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The search for new biomarkers for cognition in schizophrenia

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ABSTRACT

The search for biomarkers in cognition has been the focus of a large part of the research on patients suffering from schizophrenia. The scientific literature is heterogeneous, and few studies establishing an integrative model of pathogenesis and therapeutic response are available in this field. In this review, we aimed to summarize three essential aspects correlated with cognitive performance: 1) the relationship between inflammation and cognition in schizophrenia, 2) the role of prolactin in cognition, and 3) the association between cognition and neurotrophic factors, particularly brain-derived neurotrophic factor (BDNF).

Several studies support the association of inflammatory markers with cognitive status in schizophrenia. In recent decades, the development of effective therapies for cognitive impairment in schizophrenia has focused on the search for anti-inflammatory and immunomodulatory medications. Conversely, the implications of prolactin and its functions in cognition, the transition to psychosis and the diagnosis and prognosis of schizophrenia have been established independent of antipsychotic treatment. With regard to neurotrophic factors, a recent study has correlated BDNF levels with cognitive recovery in schizophrenic patients treated with cognitive remediation.

We conclude that although there is a diversity of biomarkers focused on cognitive function in schizophrenia, BDNF is the biomarker that has accumulated the vast majority of evidence in the current literature.

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1. The search for biomarkers for cognition

The Food and Drug Administration (FDA) defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention" (Atkinson et al., 2001). The current scientific literature suggests that the definition of biomarkers for psychiatric disorders increases the potential responses to a range of psychopharmaceuticals and improves studies focused on the development of effective therapies for these disorders through better validation of objective measures and stratification of patients as a function of these markers (Tandon et al., 2010).

During the last few decades, limited scientific evidence in the field of biomarkers has stimulated scientific contributions through investigations into the principal etiopathogenetic hypotheses of psychiatric disorders. Specifically, focusing on studies of schizophrenia and related disorders, the last few years have seen increasing interest in defining new biomarkers that are valid, reliable, and useful in clinical practice and that allow researchers to confront this century's primary challenges to psychiatric biology.

The proposed models were developed to define restrictive phenotypes that can integrate a diversity of proposed hypotheses on schizophrenia (García-Bueno et al., 2014b). A systemic and meta-analytical review reveals the existence of proinflammatory dysregulation in schizophrenia and suggests that numerous cytokines involved in these processes should be the focus of new research aimed at defining biological markers that can be used to measure disease progression (Upthegrove et al., 2014). In this context, molecular genetics, plasma and cerebrospinal fluid analysis, and structural and functional neuroimaging are attractive and promising fields in studies focused on biomarkers (Oertel-Knöchel et al., 2011; Penadés et al., 2013).

One review emphasizes that in the last few decades, candidate genes and proteins have been described that show characteristics that are in line with the nature of biomarkers (Chana et al., 2013). Those authors indicate that the relationship between the majority of biological markers and the symptomology that arises in psychiatric disorders should be the subject of careful, in-depth study. Additionally, biological psychiatry has been confronted by numerous difficulties in the study of said biomarkers, one of which is the relative inconsistency of some clinical diagnoses. The aforementioned fact has allowed some researchers to relate numerous markers with the cardinal symptoms of psychiatric disorders. A recent systemic review suggests that some discoveries indicate the presence of biological

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markers associated with poor cognitive performance in schizophrenia (Ribeiro-Santos et al., 2014).

This study serves as a review of the scientific literature focused on biomarkers of cognitive state in patients suffering from schizophrenia. The objectives of this study are as follows: (1) to highlight the need to discuss the field's primary findings, given that cognitive performance has a direct impact on schizophrenic patients' functionality, and (2) to provide evidence of markers in clinical responses to therapies established by the scientific community that may have promising and hopeful results. This review is focused on three high-interest topics in the field of biomarkers. First, we review the relationship between cognition and inflammation in schizophrenia; second, we describe the potential role of prolactin in cognition; and third, we review the link between cognition and neurotrophic factors, in particular BDNF.

