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Review article

Revisiting the wandering womb: Oxytocin in endometriosis and bipolar disorder

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ABSTRACT

Hippocrates attributed women's high emotionality – hysteria - to a 'wandering womb'. Although hysteria diagnoses were abandoned along with the notion that displaced wombs cause emotional disturbance, recent research suggests that elevated levels of oxytocin occur in both bipolar disorder and endometriosis, a gynecological condition involving migration of endometrial tissue beyond the uterus. We propose and evaluate the hypothesis that elevated oxytocinergic system activity jointly contributes to bipolar disorder and endometriosis. First, we provide relevant background on endometriosis and bipolar disorder, and then we examine evidence for comorbidity between these conditions. We next: (1) review oxytocin's associations with personality traits, especially extraversion and openness, and how they overlap with bipolar spectrum traits; (2) describe evidence for higher oxytocinergic activity in both endometriosis and bipolar disorder; (3) examine altered hypothalamic-pituitary-gonadal axis functioning in both conditions; (4) describe data showing that medications that treat one condition can improve symptoms of the other; (5) discuss fitness-related impacts of endometriosis and bipolar disorder; and (6) review a pair of conditions, polycystic ovary syndrome and autism, that show evidence of involving reduced oxytocinergic activity, in direct contrast to endometriosis and bipolar disorder. Considered together, the bipolar spectrum and endometriosis appear to involve dysregulated high extremes of normally adaptive pleiotropy in the female oxytocin system, whereby elevated levels of oxytocinergic activity coordinate outgoing sociality with heightened fertility, apparently characterizing, overall, a faster life history. These findings should prompt a re-examination of how mind-body interactions, and the pleiotropic endocrine systems that underlie them, contribute to health and disease.

1. Introduction

Egyptian medical records dating back to 1990 BCE describe cases of women experiencing erratic emotions with accompanying physical manifestations including seizures, paralysis, choking, and mutism (Novais et al., 2015). Because of their female specificity, medical and gynecological practitioners and writers of antiquity such as Aretaeus, Soranus, Plato, Hippocrates, and Galen explained these symptoms as emerging from the womb (Novais et al., 2015; Tasca et al., 2012; Gilman et al., 1993). A belief held by some of these men was that the womb was a separate being or even an animalistic entity that lived within a woman and could cause health issues by wandering around her body and disturbing other organs (reviewed in Gilman et al., 1993). Hippocrates (460–377 BCE) grouped these heterogeneous symptoms under *hysteria* (from Greek *hysterikos*, meaning 'of the womb'), a term that has since been subsumed into other diagnostic labels (Fig. 1). Debate over the nature of the womb and its ability to truly wander around a woman's body continued well into the Renaissance, informing medical treatments and influencing attitudes about women (Novais et al., 2015).

In a continuation of ascribing animalistic traits to women, the 'father of psychiatry,' Emil Kraepelin, characterized hysteria as a clash between instinct and volition, intuiting later psychoanalytic developments that emphasized the role of conflicting drives in hysteria, and psychopathology more generally (Decker, 2004). Within the frameworks of the DSM, the dissociative and somatic symptoms formerly belonging to hysteria remain, and are commonly observed in mood and personality disorders, including bipolar disorder (Fig. 1). Although severe forms of bipolar disorder are equally prevalent in both sexes (Blanco et al., 2017), women tend to report higher levels of somatic, dissociative and mood symptoms (Delisle et al., 2012; Dessotte et al., 2015; Tabassum and Farooq, 2007), and overall, meet criteria for affective disorders much more frequently than men (O'Donnell et al., 2016).

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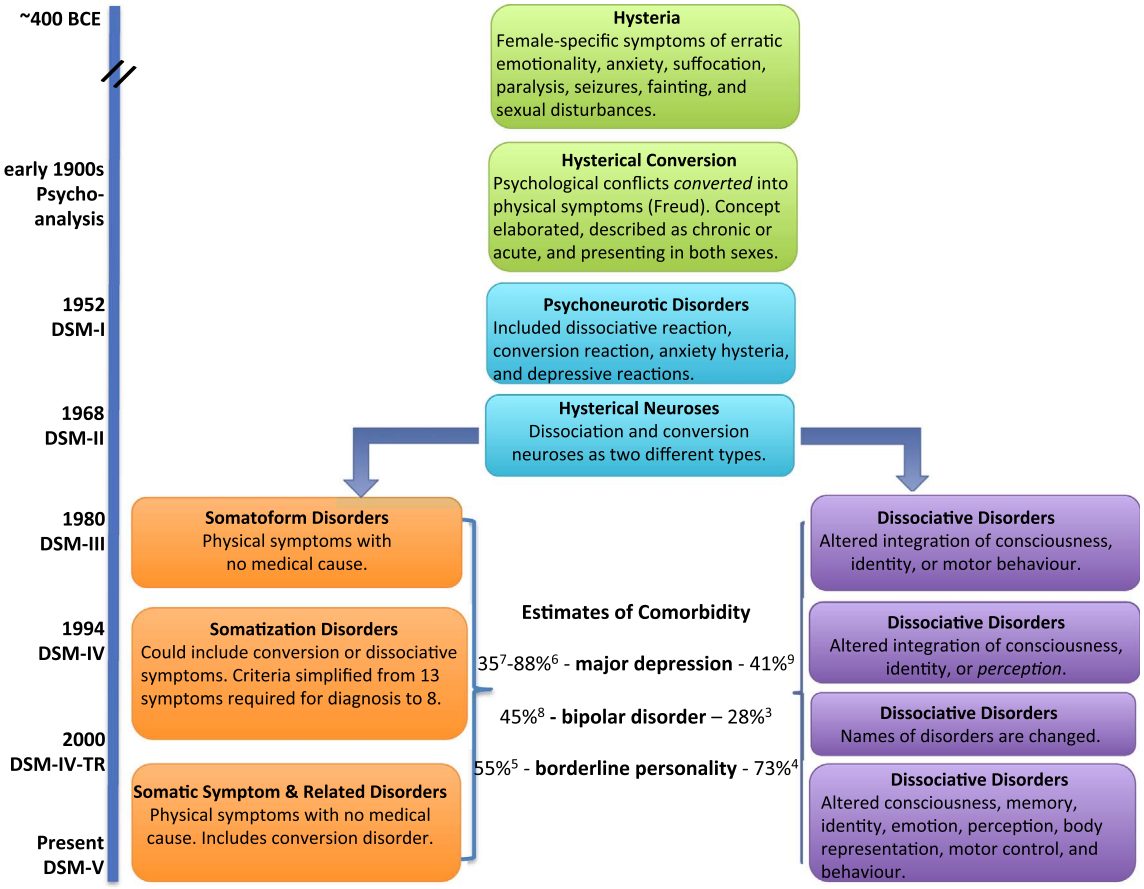

Fig. 1. Simplified timeline[1,2] and comorbidities[3–9] of hysteria-related, female-preponderant categories. Hysteria is no longer a diagnostic category but its heterogeneous symptoms still exist and have been subsumed by other diagnoses in modern versions of the DSM.
References: 1. North, 2015, 2. Kapfhammer, 2001, 3. Yayla et al., 2015, 4. Sar et al., 2006, 5. Rechlin et al., 1997, 6. Bowman and Markand, 1996, 7. Kuloglu et al., 2003, 8. Tavormina, 2011, 9. Sar et al., 2013.

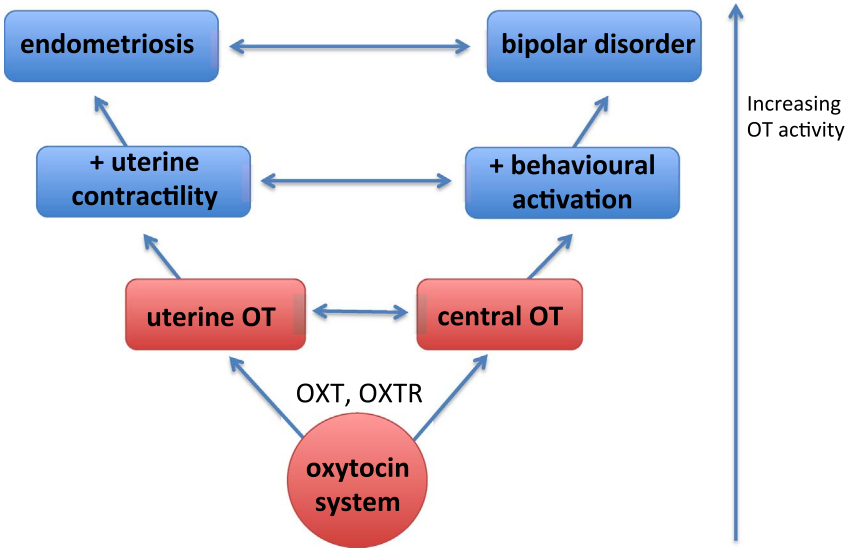

Fig. 2. Hypothesized effects of elevated oxytocin system activity on psychological and physiological traits that contribute to bipolar disorder and endometriosis. A highly simplified diagram showing how the pleiotropic genes (OXT, OXTR) that shape the oxytocin (OT) system contribute to both uterine and central OT levels and OT receptor densities. Given OT's potentiating effects on uterine contractility and social behaviour, it is hypothesized that as net OT system activity increases, through either increased OT levels or heightened OT receptor densities or both, the joint risk of endometriosis and bipolar disorder also increases. Under this model, OT-mediated physiological and psychological processes are positively associated, and jointly affected by increasing (or decreasing) oxytocin system activity.

