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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.

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).