nat Rev Neurosci* 2008;**9**:148–158.

Pfaus JG. Pathways of sexual desire. *J Sex Med* 2009;**6**:1506–1533.

Pfaus JG, Heeb MM. Implications of immediate-early gene induction in the brain following sexual stimulation of female and male rodents. *Brain Res Bull* 1997;**44**:397–407.

Phillips-Farfán BV, Fernández-Guasti A. Endocrine, neural and pharmacological aspects of sexual satiety in male rats. *Neurosci Biobehav Rev* 2009;**33**:442–455.

Phoenix CH, Goy RW, Gerall AA, Young WC. Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology* 1959;**65**:369–382.

Plunkett ER, Barr ML. Cytologic tests of sex in congenital testicular hypoplasia. *J Clin Endocrinol Metab* 1956;**16**:829–830.

Ponseti J, Bosinski HA, Wolff S, Peller M, Jansen O, Mehdorn HM, Büchel C, Siebner HR. A functional endophenotype for sexual orientation in humans. *Neuroimage* 2006;**33**:825–833.

Pope HG Jr, Cohane GH, Kanayama G, Siegel AJ, Hudson JI. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry* **160**:105–111.

Raboch J, Pietrucha S, Raboch J. Serum testosterone levels and coital activity in men with somatosexual disorders. 1. *Neuro Endocrinol Lett* 2003;**24**:321–324.

Ratcliffe SG. The sexual development of boys with the chromosome constitution 47,XXY (Klinefelter's syndrome). *Clin Endocrinol Metab* 1982;**11**:703–716.

Ratcliffe SG, Read G, Pan H, Fear C, Lindenbaum R, Crossley J. Prenatal testosterone levels in XXY and XYY males. *Horm Res* 1994; **42**:106–109.

Redouté J, Stoléru S, Pugeat M, Costes N, Lavenne F, Le Bars D, Dechaud H, Cinotti L, Pujol JF. Brain processing of visual sexual stimuli in treated and untreated hypogonadal patients. *Psychoneuroendocrinology* 2005;**30**:461–482.

Riis P, Johnsen SG, Mosbech J. Nuclear sex in Klinefelter's syndrome. *Lancet* 1956;**270**:962–963.

Romeo RD, Sisk CL. Pubertal and seasonal plasticity in the amygdala. *Brain Res* 2001;**889**:71–77.

Romundstad LB, Romundstad PR, Sunde A, von Düring V, Skjaerven R, Gunnell D, Vatten LJ. Effects of technology or maternal factors on perinatal outcome after assisted fertilisation: a population-based cohort study. *Lancet* 2008;**372**:737–743.

Rose AB, Merke DP, Clasen LS, Rosenthal MA, Wallace GL, Vaituzis AC, Fields JD, Giedd JN. Effects of hormones and sex chromosomes on stress-influenced regions of the developing pediatric brain. *Ann N Y Acad Sci* 2004;**1032**:231–233.

Ross JL, Samango-Sprouse C, Lahlou N, Kowal K, Elder FF, Zinn A. Early androgen deficiency in infants and young boys with 47,XXY Klinefelter syndrome. *Horm Res* 2005;**64**:39–45.

Rubia K, Overmeyer S, Taylor E, Brammer M, Williams SC, Simmons A, Andrew C, Bullmore ET. Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. *Neurosci Biobehav Rev* 2000;**24**:13–19.

Rupp HA, Wallen K. Relationship between testosterone and interest in sexual stimuli: the effect of experience. *Horm Behav* 2007;**52**:581–589.

Schulz KM, Molenda-Figueira HA, Sisk CL. Back to the future: the organizational-activational hypothesis adapted to puberty and adolescence. *Horm Behav* 2009;**55**:597–604.

Seidman SN, Rabkin JG. Testosterone replacement therapy for hypogonadal men with SSRI-refractory depression. *J Affect Disord* 1998;**48**:157–161.

Seidman SN, Araujo AB, Roose SP, McKinlay JB. Testosterone level, androgen receptor polymorphism, and depressive symptoms in middle-aged men. *Biol Psychiatry* 2001;**50**:371–376.

Shen D, Liu D, Liu H, Clasen L, Giedd J, Davatzikos C. Automated morphometric study of brain variation in XXY males. *Neuroimage* 2004;**23**:648–653.

Shirayama Y, Hashimoto K, Suzuki Y, Higuchi T. Correlation of plasma neurosteroid levels to the severity of negative symptoms in male patients with schizophrenia. *Schizophr Res* 2002;**58**:69–74.

