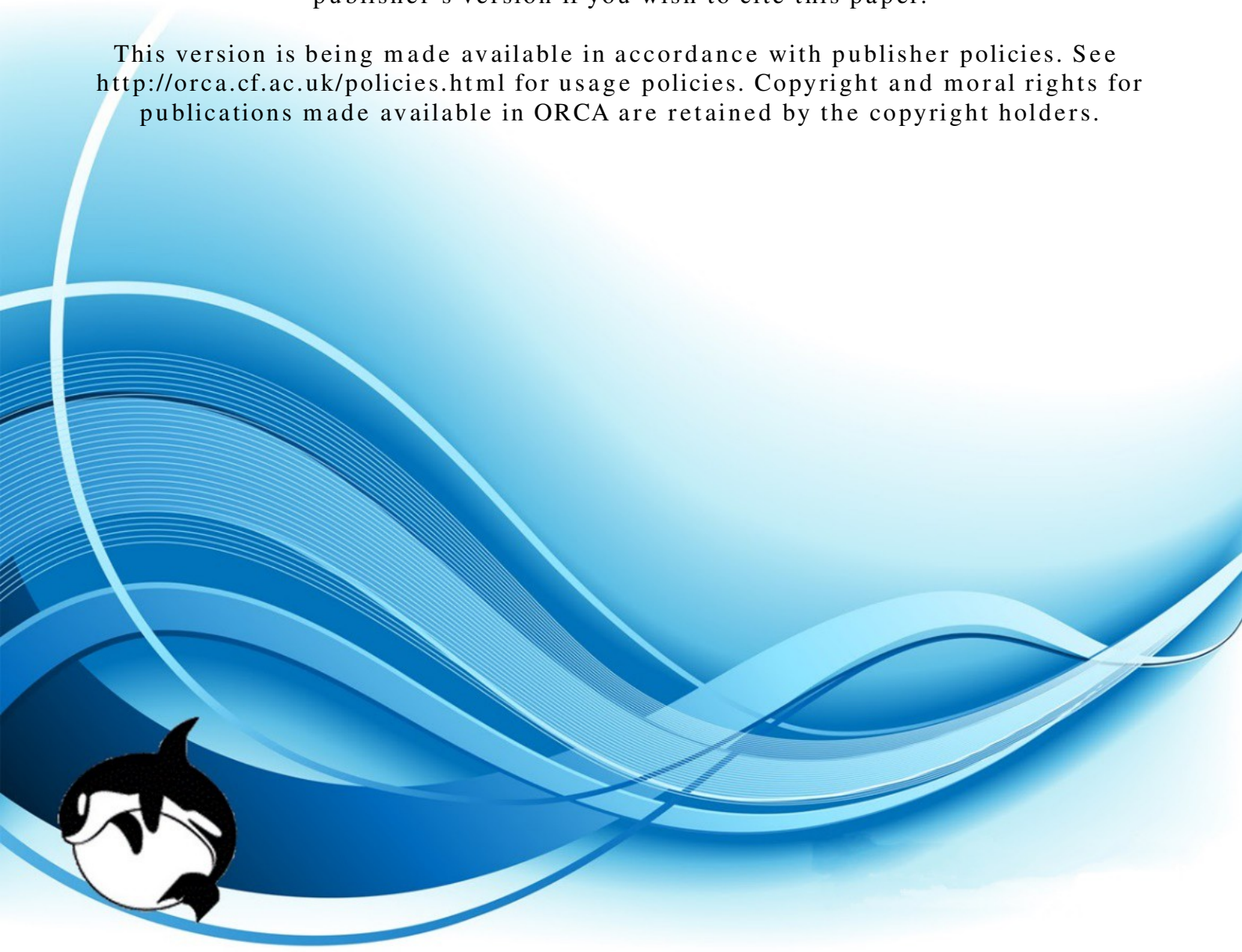

Sex differences in Attention Deficit Hyperactivity Disorder: candidate genetic and endocrine mechanisms

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Abstract

Attention Deficit Hyperactivity Disorder (ADHD) is a developmental condition characterised by severe inattention, pathological impulsivity and hyperactivity; it is relatively common affecting up to 6% of children, and is associated with a risk of long-term adverse educational and social consequences. Males are considerably more likely to be diagnosed with ADHD than females; the course of the disorder and its associated co-morbidities also appear to be sensitive to sex. Here, I discuss fundamental biological (genetic and endocrine) mechanisms that have been shown to, or could theoretically, contribute towards these sexually dimorphic phenomena. Greater understanding of how and why the sexes differ with respect to ADHD vulnerability should allow us to identify and characterise novel protective and risk factors for the disorder, and should ultimately facilitate improved diagnosis, prognosis and treatment.

Keywords

Autism, basal ganglia, imprinted gene, mouse, rat, sex chromosome, Sry, steroid sulfatase, testosterone, thalamus

Highlights

- ADHD is a common developmental disorder linked to long-term adverse consequences
- ADHD prevalence and presentation are affected by sex
- Sex-linked genetic mechanisms fundamentally contribute to establishing these biases
- Such mechanisms act directly on the brain or via intermediaries e.g. androgen levels
- Understanding sex effects in ADHD will improve diagnosis, prognosis and treatment

Introduction: what is ADHD?

Attention Deficit Hyperactivity Disorder (ADHD) is a developmental disorder that is characterised by a combination of severe inattention, extreme impulsiveness across a variety of domains, and hyperactivity (Thapar et al., 2012). The condition is complex and, like other developmental disorders such as autism, extremely heterogeneous in its presentation. Diagnosed individuals are typically assigned to one of three clinical subtypes depending upon the relative impairments observed: individuals, who predominantly, or solely demonstrate problems with attention or organisational processes will be diagnosed with the 'inattentive subtype', individuals who predominantly show heightened levels of impulsivity and hyperactivity will be diagnosed with the 'hyperactive-impulsive' subtype, and individuals who display attentional, impulsive and hyperactive symptoms will be diagnosed with the 'combined subtype'. The biological mechanisms predisposing to the three subtypes are at least partially dissociable (Baeyens et al 2006; Diamond, 2005; Woo and Rey, 2005).

Estimates for ADHD prevalence vary according to diagnostic criteria and geographical region, but rates of 1-6% appear plausible (Polanczyk et al., 2007; Simon et al., 2009; Thapar et al., 2012; Willcutt, 2012). For many years, ADHD was thought of very much as a disorder of childhood, but recently it has become apparent that the disorder and its associated endophenotypes (notably inattention and cognitive deficits such as impaired information processing) persist into adulthood in a significant proportion of cases (Modesto-Lowe et al 2012); indeed, the definition of ADHD has been updated in the recently-released DSM-5 to take into account this change in our understanding (Dalsgaard, 2013).

ADHD can potentially adversely affect an individual's function throughout life: during childhood, ADHD can cause disruption to family life, to peer relationships and to education (Leibson et al., 2001; Thapar et al., 2005), whilst during adolescence and adulthood the disorder has been associated with antisocial behaviour and later criminality, with social impairment, with drug/alcohol misuse and with employment difficulties (Barkley, 2006). Impaired functioning may be further exacerbated by comorbid psychiatric disorders or learning disabilities: disorders that are frequently associated with ADHD include autism spectrum disorders (ASDs), obsessive-compulsive disorder, Tourette's syndrome, conduct and oppositional defiant disorders, and anxiety and eating disorders (Kooij et al., 2012; Taurines et al., 2010; Thapar et al., 2012). Whilst not a core feature of the disorder, impaired motivation (avolition) is relatively frequently observed within ADHD cohorts (Carlson et al., 2002). A better understanding of the biological, psychological and psychosocial mechanisms underlying ADHD risk will therefore be vital for developing better strategies for early diagnosis and therapeutic intervention to limit these deleterious outcomes. In terms of psychology, much focus (and debate) has related to specifying primary cognitive deficits that may directly underlie disorder vulnerability; candidates include aberrant behavioural inhibition (either excessive impulse, or deficient inhibition), and defective information processing (Salum et al., 2013). Conceivably, the primary cognitive deficit could be different for the different disorder subtypes, or between the two sexes (see later).

