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# Immune and metabolic alterations in first episode psychosis (FEP) patients

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ABSTRACT

The molecular underpinnings associated to first episode psychosis (FEP) remains to be elucidated, but compelling evidence supported an association of FEP with blood alterations in biomarkers related to immune system, growth factors and metabolism regulators. Many of these studies have not been already confirmed in larger samples or have not considered the FEP diagnostic subgroups.

In order to identify biochemical signatures of FEP, the serum levels of the growth factors BDNF and VEGF, the immune regulators IL-1RA, IL-6, IL-10 and IL-17, RANTES/CCL5, MIP-1b/CCL4, IL-8 and the metabolic regulators C-peptide, ghrelin, GIP, GLP-1, glucagon, insulin, leptin, PAI-1, resistin and visfatin were analysed in 260 subjects collected in the GET UP project.

The results indicated an increase of MIP-1b/CCL4, VEGF, IL-6 and PAI-1, while IL-17, ghrelin, glucagon and GLP-1 were decreased in the whole sample of FEP patients ($p < 0.01$ for all markers except for PAI-1 $p < 0.05$). No differences were evidenced for these markers among the diagnostic groups that constitute the FEP sample, whereas IL-8 is increased only in patients with a diagnosis of affective psychosis. The principal component analysis (PCA) and variable importance analysis (VIA) indicated that MIP-1b/CCL4, ghrelin, glucagon, VEGF and GLP-1 were the variables mostly altered in FEP patients. On the contrary, none of the analysed markers nor a combination of them can discriminate between FEP diagnostic subgroups.

These data evidence a profile of immune and metabolic alterations in FEP patients, providing new information on the molecular mechanism associated to the psychosis onset for the development of preventive strategies and innovative treatment targets.



## 1. Introduction

Psychosis as diagnostic category is characterized by a high clinical and etiological heterogeneity (Insel, 2010; Maj, 2011) with the molecular underpinnings still to be elucidated. Thus, the identification of a biological signature associated to psychosis could improve the early diagnosis and could help to develop treatment strategies tailored to the individual (Fond et al., 2015). This field of research is of great interest in the clinical practice, in particular in first episode psychosis (FEP), where longitudinal studies have highlighted a critical period that ranges from two to five years after the psychosis onset for the evolution of the illness and prognosis (Abdel-Baki

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et al., 2011; Harrison et al., 2001). In this period, FEP patients are vulnerable for relapse: the rates range from 30 to 60% at two years (Vázquez-Barquero et al., 1999) to 80% at five years (Shepherd et al., 1989). For this reason, the diagnostic assessment and the beginning of an adequate and timely treatment is crucial to prevent relapse and the chronicization of the disorder (Birchwood et al., 1998).

During the last few years, several studies have been focused on search for biological markers involved in inflammatory and endocrine processes that occur at the psychosis onset to avoid the influence of confounding factors such as lifetime treatments with antipsychotics. Many studies have reported abnormal activation of the immune system in major psychosis (Howes and McCutcheon, 2017; Köhler et al., 2017; Müller, 2014; Rosenblat and McIntyre, 2016; Steiner et al., 2014), mainly at the cytokine level even at illness onset (Di Nicola et al., 2013; Garcia-Bueno et al., 2015). Furthermore, a *meta*-analysis of 40 studies (Miller et al., 2011) about the impact of cytokines upon FEP suggested the presence of an inflammatory syndrome, where some cytokines (IL-1β, IL-6, and TGF-β) can be state markers for acute exacerbations, and others (IL-12, IFN-γ, TNF-α, and sIL-2R) can be considered trait markers. A subsequent study confirmed that pro-inflammatory cytokines were elevated in antipsychotic medication-naïve FEP patients (Upthegrove et al., 2014). Moreover, it has been demonstrated that increased levels of pro-inflammatory cytokines, in particular IL-6 and IFN-γ, predict poor treatment response at the onset of psychosis (Mondelli et al., 2015) as well as it has been reported that depressive symptomatology is associated with specific immune–inflammatory abnormalities in FEP (Noto et al., 2016).

The systemic deregulation of the inflammatory balance in individuals with FEP would seem to activate compensatory mechanisms to repair neuronal damage at early stage of illness, causing systemic changes in the expression of the receptors of neurotrophins, in particular the Brain Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) (Martinez-Cengotitabengoa et al., 2015). There are several evidences of a reduction in serum BDNF in FEP and drug-naive cohorts (Toll and Mané, 2015). However, data are often contrasting since an increase of BDNF in FEP patients (Lizano et al., 2016; Theleritis et al., 2014), suggesting that alterations might be related to specific diagnostic groups.