2. Cognition and inflammation in schizophrenia

We are in the midst of experiencing a reformulation of the classic concept of schizophrenia, now seen as a mixture of symptoms that, from the beginning, has a multisystem impact (Insel, 2010; Kirkpatrick, 2009). In this context, numerous hypotheses involving the immune system and inflammatory processes of both the peripheral and central nervous systems have been proposed as etiological explanations for schizophrenia and related disorders. These processes seem to be influenced by a series of genetically predisposed and environmental factors that could make critical contributions to the progressive nature of these pathologies (Meyer, 2011).

An inflammatory response is an adaptive mechanism that enables the body to cope with numerous challenges. Under prolonged pathological conditions, however, the continued maintenance of this response could be detrimental. The precise regulation of the entire inflammatory response process involves complex endogenous counterbalancing mechanisms that control the effects of fixed, and potentially damaging, proinflammatory intermediaries (Meyer, 2011).

In the last fifteen years, renewed interest has focused on these immune and inflammatory changes and the consequences of related oxidative and nitrosative metabolic issues, including key physiopathological mechanisms involved from the onset of schizophrenia and other related psychiatric disorders. Consequently, a considerable body of study has identified a spectrum of inflammatory and immunological dysfunction in schizophrenia. The primary evidence that supports the existence of this spectrum is as follows:

a) Genetic studies, including the *Genome-Wide Association Study (GWAS)* with large population samples, that have described genetic variations of the major histocompatibility complex and of genes expressed in tissue with important roles in immune or inflammatory responses (Schizophrenia Working Group of the Psychiatric Genomics, 2014; Shi et al., 2009; Stefansson et al., 2009). There is also evidence of the upregulation of genes linked to inflammation in brain tissue (Drexhage et al., 2010; Saetre et al., 2007).
b) Ecological studies that demonstrate an increased presentation of autoimmune illnesses and serious infections in this population (Benros et al., 2011; Torrey et al., 2012).
c) At the peripheral level, multiple studies have described an elevation of plasma proinflammatory cytokines, which are key mediators in the regulation between the central nervous system and the immune system (review in Miller et al. (2011)). Given that the majority of infectious agents do not cross the placenta, prenatal studies have identified proinflammatory cytokines as potential mediators of the harmful effects of fetal brain infections (Fineberg and Ellman, 2013). Additionally, studies have recognized an increase in other peripheral proinflammatory mediators, such as prostaglandin E2 and COX activity (Das and Khan, 1998; Kaiya et al., 1989).
d) Although substantial interest has focused on proinflammatory processes activated in schizophrenia, the role of anti-inflammatory signaling has attracted somewhat less attention in this context (Meyer, 2011). The stimulation of anti-inflammatory cytokines, such as IL-4, IL-10, and IL-17, appears to be a mechanism provoked by various antipsychotics to regulate uncontrolled and potentially harmful inflammation in schizophrenia, suggesting an alternative method of action for dopaminergic blocking (Maes et al., 1995; Meyer, 2011; Sugino et al., 2009).
e) Disequilibrium has been recognized to exist in specific pro/anti-inflammatory mediators in peripheral blood (Martinez-Gras et al., 2011). This disequilibrium, which involves the inflammatory pathway of nuclear transcription factor κB (NFκB) and the anti-inflammatory pathway of prostaglandin 15-deoxy-PGJ2 (15d-PGJ2), is evident from the first psychotic episode (FPE) (Garcia-Bueno et al., 2014a) and increases as the illness progresses (García-Bueno et al., 2014b), supporting the existence of dysregulation of inflammatory equilibrium in patients at an early stage of psychotic disorder. Because of its soluble nature, one notable finding of these studies is that the anti-inflammatory mediator 15d-PGJ2 can be used as a plasma biomarker for FPEs (Garcia-Bueno et al., 2014a; García-Bueno et al., 2014b).
f) At the level of the central nervous system (CNS), the activation of cerebral microglia, the CNS's first line of defense, has been described (Benarroch, 2013) in post-mortem studies using positron emission tomography (van Berckel et al., 2008).
g) Disequilibrium of the immune response to a significant humoral response (increased levels of IL-1, -4, -6, -10, and -12 in patient plasma and a large cell ratio (LCR)), a finding that was correlated with a poor prognosis (Potvin et al., 2008).
h) These data have supported clinical trials of non-steroidal anti-inflammatory drugs (NSAIDs) as contributing treatments in psychotic disorders. Recent meta-analyses show conditional evidence of the favorable symptomatic effects of NSAIDs, especially aspirin, *N*-acetylcysteine, and estrogens, as drugs that complement antipsychotics (Nitta et al., 2013; Sommer et al., 2014).
i) Various studies have linked alterations of the endocannabinoid system (ECS) with schizophrenia (for a review, see Zamberletti et al. (2012)). The ECS has been suggested as a principal homeostatic system involved in the regulation of complex neuroimmune interactions in a range of neuropathological scenarios (Wolf et al., 2008). Studies on schizophrenia have focused primarily on the CB1 and CB2 receptors (Eggan et al., 2008; Ishiguro et al., 2010) and on principal endogenous ligands (Giuffrida et al., 2004; Leweke et al., 1999; Muguruza et al., 2013). There is also recent evidence of peripheral dysregulation of this system during FPEs (Bioque et al., 2013). Converging lines of evidence indicate that endocannabinoids modulate cognitive processes in both animals and humans (Morena and Campolongo, 2013).

