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Review Article

Investigating Neurobiological Pathways Connecting PCOS, Neurodivergence, and Mood Disorders

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Abstract

Polycystic Ovary Syndrome (PCOS) is a complex endocrine condition affecting approximately 10% of women of reproductive age. Long considered to be a gynaecological and metabolic issue, recent advances indicate a robust linkage between PCOS and neuropsychiatric comorbidity such as attention deficit hyperactivity disorder (ADHD), Generalised Anxiety Disorder (GAD) and Major Depressive disorder (MDD). This review provides an interdisciplinary perspective spanning endocrinology and psychiatry by focusing on the Ovary Brain Axis and hormonal changes associated with PCOS, which contribute to brain structure and cognitive function. The discussion focuses on three principal biological mechanisms. First, hormonal programming as suggested by the Organisational Hypothesis, suggests that prenatal exposure to increased androgens may have an impact on fetal brain development, particularly dopamine pathways associated with ADHD. Secondly, chronic low-grade inflammation with raised CRP and interleukin-6 has the potential to compromise the BBB, activate microglia and increase anxiety through modulation of the amygdala. Lastly, metabolic failure, and in particular insulin resistance, could be associated with a lower production of brain-derived neurotrophic factor, altering neuroplasticity and working memory.

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a multifaceted and very heterogeneous endocrine condition and involves a significant fraction of women in different parts of the world (Azziz et al., 2009). In the past, studies and clinical treatment have centred a lot on its xenophonic characteristics, relating to its abortion and sterility, and its xenophonic comorbidities, comprising insulin resistance and type 2 diabetes (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workgroup, 2004). Nevertheless, an emerging body of literature requires a radical extension of this point of view, which attracts the focus to the fact that PCOS significantly influences neurodevelopment, cognitive abilities, and even mental well-being. The current epidemiological evidence shows that the prevalence of neurodivergent disorders, especially attention deficit hyperactivity disorder (ADHD), in women with PCOS has been much higher and that women with this condition are at an increased risk of mood and anxiety disorders (Cesta et al., 2020; Hiam et al., 2022). The noted comorbidity raises some inherent questions regarding the biological processes underlying how the endocrine pathology of PCOS is related to changes in brain functions and structure. Can these mental health issues be seen simply as the secondary psychological responses to the physical expression of PCOS, including hirsutism, acne, or infertility? Or are they neurobiological effects, per se, of underlying hormonal and metabolic abnormalities underlying the syndrome? The paper at hand is a synthesis of the existing knowledge on the Ovary-Brain Axis of PCOS, which will take an in-depth look into the biological frontier that connects the endocrine pathology to cognitive, emotional, and behavioural phenotypes. We are going to examine three main mechanistic processes:

(1) The long-term programming consequences of prenatal androgen exposure to the developing brain, especially its dopamine circuits.
(2) The ubiquitous role of chronic low-grade neuroinflammation in regulating brain regions involved in emotional control, including the amygdala
(3) The effects of metabolic dysregulation, which is insulin resistance, on the health and functioning of neurons. Lastly, the possibility of Narrative Medicine as a supplemental form of treatment to deal with the distinct psychological burden, in addition to alleviating the so-called blame-cycle so prevalent among PCOS patients, will be considered.

The current paper aims to propose a paradigm shift in the PCOS studies/clinical practice and a comprehensive model that should be adopted, the Neuro-Endocrine model, which allows for a comprehensive approach to the multifactorial needs of individuals affected.

The PCOS-ADHD Link: Statistical and Biological Correlations

The correlation between Polycystic Ovary Syndrome (PCOS) and Attention-Deficit/Hyperactivity Disorder (ADHD) has been discussed as an important topic of study that goes beyond just being anecdotal to some form of strong statistical and biological correlation. This comorbidity insinuates mutual underlying pathogenic pathways, which mainly focus on the exposure to androgen and dysfunction of the dopamine system.

