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COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA: DISENTANGLING THE ROLE OF METABOLIC ALTERATIONS AND NEUROINFLAMMATION

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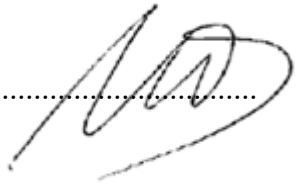

DECLARATION

This thesis has been composed by myself and has not been used in any previous application for a degree. Throughout the text I use both 'I' and 'We' interchangeably.

All the results presented here were obtained by myself, except for:

- **Determination of plasma concentrations of peripheral cytokines,** performed by Dr. Cristina Lorenzi, Psychiatry & Clinical Psychobiology Unit directed by Prof. Francesco Benedetti, Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy

- **Determination of plasma concentrations of peripheral metabolites of the Kynurenine Pathway,** performed by Dott. Stefano Comai, Department of Pharmaceutical and Pharmacological Sciences, University of Padua, Padua, Italy

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All sources of information are acknowledged by means of reference.

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"In the long history of humankind (and animal kind, too) those who learned to collaborate and improvise most effectively have prevailed." - *Charles Darwin*

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ABSTRACT

Cognitive deficits and metabolic disturbances are highly prevalent in schizophrenia, leading to severe disability and thus representing main treatment targets. A relationship between Metabolic Syndrome (MetS) and cognitive impairment has been demonstrated both at clinical and neurobiological level, with several studies showing an association of MetS with cognitive impairment and altered brain structural integrity. In this context, recent converging evidence indicates that inflammation may play a major role. Indeed, MetS is characterized by a low-grade chronic pro-inflammatory state, and inflammation has been correlated with greater severity of cognitive deficits in schizophrenia, as well as with alterations of brain structure and activity. Consistently, preliminary data brought by our previous research suggested an interplay between inflammation and MetS in modulating cognitive outcome of patients affected by schizophrenia.

Based on this evidence, this study aimed at investigating the relationship between cognition, MetS and inflammation in a sample of 75 patients with schizophrenia, also investigating in a subsample possible influences of MetS and related inflammatory biomarkers on white matter integrity and brain metabolites of the Dorsolateral Prefrontal Cortex (DLPFC).

Results showed that, among patients with schizophrenia, MetS and its components are associated with higher levels of proinflammatory cytokines and greater activation of the Kynurenine Pathway (KP). The interplay between MetS and related inflammatory biomarkers resulted to significantly influences patients' cognitive functioning, with MetS moderating the effects of Tumor Necrosis Factor-α (TNF- α) and Kynurenic Acid (KP metabolite) on Verbal Memory and global cognitive outcome. Finally, MRI analyses evidenced that MetS and levels of TNF-α and KP metabolites predicted reduced white matter integrity and neurometabolic alteration associated with neurodegenerative processes in the DLPFC.

Taken together, results of this study confirmed previous preliminary evidence indicating an association between metabolic disturbances, inflammation, and cognitive functioning in schizophrenia, thus contributing to better understand the great clinical variability of the disease. Moreover, these data further indicate the need of combined treatment strategies including interventions aimed at ameliorating metabolic status, in order to improve both health and cognitive outcome of patients with schizophrenia.

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ACRONYMS AND ABBREVIATIONS

α7nAChR = α7 nicotinic acetylcholine receptor

1H-MRS = Proton Magnetic Resonance Spectroscopy

3-HK = 3-hydroxykynurenine

ACC = Anterior Cingulate Cortex

ACR = Anterior corona radiata

AD = Axial Diffusivity

AHA = American Heart Association

ALIC = Anterior limb of internal capsule

AMPARs = AMPA receptors

AP = Antipsychotic

ATP III = Adult Treatment Panel III

BACS = Brief Assessment of Cognition in Schizophrenia

BBB = blood-brain barrier

BCC = Body of corpus callosum

BDNF = Brain-Derived Neurotrophic Factor

CC = Corpus callosum

CCL = C–C motif ligand

CGC = Cingulate gyrus

CGH = Cingulum (Hippocampal part)

CNS = Central Nervous System

CR = Corona radiata

CRP = C-Reactive Protein

CSF = Cerebral Spinal Fluid

CST = Cortico-spinal tract

DLPFC = Dorsolateral Prefrontal Cortex

DTI = Diffusion Tensor Imaging

EAATs = Excitatory Amino Acid Transporters

EC = External capsule

ED = Endothelial Dysfunction

FA = Fractional Anisotropy

FEP = First Episode Psychosis

FFAs = Free Fat Acids

FGF = Fibroblast Growth Factor

FX = Fornix

FX-ST Fornix stria terminalis

GCC = Genu of corpus callosum

G-CSF = Granulocyte Colony Stimulating Factor

Glx = Glutamate + Glutamine

GM-CSF = Granulocyte Macrophage Colony Stimulating Factor

HDL = High-Density Lipoprotein

HPA = Hypothalamic–Pituitary–Adrenal

IC = Internal capsule

IDF = International Diabetes Federation

IDO = Indoleamine 2,3 Dioxygenase

IFN- γ = Interferon-γ

IFO = Inferior fronto-occipital fasciculus

IGF-1 = Insulin-like Growth Factor 1

IL = Interleukin

Ins = Myo-inositol

IR = Insuline resistance

KATI and KATII = Kynurenine Aminotransferases

KMO = Kynurenine 3- Monooxygenase

KP = Kynurenine Pathway

KYN = Kynurenine

KYNA = Antagonist Kynurenic Acid

LDL = Low-Density Lipoprotein

MD = Mean Diffusivity

MetS = Metabolic Syndrome

NAA = N-acetylaspartate

NMDA = N-methyl-D-aspartate

OOR = Out Of Range

PANSS = Positive and Negative Syndrome Scale for Schizophrenia

PCR = Posterior corona radiata

PFC = Prefrontal Cortex

PLIC = Posterior limb of internal capsule

PTR = Posterior thalamic radiation

QUIN = Quinolinic Acid

RD = Radial Diffusivity

RLIC = Rentrolenticular part of internal capsule

ROS = Reactive Oxygen Species

SCC = Splenium of corpus callosum

SCR = Superior corona radiata

SFO = Superior fronto-occipital fasciculus

SLF = Superior longitudinal fasciculus

SNP = Single Nucleotide Polymorphism

SS = Sagittal striatum

T2DM = Type 2 Diabetes Mellitus

TDO = Tryptophan-2,3 Dioxygenase

TGF-β = Transforming growth factor beta

TNF = tumor necrosis factor

TRP = Tryptophan

UNC = Uncinate fasciculus

VEGF-A = Vascular-Endothelial Growth Factor-A

VOIs = Volumes of interest

WM = White Matter

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1. INTRODUCTION

Schizophrenia is a devastating chronic mental illness with onset in youth, affecting over 25 million people worldwide and characterized by a high burden of suffering for patients and caregivers, which also reflects the huge burden of costs (Reeder et al, 2014). According to the National Institutes of Mental Health, schizophrenia-related costs amount to almost $63 billion a year with nearly $19 billion involved in direct treatment, while the rest due to other factors, such as unemployment and social services resources (Bellack et al, 2007). Practically, the burden and costs for both the individual and the society do not derive from actual health care, but rather depend on the disability still associated to the illness even when symptoms are fairly managed by treatments. It has been widely acknowledged that such disability is mainly determined by the core cognitive deficits 3 that accompany the illness, and despite the astonishing scientific breakthroughs of recent decades and significative changes in patients' quality of life from the Kraepelin's era, cognitive deficits still represent a treatment issue in schizophrenia. Indeed, antipsychotic agents, which have unquestionable value in managing psychotic symptoms, have no or minimal effects on neuropsychological performance (Keefe et al, 2007). For this reason, it is not surprising that significant research efforts have been dedicated to both understanding the biological bases and developing new treatment targeting the cognitive impairment.

Beside persistent cognitive and functional impairments, schizophrenia is also characterized by a decreased longevity, with a life expectancy about 20% lower than the general population (61 vs 76 years). Increased mortality is due to both psychiatric and medical conditions. Indeed, on one side schizophrenia is associated with higher rates of suicide, but on the other side, people with schizophrenia show elevated metabolic risk factors and increased mortality due to cardiovascular and dysmetabolic comorbidities. Indeed, compared to general population, patients with schizophrenia are characterized by a two-fold prevalence of obesity and higher rates of Metabolic Syndrome (MetS). Different factors contribute to determine this dysmetabolic state associate with the disease, such as antipsychotic treatment, unhealthy lifestyle and dietary habits, as well as genetic predisposition to altered lipid and glucose metabolism. Metabolic alterations do not only negatively affect physical health but can lead to a worse psychopathological outcome as well. Indeed, recent findings pointed out that MetS is associated with greater

cognitive impairment, as well as with disruptions of cerebral grey and white matter. Of note, these associations are detectable also among healthy subjects and other psychiatric populations. However, to date the neurobiological correlates of MetS are still far to be defined. In this context, recent converging evidence indicates that neuroinflammation may play a major role. A growing number of genetic, neuroimaging and epidemiological studies have shown that inflammatory pathways are altered in schizophrenia, possibly contributing to the cognitive deficit that features the disease. Indeed, elevated peripheral inflammatory biomarkers and in vivo microglial activation were consistently associated with cognitive deficit, and disruption of brain structural integrity. Interestingly, metabolic alterations, particularly abdominal visceral obesity, are characterized by low-grade chronic inflammation and higher production of proinflammatory cytokines able to cross the blood brain barrier and to induce microglial activation, affecting brain plasticity and signaling processes. Based on this evidence, it has been hypothesized that metabolic alterations are able to further increase inflammation among patients with schizophrenia, which are already characterized by a proinflammatory state. However, to date only few studies investigated the neurobiological correlates of this complex relationship between cognition, metabolic alterations and neuroinflammation in schizophrenia. A better understating of the underlying mechanisms would allow identifying new potential biomolecular targets of intervention, with a potential significant impact for prognosis of the disease.

1.1 Cognitive deficit in schizophrenia

Despite cognition is not formally included among DSM-5 criteria for schizophrenia, neurocognitive deficit is a core feature of the illness, representing together with negative symptoms the most critical treatment dimension, determining high disability and being almost completely resistant to antipsychotic drugs.

Evidence of a severe functional and cognitive impairment among patients with Schizophrenia was already present in the early descriptions of the disorder as Dementia Praecox by E. Kraepelin (Kraepelin, 1919), and nowadays schizophrenia is often considered as a proper cognitive disease (Kahn & Keefe, 2013).

Indeed, cognitive impairment is often detectable before the onset of illness, is scarcely related to psychotic symptoms, and remains stable or worsens along the course of illness.

Patients with schizophrenia show deficits in a wide range of cognitive domains, spanning form neurocognitive functions to social cognitive abilities and language. Among these, neurocognitive performance in schizophrenia is reported as 1.5 to 2.5 standard deviation below general population, mainly depending on prefrontal cortex (PFC) activity. As widely described, schizophrenia is characterized by progressive gray matter reductions and cortical thinning in frontal and temporal areas (Sheperd et al, 2012), as well as by altered white matter integrity in frontal and temporal tracts (Ellison-Wright et al, 2014). Neurocognition is associated with PFC volume among both healthy subjects and patients with schizophrenia, and among patients with schizophrenia prefrontal reductions of Fractional Anisotropy (FA) correlate with neurocognitive deficits (Mazza et al, 2019).