Bipolar disorder, characterized by alternating high and low affective states, is different from hysteria, but it has long been recognized that the two phenotypes overlap, especially with respect to mood volatility (noted by Kraepelin; reviewed in Kapfhammer, 2001). Somatic symptoms, such as muscular tension and migraines, are frequently observed in people seeking treatment for bipolar disorder (Tavormina, 2011). For about half of women with bipolar disorder, shifts in menstrual cycle phase also precede symptom onset, and menstrual cycling notably impacts symptom severity (Teatero et al., 2014), highlighting the complex interplay between the body, particularly with respect to female reproductive physiology, and psychological health (Galea et al., 2016).

The interactions of mind with body - and their joint disturbance in female-preponderant psychiatric diagnoses - thus centrally contributed to the emergence of psychiatry, and at present remain both mysterious

and difficult to study and treat. Such difficulties apparently derive in part from sharp demarcation of medicine (for the body) from psychology (for the mind) and more broadly, they represent an outcome of persistent dualistic concepts of 'mind' and 'body', which constrain our abilities to accurately perceive and communicate about mind-body interactions (Van Oudenhove and Cuypers, 2010).

Although a 'wandering womb' was long ago dismissed as causing mental illness, recent evidence links oxytocin, a neuropeptide that mediates both uterine contractility and social bonding, with diverse and correlated psychological and physical symptoms and conditions that more frequently affect women than men (Seng, 2010). In this article, we propose the novel hypothesis that elevated oxytocin activity, via some combination of increased serum oxytocin and increased expression and densities of oxytocin receptors, jointly mediates risk of bipolar disorder and endometriosis in women (Fig. 2).

To evaluate this hypothesis, we draw on multiple lines of evidence. We begin by describing salient aspects of the oxytocinergic system, and provide relevant background information on the symptoms and causes of endometriosis and bipolar disorder. We then describe and evaluate evidence of comorbidity between these two disorders, and investigate evidence regarding its causes. These lines of salient evidence include: (1) oxytocin's influence on personality traits, especially extraversion and openness; (2) higher oxytocinergic activity in both endometriosis and bipolar disorder; (3) abnormal hypothalamic-pituitary-gonadal axis functioning in both conditions, including overlapping patterns of menstrual characteristics; (4) the presence of a set of medications commonly used to treat bipolar disorder that appear to improve endometriosis symptoms, and vice versa; (5) observed, and hypothesized, fitness-related impacts of endometriosis and bipolar disorder as well as their non-clinical, less-severe phenotypes; and (6) a pair of correlated reproductive and psychological disorders, polycystic ovary syndrome and autism, that appear to involve reduced oxytocinergic activity, thus representing an 'opposite' pair of conditions to endometriosis and bipolar disorder.

Finally, we explore the extent to which high oxytocin levels adaptively coordinate psychological and physiological traits within women, possibly contributing to a faster life history strategy that is characterized by a combination of high sociality and early, high fertility. Although the 'wandering womb' is now considered a historical anecdote, the proposed hypothesis highlights its apparent essential truth: uterine activity and psychological health are indeed linked, via complex and oxytocin-dependent effects.

1.1. Oxytocin, sociality, and physiology

The neuropeptide oxytocin emerged in concert with placentation, viviparity, lactation, and extended maternal care among mammals, and is well known for its role in regulating maternal-offspring interactions and sociality much more broadly (Crespi, 2016; Feldman, 2016). One of oxytocin's most conserved functions is the contraction of smooth muscles, notably of the uterus during parturition, which inspired its name, as oxytocin means '*quick birth*' in Greek (H. Lee et al. 2009a).

In addition to its modulation of reproductive processes and social behaviour, oxytocin also mediates immune functioning and wound healing (Elabd et al., 2014; Gouin et al., 2010; Li et al., 2017), cardiovascular activity (Gutkowska et al., 2014), and energy homeostasis and stress-responsiveness (Smith et al., 2015). These diverse effects are exerted through oxytocin's central release from magnocellular neurons in the neurohypophysis and its subsequent entrance into general circulation, as well as through its peripheral production in, and action upon, multiple tissues including the heart, ovaries, and uterus (Gimpl et al., 2001). Overall, oxytocin is a highly abundant chemical messenger in both the brain and the body, acting as a neurotransmitter that alters brain connectivity for extended periods of time, and as a hormone that coordinates physiological processes with behavioural states (Bethlehem et al., 2013; Gimpl et al., 2001).

A large body of research reveals that oxytocin augments prosocial behaviour such as empathy, trust, and maternal sensitivity, through both endogenous release and artificial administration (Striepens et al., 2011). Although oxytocin's effects vary widely depending on contextual and individual factors (Bartz et al., 2011), the majority of studies tend to focus on oxytocin's positive impacts on psychological and social functioning. However, a recent and comprehensive review demonstrates that elevated oxytocin levels can also predict aspects of negative emotionality, including increased interpersonal distress, relationship anxiety, and sustained attention to stressful social situations, especially in women (Crespi, 2016; Grebe et al., 2017). These findings indicate that elevated oxytocin levels can mediate either prosociality or social and relational vulnerability, motivating an individual to attend to and process social information salient to navigating complex and valuable relationships.

Aspects of social cognition and mentalizing tend to be elevated and exaggerated in psychological disorders that belong to the psychotic-affective spectrum, and several of these conditions, including schizophrenia, bipolar disorder, and depression, show associations with increased levels of oxytocin in some studies (Crespi, 2016). Oxytocin is also elevated in women with post-traumatic stress disorder, and positively correlated with dissociative symptoms as well as physical symptoms including severe nausea and vomiting during pregnancy (Seng et al., 2013). Although the detrimental effects of low oxytocin levels in psychiatric conditions are relatively well characterized (Cochran et al., 2013), the contribution of *high* levels of oxytocin to psychiatric - and physical – disease remains almost entirely underexplored.

Large quantities of oxytocin are centrally released during coitus, parturition, and suckling, revealing oxytocin's key roles in coordinating interpersonal and reproductive functions (Gimpl et al., 2001; Roney, 2016). The uterus becomes increasingly sensitive to oxytocin in late pregnancy and locally produced oxytocin may play a role in regulating the onset of labor (Kimura et al., 2013). Levels of oxytocin fluctuate with women's menstrual cycles; rising oxytocin levels coincide with peaks in estrogen prior to ovulation, coordinating sexual receptivity with oxytocin-mediated sperm transport during the fertile phase of a woman's cycle (Kunz et al., 2007; Salonia et al., 2005). Oxytocin influences other, diverse aspects of female reproductive physiology, such as luteal degradation, uterine contractility, and embryo positioning; these roles are not fully understood in humans but plausibly impact a woman's ability to become and remain pregnant, as well as to give birth at an optimal time (Bishop, 2013; Carter, 1992; Furuya et al., 1995; Saller et al., 2010).

Oxytocin is produced and its effects are exerted through the action of two genes: one gene encodes oxytocin and its precursor (oxytocin-neurophysin I; OXT), and another gene encodes oxytocin's singular receptor (the oxytocin receptor; OXTR). Because OXT and OXTR gene products each influence a diverse range of phenotypes, the oxytocin system is highly pleiotropic (Paaby and Rockman, 2013), in that changes to either or both of these genes will impact not only social behaviour, but numerous physiological processes as well. Such pleiotropy is indeed central to oxytocin's evolved functions as a neuropeptide that, among mammals, is the primary hormone for coordinating physiological processes with behavioural aspects of viviparity and maternal care (Crespi, 2016). As such, high oxytocinergic activity in the physiological domain is expected to coincide with high activity in oxytocin-mediated cognitive and behavioural domains, and conversely for low activity in both.

Generally, biological systems can be altered toward greater or reduced activity, and an evolutionary framework for health and disease suggests that diseases, as forms of maladaptation, often represent extremes of adaptive phenotypes in either of these two directions (Crespi and Go, 2015). Elevated activity of the oxytocin system may thus, through its pleiotropic nature, be expected to jointly contribute to psychological and physiological symptoms and diseases. Thus, as

described in more detail below, in endometriosis heightened oxytocinergic activity appears to increase uterine movement to an extent that fertility is disrupted, and for bipolar disorder, heightened oxytocinergic activity may increase social approach tendencies to an extent that disturbs healthy goal-seeking behaviour and mood (Fig. 2).

1.2. Endometriosis and adenomyosis

Two reproductive disorders centrally involve the movement of uterine tissue outside of the uterus. Endometriosis is an estrogen-dependent disease that involves the migration and proliferation of endometrial glands and stroma into the ovaries, fallopian tubes, and peritoneal cavity (Leyendecker et al., 2009). A leading contributor to female infertility, endometriosis causes pain in up to 80% of affected women, while up to one quarter are asymptomatic (Bulletti et al., 2010). Endometriosis ranges in severity with respect to the intensity and chronicity of pain experienced, as well with the depth and invasiveness of lesions (Koninckx et al., 2016). Adenomyosis is diagnosed when the endometrial lining breaks through the uterine muscle wall (the myometrium), enlarging the uterus and causing painful menstruation (Vercellini et al., 2006). Affecting approximately 10–18% of women, adenomyosis prevalence is difficult to assess because of differences in diagnostic criteria (Vercellini et al., 2006). Endometriosis occurs in about 80–90% of women with adenomyosis, and both diagnoses are heritable with approximately half of the variation in risk due to genetic factors (Kissler et al., 2007; Saha et al., 2015).