Statistical Correlations: Epidemiological Evidence

Recent large-scale epidemiological surveys have consistently shown a large prevalence of ADHD in people with PCOS.

Raised Risk in Childhood: A meta-analysis by Maleki et al (2024), constituting more than 300,000 individuals, found that children of mothers with PCOS had a 42-43 percent high RR of having ADHD than the controls. This correlation remained despite an intensive correction of the possible confounding variables, including maternal age, body mass index (BMI), and socioeconomic status. The observation places a strong blame on prenatal factors, which is in line with the developmental programming conception.

Adult Comorbidity: Again, in adult women with PCOS, direct research has also shown high levels of ADHD diagnosis or symptoms of clinical significance. The study by Cesta et al. (2020), based on the data of Swedish national registries, revealed that the risk of ADHD among women with a PCOS diagnosis increased by 59%. Moreover, researchers who used the Adult ADHD Self-Report Scale (ASRS) found that the inattention and impulsivity scores of women with PCOS indicate significantly higher results than those of their age equivalent control groups (Sukhapure et al 2024), which stimulates a larger burden of ADHD symptomatology.

Biological Processes: Dopamine-Androgen Axis.

The basic biological theory that underlies the PCOS-ADHD association is the effect of androgens on brain development and the neurotransmitter system, specifically the dopaminergic pathways of the brain that play an important role in attention, reward, and executive functions.

a. Prenatal Androgen Programming: The "Organisational Hypothesis"

Fetal Brain Development: The Organisational Hypothesis: The hypothetical Manipulation of Neural Circuitry. The hypothesis holds that during the critical organisational periods of fetal brain development, interventions that lead to exposure to androgens in large amounts can cause lasting, structural alterations within neural circuits. In PCOS, increased androgens in maternity (endogenously generated or exogenously injected into animals) may penetrate through the placental barrier and affect the fetal developing brain.

Targeting Dopaminergic Pathways: Animal models, especially those exposing the brain to prenatal androgen (e.g., DHEA-treated rodents), have shown a great change in the mesocorticolimbic dopamine system, which is an essential part of ADHD pathophysiology. Such developments encompass a decrease in dopamine receptor density, a change in the production of dopamine, and damage to the uptake mechanism of dopamine, especially in the prefrontal cortex (PFC) and striatum (Hiam et al 2022). The PFC takes a central role in the

executive functions, such as attention, working memory and impulse control, all affected in ADHD.

b. Dopaminergic Dysregulation in the Postnatal Period

In addition to prenatal programming, chronic androgen overexposure in adult PCOS women can persist in the functioning of the dopamine systems.

Insulin Resistance and Dopamine: It is known that hyperinsulinemia, which is a characteristic typical of PCOS, has been associated with impaired dopamine signalling. Diabetic condition may result in the decline of the D2 dopamine receptor sensitivity and/or an increase in dopamine transporter activity. Since ADHD is a condition that is defined by a deficiency of dopamine (particularly, in the prefrontal cortex), the existence of metabolic impairment in PCOS could result in an aggravation or addition to the ADHD symptoms development through further undermining of the dopamine neurotransmission.

Executive Dysfunction: Although not directly diagnosed with ADHD, it has been demonstrated that women with PCOS tend to show some mild impairments in so-called cold executive functions (e.g., working memory, inhibitory control) of neuropsychological testing (Sukhapure et al., 2024). These deficits are associated with increased levels of androgen, and there is a hint of a direct hormonal effect on the prefrontal cortical functioning.

A combination of genetic tendencies, prenatal exposure to androgens and continued metabolic and hormonal distrust thereby gives a strong biological hypothesis as to why ADHD is more prevalent in individuals with PCOS.

Neuroinflammation and Anxiety: The Amygdala Connection

The prevalence of anxiety disorders is astonishingly high among women with PCOS, and it is estimated that 45-60 per cent of PCOS women develop a clinically significant level of anxiety, which significantly exceeds that given in the general population (Cesta et al., 2020). Although psychological distress to do with somatic symptoms such as hirsutism or infertility is also obviously playing a role, the consequences of emerging research are that a sizeable portion of such comorbidity is compelled by direct neurobiological processes, namely chronic neuroinflammation and dysfunction of the amygdala.

