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# The Beginning of Psychosis: Psychological and Environmental Factors That Lead To Psychosis and Their Relationship to Biological Factors

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**ABSTRACT**

When we talk about psychosis and psychotic disorders, we have in mind patients with disorganized thinking, mental retardation, delusions, and other similar symptoms associated with damage to the brain's normal functioning. Psychosis, however, is not the only cause of dysfunction, the abnormal functioning of the brain. The onset of psychosis may be due to psychological factors, with stress to be one of the main factors. Psychological and environmental factors interact with biological ones creating fertile ground for the development of psychosis. Anxiety, stress, depression, immigration, social stress, and consequently stressful life events are the leading causes of a psychotic episode. In this article, we will try to examine the following parameters: 1) what are the psychological-environmental factors that contribute to the onset of psychosis, and 2) what is their relationship with biological factors.

**KEYWORDS:** Anxiety, psychosis, hippocampus

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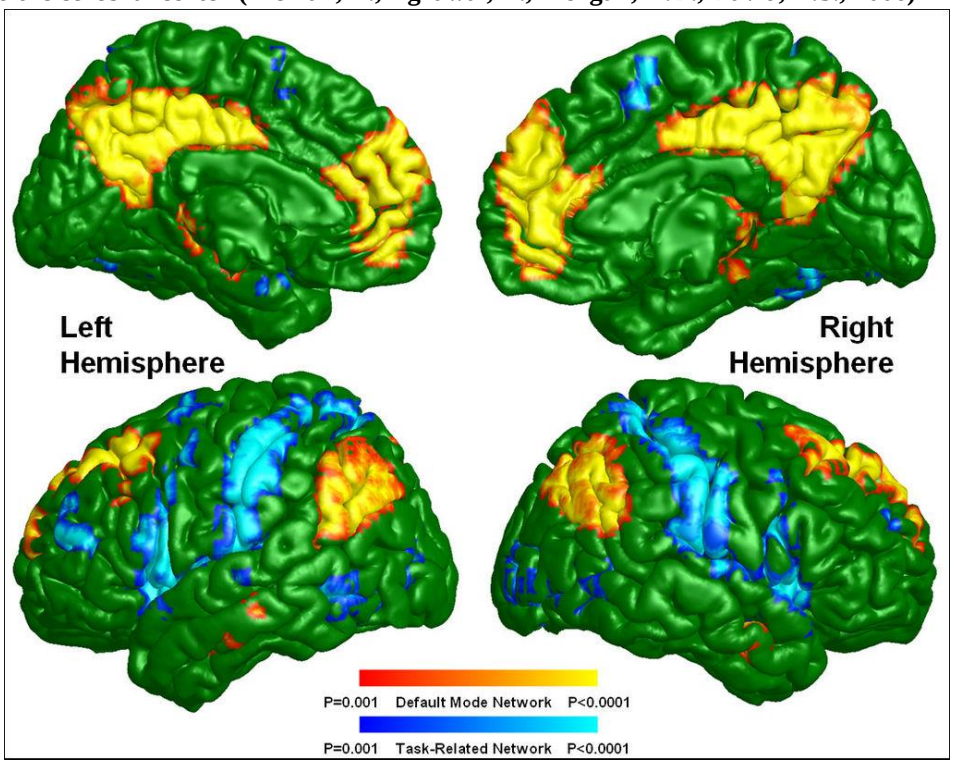
## INTRODUCTION

Psychosis or psychotic disorder is defined as a psychiatric condition that describes a mental state long intertwined with hallucinations, delusions, and constant mental retardation. Patients with psychosis show a lack of normal behavior and a continuous loss of contact with reality for long periods, often with the onset of anxiety disorders. The causes of psychosis can come from different directions:

- Pathological changes in the structure and chemistry of the brain with consequent impairment of brain function can cause the onset of psychosis in terms of the organic part of the disease (Figure 1).
- Another direction is the primary psychiatric condition and the type of the psychotic disorder or genetic predisposition. Anxiety and depression can cause psychosis.
- In addition, general medical conditions, hormones, sleep, or substance use can cause psychosis

**Figure 1. Damage to the cerebral cortex (Aleman, A., Agrawal, N., Morgan, K.D., David, A.S., 2006)**




The duration of psychosis varies. It can last for only a few days due to extreme experiences, or it can be a feature of a mental health condition such as schizophrenia, bipolar disorder, major depression.