Like most other common psychiatric disorders, ADHD has a strong genetic component, demonstrated experimentally through family, twin and adoption studies (Akutagava-Martins et al., 2013). Efforts to date, by means of Genomewide Association Studies (GWAS), have been relatively unsuccessful in

identifying common polymorphisms that might underlie ADHD risk. This lack of success is probably largely attributable to the small sample sizes used (i.e. low power), and their inability to detect what are likely to be many polymorphisms each conferring marginally elevated risk (Franke et al., 2009). However, contemporary GWAS studies have been able to show us that, in terms of common genetic variants, ADHD has more in common with major depressive disorder than ASDs (Lee et al., 2013), a somewhat surprising result given the previously assumed phenotypic and genetic overlap between the two classical developmental disorders (Rommelse et al., 2010). A second type of genetic analysis, the comparison of copy number variants (CNVs) in ADHD cases and healthy controls, has indicated a significantly higher number of large, rare variants (duplications and deletions) in the former group, several of which overlapped with such variants over-represented in cohorts with other brain disorders including autism and schizophrenia (Williams et al., 2012). One study, which combined initial GWAS and CNV data, identified *CHRNA7* (encoding the α7 subunit of the nicotinic acetylcholine receptor) as a gene whose product (or aberrant expression thereof) could modulate ADHD risk (Stergiakouli et al., 2012).

1. Sex differences in ADHD

Thomas Insel, Director of the National Institute for Mental Health in the United States, was once quoted as saying 'it's pretty difficult to find any single factor that's more predictive for….(psychiatric) disorders than gender' (Holden, 2005). Despite this, the issue of gender effects (or from a more biological standpoint 'sex effects'), on the manifestation of psychiatric illness has been relatively neglected; indeed, such effects are often investigated *post hoc* rather than *a priori*. This 'one size fits all' approach was likely fuelled by the assumption

that sex differences are small, unimportant, and difficult to measure or interpret (Cahill, 2006). However, ADHD-relevant cognitive constructs, including attention and impulsivity, are now known to vary considerably both within and between groups of healthy males and females (Trent and Davies, 2011), whilst large-scale, multimodal neuroimaging techniques applied longitudinally are beginning to define sex-specific neuroanatomical and functional trajectories (Dennis and Thompson, 2013; Giedd and Rapoport, 2010). In terms of psychiatry, investigators are increasingly recognising that sex can influence a number of relevant parameters including prevalence, age-at-onset and subsequent clinical course, frequency and type of comorbidities, underlying neurobiology, and response to therapy (Davies and Wilkinson, 2006).

Studies examining sex differences in ADHD to date have focussed on children and adolescents, have been somewhat underpowered, and have used varied diagnostic criteria; moreover, such studies may have been subject to effects arising from ascertainment biases or rater influences. These caveats notwithstanding, the current literature suggests that, in general, the presentation of the disorder is more similar than different in males and females, though there is some evidence for sex biases in terms of prevalence, clinical course, comorbidities and underlying neural substrates (Rucklidge, 2010).

1.1 Sex differences in prevalence, clinical course and co-morbidities

Within clinical samples, extreme sex biases have been observed whereby boys diagnosed with ADHD can outnumber girls by up to 10:1 (Biederman et al., 2002). The most likely explanation for such a marked skew is a stronger association between the condition and conduct disorder/disruptive behaviour in males, and hence a greater likelihood of parental or teacher referral of boys to

clinical services (Biederman et al., 2005; Derks et al., 2007; Gaub and Carlson, 1997). This bias may be further compounded by the fact that teachers appear more likely to refer males than females for treatment for ADHD, even when all other information about symptom expression is equal (Sciutto et al., 2004).

Meta-analyses in population-based samples from Europe and the United States have suggested significantly lower sex discrepancies with males being 2-4 times more likely to meet full DSM-IV criteria for ADHD than females (Catalá-López et al., 2012; Willcutt, 2012). Sex differences in ADHD prevalence appear to be most pronounced during childhood, becoming less obvious with increased age; females often receive a diagnosis of ADHD significantly later than do males which may reflect a buffering effect of their earlier developmental maturity (Nussbaum, 2012; Simon et al., 2009). One plausible explanation for this phenomenon is that childhood referrals to psychiatric services are initiated by the child's parents or teachers whereas adults self-refer, the latter process possibly precipitated by the presence of comorbid internalising disorders that tend to be more frequent in females with ADHD than in males (Rucklidge, 2010). There is some initial evidence from a large European study that reported sex differences in ADHD symptoms may be influenced by the identity of the informant, with teachers reporting more hyperactive/impulsive behaviours in boys than parents (Ullebo et al., 2012).

In addition to a sex difference in overall prevalence rate, there also appears to be a sex difference in the likelihood of being diagnosed with a particular subtype. Whilst males are more likely than females to suffer from all subtypes of ADHD (Willcutt, 2012), studies undertaken in the United States indicate that a higher proportion of females (both children and adults) than

males diagnosed with ADHD are assigned to the inattentive subtype group (45-60% vs. 35-50%) (Biederman et al., 2002; Hinshaw et al., 2006; Rucklidge, 2010; Willcutt, 2012). Whether such an effect is seen in clinic-referred individuals in different countries, or in population cohorts remains to be comprehensively studied; initial studies suggest that the effect may be reduced or absent in such cases (Biederman et al., 2005; Ghanizadeh, 2009).

In terms of ADHD-relevant cognitive constructs, a recent meta-analysis in ADHD subjects reported no significant sex effects on a continuous performance tasks assaying attention (Hasson and Fine, 2012). This result suggests that 'attention' as defined by the DSM-IV, and 'attention' as defined by the CPT, may be fundamentally distinct constructs with dissociable neural correlates. A second meta-analysis of studies assessing behavioural inhibition (assessed using the the stop-signal task) found a borderline effect of gender whereby inhibition in male ADHD patients (compared with male healthy controls) was more severely impaired than in female ADHD patients compared with female healthy controls (Lipszyc and Schachar, 2010). O'Brien and colleagues reported a similar result when assessing a population of children diagnosed with ADHD, whereby boys exhibited deficits in tasks requiring effortful, conscious behavioural inhibition, whilst girls tended to demonstrate impairments in planning (O'Brien et al., 2010). It has previously been proposed that some aspects of executive function may be particularly perturbed in individuals diagnosed with subtypes less common for sex i.e. inattentive for boys, hyperactive-impulsive for girls (Wodka et al., 2008). Boys with ADHD may be more severely and persistently affected than girls with ADHD with respect to motor skills (Cole et al., 2008). In adults with ADHD, males have been reported to show a generally greater level of

impairment across multiple cognitive domains including on distractability as indexed by Stroop interference (Balint et al., 2009). Overall, the aforementioned work suggests that males with ADHD may be affected by deficits in attentional processes and/or motor inhibitory dysfunction, whereas females diagnosed with the disorder may be affected by more selective deficits in attentional or processing capacity.

In terms of co-morbidities, affected adolescent females typically have poorer coping strategies than affected adolescent boys, whilst rates of anxiety and eating disorders, and depression may be higher in females (Rucklidge, 2010). In contrast to the male bias in prevalence seen in ADHD, major depression is approximately twice as frequently observed in females as in males (Holden, 2005); therefore, it seems unlikely that common genetic variants influencing susceptibility to both depression and ADHD (Lee et al., 2013) would affect sexually dimorphic pathways. Males diagnosed with ADHD tend to show higher rates of externalising conditions including physical aggression and oppositional and conduct disorders (Rucklidge, 2010). As both ADHD and ASDs are significantly more prevalent in males than in females, it is unsurprising that in the former sex the two conditions are more likely to be comorbid; estimates suggest that 20-50% of children with ADHD meet diagnostic criteria for ASDs, whilst 30-80% of children with ASDs meet diagnostic criteria for ADHD (Rommelse et al., 2010; Russell et al., 2013). Given this overlap at the symptom level, it is somewhat surprising to see that in terms of underlying common genetic variation, ADHD and ASDs appear to be largely independent (Lee et al., 2013); the two conditions may be more similar in terms of rarer genetic variants, including CNVs. Learning disabilities, which are generally more frequent

in males, appear to be present significantly more frequently in male than female subjects with ADHD (Pastor and Reuben, 2002).

1.2 The neurobiology of ADHD: effects of sex

A detailed discussion of the brain region and neurochemical abnormalities that are thought to underlie ADHD symptoms is beyond the scope of this review, and has been dealt with comprehensively elsewhere (e.g. Cortese 2012). Below, I summarise the key issues and findings in this area to date.