Recent studies have linked immune and inflammatory changes to cognitive performance in numerous illnesses, including schizophrenia. Specifically, cytokines such as interleukins 1 and 6 (IL-1, IL-6) and tumor necrosis factor (TNF) have been linked to cognitive deterioration and other negative symptoms (Meyer et al., 2011). Evidence suggests that IL-1, IL-6, and TNF could have a central role in maintaining biological characteristics at a molecular level; characteristics such as synaptic plasticity, neurogenesis, or neuromodulation; and cellular mechanisms involved in learning, memory, and cognition (McAfoose and Baune, 2009).

It has also been suggested that COX-2 is involved in cognitive function (Muller et al., 2005), inhibiting the strength of synaptic connectivity and affecting memory consolidation. Overall, these results link inflammatory markers to cognitive performance in schizophrenia, suggesting that the presence of inflammation is associated with poor cognitive performance (see Ribeiro-Santos et al., 2014). Various physiopathological mechanisms have been developed to attempt to explain the inflammatory mechanisms that underlie cognitive deterioration in schizophrenia and related disorders, including microglial activation, monoaminergic disequilibrium, cerebral abnormalities, and the kynurenine pathway (Ribeiro-Santos et al., 2014). Non-specific inflammatory markers, such as the elevation of C-reactive protein, have been linked to cognitive function but not to other psychopathological symptoms (Dickerson et al., 2007), thus indicating the potential use of particular inflammatory mediators as biomarkers for cognitive state.

Antipsychotic drugs (via the dopaminergic antagonism of D2-receptors) form the basis of the current treatment of schizophrenia and related disorders. Although these drugs have been shown to be effective in treating positive symptoms (such as hallucination and delirium) in the majority of patients, they have also shown to have poor results in treating both negative symptoms and cognitive deficiencies (Correll, 2014; Meyer et al., 2011). Because these neurocognitive dysfunctions have such a higher impact on the functional result than the positive symptoms of schizophrenia do (Green et al., 2000), the focus of pharmacotherapeutic treatment has shifted toward future drugs' potential efficacy in improving cognition (Correll, 2014). A few studies have produced data on the effect of anti-inflammatory or immunomodulatory drugs as complementary treatment to antipsychotics for patients with schizophrenia. The use of celecoxib (a cycloxygenase-2 inhibitor), along with risperidone treatment, has shown a beneficial effect on the Positive and Negative Syndrome Scale (PANSS) cognitive factors (Muller et al., 2002). Minocycline, an antibiotic that also produces immunomodulatory activity, can also improve cognitive functioning during the early phases of schizophrenia (Levkovitz et al., 2010). These data suggest that FPEs can be treated in the subgroup of patients who achieve the most benefit from anti-inflammatory treatments. The repeated association between inflammation and cognition supports clinical tests using immunomodulatory or anti-inflammatory drugs as procognitive drugs for schizophrenia and related disorders (Kroken et al., 2014), opening up a promising new field for the treatment of these patients and allowing clinics to monitor their progress.

