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REVIEW

Cognitive, behavioural and psychiatric phenotypes associated with steroid sulfatase deficiency

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Abstract

The enzyme steroid sulfatase (STS) desulfates a variety of steroid compounds thereby altering their activity. STS is expressed in the skin, and its deficiency in this tissue has been linked to the dermatological condition X-linked ichthyosis. STS is also highly expressed in the developing and adult human brain, and in a variety of steroidogenic organs (including the placenta and gonads); therefore it has the potential to influence brain development and function directly and/or indirectly (through influencing the hormonal milieu). In this review, we first discuss evidence from human and animal model studies suggesting that STS deficiency might predispose to neurobehavioural abnormalities and certain psychiatric disorders. We subsequently discuss potential mechanisms that may underlie these vulnerabilities. The data described herein have potential implications for understanding the complete spectrum of clinical phenotypes associated with X-linked ichthyosis, and may indicate novel pathogenic mechanisms underlying psychological dysfunction in developmental disorders such as attention deficit hyperactivity disorder and Turner syndrome.

Key words: Acetylcholine; Aggression; Attention; Attention deficit hyperactivity disorder; Dehydroepiandrosterone sulfate; Impulsivity; Hippocampus; Postpartum psychosis; Serotonin

Core tip: The enzyme steroid sulfatase (STS) cleaves sulfate groups from neuroactive steroid hormones thereby altering their activity. Here, we review cross-species evidence indicating that deficiency for this enzyme might influence behaviour and vulnerability to psychiatric illness; we then suggest potential mediating mechanisms. Understanding whether or not STS deficiency impacts upon neural function, and if so, how, has potential implications for diagnosis, counselling and treatment in cases of X-linked ichthyosis (the dermatological condition associated with STS deficiency). Moreover, this understanding may provide more general novel insights into the pathogenesis of common and disabling psychiatric disorders.

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STEROID SULFATASE AND ITS ROLE IN BRAIN FUNCTION

Steroid sulfatase (STS, formerly known as arylsulfatase C) is an enzyme that acts as a homodimer within the endoplasmic reticulum to cleave sulfate groups from a variety

of sulfated steroid hormones (notably 16α-hydroxy-dehydroepiandrosterone, dehydroepiandrosterone, estrone and cholesterol sulfates), thereby altering their biological function; the desulfation of several of these compounds represents an initial step in the biosynthesis of a number of androgens and oestrogens[1]. The STS protein is expressed in a number of tissues important in reproductive function including the placenta (highest expression), the ovaries, the testes and the mammary gland, as well as other non-reproductive tissues such as the liver and thyroid gland[2] (http://www.ncbi.nlm.nih.gov/unigene).

Besides potentially influencing the development and/or ongoing function of the aforementioned organs, STS represents an excellent *a priori* candidate modulator of brain development and behaviour: during human embryogenesis, *STS* expression occurs throughout the thalamus, in the cortical plate, throughout the basal ganglia, in the hypothalamus and anterior pituitary gland, and in the cerebellar neuroepithelium (a pattern largely consistent with that seen in other mammalian and non-mammalian species)[3], and with reported sulfatase activities in *post mortem* brain tissue of adult humans[4]. Given this persistent brain expression, STS is likely to influence neural function directly; the substrates and products of the enzyme are known to act as modulators at key sites of neurotransmission in the brain, notably at γ aminobutyric acid type A, N-methyl-D-aspartic acid and sigma (σ)receptors[1]. In addition, STS could exert a significant indirect influence on the brain *via* its role in androgen and oestrogen biosynthesis; these compounds can act systemically either to substantially and permanently alter brain development ("organisational effects") or to influence ongoing neural function *via* more subtle, potentially reversible "activational effects"[5].

In man, STS is encoded by the X-linked *STS* gene, which resides just outside pseudoautosomal region (PAR) 1 at Xp22.3. *STS* escapes X-inactivation[6], and its Y homologue is pseudogenic as a consequence of a pericentric inversion[7]. Together these attributes suggest the possibility that the gene might be expressed more highly in female than male tissues, and hence the activity of the associated enzyme may be greater in the former sex; there is some empirical evidence that this may be the case[8-10]. A recent expression analysis has suggested that alternative first exons of the *STS* gene may be employed in different tissues, with exons 0a and 1b being most abundant in the brain[11]. In rats, as in man, *STS* is X-linked, but the rat orthologue appears to be subject to X-inactivation[12]. In mice, *STS* is located within the PAR, and therefore by definition, escapes X-inactivation[13]. At the genetic level, there is considerable sequence divergence across species, although the function of the encoded enzyme appears to be largely conserved[12,13].