The brains of individuals affected by childhood disorders are rarely available *post mortem*. Therefore, information about the underlying neural substrates of these disorders must be obtained via other methods e.g. neuroimaging, extraneous recording, pharmacological techniques, or inferred from *in vitro* or animal model studies; all of these approaches have inherent limitations, somewhat restricting our confidence in the generalisability of findings emerging from them. It should be pointed out that inconsistencies and variability within the human ADHD data could be explained by disorder subtype, by psychiatric comorbidities, by past or current substance abuse or medication regime, or by age of the experimental subjects.

Recent meta-analyses of magnetic resonance imaging (MRI) structural scans in children and adults with ADHD have confirmed significant abnormalities in the corticostriatal system, and particularly in the basal ganglia (reduced globus pallidus, caudate and putamen, and anterior cingulate cortex volumes) that can be ameliorated to some extent by medication (Frodl and Skokauskas, 2012; Shaw and Rabin, 2009). Structural abnormalities in the limbic system (hippocampus and amygdala) (Shaw and Rabin, 2009), and in the thalamus

(Ivanov et al, 2010; Xia et al., 2012) and cerebellum (Bledsoe et al., 2009) have been less frequently described (Seidman et al., 2005). Multiple Diffusion Tensor Imaging (DTI) studies have revealed abnormal connectivity between regions of the basal ganglia (notably within the internal capsule), the cortex, and the thalamus (Silk et al., 2009; Tomasi and Volkow, 2012; van Ewijk et al., 2012; Xia et al., 2012).

The structural abnormalities listed above appear to predispose to altered resting state neural activity in subjects with ADHD (Zang et al., 2007; Zhu et al., 2008), and to altered brain function during neuropsychological tasks taxing executive function, motivation, impulsivity and attention (de la Fuente et al., 2013). There is now a growing appreciation that the complex constellation of symptoms associated with ADHD doesn't solely arise from locally disturbed corticostriatal circuitry, but rather from more global brain dysfunction (Castellanos and Proal 2012).

The concept that monoamine system dysfunction underpinned ADHD endophenotypes followed from early observations that the administration of stimulant medications that acted upon such systems could alleviate symptoms of impulsivity and hyperactivity (Bradley, 1937). Subsequent work showed significant perturbations of the monoaminergic system, and particularly the dopaminergic system, in the brains of individuals with ADHD (Arnsten, 2011; Del Campo et al., 2011; Genro et al., 2010; Wu et al., 2012). Today's most effective pharmacological treatments act to enhance monoamine levels (notably dopamine and/or noradrenaline) in the synaptic cleft, implicating deficiency, or impaired signalling, of one or both of these two compounds in ADHD endophenotypes: methylphenidate acts as a mixed dopamine/noradrenaline

reuptake inhibitor, atomoxetine as a selective noradrenaline reuptake inhibitor, and amphetamine and its derivatives as dopamine reuptake inhibitors and/or enhancers of dopamine levels in the pre-synaptic terminal (Del Campo et al., 2011). However, the precise subcortical and prefrontal regions through which these drugs exert their therapeutic effects remain to be fully specified (Del Campo et al., 2011). Whilst dopaminergic and noradrenergic system dysfunction has been the focus of attention for much ADHD research, a role for serotonin (5-hydroxytryptamine, 5-HT) on disorder endophenotypes, possibly via a modulatory influence on dopaminergic function, has also been suggested (Oades, 2007 and 2008). Studies in rodents have indicated that pharmacological or genetic manipulation of the 5-HT_{2c} and 5-HT_{2A} receptors can affect levels of impulsivity (Fletcher et al. 2013; Homberg, 2012; Humby et al., 2013), whilst other studies have shown that genetic polymorphisms within 5-HT genes (*TPH2*, *HTR1A*, *HTR2A* and *HTR2C*) in man are associated with impulsivity-related phenotypes (Homberg, 2012; Li et al., 2006a, 2006b).

A number of additional neurochemical systems have been implicated in ADHD pathogenesis (Cortese, 2012). Of these, perhaps the most robustly associated is the cholinergic system, a system with a well-established role in attentional and executive processes (Robbins and Roberts, 2007; Sarter and Paolone, 2011). Converging data from genetic, pharmacological, neuroimaging, behavioural and animal model studies have indicated cholinergic disturbances in individuals with ADHD (Perlov et al., 2009; Sarter and Paolone, 2011; Stergiakouli et al., 2012; Wilens and Decker, 2007).

The sexually dimorphic clinical features of ADHD described in section **1.1** may be underpinned by qualitatively different neural substrates (both structural and functional) between the sexes, or by sex differences in the extent to which the same substrates are disturbed. Dissociating between these two possibilities is fraught with a number of complications. To date, imaging and functional studies have examined sex differences *post hoc* and as such have been considerably underpowered to detect sex effects. Moreover, they have focussed on young subjects with the inattentive subtype or adults (children with ADHD, particularly those with pronounced hyperactivity, tend to be difficult to test or scan successfully). Functional measures have often failed to take into account menstrual stage (which can significantly affect aspects of cognition including attention and behavioural inhibition and underlying brain activity (e.g. Bannbers et al., 2012; Solis-Ortiz et al., 2008)). A further level of complexity comes from the fact that males and females may be subject to different medication regimes as a function of sex biases in the severity and nature of ADHD (and comorbid) symptoms (Bahmanyar et al., 2013; Garbe et al., 2012; Linares et al., 2013); these sex-biased medication regimes could feasibly impact differentially on brain development and/or ongoing function (Schweren et al., 2012; Singh and Chang, 2012).

One functional neuroimaging study that explicitly set out to examine sex differences in adults with ADHD and that employed sex-matched controls, demonstrated that whilst the sexes had a similar clinical profile and performed equivalently on a working memory task, affected males showed reduced activation relative to healthy males in frontal, temporal, subcortical, occipital and cerebellar regions, whereas affected and healthy females demonstrated

equivalent activation; exploratory analyses indicated that the task-induced activation was related to the number of hyperactive symptoms in men, but to inattentive symptoms in women (Valera et al., 2010). These data suggest the possibility that the development of the cerebellar-prefrontal-striatal networks is more seriously impaired in males with ADHD than in females with the disorder (possibly arising from the protective effects of normal sexual dimorphisms in females), and that males adopt mediating strategies in order to generate a similar behavioural/cognitive output. Further work using similarly powered studies and assaying multiple relevant cognitive domains will be required to determine whether these initial findings can be generalised across other neuropsychological tasks, and to other cohorts of different ages and with different medication histories.

There is also some evidence for sex differences in brain activity in individuals with ADHD as indexed by electroencephalography (EEG) measures; specifically girls exhibit anomalous elevated coherence in frontal and temporal regions and localised frontal theta enhancement whereas boys show little evidence of systematic coherence development, and more widespread theta wave enhancement (Barry et al., 2006; Hermens et al., 2005). These findings appear somewhat consistent with the notion of a more extensive and severe neurodevelopmental phenotype in males with ADHD.

Studies examining whether the most commonly used pharmacotherapeutics (methylpheniate and atomoxetine) show differential efficacy in males and females with ADHD have generally concluded that they do not (Bahmanyar et al 2013; Cornforth et al., 2010; Mikami et al., 2009; Wehmeier et al. 2012). These converging findings suggest that any functionally relevant sex differences in

dopaminergic and noradrenergic chemistry within this clinical population are likely to be small and indifferent to clinically-relevant doses of the drugs. However, some studies have described sex differences in response to ADHD medication e.g. in methyphenidate pharmacodynamics (Sonuga-Barke et al., 2007), for enhanced effectiveness of atomoxetine in female patients (Marchant et al., 2011), and for sex-specific effects of methylphenidate on behaviour in genetic rat models pertinent to ADHD (Chelaru et al., 2012). There may also be sex differences in response to psychological and social therapies within the ADHD clinical population. One recent study has shown that social behaviour in girls improved only in single-sex group treatment sessions, but that boys' behaviour improved more in mixed-sex sessions (Babinski et al., 2013). Once again, further larger studies are required to explicitly examine sex differences in response to various treatments that can adequately account for possible confounding effects of age, disorder subtype and comorbidites, and previous treatment history.

2. Mechanisms underlying sex differences in ADHD

A variety of ascertainment biases undoubtedly play a role in some of the sex differences seen in the ADHD clinical population. Some of these have been alluded to in section **1.1**; it is also plausible that as males generally perform more poorly than females in terms of early education (perhaps due to a greater frequency of learning disabilities (Pastor and Reuben, 2002), or underlying ADHD-like symptoms) (Gibb et al., 2008), they are more effectively screened (consciously or subconsciously) by the educational establishment and by parents for potentially deleterious behaviour, and subsequently referred to clinicians.

