Assessing gonadal hormone contributions to affective psychopathologies across humans and animal models

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Abstract

Despite increasing acknowledgement of hormonal contributions to mood and anxiety disorders, the underlying mechanisms by which gonadal hormones influence psychopathology-related behaviours remain unknown. This review focuses on recent research that examines the influence of gonadal steroid hormones, including androgens, estrogens, and progesterone, on mood and anxiety-related behaviours in human health and disease. To this aim, the literature was surveyed for studies that assess conditions with suspected underlying hormonal imbalances in otherwise healthy participants (e.g., Premenstrual Dysphoric Disorder, Postmenopausal Depression,) as well as conditions linked to congenital endocrine abormalities (e.g., Turner Syndrome, Klinefelter Syndrome, Polycystic Ovary Syndrome, Congenital Adrenal Hyperplasia, Familial Male Precocious Puberty, Androgen Insensitivity Syndrome). Furthermore, to better inform clinical work and to create a translational bridge, a second goal was to set human psychopathologies and animal models of these conditions side-by-side. In the second part of the review, based on consistencies revealed in the existing literature across conditions, a new model for the impact of gonadal hormones on anxious and depressed behavioural states is proposed. Finally, we conclude by proposing directions for future research, including the development of specific tasks suitable for cross-species comparisons to increase our knowledge of the role of gonadal hormones in mood and anxiety.

Keywords: anxiety; depression; mood disorder; sex steroids; translational; testosterone; estradiol

"The creatures outside looked from pig to man, and from man to pig, and from pig to man again; but already it was impossible to say which was which."

— George Orwell, *Animal Farm*

Introduction

The clinical picture of hormonal dysfunction of the gonads (hyper- or hypogonadism) is frequently accompanied by some presentation of psychopathology, most notably in forms of anxiety and/or depression. Awareness of comorbid psychopathology is important for the clinical care and management of affected individuals, but it may also provide valuable information on the fundamental contributions of gonadal hormones, specifically androgens, estrogens, and progesterone, to affective cognition. Conversely, some manifestations of mood disorders, such as premenstrual dysphoric disorder or postmenopausal depression have been intimately linked to underlying imbalances of the hormonal milieu. While research on basic cognitive-affective processes in human endocrine conditions is slowly increasing (Mueller, 2013), parallel research employing animal models indicates important relationships between gonadal dysfunction and the presentation of anxiety-like and depressive-like behaviours in non-human species (ter Horst et al., 2012). Surprisingly, few attempts to reconcile how human and animal literatures can inform one another have been made despite the possibility that findings obtained in one species may provide insights into the basic mechanisms that are better addressed in the other species. Such cross-species comparisons and validation of animal models are essential when aiming to develop effective therapeutic and/or pharmacological interventions for various disorders.

This review focuses on recent developments of affective processing in humans suffering from perturbations of gonadal hormones and corresponding models in non-human species, particularly rodents. As will be shown, these conditions may serve as an essential intermediary between behavioural neuroscience in animal models and basic neuroscience in human populations. To limit its scope, this review primarily focuses on changes in gonadal hormones and the HPG (hypothalamic-pituitary-gonadal) axis, however, some conditions presented here also affect HPA (hypothalamic-pituitary-adrenal) axis functioning. Given the breadth of this topic and the number of disorders and species being involved, and to emphasize similarities rather than differences, we decided to selectively focus on perturbations in sex hormones. To maintain this focus, the review will not address underlying biology or etiology or examine possible interactions between hormones and other molecular systems including neurotransmitters or immunochemistry. Instead, it will address the relevance of sex hormones for behavioural aspects of anxiety and depression. In this sense, the reviewed literature has to be regarded as being limited and only constituting one aspect of a broader, complicated scenario.

First, conditions of hypogonadism in women and men will be reviewed followed by discussion of conditions of hypergonadism in both sexes. Given the current scarcity of research in this area, inclusion of published reports in the review was guided by available studies. To obtain these available studies, we searched PubMed from 1970 onwards with the search terms for the disorder or the rodent equivalent, i.e., Klinefelter, XXY, TFM and testicular feminization model, CAH and congenital adrenal hyperplasia, PMDD and premenstrual dysphoric disorder, postmenopausal syndrome, ovariectomy, Turners Syndrome, hypogonadal, castration PLUS anxiety OR depression AND / OR psychopathology AND human OR rodent.

In addition, reference lists of identified articles were also searched for relevant literature. Thus, while some conditions are not included in this article, a secondary purpose of this review is to highlight the need for further studies of the consequences of hormonal imbalances. Following these sections, we highlight consistencies in the reviewed literature and discuss methodological challenges for future research, including the need for valid behavioural tasks that can be applied across human and rodent species.

Hypogonadism in women

Premenstrual Dysphoric Disorder

Roughly affecting 3-8% of women of childbearing age, symptoms of premenstrual dysphoric disorder (PMDD) include depression, irritability, mood swings, and feelings of tension and anxiety (Halbreich et al., 2003). These symptoms typically occur within 5-11 days before the beginning of a woman's menstrual cycle, thus during the luteal phase, and usually cease during or after menstruation. A strong contribution of gonadal hormones in PMDD has been proposed although it may not be the sole underlying factor (Halbreich et al., 2003). While variations in ovarian steroid levels have been proposed to increase sensitivity of emotional processing areas of the brain, evidence in support of this hypothesis is only slowly emerging.

An experimental paradigm that has been used to assess anxiety in both humans and animals is the startle response. In both species, the response to a loud stimulus is measured in the acoustic version of the task. In humans, the dependent measure is the eye-blink reflex (e.g., (Grillon et al., 1994), while in the rodent version of this task a whole body reaction is assessed (Koch and Schnitzler, 1997). In order to determine the anxiety levels in women, patients diagnosed with PMDD and matched

controls were presented with pleasant and unpleasant images at random intervals, which were preceded by coloured squares to indicate the valence of the upcoming image (Bannbers et al., 2011). Startle response during anticipation of negative pictures was increased in women with PMDD relative to control subjects during the luteal phase but not the follicular phase of the menstrual cycle. This effect was accounted for by an increase in the startle response to negative anticipation in women with PMDD during the luteal phase relative to the follicular phase, while control women showed no changes in startle across phases of their cycles. These data would suggest that sensitivity to negative anticipation is increased during phases of the cycle when progesterone levels are unusually low as in PMDD. The effects of PMDD also extended to other emotional processing skills such as emotional face labelling. Women diagnosed with PMDD and unaffected controls were tested during both the follicular phase and luteal phase on a task to discriminate emotional facial expressions (Rubinow et al., 2007). Women with PMDD had more difficulty discriminating emotional expressions and exhibited a greater bias in judging faces as negative during the luteal phase relative to the follicular phase. Mirroring the startle response findings by Bannbers et al. (2011), no such cycle effects were observed in the comparisons tested by Rubinow et al. (2007).