PCOS Low-Grade Chronic Inflammation.

A chronic low-grade inflammation of the entire system is a characteristic feature of PCOS (Dunaif & Binstock, 2024). This is reflected in high amounts of pro-inflammatory cytokine levels, including: C-Reactive Protein (CRP): This is a very sensitive inflammatory index of the overall system, Interleukin-6 (IL-6): Licensed cytokine, which contributes to immune reaction and inflammation and Tumour Necrosis Factor-alpha (TNF-α): There is another inflammatory mediator. The peripheral markers of inflammation are also persistently increased with PCOS in both obese and non-obese women, but they can also be aggravated by obesity (Dunaif and Binstock, 2024).

Bridging the Blood-Brain Barrier (BBB)

The classical perception of the brain as an immune-privileged organ has been put to the test. Treatment of PCOS may cause chronic inflammation of the periphery:

- **BBB Permeability:** Pro-inflammatory cytokines may cause an increase in the permeability of the blood-brain barrier (BBB), where inflammatory mediators and immune cells can enter the central nervous system (CNS).
- **Microglial Activation:** When the cytokines enter the brain, they stimulate the activity of the indigenous immune cells of the CNS, which are microglia. Microglia that become chronically activated also secrete their own range of neuroinflammatory substances, including increased cytokines, reactive oxygen species and chemokines, necessitating the development of neuroinflammation (Hiam et al., 2023).

Amygdala Hyperactivity and Anxiety

The amygdala is an important part of the limbic system that is at the heart of emotion processing, especially fear and anxiety. Hypothesis: Neuroinflammation and disrupted hormonal milieu in PCOS have a direct effect on the functioning of the amygdala.

- **Androgen Effects:** The effect of elevated androgen in female PCOS patients can alter the response of the amygdala. It has been shown that a high level of androgen may increase the responsiveness of the amygdala to stimuli of emotional states, leading to an increase in perceptions of danger and the feeling of anxiety (Stener-Victorin et al., 2023). This is done directly, via androgen receptors in the amygdala, and indirectly via stress hormones.
- **Alteration of Neuronal operation and communication mediated by Cytokines:** Cytokine-mediated neuroinflammation, such as that caused by IL-6 and TNF-a may disrupt the functioning and communication of neurons in the amygdala. This may interfere with the balance between excitatory and inhibitory signals and may result in sustained amygdala hyperactivity and sustained anxiety (Hiam et al., 2023).
- **Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation:** The HPA axis breaks because of chronic stress and anxiety, which are aggravated by the presence of an over-activated amygdala. It results in alterations of cortisol secretion patterns, which contribute to further stimulating inflammation and responding to feedback mechanisms, which are vital in ceasing the stress response.

Impaired Neuroplasticity and Cognitive Function

Besides being anxious, neuroinflammation and hormonal disproportions may damage neuroplasticity. This impacts mental functioning and can also cause depressive symptoms, as well as the brain fog described by a significant number of PCOS patients.

- **Reduced BDNF:** Recent evidence of continuous inflammation and elevated cortisol suggests diminished volumes of Brain-Derived Neurotrophic Factor (BDNF) in essential components of the brain, such as the hippocampus and prefrontal areas. BDNF plays a key role in the kind of growth and survival of neurons, and it is also a matter of the plasticity of the synapses. The inability to change, learn and heal results in cognitive issues for the brain as well as an increased likelihood of mood disorders due to reduced BDNF (Stener-Victorin et al., 2023).
- **Glutamate/GABA Imbalance:** The spontaneous imbalances of the excitatory (glutamate) and inhibitory neurotransmitters (GABA) can be brought on by neuroinflammation. This leads to more overactivity of neurons and impairs the process of cognition.