Ascertainment and diagnostic issues notwithstanding, there is now substantial support from behavioural, neuropsychological, neuroanatomical, endocrine, and genetic sources for genuine biological differences between individuals diagnosed with ADHD and healthy subjects (Purper-Ouakil et al., 2011; Thapar et al., 2013;). Importantly, sex biases in ADHD prevalence and phenotypes are apparent (though to a somewhat lesser extent) in community samples where referral biases will not be present. Hence, biological factors are likely to play a significant (though not exclusive) role in explaining some of the sex differences in ADHD described above. Excellent previous reviews (e.g. (Waddell and McCarthy, 2012)) have considered this question in depth: in the discussion below, I focus primarily on potential mediating genetic mechanisms, which have, to date, been relatively unexplored: some of these mechanisms have convincing empirical support whilst other are rather more theoretical. I also briefly describe how these genetic mechanisms could contribute towards sex differences in ADHD via their endocrinological influences, notably on sex-specific androgen levels.

2.1 (Epi)genetic mechanisms

Sex differences in neurobiology must ultimately stem from sex differences in genetic complement, either arising as a consequence of sexually dimorphic intrinsic developmental programs, or as a consequence of sex-specific reactivity to exogenous agents or processes. In mammals, males inherit a single X chromosome from their mother, and a Y chromosome from their father; females inherit two X chromosomes, one from either parent. This asymmetry of inheritance sets up the possibility of sexually dimorphic expression of sex-linked genes, and sex-specific effects on downstream autosomal gene expression and

developmental and physiological processes. Early experiments in model systems in which animals were gonadectomised, or administered androgens or oestrogens, seemed to indicate that steroid hormones of gonadal origin were the main driver of sexually dimorphic phenotypes. Over the past two decades this dogma has been challenged, and it is now increasingly being recognised that sex-linked gene products may contribute substantially towards sexually dimorphic phenotypes independently of, and in addition to, gonadal hormones (Arnold, 2004; Davies and Wilkinson, 2006). Work in model systems has shown that brain gene expression differs significantly between the sexes even prior to differentiation of the gonads, implying that from very early in development, mammalian males and females are neurobiologically distinct (Dewing et al., 2003; Wolstenholme et al., 2013). Three fundamental genetic mechanisms may result in sex-specific patterns of gene expression, and therefore might contribute towards modulation of sexually dimorphic phenotypes in healthy and clinical populations. These mechanisms might act via influencing brain function directly, or by influencing intermediary physiological systems e.g. systemic hormone levels. In the following text, I describe these mechanisms and discuss how they might impact upon ADHD risk.

2.1.1 Male limited Y-linked gene expression

The idiosyncratic inheritance pattern associated with the sex chromosomes means that genes on the Y chromosome can only be expressed in males. In man, the Y chromosome is just 60Mb in size, and is thought to house fewer than 100 protein-coding genes (together with a large number of pseudogenes, and extensive repetitive sequence)(Kopsida et al., 2009). Whilst the majority of these genes play a role in reproductive physiology, a significant

proportion are expressed in the brain, and therefore could modulate neurodevelopment (Kopsida et al., 2009).

There are several lines of evidence that implicate the Y chromosome in ADHD-related phenotypes. First, males with additional Y chromosomes (karyotypes 47,XYY or 48,XXYY) demonstrate unusually high rates of ADHD (~75% of cases), particularly the hyperactive-impulsive subtype (Ross et al., 2009; Ruud et al., 2005; Tartaglia et al., 2012), although it must be appreciated that such high rates may be an artefact of ascertainment, and/or of restricted sample size. Mice with two Y chromosomes can be produced (41,XYY) (Mahadevaiah et al., 2000) and initial studies with this model have shown that they perform worse than 40,XY controls on motor tasks (Chen et al., 2013). Future work should assess activity, impulsivity and attentional phenotypes in these mice to determine whether they resemble those seen in 47,XYY humans, and if they do, to investigate the underlying neurobiology. Together, these preliminary data hint that the over-expression of one or more Y-linked genes may predispose to motoric aspects of the ADHD phenotype. As 47,XYY subjects do not appear to show marked perturbations in their pre- or postnatal hormonal profile (androgen and growth factor levels)(Aksglaede et al., 2008; Ratcliffe et al., 1994) the effect of such over-expression may be directly upon the brain.

The majority of the Y chromosome (the non-recombining region, NRY) does not recombine at meiosis; as such, it is generally passed unchanged from father to son with both sharing the same Y-linked polymorphism profile (or 'haplotype'). Association studies have compared Y chromosome haplogroups (i.e. a group of haplotypes that share a common ancestor) in clinical and control cohorts; this approach tests whether Y chromosome polymorphisms are involved

in a particular phenotype, but cannot identify the causal variant. Y chromosome haplogroups have been associated with ADHD-relevant male-biased traits such as aggression (Shah et al., 2009) and alcohol dependence (Kittles et al., 1999), and another neurodevelopmental disorder, autism (Serrajee, 2009). However, studies in this area have been hampered by small, heterogeneous samples and the use of non-overlapping genetic markers. Our preliminary analyses have indicated a modifying effect of Y chromosome variants on IQ in a small British Caucasian ADHD sample, whereby more evolutionarily recent haplogroups are associated with higher scores (unpublished results). The modulatory effects of Y haplotype on brain function and IQ could potentially explain variability in symptomatology within males (which in turn may influence rates of diagnosis), and the male-bias towards both ADHD and low IQ. Replicating this intriguing finding in larger cohorts, and subsequently identifying causal candidate variants (based on bioinformatic signatures and animal work) will therefore be worthwhile.

One Y-linked gene of particular interest in the context of this review is *SRY* (Sex Determining Region on Y). *SRY* encodes a transcription factor which is transiently expressed within the bipotential gonad during embryogenesis; the activity of the SRY protein at specific genomic targets encourages differentiation of this tissue into testes (Wilhelm and Koopman, 2006). Subsequently, the testes secrete a variety of androgens (notably testosterone) which can act to masculinise the brain developmentally leading to large, persistent changes in structure (‘organisational effects’) or at particular timepoints leading to more labile neural changes (‘activational effects’). How differing androgen levels in

males and females might contribute towards sex-specific ADHD pathology is discussed in section **2.2**.

Besides acting in an 'indirect' hormone-mediated manner to influence neurobiology, SRY may influence neurobehavioural phenotypes directly. Studies in rodents have shown that *Sry* is expressed throughout development, initially in an untranslatable circular form, and postnatally in a translatable linear form (Mayer et al., 2000). In adult mammalian tissues, the gene is most highly expressed in brain regions rich in dopaminergic neurons, including the substantia nigra (SN) and ventral tegmental area (VTA) (Dewing et al., 2006). The expression profile in human brain appears to be similar with significant expression in the adult SN and VTA (Czech et al., 2012), and in the hypothalamus, frontal cortex and temporal cortex (Mayer et al., 1998). At the molecular level, SRY appears to act as a transcriptional activator for genes of the monoaminergic system in both man and mouse, notably *TH* (encoding tyrosine hydroxylase, the rate-limiting enzyme in dopamine biosynthesis) and *MAOA* (encoding monoamine oxidase, an enzyme whose function is to deaminate monoamines including dopamine and noradrenaline)(Czech et al., 2012; Milsted et al., 2004; Wu et al., 2009). Because of its genomic location, its expression in regions associated with cognition, emotion, motivation and motor function, and its role in dopaminergic/noradrenergic biochemistry, *a priori*, SRY represents an excellent candidate modulator for sex-related endophenotypes in ADHD (where, presumably it would act to reduce the male threshold for developing the disorder). Is there any functional evidence that supports this proposition?

Recent animal experiments assaying attention and motor impulsivity in the 5-choice serial reaction time task using the 'four core genotypes' mouse

model in which effects of *Sry* and other sex-linked genes can be dissociated (Arnold and Chen, 2009), have shown that mice possessing Sry (irrespective of sex chromosome complement) exhibit a moderately increased tendency to respond impulsively under certain conditions (Lynn, 2010); in contrast, *Sry* presence is actually associated with *decreased* locomotor activity (Kopsida et al., 2013). Work in this model, and others, has also emphasised a role for SRY in promoting aggression (Lee and Harley, 2012), in enhancing stress responsivity and exacerbating hypertension (Dickey et al., 2012), in predisposing to alcohol drinking (Barker et al., 2010), and in mediating motor function (Dewing et al., 2006). Overall, therefore, the animal literature is somewhat supportive of a possible effect of SRY on motor function and inhibition, and other associated features of ADHD. However, how reliably this data can be extrapolated to a complex disorder with uniquely human elements is open to question. To address this issue, one option would be to evaluate behaviour, cognition and psychiatric vulnerability in 46,XX males possessing an extraneous *SRY* gene, or in males with additional copies of *SRY*; however, such individuals are rare, and often exhibit multiple other confounding phenotypes. One study, describing a boy with a genetic mutation resulting in two copies of the *SRY* gene, reported that he exhibited symptoms of hyperactivity, impulsivity and anxiety somewhat consistent with the animal literature (Mulligan et al., 2008).