STS DEFICIENCY AND EFFECTS ON GENERAL PHYSIOLOGY

The vast majority of cases of STS deficiency (85%-90%) are caused by complete/partial deletions of the *STS* gene, which typically also encompass genes immediately adjacent (*HDHD1A*, *PNPLA4* and *VCX*); larger, rarer deletions may encompass more distant genes including *ARSE* (encoding arylsulfatase E), *NLGN4X* (neuroligin 4X), other members of the *VCX* family (encoding variably charged proteins) and *KAL1* (encoding anosmin-1)[14-21]. About 5%-10% of patients with STS deficiency present with a complex phenotype arising from the deletion of one or more of the disease genes listed above: altered neuroligin 4X function has previously been suggested to account for sporadic cases of autism and mental retardation[20,22,23], deficiency for the *VCX* and *VCX3A* genes has been suggested as a possible cause of mental retardation[24-26] (although there is some evidence that deletion of these genes alone is not sufficient to cause this phenotype[27-29]), arylsulfatase E dysfunction has been linked to the skeletal disorder chondrodysplasia punctata[30], and mutations within *KAL1* (encoding anosmin-1) are associated with Kallman syndrome characterised by hypogonadotropic hypogonadism and anosmia[31]. The remaining 10% of cases of STS deficiency may be caused by a either variety of point mutations within the *STS* gene resulting in aberrant gene expression/splicing or protein function[32-39], or, rarely, by a deleterious mutation in the autosomal gene encoding sulfatase modifying factor-1 (*SUMF1*) whose normal role is the posttranslational modification and catalytic activation of a host of sulfatase enzymes[40]. The majority of genetic mutations at the *STS* locus are likely to be inherited rather than arising *de novo*[41].

The main phenotype associated with STS deficiency is a comparatively benign dermatological condition (X-linked ichthyosis, XLI) in which affected individuals present with large dark brown, adherent scales (particularly on the trunk, arms and legs) as a consequence of the accumulation of cholesterol sulfate in the membranes of stratum corneum cells[42]. Unsurprisingly, given that *STS* is X-linked, the vast majority of subjects diagnosed with XLI are male, although skin dryness may be manifest in female heterozygotes. Other, less common, phenotypes associated with STS deficiency include corneal opacities which do not affect vision (10%-50% of cases), and maldescent of the testes during embryogenesis (20% of cases)[42]. Expectant mothers carrying fetuses affected by STS deficiency tend to exhibit delayed or prolonged labour as a consequence of reduced placental oestrogen production and insufficient cervical dilation[43].

Confirmation of STS deficiency in cases ascertained clinically (generally through their skin condition) may be done biochemically through showing absent enzyme activity, or genetically through identifying either a complete/partial *STS* deletion or a deleterious point mutation within the gene[42]. Prevalence estimates for XLI based on clinical ascertainment have been in the range of 1 in 3000-6000 males; however, prenatal screens identifying cases of STS deficiency through low levels of maternal serum oestrogen (unconjugated estriol) have reported higher prevalences of approximately 1 in 1500 males[44,45].

These data indicate a spectrum of phenotypic consequences of enzyme deficiency, ranging from the most severe and easily ascertained (including contiguous gene syndromes), to milder forms (skin abnormalities only), to forms with no obvious clinical implications.

As the *STS* locus escapes X-inactivation, loss of genetic material from the short arm of the X chromosome, or loss of an entire X chromosome, in females as occurs in the developmental disorder Turner syndrome (TS)[46], will result in haploinsufficiency for STS. Whilst such haploinsufficiency is unlikely to result in phenotypes as obvious as those caused by complete enzyme deficiency, it may still feasibly contribute to the physiological and psychological abnormalities seen in TS[47]. Moreover, loss of one *STS* allele in TS could expose deleterious mutations on the remaining allele.