The interrelation of the systemic inflammatory state of pathophysiology, associated neuroinflammatory condition, and direct hormonal actions on the critical and fundamental areas of emotion-processing, including the amygdala, provides a solid biological definition of the high level of anxiety and mood-related disorders in women with PCOS.

Narrative Medicine: Reducing the "Blame" Culture

Even though the biological processes that would bring about the neurodivergence and mood disorders in PCOS are decisive, the psychosocial effects of the syndrome cannot be exaggerated. Women with PCOS are often isolated, frustrated, and self-blaming because of the chronic, frequently apparent, and ongoing talk about lifestyle changes (diet and exercise) in the clinical environment (Charon, 2024). The culture has the unwitting effects of developing a culture of blame, in which it becomes the patient owning their health issues as a personal failure, as opposed to a biological issue that exists within the system. Narrative Medicine provides an effective patient-centred practice that can alleviate this psychological consequence.

The Essence of Narrative Medicine

Narrative Medicine Narrative Medicine is a clinical approach that has been developed by Rita Charon, and it relies upon narrative competence, or the skill to recognise, internalise, discern, and be affected by the narratives of illness, to promote patient care (Charon, 2006). It changes the biomedical problem-solving paradigm of the clinical encounter to one that recognises and incorporates the lived experience of the patient, personal history and the culture of the patient.

The Reframing of PCOS: Black and White to Biological.

Narrative Medicine working with PCOS might have a significant effect on patient health outcomes since it can:

- **Validating Experience:** Every recovery process that opens up, letting the patient describe their illness story, the emotional burden of symptoms, delays in diagnosis, and frustrations with treatment, is very important in giving a patient validation. It is a powerful mechanism to feel less isolated and poorly understood in this activity of being heard (Charon, 2024).
- **Decoupling Self-Blame:** Narratively competent trained clinicians can provide patients with assistance in the re-framing of their condition. Other than taking PCOS symptoms as a personal failure (e.g. I am not doing enough to lose weight), the story can focus on systemic biological basis (e.g. genetic predispositions, evolutionary Thrifty genes that served us well in the past, but now assist in insulin resistance) or environmental influences. This reframing is necessary in the reduction of internal shame and guilt.
- **Empowerment through Understanding:** Patients feel empowered when they create a common understanding of the illness. They change the roles of passive receivers of medical recommendations to active participants of their health care, knowing why some of the interventions can be helpful in the setting of the context of their own biology and life history.

Psychological and Physiological Benefits

Consistent with qualitative and nascent quantitative research proposes that the approach dependent on narratives can have practical effects:

- **Less Psychological Distress:** Research shows that interventions that help patients to develop a narrative and empathy may play a vital role in alleviating the symptoms of anxiety and depression in chronically ill patients (Charon, 2024). In part, this can be explained by the therapeutic effect of sharing challenging experiences and being able to understand.
- **Better Adherence to Treatment:** The adherence to complicated treatment has a tendency to be enhanced, when patients feel properly heard, and their opinion is taken into account to create a specific treatment plan. This is especially important in PCOS, in which the long-term management of drug therapy and lifestyle changes is critical.
- **Stress Response Stressors:** Stress can be minimised by feeling legitimate and having others on your side. This can, in its turn, positively influence the Hypothalamic-Pituitary-Adrenal (HPA) axis, which might cause the reduction of cortisol levels and alleviate some of the elements of the inflammatory response that cause mood disturbances (Charon, 2024). Although direct situation of physiological measurement is still new, the connection that exists between psychological wellness and physical wellness is well established.

With Narrative Medicine becoming a part of PCOS management, clinicians will be able to shift toward a more human-centred approach towards the biological measures by considering the deeper, more human-centred aspect of life with a chronic, complex, and misconceived illness. This holism approach helps to promote mental health, resilience, and, eventually, the effectiveness of the treatment as a whole.