Several genes on the Y have homologues on the X; these include *PCDH11Y* and *NLGN4Y*. The *PCDH11X/Y* genes are located on a hominid-specific region of the sex chromosomes, and encode proteins of the protocadherin superfamily whose function is to control cell-cell interactions during central nervous system development (Morishita and Yagi, 2007). *PCDH11X and*

PCDH11Y are not only structurally distinct, but also show dissociable expression patterns in the brain (Blanco et al., 2000); whilst both are expressed in the cortex, amygdala, hippocampus, caudate nucleus and thalamus, *PCDH11X* appears to be the preferential transcript in the cerebellum. The fact that *PCDH11Y* exhibits comparatively weak expression in the cerebellum only could potentially explain male vulnerability to mental disorders associated with cerebellar pathology, including ADHD and ASDs. In a very small-scale study examining just 61 males with ADHD, the frequency of genetic variants within *PCDH11Y* did not differ from that in healthy controls (Durand et al., 2006), although obviously larger-scale studies are necessary to completely discount the possibility that this is the case. The *NLGN4X* and *NLGN4Y* genes modulate cell adhesion processes during synaptogenesis, and ultimately synaptic function (Bottos et al., 2011). Previous studies have indicated that loss-of-function mutations within *NLGN4X* or *NLGN4Y* may contribute towards neurodevelopmental pathology, but probably only in rare cases (Avdjideva-Tzavella et al., 2012; Blasi et al., 2006; Laumonnier et al., 2004; Pampanos et al., 2009; Wermter et al., 2008; Yan et al., 2008); thus a significant role for these genes in mediating sexually dimorphic phenotypes in ADHD appears improbable.

2.1.2 Two versus one X

2.1.2.1 Male hemizygosity

Males inherit a single X chromosome, whereas females inherit two; thus, males will be hemizygous for genes on the non-recombining portion of the X chromosome (NRX). This means that the effects of polymorphisms or mutations

on the X chromosome will be expressed in males in every cell; in females, the effects of similar polymorphisms or mutations will be attenuated by the expression of a second allele. This mechanism explains why males are more likely to suffer from disorders with a known X-linked genetic component (such as colour blindness or Duchenne muscular dystrophy (Prot and Laska, 1970)). Male susceptibility to the deleterious effects of X-linked mutations could theoretically explain why this sex is more vulnerable to developmental and environmental insults across the lifespan (Austad, 2006); in particular, this phenomenon could explain sexual dimorphism in the fetal physiological responses, and the long-term adverse effects of *in utero* exposure to ADHD-promoting teratogens such as alcohol and lead (Banerjee et al., 2007; Faulk et al., 2013; Weinberg et al., 2008).

A disproportionately high number of X-linked genes in man are thought to influence neurodevelopment (Zechner et al., 2001). The effects of *de novo* mutations within these will be more apparent in males than females, and will tend to result in impaired cognition, manifest in many cases as learning disabilities. The increased presence of comorbid clinical or subclinical learning disabilities in males may reduce the threshold for expressivity of ADHD-related traits and/or may result in better ADHD diagnosis (as a consequence of greater teacher focus on educational low achievers for example). Systematic searching for such mutations in adequately-powered ADHD cohorts by chromosome-wide or exome sequencing, or by CNV analysis, has yet to be undertaken. However, studies focussed on specific CNVs, or on selected candidate genes, show that in some cases X-linked mutations are associated with a diagnosis of ADHD, or an influence on ADHD symptoms (see below). Unfortunately, in such small-scale

studies the pathogenicity and penetrance of the mutation cannot be accurately determined.

The effects of X-linked polymorphisms will also be more obvious in males than in females. Despite its abundance of neurally-significant genes, psychiatric GWAS studies have tended to neglect the X chromosome for a variety of reasons, including poor coverage on genotyping arrays and power issues as a consequence of having to stratify data by sex (Wise et al., 2013). Larger pooled sample sizes, better array coverage, enhanced imputation techniques and improved statistical methodologies in the future should enable the robust identification of X-linked risk polymorphisms that confer increased risk of ADHD to males.

Two X-linked candidate genes, identified on basis of their known role in monoaminergic function, have been investigated with regard to their possible role in ADHD phenotypes. Of the two, the best studied is *MAOA* (encoding monoamine oxidase), discussed in section **2.1.1** as a downstream target of SRY. Since the publication of a seminal study in 1993 showing that males with inactivating mutations within MAOA displayed impulsive aggression (Brunner et al., 1993), much focus has been on the association between gene variants in hyperactive-impulsive ADHD. Multiple genetic variants within MAOA, notably variable number tandem repeats within the promoter region, have been associated with ADHD vulnerability, attentional dysfunction, impulsivity, comorbid conduct disorder and neural function (Brookes et al., 2006; Das Bhowmik et al., 2007; Gizer et al., 2009; Kebir et al., 2009; Nymberg et al., 2013); several of these associations have been replicated in one or more studies. Some, or all, of these genetic variants may feasibly contribute to the

male bias in aspects of ADHD. Interestingly, particular genetic variants within *MAOA* may be associated with different outcomes in males and females with ADHD, suggesting that the same polymorphism may have functionally different consequences in the two sexes (Biederman et al., 2008; Gizer et al., 2009; Rommelse et al., 2008).

The second candidate gene of interest is *HTR2C*, encoding the serotonin 2C receptor. Pharmacological and genetic studies in rodent systems have consistently implicated this receptor in behavioural phenotypes of relevance to ADHD, including response inhibition and attention (Homberg, 2012; Humby et al., 2013; Pennanen et al., 2013; Robinson et al., 2008). To date, association studies in man have been relatively small and have produced inconclusive evidence for a role of this receptor in ADHD. There is some suggestion that variation within this gene may preferentially contribute towards the hyperactive-impulsive subtype of the disorder rather than the inattentive subtype (Li et al., 2006b; Xu et al., 2009). Recently, a missense single nucleotide change (Cys23Ser) has been associated with increased dopamine release in the striatum of healthy individuals during stress (Mickey et al., 2012), and this polymorphism could feasibly influence striatal-dependent dopamine-sensitive functions in individuals with ADHD. Large GWAS examining autosomal gene variation and vulnerability to psychiatric illness have highlighted the over-statement, inadequacy and irreproducibility of some hypothesis-led candidate gene findings (Lewis and Knight, 2012; Wilkening et al., 2009). Thus, it will be interesting to see whether future GWAS studies focussing on the X chromosome support existing findings from the *MAOA* and *HTR2C* candidate studies.

2.1.2.2 X-linked gene dosage

In female mammals, one X chromosome in each cell is silenced by the epigenetically-medicated process of X-inactivation; this process is thought to be a mechanism to ensure that males and females generally have equivalent X-linked gene expression, and therefore grossly equivalent physiology (Dupont and Gribnau, 2013). In humans, although most X-linked genes are subject to X-inactivation, a small number (perhaps 15-20%, including those within the pseudoautosomal regions), escape, and thus will be expressed from both X chromosomes (Carrel and Willard, 2005). The expression of these genes will be higher in female tissues than in male tissues; the magnitude and nature of this expression difference will depend on the extent to which the gene truly escapes silencing on the inactivated chromosome, where and when it escapes, and background physiology such as hormonal levels (Berletch et al., 2011). Theoretically, the differential expression of one or more X-linked escapees in brain may contribute to sex differences in vulnerability to mental disorders. Indeed, a new analysis has shown that there is an excess of escaping genes associated with cognitive (dys)function in man (Zhang et al., 2013). With respect to ADHD risk, we might anticipate that greater dosage of one or more X-linked genes in females than males was protective.

