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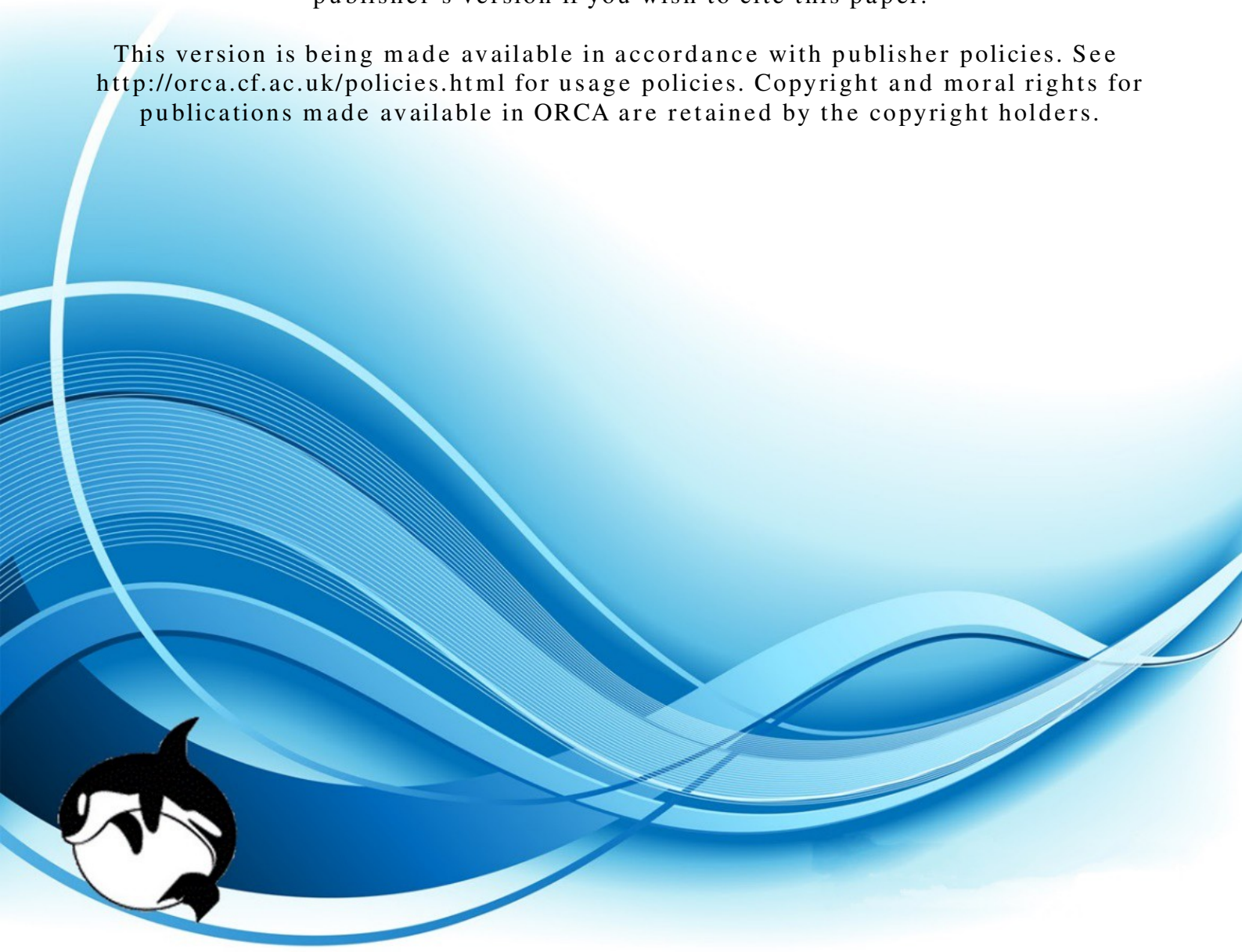

The steroid sulfate axis and its relationship to maternal behavior and mental health

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Abstract

Steroid hormones can exist in functionally-dissociable sulfated and non-sulfated (free) forms and can exert profound effects on numerous aspects of mammalian physiology; the ratio of free to sulfated steroids is governed by the antagonistic actions of steroid sulfatase (STS) and sulfotransferase (SULT) enzymes. Here, I examine evidence from human and animal model studies which suggests that STS and its major substrate (dehydroepiandrosterone sulfate, DHEAS) and product (DHEA) can influence brain function, behavior and mental health, before summarising how the activity of this axis varies throughout mammalian pregnancy and the postpartum period. I then consider how the steroid sulfate axis might impact upon normal maternal behavior and how its dysfunction might contribute towards risk of postpartum psychiatric illness. Understanding the biological substrates underlying normal and abnormal maternal behavior will be important for maximising the wellbeing of new mothers and their offspring.

