

## REVIEW ARTICLE

# Hallucinogens and the neuroendocrine system in relation to anxiety and depression: a review

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## Abstract

Psychosis is an accumulation of psychiatric symptoms that cause a loss of awareness of reality. It may be brought on by environmental, genetic, or developmental causes, including stress, substance misuse, immigrant status, infection, or the postpartum period. Their potential for logical functioning and reasoning is significantly impacted. In some situations, these effects could be temporary or persistent for a lifetime, and the cause of this anomaly could be genetic, developmental, or brought on by any other outside influences. Individuals under stress in different intensities have been shown to exhibit psychotic-like behaviour in varied conditions, where the hypothalamic-pituitary axis is activated to release the hormone cortisol in response to stress. Additionally, numerous studies have linked the involvement of hypothalamus-pituitary-adrenal axis (HPA) with anxiety and depression, establishing a link between anxiety and depression as well as psychotic disorders. Cortisol levels have been observed to be raised in both situations where anxiety- and depression-like symptoms have been reported in people experiencing psychotic episodes, suggesting that either condition may be a sign of the other. An edible hemipteran insect known as *Coridius* sp., which is enjoyed locally by the residents of Arunachal Pradesh in India as a winter delicacy, is one such external factor that could cause these psychotic disorders (hallucination/delusion). This particular insect is allegedly known to elicit a psychotic effect on its consumer, causing them to experience hallucinations/delusions, which causes them to act in abnormal behaviour such as attempting to fly, hiding under furniture etc. The metathoracic smell gland, which contains semiochemicals exclusive to insects, is thought to be the insect organ responsible for such an impact. Both the consumer's hormonal profile and the makeup of this particular insect's metathoracic scent gland have not been studied. The causal reason for the psychotic effect elicited by the insect on its consumer is still unknown. As a result, we have attempted to assemble a body of knowledge in this review article that will aid in the study of this phenomena by seeking to determine the relationship between psychosis and behaviours that resemble anxiety and depression as well as its associated hormonal components.

**Keywords:** Psychosis; Hallucination; *Coridius* sp.; Hypothalamic-Pituitary Axis; Anxiety and Depression

## 1. Introduction

A buildup of mental health symptoms known as psychosis results in a loss of consciousness of reality (Calabrese and Khalili, 2022). Hallucinations, delusions, disorganized thought (speech), drastically disorganised or aberrant motor behaviour (including catatonia), and negative symptoms are characteristics of psychotic disorders (Schrimpf et al., 2018). In all these disorders, the person's perception of reality is altered in different ways and intensities which could be due to genetic, developmental, or environmental factors (substance abuse, stress, immigration, infection, postpartum period etc. (Calabrese and Khalili, 2022). Furthermore, studies have reported that psychosis is accompanied by elevated levels of anxiety and depression (White et al., 2013). Therefore, it is one of the early noticeable psychological symptoms of psychosis. Also, the increased level of pituitary volume in response to stress during psychosis indicates the involvement of the hypothalamus-pituitary-adrenal axis (HPA) (Pariante et al., 2004), which results in the release of a high amount of cortisol. People with psychotic disorders like hallucinations and delusions become detached from reality. Hallucination is a psychological experience encounter when there is no sufficient external stimulation to elicit them whereas, delusions are ingrained, incorrect ideas for which a person lacks understanding, even in the presence of information that contradicts their veracity (Calabrese and Khalili, 2022). Hallucinogens are substances that have psychotic effects. These psychoactive substances change cognitive, emotional, and perceptual functions (Nichols, 2004). One of the most common synthetic hallucinogens is lysergic acid (LSD), which

is used as a recreational drug and is banned in many countries. However, in addition to manufactured hallucinogens, there are several naturally occurring hallucinogens, such as the mescaline-containing peyote cactus *Lophophora williamsii* (Garcia-Romeu et al., 2016), psilocybin and psilocin-containing Mexican mushrooms *Psilocybe mexicana* when taken orally help to produce a psychotomimetic effect and euphoria-inducing Tetrahydrocannabinol is the main active ingredient in marijuana (*Cannabis sativa*). Like these hallucinogenic plants, several fish species in the animal kingdom also generate hallucinogenic effects after intake. For example, a sea bream species called *Sarpa salpa* is said to have given its consumers hallucinations of vicious, howling creatures and a horrific nightmare that lasted for a few hours accompanied by nausea and vomiting. (Haro and Pommier, 2006). In the context of hallucinogenic species in the animal kingdom, there are reports of edible insects eaten in Southeast Asian nations that are supposed to have a similar hallucinogenic effect on their consumers. A species of the genus *Coridius* (= *Aspongopus*), a sap-sucking Hemipteran insect belonging to the family Dinidoridae, is colloquially referred to as "Tari" or "Gandhi puk" in the Indian state of Arunachal Pradesh. They begin mass migration from higher altitudes towards the riverbeds during winter (November to February) and then the locals harvest them for food (Gogoi et al., 2017). It has been reported that the consumption of these sap-sucking insects caused drunkenness, which caused them to act abnormally and have hallucinations (Rinchen, 2016).