This model essentially suggests that genes involved in neurodevelopment (Jones and Murray, 1991) and/or environmental attacks in early life led to abnormal brain development, which in turn predisposes to the subsequent onset of psychosis (Murray and Lewis, 1987; Bullmore et al., 1998; McDonald et al., 1999). However, the need to refer to the role of social factors such as urban upbringing, social isolation, and migration (Boydell et al., 2004), which point to an interaction between biological and psychological aspects in an increasingly divergent set of development, has also emerged. (Howes et al., 2004). In general, what is observed is the focus on the biological factors that cause and lead to the onset of psychosis. The aim of his article is to elaborate on the psychological factors that affect the onset and course of psychosis, as well as the relationship among them and biological factors.

## PSYCHOLOGICAL - ENVIRONMENTAL FACTORS

### 1. Anxiety

The influence of anxiety on the onset and course of psychosis is great and essential. From the very beginning, when we tried to define psychosis, we saw that it includes the presence of anxiety disorders, of course, along with other symptoms. Anxiety disorders and anxiety symptoms are common in people with psychotic disorders (Achim et al., 2011; Braga, Reynolds, & Siris, 2013; McEnery, Lim, Tremain, Knowles, & Alvarez - Jimenez, 2019; Temmingh & Stein, 2015). The experience of stress is usually involved in the onset and maintenance of psychotic disorders. Studies have shown that stress has a negative impact on the severity of positive and negative symptoms, social and overall functioning as well as the overall quality of life (Braga, Mendlowicz, Marrocos, & Figueira, 2005; Huppert, Weiss, Lim, Pratt, & Smith, 2001; Karpov et al., 2017; McEnery et al., 2019; Pallanti, Quercioli, & Hollander, 2004).

Comorbid anxiety is associated with positive and negative symptoms; higher stress levels were associated with greater hallucinations, withdrawal, depression, despair, and poor functioning, as well as better insight (Huppert 2001, Lysaker 2007). The association with positive symptoms is strongest, suggesting that most anxiety is associated with acute exacerbation of schizophrenia (Emsley 1999, Craig 2002). Anxiety is often considered secondary to the psychotic condition and is expected to improve along with schizophrenic symptoms. Anxiety symptoms have a significant negative impact on the quality of life of patients with schizophrenia.

The signs and symptoms of anxiety are the same in patients with psychosis as in patients with anxiety disorders. Sometimes the symptoms of psychosis are more prominent and the symptoms of anxiety do not receive full clinical attention. There is also an overlap of anxiety symptoms and a reaction to the psychotic experience (Braga et al. 2004, Muller et al. 2004). Due to the appearance of stress in a variety of medical conditions, healthcare professionals must detect any routine medical problems or medications behind the stress. Some difficulties in making an accurate diagnosis are usually associated with the effects of drug/alcohol abuse

that can mask or reduce the signs and symptoms of anxiety (self-medication) (Castle 2008).

The criteria for the diagnosis of stress in patients with psychosis, include (American Psychiatric Association 1994, Kaplan 1995):

- Severe stress and reduced functioning due to severe stress.
- Experience of diffuse and intense negative emotion, feeling out of control, trapped attention and difficulties in solving a problem.
- physical symptoms of anxiety.
- typical emotional symptoms such as panic, tension, weakness.
- Behavior issues, which are typical of stress and can boost it when avoiding stress, and preventive anxiety.

Anxiety disorders and anxiety symptoms are common in psychosis, although there are differences between cultures. Anxiety symptoms could occur in 60% of patients with chronic psychotic disorder (Siris 1991, Cassano 1999, Morey 1994). Studies have shown that emotional symptoms can predict relapse (Goldberg 1977, Johnson 1988) and suicide risk (Drake 1986, Caldwell 1990). In clinical specimens, the prevalence of obsessive-compulsive disorder in patients with schizophrenia was 15.8% (Kruger 2000), and 23.5% in hospitalized patients with chronic schizophrenia (Poyurovsky 2001). Social phobia is common in patients with schizophrenia. Some studies have shown that approximately 17% of social phobias were associated with psychotic features (Cassano 1998, Cosoff 1998). The nature and severity of social anxiety were similar in schizophrenia and patients with social phobia as their primary diagnosis (Pallanti 2004). Compared to other patients with psychosis, those with social phobia had more suicide attempts with higher mortality and lower social adjustment. Data from various studies have shown that panic attacks are also prevalent in people with schizophrenia (45%). Patients with panic attacks had increased rates of coexisting mental disorder, psychotic symptoms, and use of health services (Goodwin 2002, 2003). Panic attacks are associated with an increased risk of comorbidity of alcohol or substance use disorder. Chen (2001) found that patients with panic attacks had more depressive symptoms, greater hostility, and lower levels of function.