Word count: 140

An introduction to the steroid sulfate axis

Steroid hormones are synthesised within a number of endocrine body tissues (notably the adrenal gland, gonadal, breast, adipose and liver tissue in primates), and, as well as being utilised locally, may subsequently transported elsewhere to elicit widespread physiological effects. The hydrophobicity of free steroids limits their ability to be transported within aqueous media; hence, transport of these compounds is faciliated by the addition of negatively-charged sulfate groups through esterification by the steroid sulfotransferase (SULT) enzymes SULT1E1, SULT2A1, or SULT2B1b, or, to a lesser extent, by SULT1A1 or SULT2B1a (Salman *et al.* 2011, Mueller *et al.* 2015). In addition to increasing the solubility of steroids, sulfation processes also increase their stability: circulating concentrations of sulfated steroids are typically substantially higher than circulating concentrations of their free steroid counterparts, and the former may act as 'reservoirs' for the peripheral formation of bioactive hormones (Mueller *et al.* 2015). Many common steroids can be sulfated including cholesterol, pregnenolone, estrone and dehydroepiandrosterone (DHEA) (Mueller *et al.* 2015).

Upon influx into cells in target tissues via organic anion transporter proteins, sulfated steroids are typically desulfated by hydrolysis to their unconjugated forms, which are generally considered to be more biologically-active and which can act as precursors for a variety of androgens and estrogens. Whilst multiple sulfotransferases can facilitate sulfation according to tissue-type, there is just one ubiquitous enzyme which cleaves sulfate groups from steroids: steroid sulfatase (STS, formerly known as arylsulfatase C). In the interests of clarity and brevity, in this review I focus upon the physiological roles of STS and dehydroepiandrosterone (DHEA), whose sulfated form (DHEAS) is the most abundant circulating steroid in humans (Neunzig & Bernhardt 2014).

Steroid sulfatase: its regulation, expression and function

Steroid sulfatase is encoded by the X-linked *STS* gene (Xp22.3). As the human *STS* gene escapes X-inactivation (Shapiro *et al.* 1979), and as its Y-linked paralogue is pseudogenic (Yen *et al.* 1988), expression of STS is 1-2fold higher in female than male tissues (including brain) during development and into adulthood, although whether this expression difference translates to significantly greater enzyme activity in female tissues is debatable (Cuevas-Covarrubias *et al.* 1993, Miranda-Duarte *et al.* 1999, Ugele & Regemann 2000, Nakamura *et al.* 2003, Steckelbroek *et al.* 2004, Kriz *et al.* 2008, HE O'Brien *et al.* manuscript in preparation); nevertheless, the possibility certainly exists that the physiological consequences of STS activity modulation could feasibly be more profound in women than in men. STS is expressed in a number of tissues many of which are involved in reproductive function, including: the placenta (highest expression), brain, ovary, mammary gland, testis, adipose tissue, thyroid gland and skin (Salido *et al.* 1990, Miki *et al.* 2002, Steckelbroek *et al.* 2004, Stergiakouli *et al.* 2011, https://www.ncbi.nlm.nih.gov/unigene accessed 12th September 2017).

At the cellular level, the STS protein is largely located in the endoplasmic reticulum of the cell where it functions as a glycosylated homodimer; the catalytic activity of STS is dependent upon the presence of sulfatase-modifying factors (SUMFs) (Mueller *et al.* 2015). STS activity appears to be increased in response to stress/inflammation in various tissues with the gene being a target of NF-κB; the resultant free steroid products, notably estrogens, may act as inflammation-suppressors (Dias & Selcer 2016, Jiang *et al.* 2016). STS has long been recognised as a therapeutic target in hormone-dependent cancers, and a number of effective and specific STS inhibitors have been developed which reduce the pool of androgens and estrogens in the vicinity of the cancer and which have potential clinical benefits (Purohit & Foster 2012).

The steroid sulfatase axis: its influence on brain function and behavior

Seminal work in rodents suggested that, in mammals, some steroids (and hence their sulfate conjugates) such as DHEA(S) could be synthesised *de novo* in the brain and may be regarded as neurosteroids (Corpechot *et al.* 1981). Subsequent work has shown that, whilst DHEA biosynthesis within the brain is possible, a second route by which DHEA appears in the brain in rodents (and feasibly humans too) is through the uptake, and subsequent rapid desulfation, of circulating DHEAS by organic ion transporters and steroid sulfatase respectively in the capillaries of the blood-brain barrier (Qaiser *et al.* 2017). Whilst the expression patterns of STS in the human blood-brain barrier have yet to be systematically assessed, in the developing human brain, *STS* is highly expressed throughout the thalamus with lower expression also seen in the olfactory epithelium, the cerebral cortex, the basal ganglia, the hypothalamus and pituitary gland, the choroid plexus and the cerebellar neuroepithelium (Stergiakouli *et al.* 2011); in adulthood, high levels of *STS* expression and associated enzyme activity persist in these regions (Perumal *et al.* 1973, Steckelbroeck *et al.* 2004, Kriz *et al.* 2008). Although STS activity in the brain is likely to have important and widespread developmental and ongoing effects (see later), sulfatase activity in this tissue is apparently dominated by sulfotransferase activity, and, in support of this idea, levels of sulfated steroids in the human brain (including those of DHEAS) may be relatively high (Maninger *et al.* 2009, Mueller *et al.* 2015).