Furthermore, it has been assumed that the red bilobed structure on the ventral side of the insect causes intoxication. Hence, many people practice removing that particular organ/part before it is consumed. Previous studies on its chemical composition and nutritional value have revealed that the insect is a good source of beneficial fatty acids and minerals (Chakravorty et al., 2011). However, the root cause of its psychotic side effects is still unresolved. Another study used scanning electron microscopy (SEM), Fourier transforms infrared spectroscopy (FTIR), and X-ray diffraction (XRD) to characterize the chitin content of *Coridius nepalensis*. The chitin yield was found to be 43.9% of the dry weight of the chitin extract, which contained both chitin and chitosan (Sharbidre et al., 2021). The red-bilobed structure, the hypothesized causative organ, is the metathoracic scent gland, a common feature seen in most hemipteran insects and responsible for several tasks such as a defensive mechanism, epigamic, alarm pheromones, etc. (Raska, 2009). However, the exact biochemical compound responsible for eliciting a hallucinogenic effect on its consumer is unknown.

## 2. Psychosis in relation to anxiety and depression

There is evidence linking the effects of auditory-verbal hallucinations (hearing voices), negative critical-threatening thoughts, and self-harm in the case of a psychotic disease like schizophrenia (Scott et al., 2020). Wigman et al (2012) observed that individuals with anxiety and depression also had psychotic symptoms. According to some studies, almost 27% of those with anxiety and depression also displayed one or more psychotic symptoms, indicating that the two illnesses frequently coexist. Peters et al.'s Delusions Inventory (PDI), which measures delusional thoughts, was created using the Present State Examination as a model. It measures the individual's distress, preoccupation, and conviction in relation to psychotic illnesses like delusion (Peters et al., 1999). Based on this, several studies have been conducted to measure the psychotic symptoms in the case of an individual with anxiety and depression. Os et al (1999) used this method to examine the increase in severity of psychotic symptoms from normality through states of anxiety and depression to clinical psychosis, and their result showed a positive quantitative correlation between psychosis and anxiety or depression. Similar testing was done by Verdoux et al (1999) where a follow-up survey was performed to check whether the higher proneness for psychosis indicates the occurrence of increased anxiety or depression in subjects with no history of mood disorder. Their results also yielded similar outcomes suggesting the association of psychosis with a greater risk of depression. Based on these studies, it can be implied that anxiety and depression could be parallel indicators of psychotic conditions. Thus, studying anxiety and depression could give some insight into psychosis. Anxiety and depression are different conditions with distinct causes and consequences. Still, it is well established that they are closely associated, and thus experiments done to measure them should be done considering both the variables together and not separately (Beuke et al., 2002). There are many reasons for anxiety and depression (Pies, 1994; White et al., 2013; Wong, 2006) and these factors are said to be BioPsychoSocial that contribute to anxiety disorders. Biological causes (hereditary, neurotransmitter imbalance, illness, medications, nutritional factors), psychological causes (personality traits, low self-esteem, cognitive dissonance, negative emotions, inter/intra personal conflicts, development crisis, perception of situational factors), and social causes (adverse life experiences, a lack of social support, work stress, a lack of social skills, changing values, conflict of social norms) are the three broad categories into which these factors can be divided (Shri, 2012). An individual's capacity for logical cognition and efficient functioning is impacted by their mental health, which is affected by anxiety and depression (Dotson et al., 2015). The major depressive disorder has been related to dysregulation of the stress system, which is caused by the abnormal hypothalamus-pituitary-adrenal axis function, resulting in the release of glucocorticoid cortisol (Belmaker and Agam, 2008). Also, neuroimaging studies have revealed altered grey matter volume of brain structures like the hippocampus, insular cortex, prefrontal and amygdala areas in individuals with anxiety and depression disorders (Van Tol et al., 2010). In a review by Germeys and Os, 2007, on stress reactivity in psychosis, stress was deemed a significant factor about psychosis, leading to the apparent involvement of an altered HPA axis which is the significant mediating system involvement in stress response.