Overall, the main neurocognitive domains impaired in schizophrenia are working memory, executive functions, attention, verbal learning and memory, speed of processing and executive functions Green et al, 2004).

Working memory: refers to the cognitive abilities necessary to transiently storage and manipulate information, underlying crucial functions such abstraction, reasoning and learning. Three subcomponents of working memory are described in literature: the central-executive, the visuospatial, and the phonological, respectively implicated in integration and attentional-controlling system, visual images manipulation, and storage of verbal information (D'Esposito & Postle, 2015). A meta-analysis conducted by Forbes and colleagues showed that the impairment is present at all three levels of working memory, with no significant differences between different domains (Forbes et al, 2009)

Alteration of working memory may lead to impairments in decoding ant maintaining information, speech production, and formal thought (Acheson & MacDonald 2009). Working memory is also a critical determinant of patient's functioning, particularly of functional capacity (ability to perform under optimal conditions) (Bechi et al, 2014) and work competence. In schizophrenia, working memory deficit has been correlated with lower hippocampal volumes and reduced activity of the Dorsolateral Prefrontal Cortex (DLPFC).

Executive Functions: refer to the cognitive abilities necessary for crucial functions such as planning, problem solving, intentional behavior, abstraction, cognitive flexibility, and meaning attribution to external/internal stimuli. Executive dysfunction underlies patients'

deficits to deal with novel and complex events, and has been found to correlate with lack of insight (Young et al, 1993) as well as with poor functional and clinical outcome.

Similarly to working memory, executive dysfunction have been link to lower prefrontal volumes and DLPFC activity. Moreover, executive deficit was also associated with compensatory increased activity of rostral and dorsal anterior cingulate cortex (ACC).

Attention: refers to the abilities necessary in order to individuate and differentiate environmental relevant stimuli (selective attention), to sustain focus during information processing and acquisition (sustained attention/vigilance), and to receive different simultaneous messages (shared attention) (Sharma & Antonova, 2003). In schizophrenia, impairments in vigilance and attention lead to difficulties in learning, concentrating and following social conversations and to inability to follow instructions (Green, 1996), thus significantly negatively affecting functional outcome.

Speed of processing: Processing speed is the speed with which various cognitive tasks are performed. Two meta-analyses regarding schizophrenic patients (Dickinson et al, 2007, Knowles et al, 2010) show that the effect size of this deficit exceeds those typically found for episodic memory and executive functions, suggesting that processing speed deficit is central and of great importance in cognitive disorders in schizophrenia. Moreover, a reduction in processing speed was also found in the first and second-degree relatives of schizophrenic patients, demonstrating the heritability of this cognitive function deficit as well (Glahn et al, 2007). Alteration of the processing speed adversely affects the patient's functioning by reducing the degree of autonomy (Keefe & Harvey, 2012).

Verbal learning and Memory: refer to the abilities necessary for learning, information retaining, recognizing. In schizophrenia are frequently reported deficits in learning rather than information retention, associated with impairments in social functioning and real-world behavior. Episodic memory deficits are associated with DLPFC hypoactivation and reductions of hippocampal and frontal volumes, as well as with trophism of other subcortical structures such as amygdala and putamen (Kurtz et al, 2017).

Language: Patients with schizophrenia are characterized by deficits of lexical networks and semantic associations, underlying the presence of language alterations that translate into neologisms, bizarre speech, and eventually "word salad". Moreover, impairments are not limited to the lexical-semantic field, but they extend to the syntactic domain, as well as to communicative-pragmatic abilities (Moro et al, 2015; Bambini et al, 2016). Deficits

in the latter domain are also predictive of a poor social functioning and a reduced quality of life (De Boer et al, 2020).

Social Cognition: A large body of literature has documented a broad impairment encompassing every socio-cognitive domain and multiple processes, including: Theory of Mind (ToM, affective and cognitive) and mentalization, pragmatic abilities, emotion processing (especially negative emotions misinterpretation), experience sharing and empathy (both affective and cognitive), metacognition and attributional style (i.e., self-serving bias and a tendency to blame others), and social perception (especially with abstract cues). Social cognitive deficit has a profound impact on patients' functional outcome and especially social functioning, mediating the effect of neurocognitive deficit on overall functioning (Green et al, 2019; Pinkham et al, 2014; Bechi et al, 2017; Van Rheenen et al, 2019).

Cognitive deficit is characterized by great variability between patients, influenced by several biological and environmental factors (Carruthers et al, 2019). In line with the concept of schizophrenia as a cognitive disease, different authors hypothesized that abnormalities within several cognitive domains (i.e., working memory, set-shifting abilities, episodic verbal memory, processing speed and attentional processes) might represent different endophenotypes of schizophrenia (Allen et al, 2009; Alloza et al, 2016; Donati et al, 2020; Schmitt et al, 2016).

Concerning the role of neurocognition in patients' functional outcome, reviews and meta-analyses in the field focused on different clinical subpopulations and outcomes (i.e., both community-based functioning indicators and the ability to acquire skills in rehabilitation programs for inpatient samples) (Green et al, 2019). Studies reported a longitudinally stable association between patients' cognitive profile and functional outcome, with a possible role of increased inflammation (Jiménez-López et al, 2019; Kogan et al, 2018; Velthorst et al, 2017). Moreover, poorer neurocognitive performance has been associated with worsened treatment response and vocational abilities (Helldin et al, 2020, Spangaro et al, 2021). Although the role of specific cognitive domains on different functional domains has been pointed out (e.g., working memory and work functioning; episodic memory, verbal fluency and community living skills; processing speed and overall functioning), there is still preliminary evidence on the impact of cognitive heterogeneity (Andersen et al, 2013; Guimond et al, 2017; Keefe & Harvey, 2012; Pinkham & Penn,

2006). Specifically, cognitively impaired patients seem to be less likely to get to symptom remission, more likely to develop worse physical functioning and somatic ill health, and to die prematurely with respect to cognitively intact peers (Helldin et al, 2015; Helldin et al, 2020; Moradi et al, 2018).

1.2 Metabolic Syndrome

1.2.1 Definition and Criteria

Metabolic Syndrome (MetS) is a constellation of cardiometabolic conditions that occur together and are associated with a higher risk of cardiovascular disease, type II diabetes and overall mortality (Tahmi et al, 2021).

MetS has been described in several ways, and efforts have been made to unify its definition in order to facilitate comparisons of prevalence and impact between countries. While the concept of MetS has existed for almost a century, only in 1998 an internationally recognized definition was formulated by the World Health Organization (WHO). Several definitions were developed in the following years. While all of the different definitions acknowledge the same components (obesity or abdominal adiposity, hypertension, impaired glucose metabolism and IR and dyslipidemia), they differ are in how the components are clinically detected and, in some cases, a particular trait is emphasized and needed to meet the criteria and establish a diagnosis (Samson & Garber, 2014).

The most widespread definition of MetS was operationalized by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) in 2001 and subsequently updated in 2005 by the American Heart Association (AHA) and the National Heart Lung and Blood Institute (NHLBI) (Grundy et al, 2005).

A similar definition was formulated in the same year also by the International Diabetes Federation (IDF) (Samson & Garber, 2014).

According to NCEP/ATPIII, the diagnosis of MetS can be established if three or more of the following conditions coexist:

1. Blood glucose greater than 5.6 mmol/L (100 mg/dl) or pharmacological treatment for hypergicemia
2. HDL cholesterol < 1.0 mmol/L (40 mg/dl) in men, < 1.3 mmol/L (50 mg/dl) in women or pharmacological treatment for low HDL cholesterol

3. Blood triglycerides > 1.7 mmol/L (150 mg/dl) or pharmacological treatment for hypertrigliceridemia
4. Waist circumference > 102 cm (men) or > 88 cm (women)
5. Blood pressure > 130/85 mmHg or pharmacological treatment for hypertension (Tahmi et al, 2021).

1.2.2 Epidemiology

MetS has been defined a global epidemic by the WHO and is regarded a major public health issue. The reported prevalence of MetS varies by age, sex, region, socioeconomic status, environment (rural or urban), and ethnicity of study cohorts. Furthermore, it is often difficult to establish because of differences in the criteria used for the definition of MetS and in adiposity thresholds applied across the studies. According to the World Health Organization, 34% of the US adults (over twenty) and 9.4% of adolescents is affected by MetS (Ervin & Bethene, 2009). The National Health and Nutrition Examination Survey (NHANES) estimated the MetS prevalence among the US population between 2007 and 2014 (using NCEP-ATP III criteria) to be around 34% as well, ranging from 19% and 55% depending on the age (Shin et al, 2018).

As far as Europe is concerned, the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study, using the IDF criteria, reported a MetS prevalence of 41% in men and 38% in women at ages 47 to 71 years. The high prevalence of MetS is not limited to US and Europe. In Asia, MetS affect around one-third of the Indian population in urban settings (Samson & Garber, 2014).

1.2.3 Etiopathogenesis

MetS is acknowledged to represent a proinflammatory and prothrombotic state resulting from a complex interplay between genetic and environmental factors.

The broad variation in geographic distribution of MetS underlines the role of environmental and lifestyle factors in contributing to the development of the syndrome. The majority of patients are obese or overweight, older, sedentary, and show some degree of IR. Predisposing factors for the development of MetS are overfeeding and obesity, genetics (positive family history), aging, stress, sedentary behavior or reduced physical

activity, disturbed sleep, psychotropic drugs' treatment (especially atypical antipsychotics), and excessive alcohol consumption (Fahed et al, 2021).

MetS' pathophysiology is very complex and has not been fully clarified yet. Genetic susceptibility, IR, visceral adiposity, arterial hypertension, atherogenic dyslipidemia, endothelial dysfunction, hypercoagulability, and chronic inflammation are all factors implicated in the syndrome. However, whether the MetS individual components represent different diseases or manifestations of a shared pathogenetic pathway is still under debate. Of the different mechanisms proposed to underlie the condition, IR, chronic inflammation and neurohormonal activation, and have emerged as the main players in the development and progression of MetS, and as well as in its transition to cardiovascular disease (Armani et al, 2017; Rochlani et al, 2017; Fahed et al, 2021). IR plays a crucial part in the pathogenesis of MetS. IR is a condition characterized by a reduced tissue response to insulin action and affect several organs, including adipose tissue, skeletal muscle and liver (Rochlani et al, 2017). In normal conditions, insulin determines an increase in glucose uptake from circulation into liver and skeletal muscle tissues for glycolysis, while hepatic gluconeogenesis is inhibited. These processes together aim to restore the normal basal levels of blood glucose. Besides modulating glucose metabolism, insulin also regulates lipid metabolism, by enhancing lipogenesis and suppressing lipolysis. In an abnormal condition, IR, in adipose tissue, determines an increase in circulating Free Fat Acids (FFAs) that, in turn, inhibit the lipolysis-suppressing effect of insulin (Boden & Shulman, 2002). In skeletal muscle, FFAs suppress protein kinase activation reducing glucose uptake, while, in the liver, they induce protein kinase activation promoting lipogenesis and gluconeogenesis. These processes induce the creation of a compensatory hyperinsulinemic state that initially is able to maintain the glycaemia within the normal range, but, eventually, lead to a decrease in insulin levels. In addition, the increase in circulating FFAs determines a further reduction of insulin secretion also through a direct lipotoxic effect on pancreas □ cells, hastening the development of glucose intolerance (Tooke & Hannemann, 2000; Rochlani et al, 2017).