3. Cognition and prolactin

Prolactin is a peptide hormone that historically has been studied for its function in lactation; it is responsible for stimulating milk production during the postpartum period, thus giving the hormone its name. Although it was initially thought to be secreted only by lactotrophic cells of the anterior pituitary gland, various mammal studies have expanded the physiology of prolactin. Other cells outside the anterior pituitary have been found to produce the hormone, such as cells in the skin, the mammary glands, the myometrium, the prostate gland, the placenta, and the immune system (Bernichtein et al., 2010; Horseman and Gregerson, 2013). Its function has similarly been expanded by examining the locations of its receptors, which are found in the mammary glands, ovaries, pituitary gland, heart, lungs, thymus, pancreas, kidneys, liver, adrenal glands, uterus, skeletal muscle, vascular system, and various parts of the central nervous system (Grattan and Kokay, 2008).

In addition to its role in lactation, prolactin has been implicated in maternal behavior (Ben-Jonathan et al., 2008), sexual behavior (in equilibrium with dopamine), energetic balance, feeding behavior, stress, pain, anxiety, and neurogenesis (Bernichtein et al., 2010). Although its secretion has been linked to clinical and biological factors such as age, sex, body mass index, steroid hormones (such as luteinizing, follicle-stimulating, and thyroid-stimulating hormones), temperature, nutrition (leptin and ghrelin), and stress, its primary limiting factor is the inhibitory activity of hypothalamic dopamine. Certain endocrine neurons from the hypothalamus – i.e., the tuberoinfundibular neurons of the arcuate nucleus – secrete dopamine; through the D2 dopaminergic receptors of lactotrophic cells, these neurons inhibit the secretion of prolactin.

Prolactin levels act as a daily, oscillatory, and even seasonal circadian rhythm, with both pulsating and basal modes of secretion. The basal levels differ based on sex, with women secreting more than men (Roelfsema et al., 2012). Studies of the CNS have resulted in an increased interest in the function of prolactin and its receptors in the brain. The expression of brain prolactin receptors has been studied primarily in lower mammals (rodents), emphasizing the greater presence of receptors in specific zones – such as the choroid plexus, the hippocampus, the hypothalamus, and the preoptic area – during pregnancy and lactation; presumably, this is attributable to direct action by prolactin, placental lactogen, and sex steroids (Grattan, 2002).

The interaction between prolactin receptors and various sex-steroidal (estradiol, testosterone), leptin, ghrelin, and adiponectin receptors results in variations in the functionality of the CNS. In addition to specific functions in the regulation of energetic balance (Le et al., 2011) and physiological responses to stress (Jaroenporn et al., 2007), there are also studies that relate prolactin to cognition. Animal studies in lower mammals show an association between changes in prolactin levels and various cognitive processes. In genetically modified animals, a prolactin deficit has been associated with lowered neurogenesis in the hippocampus, along with alterations in both learning and memory (Walker et al., 2012). In another study, elevated levels of prolactin were associated with a change in the capacity for object recognition with no modification in spatial learning (Torner et al., 2013).

Studies in humans (primarily pregnant women) have also been carried out to investigate the role of prolactin on cognitive processes. These studies have indicated that variations in steroid hormones during pregnancy resulted in changes to both the neural structure and the activity of brain regions focused on information storage and the modulation of emotional responses. Initially, studies comparing cognitive function in pregnant and postpartum women with that in non-pregnant women found these changes in verbal memory and processing speed. The differences indicated poorer performance during pregnancy and the postpartum period, highlighting an inverse relationship between verbal memory and executive function on the one hand and prolactin levels on the other (Henry and Sherwin, 2011). However, the results were inconclusive because although an association with spatial recognition memory was detected, a later comparative study of cognitive function during each trimester of pregnancy and three months postpartum was unable to identify the hormones linked to these differences (Farrar et al., 2014).

