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1        **The steroid sulfate axis and its relationship to maternal behavior**  
2  
3                                    **and mental health**

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**27 Abstract**

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

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**41 Word count: 140**

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### 53 **An introduction to the steroid sulfate axis**

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

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

76

## 77 **Steroid sulfatase: its regulation, expression and function**

78 Steroid sulfatase is encoded by the X-linked *STS* gene (Xp22.3). As the human *STS* gene  
79 escapes X-inactivation (Shapiro *et al.* 1979), and as its Y-linked paralogue is pseudogenic (Yen  
80 *et al.* 1988), expression of *STS* is 1-2fold higher in female than male tissues (including brain)  
81 during development and into adulthood, although whether this expression difference  
82 translates to significantly greater enzyme activity in female tissues is debatable (Cuevas-  
83 Covarrubias *et al.* 1993, Miranda-Duarte *et al.* 1999, Ugele & Regemann 2000, Nakamura *et*  
84 *al.* 2003, Steckelbroek *et al.* 2004, Kriz *et al.* 2008, HE O'Brien *et al.* manuscript in preparation);  
85 nevertheless, the possibility certainly exists that the physiological consequences of *STS*  
86 activity modulation could feasibly be more profound in women than in men. *STS* is expressed  
87 in a number of tissues many of which are involved in reproductive function, including: the  
88 placenta (highest expression), brain, ovary, mammary gland, testis, adipose tissue, thyroid  
89 gland and skin (Salido *et al.* 1990, Miki *et al.* 2002, Steckelbroek *et al.* 2004, Stergiakouli *et al.*  
90 2011, <https://www.ncbi.nlm.nih.gov/unigene> accessed 12<sup>th</sup> September 2017).

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

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

102 Seminal work in rodents suggested that, in mammals, some steroids (and hence their sulfate  
103 conjugates) such as DHEA(S) could be synthesised *de novo* in the brain and may be regarded  
104 as neurosteroids (Corpechot *et al.* 1981). Subsequent work has shown that, whilst DHEA  
105 biosynthesis within the brain is possible, a second route by which DHEA appears in the brain  
106 in rodents (and feasibly humans too) is through the uptake, and subsequent rapid desulfation,  
107 of circulating DHEAS by organic ion transporters and steroid sulfatase respectively in the  
108 capillaries of the blood-brain barrier (Qaiser *et al.* 2017). Whilst the expression patterns of  
109 STS in the human blood-brain barrier have yet to be systematically assessed, in the developing  
110 human brain, *STS* is highly expressed throughout the thalamus with lower expression also  
111 seen in the olfactory epithelium, the cerebral cortex, the basal ganglia, the hypothalamus and  
112 pituitary gland, the choroid plexus and the cerebellar neuroepithelium (Stergiakouli *et al.*  
113 2011); in adulthood, high levels of *STS* expression and associated enzyme activity persist in  
114 these regions (Perumal *et al.* 1973, Steckelbroeck *et al.* 2004, Kriz *et al.* 2008). Although *STS*  
115 activity in the brain is likely to have important and widespread developmental and ongoing  
116 effects (see later), sulfatase activity in this tissue is apparently dominated by sulfotransferase  
117 activity, and, in support of this idea, levels of sulfated steroids in the human brain (including  
118 those of DHEAS) may be relatively high (Maninger *et al.* 2009, Mueller *et al.* 2015).

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

125 reported to act as a weaker GABA<sub>A</sub> antagonist than DHEAS (Reed *et al.* 2005, Maninger *et al.*  
126 2009). In addition to relatively weak agonistic effects at the androgen and estrogen receptors,  
127 DHEA and DHEAS may bind to, and activate, neurotrophin TrkA and p75<sup>NTR</sup> receptors to  
128 attenuate neuronal apoptosis and hence influence neurodevelopment (Lazaridis *et al.* 2011).

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

136       In humans, *STS* deficiency (arising from partial or complete deletion of the gene, or  
137 inactivating point mutations within it) results in the rare dermatological condition X-linked  
138 ichthyosis (XLI) (Fernandes *et al.* 2010). XLI chiefly affects males, and is associated with an  
139 elevated DHEAS/DHEA serum ratio, especially pre-pubertally (Idkowiack *et al.* 2016). Whilst  
140 there is currently little published literature on brain structure/function and biochemistry in  
141 individuals with XLI (Trent & Davies 2013), there is an emerging literature suggesting that boys  
142 with the condition may be at increased risk of developmental disorders such as Autism  
143 Spectrum Conditions (ASCs), Attention Deficit Hyperactivity Disorder (ADHD), and early-onset  
144 psychotic disorders (Kent *et al.* 2008, Chatterjee *et al.* 2016, Malik *et al.* 2017) whilst men with  
145 the condition may be at increased risk of both developmental and mood (unipolar depression  
146 and bipolar) disorders (Chatterjee *et al.* 2016). There is also some evidence that genetic  
147 variation within *STS* is associated with measures of attention in both clinical (ADHD) (Brookes  
148 *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



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

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

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

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

197 produced by the maternal and fetal adrenal glands and fetal liver must undergo hydrolysis 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).