The etiologies of endometriosis and adenomyosis are not fully understood, but the conditions do involve some well-characterized alterations to normal reproductive physiological processes, including hormonally regulated uterine motion (Leyendecker et al., 2004). All non-pregnant uteri are constantly in motion, but endometriosis and adenomyosis uteri express very intense patterns of contraction, which cause excess strain on tissues that elicits constant repair (Kobayashi et al., 2013; Leyendecker et al., 2009). Tissue repair, plus the cyclical growth and shedding of the endometrium, requires a balance between cellular proliferation and apoptosis; this balance is dysregulated in endometriosis uteri, resulting in a state of chronic inflammation that is maintained by estrogen production in endometriosis lesions (Kobayashi et al., 2013; Leyendecker et al., 2009). Indeed, multiple indicators of chronic inflammation, such as immune cells in the peritoneal fluid and elevated levels of prostaglandins and cytokines, are observed in women with endometriosis (Kobayashi et al., 2013). Uterine motion also creates retrograde menstruation, the backward and upward movement of menstrual secretions, which occurs in most women, but for reasons not fully understood, develops into endometrial lesions in a subset (Leyendecker et al., 2004). Elevated contractility of the uterus thus constitutes the primary phenomenon of endometriosis and adenomyosis (Kunz et al., 2007; Leyendecker et al., 1996).

1.3. Bipolar disorder

Bipolar disorder is characterized by alternating periods of depression and mania or hypomania, but high levels of heterogeneity in both the duration and severity of mood fluctuations have prompted the usage of multiple labels within this broader diagnostic category (DSM-V; APA, 2013). For example, bipolar I disorder is the most chronic and severe form, involving both manic and depressive episodes that usually begin in the second decade of life; lifetime prevalence of bipolar I disorder is around 1–2% and does not differ between the sexes (Blanco et al., 2017). Other forms of bipolar disorder include cyclothymic disorder, a relatively mild diagnosis that involves depressive and hypomanic symptoms, and bipolar II disorder, characterized by major depressive and hypomanic episodes (Angst et al., 2003). These less severe manifestations of bipolar disorder tend be more prevalent in women (S. Lee et al. 2009b; Merikangas et al., 2011), although some studies do not find a sex difference (Dell'Aglio et al., 2013). Bipolar traits and symptoms also occur in healthy people, indicating that bipolar disorder is most accurately conceptualized as a spectrum with manifestations in both clinical and non-clinical populations (Dell'Aglio et al., 2013).

For all bipolar disorders, the defining characteristic is mania, or its less extreme form, hypomania, which involve elevated mood and hyperactivity that ranges from elation and risk-taking to irritability and recklessness (DSM-V; APA, 2013). Mania is heterogeneous, involving combinations of grandiosity, racing thoughts, rapid speech, distractibility, increased goal-directed activity, agitation, risky behaviour, and altered sleep patterns (DSM-V; APA, 2013). These multiple features observed in manic episodes can be generally understood as involving behavioural and psychomotor activation and goal-seeking (Johnson et al., 2012; Scott et al., 2017).

Bipolar symptoms in women fluctuate with the menstrual cycle and both manic and depressive symptoms can be initiated by ovulatory or premenstrual phases (Teatero et al., 2014). Childbirth constitutes a high-risk period for the onset of hypomania in women with major depression, due in part to low estrogen levels following parturition, and women with postpartum psychotic symptoms respond well to estrogen supplementation (Meinhard et al., 2014; Sharma et al., 2014). Estrogen appears to exert its effects on bipolar symptoms through modulating neurotransmitter systems and intracellular signaling pathways (Frey and Dias, 2014.) Although fluctuating estrogen impacts bipolar symptoms, individual heterogeneity is high, and women with and without bipolar disorder tend to show equivalent levels of estrogen (Teatero et al., 2014). For women, bipolar disorder is thus closely linked to the reproductive cycle, though the relationship is not fully understood.

1.4. Comorbidity of endometriosis with bipolar disorder

Women with endometriosis manifest heightened vulnerability to certain psychiatric disorders, especially the tendency toward anxiety and depression, though these relationships interact with level and chronicity of pain in complex ways so it is essential that studies include measures of pain levels or pain-matched control groups (reviewed in Pope et al., 2015). In Pope et al.' (2015) meta-analysis, major depression occurred more frequently in the non-endometriosis control group (36.4% compared to 18%) while bipolar disorder was more prevalent in the endometriosis group (16.7% compared to 2.7%). Similarly, Ferrero et al. (2006) found that panic and somatoform disorders were significantly more frequent in women with endometriosis than in unaffected women; panic and somatoform disorders belong to the larger diagnostic category of somatization, which is highly comorbid with bipolar disorder (Fig. 1).

This apparent comorbidity between endometriosis and bipolar disorder has been specifically examined in four studies, with mixed results. Lewis et al. (1987) first documented comorbidity between the two conditions, reporting that 62.5% of endometriosis patients from a small sample (n = 16) drawn from a university clinic met bipolar criteria or had already been diagnosed, while only 12% met criteria for major depression. Furthermore, 56% of the endometriosis patients reported having a first-degree relative with a mood disorder. The lack of control or comparison group in Lewis and colleagues' study however makes it difficult to assess the specificity of the bipolar-endometriosis link. A subsequent attempt to replicate these findings (Walker et al., 1989) included a control group, but failed to find evidence for either increased prevalence of bipolar disorder, or for higher rates of first-degree relatives with affective disorders, in endometriosis patients. While the inclusion of control subjects (n = 55) strengthens these findings, the control group included women with and without pelvic pain, and the pain levels of subjects - including the endometriosis patients (n = 14) - were not assessed, rendering possible interactions between psychiatric features and pain unknown.

To expand upon these contradictory findings, Kumar et al. (2011) assessed the prevalence of bipolar disorder in women with endometriosis (n = 27) and women with pelvic pain but no endometriosis

(n = 12). Importantly and in contrast to Walker and colleagues, Kumar's team assessed pain levels and found no group differences, so the results on bipolar prevalence cannot be attributed to pain. Bipolar disorder was significantly more prevalent in endometriosis patients than expected (8.3 expected, 12 actual; $\chi^2 = 7.96$, $p < 0.019$). In a recent study, Osório et al. (2016) found that women with chronic pelvic pain (n = 50) were more likely than pain-free women to meet criteria for mood disorders, including bipolar disorder and major depression. However, Osório and colleagues did not find evidence for increased prevalence of bipolar disorder among a subgroup of women with endometriosis (n = 24), though the control group against which they compared bipolar prevalence (endometriosis versus pelvic pain, endometriosis versus no pelvic pain, or both) was not mentioned.

Patterns of comorbidity can be further examined by assessing personality traits in women with endometriosis, as some women may not meet psychiatric diagnostic thresholds but might manifest elevated levels of certain personality traits that tend to predict increased susceptibility to psychiatric disorders. Low et al. (1993) reported elevated levels of psychoticism, introversion, and anxiety in women with endometriosis compared to women with matched levels of pelvic pain but no endometriosis. Psychotic features and symptoms do overlap with the bipolar spectrum, affecting approximately half of people with a bipolar diagnosis (Özyildirim et al., 2010); increased psychoticism in women with endometriosis is consistent with a link to bipolar disorder. In contrast, Cavaggioni et al. (2014) did not find differences in psychotic, or somatic, symptoms between endometriosis patients and control subjects, but women with endometriosis showed significantly higher levels of obsessive-compulsive and depressive traits. Facchin et al. (2015) measured novelty-seeking and self-transcendence in women with endometriosis, two traits which are uniquely elevated in bipolar disorder relative to major depressive disorder (Zaninotto et al., 2016). Because Facchin et al. (2015) were interested in the relationship between pain and personality in women with endometriosis, they measured but did not compare or discuss personality differences between women with pain-free endometriosis and healthy pain-free subjects. Comparing these two groups can reveal personality traits unique to endometriosis without the confounding influence of pain.

We analyzed Facchin et al.'s (2015) published data to examine whether or not bipolar spectrum traits were associated with endometriosis. For the dimension of novelty-seeking, total scores did not significantly differ between unaffected women and women with pain-free endometriosis; however, impulsiveness, a subscale of novelty-seeking, was higher in women with pain-free endometriosis ($n = 24$, $\bar{x} = 25.9$) relative to unaffected women ($n = 51$, $\bar{x} = 24.1$) at a trend level of significance ($t = 1.34$, $p = 0.09$). Mean self-transcendence scores were four points higher in women with pain-free endometriosis ($\bar{x} = 72.2$) than unaffected women ($\bar{x} = 68.1$) but this difference was not significant ($t = 1.19$, $p = 0.12$). However, scores on transpersonal identification, a subscale of self-transcendence that refers to a sense of unity with objects beyond the self (Cloninger et al., 1993), were elevated in women with pain-free endometriosis ($\bar{x} = 21.4$) relative to healthy controls ($\bar{x} = 19.4$), at a trend level of significance ($t = 1.41$, $p = 0.08$). These data suggest that women with endometriosis express elevated levels of some bipolar spectrum traits.

Research examining the relationship between endometriosis and bipolar disorder is summarized in Table 1 and is notably suggestive of comorbidity between the two conditions. Personality traits of women with endometriosis appear to differ from unaffected women, and some of these differences are unique to the bipolar spectrum. Given that two of four studies found increased prevalence of bipolar disorder in endometriosis (Kumar et al., 2011; Lewis et al., 1987), and that one of these studies controlled for pain levels (Kumar et al., 2011), and that across multiple studies, bipolar disorder - but not major depression - appears more frequently in women with endometriosis relative to unaffected women (Pope et al., 2015), the connection between these two conditions is, we believe, sufficiently compelling to warrant further examination.