As mentioned above, various clinical factors can modify prolactin levels, including age, sex, body-mass index (Roelfsema et al., 2012), and gonadal estrogen levels. According to this line of argument, the lowering of prolactin levels in menopausal women is linked to decreased estrogen secretion, just as in older men in which a slight increase in the levels of prolactin is associated with higher amounts of estradiol (Vermeulen et al., 2002). Aging is also associated with changes in circadian rhythm, reflecting variations in nocturnal dopaminergic activity and, consequently, in the secretion of prolactin. Similarly, a Portuguese study has correlated the combination of prolactin and sex estrogens in adulthood with cognitive patterns during old age (Castanho et al., 2010). In this study, both prolactin and dehydroepiandrosterone were the two hormones that were the most correlated with cognitive patterns. In men, elevated levels of prolactin

were associated with poor cognitive performance, lower levels of wellbeing and poorer moods. A study assessing cognition and mathematical abilities in university students found a significant difference between the sexes at the cognitive and hormonal levels; women with low levels of prolactin had higher mathematical ability, whereas those with high levels of prolactin had higher spatial ability (Amani et al., 2012).

Because of prolactin's functional and physiological abilities, its study in the field of neuroscience has historically been limited to the hyperprolactinemia associated with the dopaminergic block caused by antipsychotic drugs. The consequences of this pathologic increase in prolactin depend on the patient's sex and can produce a wide variety of clinically relevant adverse effects, including galactorrhea, amenorrhea, infertility, sexual dysfunction, osteopenia, and cardiovascular pathologies in both sexes (Byerly et al., 2007).

Nevertheless, during the last few years, with increased research into cognition as a nuclear dimension of serious mental disorders (schizophrenia and related psychotic disorders, bipolar disorder), various studies have evaluated the function of prolactin in the cognition spectrum. One study of patients with early psychosis (less than three years since the first signs of symptoms) showed that elevated levels of prolactin were associated with deficits in processing speed independent of the use of antipsychotic drugs (Montalvo et al., 2014). There is considerable controversy surrounding these results, however, because another study of cognition in male patients with schizophrenia demonstrated that prolactin did not interfere with the link between sex steroids, such as testosterone, and cognitive function (Moore et al., 2013). A critical evaluation of those results, however, highlights the possibility of a beta-error in using subgroups with small sample sizes. Similarly, an investigation of patients of both sexes diagnosed with chronic schizophrenia and actively treated with antipsychotics found a link between prolactin and cognitive function; nevertheless, it could not demonstrate a direct association using the cognitive parameters measured with the Mini-Mental test (Ichioka et al., 2012).

Broadly speaking, this finding will have future implications in the field of cognitive function because earlier studies involving patients treated with antipsychotics showed a link between the use of a partial dopaminergic agonist (aripiprazol), which could decrease prolactin levels, and an effective reduction in hyperprolactinemia, better clinical psychopathology, and reduced secondary motor effects but no improvement in cognitive function (Lee et al., 2013). A previous, similar approach did not evaluate prolactin levels (although, a priori through pharmacodynamics, reduced prolactin levels were expected) but did associate the concomitant use of partial dopaminergic agonists with improved processing speed but worsened (certain) cognitive functions (Yasui-Furukori et al., 2011). This same group had previously evaluated decreased prolactin levels in women undergoing antipsychotic treatment; the decrease was linked to the use of a partial dopaminergic agonist, but no differences were found in the women's cognitive evaluations (Yasui-Furukori et al., 2010).

In summary, prolactin is a peptide hormone whose physiology is the subject of continuous study and widespread development. It shows numerous functions at the level of the CNS involved in hormonal interaction with systems of energetic balance, stress, or reward. However, recent data suggest new implications in the relationship between neurogenesis and cognition that, in the future, could modify our understanding of this hormone as a key element in the transition to (Aston et al., 2010), prognosis of, and diagnosis of (Garcia-Rizo et al., 2012) schizophrenia.

4. Cognition and neurotrophic factors: BDNF

Neurotrophins are growth factors that facilitate the development and survival of nerve cells. They are thus essential for proper neuron functioning and improve their survival by preventing the triggering of cell death. BDNF is likely the best-studied neurotrophin both in basic research and in relation to various clinical syndromes, including schizophrenia. Its relevance has been highlighted both in more basic neurobiological processes, such as neural plasticity, differentiation, and survival, and in higher cognitive processes, such as learning and memory (Bekinschtein et al., 2008; Nakajo et al., 2008). There is not yet a complete consensus on how to measure BDNF, nor even a standard protocol for collecting plasma BDNF. Nevertheless, the enzyme-linked immunosorbent assay (ELISA) techniques – based on the methods described by Metzger et al., 1981 – are the most prevalent within the BDNF literature; these techniques have been shown to have a high degree of sensitivity and reliability in determining serum and plasma levels within blood samples. Additionally, the procedure has been validated in significant demographic samples (Trajkovska et al., 2007). Samples tend to be extracted from peripheral activity because of the supposed difficulty of obtaining BDNF from the brain. The data suggest a correlation between BDNF levels in the brain and in peripheral plasma (Karege et al., 2002).