Various diagnostic and standard self-report tests are available to evaluate the symptoms of anxiety. Stress could be investigated by the Beck Hopelessness Scale (Beck 1974), the Beck Anxiety Inventory (Beck 1985), and the Generalized Anxiety Disorder Screener (GAD-7) (Spitzer 2006). For psychological interventions, a careful evaluation of what patients report about their subjective experience and the problems they face is necessary. Research studies have shown that such reports are reliable and consistent even in patients with more severe issues (MacCarthy 1986).

**2. Life events**

In studies with psychotic disorders, the most common way to measure stress is to approach "life events". Life events are significant life changes that are not uncommon but can occur out of the individual's control (such as the death of a loved one or dismissal from work) or may be influenced by the person's actions (such as divorce or having a child) (Lazarus & Folkman, 1984). This approach to measuring stress assumes that some events are associated with a period of adjustment and, often, with some degree of risk, even if the event is positive. When investigating possible causal relationship between the experience of stress and the health outcome, researchers compare the number of life events that occurred before the onset of the disease with the number of events observed during periods of good health (or absence of the condition of interest). A judgment is often made on whether events occur depending on or independent of the health issue being investigated.

It is well known that patients with psychosis have many negative experiences in their lives. Some studies show that people with schizophrenia tend to experience significant stress levels. A history of childhood sexual abuse may predispose some people with schizophrenia to experience substantial statuses of persistent stress. It is not clear whether childhood sexual abuse is more closely linked to specific forms of stress, including symptoms of post-traumatic stress disorder (Janssen 2004; Lysaker 2005; Lysaker 2007). In addition, cumulative trauma may further increase the risk, given the positive correlation between the number of traumatic experiences and the risk of psychotic illness (Shevlin 2008).

**2.1 Retrospective studies**

A predominant and innovative study that investigated the relationship between experiencing life events and the onset of a psychotic episode was conducted more than three decades ago. Brown and Birley (1968) reported that people with the pre-existing psychotic disorder had almost twice the number of life events during the three months before admission to a psychiatric ward, compared with a group of the same age. 46% of patients experienced at least one independent event in the three weeks just before the onset of the episode. Still, only 12% experienced an event in any of the three weeks of the previous study period. The incidence rate did not differ during the evaluation period for the comparison team. The authors concluded that there was "reasonable evidence" that although stressful events were not sufficient causes of a psychotic episode on their own, they contributed and probably coincided with other factors to produce the necessary conditions for the onset of the episode and caused episode on average 10 weeks earlier (Brown, Harris, & Peto, 1973). Although the results of this study are often cited as evidence of a causal relationship between the experience of stress and the first onset of a psychotic disorder, such

conclusions are erroneous given that participants were mixed, in terms of the number ofs episodes.

The results of other retrospective studies on the relationship between stressful life events and the onset of a psychotic episode vary. Some have found an increase in the number of life events experienced before the beginning of an acute psychotic episode (Bebbington et al., 1993; Canton & Fraccon, 1985; Chaven & Kulhara, 1988; Day et al., 1987; Mazure, Quinlan & Bowers, 1997; Michaux, Gansereit, McCabe, & Kurland, 1967; Schwartz & Myers, 1977), while others do not (Chung, Langeluddecke, & Tennant, 1986; Gruen & Baron, 1984; Malzacher, Merz, & Ebonther), 1981 ). Al Khani, Bebbington, Watson, and House (1986) reported that female patients were more likely to report events before the onset of the episode. The same was not observed in male patients. Jacobs and Myers (1976) reported that newly diagnosed patients with schizophrenia had more life events in the year before hospitalization than a healthy control group. Still, this difference was only significant when dependent events were considered. Finally, van Os et al. (1994) reported that people with schizophrenia who had experienced a stressful life event in the three months before the disease onset had milder symptoms, less hospitalization time, and received fewer antipsychotic medications than those who did not.