IR exerts an action also directly on small blood vessels, causing an increase in blood pressure. As a consequence of the FFAs-induced vasoconstriction and on loss of insulin's vasodilator activity, IR plays a role in the development of arterial hypertension. Additional involved mechanisms include renal sodium reabsorption and increase

sympathetic activation. Furthermore, IR contributes to the creation of a prothrombotic state, determines an increase in serum viscosity, and induces the release of pro-inflammatory cytokines from the adipose tissue, thus leading to an increased cardiovascular risk (Juhan-Vague et al, 2003; Rochlani et al, 2017).

Abdominal obesity and IR are particularly interrelated. Visceral adipose tissue contribute to IR to a greater extent than subcutaneous fat, as visceral lipolysis increases the supply of FFAs to the liver, thus leading to a raise in the synthesis of triglycerides and the production of triglycerides, apolipoprotein B and low-density lipoprotein (LDL). IR, thus, indirectly contributes to an increase in LDL cholesterol and a reduction in High Density Cholesterol (HDL) as a consequence of the disrupted lipid metabolism in the liver. Finally, visceral fat, which is more metabolically active than subcutaneous fat, is itself involved in the promotion of a prothrombotic state through the synthesis of high amounts of mediators such as plasminogen activator inhibitor (Rochlani et al, 2017).

The discovery of the endocrine and immunological activity of adipocytes has shed more light on the pathogenesis of MetS. Visceral fat is associated with increased levels of leptin, an adipokine associated with increased cardiovascular risk, and reduced levels of adiponectin, an anti-inflammatory and antiatherogenic adipokine with effects opposite to those of leptin. Leptin not only regulates energy homeostasis and food intake, but also enhances the stress response by activating the cerebral corticotrophin-releasing factor pathway, thereby strengthening both sympathetic nervous system and the HPA axis (Leonard et al, 2012; Rochlani et al, 2017).

The activation of the renin-angiotensin system and the increased production of Angiontensin II, caused by obesity and IR and resulting in an increased production of reactive oxygen species, are other relevant pathways involved in the development of MetS. All these mechanisms together result in increased activation of downstream signaling cascades causing tissue fibrosis and atherogenesis (Rochlani et al, 2017).

The activation of various pro-atherogenic signaling pathways in MetS eventually leads to a common inflammatory pathway that contributes to the development of hypertension, dyslipidemia, diabetes, and cardiovascular disease, ultimately leading to the development of MetS. Inflammation plays a crucial part in the pathogenesis of cardiovascular disease and, although their specific role is still controversial, several inflammatory markers have been demonstrated to be increased in subjects with MetS. The increase in

proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), and C-reactive protein (CRP) is the result of an overproduction by the expanded adipose tissue mass, also in response to leptin activity. Tumor necrosis factor alpha (TNF-α), produced by macrophages in the adipose tissue, inactivates insulin receptors in the smooth muscle and adipose tissues, inhibits adiponectin release and induces lipolysis, thus incrementing the FFAs load. IL-6, produced by adipocytes and immune cells, exerts its action on several tissues, including liver, endothelium and bone marrow, where it promotes the production of fibrinogen and of acute phase reactants, such as CRP, inducing a prothrombotic and proinflammatory state. Consistently, high CRP levels have been correlated with the development of MetS, cardiovascular disease and diabetes. (Rochlani et al, 2017, Eckel et al, 2005).

1.2.4 Metabolic Syndrome in Schizophrenia

Subjects suffering from psychiatric disorders represents a population at high risk for the development of metabolic abnormalities and, among them, patients with schizophrenia seem to be the most affected. It is well-established fact that subjects with schizophrenia have premature morbidity and mortality, being their life expectancy approximately 80-85% of that of the general population (Laursen et al, 2014). While the increased risk of death in schizophrenia has long been ascribed to the higher incidence of accidents and suicide, research in the last decades has focused on the impact of the numerous medical comorbidities of the illness, identifying cardiovascular risk factors as the main cause of mortality in schizophrenia (Laursen et al, 2011). MetS among patients with schizophrenia contributes to some of this increased cardiovascular risk. In subjects with schizophrenia, the risk of developing MetS was found to be two to three times higher than the general population (De Hert et al, 2009; Vancampfort et al, 2013).

Recent meta-analytic evidence reported an average prevalence of MetS of over 30% (Mitchell et al, 2013, Vancampfort et al, 2015, Santini et al, 2016) in patients with schizophrenia. Moreover, they have a significantly higher risk of abdominal obesity, hypertension, hyperglycemia and dyslipidemia.

Despite the numerous attempt made to identify factors predisposing to MetS in subjects with schizophrenia, reliable predictors are still lacking. Among the different sociodemographic variables investigated, the most consistently reported are older age

(Arango et al, 2008) and longer duration of illness, while no conclusive evidence has emerged on the association between gender and MetS.

The mechanisms underlying the increased prevalence of MetS among subjects with schizophrenia are still under investigation. Several factors have been proposed as responsible to its higher prevalence, including environmental factors such as sedentary lifestyle and unhealthy eating habits that promote the development of obesity, disruption of the hypothalamic pituitary-adrenal axis (HPA) leading to hypercortisolemia and direct action of antipsychotic treatment on lipid and glucose metabolism (Malhotra et al, 2013). Moreover, research has shown that elevated insulin levels and glucose alterations, abnormal waist-hip ratio and increased visceral adiposity may occur early in the course of the disease, in first-episode drug-naïve patients and their first-degree relatives (Castillo et al, 2016). This led to the hypothesis that, besides epigenetic, also genetic variability could be related to MetS in schizophrenia patients. Antipsychotic (AP) drugs certainly play a central role in the susceptibility of patients with schizophrenia to develop MetS and its components. Indeed, the prevalence of MetS in schizophrenia subjects ranges between 3-26% in drug-naïve patients to 69% in medicated patients. APs influence glucose homeostasis, lipid metabolism and body weight through several receptor pathways and hormonal systems (Stahl, 2008; Ventriglio et al, 2015). The molecular mechanisms involved in these complex metabolic changes virtually affect all the organs involved in metabolism, such as pancreas, liver, muscle, nervous system, and adipose tissue (Carli et al, 2021).

First, APs act as antagonists on histamine H1 and serotonin 5-HT2C and receptors, promoting appetite and weight gain. Furthermore, they can antagonize M3 muscarinic receptors located on pancreatic cells, thus directly influencing insulin secretion and brain metabolism (Ventriglio et al, 2015; Stahl, 2008). The antagonistic activity on H1, M1 and α1 adrenergic receptors can also induce sedation, contributing to a sedentary lifestyle (Henderson et al, 2015). An additional receptor mechanism with possible synergistic effects may be dopamine D2-receptor antagonism which may potentiate 5-HT2C-mediated effects on food assumption, and affect glucose and lipid metabolism by disinhibiting prolactin release (Reynolds & Kirk, 2010).

Although the association between MetS and a specific atypical antipsychotic or the average chlorpromazine dose has not been consistently demonstrated, some literature

suggests that the propensity to induce MetS differs depending on the antipsychotic. Among them, clozapine and olanzapine, due to their high affinity for 5-HT2C, H1 and M3 receptors, have the highest potential to induce weight gain by dysregulating adipose tissue homeostasis, (Aringhieri et al, 2018; Stahl 2008). The prevalence of clozapine and olanzapine-induced MetS has been reported to be between 25% and 50% (Rummel-Kluge et al, 2010; De Hert et al, 2006).

Numerous studies and meta-analyses have unquestionably demonstrated a significant increase in MS and its components after the introduction of an AP treatment (Mitchell et al, 2013; Malhotra et al, 2013). AP treatment contribute to induce weight gain, dyslipidemia and fasting hyperglycemia and IR. Although the alteration of glucose homeostasis is not strictly dependent on weight gain, this latter becomes an aggravating risk factor for diabetes over the years.

MetS represents one of the main challenges in the treatment of schizophrenia nowadays due to several reasons. First, MetS increases the risk of cardiovascular disease, which has become the leading cause of mortality in schizophrenia patients. Subjects with schizophrenia aged 16 to 50 years have a three-fold higher risk of dying from cardiovascular disease than general population (Kritharides et al, 2017).

Second, MetS patients show significantly higher psychopathological severity, as assessed with PANSS, than those without MetS (Arango et al, 2008).

Furthermore, previous studies shown that patients treated with antipsychotic drugs consider weight gain one of the most bothersome side effects of the treatment and, thus, one of the main reasons responsible for treatment discontinuation (Read & Sacia, 2020). Consistently, MetS patients have been reported to have a reduced adherence to pharmacological treatment, and, consequently, to be at greater risk of symptomatic exacerbation (Dibonaventura et al, 2012, Godin et al, 2018). Finally, growing evidence suggests that MetS and its components represent risk factors for cognitive impairment both in healthy subjects and in patients with schizophrenia (Li et al, 2014; Bora et al, 2017).

1.2.5 Metabolic Syndrome and Cognition

MetS is a well-established significant risk factor for cognitive impairment. In the last decade, a growing amount of evidence pointed out an inverse association between the

MetS and global and domain-specific cognitive functioning, with some heterogeneity mainly due to the different neuropsychological assessment tools used. Lower performance across different cognitive functions, including memory, attention/speed and executive function, as well as global cognition, was reported in subjects affected by MetS. Age and sex have been identified as important factors influencing the relationship between cognitive functioning and MetS (Tahmi et al, 2021).

Studies among both middle-aged and older adults reported a worse cognitive performance in subjects with MetS. Although somehow counterintuitive, the association between cognition and MetS has been found to be more robust among middle-aged than older adults, especially in verbal domains. Differences in the magnitude and strength of associations could be ascribed to different factors including the modification of some MetS components over the lifespan. For instance, waist circumference and triglyceride levels could decrease in older adults as a result of inadequate nutrition. Although associations between MetS and cognition have been described also in longitudinal studies, results are inconsistent. Indeed, while some studies reported that the presence of MetS or some of its components in midlife was associated with an accelerated decline in some cognitive domains over time, other showed no significant cognitive deterioration in individuals with MetS compared with those without (Tahmi et al, 2021). These inconsistencies could be ascribed to differences in the study populations or follow-up time. Moreover, MetS has been linked to an increased risk of mild cognitive impairment and progression to dementia, in particular vascular one.

Besides midlife and late life, MetS has been reported to have a detrimental effect on cognitive functioning also in adolescents. Some studies reported lower performance in reading, working memory, attention, cognitive flexibility and executive function among adolescents with MetS or some of its components (Yau et al, 2012, Tahmi et al, 2021).

Concerning sex, literature shows mixed results as well. Indeed, while some studies found worse cognitive performance only in women with MetS or some of its components compared to women without MetS (Schuur et al, 2010; Segura & Jurado, 2009), others described greater cognitive impairment in men only (Cavalieri et al, 2010) and some failed find significant differences (Hassenstab et al, 2010).