2. Review of evidence

2.1. Oxytocin, personality traits, and psychiatric diagnoses

Oxytocin promotes social behaviour and bonding through affective and cognitive pathways. The release or administration of oxytocin can reduce fear and anxiety via attenuation of amygdala activity, as well as enhancing attention to and processing of socially salient stimuli (Domes et al., 2007; MacDonald and MacDonald, 2010; Shamay-Tsoory and Abu-Akel, 2016). Oxytocinergic neurons in the hypothalamus project to the ventral tegmental area (VTA), a key region of the reward pathway rich in both dopaminergic neurons and oxytocin receptors, as well as to the nucleus accumbens (NAc), amygdala, hippocampus, and prefrontal cortex, all of which also receive projections from dopaminergic neurons (Skuse and Gallagher, 2009). These complex oxytocin-dopamine interactions imbue social stimuli with reward and facilitate approach-avoidance behaviours (Love, 2014), promoting long-term memory formation, social recognition, and behavioural synchrony; together, these processes support bonding across interpersonal contexts such as mother-offspring, mating, and friendship (Feldman, 2016). Together, the anxiolytic, stress-reducing, and rewarding properties of oxytocin release can function to reduce the threshold for social approach behaviours (Kemp and Guastella, 2011), though these prosocial effects depend on contextual and individual factors such as familiarity and attachment (Bartz et al., 2011).

Oxytocin's modulation of social approach tendencies is evident through its relationship to specific personality dimensions, especially extraversion, openness, and creativity. Extraversion is a relatively stable personality trait that encompasses facets of warmth, positive affect, gregariousness, and responsiveness to reward, while openness to experience reflects intellectual curiosity and imagination (Power and Pluess, 2015).

Andari et al. (2014) reported that levels of plasma oxytocin positively predict self-reported ratings of extraversion, and together, plasma oxytocin levels and extraversion scores negatively predict volumes of the amygdala and hippocampus, brain regions important in fear processing and memory consolidation. Interestingly, oxytocin administration also influences beliefs about one's social behaviour: Cardoso et al. (2012) found that people self-reported higher levels of extraversion and openness to experience if they had received oxytocin relative to a placebo. In a recent review, De Dreu et al. (2015) also proposed that the oxytocin system underlies creativity through its engagement of divergent and flexible cognitive pathways. Oxytocin, through interacting with dopamine-mediated neural pathways, thus shows evidence of contributing to extraversion, openness, and creativity.

Psychological disorders are increasingly considered as reflecting extremes of normally adaptive psychological and personality traits (Widiger and Trull, 2007). Mania, as the defining feature of bipolar disorder, may thus be conceptualized as reflecting high extremes of extraversion, openness, and creativity, in the general context of seeking fitness-related goals in one's environment. Both extraversion and mania involve reduced thresholds for behavioural approach, such as increased sexual activity (Kopeykina et al., 2016; Raynor and Levine, 2009), impulsivity and sensation-seeking (Strakowski et al., 2010; Zuckerman and Glicksohn, 2016), and elevated creativity (Ma, 2009; McCraw et al., 2013). In numerous self-report studies using validated personality and diagnostic surveys, extraversion and openness positively predict levels of hypomanic personality traits such as energetic temperament, cheerfulness, irritability, and recklessness (Durbin et al., 2009; Meyer, 2002; Quilty et al., 2009). Approximately half of the variation in openness and extraversion can be attributed to genetic factors (Jang and Livesley, 1996; Vernon et al., 2008), and genes underlying both traits also contribute to bipolar disorder risk. For example, Lo et al. (2017) reported significant, positive genetic correlations between

Table 1
Summary of findings from studies investigating personality and mental illness in women with endometriosis.

Author	Year	Method	Key finding
Lewis et al.	1987	Clinical sample with no control group	High rates of bipolar disorder in women with endometriosis
Walker et al.	1989	Study included control group but did not measure or match pain levels	No difference in rates of bipolar disorder in women with or without endometriosis
Low et al.	1993	Study included control group and matched for pain levels	Elevated psychoticism, introversion, and anxiety in women with endometriosis
Ferrero et al.	2006	Study with control group and measures of pain levels	Increased rates of panic and somatoform disorders in women with endometriosis
Kumar et al.	2011	Study with control group and matched for pain levels	Bipolar disorder more prevalent in women with endometriosis than expected
Cavaggioni et al.	2014	Study with control group and measures for pain levels	Elevated levels of obsessive-compulsive and depressive traits in women with endometriosis
Pope et al.	2015	Meta-analysis	Increased rates of bipolar disorder in women with endometriosis
Facchin et al.	2015	Study with control group and measures of pain levels	Trend of higher levels of bipolar spectrum traits, including impulsiveness and spiritual experiences, in women with endometriosis

extraversion and bipolar disorder ($r = 0.18$, $p < 0.05$) and openness and bipolar disorder ($r = 0.34$, $p < 0.001$). A novel model of personality found that both openness and extraversion were positively associated with a curious/energetic temperament, and the authors suggest that this temperament reflects the dopamine system, likely predisposing to mania as well as the broader psychotic-affective spectrum (Fisher et al., 2015).

Enhanced creativity is notably related to the bipolar spectrum (Greenwood, 2017; Taylor et al., 2015), among other psychotic-affective spectrum conditions (ie. Nettle and Clegg, 2006), and mood disorders including bipolar tend to be more prevalent in families of artists and writers (Post, 1996). In a recent meta-analysis on personality dimensions in mood disorders, Zaninotto et al. (2016) reported that bipolar disorder was specifically predicted by elevated scores on measures of novelty-seeking, which includes impulsiveness and extravagance, as well as self-transcendence, which involves creativity and the tendency to experience a sense of unity or spirituality (Cloninger et al., 1993). The human capacity to have spiritual experiences is regulated in part by oxytocin (Crespi and Summers, 2014; Van Cappellen et al., 2016). These findings suggest that mania and the bipolar spectrum represent extreme variants of personality traits, including creativity, spirituality, openness, and extraversion, that are known from other work to be strongly mediated by oxytocin.

Consistent with the above patterns, people with bipolar disorder have been reported to exhibit heightened serum oxytocin levels. Turan et al. (2013) found that overall, oxytocin levels were higher in people with bipolar disorder than people without, and even after patients positively responded to treatment, serum oxytocin remained significantly elevated in patients. Oxytocin was highest in patients currently in a manic episode, and oxytocin levels in both remitted patients and currently-depressed patients were significantly higher than non-patient levels. Similarly, Lien et al. (2016) reported higher serum oxytocin in patients with bipolar II disorder relative to patients with major depression and healthy controls. In contrast to Turan and colleagues' finding however, Lien and colleagues found that following treatment, oxytocin levels of bipolar patients, but not depressed patients, were reduced.

Higher levels of serum oxytocin have also been observed in adolescents with treatment-resistant depression – which predicts later development of bipolar disorder, major depression, and schizophrenia – when compared to healthy control subjects and subjects with treatment-responsive depression (Sasaki et al., 2016). Subclinical manic symptoms tend to predict poor response to depression treatment in both adolescents and adults (Correa et al., 2010; Maalouf et al., 2012). If mania is associated with elevated oxytocin as noted above, and if mania predicts poor response to treatment, then treatment-resistant depression is indeed expected to involve elevated levels of oxytocin.

Increased oxytocin levels are also associated with traits, symptoms, and disorders that belong to the psychotic-affective spectrum, of which bipolar disorder overlaps with in terms of symptoms and causes, including the tendency toward hyperactive social cognition (reviewed in Crespi, 2016). Findings on the link between elevated oxytocin and psychotic-affective symptoms are heterogeneous but compelling. For example, serum oxytocin positively predicted schizotypal traits in healthy females (Tseng et al., 2014) as well as delusional ideation in patients with schizophrenia (Walss-Bass et al., 2013). In patients with bipolar disorder, plasma oxytocin levels have been positively associated with the ability to accurately recognize fearful emotions, but not other kinds of emotions (Tas et al., 2015), which is consistent with oxytocin as a signal of social vulnerability. Evidence from psychiatry, personality, and genetic research thus indicates that oxytocin, in conjunction with dopamine, contributes to extraversion, openness, and creativity, which together involve behavioural activation, and when expressed in more extreme levels, underlie risk and expression of mania and bipolar spectrum disorders. Additional integrative endocrine, personality, and psychiatric studies are required, however, to evaluate these ideas further, especially in the contexts of sex differences, and mania and hypomania in relation to depression.

2.2. Oxytocin and endometriosis

Both endometriosis and adenomyosis centrally involve altered and increased uterine peristalsis, a complex and cyclical process necessary for sperm transport and embryo positioning that is regulated through oxytocin's interactions with gonadal hormones (Kunz et al., 1998; Kunz and Leyendecker, 2002; Leyendecker et al., 1996). Uterine peristalsis involves continuous wave-like patterns of rhythmic contractions that shift according to the phase of the menstrual cycle (Kunz and Leyendecker, 2002; Leyendecker et al., 2004). In healthy uteri, contractions move from the cervix to the fundus after menstruation until ovulation; this upward motion during the proliferative phase assists sperm transport from the vagina toward the fallopian tube ipsilateral to the dominant follicle. After ovulation (during the secretory phase), contractions move from the isthmus (above the cervix) to the fundus, encouraging implantation near the top of the uterus. If fertilization does not occur in a given menstrual cycle, contractile waves then move from the fundus toward the cervix, supporting the flow of menstrual blood out of the uterus.