Recognizing some of the limitations of the life events approach, the experience of "small" events has been evaluated in several studies. Norman and Malla (1993) suggested that people with schizophrenia are more likely to be adversely affected by chronic difficulties and stress experienced under physiological conditions than the most unusually significant life changes and challenges. They showed that the level of discomfort reported by people with schizophrenia was significantly correlated with the number of minor stresses experienced, but not with the number of life events (Norman & Malla, 1991). Similarly, Beck and Worthen (1972) reported that people with schizophrenia are more likely to attribute worsening symptoms to "low-severity" stressors. Some studies have shown that minor stressors or distress are associated with increased comorbid psychotic symptoms such as depression and anxiety.

**3. Immigration**

Immigration is another situation that provides an opportunity to assess the relationship between stress and the onset of psychotic disorders. Studies focusing on refugees showed that the onset of psychosis is more common in those exposed to extreme stress before immigration (Bhui et al., 2003; Zolkowska, Cantor-Graae, & McNeil, 2003). Other studies have shown that, in some cases, the development of post-migration psychosis is caused by socially disadvantaged stress and is found in a group of cultural minorities in a new environment (Cantor-Graae & Selten, 2005; Hutchinson & Haasen, 2004). One difficulty with immigration studies is that people who are predisposed to developing schizophrenia or are in the precursor phase may be more likely to move away from where they live (Ödegaard, 1932), although this explanation has recently been challenged (Cantor- Graae & Selten, 2005; Selten, Cantor-Graae, Slaets, & Kahn, 2002).

The risk associated with migration may be exceptionally high in second-generation migrants, migrants from developing countries, and migrants from predominantly black countries. It has been shown that the association between immigration status and psychosis is not solely due to choice (selective migration of people at risk for psychosis). Epidemiological evidence suggests that immigration-related discrimination may be implicated in the risk of developing psychosis, due to the association between the degree of ethnicity discrimination and the relative risk of psychosis.

**4. Model of Vulnerability**

Although psychotic disorders, such as schizophrenia, are undoubtedly related to biological factors, psychological factors can also influence their onset and course (Arieti, 1974; Bentall, Corcoran, Howard, Blackwood, & Kinderman, 2001; Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001; Kinderman, 2005). Particular attention has been paid to the possible interaction between the experience of "stress" and the course of psychosis. The stress vulnerability model developed by Zubin and Spring (1977) suggests that their understanding of stress is vital for onset of acute psychosis. According to the model, an endogenous, organic mood or vulnerability interacts with internal or external stressors in developing psychotic disorders. Zubin and Spring stated: "Each of us has a degree of vulnerability that, under appropriate conditions, will manifest itself in an episode of schizophrenia" (1977, p. 109). The meaning is that stressful experiences that are not well managed and lead to anxiety and stress can cause psychotic symptoms in people with pre-existing increased vulnerability.

Notably, the model of anxiety vulnerability also creates opportunities for symptom treatment and preventive intervention, primarily through psychological strategies that enhance stress management. For example, researchers in the UK have developed a cognitive psychological model of the role of stressors in the development and maintenance of psychotic symptoms (Freeman, Garety, Kuipers, Fowler, & Bebbington, 2002; Garety et al., 2001). They suggest that the experience of victimization may lead individuals to believe that they are vulnerable and to view the world and others as hostile and threatening. Subsequent stressful events are thought to cause psychotic symptoms under these conditions. Recent studies have supported this model (Dudley & Over, 2003; Freeman et al., 2004), with clear implications for treatment.

**5. Behavioral Awareness Model in Stress**

Awareness refers to the process by which (repeated) exposure to a particular event increases the behavioral and biological response to subsequent exposure to a similar event, even if the subsequent exposure is less severe. The results of such a behavioral awareness process can be increased emotional and psychotic reactions to stress, which occurs when previous exposure to severe or persistent stress results in increased responses to the small stresses of everyday life. Indeed, prior exposure to childhood trauma or life events has been said to increase sensitivity to minor stresses in daily life, which if accumulated may lead to the need for care and impairment of individuals in primary subclinical or schizotypal levels of psychosis.