STS DEFICIENCY: EFFECTS ON BEHAVIOUR AND VULNERABILITY TO PSYCHIATRIC DISORDER

Possible role in disorders of attention

Emerging data from a variety of experimental sources is providing converging evidence for a role for STS in the modulation of attention. In the first systematic study of behaviour in individuals with XLI, Kent *et al*[20] showed that within a sample of 25 affected boys, ten met DSM-IV criteria for diagnosis of attention deficit hyperactivity disorder (ADHD), a neurodevelopmental condition characterised by inattention, pathological impulsivity and hyperactivity[48]; crucially, this sample was originally ascertained on the basis of low unconjugated estriol levels in their pregnant mothers and not on the basis of the boys' behaviour. Of the ten individuals affected by ADHD, eight were diagnosed with primarily inattentive subtype of the disorder, whilst the remaining two were diagnosed with the combined subtype (exhibiting evidence of inattention, and impulsivity and/or hyperactivity). Although this study did not employ a matched-control group, the 40% overall ADHD diagnosis rate (and 32% inattentive ADHD diagnosis rate) within the XLI group was substantially higher than that typically observed within the United Kingdom general population (4%-6% overall, 0.5% inattentive). Importantly, whilst most boys diagnosed with inattentive ADHD had deletions spanning multiple genes, two individuals within this subgroup had presumed inactivating point mutations within *STS*, indicating that STS dysfunction *per se* might predispose to inattention rather than the lack of gene product from a contiguous gene. The findings of the Kent *et al*[20] study are consistent with previous, more limited, case reports in the literature that have described individuals with contiguous Xp22.3 gene deletions and ADHD[49-51]. These initial data indicate that genetic screening of large, behaviourally-ascertained ADHD samples and appropriate control samples to investigate the relative prevalence of *STS* deletions/point mutations may be worthwhile.

Whilst work stimulated by the initial XLI findings has indicated no significant association between polymorphisms within *STS* and overall ADHD risk after correction for multiple testing[3,11], there does appear to be a significant, and replicable, association between variation at rs17268988 (located within intron 9 of *STS*) and number of inattentive symptoms within ADHD cohorts[3,52]; specifically, possession of the minor G allele at this site (allele frequency about 0.25) is associated with a greater number of inattentive symptoms, particularly in older children (> 9 years of age). Whilst the genetic, cellular and neural mechanisms through which this association is mediated remain obscure, this finding provides further evidence for a role of STS in attentional function in neurodevelopmentally-compromised subjects; the extent to which an association between this genetic variant and attention exists in healthy individuals remains to be tested. Other polymorphisms across the *STS* gene (rs12861247, rs5978405 and rs5933863) have been shown to be significantly associated with aspects of cognitive function in males with ADHD as indexed by their performance on the comprehension, verbal IQ and picture completion Wechsler subtests, respectively[3]; as a small sample size was employed in this study these findings could be spurious, but if confirmed, these associations could feasibly also be mediated *via* effects on attention.

One of the most consistently reported neuropsychological findings in women with TS is inattention[53] which can be manifest as heightened distractability in real-life situations[54]. Rates of ADHD have been reported to be up to eighteen-fold higher in the TS population than in a control female population[55]. By correlating individual TS subjects' aggregate cognitive scores (partly based upon measures of attention) with their karyotype, Zinn *et al*[56] concluded that haploinsufficiency for an 8.3Mb region of chromosome Xp22.3 housing just 31 annotated genes (including *STS*) was critical in the development of the characteristic TS cognitive profile. Given the results arising from the XLI and ADHD studies described above, *STS* is a candidate for the attentional component of this profile. As such, it will be interesting to test whether those subjects with TS at greatest risk of attention deficits are hemizygous for the previously-identified risk alleles or deleterious mutations within *STS*. Should this prove to be the case, it would offer an opportunity to provide better genetic counselling and earlier clinical intervention in cases of TS.

Attention deficits are a prominent clinical feature of neuropsychiatric disorders other than ADHD, including autism[57-59] and schizophrenia[60]; cytogenetic deletions encompassing *STS* have been reported in individuals affected by both disorders[20,61-65]. Psychiatric disorders associated with attention problems are more common (*e.g.,* ADHD and autism[66]) or more severe (*e.g.,* schizophrenia[67,68]) in males than in females. Thus, it is plausible that the lower expression/activity of STS in males reduces their threshold of vulnerability to attentional dysfunction.