Changes in the direction, frequency, and amplitude of uterine contractions depend in part on temporal and spatial changes in the density and distribution of uterine oxytocin receptors (Kunz et al., 1998). In women with endometriosis or adenomyosis, uterine peristalsis is stronger and faster (hyperperistalsis) as well as asynchronous with the menstrual cycle (dysperistalsis). Table 2 compares oxytocin-mediated uterine and menstrual characteristics in women with and without endometriosis. Although Table 2 focuses on endometriosis, women with adenomyosis show similar alterations to oxytocin-mediated uterine peristalsis (Zhang et al., 2015), including overexpression of oxytocin receptor in the myometrium that positively predicts both intensity of uterine contractions and severity of dysmenorrhea (Guo et al., 2013;

Table 2
Comparison of uterine activity and oxytocin characteristics in women with and without endometriosis.

Women with healthy uteri	Women with endometriosis
Temporal and spatial changes in uterine oxytocin receptor (OXTR) expression across the cycle[a,b] • Proliferative > secretory • Proliferative: fundus < isthmus • Secretory: fundal > isthmus	Higher OXTR expression in proliferative and secretory phases relative to healthy uteri[a] and no change across cycle • Proliferative = secretory • Proliferative: fundus ≥ isthmus • Secretory: fundus ≥ isthmus
Smooth, wave-like uterine contractions that shift in direction and intensity across the cycle	At proliferative phase, wave frequency is doubled relative to healthy uteri and prior to ovulation, contractions are convulsive[e]
Directed sperm transport coincides with ovulation	At early proliferative phase, labeled particles move very rapidly relative to healthy uteri, but prior to ovulation, transport is absent[e]
Clinically non-significant menstrual pain	Dysmenorrhea[d] severity positively associated with uterine OXTR expression[a]
Mild retrograde menstruation occurs in nearly all women[c]	Retrograde menstruation results in endometrial tissue proliferating into lesions outside the womb[c]
Normal plasma oxytocin levels	Elevated plasma oxytocin levels[f]

References
[a] Huang et al., 2017.
[b] Zhang et al., 2015.
[c] Leyendecker et al., 2004.
[d] Harada, 2013.
[e] Leyendecker et al., 1996.
[f] He et al., 2016.

Mechsner et al., 2010; Nie et al., 2010). Elevated oxytocinergic activity thus significantly contributes to the primary features – uterine hyperperistalsis and dysperistalsis - of endometriosis and adenomyosis.

2.3. Overlapping menstrual characteristics between endometriosis and bipolar disorder

Some menstrual features appear to overlap between bipolar disorder and endometriosis, possibly reflecting shared disruptions of the hypothalamic-pituitary-gonadal (HPG) axis. Shorter menstrual cycles (≤ 28 days) are associated with endometriosis (Arumugam and Lim, 1997; Cramer et al., 1986; Wei et al., 2016; Yasui et al., 2015); and adenomyosis (Templeman et al., 2008), though the causal direction of this relationship is unclear. Treloar et al. (2010) reported a similar but non-significant trend of short menstrual cycles predicting endometriosis risk, and also reported that earlier onset of menarche predicted later endometriosis. Similarly, Templeman et al. (2008) found that early menarche (≤ 10 years) predicted later adenomyosis but not endometriosis, while Missmer et al. (2004) reported that early menarche was a risk factor for endometriosis.

Women with bipolar disorder experience early onset menstrual dysfunction significantly more frequently than both non-depressed women and women with major depression, which may be due to bipolar disorder-specific alterations in HPG axis functioning (Joffe et al., 2006). Short menstrual cycles (≤ 28 day cycles) were associated with an almost doubled risk of mood and substance abuse disorders in Caucasian women, but not in African-American women (Barron et al., 2009). Early menarche did not predict later onset of bipolar disorder, but was associated with longer depressive episodes and more severe depressive and cyclothymic symptomology (Kesebir et al., 2013). These lines of evidence suggest that menstrual features and menstrual dysfunction overlap between endometriosis and bipolar disorder, indicating that HPG axis dysfunction may underlie important aspects of both conditions.

2.4. Effects of estrogenic and other medications on endometriosis and bipolar disorder

Additional, indirect evidence for HPG axis alterations in endometriosis and bipolar disorder comes from the pharmaceutical literature, as medications that treat these conditions often target this axis. Table 3 lists several medications that interact with the HPG axis, including drugs that alter estrogen levels, which have shown positive effects on both bipolar disorder and endometriosis symptoms. For example, tamoxifen, a selective estrogen receptor modulator, is an effective anti-manic that paradoxically can both treat and induce endometriosis and adenomyosis symptoms (Table 3). These mixed effects are attributable to tamoxifen's interactions with estrogen: normal rats with induced endometriosis show lesion reduction when treated with tamoxifen, but after an ovarectomy, tamoxifen treatment causes the recurrence of endometriosis lesions (Kadaba and Simpson, 1990). The ability of tamoxifen to reduce endometriosis lesions in both humans and rats, under specific hormonal conditions, are likely due to the drug's inhibiting effects on estrogen-dependent cellular proliferation, an effect that is potentiated by oxytocin (Gimpl et al., 2001).

Endometriosis is an estrogen-dependent disease and estrogen is known to influence bipolar spectrum traits in women, often eliciting both depressive and manic episodes (Kumar et al., 2011; Meinhard et al., 2014; Teatero et al., 2014). Estrogen potentiates the effects of oxytocin, and its presence is often required for oxytocin-dependent traits to emerge (e.g. lordosis in rats; reviewed in Gordon et al., 2011). For example, the uterine hyperperistalsis typical of endometriosis is similar to that observed in healthy women with naturally high estrogen levels who have received intravenous injections of oxytocin (Leyendecker et al., 1998). The oxytocin antagonist, atosiban, reduces endometriosis lesions in rats (Simsek et al., 2012), but in contrast, Yeniel et al. (2014) found that oxytocin itself reduced endometriosis lesions in rats, possibly through its anti-inflammatory effects. Whether or not oxytocin antagonists could be used to reduce manic symptoms is currently unknown. These medications highlight complex interactions between oxytocin and estrogen, and the HPG axis more generally, and while their effects are not fully understood, these medications are suggestive of etiological overlap between endometriosis and bipolar disorder.

2.5. Fitness correlates and impacts of bipolar disorder and endometriosis

An evolutionary perspective on health and disease can help to explain why diseases persist even when they produce deleterious effects on individual fitness (Williams and Nesse, 1991). One hypothesis for the persistence of mental illness is that genetic variants contributing to psychiatric disorders also confer reproductively beneficial traits, such as enhanced creativity or intelligence, as evidenced by increased fecundity or elevated levels of beneficial traits in families of people with psychiatric diagnoses (e.g. Greenwood, 2017). Variation in personality traits such as extraversion may be maintained through trade-offs in

Table 3
Effects of medications on bipolar disorder, endometriosis, and adenomyosis.

Medication & mechanism	Effect on bipolar disorder	Effect on endometriosis	Effect on adenomyosis
Valproate (suppresses estrogen)	Commonly prescribed to treat bipolar disorder	Suppressed proliferation of endometrial stromal cells[a]	Eradication of dysmenorrhea and 1/3 reduction in uterus size[b]
Danazol (androgenic properties)	Alleviated rapid-cycling affective symptoms and manic grandiosity in one female patient[c]	Long history of use in endometriosis; reduces pain and lesion volume[d]	Reduced pain, bleeding, and uterine size[g]
Tranylcypromine (monoamine oxidase inhibitor)	Improved depressive symptoms and reduced switching into hypomania[f]	Significantly reduced lesion size and proliferation and pain in mice with induced endometriosis[e]	Unknown
Mifepristone (anti-progesterone)	Improved spatial working memory, which tends to be reduced in bipolar[h]	Alleviated symptoms when used alone, and improved pregnancy rate when combined with other therapies[i]	Initiated cell apoptosis via increasing caspase 3 expression, which could inhibit adenomyosis[j]
Medroxy-progesterone (progesterone like, anti-estrogenic)	Reduced acute mania in women with schizoaffective disorder and bipolar affective disorder when used with mood stabilizers[k]	Causes endometrial tissue atrophy but high recurrence rates after discontinuation of use[p]	Unknown
Tamoxifen (complex anti-estrogenic and estrogenic effects)	Produced anti-manic effects in 4 studies[l]	Improved symptoms in two women[o] but worsened symptoms in post-menopausal women[m]	Induces adenomyosis in mice[n]

References
[a] Wu and Guo, 2008.
[b] Liu and Guo, 2008.
[c] Goldstein, 1986.
[d] Godin and Marcoux, 2015.
[e] Sun et al., 2016.
[f] Heijnen et al., 2015.
[g] Pontis et al., 2016.
[h] Watson et al., 2012.
[i] Zhang, 2016.
[j] Wang et al., 2014.
[k] Kulkarni et al., 2014.
[l] Meinhard et al., 2014.
[m] Rose et al., 2000.
[n] Parrott et al., 2001.
[o] Haber and Behelak, 1987.
[p] Rodgers and Falcone, 2008.

different combinations of fitness costs and benefits; for example, higher extraversion in women predicts higher numbers of lifetime sex partners, but also increases offspring exposure to step-parents, which constitutes a 'risky' parenting strategy (Nettle, 2005). Extraversion genes contribute to the bipolar spectrum (Lo et al., 2017), and non-affected twins of individuals with bipolar disorder demonstrate elevated positive temperaments and enhanced verbal intelligence (Higler et al., 2014). These 'attractive' traits appear to enhance mating opportunities (Nettle, 2005), helping to account for the persistence of bipolar spectrum traits and alleles in the general population.