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

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

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

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

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

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

269 impaired performance on attentional set-shifting and startle/prepulse inhibition tasks, whilst  
270 increased maternal care (pup-licking) is related to reduced motor impulsivity (Lonstein *et al.*  
271 2015). In non-primate species, and in primates to a lesser extent, these behaviors are driven  
272 by hormonal mechanisms acting via a multitude of brain regions and neurochemical systems,  
273 including the prefrontal cortex, the amygdala, the cholinergic basal forebrain activating  
274 system and the GABAergic and serotonergic systems (Bridges 2015, Lonstein *et al.* 2015). The  
275 fact that manipulation of the STS axis in males affects many of the cognitive/behavioral  
276 phenotypes and neurobiological systems listed above (notably attention, social interaction,  
277 emotional reactivity, aggression, memory, behavioral flexibility and motor impulsivity  
278 (Mortaud *et al.* 1996, Rhodes *et al.* 1997, Kent *et al.* 2008, Davies *et al.* 2009, Trent *et al.*,  
279 2012a,2012b, Trent *et al.* 2013, Davies *et al.* 2014, Chatterjee *et al.* 2016)) supports the  
280 argument that the STS axis influences neural processes pertinent to maternal care efficacy in  
281 females. To explicitly test the idea that the STS axis influences maternal perinatal behavior,  
282 studies will need to be undertaken in non-pregnant (control), pregnant and postpartum  
283 female animal models and human subjects in which STS activity is compromised, or in which  
284 DHEA(S) levels are systematically varied and assayed.

285         To date, the only available *Sts*-deficient genetic rodent models have been  
286 chromosomally-mutant mice that are necessarily male (Trent *et al.* 2012b), but new gene  
287 editing technology should hopefully allow the generation of *Sts*-deficient female rodents  
288 (Baud & Flint 2017). The expectation that such genetically-modified female rodents may  
289 exhibit STS-dependent abnormal maternal behaviors has been raised by a recent  
290 pharmacological study in our laboratory. Briefly, we showed that acute inhibition of STS in  
291 new mouse mothers resulted in anxiety-related phenotypes (a reduced startle response, and  
292 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

### 317 **Postpartum psychiatric disorders**

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

### 331 **The nature and etiology of postpartum psychosis**

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

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

#### 352 **Steroid sulfate axis dysfunction and postpartum psychosis risk**

353 There are several lines of basic and clinical evidence suggesting that abnormalities with the  
354 steroid sulfate axis (and most likely steroid sulfatase deficiency (Davies 2012)) may influence  
355 PP risk: a) the axis appears to exert disproportionately large effects in the late  
356 pregnancy/early postpartum period, so any disruption to it may impact relatively specifically  
357 on this timepoint, b) estrogens are generally thought to be protective against psychosis  
358 (Reicher-Rossler 2017) and STS deficiency, in women, as in men (Lykkesfeldt *et al.* 1985), is  
359 expected to result in lower levels of circulating estrogens as a consequence of reduced levels  
360 of DHEA precursor, c) genetic deletions encompassing *STS* have been associated with  
361 psychotic disorders (paranoid and early-onset schizophrenia) in case studies (Milunsky *et al.*  
362 1999, Malik *et al.* 2017), d) *STS* brain expression is high in regions previously implicated in  
363 psychotic disorders (Fusar-Poli *et al.* 2011, Dietsche *et al.* 2017), e) the neurochemical  
364 abnormalities associated with psychosis and remediable by antipsychotic treatment overlap



365 considerably with those influenced by STS and DHEA(S) i.e. of the serotonergic system  
366 (notably the 5-HT<sub>2c</sub> receptor)(Meltzer *et al.* 2012, Selvaraj *et al.* 2014), the hippocampal  
367 cholinergic system (Olincy & Freedman 2012, Carruthers *et al.* 2015), the GABA<sub>A</sub> system  
368 (Egerton *et al.* 2017), and of NMDA receptor signalling (notably in the thalamus)(Vukadinovic  
369 2014, Harrison 2015), f) STS-deficient humans and mice exhibit a range of PP-relevant  
370 phenotypes including inattention and emotional instability, whilst genetic variants within *STS*  
371 in man are associated with cognitive disorganisation (see above), g) STS is highly-expressed in  
372 the hypothalamus, pituitary gland and the thyroid gland (Stergiakouli *et al.* 2011) and its  
373 absence in these tissues could potentially explain high rates of hypothalamus-pituitary-  
374 thyroid axis dysfunction and autoimmune thyroid dysfunction in PP, h) abnormal placental  
375 and whole blood STS expression is associated with pre-eclampsia (Gratton *et al.* 2016), i)  
376 levels of salivary DHEAS during late pregnancy and in the early postpartum period (10 days  
377 after birth) positively correlate with measures of anxiety, phobia, paranoia and psychoticism  
378 in previously-healthy women, with highest DHEAS levels (consistent with impaired or absent  
379 STS activity) being associated with significant psychiatric distress (Marrs *et al.* 2009, Marrs *et*  
380 *al.* 2010), j) lithium, an established effective treatment for mania in bipolar disorder and PP,  
381 enhances the serum DHEA/DHEAS ratio in rats consistent with a stimulatory effect on STS,  
382 whilst reducing both brain and serum levels of DHEAS (Maayan *et al.* 2004b), k) pathologically-  
383 reduced levels of immunosuppressive DHEA in the postpartum period as a consequence of  
384 STS deficiency may feasibly contribute towards the immune hyper-activation seen in PP and  
385 l) *STS* and the *HTR2C* (5-HT<sub>2c</sub>) gene lie under candidate quantitative trait loci linkage peaks in  
386 a porcine model of PP (Quilter *et al.* 2007). Finally, the prevalence of STS deficiency i.e.  
387 heterozygosity or homozygosity for null mutations in women is estimated to be ~1 in 950  
388 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 candidate 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

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

#### 447 **Conclusions and future work**

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

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

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

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**485 Declaration of interest**

486 There is no conflict of interest that could be perceived as prejudicing the impartiality of this  
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