Recent data from animal model work appears to

substantiate the link between STS dysfunction and inattention. Performance deficits in the 39, XO mouse (a model of TS[69]) on the 5-choice serial reaction time task (5-CSRTT) assaying visuospatial attention could be rescued by the addition of a small chromosome containing a small number of additional genes including *STS*[70]. Subsequent work in another genetic model, the 39, $X^{Y*}O$ mouse (in which the *STS* gene is deleted as a consequence of an end-to-end fusion of the X and Y chromosomes within the PAR), revealed that these mice are less able to detect stimuli of short duration than wildtype mice[71]. Parallel studies in mice in which the STS axis was acutely pharmacologically modulated also showed effects on attention; specifically, administration of the enzyme substrate dehydroepiandrosterone sulfate (DHEAS) enhanced a main index of attention, whilst administration of the specific enzyme inhibitor COUMATE impaired response accuracy under attentionally-demanding conditions[71]. These pharmacological data, besides hinting that brain DHEA(S) levels may be a pertinent factor in attentional function, also indicate that ongoing STS activity could influence this psychological process. Given that peripherally-administered DHEAS is rapidly converted to DHEA within the mammalian brain[72], it is plausible that high levels of the latter compound within the brain are associated with enhanced attention, but that low levels (as presumably occur in XLI patients and 39, $X^{Y*}O$ mice) are associated with impaired attention. Whilst animal model work has provided some preliminary clues as to brain pathways that might be affected by STS and hence which might underpin its effect on attention (see later), more in-depth analyses are clearly required. As STS appears to influence ongoing attentional processes, such analyses may feasibly identify novel therapeutic targets that could be acutely pharmacologically modulated in adolescents and adults affected by disorders of attention.

Aggression

Early genetic evidence in mice examining inter-male aggression indicated that the Y chromosome PAR played an important role[73]; in mice, the PAR was originally thought to house just one gene (*STS*), but recently a second mouse PAR gene *Asmt* (encoding the enzyme acetylserotonin O-methyltransferase involved in the biosynthesis of melatonin from serotonin) has been identified[74]. However, in support of STS as a candidate mediator of this phenotype, a strong relationship between protein levels and aggression has been noted across several inbred mouse strains[75] and co-administration of both DHEAS and COUMATE resulted in heightened aggression in the inbred CBA/H strain[76]; this latter result suggests that, in addition to modulating ongoing attentional function in mice, STS may also modulate ongoing levels of aggressive behaviour. Consistent with the results of this pharmacological study, 39, $X^{Y*}O$ male mice, which have low levels of DHEA (and presumably elevated levels of DHEAS), are hyper-aggressive towards their cagemates[77].

To date, there is little evidence from human studies that suggests an equivalent role for STS in modulating aggression: to our knowledge, abnormally high levels of overt aggression have not been reported in cases of *STS* deletion, and within our Cardiff ADHD sample we did not detect association between a number of polymorphisms within *STS* and DSM-IV aggressive symptoms (albeit the case that the sample displayed low overall levels of aggression)[3]. There are two possible reasons for this apparent cross-species discrepancy: first, mouse brain function may be differentially affected by changes in STS levels, or the social structures imposed within groups of laboratory-housed mice might be conducive to eliciting aggression. Alternatively, the phenotype of elevated aggression may be present in *STS*-deficient humans but it may be more subtle than in mice, or only observable upon provocation.

Whilst there is fairly convincing cross-species evidence indicating a role for STS in attentional processes, and some data consistent with a role for the enzyme in aggression (in rodents at least), data suggesting a modulatory role in other behavioural phenotypes is more limited; this preliminary evidence is summarised below.

Impulsivity

In addition to being inattentive relative to 40, XY control mice, *STS*-deficient 39, $X^{Y*}O$ mice appear to be less impulsive, as indexed by their tendency to make fewer premature responses to a stimulus in the 5-CSRTT[71], and to better withhold responding on a murine analogue of the human Stop Signal Reaction Time Task (SSRT); pharmacological manipulation of the STS axis (*i.e.,* COUMATE and DHEAS administration) also enhanced behavioural inhibition on the SSRT. These data hint that STS deficiency in humans may also confer reduced impulsivity. Most research in psychiatry has focussed on pathological hyper-impulsiveness rather than the consequences of hypo-impulsivity, so exactly how this might be manifest is unclear - perhaps such individuals would show a tendency towards apathy or extreme risk aversion? To date, there is no information available regarding whether XLI patients are particularly apathetic or cautious. At the neuropsychological level, we might predict that *STS*-deficient subjects, like 39, $X^{Y*}O$ mice, would demonstrate enhanced "stopping" on the SSRT. Testing for association between polymorphisms across the *STS* gene and DSM-IV impulsive symptoms in a small sample of boys with ADHD revealed no significant findings[3]. However, such a result is perhaps not surprising if *STS* variation does generally result in reduced impulsivity, given that the ADHD population is, by definition, ascertained on the basis of abnormally high levels of impulsivity.