At the molecular level, free and sulfated steroid hormones can modulate receptors influencing acute neuronal inhibition and excitation, as well as neurodevelopmental processes. For example, both DHEAS and pregnenolone sulfate act as antagonists at $GABA_A$ receptors, as agonists at σ receptors, and as positive modulators at N-methyl-D-aspartic acid (NMDA) receptors (Reed *et al.* 2005, Qaiser *et al.* 2017). Importantly, the sulfated and unconjugated steroids may have differential effects and potencies e.g. DHEA has been

reported to act as a weaker $GABA_A$ antagonist than DHEAS (Reed *et al.* 2005, Maninger *et al.* 2009). In addition to relatively weak agonistic effects at the androgen and estrogen receptors, DHEA and DHEAS may bind to, and activate, neurotrophin TrkA and $p75^{NTR}$ receptors to attenuate neuronal apoptosis and hence influence neurodevelopment (Lazaridis *et al.* 2011).

Insights into the behavioral and brain processes that are mediated by STS and DHEA(S), potentially via the aforementioned molecular mechanisms, can be obtained by examining phenotypes in individuals in which: a) the *STS* gene is rendered non-functional (by natural or experimental means), b) the STS enzyme is acutely inhibited by a selective drug, or c) DHEA(S) has been administered. Less convincingly, it is possible to investigate the extent to which (peripheral) levels of DHEA(S) correlate with brain/ behavioral phenotypes of interest, and hence the extent to which changes in the former may cause the latter.

In humans, *STS* deficiency (arising from partial or complete deletion of the gene, or inactivating point mutations within it) results in the rare dermatological condition X-linked ichthyosis (XLI) (Fernandes *et al.* 2010). XLI chiefly affects males, and is associated with an elevated DHEAS/DHEA serum ratio, especially pre-pubertally (Idkowiack *et al.* 2016). Whilst there is currently little published literature on brain structure/function and biochemistry in individuals with XLI (Trent & Davies 2013), there is an emerging literature suggesting that boys with the condition may be at increased risk of developmental disorders such as Autism Spectrum Conditions (ASCs), Attention Deficit Hyperactivity Disorder (ADHD), and early-onset psychotic disorders (Kent *et al.* 2008, Chatterjee *et al.* 2016, Malik *et al.* 2017) whilst men with the condition may be at increased risk of both developmental and mood (unipolar depression and bipolar) disorders (Chatterjee *et al.* 2016). There is also some evidence that genetic variation within *STS* is associated with measures of attention in both clinical (ADHD) (Brookes *et al.* 2010, Stergiakouli *et al.* 2011, Wang *et al.* 2017) and healthy (Humby *et al.* 2017)

149 populations. These behavioral findings are consistent with the high expression of STS in brain
150 regions involved in integrating and acting upon sensory information, and executive function.

151 Recapitulating the clinical findings in XLI, mice in which the *Sts* gene is deleted (or in
152 which the STS enzyme is inhibited) show significantly reduced levels of serum DHEA and
153 associated impairments in attention, altered response inhibition, hyperactivity, heightened
154 emotional reactivity and aggression, and increased levels of behavioral perseveration (Davies
155 *et al.* 2009, Trent *et al.* 2012b, Trent *et al.* 2013, Davies *et al.* 2014). Animal models allow the
156 neurochemistry underlying behavioral abnormalities to be studied. *Sts* deletion in mice is
157 associated with higher serotonin levels in the striatum and hippocampus (together with
158 elevated hippocampal expression of the serotonin receptor 2c (*Htr2c*) gene), and reduced
159 striatal noradrenaline turnover; the extent of serotonergic perturbation in *Sts*-deficient mice
160 seems to correlate with the severity of some behavioral phenotypes (Trent *et al.* 2012a).
161 Pharmacological studies in rats in which the STS enzyme was acutely inhibited have revealed
162 changes in hippocampal acetylcholinergic release together with parallel changes in memory
163 function (Rhodes *et al.* 1997, Babalola *et al.* 2012, Yue *et al.* 2016).

164 Experimental and correlational studies in animal models and human populations have
165 linked altered DHEA(S) levels to a diverse and important range of behavioral phenotypes
166 including: sexual function (Peixoto *et al.* 2017), aggression (Nicolas *et al.* 2001, Soma *et al.*
167 2015), locomotor activity (Strous *et al.* 2001, Trent *et al.* 2012b, Trent *et al.* 2013) and
168 numerous aspects of mood and cognition (including attention) (Rhodes *et al.* 1996, Davies *et*
169 *al.* 2009, Pluchino *et al.* 2015, Starka *et al.* 2015).