Complementing these behavioural findings, Gingell and colleagues (2013), aimed to assess the underlying neurobiological basis of low progesterone levels on anxiety in PMDD. Using a similar behavioural protocol to probe anticipation of negative and positive images, women with PMDD showed greater activation in the medial and dorsolateral prefrontal cortices during negative anticipation in the luteal phase relative to controls (Gingnell et al., 2013). Similarly, in another study of PMDD by these researchers that to assess emotional responding (Gingnell et al., 2012),

depression scores of women with PMDD correlated with amygdala activity during the luteal phase. By comparison, during the follicular phase, amygdala activation was correlated with progesterone levels while completing an emotional matching task. These authors suggested that, in PMDD, the amygdala may be more prone to habituation as indicated by a larger decrease of activity between phases of the cycles for affected women relative to healthy comparisons (Gingnell et al., 2012).

In rodents, PMDD can be modeled either by manipulating the hormonal profile of female rats following ovariectomy to induce a state of progesterone withdrawal, or by tracking the stages of the rodent estrous cycle to mirror stages of the human menstrual cycle. In a study that neatly parallels the human startle response findings by Bannbers et al. (2011), gonadally-intact female rats experiencing induced withdrawal from exogenous progesterone displayed increased startle reflexes relative to control females, while gonadally-intact males failed to display similar changes when withdrawn from progesterone (Gulinello et al., 2003). Moreover, the startle response in female rats was accompanied by up-regulation of $GABA_A$ receptors in the amygdala suggesting an underlying neurochemical mechanism in neurocircuitry in mood and anxiety disorders. Complementing these data, other evidence supports the hypothesis that both anxiety and depression are increased in rodent models of progesterone withdrawal. Anxiety-like behaviour was indicated by shorter latencies to bury novel objects by rodents undergoing withdrawal from progesterone compared to control subjects receiving vehicle treatment (Schneider and Popik, 2007). Similarly, increased depressive-like and anhedonic behaviours were reported during progesterone withdrawal in female rats tested on the forced swim test, the social withdrawal test, and the saccharin preference test (Li et al., 2012; Schneider and Popik, 2007)(for overview of common paradigms used in rodents see Figure 1).

Interestingly, these rodent studies suggest that it may not necessarily be the low levels of progesterone or estradiol per se but that mood dysregulation during the luteal phase of PMDD may be caused by the decline or withdrawal of these hormones. Taken together then, these findings suggest that low progesterone or withdrawal of such may significantly impact mood and anxiety levels and increase the way in which negative information is being processed. However, changes in mood symptoms are not only associated with perturbations of gonadal hormones during different phases of the menstrual cycle, but also when menstruation has ceased.

Postmenopausal Depression

It has long been known that the transition into menopause is associated with a variety of symptoms including feelings of irritability, anxiety, depression, decreased interest in sexual activity, irregular heartbeat, and sleeping problems (Woods and Mitchell, 2005). In some women the severity of these symptoms may lead to a diagnosis of postmenopausal depression. The onset of depression may be linked to the cessation of regular hormonal fluctuations characteristic of the menstrual cycle, which leads to rather abrupt reductions in progesterone and estrogen levels. Surprisingly, few experimental attempts have been made to "utilise" these changes in postmenopausal hormonal levels to examine relationships between ovarian steroids and basic affective functioning. However, the studies that have investigated the role of postmenopausal hormones on affect reported only a weak association between higher-level cognitive function and ovarian hormones (Henderson et al., 2013). In their large sample of post-menopausal women, progesterone levels were positively associated with verbal memory and global cognition, while no relationships were found between cognitive performance and estrogen (Henderson et al., 2013). Nevertheless, a clear

interpretation of these findings was limited by the study design, which compared two groups of postmenopausal women but failed to include groups of peri- or premenopausal women. Moreover, to our knowledge, the neurobiological correlates of affective processing in the postmenopausal period remain elusive in human studies.

By comparison, various animal models have employed designs intended to simulate the hormonal features of the human postmenopausal period. Providing a bridge that spans human and non-human primate research is a study of ovariectomised cynomolgus macaques (Willard et al., 2011). Macaques were ovariectomised at 3 months of age, treated daily for two months with estradiol, progesterone, or vehicle using dosage equivalents commonly prescribed to postmenopausal women. Animals then were assessed for behavioural signs of depression and classified as depressed or non-depressed prior to undergoing MRI scanning. Macaques classified as depressed had significantly smaller hippocampal volumes relative to non-depressed counterparts, however, the effects of hormone treatments on behavioural and structural measures were unfortunately not reported. As in humans and non-human monkeys, aging female rodents also undergo a change in reproductive status known as estropause. However, this condition is a weak model of human menopause primarily because of the prolonged course of estropause, as well as significant individual variation between females. Therefore, in aged female rodents, the method to simulate the postmenopausal status of humans is typically induced by removal of the ovaries, their endogenous source of gonadal estrogen.

Following ovariectomy, female rodents receive treatments with estradiol or vehicle administered in various forms and routes and for various periods. Elevations in anxiety-like (de Chaves et al., 2009; Diz-Chaves et al., 2012; Walf et al., 2009) and depressive-like (de Chaves et al., 2009; Walf et al., 2009) behaviours have been

reported when estrogen is absent following ovariectomy, compared to rats that received estrogen replacement. However, not all studies are in agreement, with reports of increases in anxiety-like behaviours, but not in depressive-like behaviours, following ovariectomy without estrogen replacement in aged female rats (Diz-Chaves et al., 2012). Other studies have examined the effects of long-term absence of estrogen following ovariectomy during young adulthood, reporting increases in anxiety-like and depressive-like behaviours following exposure to stressors in aged females without estrogen, compared to those with estrogen present (Lagunas et al., 2010). Overall, results indicate that an absence of estrogen in female rodents is associated with a greater incidence of anxiety-like behaviours, and some indication of more depressive-like symptoms in rodent models of postmenopausal syndrome. A further consideration in studies of postmenopausal depression may be the timing and duration of estrogen replacement in non-human comparisons, as recent evidence from studies of cognition in aged female rats indicate that the beneficial effects of estradiol are present primarily when hormone replacement is initiated shortly after ovariectomy (Daniel, 2013). In summary, surprisingly little information is available on the impact of changes in gonadal hormones during menopause on cognitive-affective processing. In addition, findings in rodent models may not be ideal counterparts to humans but suggest some associations with mood and anxiety. Complementing these variations in mood and anxiety symptoms during the normal cycle or during menopause, endocrine conditions of estrogen absence provide further evidence of the impact of gonadal hormones on affective cognition.

Estrogen Deficiency

Women suffering from estrogen deficiencies due to partial or complete loss of the second X-chromosome in Turner Syndrome (TS) express high rates of lifetime psychopathology (~69%) and current depression (~17%)(Downey et al., 1989). Complementing this clinical profile, evidence has suggested aberrant affective processing in TS. For example, relative to matched-controls, women with TS have difficulty identifying negative emotional facial expressions that indicate fear or anger (Good et al., 2003; Hong et al., 2013). However, affective processing difficulties are not limited to the visual domain. In a study of emotional prosody during speech, adolescent girls with TS performed more poorly in recognizing the valence of emotional speech compared to matched-comparisons (Ross et al., 1995). These behavioural alterations of affective processing are synchronous with changes in affective regions at the neuroanatomical level implicating a brain-behaviour link.