Unfortunately, studies on the concentrations of BDNF serum levels in patients with schizophrenia have had contradictory results, leaving open the question of this relationship and necessitating additional research and data. Most of the studies that compare levels of BDNF in samples of schizophrenic patients and healthy controls showed that patients with schizophrenia have a lower concentration of BDNF (Grillo et al., 2007; Ikeda et al., 2008; Tan et al., 2005; Xiu et al., 2009; Zhang et al., 2007). Other studies have not found differences between the two groups, instead showing that levels are elevated in patients with schizophrenia (Gama et al., 2007; Reis et al., 2008). These apparently contradictory results and conclusions have been analyzed extensively in a meta-analysis study that provided a better interpretation of the results. Green et al. (2011) performed a rigorous selection of the published reports and concluded that the serum concentration of BDNF in patients with schizophrenia was found to be lower than that in healthy patients. This result seems to apply not only to patients undergoing pharmacological treatment but also to patients who have never been medicated. The results also seem to apply evenly regardless of sex. Finally, Green et al. (2011) used meta-regression techniques to demonstrate that BDNF and age were significantly correlated, with lower levels of BDNF corresponding to older age. However, no relationship was found between BDNF levels and antipsychotic dosage. We can conclude that in light of the published studies and the meta-analysis performed on them, and after controlling for methodological aspects and sample heterogeneity, blood BDNF levels are lower in patients with schizophrenia than in healthy individuals.

The consequences of this potential decrease in BDNF levels in patients with schizophrenia are important in light of this neurotrophic factor's impact on cognition. Tests have linked BDNF with the formation of dendritic spines and branches, indicating that BDNF acts as an authentic regulator of axonal growth. For example, it has been suggested that learning and memory procedures produce a synapse strengthening effect, resulting in long-term potentiation. Specifically, the process of synaptic strengthening appears to be mediated by receptors linked to BDNF, such as tyrosine-receptor kinase B (TrkB) (Gärtner et al., 2006; Minichiello et al., 1999). Numerous studies have even obtained correlations between the levels of BDNF and various aspects of cognition in patients diagnosed with schizophrenia. Zhang et al. (2012) found a significant correlation between reduced BDNF levels and the presence of cognitive changes in a large sample of admitted patients. Niitsu et al. (2011) used a patient sample to successfully predict cognitive functioning based on the levels of a precursor to BDNF; their results demonstrated considerable sensitivity and specificity.

Because BDNF is found at low concentrations in patients with schizophrenia and plays a crucial role in cognitive processes, it has been proposed as a biomarker for this mental disorder and, more specifically, as a biomarker for cognitive variability in schizophrenia. However, it does not appear that sufficient information exists to support this proposal, which, although promising, is unsatisfactory. At any rate, as we have indicated previously, a biomarker should have the characteristics of indicating normal biological processes, pathological processes, and therapeutic responses. With respect to the first characteristic, BDNF seems to play a large role in the processes responsible for cognition, especially in learning and memory. Its role as a regulator of axonal and dendritic growth has been demonstrated, as has its role of regulating neurogenesis in adults. Tests illustrate that long-term potentiation produced in the hippocampus as a result of learning is associated with the TrkB BDNF receptor. The second biomarker characteristic is demonstrated in the finding that the BDNF serum levels of patients with schizophrenia are lower than those of healthy subjects. This result is observed both in chronic patients and in those suffering their first psychotic episode. Specifically, neuroimaging studies link low levels of serum BDNF with reduced hippocampal volumes. The final step, therefore, is to determine the role of BDNF as a marker of therapeutic response. Numerous studies indicate that typical antipsychotics could diminish BDNF expression, whereas atypical drugs increase it. These data are still preliminary, however, and have only been investigated in animal models. Another study investigated the ability of cognitive treatment to augment serum levels of BDNF. The study sought to establish a statistically significant correlation between improved cognition and an increase in BDNF levels in the group that was provided with cognitive therapy. Although the study has yet to be duplicated, it has opened the door to promising research (Vinogradov et al., 2009).