Other studies report associations between enhanced fecundity and the bipolar spectrum. Power et al. (2013) investigated the relationship between several psychiatric diagnoses and number of offspring in a cohort of over two million people from a Swedish registry. While people with a bipolar diagnosis had fewer children relative to the general population, sisters - but not brothers - of people with bipolar disorder had more children relative to the general population. Increased fecundity in sisters of people with bipolar disorder suggests that genes contributing to the bipolar spectrum differentially affect female and male fitness. However, another dataset drawn from the National Comorbidity Study (n = 8098) revealed that bipolar symptoms positively predicted increased fertility, and reduced parenting effort, at younger ages in both sexes (Jacobson, 2016). Association of bipolar symptoms with reduced parenting effort is consistent with Nettle's (2005) finding that extraversion predicts riskier parenting strategies. Overall, bipolar spectrum features appear to enhance mating opportunity and fecundity, while severe bipolar disorder leads to reduced reproductive success.

Endometriosis is clearly associated with significant reductions in fertility, making its relatively high prevalence puzzling from an evolutionary perspective. Rates of mild endometriosis appear to be increasing in North America over the past few decades, but prevalence rates are difficult to accurately estimate due to changes in diagnostic criteria over the same time period (Koninckx et al., 2016). Modern environmental factors such as stress, chemical disruptors, and delayed pregnancy appear to contribute to rising rates of mild, but not severe, endometriosis (Koninckx et al., 2016). Because pregnancy-mediated progesterone release inhibits estrogen-dependent endometrial proliferation, pregnancy can prevent and improve endometriosis symptoms, and due to the social trend of women postponing childbirth to develop professionally, endometriosis has been dubbed the ‘career woman's disease’ (Koninckx et al., 2016). Even if current rates of endometriosis partially reflect environmental factors, evolutionary pressures are still expected to have shaped the physiological mechanisms that are sensitive to disruption in this condition.

Sperm transport mechanisms, which are essential to fertility, appear to be overdeveloped, and thus dysfunctional, in women with endometriosis (Kissler et al., 2007; Kunz et al., 2007; Leyendecker et al., 1996). Fertility depends upon cyclical uterine activity: in healthy women, elevated uterine peristalsis prior to ovulation promotes rapid sperm transport and reduced uterine peristalsis after ovulation supports conception and implantation (IJland et al., 1997; Leyendecker et al., 1996; Kunz and Leyendecker, 2002; Kissler et al., 2007). In endometriotic uteri, hyperperistalsis is sustained throughout the cycle, promoting extremely rapid uptake of sperm-like particles too early in the ovulatory cycle (Table 2; Leyendecker et al., 1996), and following ovulation, peristaltic dampening fails to occur, which appears to prevent implantation (Kunz and Leyendecker, 2002). Uterine hyperperistalsis and dysperistalsis thus interfere with the normal functioning of the sperm transport mechanism - specifically in the direction of hyperactivity - in women with endometriosis.

These features of endometriosis and the bipolar spectrum that demonstrate important associations with fertility and fecundity are regulated by oxytocin. Polymorphisms in the oxytocin receptor gene (OXTR) show associations with childbirth at younger ages, plus reduced

usage of contraceptives (Prichard et al., 2007). A recent study found that women with the A allele of the widely studied OXTR SNP rs53576 reported higher rates of orgasm and sexual arousal when the allele co-occurred with a specific estrogen receptor allele (Armeni et al., 2017). Relative to the G allele of OXTR rs53576, the A allele predicted generally reduced prosocial behaviour in a meta-analysis (Li et al., 2015). Two studies have found associations between duration of labour and rs53576 alleles, but the results were in opposite directions (Reitman et al., 2011; Terkawi et al., 2012). Variation in oxytocin genes thus jointly influence sociality, sexual behaviour, and reproductive functioning in women, and though results are mixed and effect sizes small, these findings highlight the diverse, pleiotropic, and fitness-relevant effects of the oxytocinergic system.

2.6. Oxytocin, autism, and polycystic ovary syndrome

If elevated oxytocinergic activity jointly contributes to bipolar disorder and endometriosis, then reduced oxytocinergic activity should jointly underlie diseases with symptoms and causes opposite to those observed in bipolar disorder and endometriosis. A pair of psychological and reproductive disorders, autism and polycystic ovary syndrome (PCOS), appears to fit this pattern. Both autism and PCOS involve elevated androgen activity, and testosterone, one of the main androgens, demonstrates opposite effects to oxytocin across diverse cognitive, behavioural, and physiological domains (Crespi, 2016). Autism is characterized by diminished social interest, communication difficulties, and restricted or repetitive interests and behaviours (Cochran et al., 2013), and generally involves reduced activity of the oxytocinergic system (Gordon et al., 2016; Parker et al., 2014). Repetitive behaviour and restricted interests in autism can be contrasted with increased novelty-seeking in bipolar disorder (Zaninotto et al., 2016), and the autism spectrum involves reduced levels of extraversion and openness (Schwartzman et al., 2016; Strunz et al., 2015), and reduced goal pursuit through social reward (e.g. Dölen, 2015), in contrast to the elevations of these three phenotypes in bipolar disorder, as described above.

Women with autism spectrum conditions are also more likely to identify as 'asexual' compared to non-autistic women (Ingudomnukul et al., 2007), and tend to exhibit lower levels of sexual interest and activity overall (Byers et al., 2013); these findings contrast with elevated sexual motivation - sometimes to an extent that is characterized as hypersexuality - in women with bipolar disorder (Kopeykina et al., 2016; Mazza et al., 2011). Sexual interest is mediated by oxytocin-dopamine interactions (Borrow and Cameron, 2012; Pfaus, 2009; Veening et al., 2015). These findings indicate that some oxytocin-mediated psychological and behavioural features show evidence of opposite patterns in autism and bipolar disorder, though comparisons between these two disorders should be interpreted with caution due to significant differences in age of onset between the two conditions.

Women with autism spectrum conditions, as well as their female relatives, frequently display comorbid testosterone-related disorders, including PCOS (Ingudomnukul et al., 2007), and offspring of mothers with PCOS demonstrate elevated levels of autistic features and autism diagnoses (Kosidou et al., 2016; Palmoba et al., 2012). PCOS is a reproductive condition affecting 4–18% of women of reproductive age that involves symptoms related to hyperandrogenism including increased body hair (hirsutism), irregular or absent menstruation, ovarian dysfunction with irregular or absent ovulation, and metabolic alterations including insulin resistance and increased risk of cardiovascular disease (Teede et al., 2010). Although oxytocin levels in women with PCOS have not been assessed to the best of our knowledge, several key features of the condition are suggestive of low oxytocinergic activity, and these contrast with features of endometriosis.

First, uterine peristalsis in women with PCOS was undetectable in one study, which may indicate reduced uterine contractility in women with this condition (Leonhardt et al., 2012). Second, women with PCOS display thinner endometria (Leonhardt et al., 2012), while women with adenomyosis tend to have thicker endometria (Benagiano et al., 2014). Endometrial thinning in PCOS may be due to high levels of the testosterone precursor androstenedione, as androstenedione inhibits human endometrial cell growth (Tuckerman et al., 2000), and is elevated in people with autism and in women with PCOS (Georgopoulos et al., 2014; Ruta et al., 2011). Third, women with PCOS tend to have irregular menstrual cycles with infrequent or absent ovulation (Teede et al., 2010), while women with endometriosis tend toward shorter cycles with intact ovulation (Hughes et al., 2007). Fourth, while valproate reduces the size of endometriosis lesions and treats symptoms of bipolar disorder (Table 3), it can induce polycystic ovaries when taken by women for epilepsy (Isojärvi et al., 1993); prenatal valproate also represents a well-validated cause of high autism risk in offspring (Roullet et al., 2013).

Polycystic ovary syndrome contrasts notably with endometriosis for the hormone-related physical characteristics waist-to-hip ratio and body mass index, such that these two indices are increased in the former condition but decreased in the latter, compared to controls (Backonja et al., 2016; Ezeh et al., 2014; Shah et al., 2013; Velázquez et al., 2000); these findings are also of interest given evidence of higher fertility being associated with lower waist to hip ratios, in a typical population (Jasienska et al., 2004). Lower levels of serum testosterone (and high estradiol) have also been reported in endometriosis patients (Ono et al., 2014), in comparison to the high testosterone characteristic of women with PCOS. Serum oxytocin is lower in women with obesity or newly-diagnosed type 2 diabetes, compared to controls (Qian et al., 2014), which is consistent with its demonstrated effects on metabolism, energy balance, and body weight (Blevins and Ho, 2013); however, as noted above, the oxytocin system remains virtually unstudied in patients with PCOS.

Considered together, these findings demonstrate that physical, physiological and behavioural features of co-occurring autism and PCOS contrast with features of bipolar disorder and endometriosis, and further, that these diametric patterns of features may be associated with relatively reduced versus elevated oxytocinergic activity. Future joint studies of endometriosis, and PCOS, in relation to controls, are clearly warranted.

3. Discussion

We have described diverse lines of evidence from personality research, endocrinology, psychiatry, and medicine that converge to support the hypothesis that elevated oxytocinergic activity contributes to the symptoms and features of, and the comorbidity between, bipolar disorder and endometriosis (Fig. 3). Evidence for shared etiology of these conditions is especially valuable when considered in two contexts. First, endometriosis and bipolar disorder provide a paradigmatic example of how comorbid diseases can arise through altered activity of a pleiotropic system. Further, the symptoms of these conditions reveal evidence for apparently-adaptive pleiotropy in the female oxytocin system, as bipolar and endometriosis features appear to reflect extreme - and disrupted - manifestations of phenotypes that normally enhance reproduction when co-occurring within individuals. Second, the oxytocin system emerges as a key research avenue for elucidating the causes of women's increased susceptibility to conditions that centrally involve joint mind-body disturbances.