In an fMRI study of cognitive appraisal of emotional information, Skuse and colleagues (2005) asked women with TS and matched-comparisons to complete a gender identification task (i.e., whether a presented face was male or female) while ignoring the emotional valence of the presented face (e.g., fearful or neutral). Not only were patients less able to identify fearful or angry emotions relative to controls, but groups also differed in neuronal responses to fearful faces. While healthy women showed brief but intense activation of the amygdala to a fearful face, the response of women with TS was weaker and less intense but more prolonged. Given that the stimuli evaluated by subjects concerned human faces, the coupling or connectivity between the amygdala and face processing regions (such as fusiform gyrus) was also altered. For healthy women, activity in the fusiform area was positively correlated with the amygdala response, an effect that was absent in women with TS. Such data would suggest that estrogen deficiency alters the intensity and duration in which

affective stimuli are processed and affects *down-stream* areas of the brain further implicated in the processing of affective material. Differences in activation patterns in affective brain regions associated with estrogen deficiency were paralleled by differences in underlying brain structure. Amygdala volumes were significantly enlarged while hippocampal volumes were reduced in women with TS expressing estrogen deficiency relative to matched-controls (Kesler et al., 2004), a finding reported previously (Good et al., 2003).

In rodents, the study of Turner Syndrome is sparse, however, one mouse model has been proposed. The 39, XO mouse parallels some of the same behavioural and neurobiological traits presented by humans with Turner Syndrome (Lynn and Davies, 2007). Mirroring findings in humans (Keysor et al., 2002; Rovet and Ireland, 1994), XO mice exhibited higher anxiety-like behaviour compared to XX mice on the elevated plus maze test, spending less time on the open arms of the maze (Isles et al., 2004). Cognitively, XO mice displayed deficits in attention on a five-choice serial reaction time task (5-CSRTT) compared to XX controls (Davies et al., 2007). While the XO mouse model of Turner Syndrome shows promise, further studies to determine the cognitive and affective profiles of these mice are urgently needed. In summary, while additional work is required in rodent models, studies in human females with estrogen deficiency have consistently shown decrements in the ability to process affective information. This effect may be grounded in changes at the underlying neurobiological level of affective circuitry. Similar to such effects in women, the next section will review the evidence that men can also be affected by reduction or absence of native testosterone.

Hypogonadism in Men

Testosterone Deficiency

Human males with androgen deficiency due to a supernumerary X chromosome, such as in men carrying the 47 XXY genotype or Klinefelter Syndrome (KS), show high rates of various psychopathologies, particularly language disorders (65%), attention deficit hyperactivity disorder (63%), autism spectrum disorder (27%), depression, (24%) and anxiety disorders (18%)(Bruining et al., 2009). In an interesting series of studies, Van Rijn and colleagues have assessed affective processing, emotion regulation, and decision making in men with KS and documented their difficulties in labeling affective facial expressions (van Rijn et al., 2006), similar to the profile observed in women with estrogen deficiency (TS)(Skuse et al., 2005). Paralleling this behavioural profile of women with TS, males with androgen deficiency expressed difficulty in the visual domain as well as in the auditory domain indicated by detection of emotional states based on prosody of speech (van Rijn et al., 2007). Moreover, impairments extend to higher-level affective processes such as emotional regulation. In a prior study (van Rijn et al., 2006), emotion regulation, as measured by a self-assessment questionnaire, revealed that men with KS were prone to become more easily aroused. Furthermore, men with KS rejected more offers from co-players for financial gain on a social cooperation task. These data suggest that testosterone deficiency impacts a variety of social-affective processes spanning affective labelling, speech processing, emotion regulation, and social cooperation.

While functional imaging data on affective function in men with KS are unfortunately unavailable to link androgen deficiency to underlying neurobiology, structural studies of men with KS are consistent with behavioural findings. A recent, comprehensive study reported higher rates of anxiety and depression in men with KS (Skakkebaek et al., 2014). Corresponding MRI data revealed that men with KS had

lower grey matter volume compared to controls matched for age and education in a variety of affective regions including the hippocampus, the insula, and the corpus striatum (Skakkebaek et al., 2014). Although these researchers did not find ameliorating effects of testosterone treatment, further longitudinal work is required to establish whether hormonal treatment can normalise affective brain function in pediatric and adult males with KS.

Mirroring findings in humans, multiple studies have examined the effects of testosterone exposure during adulthood on anxiety-like and depressive-like behaviours in male rodents (Aikey et al., 2002; Fernandez-Guasti and Martinez-Mota, 2005; Frye et al., 2008; Hodosy et al., 2012). A recently-developed mouse model of KS has extended the understanding of the phenotypic profile of rodents with low testosterone in early life. However, only one study to date has included behavioural endpoints using this mouse model. Lewejohann and colleagues (2009) compared the performance of supernumerary XXY male mice and normal XY male mice on both the open field task and elevated plus maze task and found no differences in anxiety-like behaviours. These results indicate that low testosterone in early life does not reflect the same elevations in anxiety seen in rodents with low levels of testosterone in adulthood.

Hypogondal syndromes in humans are also comparable to castration in male rodents, as a result of removing the endogenous source of androgens in adulthood. A higher incidence of anxiety-like behaviours was evident in male mice castrated in adulthood, compared to males undergoing sham surgery (Slack et al., 2009). Interestingly, the effects of castration on anxiety-like behaviour were influenced by the age at castration thus providing some hypotheses for potential age differences in affective processing in patients with KS. When castrated before puberty, mice

displayed lower anxiety-like behaviour on the elevated plus maze compared to gonadally-intact males. However, when castrated as adults, mice displayed more anxiety-like behaviours on the elevated plus maze when compared to sham-castrated controls (McDermott et al., 2012). Further investigation of affective behaviours in castrated adult male rats indicates elevations in anxiety-like and depressive-like behaviours following chronic stressors, compared to sham males that experienced the same chronic stress paradigm (Wainwright et al., 2011). These findings suggest that androgen deficiencies in adult male rodents increase their vulnerability to chronic stressors and resulting anxiety and/or depression. Furthermore, given findings that rats deficient in testosterone demonstrate spatial memory deficits that were rescued by testosterone administration (Hawley et al., 2013; McConnell et al., 2012; Spritzer et al., 2011), elevations in anxiety as a result of low or absent testosterone levels could impact cognition as well. Taken together, while studies in men with testosterone deficiencies suggest changes in affective processing, neurobiological evidence is currently lacking. Complementary studies in rodents, however, support an increase in anxiety with lack of testosterone, particularly in adulthood. The previous section has consistently revealed increases in mood and anxiety symptoms with lack of gonadal hormones. The following sections will examine changes in mood during hypergonadism.