Furthermore, stress is closely related to anxiety and depression, creating a vicious cycle of never-ending mental and physical illness (Wheatley, 1997). With all these components interlinking with each other, it can be somewhat said that stress is a common causal and consequential reaction to psychosis, as well as anxiety and depression, which indicates that studying the stress response caused by anxiety and depression could stipulate the presence of psychotic results as well.

## 3. Involvement of HPA in stress response to anxiety and depression

The neuroendocrine system consists of the HPA axis, which produces glucocorticoid (cortisol) in our body as a product. It plays a primary role in maintaining stress-related homeostasis (Nicolaidis et al., 2015). Long-term stressful life events can contribute to potential depressive illnesses and impact the brain's structure and function (Ding and Dai, 2019). This is particularly true in the case of chronic stress and depression. Desensitization of glucocorticoid receptors to the negative feedback regulation of the HPA axis that follows hyper-glucocorticoid production leads to increased stimulation of the HPA axis (Leonard, 2005).

In a study, the cortisol levels of 99 individuals, including children and adolescents with anxiety disorder, were assessed to examine the association between HPA axis functioning and level of anxiety. As a result, it was determined that girls had significantly lower levels of anxiety and cortisol than boys (Kallen et al., 2008). The sexual dimorphism in anxiety and depression linked with changes in HPA axis activity was studied in male and female rats to address this phenomenon. Corticosterone was monitored, and behavioural performances were examined by conducting the open field test (OFT) and forced swim test (FST), which revealed that in comparison to males, females typically display less anxiety-like behaviour and more depression-like symptoms (Kokras et al., 2012). It might be a result of the underlying hormonal variations playing a secondary functional role in HPA activity (Kajantie and Phillips, 2006), highlighting the significance of sexual differences and reproductive biology when anxiety, depression, and other associated illnesses are considered. With the help of behavioural models like OFT, FST, and others, experiments for studying mental diseases in mice have proven to be particularly beneficial in drawing parallels between human anxiety and depression-related symptoms (Cryan and Holmes, 2005; Wang et al., 2017).

According to a review paper on animal models of anxiety and depression, there are sex differences in the organizational and activation effects of steroid hormones on neuropsychiatric behaviour. Females are more likely to display anxiety-depression-like symptoms in response to stress. The study suggests the influence of gonadal hormones in neuropsychiatric disorders (Palanza, 2001). Therefore, any abnormality in the production and release system of gonadal hormones, i.e., the Hypothalamic Pituitary-Gonadal (HPG) axis, will consequently cause possible neuropsychiatric symptoms like anxiety and depression. Also, it is found that there is an interlinked association between the gonadal and stress hormones modulating anxiety and depression-like behaviours (Solomon and Herman, 2009). It has been well studied that Estrogen has many effects on the central nervous system, including anxiety and depression behaviour, the level and amount of Estrogen present in different menstrual/estrous cycles affect the mood and mental state of the person. An individual with lower amounts of estrogen has been proven to be more prone to depressive episodes, whereas additional estrogen administration demonstrated to produce a comparatively lower degree of depression (Walf and Frye, 2006). The relationship between stress and cortisol was first described by Board et al (1957). In addition to gonadal hormones, cortisol activation is also known to act as an index of stress. Its level in blood plasma is significantly higher in people suffering from neuropsychiatric disorders.

In a subsequent study, Chronister et al (2021), attempted to investigate the relationship between sex and adrenal hormones and anxiety and depression. They observed that elevated levels of cortisol, estradiol, and testosterone increase the likelihood of experiencing elevated symptoms of anxiety and depression and significantly impact mood. To compare and examine the influence of different ages, sexes, and gonadal hormones in anxiety and depression-like behaviour during puberty in mice, Boivin et al (2017) used behavioural tests like the EPM, FST, and MBT and observed the influence of gonadal hormones on anxiety and depression-like behaviour. The influence of sex and symptomatic state on cortisol stress reactivity was examined in a systematic

review and meta-analysis that included data from numerous studies on anxiety, major depressive disorders (MDD), and schizophrenia. The results revealed a positive relationship between cortisol stress reactivity and psychiatric disorders (Zorn et al., 2017). It is not surprising to assume that deregulation of HPA could be related to psychotic symptoms, where abnormal levels of cortisol and pituitary or hippocampal volume have been observed. Stress is one of the precipitators for psychotic disorders, which consequently activates HPA for the release of cortisol (Philips et al., 2006; Borges et al., 2013).