Furthermore, evidence suggests an association between the severity of MetS, quantified as the total number of MetS components present, and lower cognitive functioning. Some

studies reported that the number of MetS components present was more strongly associated with worse cognitive performance than the presence of MetS itself. Among the MetS components, hyperglycemia, high blood pressure, and high waist circumference resulted the most robustly associated with cognitive functioning (Tahmi et al, 2021).

Finally, it should be noted that few studies failed to demonstrate associations between the presence of MetS and cognitive functioning. These results may be attributable to the characteristics of the sample population, the covariates considered in the models, the use of different MetS definitions, and the low sensitivity of the selected test battery. Indeed, these studies utilized less sensitive screening tests for global cognition, such as the Montreal Cognitive Assessment (MoCA) or the Mini Mental Status Exam (MMSE), instead of validated and standardized neuropsychological tools. These assessment scales are generally used as screening instrument for cognitive impairment and, are unable to detect the subtle cognitive changes that may occur before cognitive impairment is manifest (Tahmi et al, 2021). Several explanatory models have been proposed on cognitive impairment in the metabolic syndrome. These include: neuroinflammation, oxidative stress, abnormalities in brain lipid metabolism brain and altered vascular reactivity (Yates et al, 2012). One of these models hypothesized that the cognitive impairment found in people with MetS could be at least partially attributable to vascular alterations leading to brain structural damage. Alterations in cerebrovascular reactivity and thickness reported in adults with MetS support this hypothesis. According to this model, dysfunctions in vascular reactivity, typical of MetS and DM2, leads to altered cerebral vasodilation with a reduced blood supply to the activated brain areas, particularly in times of greater cognitive demand. The authors propose that this reduction in vascular reactivity may be caused both by the direct or indirect detrimental effects of IR and the inflammation related to obesity on the micro-vessels. Endothelial dysfunction, in co-occurrence with dysregulations of the hypothalamus-pituitary-adrenal axis, or with increased oxidative stress, could result in brain damage and cognitive impairment (Yates et al. 2012).

In addition, the proinflammatory effect on MetS and the associated insulin and leptin resistance and hyperglycemia profoundly affect the blood brain barrier, whose breakdown leads to the infiltration of immune cells into the brain parenchyma and neuronal death, contributing to cognitive decline (Van Dyken & Lacoste, 2018).

Whatever the mechanisms involved, neuroimaging studies demonstrate that MetS and its components, including diabetes, hypertension, increased visceral adiposity, IR and hyperlipidemia, are associated with white matter microstructure and functional connectivity abnormalities and reductions in grey matter volume (Friedman et al, 2014, Rasgon et al, 2011, Kotkowski et al, 2019).

1.2.6 Metabolic Syndrome and cognition in Schizophrenia

As already mentioned, cognitive impairment is a hallmark of schizophrenia, which remains stable despite the reduction of positive and, to a lesser extent, negative symptoms obtained with antipsychotic drugs (Keefe et al, 2007), and significantly contributes to the functional deficit in the disorder. Moreover, as previously pointed out, subjects with schizophrenia have a higher prevalence of MetS and its constituent components than the general population. If detrimental effects of MetS on cognitive functioning have been established in all age groups in the non-psychiatric population, their investigation and management is of considerable importance even more in subjects with schizophrenia, given both the high prevalence of comorbidity and the higher risk of cognitive impairment in this population. However, to date, studies investigating this relationship are scarce and results conflicting. One of the most extensive studies, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), conducted in 2005, reported no relationship between MetS and cognitive deficit in schizophrenia (Meyer et al, 2005). However, many subsequent studies described associations between MetS as a whole or its individual components and some cognitive functions (Friedman et al, 2010; Lindenmayer et al, 2012). Once again, methodological differences across the studies may be responsible for these discrepancies. Recent meta-analytic evidence shows that comorbid MetS and diabetes are associated with cognitive deficits in subjects with schizophrenia. Moreover, a significant relationship emerged also between cognitive dysfunction and the singular components of MetS including dyslipidemia, hypertension, diabetes and abdominal obesity (Bora et al, 2017). A subsequent systematic reviews and meta-analysis investigating the association between cognitive performance and risk factors for cardiovascular disease, including MetS, confirmed greater global cognitive impairment in schizophrenia patients with MetS compared to those without. Moreover, the authors

reported a significant association of some of MetS components, such as diabetes and hypertension with cognitive deficit (Hagi et al, 2021).

Overall, these findings suggest that MetS and its components may represent an additional risk factor for cognitive impairment in some schizophrenia patients. However, it should be noted that the relationship may not be unilateral, since cognitive dysfunction may also contribute to the increased prevalence of MetS and its components in individuals with schizophrenia. Indeed, cognitive deficits, often detectable already at illness onset, may lead to impaired decision-making, which, in turn, could result in unhealthy lifestyle choices. Longitudinal studies investigating the impact of the development of MetS and its components starting from illness onset could help to distinguish the characteristics of the neurodevelopmental cognitive dysfunction from the cognitive deficits that arise as a consequence of MetS development (Bora et al, 2017).

1.2.7 Effects of metabolic alterations on Central Nervous System (CNS)

As previously discussed, MetS and its components have been associated with several alterations of neural substrates, among both healthy subjects and patients affected by schizophrenia.

In general population, different studies reported in MetS reduced total brain volumes and cortical thickness, lower white matter integrity and higher rates of subcortical and lacunar lesions (Alfaro et al, 2018; Schwarz et al, 2018). Concerning MetS single components, hyperglycemia, dyslipidemia, and abdominal obesity have been associated with lower gray matter volumes and altered Fractional Anisotropy (FA) (Friedman et al, 2014). In this context, a large body of literature have been focusing on neural correlates of obesity as well, reporting a widespread alteration of white matter integrity and reduced grey matter volumes, particularly localized to hippocampus, thalamus, frontal cortex and anterior cingulate gyrus (Willette & Kapogiannis, 2015). Interestingly, these areas are region of main interest in schizophrenia since onset disease, implicated in cognitive dysfunction and psychopathology (Minichino et al, 2017). Consistently, we recently reported that among patients with schizophrenia, overweight and obesity resulted associated with reduced FA and Axial Diffusivity (AD) in several fibers' tracts including longitudinal fasciculus, uncinate fasciculus, corona radiata, thalamic radiation, fronto-occipital fasciculus, cingulum and corpus callosum (Figure 1).

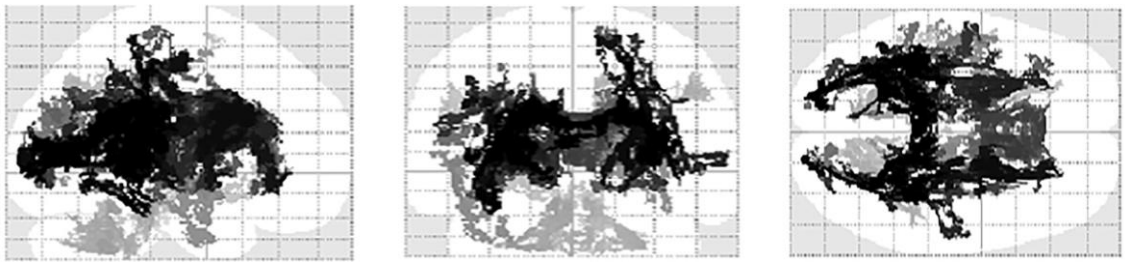

Figure 1. Glass brain images of white matter tracts where the normal-weight group showed a higher AD than obese group (Spangaro et al, 2018)

Results of this study have been recently replicated in an independent Japanese sample of patients with schizophrenia, wherein were additionally reported also significant effects on Radial and Mean Diffusivity (RD, MD), thus further suggesting a potential demyelinating effect of obesity in schizophrenia.

MetS and its components negatively affect brain structure and functioning by multiple pathways, including insulin-resistance, hypothalamus-pituitary-adrenal (HPA) axis alteration, oxidative stress, vascular damage, and chronic neuroinflammation (Arshad et al, 2018). MetS-related disruptive processes have been reported among both healthy and psychiatric populations. Still, it is to note that alterations of these pathways result independently associated with schizophrenia, thus suggesting that the co-occurrence of metabolic diseases may lead to more severe brain structural and functional impairments (Minichino et al, 2017).

Insulin resistance leads to disturbances of cerebral insulin receptor signaling, causing reduced brain glucose uptake, associated with cerebral atrophy and reduced cortical volumes. Moreover, high circulating glucose levels have been associated with neuronal mitochondrial dysfunction, as well as with increased levels of oxidative stress, monoamine oxidases and dopamine clearance (Arshad et al, 2018). Another significant consequence of IR is the reduced expression of insulin-like growth factor 1 (IGF-1), crucial for modulating synaptic plasticity, neuronal apoptosis and nerve cell growth. Consistently, lower IGF-1 levels have been associated with cognitive deficit, and implicated in the etiopathogenesis of neurodegenerative diseases (Arshad et al, 2018).

MetS and obesity and strongly related to HPA axis abnormalities, particularly to increased cortisol levels, associated with reduced hippocampal and frontal volumes (Minichino et al, 2017). Concerning psychosis, HPA axis alterations were hypothesized to determine lower BDNF expressions and increased glutamatergic excitotoxicity, leading to lower hippocampal, amygdala and PFC volumes. Interestingly, IR have been suggested to potentiate cortisol's cerebral disruptive effects (Arshad et al, 2018), as evidenced in murine models of Diabetes that developed extensive cortisol-induced hippocampal damage three times faster than controls.

MetS patients are also characterized by endothelial dysfunction (ED), due to dyslipidemia, hyperglycemia, and reduced expression of nitric oxide. ED is associated with higher risk of cerebral vascular events, as well as with brain microvasculopathy, thus leading to impaired oxygen supply, reduced neuronal excitability and eventually neurodegeneration.

Adipokines, particularly leptin and adiponectine, play a central role in the connection between MetS and brain alterations. These compounds are produced in the adipose tissue, proportionally to body fat mass. Leptin is able to cross the blood-brain barrier (BBB) and influences hippocampal and mesolimbic activity. Moreover, in the CNS leptin determines both pro-cognitive effects and microglial pro-inflammatory changes, whereas adiponectine shows anti-inflammatory properties. Obesity and MetS are associated with fat cells hypertrophy, IR, and higher levels of free fatty acids, that taken together lead to lower adiponectine and increased leptine levels, and leptin resistance, negatively affecting cortical volumes and brain function (Stranahan, 2022).

IR, ED, HPA axis abnormalities, and adipokines alterations together converge on a down-stream common pathway, that is inflammation, both central and peripheral. As previously described, MetS determines a global inflammatory, that potentially negatively affects brain structure and function by inducing neuroinflammatory processes. Moreover, beside adipokines, adipose tissue is also responsible for production of cytokines, able to cross the BBB and to influence cerebral processes. MetS and obesity are characterized higher cytokine production and chronic low-grade inflammation, as well as with reduced synaptic markers and proinflammatory microglial alteration (Bocarsly et al, 2015).

In order to better understand the interplay between metabolic alterations, cognition and inflammation, the next section will discuss basic mechanisms of neuroinflammation and its related major findings in the context of schizophrenia and related cognitive deficit.