Hypergonadism in Women

Polycystic Ovary Syndrome

One in five women of reproductive age suffer from Polycystic Ovary Syndrome (PCOS), which includes symptoms of anovulation, irregular menstrual periods, exposure to large amounts of androgens, and insulin resistance. Frequent associated

psychopathologies include anxiety and depression as well as eating disorders relative to women without this condition (Barry et al., 2011; Mansson et al., 2008). Importantly, a 7-fold increased risk for suicide attempts in affected individuals relative to matched controls has been documented (Mansson et al., 2008) warranting close attention to the mental health of affected individuals.

Despite the high prevalence of anxiety and depression symptoms in PCOS (Barry et al., 2011), surprisingly, we are aware of only one neurocognitive study of patients with PCOS that assessed emotional functioning. Participants were asked to rate stimulus pictures as either neutral or negative while undergoing fMRI scanning. In the fMRI, patients with PCOS relative to matched controls had significantly greater activity in the prefrontal cortex and ventral anterior cingulate and a trending reverse effect of lower amygdala activation in response to negative pictures (Marsh et al., 2013). Nicely complementing this study, Livadas and colleagues (2011) assessed associations between state and trait anxiety and hormonal profiles such as the free androgen index and the homeostasis assessment model - insulin resistance. Their unique data revealed a positive correlation suggesting that higher state anxiety corresponded to higher free androgen titers. However, comparing the two studies raises an important question. PCOS is not only associated with mood and anxiety disorders but also with eating disorders induced by insulin resistance. If treating an eating disorder with an anti-diabetic medication resolves associated psychopathology, the effect of treatment could be via a direct or indirect mechanism. In other words, treatment of insulin resistance could directly elevate mood, or alternatively, peptide and steroid hormones could interact in such a way that re-balancing insulin homeostasis affects steroid hormone levels, thereby altering mood level. As these two

studies do not resolve this issue, more work on the interaction between different hormonal classes seems warranted.

Though rodent models of PCOS exist (Foecking et al., 2008; McNeilly and Duncan, 2013; Shi and Vine, 2012), to date, no studies of PCOS in rodents have examined behavioural endpoints. Further study of the behavioural profile of existing PCOS rodent models is necessary to determine if parallels exist between the human and rodent models of this endocrine disorder. Similar to hypergonadic function associated with increased levels of progesterone in females, increases in androgens in both males and females also leads to significant changes in affective processing.

Hypergonadism in Men and Women

Congenital Adrenal Hyperplasia and Familial Male Precocious Puberty

Similar to hypogonadism in males, evidence also supports increased rates of psychopathologies associated with exposure to excess androgen, particularly during early developmental stages of life. Pathogenesis of hyperandrogenism can have different origins. In Congenital Adrenal Hyperplasia (CAH), both males and female fetuses are exposed to abnormally high levels of androgens *in-utero*. While CAH may affect both sexes, effects are particularly severe in females who may be born with ambiguous genitalia due to the excess androgen leading to significant virilization. In parallel, the endocrine imbalance extends to mineralocorticoids and glucocorticoids leading to cortisol deficiency, and in some cases, aldosterone deficiency (Merke and Bornstein, 2005). By comparison, a selective form of hyperandrogenism, familial male precocious puberty, only affects males and is limited to excess androgens due to higher production of testosterone by testicular Leydig cells. Dramatic effects become apparent early in life when individuals enter puberty as early as 2 to 4 years of age,

expressing pubescent characteristics including acne, deepening of the voice, hair growth, and penile erections among others (Leschek, 2004).

Both forms of hyperandrogenism have been associated with increased rates of anxiety disorders, disruptive behavioural disorders, and ADHD relative to general population rates (Mueller et al., 2010). Importantly, rates of ADHD were reported to be higher in both groups when compared to teenagers with other chronic disorders, suggesting a hormonal contribution to the development of ADHD. In another survey of disorders of sexual development (DSD), Johannsen et al (2006) reported that the degree of virilization in DSD was positively correlated with anxiety and depression as well as previous suicidal thoughts. In the laboratory, emotional tasks indicate that patients with CAH and FMPP show accelerated threat processing when assessing angry or fearful faces (Ernst et al., 2007; Mueller et al., 2009a). At the neurobiological level, these effects were associated with changes in amygdala-hippocampal activation (Ernst et al., 2007; Mueller et al., 2009a). Consequently, a higher level of clinical anxiety in some forms of hyperandrogenism was mirrored behaviourally and neurobiologically by more rapid processing of threat. Of note, changes in affective processing do not seem to be limited to negative stimuli but also extended to positive, rewarding material.

Although the effects of androgens on positive emotion have received limited attention, one study linked circulating testosterone levels to personality traits indicative of high reward processing such as novelty-seeking and reward dependence (Maattanen et al., 2013). Moreover, when early (i.e., fetal) testosterone levels fall within the normal, non-pathological range, they are associated with preferential processing of positive emotional faces and activation of reward structures such as the caudate, the putamen and the nucleus accumbens later on during childhood

(Lombardo et al., 2012). In addition, testosterone administration to healthy women leads to increases in reward processing in mesolimbic circuitry, most notably in individuals with low appetitive motivation (Hermans et al., 2010). However, when testosterone levels exceed the normal range, they negatively affect reward processing. In experimental studies of inhibitory control, healthy volunteers can improve their performance if a monetary incentive is provided on a trial-by-trial basis, while such an effect is shown to be absent in CAH youths (Mueller et al., 2013). Taken together, these findings are noteworthy because of recent, parallel work, which has slowly begun to investigate the role of reward and associated brain circuitry such as the striatum in clinical anxiety (Sripada et al., 2013).

Though the CAH paradigm proves difficult to mirror in rodents, recently, a mouse model of CAH has been proposed, in which mice are genetically modified and lack the Cyp11b1 gene, resulting in a deficiency of 11β-hydroxylase (Mullins et al., 2009). This genetic mutation serves to convert deoxycorticosterone to corticosterone in rodents. Therefore, although this mouse model provides insight into the neurobiological and physiological changes associated with reduced corticosterone production, analogous to reduced cortisol production in humans with CAH, it is of limited value in the study of behaviour related to androgen excess. However, experiments that study the impact of testosterone exposure postnatally can provide insight into the impact of excess androgen exposure in early life. Exposure to testosterone shortly after birth masculinizes the sexual and cognitive behaviours of female rodents (Bodo and Rissman, 2008; Dawson et al., 1975; Phoenix et al., 1959; Roof, 1993) and results in structural changes to the hippocampus (Roof, 1993). However, organizational effects are not as robust in terms of anxiety-like or depressive-like behaviours. Tests of baseline anxiety comparing females treated

neonatally with testosterone or vehicle failed to indicate any differences in anxiety-like behaviours on the open field test, elevated plus maze test, or light/dark box (Figure 1)(Goel and Bale, 2008). However, the results of a marble-burying task revealed that females treated neonatally with testosterone displayed significantly more burying behaviour compared to vehicle-treated females, and similar to the behaviour of males (Goel and Bale, 2008). The higher level of this anxiety-like behaviour was found when tests were conducted in adulthood (Goel and Bale, 2008) as well as prior to puberty (Grissom et al., unpublished results). Interestingly, when subjects were stressed as adults, differences in anxiety-like and depressive-like behaviours were more pronounced in females treated neonatally with testosterone compared to vehicle (Goel and Bale, 2008; Seney et al., 2012), indicating that though exposure to androgens during the early stages of development may not directly alter later anxiety and depression, early androgen may increase these behaviours by changing the vulnerability to stressors. Taken together, these findings suggest that androgen supplementation in human and female mice increases sensitivity of threat processing and increases anxiety-like and depressive-like behaviours. In addition, while normal variation of testosterone may show a positive association with reward processing, it appears to become perturbed when levels fall outside the limits.