Methodology for Investigating the Ovary-Brain Axis

To investigate a biological relationship between PCOS and neurodivergence, specifically ADHD and mood disorders, we propose a multidisciplinary observational cohort study design. The study will consist of two groups, (1) PCOS diagnosis based on Rotterdam criteria: hyperandrogenism and ovulatory dysfunction and/or polycystic ovarian morphology (PCOM), and (2) an age- and BMI-matched control group of healthy women with normal menstrual cycle. Eligibility Women aged 18 to 40 years will be eligible. Exclusion criteria are any primary psychiatric disorder not related to PCOS, use of hormonal contraceptives in the past three months and current treatment with psychotropic drugs. Biochemical evaluation will include thorough hormonal measurement (hormonal profiling) of total and free testosterone, dehydroepiandrosterone sulfate, and sex hormone–binding globulin by using liquid chromatography–mass spectrometry along with the measurement of selected inflammatory markers including high-sensitivity CRP, interleukin-6, and tumor necrosis factor-alpha. Blood oxygen level–dependent functional MRI derived neuroimaging will be applied to assess amygdala reactivity and connection with the prefrontal cortex. Neuropsychological assessment will involve sprecifically validated ADHD and mood rating scales.

DISCUSSION

The conventional learning of Polycystic Ovary Syndrome as a reproductive and metabolic disorder is becoming less and less viable in the face of overwhelming evidence that suggests it is a factor in neurodivergence and pervasive mood disorders. It has been demonstrated in this paper that the biological border of neurobiology concerns the direct crossover between the physiology and pathology of PCOS and the mechanisms of the brain, despite the widespread current understanding regarding the psychosocial nature of the latter being a secondary response. Rather, we will suggest they are manifestations of inherent expressions of the underlying hormonal, inflammatory and metabolic disturbances of the syndrome. There is a strong body of evidence to back the claims that the link between PCOS and ADHD is strong, in both epidemiological correlations and biological mechanisms. The Organizational Hypothesis offers a potent model, which is that excess androgens in the fetus can program the brain of the fetus, especially the dopaminergic systems in the prefrontal cortex, so that people become susceptible to symptoms akin to ADHD. Combined with continued insulin resistance that affects dopamine receptor sensitivity in adulthood, this prenatal programming gives us the entire picture of how PCOS induces a dopamine deficit condition that resembles that of ADHD neurobiology. The acknowledgement of ADHD as a component of PCOS in a significant proportion of patients requires a paradigm change in the screening and management tools, beyond symptom suppression to the Neurotransmitter dysregulation at the root causes. On the same note, the abundance of anxiety and mood disorder cases in PCOS cannot be simply explained by the mental pain of having chronic manifestations. The inflammatory changes that are chronic and low-grade of PCOS is crucial. Higher pro-inflammatory cytokines impair the soundness of blood-brain barrier, which results in neuroinflammation. Such neuroinflammatory condition, along with the direct effect of high androgens, preconditions the amygdala to hyper-react to the perceived threats, which directly contributes to anxiety. Moreover, the effect on the levels of BDNF and the assessed impairment of neuroplasticity is a contribution to the mental impairment as well as heightened susceptibility to depression. This puts emphasis on the necessity of attacking neuroinflammation as a treatment option, in conjunction with standard psychiatric treatment.

The special psychological burden of PCOS complicated by a widespread sense of blame culture nearly always unintentionally encouraged in a clinical context characterizes the importance of Narrative Medicine. Clinicians can achieve a great deal in fostering better health and supplanting internalized shame by enhancing the expression of patients, who can then frame their illness as a complicated biological issue with a roots in evolutionary history, as well as by reframing the understanding of patient experience as not a personal failure but instead as a sophisticated biological effort to adjust with a complex adaptive response. Besides reducing distress, this patient-centered care means greater involvement and compliance to the treatment which can ultimately lead to healthier living. Incorporating the narrative competence in the clinical practice can be used to humanize the PCOS care and tackle the emotional and psychological distress that remains invisible. Figure 1 refer to the neurological, neurochemical, and emotional impacts of communication disorders (CDs) which are associated with structural and functional alterations in key brain regions, including the prefrontal cortex, motor cortex, and language areas (Broca's area, Wernicke's area, primary auditory cortex, primary visual cortex, and the angular gyrus) which are essential for language processing and executive functions (Bertollo et al., 2025).