Psychotic and mood disorders

Postpartum psychosis (PP) is a severe psychiatric condition occurring shortly after birth in 1-2 of every 1000 new mothers; it is characterised by hallucinations/delusions, cognitive disorganisation, mood changes and

sleep abnormalities and can occasionally result in self- or infant-directed harm[78]. Whilst biology undoubtedly plays a role in PP susceptibility, as yet, well-defined risk factors are few and far between. The biggest risk factor appears to be a personal or family history for psychiatric (psychotic) illness, with a strong and consistent relationship between prior bipolar disorder diagnosis and vulnerability to PP; other risk factors include the extent to which circulating maternal oestrogen levels plummet following expulsion of the placenta, and levels of maternal stress[78]. It has been proposed that maternal STS deficiency might influence PP risk on the basis of several observations (described in detail in a recent paper[79]): (1) levels of the STS enzyme in the mammalian maternal brain specifically increase following parturition, hence perturbation of the STS axis as a consequence of enzyme deficiency may particularly impact upon behaviour at this timepoint; (2) the enzyme is highly expressed in the placenta where it is involved in the biosynthesis of oestrogen precursors; decreased levels of circulating oestrogens during pregnancy and in the postpartum period as a consequence of Sts deficiency may predispose to psychosis; (3) *STS* is a candidate gene underlying a quantitative trait locus for postpartum behavioural disturbance in pigs; (4) as discussed above, *STS*-deficiency in mice and humans predisposes to inattention (or "cognitive disorganisation") and occasional aggression; and (5) *STS* is highly expressed in the thyroid gland, an organ whose dysfunction is often noted in cases of PP. Given the overlap between bipolar disorder and PP, it is interesting to note that in a recent meta-analysis of gene expression data from *post mortem* brain samples from patients with bipolar disorder, *STS* was one of just a handful of genes whose expression was consistently downregulated[80]; thus it plausible that *STS* deficiency predisposes primarily to bipolar disorder and thereafter to PP, or to PP directly, or to both disorders *via* shared neurobiological mechanisms. It is also noteworthy that the estimated prevalence of female heterozygosity for a deleterious *STS* mutation (based on prenatal screening and XLI rates) is comparable to that of PP (*i.e.,* about 1 in 750-3000 females), that the neurosteroid system has previously been implicated in psychotic disorders and in other postpartum conditions[81], that two female cases of paranoid schizophrenia possessed cytogenetic deletions spanning *STS*[61], and that deficiency for the *STS* paralogue, *ARSA* (arylsulfatase A), has been linked to psychotic phenotypes and postpartum depression[82-84].

A relationship between STS deficiency and a second mood disorder, unipolar depression, might also be considered, although currently the evidence for such a link is weak or anecdotal. One of two females completely deficient for enzyme activity according to biochemical measurements (and therefore homozygous for an undefined *STS* mutation) was reported to have a history of depression[85]. Moreover, we are aware of one United Kingdom family in which X-linked ichthyosis appears to co-segregate with debilitating depression/anxiety.

Other behavioural endophenotypes

39, $X^{Y*}O$ mice are hyperactive, particularly within a novel environment and during the night (*i.e.,* during their active phase)[77], and there is a significant inverse relationship between evening activity in a novel environment and systemic levels of the STS product DHEA[86]. 39, $X^{Y*}O$ mice also exhibit increased response rates within operant behavioural tests where only one type of response is required, which may reflect a greater tendency towards perseverative responding[86,87]. Finally, these mice tend to show heightened emotional reactivity relative to wildtype controls as indexed by their lack of willingness to enter aversive (open, brightly-lit) spaces, and their increased levels of urination and defecation in such spaces[77]. As 39, $X^{Y*}O$ mice also lack the PAR gene *Asmt*[86], theoretically, the hyperactivity, perseverative and emotional reactivity phenotypes in 39, $X^{Y*}O$ mice could be due to the loss of *STS* and/or *Asmt* (particularly given that the former and latter phenotypes are not elicited upon acute COUMATE administration[77]). However, the inverse association between DHEA levels and hyperactivity tends to argue for a specific role for STS in this behaviour. To date, it has not proved possible to generate single-gene *STS* and *Asmt* knockout rodents; should such animals be created in the future, they could be used to dissociate between behavioural effects arising dues to STS and/or ASMT deficiency.

Hyperactivity and behavioural inflexibility (perseveration) have not consistently been reported as (endo) phenotypes associated with cases of STS deficiency in humans. This could be because these phenotypes in mice are largely due to ASMT deficiency, because there is no association, because the phenotypes are relatively minor and do not impair everyday function, or because no systematic, objective, case-controlled behavioural studies have yet been performed for XLI (*e.g.,* using activity monitors). The observation that 39, $X^{Y*}O$ mice exhibit more anxiety-related behaviours than their wildtype counterparts is consistent with anecdotal evidence suggesting anxiety in XLI patients, but clearly the veracity and magnitude of this association requires further exploration.