Androgen Insensitivity

Although humans can experience both over- and under-production of gonadal steroids, another form of gonadal hormone perturbation occurs when sufficient levels of gonadal steroids are present but dysfunction of hormone receptors precludes their effects. A well-known form of insensitivity in humans is Androgen Insensitivity Syndrome (AIS), which presents in partial or complete forms. Despite having a 46,

XY karyotype and the presence of a Y chromosome, individuals with the complete form of this syndrome (CAIS) will develop phenotypically as females, often characterized by well-formed external female genitalia. In the partial form of the syndrome (PAIS), external male genitalia are only partially masculinized or ambiguous (Fliegner et al., 2013). To date, due to the rarity of the disorder, few reports on the mental health of patients with CAIS are available. However, in a recent report, Fliegner et al. (2013) described critical levels of depression in 36% of individuals with CAIS. By comparison, in a Danish cohort, Johannsen et al (2006) documented reduced levels of anxiety and depression in individuals with CAIS relative to matched controls but a higher number of visits to mental health care professionals. To date, no studies exist on affective processing in individuals with AIS leaving a large gap in our understanding of the effects of androgen insensitivity on affective processing.

Despite this scarcity of evidence in humans, in rodents, androgen insensitivity syndrome has been modelled by the testicular feminization model (TFM). In this model, TFM rats or mice carry a genetic mutation of the androgen receptor, resulting in insensitivity to androgens. Investigations of the affective behaviours characteristic of TFM male rodents compared to their wild-type counterparts revealed higher anxiety-like behaviours in TFM animals (Hamson et al., 2014; Rizk et al., 2005; Zuloaga et al., 2011a; Zuloaga et al., 2011b). Studies document higher anxiety-like behaviour on the elevated plus maze in TFM rats (Hamson et al., 2014; Zuloaga et al., 2011b), a behavioural difference that was not apparent in mice with the same mutation (Zuloaga et al., 2008). Similarly, on another task of anxiety, TFM rats displayed higher anxiety-like behaviour compared to their wild type counterparts, on the open-field task (Zuloaga et al., 2011a; Zuloaga et al., 2011b), an effect that again

was not observed in TFM mice on the same task (Zuloaga et al., 2008). Alternatively, measures of anxiety on a third indicator of rodent anxiety, the light-dark box task, agree across rats and mice with both species displaying higher anxiety-like behaviour in TFM males compared to wild-type males (Figure 1)(Zuloaga et al., 2011a; Zuloaga et al., 2008; Zuloaga et al., 2011b). Overall, male TFM rats consistently displayed higher levels of anxiety-like behaviours compared to wild-type control males, while the effects of androgen insensitivity in male TFM mice is less consistent. Thus, the influence of androgen insensitivity on anxiety-like behaviour appears to vary across rodent species and requires further investigation.

**********Figure 1 about here please **********

Synthesis of human and animal data across the life-span on hormonal effects on affective and neurocognitive function

In this review, several consistencies across the surveyed literature emerged. In humans, low androgens in males with Klinefelter Syndrome (KS), low estrogen in females with Turner Syndrome (TS), and low progesterone in females with Premenstrual Dysphoric Disorder (PMDD) increased manifestations of depression and anxiety (Bruining et al., 2009; Downey et al., 1989; Halbreich et al., 2003). Each of these disorders was reported to be associated with difficulties in labelling emotional facial expression (Good et al., 2003; Hong et al., 2013; Rubinow et al., 2007; Skuse et al., 2005; van Rijn et al., 2006) and assessing emotional prosody in speech (Ross et al., 1995; van Rijn et al., 2007). Likewise, excess androgen exposure in males with Male-Limited Precocious Puberty (FMPP) and females with Congenital

Adrenal Hyperplasia (CAH) or Polycystic Ovary Syndrome (PCOS) revealed higher rates of anxiety disorders (Barry et al., 2011; Mansson et al., 2008; Mueller et al., 2010) and cognitively faster processing of threat in some cases (Ernst et al., 2007; Mueller et al., 2009a). Such results strongly support the hypothesis that mood and anxiety disorders are often associated with disorders of gonadal dysregulation. In addition, these studies suggest that gonadal steroids affect a variety of cognitive and non-cognitive processes at behavioural and neurobiological levels involved in the regulation of negative affect.

On the flip side, another valuable avenue of study that has received almost no attention is the potential effects of gonadal steroids on affective processing of positive, rewarding stimuli. For example, some studies of hypogonadal men reported increases in sexual interest and sexual desire concurrent with decreases in depression scores after starting testosterone supplementation (Jockenhovel et al., 2009). Such findings are supported experimentally by studies showing that testosterone supplementation not only increased sexual enjoyment but also increased selective attention to sexual stimuli in an auditory listening task (Alexander et al., 1997). Conversely, exposure to supra-threshold levels of androgens decreased the ability to process motivational cues for cognitive performance (Mueller et al., 2013). Additional investigations of the effects of testosterone and estrogen deficiencies and excesses on processing of positive affect are clearly indicated.

Although some consistencies emerged in the human literature, this review also revealed a variety of contradictory findings that deserve further investigation and clarification. For example, memory recall of threatening images increased during a stressor task in women with high levels of progesterone when tested at the mid-luteal phase of menstrual cycle relative to women with low levels of progesterone tested

during their non-luteal phase or compared to control participants who were not exposed to stressors (Felmingham et al., 2012). By contrast, in another study, recognition accuracy for emotional expressions was increased in women in their follicular phase when progesterone levels are low relative to the luteal phase when progesterone levels are elevated (Derntl et al., 2008). In addition, amygdala activation in response to fearful faces was negatively correlated with progesterone levels, indicating greater amygdala activation is associated with lower progesterone levels (Derntl et al., 2008). Thus, the interaction of the amygdala and fluctuating progesterone levels across the human menstrual cycle in the regulation of affective cognition, remains unclear.