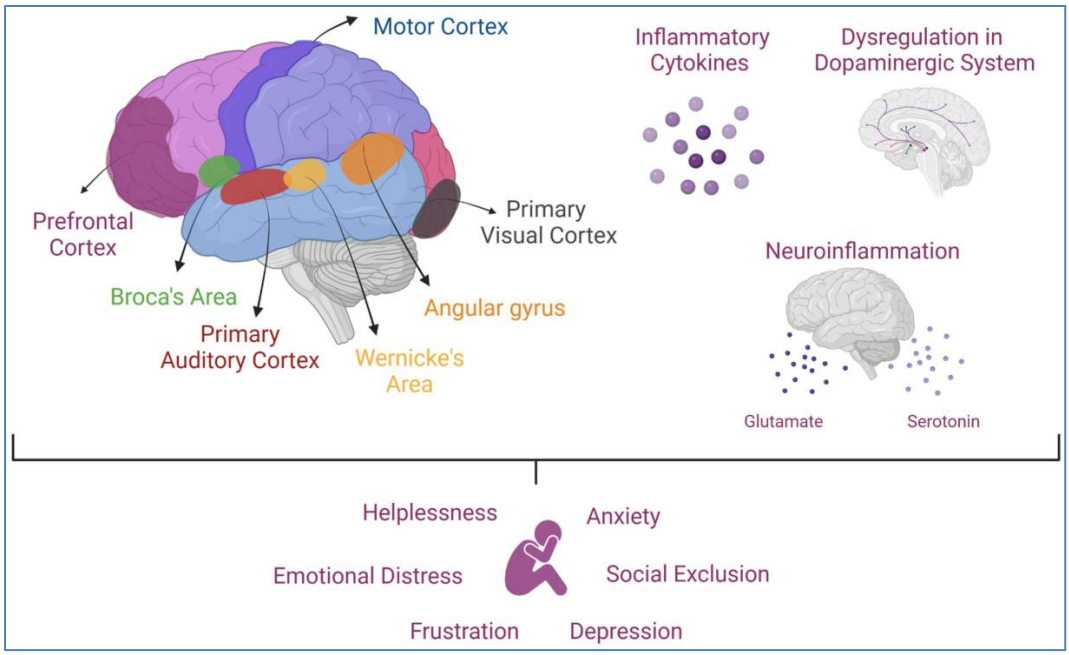

Figure 1. The neurological, neurochemical, and emotional impacts of communication disorders (Adapted from Bertollo et al., 2025).

CONCLUSION

The neurobiological frontier of Polycystic Ovary Syndrome is a very important and developing field of study. In this paper, strong and multidimensional connections have been enlightened between PCOS and elevated levels of neurodivergence, namely ADHD, and widespread mood disorders. The data is consistent with a paradigm shift, and the understanding that these endocrine and metabolic alterations inherent with PCOS have direct, intense consequences on the development and functioning of the brain, as curved by the prerenal androgen programming, neuroinflammation acutely, and insulin resistance. Going forward, the PCOS management needs to get out of its conventional limits to adopt a holistic Neuro-Endocrine approach. This requires thorough screening of neurodevelopmental and psychiatric comorbid conditions, individualized treatment plans taking into account both the systemic and neural effects, and the caring, narrative-based model of the clinical model. By realizing and directly intervening on the neurobiological aspects of PCOS we can significantly increase the level of diagnosing the syndrome, therapeutic response, and, finally, standard of living of millions of women with the syndrome. The future of PCOS management will be characterized by the incorporation of the most innovative and advanced endocrinology, neuroscience, and humanistic practices.

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