EFFECTS ON NEUROANATOMY AND NEUROCHEMISTRY: INSIGHTS FROM ANIMAL MODELS

The comparative rarity of XLI patients, together with the relative inaccessibility of the human brain, means that, to date, little is known about the neuroanatomical and neurochemical sequelae of STS deficiency in man. Individuals in which *STS* is deleted have been reported to exhibit cortical malformations including polymicrogyria[88] and heterotopia[89,90]; whilst these manifestations may be consistent with a role for STS in the developing cortex[3], given that these individuals lack multiple genes at Xp22.3, these abnormalities might equally likely be a consequence

of the absence of function of one or more contiguous brain-expressed genes (*e.g., HDHD1A*). To uniquely ascribe these cortical phenotypes to STS deficiency, it will be necessary to examine the brains of individuals with nonsense point mutations within *STS* either by *in vivo* neuroimaging or through analysing *post mortem* tissue.

Rodent models are far more amenable to neurobiological investigation than humans, and ongoing studies in genetic and pharmacological models have provided interesting initial clues as to the neurochemical mechanisms underlying STS deficiency effects on behaviour. Relatively crude analyses of whole tissue monoamine levels in the 39, $X^{Y*}O$ mouse have identified brain region-specific changes in the serotonin (5-HT) system (notably elevated 5-HT levels in the striatum and hippocampus)[86,87]; these mutant mice also have increased hippocampal expression of the *Htr2c* gene (encoding the 5-HT_{2c} receptor) and reduced striatal levels of the noradrenaline metabolite 4-hydroxy-3-methoxyphenylglycol[87]. Correlational analyses have indicated a positive linear relationship between hippocampal 5-HT levels and response rate/behavioural perseveration across two independent behavioural paradigms[86,87] and between striatal 5-HT levels and activity[87]; whilst these observations suggest that the 5-HT system abnormalities may affect these behavioural endophenotypes, an explicit causal link between the variables has yet to be established. Interestingly, serotonergic system dysfunction (including disruption of 5-HT_{2c} receptor expression/function) has been implicated in many of the psychiatric phenotypes linked to STS deficiency including inattention[91,92], aggression[93], impulsivity[94], PP[95], anxiety and depression[96,97]. More refined analyses of the relationship between analogues of these behavioural/psychiatric outcomes and 5-HT perturbation in the 39, $X^{Y*}O$ mouse will be useful, notably investigating whether neurochemical changes within specific sub-regions of the hippocampus and striatum underlie the behavioural abnormalities. Although the most parsimonious explanation for the neurochemical findings is STS deficiency[86], it is formally possible that they could arise due as a consequence of *Asmt* gene deletion. Again, examining single gene knockouts and/or assaying whether 39, $X^{Y*}O$ phenotypes are recapitulated by acute enzyme inhibition will aid in distinguishing between these scenarios. Should a discrete STS-dependent change in 5-HT function be confirmed in mice, its potential functional relevance to human phenotypes might be tested through using positron emission tomography with serotonergic ligands in XLI patients[98].

To date, the neuroanatomy of the 39, $X^{Y*}O$ mouse has not been examined; future analyses might initially look for gross abnormalities in hippocampal and striatal morphology for example, before investigating more subtle changes in cell number or subtype in these regions. Given the suggestion above that XLI may be associated with cortical abnormalities, examining the development and structure of the cortex in *STS*-deficient mice may also be warranted.

Rat studies in which STS is inhibited have also begun to shed some light on the neurochemical pathways influenced by enzyme dysfunction. Again, these have emphasised the hippocampus, a key site of neurosteroid-mediated neurogenesis[99], as an important locus of ongoing Sts action. Initial studies using estrone-3-O-sulfamate (EMATE) as an inhibitor indicated that inducing acute enzyme dysfunction, particularly in combination with substrate (DHEAS) administration, could benefit learning and/or memory formation[100]. However, EMATE is oestrogenic[101], and thus it is difficult to ascertain whether its effects on cognition are due to its inhibitory and/or its oestrogenic role. In later studies, systemic enzyme inhibition using the compound [p-O-sulfamoyl-N-tetradecanoyl tyramine (DU-14), a compound with lower oestrogenicity than EMATE] administered chronically was shown to increase brain levels of DHEAS[102], enhance hippocampal release of the neurotransmitter acetylcholine[103], and result in improved learning, spatial memory and context-dependent fear memory[104,105]. The acetylcholine system has a long association with attentional function, and one obvious route through which STS axis variation might influence attention is *via* this intermediary mechanism[106]. Thus, future work might examine the effects of STS inhibition, or *STS* gene deletion, on acetylcholinergic function in the hippocampus and other brain regions implicated in attention, and how these induced neurochemical changes might then relate to measures of (in) attention. Within the hippocampus, various serotonergic receptors are involved in controlling acetylcholine release[107]; hence, it will also be interesting to see whether there is any relationship between serotonergic and acetylcholinergic abnormalities induced as a consequence of STS deficiency in this structure.