Such consistencies and inconsistencies were also present in the reviewed rodent literature. In terms of hypogonadism, reduction or removal of estrogen and androgen, or the withdrawal of progesterone all resulted in increases in anxiety-like behaviours when compared to control subjects (de Chaves et al., 2009; Diz-Chaves et al., 2012; Gulinello et al., 2003; Isles et al., 2004; Lagunas et al., 2010; Lewejohann et al., 2009; Li et al., 2012; McDermott et al., 2012; Schneider and Popik, 2007; Slack et al., 2009; Wainwright et al., 2011; Walf et al., 2009). Measures of depressive-like behaviours were less consistent, for example, aged female rodents did not display increases in depressive-like symptoms when estradiol was absent (Diz-Chaves et al., 2012) though this effect differed depending on the age at ovariectomy and the duration of estradiol replacement (Lagunas et al., 2010). Inconsistencies were apparent as well in terms of the TFM rodent model. Though both rats and mice exhibited increased anxiety on the light-dark box, differences between rats and mice were apparent on other anxiety tasks and measures of anhedonic depression (Hamson et al., 2014; Zuloaga et al., 2011a; Zuloaga et al., 2008; Zuloaga et al., 2011b). In

comparisons of the human and rodent literature, it is important to consider the species of rodent as well. Though very similar, as illustrated in this review, mice and rats demonstrate differences in their responses to gonadal steroids, serving to make comparisons across species more complex.

Nevertheless, our review of the human and non-human literature regarding psychopathological behaviours and gonadal hormones reveals more agreement than dissention. These areas of concordance hold promise for the translational nature of animal research to elucidate mechanisms by which gonadal hormones act on the brain of both non-humans and humans. In both humans and rodents, there is evidence for an interaction of the hippocampus and amygdala in anxiety and depression (McEwen et al., 2012), specifically, both brain areas that are responsive to fluctuations in gonadal hormones (McEwen, 2010). Furthermore, reports from the rodent literature highlight that stressors can exacerbate psychopathologies resulting from gonadal hormone dysregulation, regardless of whether this dysregulation results in hormonal deficiencies or excesses (Goel and Bale, 2008; Lagunas et al., 2010; Seney et al., 2012; Wainwright et al., 2011). Additionally, recent evidence confirms that the rodent brain expresses all the molecular mechanisms necessary to synthesize gonadal hormones *de novo* (Konkle and McCarthy, 2011). The impact of brain synthesis of hormones historically associated with the gonads is only beginning to be studied and understood in rodents. Meanwhile, the implications for human psychopathologies that are influenced by these hormones represent an exciting new direction for future research.

**********Figure 2 about here please **********

A proposed model of gonadal hormone effects on anxious/depressed behaviour

Summarizing the findings of this review, the model displayed in Figure 2 proposes a U-shaped relationship to describe the role of gonadal steroid hormone perturbations in the manifestations of depression and anxiety. The reviewed literature consistently indicates higher levels of depression and anxiety across conditions with a strong, inherent hormonal component. While most studies documented the presence of psychopathology in affected individuals (Barry et al., 2011; Bruining et al., 2009; Downey et al., 1989; Fliegner et al., 2013; Halbreich et al., 2003; Mueller et al., 2010; Skakkebaek et al., 2014; Woods and Mitchell, 2005), another study found state measures to directly correlate with circulating androgens (Livadas et al., 2011). Yet another line of work supports this model by showing that testosterone administration may be beneficial for mood status in hypogonadal men when their hormonal levels are below the normal range of values but less beneficial if hormonal levels are within the normal range (Alexander et al., 1997). Similarly, testosterone supplementation for men with depression and low baseline levels of testosterone also alleviated depressive symptoms significantly (Pope et al., 2003). Therefore, the levels of gonadal hormones necessary to support optimal affective and cognitive functioning may be reflected by regular or inverted U-shaped functions. Another example of such a function for a hormone-cognition relationship has previously been suggested to underlie the interaction between cortisol exposure and memory (Lupien et al., 2005). Of course, it is important to note that a direct link between depression and anxiety on the one hand and gonadal dysfunction on the other hand might not apply to all conditions. In fact, a limitation of the proposed model is that the pathogenesis and the course of a disease are likely to differ between conditions and have different underlying mechanisms.

For example, androgen excess and cortisol deficiency in CAH are co-occuring symptoms, a combination that is difficult to disambiguate (Merke et al., 2003). Moreover, reward processing in CAH is impaired suggesting a possible interaction of these hormones with neurotransmitters involved in reward and motivation such as dopamine (Mueller et al., 2013). Likewise, during stressor tasks, females with PCOS exhibited elevated ACTH and cortisol responses relative to control females, which interacted with interleukin (IL-6) levels in patients but not in control participants (Benson et al., 2009). Neurobiological investigation of XO mice (TS) demonstrated higher anxiety-like behaviour compared to XX control mice paralleled by reductions in the expression of GABA receptor genes (Isles et al., 2004), which provides insight into alterations that may exist in GABAergic function in humans as a result of features specific to the HPG axis of individuals with TS. Yet other studies have documented the involvement of opioid peptides and immune dysfunction in patients with anxiety disorders and depression (Castilla-Cortazar et al., 1998). The value of animal models becomes apparent here to assess interactions between hormones and fundamental biochemistry including hormone-hormone, hormone-cytokine, hormone-opioid, or hormone-neurotransmitter interactions. Therefore, the present model represents a simplification of consistent trends of findings observed in the literature. In addition to the alluded interactions of hormones with other biochemical systems, additional factors such as acute vs. chronic or delayed vs. immediate changes in sex hormones are likely to play a role. Controlled studies in rodents are necessary to disentangle these complex interactions to better understand potential hormonal signaling cascades and their influence on other biochemical systems, which may be informative in fostering therapeutic development.

However, on a more basic neuroscience level, one aim of future research should be to move beyond the limitations provided by, and specific to, each hormonal disorder. Applying across-disorder comparisons to "average out" disease-specific characteristics might serve as an effective strategy to gain better understanding of related pathologies. Using the same or similar paradigms across disorders (e.g., threat processing in CAH and FMPP (Ernst et al., 2007; Mueller et al., 2009a) or emotional prosody in KS and TS (Ross et al., 1995; van Rijn et al., 2007) has provided converging findings that allow for extrapolation of the impact of hormone mechanisms on affective function. In addition, such studies can be complemented by testosterone supplementation studies in healthy women, which reveal transient changes in affective responding when levels are within the normal range (Hermans et al., 2006; van Honk et al., 2005). Of course, the precise pathways of how testosterone alters affective processing in health and disease may differ and it cannot be completely ruled out that some other but similar biochemical processes (e.g., hormone-neurotransmitter interaction) underlie the observed effects. Thus, more and larger-scale collaborative efforts are needed to synthesize and coordinate findings across studies given the limitations placed on previous research by small patient sample sizes and localised specialised clinical centers. Using paradigms that are translatable to humans from rodents as described in the following section might facilitate a leap in the knowledge that can be gained by probing the underlying neurochemical mechanisms in valid animal models.