170 The data presented above establish that steroid sulfatase (and its dysfunction) can
171 impact extensively upon normal brain function via multiple neural and neurochemical
172 pathways; this action may be direct (i.e. within the brain itself), or, alternatively, may result

from extra-brain STS activity impacting upon the production and action of circulating levels of sulfated and free steroids including DHEA(S).

Changes in the steroid sulfate axis throughout mammalian pregnancy and the postpartum period

Throughout the childbearing process, women experience considerable hormonal fluctuations, including with regard to the steroid sulfate axis (Tal *et al.* 2000). However, longitudinal studies in which the levels, and sulfation status, of multiple hormones are measured across pregnancy and the postpartum period are scarce. Due to ethical and practical issues, most information in humans comes from analysis of peripheral tissues (blood, serum/ plasma, saliva and rarely cerebrospinal fluid) and therefore its relevance to the hormonal milieu experienced directly by the brain is questionable. Moreover, peripherally-detected maternal hormone levels may be influenced by multiple variable factors including: breastfeeding, stress exposure, use of recreational and therapeutic drugs, parity, maternal age and diet, and gender/number/size of the fetus(es), and understanding how unstable hormone levels relate to specific physiological phenotypes is therefore challenging. Whilst the use of neurobiologically-amenable mammalian animal models in which experimental variables can be controlled may circumvent these issues to some extent in *in vivo* systems, such models differ from humans in terms of both circulating hormone levels and reproductive traits such as number of offspring per pregnancy, or the extent and duration of postnatal maternal care; hence, extrapolating from models to man (or woman) should be done with caution.

In humans, from around nine weeks of pregnancy, a key role of the steroid sulfate axis is to generate precursors for the production of estrogens to be secreted into the maternal and fetal bloodstreams. Initially, sulfated C-19 steroids including DHEAS and 16α-OH-DHEAS

197 produced by the maternal and fetal adrenal glands and fetal liver must undergo hydrolyis in
198 the STS-rich syncytiotrophoblast of the placenta (Salido *et al.* 1990) before conversion by a
199 series of enzymatic reactions to estrogens including estrone, estriol and estradiol; estrone,
200 but not estradiol, is subsequently sulfated in the mother (Geyer *et al.* 2017).

201 As healthy pregnancies progress, there is a consistently-observed decrease in
202 maternal DHEAS serum levels from non-pregnancy levels (apparently independent of fetal
203 gender), perhaps as DHEAS is increasingly utilised for estrogen synthesis in the developing
204 placenta; after parturition, maternal serum DHEAS levels rapidly rebound to pre-pregnancy
205 levels (Tagawa *et al.* 2004, Soldin *et al.* 2005, Kuijper *et al.* 2013, Farrar *et al.* 2014). The data
206 regarding systemic maternal DHEA levels throughout pregnancy and the postpartum period
207 are less consistent. Some studies have demonstrated elevated serum/plasma DHEA levels
208 during early-mid pregnancy, with a subsequent gradual decline up to one year postpartum
209 (Nieschlag *et al.* 1974, Buckwalter *et al.* 1999, Tagawa *et al.* 2004); given DHEA's
210 immunosuppressive effects and an increase in maternal cytokine markers after childbirth, this
211 pattern of effects has been postulated to provide maximum protection for the incipient fetus
212 from maternal immune surveillance (Tagawa *et al.* 2004). Other studies have suggested that
213 peripheral DHEA levels are relatively unaffected by pregnancy and parturition (Buster *et al.*
214 1979, Soldin *et al.* 2005) or even that they increase across pregnancy and towards parturition
215 in peripheral tissues (saliva or plasma) (Bird *et al.* 1980, Hampson *et al.* 2013). If DHEAS levels
216 do fluctuate as outlined above during pregnancy/postpartum period, and DHEA levels remain
217 in a comparatively steady state, then the DHEA/DHEAS ratio would be expected to be high
218 during pregnancy and low during the postpartum period relative to values in non-pregnancy;
219 in healthy populations where this ratio has been assessed longitudinally, this pattern of
220 effects is indeed observed (Hill *et al.* 2002, Tagawa *et al.* 2004).

Presumably the above changes in DHEA/DHEAS ratio over the course of pregnancy and the postpartum period are related to the relative abundance and/or activity of the steroid sulfatase and sulfotransferase enzymes in cells contributing towards the hormonal milieu of the periphery. A main contributor to this ratio is the syncytiotrophoblast cells of the placenta, and expulsion of the STS-rich placenta after birth likely explains the rapid restoration of circulating maternal DHEAS levels. However, other tissues may also contribute: in healthy women, STS activity in leukocytes has been reported to be greater in third trimester pregnant women than in first trimester pregnant, or non-pregnant, women (Miyakawa *et al.* 1994), a finding consistent with the observed high DHEA/DHEAS ratio during late pregnancy. To the best of my knowledge, there has not yet been any systematic analysis of peripheral (leukocyte) STS activity throughout the postpartum period in humans.