CONCLUSIONS AND FUTURE DIRECTIONS

In the preceding text we have marshalled evidence from a variety of sources which indicates that STS deficiency may elicit a multitude of brain and behavioural phenotypes of relevance to psychiatric vulnerability. Clearly there is a need for further systematic work to specify the precise neural, behavioural and psychiatric endophenotypes arising from this molecular abnormality, and to investigate their prevalence; such work may provide more general insights into behavioural and cognitive processes that commonly go awry in psychiatric conditions (*e.g.,* attention). Ideally, this work would involve the examination of individuals with discrete mis-/nonsense point mutations within the *STS* gene, or deletions solely encompassing *STS*, in whom any phenotype could not be ascribed to missing contiguous genes; however, given the low frequency of such mutations within the population, identifying such individuals will be difficult, and establishing reliable prevalence figures for particular phenotypes will be challenging. In light of the arguments outlined above,

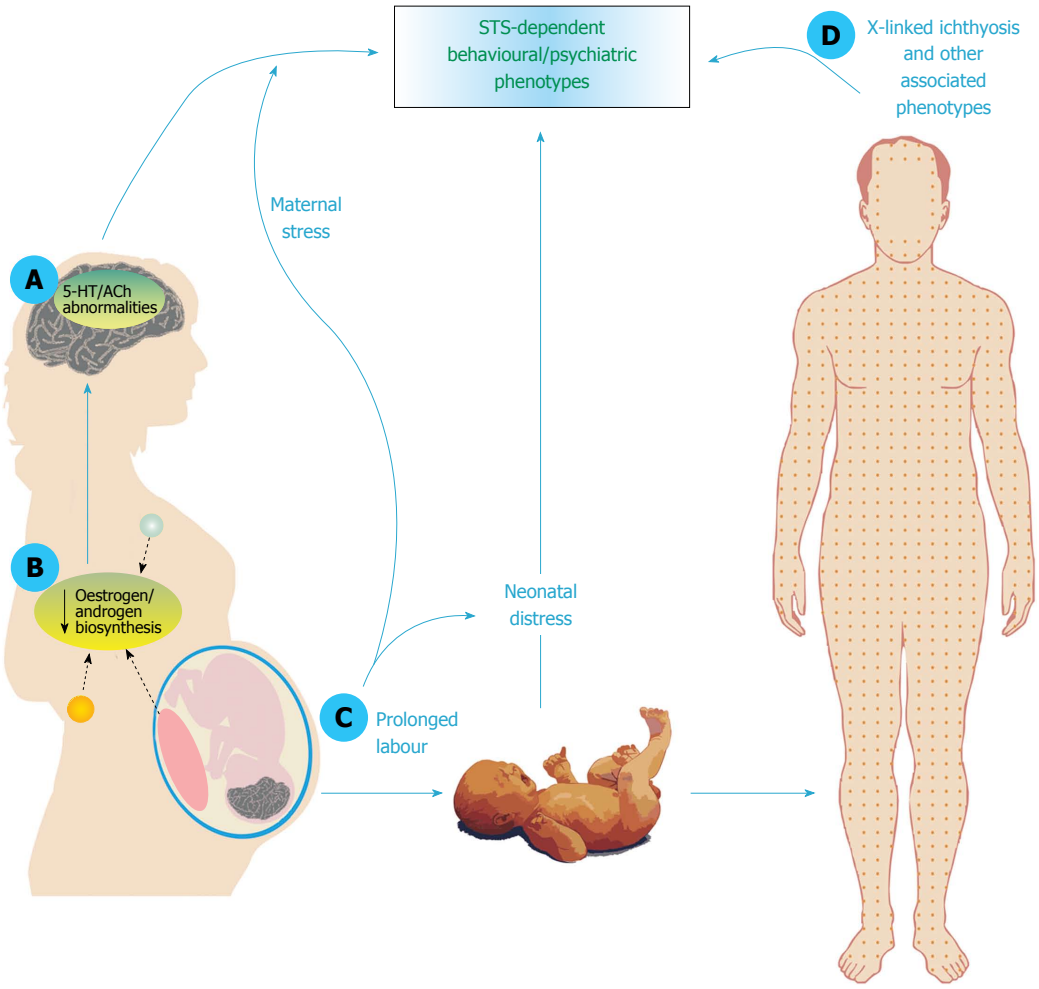

Figure 1 Mechanisms through which steroid sulfatase deficiency could theoretically influence neurobehavioural and psychiatric phenotypes. A: Loss of activity in the brain could directly influence neurodevelopment or ongoing function (*e.g., via* effects on the serotonergic or acetylcholinergic systems); B: Loss of activity in steroidogenic tissues (*e.g.,* placenta, ovaries, mamary gland) could affect neurodevelopment and brain function *via* effects on levels of circulating oestrogens and androgens; C: High levels of stress associated with prolonged labour (as a consequence of enzyme dysfunction in the fetal portion of the placenta) could both potentiate the development of postpartum illness in the mother, and could adversely affect neurodevelopment in the offspring; D: Living with potentially stigmatising conditions such as ichthyosis and male pattern baldness could feasibly increase the risk of developing disorders such as depression and anxiety. STS: Steroid sulfatase.

we propose that it would be worthwhile for patients with confirmed/suspected XLI to be asked by clinicians about any behavioural problems that they might have experienced, given that any link between dermatologic abnormalities and such difficulties may not be intuitive.

Should elevated rates of psychiatric illness be identified in enzyme-deficient individuals, it will be important to characterise their mechanistic basis *i.e.,* whether they are related to loss-of-function of the enzyme in the brain *per se*, to the pleiotropic, non-brain effects of protein dysfunction, or to both (Figure 1). STS deficiency could influence brain function and behaviour directly (*e.g.,* through modulating the serotonergic or acetylcholinergic systems). Alternatively, lack of enzyme expression in steroidogenic organs such as the placenta, gonads and mammary gland[108] could result in reduced levels of circulating steroid hormones (notably androgens and oestrogens) and subsequent downstream organisational and/or activational