Together with alterations in inflammatory response system and in neurotrophins, patients affected by psychosis have shown an increased risk of developing cardiovascular disease and type 2 diabetes compared to the general population (Morris, 2017; Rado, 2017) . Accumulating evidence has showed abnormal glucose metabolism in drug-naïve subjects with schizophrenia (Fernandez-Egea et al., 2009; Spelman et al., 2007), the presence of insulin-resistance (Ryan et al., 2003; Verma et al., 2009) and increased levels of insulin-related peptides (Chen et al., 2013; Guest et al., 2010).

Also in bipolar disorder, high serum levels of some adipokines (as leptin and adiponectin) have been observed (Barbosa et al., 2012) and a reduction of glucagon, glucagon-like peptide-1 (GLP-1) and ghrelin has been associated with increased gastric inhibitory peptide (GIP) levels (Rosso et al., 2015). Interestingly, the abnormal levels of GIP, GLP-1 and ghrelin found in these patients do not appear to be associated with the medication used neither with the presence of diabetes, hypertension or metabolic syndrome (Rosso et al., 2015).

Some reports show abnormal glucose and lipid metabolism even in FEP patients (Garcia-Rizo et al., 2017; Petrikis et al., 2015a; Pillinger et al., 2017). A recent study (Keinänen et al., 2015) has investigated baseline metabolic differences in FEP patients and alterations during the first year of treatment, suggesting that insulin resistance may be an early marker of increased vulnerability to weight gain and abdominal obesity.

On the basis of this rationale, the aims of the study were: 1) the identification of biochemical signatures in immune markers, growth factors and metabolic regulators in a large sample of FEP patients in order to replicate and extend with new markers the knowledge about the biological underpinnings associated to the psychosis onset; 2) the individuation of possible molecular markers associated to FEP specific diagnostic subgroups for the implementation of the diagnostic assessment.

## 2. Materials and methods

This study was conducted within the framework of the Research Program "Genetics Endophenotypes and Treatment: Understanding early Psychosis" (GET UP), which was constituted by four partner projects including "Psychosis early Intervention and Assessment of Needs and Outcome" (GET UP PIANO) Trial and "Genetic data Utilization and Implementation of Targeted drug Administration in the clinical Routine" (GET UP GUITAR) Project. FEP patients were recruited and assessed at baseline and after 9 months with a set of standardized instruments within the context of the GET UP PIANO Trial, a large multicenter controlled trial, which details on the protocol and on the main results are given elsewhere (Ruggeri et al., 2015, 2012).

The GUITAR project, focused on the identification of molecular markers and genetic variants associated to psychosis onset and response to medication, was conducted on the enrolled sample of the GET UP PIANO Trial and blood samples were collected in patients who accepted to participate to these biological studies. This manuscript describes the biochemical analyses of the GUITAR project performed in the serum of FEP patients at the admission of the GET UP PIANO Trial (baseline). The GET UP Research Program was approved by the Ethics Committees of the coordinating center (Azienda Ospedaliera Universitaria Integrata di Verona) and of each participating unit.

### 2.1. Subjects

Based on the WHO 10-Country study (Jablensky et al., 1992), the initial target group comprised people, with potential psychosis, who had had a first contact with any CMHCs during the index period (Apr 1, 2010-Mar 31, 2011). Inclusion criteria were: (a) age 18–54 years; (b) residence within the catchment areas of CMHCs; (c) presence of at least 1 of the following symptoms: hallucinations, delusions, qualitative speech disorder, qualitative psychomotor disorder, bizarre, or grossly inappropriate behavior; or 2 of the following symptoms: loss of interest, initiative, and drive; social withdrawal; episodic severe excitement; purposeless destructiveness; overwhelming fear; or marked self-neglect; and (d) first lifetime contact with CMHCs, prompted by these symptoms.

Exclusion criteria were: (a) pre-existing anti-psychotic medication (>3 months) prescribed by any psychiatric or other medical agencies for a mental disorder identical or similar to the current one; (b) mental disorders due to a general medical condition; (c) moderate-to-severe mental retardation assessed by clinical functional assessment; and (d) psychiatric diagnosis other than ICD-10 for psychosis.

A control group of unrelated volunteers was also enrolled. Inclusion criteria were: (a) age 18–54 years; (b) residence within the catchment areas of CMHCs. Exclusion criteria were: (a) diagnosis of any mental disorders, moderate-to-severe mental retardation, dementia, cognitive deficits, neurological disorders, previous head injury with loss of consciousness for ≥15 min; (b) first degree relatives' anamnesis for psychiatric disorders; (c) presence of

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