Some empirical evidence from individuals with sex chromosome anomalies supports the idea that the expression of X-linked escapees can influence behavioural phenotypes of relevance to ADHD. Individuals with the genetic condition Turner syndrome (TS), in which part, or all (karyotype 45,X), of one X chromosome is missing, are at significantly elevated risk (~18-fold) of being diagnosed with ADHD (Russell et al., 2006), and of presenting with attentional

and motor deficits (Nijhuis-van der Sanden et al., 2003). The most parsimonious explanation for these data is that haploinsufficiency for the products of one or more X-linked escapees contributes towards ADHD risk in the TS population, although the presence of Y chromosome sequences undetectable by conventional karyotyping in up to 30% of affected individuals (El-Eshmawy et al., 2013; Freriks et al., 2013; Zhong and Layman, 2012) and the unmasking of deleterious X-linked alleles may also plausibly contribute towards higher ADHD rates in TS. Through examining the neurocognitive profile (encompassing measures of attention) of TS individuals with various sizes of X chromosome deletion, Zinn and colleagues have implicated a small genetic region of the short arm of the X chromosome (Xp22.3) encompassing just 31 annotated genes in these deficits (Zinn et al., 2007). The cognitive deficits in TS could feasibly arise due to altered hormone levels associated with the genetic mutation: subjects with TS generally have ovarian dysfunction, resulting in low levels of circulating gonadal hormones, notably oestrogens (Bondy, 2009). However, attentional and other executive function deficits in TS appear somewhat resistant to adolescent or adult oestrogen or androgen supplementation, and subjects with premature ovarian failure (and hence a similar hormonal profile to that of TS) do not exhibit analogous cognitive deficits (Ross et al., 2003,2004; Rovet et al., 2004). These data suggest that organisational hormone deficiencies may account for the observed TS neurocognitive phenotypes, or alternatively, that they are due to direct genetic effects on the brain.

Males possessing two X chromosomes instead of the usual one (Klinefelter's syndrome, 47,XXY), and females possessing three X chromosomes (47,XXX) in which the expression of X-linked escapees is elevated, appear to be

at increased risk of developing psychiatric symptoms, including those associated with ADHD (Tartaglia et al., 2012). Again, as 47,XXY and 47,XXX karyotypes result in hormonal abnormalities, the effects of the abnormal genetic constitution could be mediated by hormonal factors, or could be a direct effect of gene dosage on the brain. Taken together, the TS, Klinefelter and 47,XXX data imply that X-linked gene dosage (both under-dosage and over-dosage) is likely to be a significant contributor to ADHD pathophysiology, and therefore to sex differences in the disorder endophenotypes. Correlating genetic, hormonal and neuropsychological measures in these genetically informative populations should partially enable the dissociation of mediating mechanisms; this venture could be further facilitated by work in corresponding animal models. As an illustration of the utility of this additional approach, using the four-core genotypes model, in combination with a 39,XO mouse model of Turner syndrome possessing just one X chromosome (Lynn and Davies, 2007), Chen and colleagues showed that the expression of genes encoding important neurochemicals or neurotransmitter receptors in the striatum (and presumably striatal physiology) was dependent upon X chromosome dosage (Chen et al., 2009).

Altered fronto-striatal circuitry could potentially explain why 39,XO mice differ from their wildtype female (40,XX) counterparts in terms of their behaviour. Some years ago, we showed that the 39,XO mouse demonstrated specific deficits in visuospatial attention, and that these deficits could be rescued in 40,XY*^{X} mice (essentially mice with a single X chromosome, and a handful of additional genes on the pseudoautosomal region and adjacent sequence). As the pseudoautosomal gene *Sts* was known to escape X-inactivation in mice and be located on the small Y*^{X} chromosome, we hypothesised that haploinsufficiency

for its product in 39,XO mice could account for the observed attentional deficits (Davies et al., 2007). Follow-up genetic and pharmacological experiments investigating the attentional performance of mice lacking *Sts*, or administered an STS inhibitor acutely, confirmed this idea (Davies et al., 2009). *Sts* encodes the protein steroid sulfatase, an enzyme responsible for cleaving sulfate groups from a variety of steroids (e.g. dehydroepiandrosterone sulfate, DHEAS), thereby altering their activity and/or potency; these sulfated and non-sulfated compounds may act as modulators at a number of neurotransmitter receptors, including gamma-aminobutyric acid A ($GABA_A$), N-methyl-D-aspartatic acid (NMDA) and sigma-1 receptors (Davies, 2012). Products of STS (e.g. DHEA) may also act as precursors for a variety of oestrogens and androgens (Reed, 2005); deficiency for the STS enzyme is predicted to result in elevated levels of steroid sulfates (e.g. DHEAS), and reduced levels of free steroid (e.g. DHEA). In both man and mouse, *STS* is expressed in regions of the developing and adult brain pertinent to ADHD, notably the cortex, basal ganglia, thalamus and cerebellum (Compagnone et al., 1997; Perumal et al., 1973; Stergiakouli et al., 2011).

Boys with deletions encompassing *STS*, or with inactivating mutations within the gene, are at elevated risk of ADHD (Doherty et al., 2003; Kent et al., 2008; Lonardo et al., 2007; Tobias et al., 2001); individuals possessing such mutations are masculinised normally, exhibiting equivalent testosterone levels, sexual development and fertility to males lacking such genetic variants (Fernandes et al., 2010). Additionally, polymorphisms within the gene have been associated with disorder risk, inattentive symptoms and cognitive abnormalities in children with ADHD (Brookes et al., 2010, 2008; Stergiakouli et al., 2011).

In subjects with ADHD, levels of salivary DHEA are lower than in neurotypical controls (Wang et al., 2011b) and levels of DHEA(S) inversely correlate with some ADHD symptomatology (hyperactivity and attention/impulsivity scores on the Continuous Performance Test) in children with ADHD (Strous et al., 2001; Wang et al., 2011a). Moreover, methylphenidate administration appears to boost circulating levels of DHEA(S) (Lee et al., 2008; Maayan et al., 2003; Wang et al., 2011a). Recently, we have shown that mice lacking *Sts* exhibit a number of additional phenotypes associated with ADHD: hyperactivity, heightened emotional reactivity, aggression, perseveration, reduced serum DHEA levels and perturbed striatal and hippocampal neurochemistry (Trent et al., 2012a, 2012b). Activity levels in these mice postively correlated with striatal 5-HT levels, and inversely correlated with serum DHEA levels (Trent et al., 2013, 2012a), whilst perseverative behaviour positively correlated with levels of hippocampal 5-HT (Trent et al., 2013, 2012a). Studies in rats have shown that acute administration of DHEAS (Rhodes et al., 1996) or a steroid sulfatase inhibitor (Rhodes et al., 1997) can enhance acetylcholine release in the hippocampus.

In summary, these cross-species data suggest that a reduction in levels of functional STS, leading to reduced levels of circulating DHEA and subsequent effects on the serotonergic and/or cholinergic systems, could lower the threshold of vulnerability for developing ADHD and promote the presence of specific endophenotypes including inattention, hyperactivity and perseveration. What relevance might these findings have to male-female differences in ADHD? In man, the *STS* gene (located at Xp22.32) escapes X-inactivation (Mohandas et al., 1980); thus, it is an excellent candidate for the neurocognitive deficits seen

in Turner syndrome (Zinn et al., 2007). Whilst *STS* has a homologue on the long arm of the Y chromosome, this appears to be a non-expressed pseudogene as a consequence of a pericentric inversion (Yen et al., 1988). Therefore, from first principles, we would expect *STS* gene expression to be higher in females (two alleles expressed) than in males (one allele expressed); in turn, this could feasibly lead to greater protein expression, and higher enzyme activity in the former sex. Levels of STS activity do appear to be higher in female than male tissues in humans and non-human primates, and there is some suggestion that this sex difference may be of a greater magnitude in the pre-pubertal period (Cuevas-Covarrubias et al., 1993; Kriz et al., 2005; Steckelbroeck et al., 2004). Thus, it is plausible that reduced STS activity in males may partially account for their greater vulnerability to inattention, hyperactivity and perseveration in ADHD. Future studies might specifically test for association between enzyme activity and the aforementioned behavioural phenotypes in males and females with ADHD.