Comparing conditions of hyper- and hypogonadism casts doubt on current theories of testosterone involvement in psychopathology. For example, the "extreme-male" brain theory suggests that high androgen levels play some role in the manifestation of disorders on the autism spectrum (Baron-Cohen, 2002). However,

this hypothesis is not supported by consistent reports of autism spectrum behaviour in men with testosterone deficiencies (Bruining et al., 2009; Skakkebaek et al., 2014; Van Rijn et al., 2012). Therefore, it is not clear how disproportionately high rates of autism spectrum in testosterone deficient men are reconcilable with the extreme-male brain theory. Rather, when viewed along the continuum of a traditional U-shaped curve, excess as well as deficiency in androgen may alter the behavioural profile on the autism spectrum as well as other pathologies. Future experimental and epidemiological studies are needed to replicate these reported effects, as in other conditions of gonadal dysfunction.

**********Figure 3 about here please **********

A continuing search for translatable paradigms and open questions for future research

One issue for enabling straightforward comparisons across species to facilitate future research is the search for valid and translatable paradigms of interest to psychoneuroendocrinology. As shown in Figure 3, a variety of paradigms currently are available to compare humans and rodents that tap into learning and memory processes (panel a) and fear conditioning and startle response (panel b), or other behaviours such as sexual function and arousal (kinky picture not shown). In areas of learning and memory, attempts to compare spatial learning and learning strategy across humans and rodents have shown remarkable similarities and supported the use of rodents to model human spatial memory (Schwabe et al., 2008; Shore et al., 2001). Within the context of anxiety, neurobiological theories focus on the roles of the amygdala and hippocampus in anxious behaviour (Gray and McNaughton, 2000) and

both regions are known to play important roles in spatial learning and memory as well as startle reflexes (panels a/b). Indeed, some studies have demonstrated spatial learning and memory deficits associated with anxiety and depression in rodents and humans (Gould et al., 2007; Gray and McNaughton, 2000; Mueller et al., 2009b). The classic Morris Water Maze task, which assesses learning and memory over multiple trials by tracking the time and distance required by rodents to escape a water environment by finding a hidden platform within a pool of water has been used extensively (D'Hooge and De Deyn, 2001). More recently, virtual or computerised versions based on the rodent water maze task have become available for human study (e.g., (Skelton et al., 2000). Therefore, the water maze task allows for direct comparisons of performance in rodents and humans as the same performance parameters can be applied to both species including latency and distance to reach the escape platform, heading error, number of failed trials, etc. In addition, probe trials administered after rodent or human subjects have learned the task can be employed to assess memory for the platform location while the use of a visible platform allows assessment of the strategy used by subjects to learn the platform location (Grissom et al., 2012). Within anxiety and depression, human adolescents suffering from an anxiety disorder (Mueller et al., 2009b) or adults with depression (Gould et al., 2007) show impairments in spatial learning and memory relative to healthy comparisons. In parallel, assessment of learning strategy in pre-pubertal and adult male rats indicated that males high in anxiety on the open field task were more likely to use striatal-based habit learning rather than hippocampus-based spatial learning to remember the location of an escape platform when compared to their less-anxious counterparts (Grissom et al., 2012; Hawley et al., 2011). Taken together, studies support the idea that spatial memory is modulated by anxiety in both humans and rodents. Future work

in this area could utilise versions of the water maze task to determine the effects of gonadal hormones on spatial learning and memory in both rodent and human subjects expressing anxious and/or depressed behaviours.

A second standard paradigm that has been used in both humans and rodents is the acoustic startle response task. Here, both women with PMDD (Bannbers et al., 2011) and female rats under progesterone withdrawal (Gulinello et al., 2003) showed increased startle reactivity, whereas healthy women with supplementation of testosterone showed reduced startle reactivity (Hermans et al., 2006). In addition, parallel investigations across the life-span in humans and mice revealed consistent evidence across species of reduced extinction learning in adolescent humans and mice possibly due to altered plasticity in the PFC during the adolescent period (Pattwell et al., 2012). In that study (Pattwell et al., 2012), the mice model also provided mechanistic insight by revealing altered synaptic plasticity of the prefrontal cortex. Despite these promising findings, fear conditioning and startle paradigms have received surprisingly little attention in the study of human endocrine conditions and may prove a fruitful avenue for future research; specifically to examine the effects of perturbations of gonadal steroids on anxious behaviour.

A third intriguing area of future study is sexual and non-sexual reward. While sexual behaviour serves the goal of procreation the rewarding properties of sexual activity place this behaviour on the positive end of the spectrum of emotional behaviour juxtaposed against negative affective processing (e.g., fear and threat). Of course, comparison of sexual activity across species, particularly when including human sexuality, presents its own assortment of unique issues. For one, human sexuality is more complex consisting not only of the act itself but can include attraction to the same or the opposite sex (or both), and include differences in sexual

arousal and desires. Although sexual health has been assessed in some endocrine populations (Fliegner et al., 2013; Wierckx et al., 2011), these are mostly limited to questionnaire-based information and not experimental tasks despite relevant clinical implications. Many questions not only remain to be answered but have yet to be addressed in well-controlled studies. Although early work has for example assessed perception of erotic material in transgender individuals (Barr and Blaszczynski, 1976), it is unclear how cross-sex hormone therapy in human adults changes the neurobiology underlying sexual arousal. For instance, preliminary studies in transgender individuals have documented sexual behaviour before and after sex reassignment surgery (Wierckx et al., 2011). Similarly, other studies have reported that testosterone supplementation in androgen-deficient men decreased symptoms of depression and simultaneously increased sexual arousal (Alexander et al., 1997). However, further evidence of how gonadal steroid replacement affects cognitive processing of sexual stimuli may provide valuable information on how quality of life and sexual health can be enhanced in affected populations.

General summary

In summary, studies investigating affective processes in humans indicate higher rates of mood and anxiety disorders in pathologies that express abnormalities in gonadal hormone levels or tissue sensitivities. Rodent models parallel many of the hormonal and behavioural characteristics of these human pathologies, offering experimental approaches to gain a better understanding of these conditions and the underlying mechanism. Nevertheless, there continues to be a dearth of research that applies non-human models to the study of hormone-based human psychopathologies.

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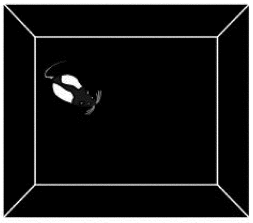
Figure Captions

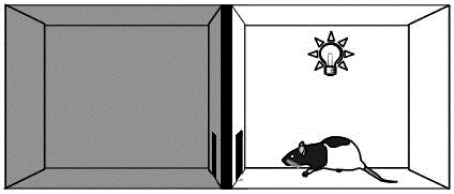
Figure 1. A series of commonly used tasks to measure anxiety-like behaviour in rodents. On the **open field task** (A) a rodent is placed in a large open arena for a period of time. The time spent and the number of entries into the center of the open field are measured as rodents that are anxious or fearful of the new environment are more likely to stay near the corners or walls. The **light/dark apparatus** (B) is a box divided into two compartments with a door that allows passage from one compartment to the other. One compartment of the box remains dark, where the other compartment is illuminated. As nocturnal animals, rodents prefer the dark, therefore anxiety-like behaviour is indicated based on the amount of time and number of entries into the illuminated compartment. Both the **elevated plus** (C) and **zero maze** (D) are elevated above the ground at a height that rodents find aversive. Both mazes have open areas where the rodent is exposed and more vulnerable and enclosed areas where the rodent is not exposed and would be less vulnerable. The time spent and number of excursions into open areas are measured to assess anxiety, with less anxious rodents spending more time and making more excursions into open areas. On the **probe burying task** (E) the latency to begin burying and the time spent burying unfamiliar objects are used as indices of anxiety, with more anxious rats being quicker or more efficient at burying novel objects. This task capitalizes on the behaviour that when confronted with an unfamiliar object, such as a marble, a rodent high in anxiety is more likely to bury the object with bedding.