Peripheral levels of sulfated and free steroids cannot provide reliable information on the activity of steroid sulfatase in the brain, and direct measurement of brain STS activity throughout pregnancy and the postpartum period in humans is currently unachievable. However, animal models, such as rodents, might provide some insights into human physiology (bearing in mind the caveats discussed above with respect to cross-species extrapolation). Mortaud and colleagues (1996) showed that, in whole female mouse brain, STS protein levels were more than two-fold higher in the lactating (postpartum) state relative to the pregnant (stage not specified) or non-pregnant state; whether this increase in protein level corresponded to an increase in enzyme activity in this state, or with brain DHEA(S) levels, was not assessed. Conversely, in rats, neither STS brain activity nor sulfotransferase liver activity appear to be affected by pregnancy or parturition although only cortical (as opposed to whole) brain tissue was analysed (Maayan *et al.* 2004a). Interestingly, data on STS activity in rat leukocytes partially resemble those seen in humans, in that activity is significantly higher

in late-pregnancy animals (18 days post conception) than in non-pregnant animals, and activity becoming even more pronounced 24hrs after giving birth (Maayan *et al.* 2004a). In rat serum and brain cortex, the DHEA/DHEAS ratio is significantly, and equivalently, elevated in late pregnancy and early postpartum animals compared to non-pregnant control females (Maayan *et al.* 2004a).

In summary, the sparse human and rodent data presented above are reconcilable with the proposal that in non-cortical regions of the mammalian brain, and in certain cells of the immune system, STS levels/activity increase over the course of pregnancy before peaking during late pregnancy and into the early postpartum period.

A possible role for the steroid sulfate axis in normal maternal behavior

Androgen-related metabolic pathways, including the STS/DHEA(S) axis, are known to modulate physiological processes asociated with parturition (Makieva *et al.* 2014). Given the previously-described role of the steroid sulfatase axis in brain and behavioral function, its increased activity in the perinatal period may be related to, and potentially be causal for, the emergence of maternal behaviors designed to nourish and protect their offspring. These behaviors, many of which are highly-conserved across mammalian species, include: nest-building, huddling, nursing and social interaction with the offspring mediated by olfactory, visual, auditory and somatosensory cues, altered (generally decreased) levels of anxiety with increased exploratory behavior, and aggression directed towards threatening predators/society members but not offspring (Bridges 2015, Lonstein *et al.* 2015). In rodents, and probably also in humans, the quality and intensity of expressed maternal behaviors is related to maternal cognitive (executive) function, particularly in the domains of offspring-related learning and memory processes, attention to relevant care cues, behavioral flexibility and impulse regulation; interestingly, in rats, reduced maternal behavior is associated with

impaired performance on attentional set-shifting and startle/prepulse inhibition tasks, whilst increased maternal care (pup-licking) is related to reduced motor impulsivity (Lonstein *et al.* 2015). In non-primate species, and in primates to a lesser extent, these behaviors are driven by hormonal mechanisms acting via a multitude of brain regions and neurochemical systems, including the prefrontal cortex, the amygdala, the cholinergic basal forebrain activating system and the GABAergic and serotonergic systems (Bridges 2015, Lonstein *et al.* 2015). The fact that manipulation of the STS axis in males affects many of the cognitive/behavioral phenotypes and neurobiological systems listed above (notably attention, social interaction, emotional reactivity, aggression, memory, behavioral flexibility and motor impulsivity (Mortaud *et al.* 1996, Rhodes *et al.* 1997, Kent *et al.* 2008, Davies *et al.* 2009, Trent et al., 2012a,2012b, Trent *et al.* 2013, Davies *et al.* 2014, Chatterjee *et al.* 2016)) supports the argument that the STS axis influences neural processes pertinent to maternal care efficacy in females. To explicitly test the idea that the STS axis influences maternal perinatal behavior, studies will need to be undertaken in non-pregnant (control), pregnant and postpartum female animal models and human subjects in which STS activity is compromised, or in which DHEA(S) levels are systematically varied and assayed.