2.1.3 X-linked genomic imprinting and downstream effects on autosomal imprinting

In mammals, autosomal genes are inherited in duplicate i.e. one allele being inherited from each parent, and these two alleles are approximately equally expressed. Genes that are subject to the epigenetically-mediated process of 'genomic imprinting' (so-called 'imprinted genes') are inherited in duplicate, but only one of their two alleles is expressed in a parent-of-origin dependent manner. Approximately 50% of imprinted genes are solely (or predominantly) expressed from the allele inherited from the father ('paternally expressed genes'), whilst the remainder of the imprinted gene complement is

chiefly expressed from the maternally inherited allele (‘maternally expressed genes’) (Kopsida et al., 2011). Imprinted genes appear to be disproportionately involved in growth and developmental processes, and their (dys)function can substantially influence neurodevelopment and associated psychiatric and neurological phenotypes (Wilkinson et al., 2007). Theoretically, genomic imprinting of X-linked genes could give rise to sexually dimorphic brain expression, and sex-specific brain and behavioural phenotypes: paternally expressed X-linked genes can only be expressed in the female brain, whilst maternally expressed X-linked genes will be more highly expressed in male than female brain provided they are subject to X-inactivation (Davies et al., 2006).

As yet, no X-linked imprinted genes have been identified in man, although there is tantalising evidence to suggest that one or more X-linked imprinted genes exist and that they might affect neurobiological features pertinent to ADHD (Davies, 2010). For example, work comparing girls with Turner syndrome (45,X) in which the single X chromosome was either of paternal (45,X^{P}) or maternal (45,X^{M}) origin, has suggested that the former group display superior social cognitive capabilities, reduced vulnerability to ASDs and better academic achievement (Sagi et al., 2007; Skuse et al., 1997) but worse visuospatial memory performance (Bishop et al., 2000). A recent study using the same experimental paradigm has indicated X-linked parent-of-origin effects on temporal cortical thickness, and superior frontal gyrus grey matter volume (Lepage et al., 2013).

Work in the more experimentally-tractable 39,XO mouse model initially identified an X-linked parent-of-origin effect on a behavioural task taxing inhibitory processes and sensitive to frontal cortex function, and identified a

novel imprinted candidate gene from the *Xlr3* family, *Xlr3b*; the closest human orthologue of *Xlr3b*, *FAM9B*, does not appear to be expressed in the brain and its imprinted status is unknown (Davies et al., 2005; Raefski and O'Neill, 2005). Later work using a reciprocal cross mouse model (in which between-strain polymorphisms could be used to identify parental origin of transcripts with next generation sequencing) has indicated a number of further X-linked imprinted gene candidates (Gregg et al., 2010a, 2010b), although given the tendency of screens like this to produce false positives in the absence of stringent statistical controls (DeVeale et al., 2012), means that these candidates have yet to be verified in mouse and man. The studies by Gregg and colleagues, statistical concerns notwithstanding, also served to emphasise the concepts that: i) imprinted genes in general, and X-linked imprinted genes in particular, could be expressed in brain regions associated with higher cognitive functions and inhibitory processes, and ii) that offspring sex could modulate the extent to which autosomal genes displayed imprinted expression patterns, a previously unappreciated viewpoint (Davies, 2013).

Whilst the notion that X-linked imprinted genes could influence ADHD risk and symptomatology is an interesting one, to date little work has been done in this area, and consequently there is little empirical evidence to support it. The single study that has explicitly compared rates of ADHD in $45,X^{P}$ and $45,X^{M}$ subjects found no difference between the two groups, although only 50 girls were studied, and only 24% of these met DSM-IV criteria for the disorder (Russell et al., 2006). In future, larger-scale, work making use of this 'experiment of nature', it may be informative to examine whether ADHD risk/presentation, behavioural endophenotypes such as

distractability/organisation and hyperactivity, or cognitive functions such as attention, behavioural inhibition and processing efficiency, are affected by the parental origin of the X chromosome. Ongoing molecular biological and bioinformatic analyses are attempting to identify novel X-linked imprinted genes on the human X chromosome. Should these be discovered, an important next step would be to determine whether their expression patterns and functions are consistent with the parent-of-origin dependent neurobiological phenomena and sex differences in neurodevelopmental disorders described above.

2.2 Endocrine mechanisms

The genetic mechanisms referred to above initiate a scenario whereby the cells of the two sexes are bathed in dissociable hormonal milieu. This stimulates a series of complex interactions whereby sex-linked genes, hormones and exogenous factors (e.g. maternal hormones or toxins) can act independently, reciprocally or (ant)agonistically to influence the physiology and behaviour of the developing subject (Bao and Swaab, 2011). For example, testosterone and its metabolites, the levels of which are considerably higher in males than females, can act to masculinise regions of the brain including subdivisions of the hypothalamus, amygdala and hippocampus by binding to the androgen receptor; the androgen receptor is encoded by an X-linked gene (*AR*), and its expression in human brain can be modulated by sex (Fernandez-Guasti A et al., 2000). In rodents and many other mammalian species (excluding primates), brain development can be significantly influenced via the conversion of androgens to estrogens, which then act at estrogen receptors (McCarthy, 2013). Furthermore, there is some evidence that, in rodents at least, *Sry* can influence testis size

(Suto, 2011), and that testis size is associated with circulating testosterone levels under arousing conditions (Preston et al., 2012).

Elevated levels of androgens in the developing male compared to the developing female as a consequence of male-limited *SRY* expression represents an obvious, though by no means exclusive, downstream biological candidate mechanism by which ADHD prevalence may be greater in males than in females. Is there any evidence that elevated exposure to androgens is associated with increased vulnerability to neurodevelopmental disorders, including ADHD?

Work in clinical and healthy human populations has hinted that exposure to elevated androgen levels during embryogenesis (and maybe also into adulthood) could predispose to male-specific behaviour patterns and to ASDs (Baron-Cohen et al., 2011; Hines, 2008). Many of the same arguments and experimental paradigms used in this ASD research are equally applicable to ADHD.

A commonly used surrogate index of fetal testosterone exposure is the ratio of the length of the index finger (2D) to the length of the ring finger (4D), with higher levels of *in utero* exposure being associated with lower 2D:4D ratios (Breedlove, 2010). However, the value of this measure as an index of prenatal androgen exposure in humans is somewhat controversial (Berenbaum et al., 2009).

Whatever underlying biology the 2D:4D ratio reflects, it appears to correlate inversely with ADHD symptoms in both healthy and clinical populations, whereby individuals with a lower, more male-typical, ratio tend to exhibit a greater number of ADHD features (de Bruin et al., 2006; Romero-

Martinez et al., 2013; Stevenson et al., 2007). One study has suggested that the association between 2D:4D ratio and inattentive symptoms may be mediated by the trait mechanism of conscientiousness (Martel, 2009). Preliminary observations within our laboratory have indicated that lower 2D:4D ratios are associated with longer latencies to inhibit a pre-potent response on a stop-signal reaction time task i.e. greater motor impulsivity in healthy individuals; the strength of the correlation was greater in females than males, potentially suggesting that fluctuations in fetal testosterone exposure may have proportionally greater long-term effects on ADHD-associated psychologies in the former sex (unpublished). Interestingly, maternal smoking during pregnancy, a known risk factor for ADHD in the offspring (Banerjee et al., 2007), has been shown to reduce the 2D:4D ratio in boys but not in girls, suggesting a potential modulatory effect on *in utero* testosterone levels (Rizwan et al., 2007). Whether this is a robust phenomenon, and if so, what the underlying molecular mechanisms by which this occurs might be (and what the downstream effects on sex-specific behaviour might be) remain open questions.

In the autism literature, levels of *in utero* testosterone have been directly measured during amniocentesis and have been shown to correlate with relevant postnatal neural (e.g. Chura et al., 2010), and behavioural (e.g. Auyeung et al., 2012b) measures; for autistic traits, there appeared to be a correlation with prenatal testosterone exposure, but not with postnatal salivary testosterone levels, implying that androgen exposure during critical developmental periods *in utero* development is a key determinant of later brain function and psychiatric vulnerability (Auyeung et al., 2012a). Conceptually similar studies could reasonably be undertaken focussing more upon ADHD-associated parameters

(particularly given evidence for putative association between fetal testosterone exposure as determined by this technique and striatal function (Lombardo et al., 2012)). However, limitations of the technique should be appreciated, notably that, given the possibility of associated miscarriage, amniotic fluid sampling can only be ethically undertaken in women with high-risk pregnancies whose physiology may not necessarily be representative of the general population.

A number of genetic conditions may result in hyperandrogenism; children affected by such disorders appear to be at significantly increased risk of developing ADHD (Mueller et al., 2010) and exhibit increased striatal grey matter volume (Mueller et al., 2011). Moreover, positive correlations have been noted between salivary testosterone levels and behavioural measures associated with, but not specific for, ADHD such as aggression in disruptive children (Scerbo and Kolko, 1994). Finally, candidate gene studies have indicated significant association between genes involved in androgen biosynthesis or action e.g. *AR* and risk for neurodevelopmental disorders (Baron-Cohen et al., 2011; Comings et al., 1999).