**BIOLOGICAL FACTORS**

**1. Hypothalamic-pituitary-adrenal axis**

The hypothalamic-pituitary-adrenal axis (HYP) is one of the major stress response systems in the human body. Research on its function shows the biological connection with the psychological factor in the development of psychosis. It is a biological system proposed as a link between the psychological experience of stress and the development of psychosis. The HYE axis is a biological mechanism that mediates the main adaptive response to perceived psychological or physiological stress.

Nerve signals associated with a stressful event are transmitted in an endocrine response at the hypothalamic level (Figure 2). The supraventricular nucleus in the hypothalamus is a complex integration center that receives and coordinates neuroendocrine, autonomic, cognitive, and emotional energy and is responsible for initiating glucocorticoid secretion. The release of the hormone corticotropin and, to a lesser extent, arginine-vasopressin from the hypothalamic parenchyma is secreted into the pituitary-portal system where they reach the anterior pituitary gland and synergistically stimulate the release of the hormone adrenoprotein. The hormone adrenocorticotropin is then transported into the bloodstream, where it elicits the release of glucocorticoids from the adrenal gland. A negative feedback mechanism ultimately inhibits glucocorticoid release. The glucocorticoid cortisol is an essential mediator of the normal stress response and affects many physiological systems to allow the body to respond to a stressor. Cortisol is a biological stress indicator, the product of the YYE axis in the stress response, and can be obtained through plasma, saliva, and urine. Cortisol has a typical daily rate that can be assessed when samples are collected throughout the day

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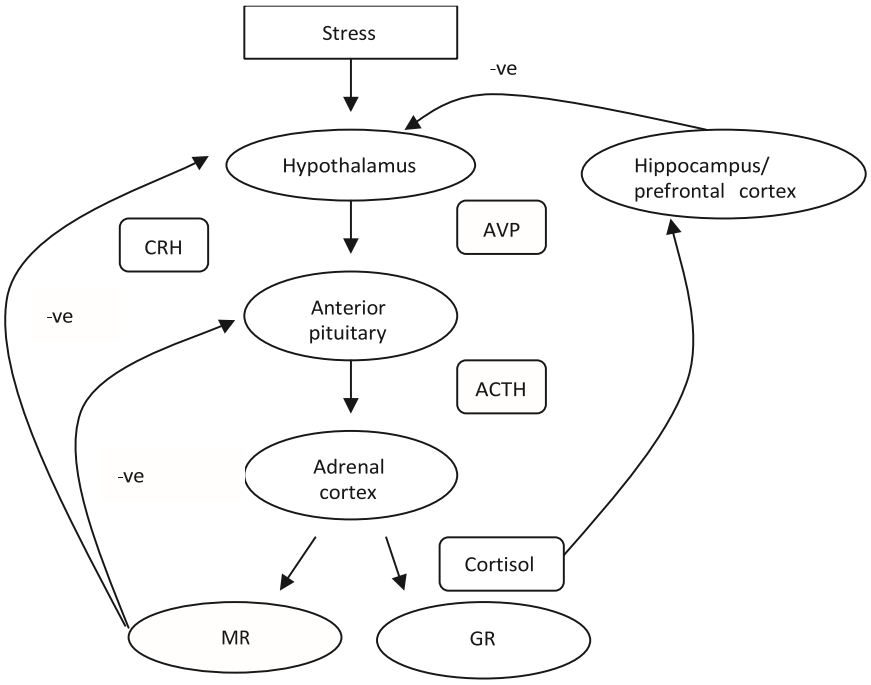


**Figure 2.** The ACTH HF axis, adrenocorticotropin hormone AVP, arginine vasopressin; CRF, corticotropin-releasing hormone; GR, glucocorticoid receptors; MR, mineralocorticoid receptors; -ve, negative feedback.