To date, the only available *Sts*-deficient genetic rodent models have been chromosomally-mutant mice that are necessarily male (Trent *et al.* 2012b), but new gene editing technology should hopefully allow the generation of *Sts*-deficient female rodents (Baud & Flint 2017). The expectation that such genetically-modified female rodents may exhibit STS-dependent abnormal maternal behaviors has been raised by a recent pharmacological study in our laboratory. Briefly, we showed that acute inhibition of STS in new mouse mothers resulted in anxiety-related phenotypes (a reduced startle response, and increased rearing and exploratory drive on the elevated plus maze), but no gross

293 abnormalities in nest maintenance or in mother-pup interactions (Humby *et al.* 2016). At this
294 stage, we cannot discount the fact that there were subtle, undetectable, irregularities in dam-
295 pup interactions, especially in light of the fact that inhibitor-treated mothers exhibit
296 substantial dysregulation of olfactory-related gene expression in the brain (W Davies,
297 unpublished results). Furthermore, as we did not examine the behavioral effects of acute STS
298 inhibition in female mice with other physiological statuses (virgin, non-virgin but non-
299 pregnant, and pregnant), we cannot definitively say that the behavioral effects mediated by
300 the STS axis are specific to the postpartum period; this extended analysis is ongoing. We are
301 currently undertaking a parallel systematic study of behavior, including perinatal behavior, in
302 STS-deficient women with a view to determining which, if any, psychological processes are
303 affected by their genetic mutation.

304 Additional evidence that DHEA(S) participate in normal perinatal maternal behaviors
305 in humans may be obtained by showing behavioral effects elicited by administration to new
306 mothers, or through identifying significant correlations between systemic DHEA(S) levels and
307 behavioral/cognitive measures in healthy (or general population) postpartum mothers.
308 Although DHEAS administration has been performed in postpartum women (e.g. Aisaka *et al.*
309 1984) there is no reliable published data available regarding parallel behavioral changes. In
310 healthy women selected from the general population, there is some evidence for an
311 association between higher serum DHEA levels, enhanced mood and aspects of better
312 cognitive performance during late pregnancy (~20 days prior to delivery) and the postpartum
313 period (~26 days after delivery) (Buckwalter *et al.* 1999), although no similar relationship
314 seems to exist for DHEAS levels (Farrar *et al.* 2014).

315

316

Postpartum psychiatric disorders

A significant proportion of women experience mental health issues manifesting in late pregnancy and/or in the postpartum period. These can range from relatively common and comparatively mild conditions which do not require medical intervention (so-called 'baby blues') to rarer, more severe, persistent and disabling disorders which require urgent medical care; the latter category of disorders includes postpartum depression, obsessive-compulsive disorder and anxiety disorders (Sharma & Sommerdyk 2015, Stewart & Vigod 2016, Pawluski *et al.* 2017). If the steroid sulfate axis is indeed a major player in maternal brain and behavioral function in late pregnancy and the postpartum period as has been argued above, then, logically, its dysfunction might reasonably be considered a risk factor for vulnerability to maternal mental health conditions in this period. In the following section, I discuss the nature and aetiology of one extremely severe and poorly-understood psychiatric disorder associated with childbirth, postpartum (or puerperal) psychosis, and consider evidence implicating steroid sulfate axis abnormalities in its pathogenesis.

The nature and etiology of postpartum psychosis

Postpartum psychosis (PP) is estimated to affect 1-2 in every 1000 new mothers (VanderKruik *et al.* 2017). Symptoms associated with the condition include hallucinations, delusions (often related to the newborn child), cognitive disorganisation, anxiety, and mood abnormalities, and these tend to present within the first two weeks (and frequently within the first few days) of childbirth; PP symptoms can impact massively upon normal mother-child bonding and family life, and affected mothers are at elevated risk of commiting suicide or infanticide (Bergink *et al.* 2016). Whilst there is thought to be a considerable biological component to disorder vulnerability, the exact nature and contribution of underlying biological risk factors is currently obscure (Jones *et al.* 2014, Bergink *et al.* 2016). Understanding these may help to

develop better predictive biomarkers for the condition, as well as more effective and safer treatment options (Davies 2017). Epidemiological data has suggested considerable overlap with bipolar disorder, autoimmune thyroid conditions, and pre-eclampsia (Jones *et al.* 2014, Bergink *et al.* 2016); other studies have implicated an abnormal (over-active) immune system (Bergink *et al.* 2013, Kumar *et al.* 2017), autoimmune anti-NMDA receptor encephalitis (Bergink *et al.* 2015), and serotonergic system dysfunction (Kumar *et al.* 2007, Davies 2017) in risk. A genetic linkage study in bipolar postpartum psychosis implicated significant and suggestive loci at 16p13 and 8q24 respectively (Jones *et al.* 2007), but, to date, findings from small-scale (and therefore underpowered) candidate gene and genome-wide association studies have been unconvincing or non-significant, and none have yet implicated X-linked genetic risk variants.