The evidence for comorbidity between endometriosis and bipolar disorder is intriguing but not unambiguous (Table 1), as two studies found support for their linkage (Kumar et al., 2011; Lewis et al., 1987) and two did not (Osório et al., 2016; Walker et al., 1989). Chronic pelvic pain is generally predictive of mood disorders (Osório et al., 2016), so the specificity of the linkage between endometriosis and the bipolar spectrum requires further testing. All four studies that assessed bipolar disorder prevalence in women with endometriosis invoked clinical instruments and diagnostic thresholds, meaning that women

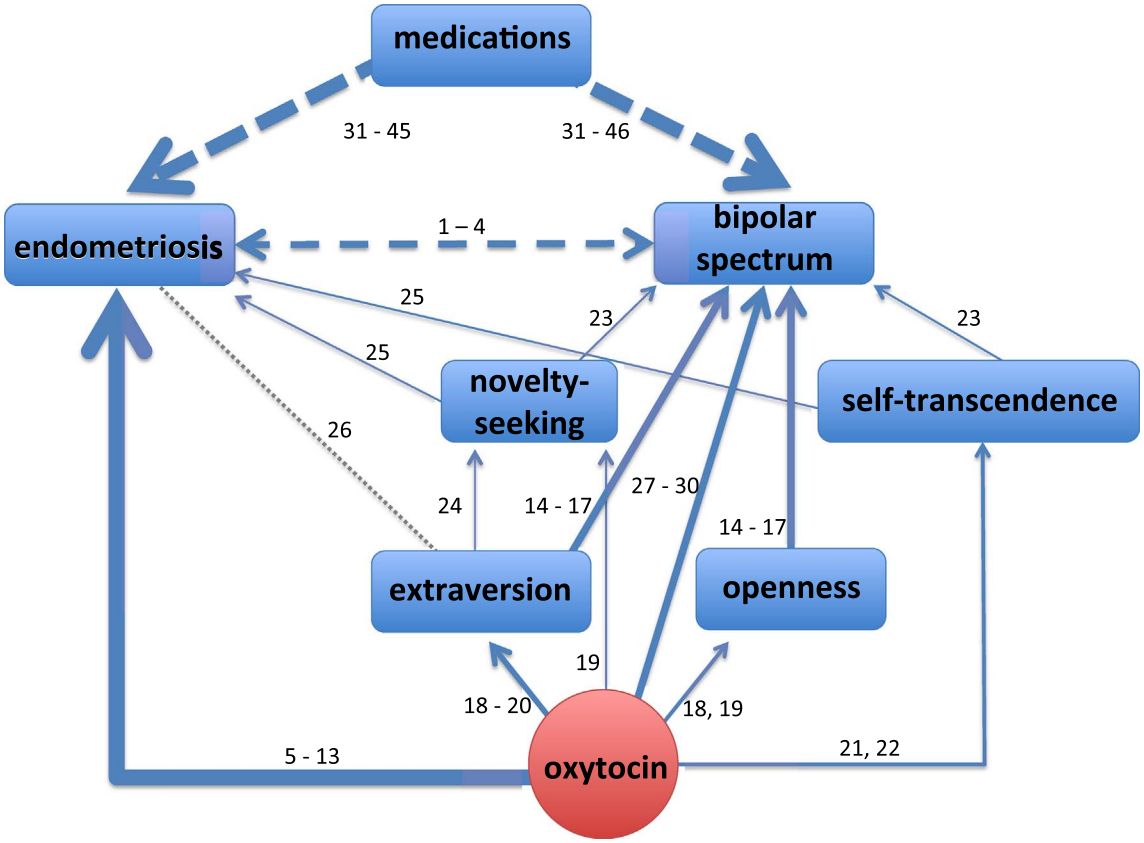

Fig. 3. Evidence-based, oxytocin-mediated interrelationships between personality traits, endometriosis, and the bipolar spectrum. The weight of the arrows between variables estimates the relative strength of evidence for positive associations between the variables, based on the number of studies reviewed. Because the arrow widths are based only on the studies included in our review, some of the arrow weights are underestimated (e.g. novelty-seeking with extraversion and bipolar), as the extensive literature documenting their overlap was not central to our review. Dashed lines represent mixed evidence, and the single doCed line (between endometriosis and extraversion) signifies negative evidence, as Low et al. (1993) reported that women with endometriosis displayed reduced extraversion relative to unaffected women.

References: 1. Kumar et al., 2011, 2. Lewis et al., 1987, 3. Walker et al., 1989, 4. Osório et al., 2016, 5. Huang et al., 2017, 6. Zhang et al., 2015, 7. Leyendecker et al., 2004, 8. Harada, 2013, 9. Leyendecker et al., 1996, 10. He et al., 2016, 11. Guo et al., 2013, 12. Nie et al., 2010, 13. Mechsner et al., 2010, 14. Quilty et al., 2009, 15. Durbin et al., 2009, 16. Meyer, 2002, 17. Lo et al., 2017, 18. Cardoso et al., 2012, 19. De Dreu et al., 2015, 20. Andari et al., 2014, 21. Van Cappellen et al., 2016, 22. Crespi and Summers, 2014, 23. Zaninotto et al., 2016, 24. Zuckerman and Glicksohn, 2016, 25. Facchin et al., 2015, 26. Low et al., 1993, 27. Turan et al., 2013, 28. Sasaki et al., 2016, 29. Tas et al., 2015, 30. Lien et al., 2016, 31. Wu and Guo, 2008, 32. Liu and Guo, 2008, 33. Goldstein, 1986, 34. Godin and Marcoux, 2015, 35. Sun et al., 2016, 36. Heijnen et al., 2015, 37. Pontis et al., 2016, 38. Watson et al., 2012, 39. Zhang, 2016, 40. Wang et al., 2014, 41. Kulkarni et al., 2014, 42. Meinhard et al., 2014, 43. Rose et al., 2000, 44. Parrott et al., 2001, 45. Haber and Behelak, 1987.

presenting with mild bipolar symptoms may miss diagnostic thresholds, which could underestimate overlap between endometriosis and the bipolar spectrum. Diagnostic categories do not reflect underlying etiological factors, but rather involve heterogeneous collections of symptoms that tend to cluster together while engendering significant levels of personal impairment (Wardenaar and de Jonge, 2013). The hypothesis addressed here does not require that women with endometriosis meet criteria for a clinically significant bipolar disorder, but rather predicts that women with endometriosis manifest personality traits and psychological features that are caused, in part, by increased oxytocinergic activity. Examining women with endometriosis using dimensional assessments of oxytocin-mediated bipolar spectrum traits would provide a stronger test of the hypothesis, compared to categorical instruments that apply strict thresholds. Such an approach did support the hypothesis, as women with endometriosis demonstrated higher levels of psychoticism, impulsiveness, and aspects of self-transcendence (Facchin et al., 2015; Low et al., 1993), but also reduced extraversion (Low et al., 1993), which contrasts with predictions. These preliminary trends thus need to be further clarified in larger samples of women, with appropriate controls for pain, using a broader range of questionnaires that quantify oxytocin-mediated, bipolar spectrum personality features, such as mania and hypomania, the tendency to exhibit spiritual experiences, novelty-seeking, creativity, extraversion, and openness (Table 4).

Emerging evidence reveals oxytocin's role in motivating complex social cognition (Crespi, 2016). Under our hypothesis, women with endometriosis are predicted to display heightened mentalistic and emotion-recognition skills, and perhaps elevated rumination concerning social interactions (Table 4). These elevations may only occur for specific domains of social cognition, such as enhanced recognition of negative but not positive emotions (e.g. Tas et al., 2015), or they might involve increased attention to social threats or relationships, as elevated oxytocin levels can be indicative of prolonged social stress and relationship vulnerability (Crespi, 2016; Grebe et al., 2017). To the best of our knowledge, mentalizing has not been studied in women with endometriosis, and careful controls for pain levels must be included as pain could diminish concentration and performance in a variety of tasks. Another approach to testing the hypothesis involves studying cognitive phenotypes, such as visual-spatial skills, in women with endometriosis, as social and non-social cognition display diametric associations with oxytocin and appear to trade off with one another (Crespi, 2016). Visual-spatial abilities are negatively related to serum oxytocin in post-menopausal women (Kocoska-Maras et al., 2013), reduced in people with bipolar disorder (Watson et al., 2012), and disrupted in rats following oxytocin administration (Wu and Yu, 2004), so under the hypothesis addressed here, women with endometriosis are predicted to show diminished visual-spatial abilities (Table 4).

Evidence for the role of increased oxytocin receptor densities in

Table 4
Predictions and suggested data collection to test the proposed hypothesis.