A recently updated Walker and Diforio contribution suggests a "neurological mood-stress model," suggesting that the HPA axis can cause many events that lead to neural circuit dysfunction, including changes in dopamine signaling. This model is based on data on the effects caused by HYP hormones, in particular cortisol, on the brain and behavior. The authors conclude that several indications show a relationship between HYE axis activity and psychosis. First, diseases associated with elevated cortisol and corticosteroid administration have been observed to cause psychotic symptoms. Second, patients with schizophrenia and other psychotic disorders exhibit HYE dysfunction, such as high

levels of cortisol and adenocorticotropic hormone, increased cortisol response to pharmacological challenges, and possibly glucocorticoid receptor abnormalities. Furthermore, severe reductions in hippocampal volume, an area of the brain that plays a crucial role in reducing HYP activity, have been described. The volume of the hippocampus is partly determined genetically. Still, the environmental contribution to the volume of the hippocampus is more significant, suggesting a possible role for the stress reactions caused by the HYP. Third, there may be a synergistic relationship between activation of the HYE axis and activation of dopaminergic circuits involved in psychosis. Although the exact mechanisms have not yet been elucidated, evidence suggests that glucocorticoid secretion may increase dopamine activity in certain regions of the brain, particularly the mesolimbic system. Fourth, factors involved in the etiology of schizophrenia, especially prenatal factors, may contribute to HYE dysfunction. These factors include prenatal exposure to maternal stress or glucocorticoid administration, substance use, and various forms of prenatal and perinatal complications.

**Survey results**

The results of studies that have evaluated the function of the HYE axis in combination with various psychotic disorders through the evaluation of cortisol levels in plasma, urine, or saliva, vary. Higher cortisol levels and abnormal circadian rhythms of cortisol have been reported in patients with schizophrenia compared with healthy controls in some studies but not in others. Compared to other psychiatric patient groups, one study reported that patients with schizophrenia had lower urinary cortisol levels than patients with bipolar disorder and major depressive disorder. However, no differences in salivary cortisol levels between patients with schizophrenia and schizophrenia. disorder in another study. Three studies have reported a blunt cortisol response to psychosocial, psychological, and physical stressors in patients with schizophrenia. The blunt cortisol response to stress may reflect a reduced ability to adapt to stress at the biological level. Once again, it should be noted that some studies had different results. Three studies failed to show any difference in cortisol responses to metabolic stress between patients and controls.

People with major depressive disorder with psychotic features were found to have significantly higher plasma cortisol levels than people with non-psychotic major depressive disorder and healthy controls in a study by Belanoff et al. Also, patients with schizoaffective disorder (manic subtype) had significantly higher plasma cortisol levels than the control group in a Whalley study.

Studies on the neurochemical effects of tetrahydrocannabinol, which is increasingly recognized as a factor that increases the risk of psychosis, show that it increases cortisol release in both non-clinical populations and people with schizophrenia. Stimulants such as amphetamines, associated with an increased risk of psychosis, also increase cortisol secretion in humans.

In contrast, opiates appear to have little or no psychogenic effect but suppress cortisol secretion in humans. Some studies show that childhood abuse and neglect affect the function of the HR axis. Evidence that childhood trauma is a risk factor for psychosis remains controversial, but early, prolonged, and severe trauma may increase the risk of subsequent psychosis through persistent effects on the HR axis.

The heterogeneous nature of psychotic disorders may explain some of the various effects reported in the studies, mentioned above. For example, some studies have reported that people with schizophrenia who also experience depression or high levels of adverse symptoms are more likely to experience non-suppression of cortisol with the Dexamethasone Suppression Test (DST) by psychotic individuals without any of these symptom profiles. Although not all studies support these findings, methodological differences may explain some of these inconsistencies. The duration of the disease may also be important in determining the function of the HYE axis in relation to psychotic disorders. The duration of psychotic symptoms was negatively correlated with cortisol levels in one study, and HYE axis hyperactivity has been reported more consistently in patients who have recently been hospitalized or are experiencing their first psychotic episode as opposed to patients with chronic disease.

**2. Hippocampus**

The hippocampus plays a crucial role in the negative feedback loops that ultimately terminate the normal stress response and is particularly important in regulating glucocorticoid levels. In humans, high plasma cortisol levels appear to be associated with reduced hippocampal tumors and cognitive impairment. For example, people with acute Cushing's disease (characterized by chronic high cortisol levels) experience a reduction in hippocampal volume, which is associated with poor performance on verbal memory tests. Decreased hippocampal tumors and deficits in aspects of memory have also been described in naturally healthy elderly individuals with high cortisol levels, and prolonged exposure to cortisol at plasma concentrations similar to those observed during physical and psychological stress has been shown to reduce memory performance. Non-psychiatric patients treated with corticosteroids have been shown to reduce hippocampal volume and impaired knowledge compared with controls. Further evidence of changes in the hippocampus combined with the experience of stress comes from many structural imaging studies that have shown reduced volume in the brain's hippocampus in anxiety disorders such as post-traumatic stress disorder and obsessive-compulsive disorder. Finally, treatment of Cushing's disease and subsequent reduction in cortisol levels are associated with increased hippocampal volume.