The lines of evidence above support the idea that elevated androgen levels (especially prenatally) may confer increased vulnerability to ADHD. However, some studies appear to contradict this contention: for example, Lemiere and co-workers have reported no significant correlations between 2D:4D finger length and attentional capabilities in ADHD subjects (Lemiere et al., 2010), whilst Attermann and colleagues have demonstrated that females with a male co-twin (and therefore presumably exposed to relatively high levels of *in utero* testosterone) were surprisingly at *reduced* risk of displaying later ADHD traits than females with a female co-twin (Attermann et al., 2012). These

discrepant findings may be related to the fact that human studies have often employed small sample sizes, have been necessarily correlational due to the ethical limitations associated with manipulating steroid hormone axes in humans, have often examined disorder traits in ostensibly healthy individuals, and have been conducted in atypical populations (e.g. in women with high-risk pregnancies). As such, the magnitude and veracity of most reported effects remains to be confirmed.

Animal studies, in which intrinsic and exogenous hormone levels can be experimentally manipulated and in which the digit ratio is better established as an index of prenatal androgen exposure (Zheng and Cohn, 2011), provide an opportunity to explicitly test for a relationship between testosterone exposure and neurobehavioural measures related to ADHD. Overall, these have indicated that administering testosterone to young rats, and specifically to genetically ADHD-prone male rats, potentiates later hyperactivity, cognitive (working memory) abnormalities, abnormal stress responses and dopaminergic dysfunction in the frontal cortex (Aubele and Kritzer, 2011; Bucci et al., 2008; Li and Huang, 2006; King et al., 2000). During adolescence, increased testosterone levels can upregulate the expression of ADHD-associated genes (*TH*, *MAOA* and *COMT*) in dopamine-rich brain regions, suggesting a tentative mechanistic link (Purves-Tyson et al., 2012). As yet, the effects of pre- and postnatal testosterone exposure on the performance of adolescent male and female rodents on assays taxing constructs of direct relevance to ADHD e.g. attention, behavioural inhibition or response to delayed gratification have not been examined despite elegant rodent tests now being available (Humby et al., 1999; Humby and Wilkinson, 2011; Isles et al., 2003). The advent of better

genetic animal models for ADHD based on emerging GWAS results, more elegant neuroscience techniques such as optogenetics allowing for highly-controlled spatiotemporal regulation of candidate gene expression, and more clinically-relevant behavioural assays, should allow us to answer more accurately the question of whether elevated testosterone exposure increases the risk of ADHD-associated traits, and if so, at which critical developmental window(s) and through which molecular and neural mechanisms.

Clearly, other endocrine mechanisms differ between the sexes and their disturbance may affect vulnerability to developmental disorders e.g. the thyroid and growth hormone systems (Lichanska and Waters, 2008; Rogol, 2010); however, their role in the pathogenesis of ADHD has only been superficially examined (Colborn T, 2004; Jensen and Garfinkel, 1988), and sex differences within them are downstream consequences of the sexually dimorphic gene and androgen expression already discussed above. Hence, these systems will not be discussed in further detail here.

Sexually dimorphic neurobiology arising as a consequence of sex-specific gene/hormone expression profiles, can modulate how autosomal risk variants affect disorder presentation in males and females. Recently, associations between polymorphisms within the dopamine receptor 2 gene (*DRD2*) and behaviour within ADHD have been shown to be sex-specific (Nyman et al., 2012), whilst different regions of the gene encoding the noradrenaline transporter (*SLC6A2*) were associated with distinct behavioural outcomes in girls and boys (Sengupta et al., 2012). Differential association in males and females for the gene *COMT*, encoding the catecholamine-degrading enzyme catechol O-methyltransferase, has also been proposed (Biederman et al., 2008), consistent

with significantly higher *COMT* expression in female than male *post mortem* brain (Dempster et al., 2006). As impaired COMT function seems to predispose to heightened aggression (Volavka et al 2004), it seems reasonable to speculate that the inheritance of a male XY karyotype, resulting in a male-specific hormonal profile, acts to attenuate *COMT* expression, and that further attenuation of this expression by gene-specific mutations or polymorphisms contributes towards the increased male prevalence of conduct disorder within ADHD (Eme, 2007).

3. Summary and future directions

There is a pronounced sex bias in ADHD prevalence whereby males are significantly more likely to be diagnosed than females; there are also (less clear-cut) sex differences in the way the disorder manifests in males and females. These sex differences may be partially accounted for by diagnostic and ascertainment biases, but are likely, in large part, to be due to biological differences between males and females. Hence, the biological pathways disturbed in male and female ADHD are likely to be affected to different extents, or to be partially dissociable. Differences in chromosomal complement, and in the subsequent early hormonal milieu, represent obvious fundamental mechanisms that could explain why ADHD manifests differently between the sexes. The specific genetic and endocrine mechanisms discussed herein that could give rise to this sexually dimorphic disorder presentation are summarised in **Figure 1**.

In order to study abnormal psychology, it is first necessary to define 'normality'. Multiple studies such as the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK, have attempted in to study large,

comprehensively-phenotyped cohorts of healthy individuals in order to better characterise typical sex-specific behavioural, cognitive and brain development over time, with a view to enabling the identification and classification of deviations from it. Projects such as these need to be supported and will be invaluable in understanding the extent and nature of pathophysiology within populations.

In man, there is a need for sex to be considered as a dependent variable in all future ADHD studies, and for genetic associations emerging from planned GWAS and CNV studies to be routinely stratified by sex in order for potential interactions between sex and genetic vulnerability to be clarified. Together with improved sample sizes, new statistical methodologies for examining genetic variation on the sex chromosomes should allow for the identification and characterisation of novel polymorphisms that may influence disorder risk and/or presentation. If we can identify robust genetic variants that are associated with the disorder, we should be able to undertake longitudinal studies on boys and girls at high genetic risk to explicitly examine how sex and might influence disorder presentation over time; these might encompass sophisticated behavioural, neuropsychological, neuroimaging and (epi)genetic experiments, as well as studies designed to tease apart the relative contributions of genes and environmental factors in mediating sex-biased endophenotypes.

Parallel experiments in animal models in which genetic, hormonal and environmental factors can be systematically varied will be of great utility in determining the relative importance of each of these factors in sex-specific vulnerability to ADHD-related phenotypes. Work in rodents, which possess a genomic and neural structure analogous to that of man, will be of particular

importance (Davies, 2013). The rodent experiments described within this review are associated with a number of caveats. For example, a variety of background strains have been used and in some of the mouse models (e.g. the four core genotypes model) the Y chromosome is of a different strain to the other chromosomes. Future work should assess the extent to which the findings emerging from these models can be generalised across strains and across species. The recent development of 'knockout' technologies for use in rats (Jacob et al., 2010) and strategies for affecting brain gene expression in a spatiotemporally-restricted manner, in parallel with the use of newly-developed behavioural paradigms taxing cognitive functions of relevance to ADHD (Mar et al., 2013) will allow the effects of disorder-associated genetic variants on brain function to be comprehensively characterised.

Over the course of the next decade or so, studies like those outlined above should enable more accurate diagnosis and prognosis for boys and girls with ADHD. Moreover, they should highlight novel protective and risk factors for aspects the disorder; knowledge of such factors may provide clues as to unrecognised, potentially druggable, disorder pathways and alternative approaches for treatment.

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Figure 1. Males (**A**) inherit a single X chromosome (dark grey) from their mother, and a Y chromosome from their father (light grey); females (**B**) inherit two X chromosomes, one from either parent. Y-linked genes (e.g. *PCDH11Y* and *NLGN4Y*) are only present, and expressed, in male brain. Only one allele of X-linked genes including *MAOA*, *AR* and *HTR2C* are present in male brain, compared to two in female brain; this means that these genes may be sexually dimorphically expressed, and that mutations or polymorphisms within them are more likely to have functional consequences in hemizygous males. The Y-linked homologue of *STS* is a non-expressed pseudogene. The expression of the Y-linked SRY gene in males causes the bipotential gonad to differentiate into a testis; this organ then secretes high levels of androgens (notably testosterone) during development and into adulthood, which have organisational and activational effects on the brain. Environmental factors of relevance to ADHD pathogenesis e.g. maternal smoking during pregnancy have been suggested to influence prenatal circulating testosterone levels.