1.3 Neuroinflammation

Neuroinflammation refers to an inflammatory state affecting the CNS, that can be due to both central and\or peripheral triggers. A crucial role in neuroinflammation is played by microglial cells, representing the macrophages of the CNS and responsible for great majority of cytokine and chemokine production. Cytokines and chemokines are proteins that constitute the main signaling pathway of the immune system, modulating activity of immune system and other functions such as cell differentiation. A wide range of cytokines have been described to date, divided according to their function: primary inflammatory cytokines, such as Interleukin 1 (IL-1), IL-6, IL-8, and Tumor Necrosis Factor alfa (TNF-α); anti-inflammatory cytokines, such as IL-10, Transforming growth factor beta (TGF-β); hematopoietic\grow factors cytokines; signal-specific cytokines, such as IL-2 that modulates T-cells activity and differentiation (Dhabhar et al, 2012).

Chemokines are responsible for directing immune cells by guiding them through tissues or fluids according to a chemotactic gradient. Two main groups of chemokines are described, according to activity and structure: CC chemokines, involved in regulation of mononuclear cells in sites of chronic inflammation; CXC chemokines, mainly involved in acute inflammations, responsible for attracting mainly polymorphonuclear cells (Bottaccioli & Bottaccioli, 2017). Under normal conditions, microglial cells are in a quiescent state, with multiple, motile, branch-like spines constantly monitoring the local environment. External stimuli such as traumatic and immunological stressors can lead to microglial activation, characterized by glial cell boy enlargement and protrusion retraction. Two different activated states of microglia are described: proinflammatory M1, and immunosuppressive M2 (Howes & McCutcheon, 2017). M1 is observed in response to inflammatory processes and neural injury, characterized by production and release of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, TNF-α, and Interferon-γ (IFN- γ) (Laskaris et al, 2016). M1 induces a shift to M2 state, wherein microglial cells promote anti-inflammatory processes by secreting immunosuppressive cytokines such as

IL-4, IL-10, TGF-β, Brain-derived neurotrophic factor (BDNF) and other neurotrophic factor, thus also inducing cell repair, debris clearance, and extracellular matrix reconstruction. Both activation states of microglia (M1 and M2) are necessary for adequate immune response, and alteration of M1\M2 balance can lead to pathological conditions.

Indeed, a persistent M1 state could lead to a cytotoxic environment with massive production of reactive oxygen species (ROS), synaptic loss and neuronal death. Moreover, impaired M2 activity may lead to lower phagocytosis and cleaning of cellular debris, thus determining their accumulation and potentially paving the way to neurodegenerative disease such as Alzheimer's disease (Heneka et al, 2014).

Beside microglial cells, also astrocytes are involved in neuroinflammation end central immune response. Similarly to microglia, it is possible to individuate two astrocyte subtypes: A1, producing proinflammatory cytokines, and A2, promoting immunosuppression, synaptic repair and neuronal growth (Stephenson et al, 2018).

Neuroinflammation can be triggered not only by events occurring inside the CNS, but also by peripheral events. Indeed, despite the old concept of the impermeability of the BBB, to date it is well known that peripheral molecules can be transported into the CNS through vessels' specific transport systems (Bottaccioli & Bottaccioli, 2017), through Cerebral Spinal Fluid (CSF), and through brain regions that do not have BBB such as circumventricular organs, pineal gland and hypothalamus. Moreover, inflammatory states can disrupt BBB permeability, allowing entrance of immune cells and peripheral cytokines, thus inducing microglial activation.

One of the main downstream effects of microglial activation and secretion of pro-inflammatory cytokines is the activation of the kynurenine pathway (KP) of tryptophan (TRP) degradation, with formation of neuroactive compounds such as the N-methyl-D-aspartate (NMDA) receptor agonist quinolinic acid (QUIN), and antagonist kynurenic acid (KYNA), thus also reducing synthesis of serotonin (5-HT) (Figure 2). Specifically, inflammatory processes promote the synthesis of kynurenine (KYN) by activating the KP enzymes indoleamine 2,3 dioxygenase (IDO) and tryptophan-2,3 dioxygenase (TDO). KYN is then metabolized either by kynurenine aminotransferases (KATI and KATII, mainly located in astrocytes) to KYNA, or by kynurenine 3- monooxygenase (KMO, mainly located in microglia) to 3-hydroxykynurenine (3-HK) and eventually to QUIN.

Beside NMDAr, KYNA is also antagonist of AMPA receptors (AMPARs) α7 nicotinic acetylcholine receptor (α7nAChR), showing antiapoptotic, anti-inflammatory and antioxidative properties. On the other side, as NMDAr agonist, QUIN is associated with excitotoxicity, inflammatory processes, lipids peroxidation and production of ROS (Schwarcz et al, 2012; Kindler et al, 2020).

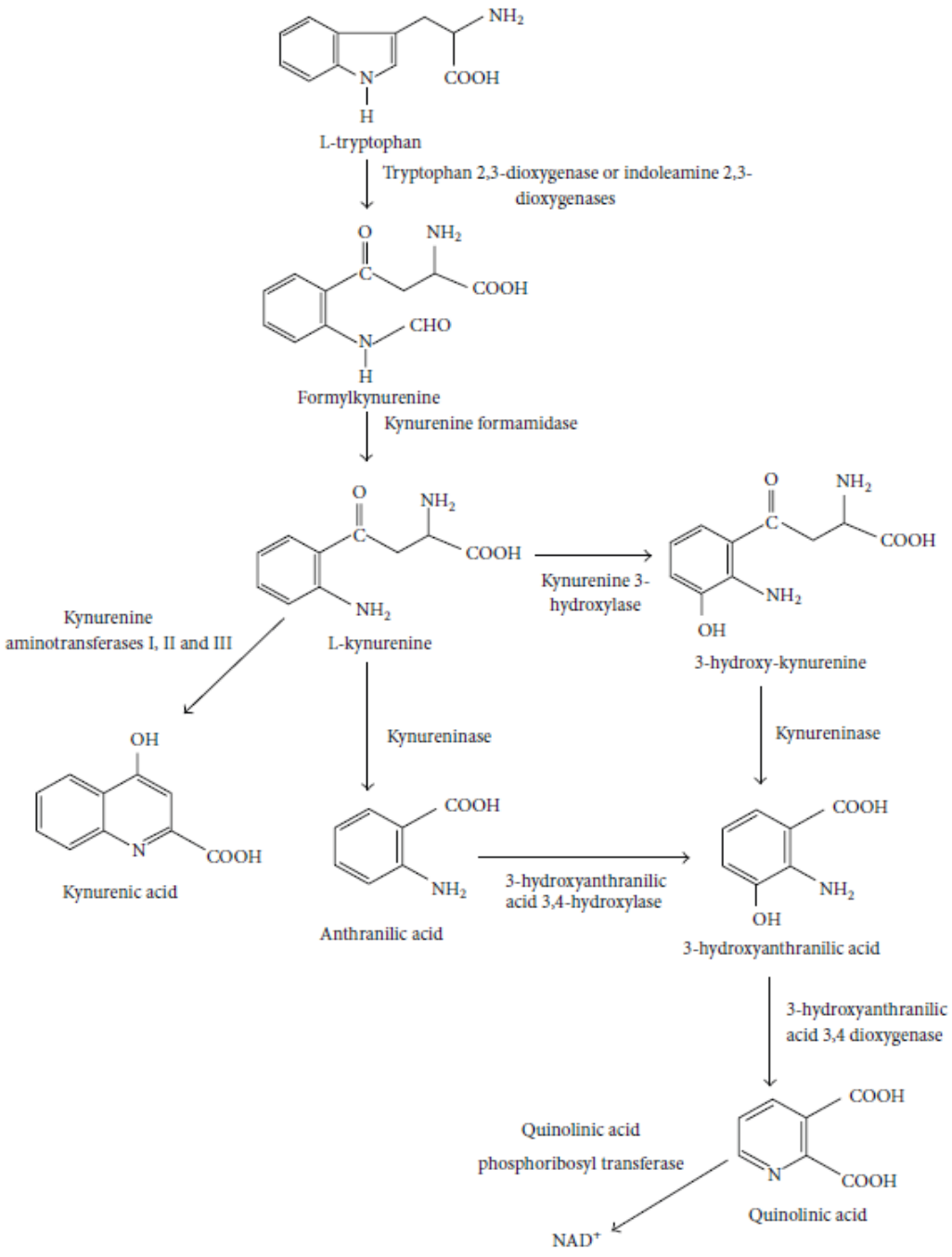

Figure 2. The Kynurenine Pathway (Lugo-Huitrón et al, 2013)

1.3.1 Neuroinflammation in schizophrenia

In the last decade, a growing number of studies have been focusing on the role of neuroinflammation in schizophrenia, largely documenting a dysregulation of the immune response, as well as an involvement of the immune system in almost every aspect of the disease. Indeed, microglial activation has been hypothesized to be involved in etiopathogenesis of schizophrenia by a "two-hit" mechanism, rethinking the vulnerability-stress theory proposed by Zubin and Spring almost 40 years ago. The first hit, occurring during prenatal\perinatal stages, induce a M1 state secondary to infections, maternal stress and\or early brain injury. In murine models, this early glial activation determines an immune priming, leading to increased and excessive proinflammatory immune response in case of a second hit, occurring during peripubertal period. Glial reactivation during this critical developmental period is thought to negatively affect synaptic pruning, thus paving the way to future development of schizophrenia (Howes & McCutcheon, 2017). This second hit could be triggered by infective, physical or even psychosocial stressors such as migration, urbanicity, and childhood trauma. This theory is also consistent with the higher rates of stress vulnerability observed among schizophrenic subjects. Microglial activation in schizophrenia has been investigated in the context of post-mortem studies, observing increased microglia density, activation, and neural degeneration. On the other hand, PET in vivo studies reported conflicting results, possibly due to the microglial inactivating properties of antipsychotics. Nonetheless, among ultra-high risk drug naïve subjects were observed associations between microglial activation and psychotic symptom severity (Muller, 2018).

However, PET studies are not able to determine the type of microglial activation characterizing patients with schizophrenia, but a large body of research concerning peripheral circulating cytokines suggest the presence of an imbalance in favor of M1 pathway. Indeed, a meta-analysis of Upthegrove and colleagues including 570 FEP patients found increased levels of pro-inflammatory cytokines, specifically IL-1β, IL-2r, IL-6, and TNF-α. Consistently, a subsequent recent study reported elevated levels of both pro-inflammatory (ie IL-6, IL-8, IL-13, IFN-γ) and anti-inflammatory cytokines (ie IL-1ra, IL-10, VEGF-A) among multi-episode schizophrenia patients, suggesting a progressive immune dysregulation during the course of illness that could be associated either to persistent chronic low-grade inflammation or to chronic antipsychotic treatment

(Upthegrove et al, 2014; Frydecka et al, 2018). Results are also in line with another recent meta-analysis by Wang and Miller (2018), showing elevated IL-1β, IL-6, IL-8, and KYNA in CSF of patients with schizophrenia.