Steroid sulfate axis dysfunction and postpartum psychosis risk

There are several lines of basic and clinical evidence suggesting that abnormalities with the steroid sulfate axis (and most likely steroid sulfatase deficiency (Davies 2012)) may influence PP risk: a) the axis appears to exert disproportionately large effects in the late pregnancy/early postpartum period, so any disruption to it may impact relatively specifically on this timepoint, b) estrogens are generally thought to be protective against psychosis (Reicher-Rossler 2017) and STS deficiency, in women, as in men (Lykkesfeldt *et al.* 1985), is expected to result in lower levels of circulating estrogens as a consequence of reduced levels of DHEA precursor, c) genetic deletions encompassing *STS* have been associated with psychotic disorders (paranoid and early-onset schizophrenia) in case studies (Milunsky *et al.* 1999, Malik *et al.* 2017), d) STS brain expression is high in regions previously implicated in psychotic disorders (Fusar-Poli *et al.* 2011, Dietsche *et al.* 2017), e) the neurochemical abnormalities associated with psychosis and remediable by antipsychotic treatment overlap

considerably with those influenced by STS and DHEA(S) i.e. of the serotonergic system (notably the 5-HT_{2C} receptor)(Meltzer *et al.* 2012, Selvaraj *et al.* 2014), the hippocampal cholinergic system (Olincy & Freedman 2012, Carruthers *et al.* 2015), the $GABA_A$ system (Egerton *et al.* 2017), and of NMDA receptor signalling (notably in the thalamus)(Vukadinovic 2014, Harrison 2015), f) STS-deficient humans and mice exhibit a range of PP-relevant phenotypes including inattention and emotional instability, whilst genetic variants within *STS* in man are associated with cognitive disorganisation (see above), g) STS is highly-expressed in the hypothalamus, pituitary gland and the thyroid gland (Stergiakouli *et al.* 2011) and its absence in these tissues could potentially explain high rates of hypothalamus-pituitary-thyroid axis dysfunction and autoimmune thyroid dysfunction in PP, h) abnormal placental and whole blood STS expression is associated with pre-eclampsia (Gratton *et al.* 2016), i) levels of salivary DHEAS during late pregnancy and in the early postpartum period (10 days after birth) positively correlate with measures of anxiety, phobia, paranoia and psychoticism in previously-healthy women, with highest DHEAS levels (consistent with impaired or absent STS activity) being associated with significant psychiatric distress (Marrs *et al.* 2009, Marrs *et al.* 2010), j) lithium, an established effective treatment for mania in bipolar disorder and PP, enhances the serum DHEA/DHEAS ratio in rats consistent with a stimulatory effect on STS, whilst reducing both brain and serum levels of DHEAS (Maayan *et al.* 2004b), k) pathologically-reduced levels of immunosuppressive DHEA in the postpartum period as a consequence of STS deficiency may feasibly contribute towards the immune hyper-activation seen in PP and l) *STS* and the *HTR2C* (5-HT_{2C}) gene lie under candidate quantitative trait loci linkage peaks in a porcine model of PP (Quilter *et al.* 2007). Finally, the prevalence of STS deficiency i.e. heterozygosity or homozygosity for null mutations in women is estimated to be ~1 in 950 individuals (based upon the general population frequency of STS deficiency in males (Langlois

389 *et al.* 2009, Craig *et al.* 2010) and *de novo* versus inherited mutation rates (Cuevas-
390 Covarrubias *et al.* 1999)); this rate is consistent with it being a risk factor for PP, although
391 clearly, as for most mood and psychotic disorders, multiple interacting genetic and
392 environmental risk factors are likely to influence overall PP vulnerability.

393 Future analyses, in STS-deficient women or in *Sts*-deficient female rodents, are likely
394 to provide evidence for or against the hypothesis that this molecular perturbation increases
395 PP risk, although such studies will likely be limited by available sample size, by the infrequency
396 of the condition, and by cross-species extrapolation issues. Further studies in healthy women
397 in late pregnancy and the postpartum period, which will be less constrained by sample size,
398 might examine if, and how, peripheral steroid sulfatase activity (in addition to DHEA(S) levels)
399 correlate with dimensional behavioral measures related to PP (e.g. psychoticism). Alternative
400 complementary work in clinical PP populations might investigate: a) variability within the *STS*
401 gene (where rates of causal polymorphisms/mutations might be expected to differ from
402 control women), b) STS activity in accessible tissues such as leukocytes (lower activity
403 anticipated in women affected by PP than in controls) or c) peripheral baseline and stress-
404 evoked levels of DHEA(S)(higher DHEAS/DHEA ratios expected in affected women versus
405 control subjects).

406 Our mouse studies have provided preliminary evidence somewhat supportive of the
407 notion of STS deficiency as a risk factor for PP. Briefly, we found that the behavioral
408 phenotypes elicited by STS inhibition in new mothers could be partially reversed by
409 administration of the clinically-efficacious antipsychotic drug ziprasidone, thus indicating
410 their potential relevance to PP (Humby *et al.* 2016). Additionally, and intriguingly, STS-
411 inhibited mice demonstrated abnormal gene expression within a small region of chromosome
412 15 (equivalent to the 8q24 candiate genomic region implicated by linkage in PP), which could

413 also be normalised by ziprasidone administration, providing further support for the model's
414 face and predictive validity and thus its utility for understanding the mechanistic basis of PP
415 risk (Humby *et al.* 2016).