**2.1 Studies**

Neurocognitive studies strongly suggest that the hippocampus is affected in people with psychotic disorders. People with psychotic disorders usually experience impairments in attention and memory. In addition, hippocampal-dependent verbal memory is a strong predictor of functional outcome.

Studies of brain structure provide more robust evidence for the role of the hippocampus in initiating or maintaining psychosis. One review reported that psychotic disorders were characterized by reductions in hippocampal and Para hippocampal volume, disturbance of hippocampal pyramidal neurons, the smaller size of hippocampal neurons, and lower levels of these proteins at synapses in require further confirmation. Structural neuroimaging studies have repeatedly found reduced hippocampal volume in psychotic patients. These findings are supported by spectroscopy, functional imaging, and shape analysis studies, which have also demonstrated hippocampal abnormalities in schizophrenia. The most substantial results came from high-resolution magnetic resonance imaging studies in patients with chronic schizophrenia, using slices smaller than 1.5 mm. Only one published study of 1.5 mm slices reported no difference in hippocampal volume between schizophrenia. and individuals in the control group. The difference in hippocampal tumors is apparent when comparing individuals experiencing a first psychotic episode with the control group. Still, a recent cross-sectional comparative study showed that structural changes in middle temporal regions, including the hippocampus, occur only after the onset of acute episodes of psychosis. The pattern of structural change varies depending on the type of the developing psychosis. This is supported by the results of the only study to date that evaluated the changes in the structure of the brain during the transition to acute psychosis. This study showed that left ventricular parietal, orbital, and cerebral cortices in young people identified as "extremely" at high risk for psychosis decreased after the onset of acute psychosis.

## ANXIETY AND COGNITIVE PERFORMANCE

The harmful effects of stress and glucocorticoids on the brain (especially the hippocampus) are well known in the literature, and disorders characterized by increased stress exposure include depression, post-traumatic stress disorder, chronic fatigue disorder, cognitive impairment, especially cognitive impairment in the executive mode. Stress can affect cognitive skills and predispose to psychotic interpretations (Hall, 2017) and affect cognitive performance by attenuating attention control. One study found that stress in the first episode of psychosis was associated with lower speech processing speed but not with memory and programming functions or overall neurocognitive performance (Stouten et al., 2017). In addition, a recent meta-analysis reported a significantly higher prevalence of comorbidity for social anxiety disorder in outpatients than inpatients, leading to a debate about the potential impact of greater insight and awareness of anxiety symptoms (McEner). et al., 2019). These results suggest that in individuals with good insight - associated with higher cognitive ability (Aleman et al., 2006; Rajji et al., 2014) - stress may develop in possible stigma associated with it (Birchwood et al., 2007).

## CONCLUSION

In this article we elaborate the psychological and environmental factors that are associated with the onset of psychosis. The main goal was to highlight the relationship and consequently the interaction between psychological/environmental and biological factors. Stress seems to play a dominant role and combined with other psychological and environmental factors, creates unfavorable conditions for people with psychotic disorders (e.g., migration, psychosocial stress, life events). Stress is joint in patients with psychosis, and its treatment can improve their quality of life. The HYP axis, as already mentioned, is a biological system proposed as a link between the psychological experience of stress and the development of psychosis. The hippocampus is strong evidence for the relationship and interaction between biological and psychological factors. The key points that emerged through our literature review, are: 1) the HR axis is dysfunctional in at least some patients with established psychotic disorders; 2) the hippocampus is an area of the brain that appears to be involved in the onset and maintenance of psychotic disorders; a psychotic episode in some people. There is also some evidence that the onset of psychotic disorders may be associated with higher stress levels and changes in the hippocampus. The hippocampus is an area of the brain that is closely involved in regulating the stress response and may also play a central role in developing and maintaining schizophrenia and other psychoses. Thus, the HYE axis and the hippocampus may mediate between the experience of stressful events and the onset of psychotic illness. Finally, the relationship and interaction are shown by how stress affects cognitive performance and leads to cognitive deficits in patients with psychotic disorders.

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