Immune dysregulation has been associated with alterations of both gray and white matter in schizophrenia. Particularly, microglial proinflammatory state resulted to correlate with lower prefrontal and hippocampal volumes and thickness (Howes & McCutcheon, 2017), with reduced white matter volumes, and with a disruption of white matter integrity of orbitofrontal, subgenual cingulate, and anterior corpus callosum traits (Najjar & Pearlman, 2015).

Given this evidence, several studies attempted to investigate influence of neuroinflammation on clinical outcome in schizophrenia. Elevated levels of pro-inflammatory cytokines have been associated with a more severe course of illness in terms of positive symptoms (IL-6, IL-1ß, IL-33, IL-17, and TNF-α) and negative symptoms (IL-6, TNF-a, IL-1ß, IL-8, IFN-g, IL-4, and TGF-β). Interestingly, higher levels of IL-6, IFN-γ, IL-8 and IL-2 have been linked to treatment resistance and poor antipsychotic response, suggesting the presence of an underlying neuroinflammatory substrate that determines a more severe and less responsive subtype of illness (Momtazmanesh et al, 2019). In this context, smoking may play a major role as well, given its high prevalence in schizophrenia and its association with chronic low-grade peripheral inflammation, in terms of elevated levels of highly sensitive C-reactive protein (Fond et al, 2017).

An involvement of neuroinflammation in the etiopathogenesis of schizophrenia arises also from studies concerning the role of KP in the disease. Indeed, due to its NMDAr antagonism, increased KYNA was hypothesized to induce psychotic and cognitive symptoms, similarly to other NMDAr compounds such as ketamine and PCP. In line with this theory, post-mortem studies observed higher KYN and KYNA levels in the CSF and in frontal and anterior cingulate cortices. However, several other studies reported conflicting results, such as a reduction of KYNA and QUIN associated with acute psychotic phases among patients with schizophrenia (De Picker et al, 2020).

A recent meta-analysis of Cao and colleagues including 4217 patients found a positive correlation between KYN and antipsychotic treatment, as well as higher KYN and KYNA in the CSF but lower plasmatic KYN. Moreover, after antipsychotic introduction, KYN

levels resulted increased, compared to drug-naïve state, possibly due to antipsychotic inhibition of KAT II agents.

Overall, meta-analytic evidence confirms an involvement of KP alteration in schizophrenia and also suggest an inverse correlation between plasmatic and brain KP levels, consistently with the poor ability of these compounds to cross the BBB.

1.3.2 Neuroinflammation and Cognition

Beside immune response, microglia is also necessary for physiological brain activity, being able to directly modulate neurotransmission. Moreover, microglial cytokines are highly involved in normal processes of cognition. Indeed, in murine models both elevation and reductions of pro-inflammatory cytokines, such as TNF-α, IL-1 β, and IL-6, have been associated with reduce learning and memory abilities. Consistently, among healthy subjects, microglial activation resulted to impair hippocampal plasticity and related cognitive functions. In line with these observations, alterations of physiological concentrations of these pro-inflammatory cytokines hamper Long Term Potentiation and Long Term Depression, thus suggesting that both M1 and M2 pathways could affect cognitive processes. On the other hand, immunosuppressive cytokines have been reported to influence hippocampal function as well, with higher levels associated with better cognitive abilities (Fourrier et al, 2019).

Consistently with these data, meta-analytic evidence shows an increased risk of dementia associated with higher peripheral levels of CRP and IL-6 (Borshchev et al, 2019).

Microglial cytokines may influence cognition also by indirect pathways, such as the modulation of expression neurotrophic factors as BDNF, highly implicated in neural plasticity and connectivity.

Furthermore, as previously reported, pro-inflammatory pathways activate the KP pathway, with increased production of the neuroactive metabolites KYNA, QUIN, and 3-HK. Among these, KYNA levels were associated with cognitive functioning among both preclinical models and general population. Administration of KYN to rats impaired abilities of learning, working memory, and sensory gating, due to inhibition of dopaminergic, cholinergic and glutamatergic neurotransmission. Consistently, inhibition of KATII, responsible for KYNA production, was reported as associated with better cognitive functions. On the other side, also increased QUIN levels appear to lead to

disruption of physiological functioning. Indeed, patients from different neurological disorder such as Alzheimer Disease and Huntington Disease showed higher QUIN levels and increased QUIN\KYNA ratio, associated to glutamatergic excitotoxicity and pro-inflammatory microglial activation. Taken together these data indicate that rather than higher KYNA or QUIN, in order to favor cognitive functioning is necessary to maintain a tight regulation of KYN and its metabolites. Concerning the relationship between neuroinflammation and cognition in schizophrenia, meta-analytic data showed an inverse correlation between CRP and cognitive performance of learning, attention, and memory (Fourrier et al, 2019).

To date only few and inconsistent studies focused on the relationship between cognition and cytokine levels are available, reporting conflicting results. Indeed, cognitive deficit has been associated with both M1 and M2 pathways, and more research is needed in order to better understand this topic of main interest (Momtazmanesh et al, 2019). Of note, add-on anti-inflammatory treatments have been reported to improve cognitive functioning of patients with schizophrenia, but evidence is still limited.

Studies focused on the role of KP in schizophrenia reported an inverse correlation between KYNA levels and working memory, attention/vigilance and between KYNA levels and cortical thickness in frontal areas (Huang X et al, 2021, Huang J et al, 202, Kindler et al, 2020). In addition, Cathomas et al. showed that also QUIN impacts on cognition, as suggested by preclinical observations. Specifically, QUIN levels resulted inversely related to composite cognitive score in schizophrenia (Cathomas et al, 2021).

1.3.3 Metabolic Syndrome, Neuroinflammation and Cognition

As previously discussed, MetS and metabolic alterations are associated with a chronic inflammatory state, affecting also brain structure and function. Beside the pathways previously described (IR, adipokines, HPA axis alterations, ED), visceral obesity and hypertriglyceridemia are characterized by a greater number of adipocytes, responsible for cytokines production and therefore subsequent neuroinflammatory processes. Dysmetabolic upregulation of IL-1β, TNF-α, and IL-6 has been correlated with increased BBB permeability and central oxidative stress (Van Dyken & Lacoste, 2018). As a matter of fact, in obesity studies have been described infiltrations of macrophages and lymphocytes in the CNS.

Beumer and colleagues reported an elevation of a greater number of inflammatory cytokines among patients with schizophrenia also affected by MetS or its components (Beumer et al, 2012).

Proinflammatory cytokines IL-1β and TNF-α appear the molecules most consistently involved in mediating the relationship between metabolic alterations and neuroinflammation. Both these cytokines are produced also by visceral adipose tissue, and are able to cross the BBB inducing microglial activation and thus influencing central processes. In this view, we recently analyzed the relationship between genetic variability of IL-1β, Metabolic syndrome and cognitive abilities among patients with schizophrenia (Bosia et al, 2021). Specifically, in this study we analyzed the effect of IL-1β C-511T Single Nucleotide Polymorphism (SNP), previously correlated with metabolic alterations and cognition among healthy subjects. The SNP is located in the promoter region of the cytokine, with the T allele associated with higher levels of expression. Among both general population and patients with dementia, subject carrying the C allele showed better cognitive functions and white matter integrity, and in line with these data Papiol and colleagues found decreased DLPFC activity among T carrier patients with schizophrenia (Bosia et al, 2021). Consistently, studies concerning metabolic alterations found the T allele associated with T2DM in healthy subject, and with antipsychotic-induced wight gain in patients with schizophrenia. Taken together, these studies suggested that the T allele, linked to higher cytokine expression, is also associated with metabolic alterations and worse cognitive functioning, according to the molecular mechanism discussed above. However, no study previously investigated a possible interplay of these pathways in schizophrenia. Of note, IL-1β levels are also modulated by sex. Indeed, estradiol and progesterone suppress cytokine production by inducing anti-inflammatory prostaglandin E2 expression. Given this evidence, this study aimed to evaluate the effects of the IL-1β C-511T polymorphism on both cognition and metabolic syndrome in a sample of 138 patients affected by schizophrenia, also taking into account possible influences of sex. Results showed a significant interaction between sex and IL-1β genotype on processing speed and executive functions. Specifically, among subjects carrying the CC genotype, female patients showed better processing speed performance, whereas among T carriers females showed worse executive functions. Moreover, worse executive functions were also observed among T carrier female patients with MetS. In this study we did not observe

any direct correlation between cognition and MetS or IL-1β C-511T polymorphism (Figure 3). However, result of this study further indicated the central role of the interaction between metabolic syndrome and inflammation in modulating cognitive functioning of patients of schizophrenia (Bosia et al, 2021).

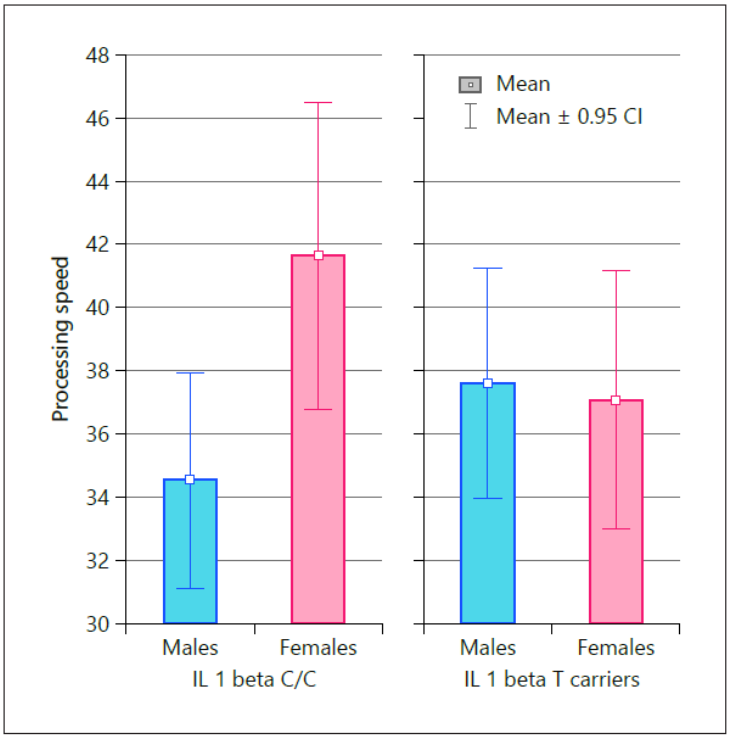

Figure 3. Symbol coding task performance stratified by sex and IL-1β genotype (Bosia et al, 2021; Work performed by Dr. Marta Bosia was in partial fulfillment of the requirements for obtaining the PhD degree at Vita-Salute San Raffaele University, Milano, Italy)

In this view, the KP could represent another potential connection between metabolic alteration, inflammation and cognition. Indeed, KP, activated by pro-inflammatory cytokines such as IL-1 β, is also implicated in etiopathogenesis of MetS, due to diabetogenic, pro-obesity and pro-oxidative activities of KYN and KYNA. Zhang and colleagues recently evaluated the relationship between MetS in a sample of 160 patients with schizophrenia, reporting a positive correlation between MetS and QUINA and QUINA\KYN ratio (Zhang et al, 2021).