#### 4. Hallucinogen affecting Neuroendocrine System

Hallucinogens are known to affect the brain's serotonin receptors which are responsible for eliciting effects like distorted sensory perception, the altered sensation of colour, sound and shapes, ultimately developing complex hallucinatory effects. It has been well established that cortisol is released from the brain's HPA system in response to stress, suggesting that cortisol is a neuroendocrine system stress hormone (Guilliams and Edwards, 2010). In relation to its effect on the neuroendocrine system, it was reported that a healthy individual under the influence of hallucinogens (MDE, Psilocybin, and d-methamphetamine) experience a hallucinatory effect due to a significant rise in cortisol (Gouzoulis-Mayfrank et al., 1999). A study explored the effect of a hallucinogen (ecstasy-polydrug) on psychological distress and basal functioning of HPA by assessing the secretion of cortisol and it was concluded that cortisol dysregulation may be indicative of increased psychological and physical morbidity associated with hallucinogens after discovering that the person affected by the drug showed hypersecretion of cortisol and a noticeably higher level of anxiety and depression than the control group (Wetherell and Montgomery, 2014). Another similar study on the effects of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') on individuals without any history of drug dependencies and prolonged alcohol abuse has revealed an elevated level of adrenocorticotrophic hormone (ACTH) and cortisol release, suggesting that HPA is responsive to stress and may be caused by the hallucinogenic factor (Gerra et al., 2003). In addition to altering perception, hallucinogens can also affect mood, such as causing outward aggression.

#### 5. Conclusion and future direction

A buildup of mental health symptoms called psychosis results in a loss of consciousness of reality. It can be brought on by genetic, developmental, or environmental factors, such as substance addiction, stress, immigration, infection, or the postpartum period. According to studies, anxiety and depression are more severe when someone is experiencing psychosis. One such psychotic phenomenon i.e. hallucination could be because of external factors like hallucinogens substances that have psychotic effects, such as lysergic acid (LSD), mescaline-containing peyote cactus *Lophophora williamsii*, psilocybin and psilocin containing Mexican mushrooms *Psilocybe mexicana*, and Tetrahydrocannabinol *Cannabis sativa*. There have also been reports of hallucinogenic effects from eating some fish species in the animal kingdom. A sap-sucking hemipteran bug from the family Dinidoridae called *Coridius nepalensis* has been known to induce intoxication and hallucinations when consumed. While earlier studies have indicated that the insect is an excellent source of beneficial fatty acids and minerals, the fundamental cause of its psychotic side effect is still unknown. Evidence points to a connection between mental illnesses and auditory-verbal hallucinations, negative critical-threatening thinking, and self-harm. It has been shown that people with anxiety and depression also exhibited psychotic symptoms. Biological causes, psychological causes, and social causes are the three main groups into which these elements can be separated, according to studies that were done to quantify the psychotic symptoms in the case of a person with anxiety and depression. An altered HPA axis, the mediating mechanism involved in the stress response, is a typical causative and consequence reaction to anxiety and depression. This implies that investigating the stress response brought on by anxiety and depression may reveal the presence of psychotic outcomes. The HPA axis is a component of the neuroendocrine system and is responsible for producing the hormone cortisol, which is crucial for preserving the homeostasis of the stress response. An increase in HPA axis stimulation results from the

desensitization of glucocorticoid receptors to hyper-glucocorticoid synthesis. Females are more prone to exhibit anxiety and depression-like symptoms in response to stress, according to a review article on animal models of anxiety and depression. The central nervous system is affected by estrogen in a variety of ways, including the behaviour associated with anxiety and depression. Board et al (1957) first identified the link between stress and cortisol; increased levels of cortisol, estradiol, and testosterone increase the risk of feeling elevated symptoms of anxiety and depression. Cortisol stress reactivity and psychiatric diseases have been linked positively, according to a thorough study and meta-analysis. When abnormalities in cortisol, pituitary, or hippocampus volume are present, deregulation of the HPA may be connected to psychotic symptoms. To clearly link the participation of the HPA axis with biological hallucinogens that cause psychosis, more investigation is required.

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#### Authors' contributions

PK and MY conceptualized the work, wrote and edited the manuscript while ML wrote the first draft of the manuscript. All the authors read the final edited manuscript and approved the same. PK supervised the research work.

#### Conflict of interests

The authors declare no conflict of interest.

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