BDNF's role as a biomarker has not been completely established by the data and results obtained thus far. For example, its specificity to schizophrenia has not been demonstrated; decreased levels of BDNF have also been found in patients with neurodegenerative disorders and other neuropsychiatric ailments. Nevertheless, BDNF's characterization as a biomarker for the cognitive dimension of schizophrenia appears to be a promising line of investigation, although more study and analysis on this relationship need to be performed (Penadés et al., 2013). Choosing BDNF as an indicator of the cognitive dimension of schizophrenia, while tempting, remains premature.

5. Conclusions

In the last decade, primarily because of debates around current clinical diagnostic criteria and psychopathological multidimensionality, there has been growing interest in the study of biological markers related to schizophrenia, specifically in certain quantifiable aspects of schizophrenia such as cognitive function. The interest in presenting objective biomarkers that are distanced from potential inter-observer subjectivity has spurred the development of specific fields within mental pathology that are more easily correlated with biological markers. First, numerous studies support the hypothesis that the inflammatory response could have a strong influence on the outset and development of schizophrenia and related disorders, and numerous inflammatory markers have been linked with the cognitive state of patients with these illnesses. Because cognitive deterioration has a direct impact on overall functioning in schizophrenia, the development of efficient therapies over the last few years has focused on locating immunomodulatory or anti-inflammatory drugs with promising and hopeful results. However, there are still numerous significant aspects that need to be investigated further in future studies, the most important of which include the following: (i) the role of prolonged antipsychotic treatment in the inflammatory response of patients with schizophrenia and their cognitive function; (ii) the type and timing (with respect to disease stage) of the delivery of anti-inflammatory or immunological therapies that are the most suitable for producing short/long-term improvement in cognitive responses; and (iii) whether dysregulation of the immune response is a common characteristic of recently diagnosed patients or only of particular pathological trajectories.

Second, the continued understanding of prolactin and its receptor has greatly illuminated prolactin's role in cognitive processes, specifically in patients with schizophrenia and related disorders. Recent studies have demonstrated prolactin's importance both in the transition to psychosis and in the prognosis and diagnosis of schizophrenia independent of antipsychotic drug use, highlighting the potential for it to become a schizophrenia-specific biomarker.

Despite the diversity of biomarkers associated with cognitive state in schizophrenia, the current literature has gathered the greatest amount of evidence for BDNF. Patients with schizophrenia demonstrated lower concentrations of BDNF compared to healthy controls, and a recent study correlates the levels of BDNF with improved cognition in patients treated with cognitive rehabilitation

Taking into account the possible counterbalancing role of neurotrophins, it is plausible both that early inflammation could activate a response to increase the concentration of neurotrophic factors and that this response could affect the response to treatment. Therefore, it would be beneficial to study the potential consequences of the inflammatory state in the initial phases of psychosis and the relevance of neurotrophic receptors in cognitive function and treatment response. It is also necessary to understand the role played by psychosocial stress as a trigger for these biological responses and its detrimental consequences when, for example, stress is either particularly acute or maintained for extended periods of time.

We thus expect considerable development in basic and clinical research both on cognitive function and on potentially related biomarkers, intended to transfer advances in neurosciences to the field of mental health, specifically the development of a greater understanding of schizophrenia.

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Contributors

RP,CG, MB, AG-R, BC, GM and MB wrote the first draft of the manuscript and reviewed it.

Conflict of Interest

R Penadés has received honoraria/travel suport from Otsuka-Lundbeck. C Garcia Rizo has received honoraria/travel support from Janssen--Cilag, Lundbeck and Ferrer. Alexandre González-Rodríguez has received honoraria or paid for travels from Pfizer, Ferrer, Janssen-Cilag, and Lundbeck-Otsuka.

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