Figure 2. Simplified model of a proposed relationship between anxiety or depressive symptoms, androgen or estrogen levels based on trends observed in neuroendocrine disorders.

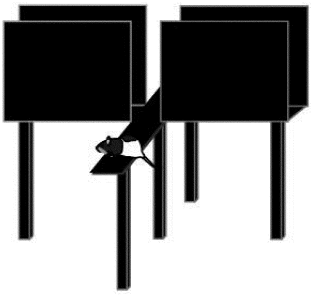
Figure 3. Comparison of translatability of tasks suitable for both humans and rodents. (A) A virtual, computerized version of the Morris Water Maze task and the original Water Maze task in rodents. (B) Measuring of startle response in humans via the conditioned eye-blink reflex and the whole body startle response in rodents.



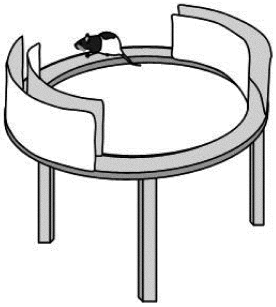
(A) Open Field



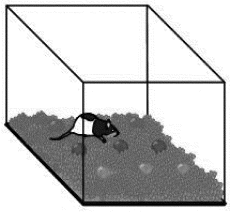
(B) Light/Dark Box



(C) Elevated plus maze

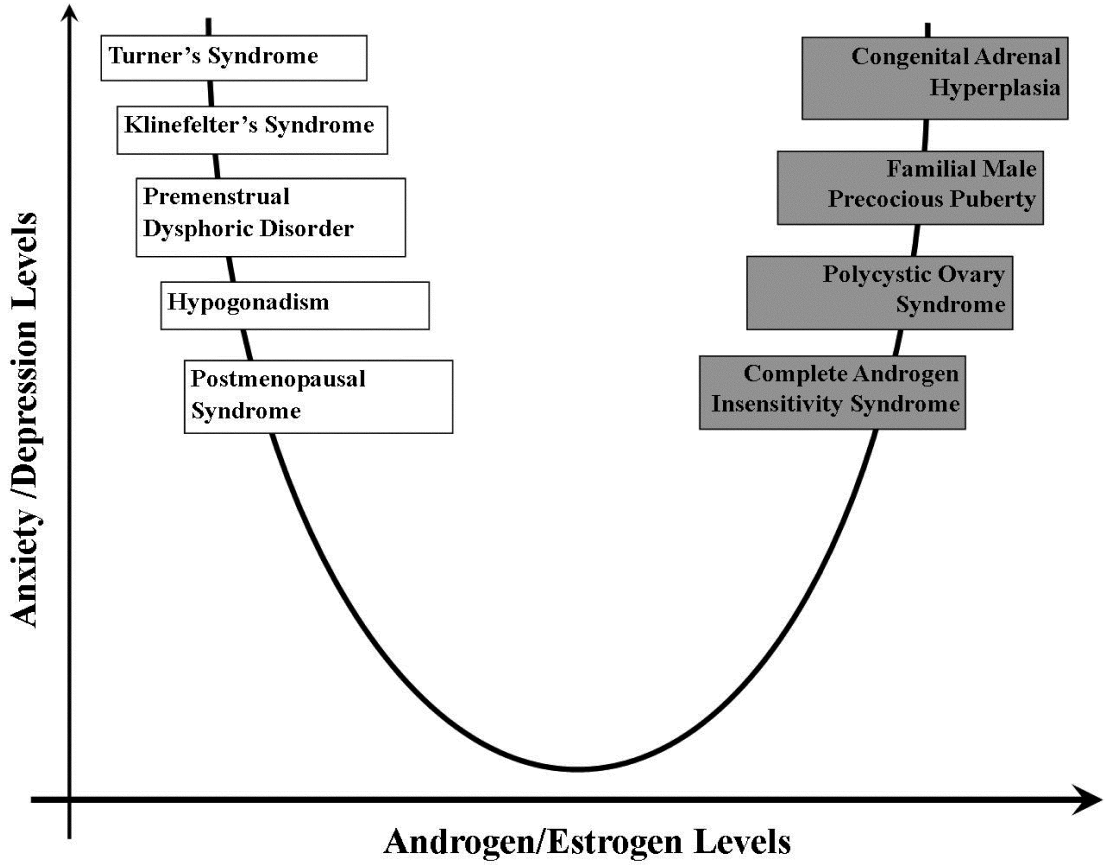


(C) Zero maze

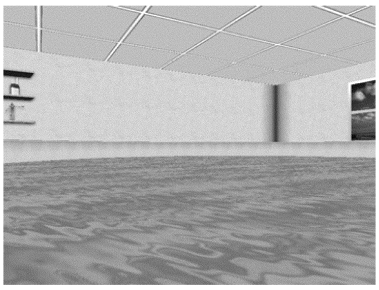


(D) Marble burying

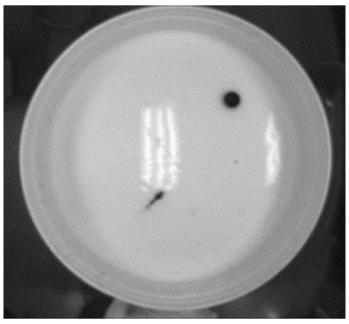
Hormonal contribution to affective psychopathologies across species



(A) Water Maze—Spatial Memory

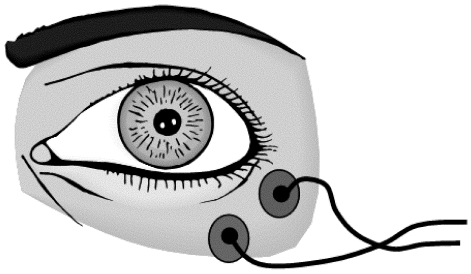


(A1) Virtual Water Maze—Humans

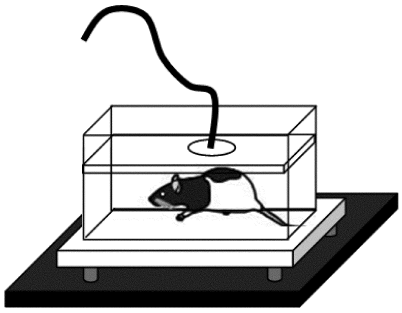


(A2) Water Maze—Rodents

(B) Startle Response—Fear



(B1) Conditioned Eye Reflex—Humans



(A2) Whole Body Startle Response—Rodent