2. AIM OF THE STUDY

Cognitive deficits are a core feature of schizophrenia and a critical determinant of global functional outcome, characterized by high interindividual heterogeneity and poor treatment response. Higher rates of metabolic alterations and increased levels of inflammatory biomarkers have been consistently reported among patients with schizophrenia. Both MetS and inflammation have been correlated with greater severity of cognitive deficits in schizophrenia, as well as with alterations of cerebral structure and activity. Of note, MetS is associated with a low-grade chronic pro-inflammatory state, and neuroinflammation represent one of the pathways through which metabolic alterations negatively affect brain processes and activity.

Preliminary evidence brought by our previous research suggests an interplay between inflammation and MetS in modulating cognitive outcome of patients affected by schizophrenia. However, to date no study has yet thoroughly investigated the relationship between these factors and its effects on neurocognition in schizophrenia.

Therefore, this project aims to investigate, in patients with schizophrenia, the direct and indirect relationship between metabolic alterations, markers of inflammation and cognition, also exploring their effects on white matter integrity and DLPFC neurometabolites.

Specific aims will be:

1) To evaluate the relationship between MetS and peripheral inflammatory biomarkers (plasmatic cytokines and KP metabolites), as well as their interplay on cognition in a sample of 75 subjects with schizophrenia

2) To evaluate the main and interactive effects of both MetS and peripheral inflammatory biomarkers on MRI multimodal parameters (DTI and 1h-MRS) in a subsample of 39 patients with schizophrenia.

Results of this study may lead to a deeper knowledge of the neurobiological processes and of the variability of the illness, potentially individuating novel therapeutic targets and treatment strategies for patients with schizophrenia

3. RESULTS

The sample was composed of 75 patients, 55 males and 20 females. Table 2 shows demographic and clinical variables of the sample. 45.3% were treatment-resistant, treated with clozapine, 54.7% of patients were smokers.

Table 1. Demographic and clinical variables of the sample

	MEAN	S.D.
Age	37.40	12.98
Years of education	12.36	2.33
Duration of illness	16.03	12.15
Antipsychotic load (CPZ) mg	499.60	258.78
PANSS Positive score	17.67	4.98
PANSS Negative score	21.43	5.15
PANSS General Score	41.61	7.72
PANSS Total score	80.71	14.69

Cognitive performance of the overall sample corrected for age, education and sex is reported in Table 2. (BACS equivalent scores).

Table 2. Cognitive performance of the sample corrected for age, education and sex

BACS	Equivalent score Mean	Equivalent score S.D.	Deficit (% sample)
Verbal Memory	2.13	1.55	33.3%
Working Memory	1.42	1.35	59.3%
Psychomotor speed	0.65	1.01	75.9%
Verbal Fluency	1.67	1.28	38.9%
Attention	0.84	1.16	69.8%
Executive functions	2.13	1.49	35.2%
Cognitive Index	1.48	0.85	31.9%

In table 3 the prevalence of each diagnostic criteria for Metabolic Syndrome is reported. 36.49% of patients satisfied criteria for MetS, whereas the most prevalent criteria resulted abdominal obesity (52% of the sample).

Table 3. Prevalence of diagnostic criteria for Metabolic Syndrome in the sample

MetS Criteria (ATP III)	% of patients
Waist circumference	52.00%
Triglycerides	39.19%
HDL Cholesterol	37.84%
Hypertension	32.43%
Fasting glucose	25.67%
Metabolic Syndrome	**36.49**%

Chi-squared showed a significant difference between males (43% MetS) and females (15% MetS), in MetS prevalence (Pearson Chi-Square=5.46, p=.019). ANOVA showed higher age (F=33.03; p<.0000; 31.77±11.63 vs 46.8±9.30) and duration of illness (F=28.81; p<.000; 11.04±10.81 vs 8.03±10.51) among patients with MetS.

ANOVAs showed no significant differences between MetS groups concerning antipsychotic load, treatment with clozapine, education, psychopathology (PANSS scores), and cognition (BACS scores). Of note, higher levels of CRP resulted significantly associated with MetS (ANOVA: F=9.34, p=.003), as well as positively correlated with the number of satisfied criteria (Pearson: r=0.30, p=.010).

Table 4 reports the plasmatic concentrations of peripheral inflammatory biomarkers analyzed in this study.

Table 4. Levels of peripheral inflammatory biomarkers

Plasmatic inflammatory biomarker	Mean	S.D.
IL-1β (pg/mL)	1.23	1.33
IL-1ra (pg/mL)	325.31	260.91
IL-6 (pg/mL)	8.73	15.37
IL-8 (pg/mL)	2.83	2.09
IL-10 (pg/mL)	3.63	2.82
IFN-γ (pg/mL)	2.61	1.77
TNF-α (pg/mL)	27.73	7.14
Triptophan (Trp) (µg/mL)	12.75	2.68
5-HT (µg/mL)	0.41	0.24
Kynurenine (Kyn) (ng/mL)	99.07	33.97
Kyn/Trp ratio *1000	8.06	3.16
3-hydroxykynurenine (ng/mL)	8.93	4.79
Quinolinic acid (QUINA) (ng/mL)	97.71	42.95
Kynurenic acid (KYNA) (ng/mL)	10.39	3.88
KYNA/Quin ratio	0.19	0.41
Kynurenic acid/Kynurenine*1000	122.84	81.33

Concerning demographic variables, no influences of sex (ANOVA) were observed (ANOVA). Age resulted significantly positively correlated with IL-1ra ($r=0.33$, $p=.004$), IFN-γ ($r=0.24$, $p=.036$) and TNF-α ($r=0.35$, $p=.003$) levels. Duration of illness resulted positively correlated with IL-1ra ($r=0.31$, $p=.004$) and TNF-α ($r=0.29$, $p=.012$). Finally, a positive correlation was also observed between antipsychotic load and IL-1β level ($r=0.36$, $p=.002$). Of note, metabolites of KP did not show any significant correlation with demographic and pharmacological variables.

ANOVA also revealed no significant differences of inflammatory biomarkers between smokers and non-smokers patients.

3.1 Metabolic Syndrome and inflammation

In order to investigate possible associations between MetS and peripheral inflammatory biomarkers, multiple ANOVAs were performed, with presence of MetS included as categorical predictor. Results showed that MetS resulted associated with higher IL-1β, IL-1ra, TNF-α, Kyn levels, and Kyn/Trp ratio, as well as with reduced KYNA level and KYNA\Kyn ratio (Table 5).

Table 5. Peripheral inflammatory biomarkers associated with MetS (ANOVA)

Plasmatic inflammatory biomarker	**MetS +**		**MetS -**		**ANOVA**	
	Mean	S.D.	Mean	S.D.	F	p
IL-1β (pg/mL)	1.68	1.67	0.98	1.04	4.85	0.03
IL-1ra (pg/mL)	406.19	227.79	274.26	270.67	4.53	0.04
TNF-α (pg/mL)	30.24	6.85	26.35	7.04	5.30	0.02
Kynurenine (Kyn) (ng/mL)	111.30	36.34	91.96	31.14	5.85	0.02
Kyn/Trp ratio *1000	9.42	3.31	7.35	2.83	8.06	0.01
Kynurenic acid (KYNA) (ng/mL)	9.17	3.71	11.01	3.86	4.00	0.05
Kynurenic acid/Kynurenine*1000	92.60	48.35	139.87	92.09	6.12	0.02

Consistently, the number of satisfied MetS criteria (MetS score) resulted correlated with levels of peripheral inflammatory biomarker as well (Pearson's correlations). Specifically, MetS score resulted positively correlated with proinflammatory biomarkers such as IL-1β (r=0.30, p=.013), IL-1ra (r=0.29, p=.013), TNF-α (r=0.29, p=.013), Kyn

(r=0.29, p=.012), Kyn/Trp ratio (r=0.35, p=.002), and negatively correlated with KYNA/Kyn ratio (r=-0.25, p=.030).

In order to investigate which of the single MetS components was involved in the previous observed associations, multiple ANOVAs were performed between altered cytokines/KP metabolites and presence of MetS criteria. Results showed that Waist circ. criterion was associated with alterations of IL-1ra, TNF-α, Kyn, Kyn/Trp ratio, and KYNA/Kyn; TG criterion with altered IL-1β, IL-1ra, TNF-α, Kyn/Trp ratio, and KYNA\Kyn ratio; HDL criterion with altered IL-1β, Kyn, Kyn/Trp, and KYNA/Kyn; FPG criterion with Kyn/Trp ratio. No associations were observed concerning presence of Hypertension criterion.

Table 6. Associations of MetS-inflammatory biomarkers with MetS criteria (ANOVAs)

Inflammatory biomarker	Waist circ.	TG	HDL	FPG	PA
IL-1β	-	F=13.87, p=.00	F=11.54, p=.00	-	-
IL-1ra	F=12.49, p=.00	F=8.52, p=.00	-	-	-
TNF-α	F=8.03, p=.01	F=7.17, p=.01	-	-	-
Kynurenine	F=7.60, p=.01	-	F=4.29, p=.04	-	-
Kyn/Trp ratio	F=12.30, p=.00	F=7.37, p=.01	F=5.83, p=.02	F=4.77, p=.03	-
Kynurenic acid	-	-	-	-	-
KYNA/Kyn	F=7.36, p=.01	F=4.18, p=.04	F=4.56, p=.04	-	-

Finally, in order to analyze which of the different metabolic and clinical-demographic influencing factors significantly predicted alterations of peripheral inflammatory biomarkers, multiple general regressions models (GRM) (backward stepwise) were performed (Table 7). Abdominal obesity resulted to significantly predict alterations of

IL-1ra, Kyn, Kyn/Trp ratio, and KYNA/Kyn, whereas hypertriglyceridemia was reported to predict IL-1β levels.

Table 7. GRMs, significant results: MetS criteria and inflammatory biomarkers

	Adj R^2	F	p	Regressors	β	p
IL-1β	0.23	11.93	<.000	TG -	-0.35	.001
				CPZeq	0.30	<.005
IL-1ra	0.15	13.35	<.000	Waist circ +	-0.40	<.000
TNF-α	0.11	10.11	.002	AGE	0.35	.002
Kynurenine	0.08	7.72	.006	Waist circ +	-0.31	.006
Kyn/Trp ratio	0.13	11.38	.001	Waist circ +	-0.37	.001
KYNA/Kyn	0.08	7.23	.009	Waist circ -	0.30	.009

3.2 Inflammation, cognition and Metabolic Syndrome

In order to investigate possible differential effects on cognition of the inflammatory biomarkers previously associated with MetS, multiple Separate Slope Models (SSM) were performed. Results showed significant differential effects of the inflammatory biomarkers, particularly among patients without MetS. Specifically, among MetS- subjects negative effects were observed for: KYNA on Verbal Memory; TNF-α, Kyn, Kyn/Trp, and KYNA/Kyn on Working Memory; TNF-α on overall Cognitive Index. Conversely, TNF-α resulted positively correlated with Verbal Memory among MetS+ patients. Finally, absence of MetS was found to positively influence Cognitive Index.