Prediction	Data Required
Women with endometriosis show higher levels of bipolar spectrum traits such as hypomania, impulsivity, openness, extraversion, self-transcendence and creativity.	Compare personality traits between women with and without endometriosis, including controls for pain levels, such as a pain-free endometriosis group, or a control group with pelvic pain but no endometriosis.
Women with endometriosis show conserved or elevated mentalizing skills relative to women without endometriosis.	Compare 'Reading the Mind in the Eyes' performance between groups, or emotion recognition tasks, with controls for pain.
Women with endometriosis show cognitive phenotypes that are associated with high oxytocin levels and bipolar disorder, including reduced visual-spatial skills.	Compare mental rotation test scores between women with and without endometriosis. Include measures of pain as a possible confounding variable.
First-degree, unaffected relatives of women with endometriosis show higher levels of bipolar spectrum traits such as hypomania, impulsivity, openness, self-transcendence, extraversion, and creativity.	Assess personality traits of first-degree relatives of women diagnosed with endometriosis.
First-degree female relatives of people with bipolar disorders have elevated rates of endometriosis compared to families without a history of bipolar disorders.	Large epidemiological study assessing rates of endometriosis relative to bipolar disorder.
Women with bipolar disorder have elevated uterine contractility relative to women without bipolar disorder.	Assess uterine contractility in women with bipolar disorder compared to healthy controls using transvaginal sonography.
Unaffected female relatives of women with endometriosis have increased fecundity.	Large population study of birth rates in relatives of women with endometriosis.
Subclinical endometriosis is associated with increased fertility.	Difficult to assess as the boundary between subclinical and clinical endometriosis can depend on pain, and women not experiencing pain may not visit clinics or be aware of possible endometriosis.
Oxytocin antagonists improve bipolar symptoms, specifically mania.	If deemed safe and ethical, give oxytocin antagonists to people with bipolar disorder and measure effect on manic symptoms.

endometriosis uteri, and their role in altering uterine contractility and contributing to the symptoms of endometriosis is strong and consistent (Table 2). Whether or not increased oxytocin receptor densities in the uterus consistently correspond to elevated serum oxytocin remain unknown, but given the dependence of both uterine and serum oxytocin on oxytocin system genes (OXT and OXTR), it is expected that there is some general tendency toward higher oxytocin levels and higher uterine oxytocin receptor densities in women with endometriosis, and in women with bipolar disorder. Under the hypothesis addressed here, it is expected that women with bipolar disorder have elevated levels of uterine peristalsis relative to women without bipolar disorder, as measured using ultrasound or other approaches (Table 4). Such a study would help elucidate the relationships between serum oxytocin, uterine oxytocin, and uterine activity.

Evolutionarily framing the connection between endometriosis and the bipolar spectrum means understanding the features of each condition, as well as their comorbidity, as extensions or alterations of normally adaptive psychological and reproductive processes. Both endometriosis and bipolar disorder are intimately tied to the female reproductive cycle, in that the onset and symptoms of each condition are influenced by hormonal fluctuations and reproductive phase (Bloski and Pierson, 2008; Teatero et al., 2014). The pronounced, hormonally regulated, cyclical growth and shedding of the endometrium in human females was likely an evolutionary response to the deep and invasive placentation characteristic of our species, which supported the evolution of our species' large and socially intelligent brains (Strassman, 1996; Cole, 2015). Both endometriosis and bipolar disorder involve alterations to the cyclical nature of female reproduction. Endometriosis is associated with shorter menstrual cycles (Arumugam and Lim, 1997; Cramer et al., 1986; Wei et al., 2016; Yasui et al., 2015). Women with bipolar disorder experience rapid cycling between depressive and manic states more frequently and more severely than men with bipolar disorder (Erol et al., 2015). That both endometriosis and bipolar disorder involve altered, rapid cycling, with associated affective and reproductive features, suggests that the relatively recent evolution of especially-invasive placentation in the human lineage, and the sensitive mechanisms that interact with it, especially high endometrial proliferation and copious menstruation, has generated new vulnerabilities to disease-related disruption.

Considering the large body of evidence for oxytocin's diverse positive effects on sociality and reproduction, selection on the oxytocin system may involve a 'cliff-edged' fitness function (Nesse, 2004) where increasing levels of oxytocin are associated with increasing fitness benefits until a certain threshold, where fitness drastically drops. For example, stronger cervico-fundal contractions are associated with increased pregnancy rates in women undergoing intrauterine insemination (Kim et al., 2015), which may or may not be true for natural pregnancies (see IJland et al., 1997); if increased uterine contractility, up to a certain threshold, enhances sperm transport and conception, selection may have driven oxytocin-mediated uterine contractility to this 'cliff-edge'. Assessing the fecundity of unaffected female relatives of women with endometriosis would help explore this hypothesis (Table 4), because if sperm transport in women with endometriosis has surpassed the cliff edge, then it might be expected that unaffected relatives share oxytocinergic genetic variation that improves sperm transport and thus fertility.

Oxytocin, through its interactions with gonadal hormones, enhances sexual interest and promotes sperm transport during the fertile window of the ovulatory cycle (Borrow and Cameron, 2012; Salonia et al., 2005). These features suggest adaptive coordination in the female oxytocinergic system, such that women who are relatively highly motivated to engage in sexual and social relationships may also demonstrate enhanced fertility. Together, endometriosis and bipolar disorder may thus reflect an extreme, dysfunctional manifestation of a highly social/highly fertile, 'fast' life history strategy. Characterizing bipolar disorder as a fast life history strategy is consistent with Del Giudice's (2014) placement of psychological disorders along a life history axis, and may contrast with a less social, low fertility, and 'slow' life history strategy represented by the autism spectrum (Del Giudice, 2014) and co-occurring PCOS.

The primary limitations of the hypothesis presented and evaluated here are that many of the predictions have yet to be subject to targeted tests, that much of the evidence is correlative and indirect, and that both endometriosis and bipolar disorder are mediated by a range of causal factors, many of which are certainly independent of the oxytocinergic system. Notwithstanding, a notable diversity of convergent evidence supports the hypothesis, and the predictions that it makes, with regard to these disorders, as well as autism and PCOS, are clear, specific, and testable, with important implications in both clinical and non-clinical domains.

Although we know that the womb in its entirety does not migrate throughout the body to cause female distress, it is interesting, given the contributions of oxytocin to both endometrial activity and psychological traits, that early observers and medical practitioners assumed a connection between uterine activity and mental health. Indeed, somatic symptoms are highly prevalent in female-preponderant mental

disorders, especially in disorders linked to trauma, such as dissociative disorder, post-traumatic stress disorder, borderline personality disorder, and also depression and anxiety (Seng, 2010). Comorbid physical health issues such as irritable bowel syndrome, gastrointestinal issues, genitourinary issues, pelvic pain, and increased nausea and vomiting during pregnancy are commonly observed in these female-biased psychiatric diagnoses (Seng, 2010; Seng et al., 2013). Seng (2010) and Seng et al. (2013) proposed that trauma dysregulates the oxytocinergic system and due to oxytocin's multiple effects in the brain and body, heterogeneous physical, emotional, and interpersonal symptoms tend co-occur in people who have experienced trauma. This hypothesis overlaps with the one addressed here, in terms of oxytocin's ability to jointly regulate reproductive and psychological traits that when disturbed, become symptoms of multiple disorders. The oxytocin signal is crucial to female reproductive success because of its joint roles in parturition, lactation, and maternal care; these female-specific functions may help explain, in part, why women are especially vulnerable to symptoms and conditions that centrally involve joint mind-body disturbances.

Interpretations of medical causes that focus upon sex-specific biology should be critically approached, because the environment - including societal and cultural factors - also influences the onset, course, symptoms, and diagnosis of disease (Kirmayer and Pedersen, 2014). For example, in Hippocrates' era, it was accepted that only women could suffer from hysteria (Fig. 1), and this belief promoted female-specific explanations and treatments for hysteria, while simultaneously justifying the reduced participation of women in society (Allison and Roberts, 1994; Devereux, 2014). Much later, during the Industrial Revolution, psychoanalysts observed hysteria in males as well, which motivated alternative explanations for hysteria's etiology (Novais et al., 2015). More recently, it has been observed that people in countries undergoing westernization, a process that involves sudden and massive changes to traditional ways of life, express higher rates of hysteria-like symptoms than people in westernized societies (reviewed in Tasca et al., 2012). Furthermore, the somatic and dissociative symptoms formerly labeled as hysteria show significant and compelling overlap with the human response to trauma (Vanderkolk et al., 1996; Vanderkolk et al., 2005). These fluctuating and environmentally dependent incidences of hysteria-related symptoms have been used to support the idea that one can use the prevalence of hysteria-like conditions in a given region as an index of the current level of social restrictiveness experienced by a population (Devereux, 2014). These findings, considered together with evidence for early-life organizational effects on the oxytocinergic system (Johnson and Buisman-Pijlman, 2016), indicate that future studies of bipolar disorder and endometriosis should take into account societal and cultural factors, in addition to individual factors, especially those involving exposure to trauma.

The hypothesis evaluated here intersects with multiple challenges in the study of health and disease, including the limitations of diagnostic categories, the problematic nature of studying 'mind' as separate from 'body', and the complex role of evolved sex differences in shaping differential susceptibility to disease. If supported by further evidence, the hypothesis has immediate practical applications, as women diagnosed with endometriosis might be assessed for comorbid bipolar disorder, and if women with bipolar disorders experience pelvic pain, the possibility of endometriosis could be investigated. Also, treatments and therapies that address women's health from an integrated mind-body perspective may be beneficial to women with these conditions (Meissner et al., 2010; Rusner et al., 2010). Although the hypothesis oversimplifies the complexity of the oxytocinergic system, it should help to guide future research toward novel and productive avenues, to further explore how positively pleiotropic systems underlie correlated patterns of disease. The 'wandering womb' of the past may indeed contain some truth, as enhanced well-being of women emerges through the joint optimization of reproductive, physiological, and psychological health.

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