effects on brain development and function. Animals models in which STS function is perturbed will be of use in distinguishing between these two possibilities. Furthermore, it is conceivable that an increased risk of some psychiatric disorders (*e.g.,* depression and anxiety) could result from individuals having to live with potentially disfiguring somatic conditions associated with enzyme deficiency including ichthyosis[42], hypogenitalism[109], or male-pattern baldness[110]; in support of this notion, one study has shown that patients with ichthyosis have a lower health-related quality of life[111]. Finally, it is conceivable that STS deficiency in the offspring could both result in increased risk of psychiatric illness in that individual simply as a consequence of neonatal distress arising from prolonged maternal labour[112-114], and, by the same general stress-inducing mechanism, could increase risk of postpartum mental illness in the mother[115]. To determine whether these latter mechanisms may be important, comparison of rates of behavioural/psychiatric abnormalities in STS-deficient cases with those in subjects with other similar skin conditions for example, or exposed to other causes of prolonged labour, may be valuable.

An alternative strategy for determining the consequences of acutely impaired STS function may be to explicitly test for brain and behavioural alterations in subjects administered enzyme inhibitors. 667-COUMATE (Irosustat) has been proposed as a treatment for hormone-dependent cancers[116,117] and for endometriosis[118], conditions where biosynthesis of oestrogens and androgens must be restricted. Although no obvious psychological side-effects of 667-COUMATE treatment were reported in the first clinical trial of the drug in breast cancer patients[119], the animal data discussed above suggest that subtle effects on cognition (attention, impulsivity) and behaviour (aggression) might be anticipated. In assessing whether this is the case, potential confounding variables such as baseline rates of depression, age, or the potential behavioural effects of co-administered therapeutic drugs, in patients would have to be considered.

Finally, taking a conceptually different approach, it will be interesting to see whether subjects with cytogenetic duplications encompassing *STS* exhibit any clear brain or behavioural phenotypes. However, in most, if not all, of these cases, any data will be confounded by duplication of contiguous brain-expressed genes. To date, the small number of cases with Xp22.3 duplications reported in the literature either do not appear to exhibit any severe neuropsychological phenotypes[120], or present with relatively non-specific phenotypes such as learning disability and/or developmental delay[121] depending upon the size of the duplication.

Understanding if, and how, STS deficiency influences vulnerability to psychiatric illness will be important in terms of counselling for XLI (and potentially TS), and additionally may highlight novel therapeutically-amenable targets for common aspects of psychological dysfunction.

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