Skakkebaek NE, Bancroft J, Davidson DW, Warner P. Androgen replacement with oral testosterone undecanoate in hypogonadal men: a double blind controlled study. *Clin Endocrinol* 1981;**14**:49–61.

Smyth CM, Bremner WJ. Klinefelter syndrome. *Arch Intern Med* 1998; **158**:1309–1314.

Sørensen K, Nielsen J, Frøland A, Johnsen SG. Psychiatric examination of all eight adult males with the karyotype 46,XX diagnosed in Denmark till 1976. *Acta Psychiatr Scand* 1979;**59**:153–163.

Sudbrak R, Wieczorek G, Nuber UA, Mann W, Kirchner R, Erdogan F, Brown CJ, Wöhrle D, Sterk P, Kalscheuer VM *et al.* X chromosome-specific cDNA arrays: identification of genes that escape from X-inactivation and other applications. *Hum Mol Genet* 2001;**10**:77–83.

Swanson LW. The amygdala and its place in the cerebral hemisphere. *Ann N Y Acad Sci.* 2003;**985**:174–184.

Swerdlow AJ, Hermon C, Jacobs PA, Alberman E, Beral V, Daker M, Fordyce A, Youings S. Mortality and cancer incidence in persons with numerical sex chromosome abnormalities: a cohort study. *Ann Hum Genet.* 2001;**65**:177–188.

Thornton J, Zehr JL, Loose MD. Effects of prenatal androgens on rhesus monkeys: a model system to explore the organizational hypothesis in primates. *Horm Behav* 2009;**55**:633–645.

Traish AM, Guay AT. Are androgens critical for penile erections in humans? Examining the clinical and preclinical evidence. *J Sex Med* 2006;**3**:382–407.

van Honk J, Tuiten A, Verbaten R, van den Hout M, Koppeschaar H, Thijssen J, de Haan E. Correlations among salivary testosterone, mood, and selective attention to threat in humans. *Horm Behav* 1999;**36**:17–24.

van Rijn S, Aleman A, Swaab H, Kahn R. Klinefelter's syndrome (karyotype 47,XXY) and schizophrenia-spectrum pathology. *Br J Psychiatry* 2006; **189**:459–460.

van Wingen G, Mattern C, Verkes RJ, Buitelaar J, Fernández G. Testosterone reduces amygdala—orbitofrontal cortex coupling. *Psychoneuroendocrinology* 2009;**35**:105–113.

Vignozzi L, Corona G, Petrone L, Filippi S, Morelli A, Forti G, Maggi M. Testosterone and sexual activity. *J Endocrinol Invest* 2005;**3**:39–44.

Vogel W, Klaiber EL, Broverman DM. A comparison of the antidepressant effects of a synthetic androgen (mesterolone) and amitriptyline in depressed men. *J Clin Psychiatry* 1985;**46**:6–8.

Walker E, Bollini AM. Pubertal neurodevelopment and the emergence of psychotic symptoms. *Schizophr Res* 2002;**54**:17–23.

Welling LL, Jones BC, DeBruine LM, Smith FG, Feinberg DR, Little AC, Al-Dujaili EA. Men report stronger attraction to femininity in women's faces when their testosterone levels are high. *Horm Behav* 2008; **54**:703–708.

Wikström AM, Dunkel L. Testicular function in Klinefelter syndrome. *Horm Res* 2008;**69**:317–326.

Witte AV, Savli M, Holik A, Kasper S, Lanzenberger R. Regional sex differences in grey matter volume are associated with sex hormones in the young adult human brain. *Neuroimage* 2010;**49**:1205–1212.

Wu FC, Bancroft J, Davidson DW, Nicol K. The behavioural effects of testosterone undecanoate in adult men with Klinefelter's syndrome: a controlled study. *Clin Endocrinol (Oxf)* 1982;**16**:489–497.

Yoshida A, Miura K, Nagao K, Hara H, Ishii N, Shirai M. Sexual function and clinical features of patients with Klinefelter's syndrome with the chief complaint of male infertility. *Int J Androl* 1997;**20**:80–85.

Zitzmann M, Nieschlag E. Androgens and bone metabolism. In: Nieschlag E, Behre HM, Nieschlag S (eds)., *Testosterone: Action, Deficiency, Substitution*, Vol. 2004, 3rd edn. Cambridge: Cambridge University Press, 2004. 233–254.

Zitzmann M, Brune M, Vieth V, Nieschlag E. Monitoring bone in hypogonadal men by quantitative phalangeal ultrasound. *Bone* 2002;**31**: 422–429.