416 **Steroid sulfate axis dysfunction in other postpartum psychiatric disorders**

417 Postpartum psychosis is an umbrella term covering a wide variety of behavioral and
418 psychiatric symptoms, in addition to psychosis, that present shortly after childbirth. Many of
419 these symptoms (which can include depressive and manic episodes, anxiety and obsessive-
420 compulsive tendencies) may also be seen, to varying extents, in cases of other differentially-
421 defined postpartum psychiatric conditions such as postpartum depression, and could be
422 underpinned by common biological processes. Much of the logic implicating steroid sulfate
423 axis dysfunction in general, and STS deficiency in particular, in PP pathophysiology may be
424 equally applied to these alternative disorders, especially considering that their occurrence
425 may, in part, be due to abnormalities in physiological and neurochemical systems affected by
426 this axis i.e. steroid hormone levels, the hypothalamic-pituitary-adrenal axis, the thyroid
427 system, markers of inflammation and the GABAergic, noradrenergic and serotonergic systems
428 (Speisman *et al.* 2011, Skalkidou *et al.* 2012, Pawluski *et al.* 2017). The observed effects of STS
429 deficiency on mood modulation (Chatterjee *et al.* 2016), behavioral (in)flexibility (Trent *et al.*
430 2013) and anxiety-related processes (Trent *et al.* 2012b, Chatterjee *et al.* 2016) implicate it as
431 a candidate risk factor in postpartum depression, OCD, and anxiety respectively. The steroid
432 sulfate axis could also feasibly mediate the effects of environmental factors (e.g. stressors
433 such as childhood maltreatment) on mothers' vulnerability to a range of postpartum
434 psychiatric illnesses, and potentially even on their infants health (Sexton *et al.* 2015, Schury
435 *et al.* 2017).

436

Evidence examining rates of these various postpartum psychiatric conditions and associated behavioral and physiological markers remains to be collected in STS-deficient individuals and animal models; conversely, rates of STS deficiency remain to be determined in patients ascertained on the basis of having been diagnosed with such postpartum conditions. However, there is some limited existing data, consistent with the STS deficiency risk hypothesis, suggesting that circulating maternal DHEA plasma levels may be abnormally low prior to, and during the onset of, postpartum depression (Gelman *et al.* 2015), and that DHEA supplementation can benefit mood in depressed individuals (although consistent therapeutic benefits of this intervention in the postpartum period have yet to demonstrated)(Soares & Phillips 2006, Peixoto *et al.* 2014).

Conclusions and future work

Above I have discussed the mounting evidence (admittedly mainly obtained in male test subjects to date) that steroid sulfatase, and the reactions it catalyses, have important roles in a wide variety of important brain and behavioral functions. As the activity of the STS axis fluctuates across numerous tissues (including brain) during pregnancy, and into the postpartum period, it is conceivable that this axis bears upon normal maternal behavioral phenotypes and its influence in this respect remains to be tested using genetic and pharmacological approaches in clinical and model populations. In particular, gene expression changes elicited by manipulations of the steroid sulfate axis may be compared against those seen in the healthy postpartum maternal brain (Gammie *et al.* 2016). It also follows that, potentially, STS axis dysfunction may be associated with postpartum psychiatric conditions, and there is some circumstantial evidence, notably in postpartum psychosis, that this may be the case. Genetic and endocrine analyses in women previously affected by, or at high of

developing, postpartum psychiatric conditions should be able to experimentally test this hypothesis.

Of course, whilst I have focussed upon the possible impact of STS and DHEA(S) on maternal behavior here, it is naïve to think that these molecules act in isolation to affect this phenotype. As such, future studies should aim to supplement the currently available, very limited, data relating to the brain and peripheral expression and activity of enzymes and compounds involved in DHEA(S) biosynthesis and metabolism (notably the SULTs and SUMFs) across pregnancy and the postpartum period in healthy women, women affected by postpartum psychiatric illness, and relevant mammalian animal models, with a view to understanding how these components interact to generate healthy or abnormal behaviours. Work in model systems in particular may highlight molecules and pathways which mediate the behavioral effects of the steroid sulfate axis, and which could theoretically comprise novel therapeutic targets. For example, our nascent mouse work has implicated the CCN family of proteins as potentially-druggable targets in cases of PP (Davies, 2017). Pharmacological or genetic targeting of such mediators might result in lower levels of side-effects compared to the systemic administration of compounds such as DHEA or estrogens which have androgenic/estrogenic potential and which elicit widespread effects on multiple physiological systems (Gentile 2005, Rutkowski *et al.* 2014).

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