Table 8. Separate Slope Models, significant results

BACS	Separate Slope	Effect	F	p	β	p
Verbal Memory	MetS*TNFα	MetS -	11.39	<.00	1.68	<.00
		TNFα (MetS+)	8.85	<.00	0.97	0.02
	MetS*KYNA	KYNA (MetS-)	4.13	0.05	0.63	0.01
Working Memory	MetS*TNFα	TNFα (MetS-)	4.13	0.05	-0.76	0.01
	MetS*Kyn	Kyn (MetS-)	4.44	0.02	-0.68	0.01
	MetS*Kyn/Trp	Kyn/Trp (MetS-)	4.50	0.01	-0.65	<.00
	MetS*KYNA/Kyn	KYNA/Kyn (MetS-)	6.50	<0.00	0.54	<.00
Cognitive Index	MetS*TNFα	MetS -	10.16	<.00	1.61	<.00
		TNFα (MetS-)	9.01	<.00	-0.78	0.01

Significant results of SSMs were then further investigated in the context of different Moderation Analyses, including inflammatory biomarkers as continuous predictors, MetS as categorical moderator and SSM-significant cognitive outcomes (Verbal Memory, Working Memory, and Cognitive Index) as dependent variables. Among the different moderations performed, the following models resulted significant.

TNFα/MetS on Verbal Memory

Table 10 reports moderation model results. MetS resulted to negatively affect Verbal Memory (β=-5.19), and its interaction with TNF-α increased explained variability of 11%. TNF-α was found to positively correlated with Verbal Memory only among MetS+ patients (β=-0.09, p=.026)

Table 9. Results of TNFα/MetS moderation on Verbal Memory

R^2	**F**	**p**	**Int. R^2 change**
0.17	3.38	0.014	0.11
Regressor	**β**	**t**	**p**
TNF-α	-.06	-1.80	.08
MetS+	-5.19	-3.25	.00
Interaction	.15	2.38	.02

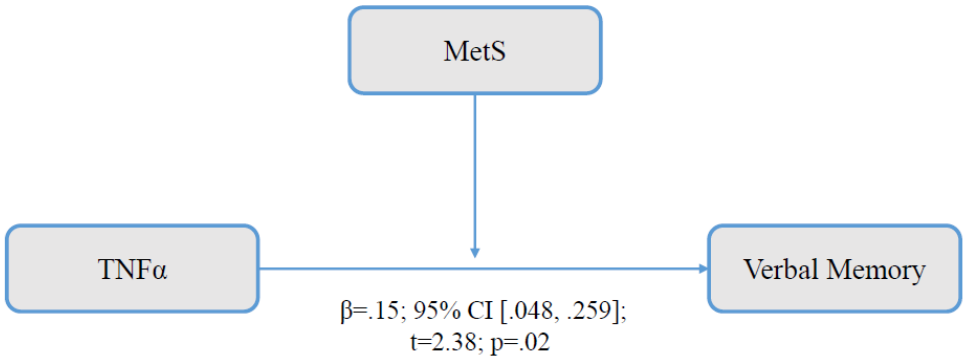

Figure 4. Moderation analysis: TNFα/MetS on Verbal Memory

KYNA/MetS on Verbal Memory

Table 11 reports moderation model results. KYNA resulted to positively correlate with Verbal Memory (β=0.12), and its interaction with MetS increased explained variability of 6%. KYNA was found to positively correlated with Verbal Memory only among MetS- patients (β=0.13, p=.031)

Table 10. Results of KYNA/MetS moderation on Verbal Memory

R^2	F	p	Int. R^2 change
0.14	2.73	0.036	0.06
Regressor	**β**	**t**	**p**
KYNA	0.12	2.19	.03
MetS+	-	-	N.S.
Interaction	-.22	-2.20	.03

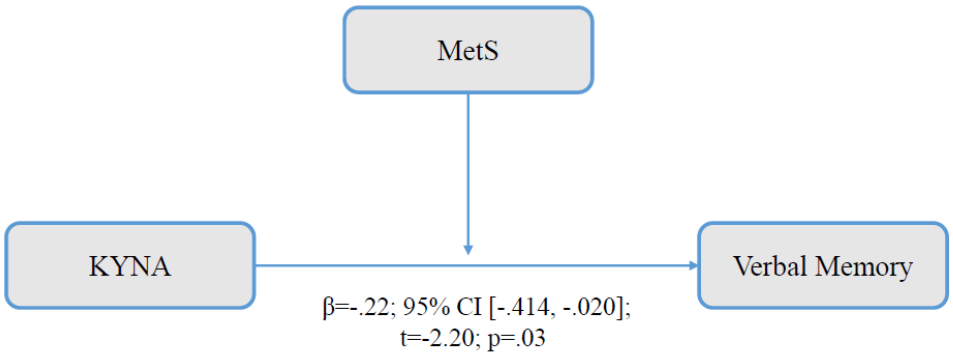

Figure 5. Moderation analysis: KYNA/MetS on Verbal Memory

TNFα/MetS on Cognitive Index

Table 12 reports moderation model results. Both TNF-α (β=-0.05) and MetS (β=-2.83) resulted to negatively affect Cognitive Index, and their interaction increased explained variability of 12%. TNF-α was found to negatively correlated with Verbal Memory only among MetS- patients (β=-0.05, p=.009). Figure 7 illustrates the moderation effects of MetS on TNF-α in influencing Cognitive Index.

Table 11. Results of TNFα/MetS moderation on Cognitive Index

R^2	F	p	Int. R^2 change
.15	2.90	0.028	.12
Regressor	**β**	**t**	**p**
TNF-α	-.049	-2.68	.01
MetS+	-2.82	-3.17	.002
Interaction	.09	3.00	.003

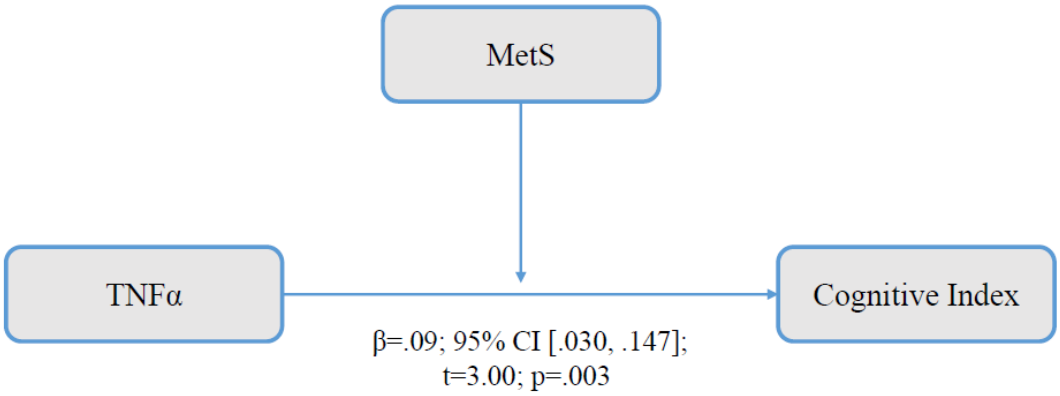

Figure 6. Moderation analysis: TNFα/MetS on Cognitive Index

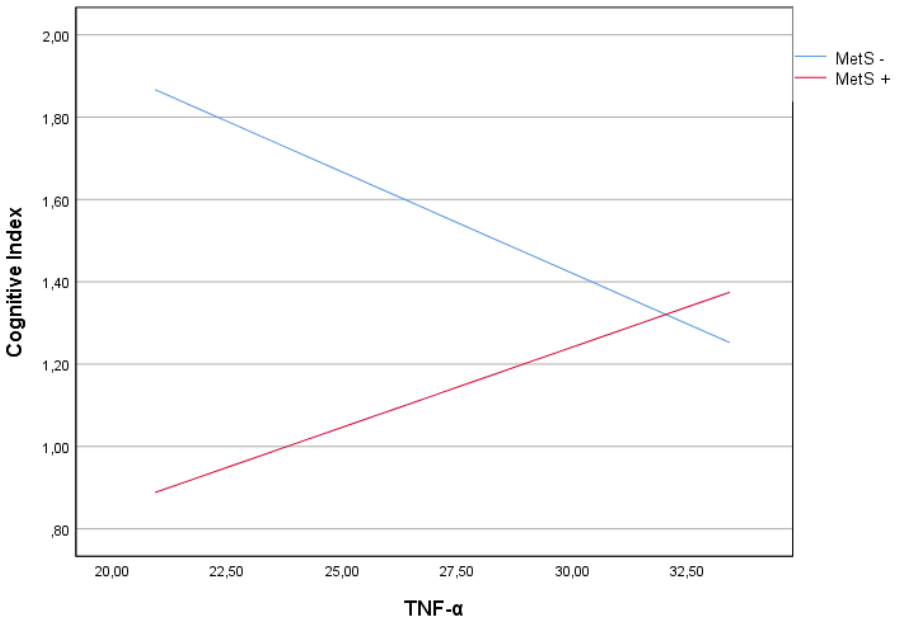

Figure 7. Cognitive Index: Single slopes, moderation effect of MetS on TNF-α

3.3 MRI Results

The MRI subsample was composed by 39 patients (8 females), with 10 patients meeting criteria for MetS (25.6%). Table 12 reports demographic features of the subsample.

Table 12. Demographic features of the subsample

	MEAN	**S.D.**
Age	34.51	11.51
Years of education	12.74	2.23
Duration of illness	13.03	10.68

3.3.1 1H-MRS data

Pearson's correlation between demographic and therapeutic variables showed significant correlations in the DLFPC for age with NAA (r=-0.59, p=<.000) and Ins (r=0.44, p=.007); duration of illness with Ins (r=0.57, p=<.001) and NAA (r=-0.52, p=.001). No effects of sex or antipsychotic load were observed.

Concerning the relationship of neurometabolites with peripheral markers of inflammation previously associated with MetS in the whole sample, significant correlations were observed for NAA with TNF-α (r=-0.48, p=.003) and IL-1ra (r=-0.47, p=.004); Glx with Kyn (r=-0.33, p=.045), Kyn/Trp (r=-0.37, p=.028) and KYNA/Kyn (r=0.47, p=.004),

ANOVA showed that patients affected by MetS showed higher Ins levels (F=4.78, p=.036) and lower NAA (F==9.04, p=.005).

Multiple general regression models (GRM) were then performed in order to individuate significant predictors of DLPFC neurometabolites, including the variables previously correlated. TNF-α and age were found to negatively affect NAA levels, whereas KYNA/Kyn ratio was positively correlated with Glx levels in the DLPFC.

Table 13. GRMs results: significant predictors of neurometabolites

DLPFC	Adj R^2	F	p	Regressors	β	p
NAA	0.40	12.41	**<.000**	TNF-α	-0.47	**.002**
				AGE	-0.33	.022
GLX	0.19	9.38	**.004**	KYNA/Kyn	0.47	.004

3.3.2 White matter – FA data

Pearson's correlation showed a widespread negative correlation of TNF-α peripheral levels with FA (Table 14), and a positive correlation of KYNA with IFO-L FA (r=0.42, p=.007).

Table 14. Pearson's significant correlation of TNF-α with FA

	r	p
Mean FA	-.46	.003
ACR	-.46	.004
CR	-.38	.019
EC-L	-.44	.006
FX-ST	-.33	.040
RLIC	-.48	.002
SLF-L	-.32	.048
SS-L	-38	.018

ANOVA showed lower FA in IFO-L of patients with MetS (F=7.65, p=.009).

Multiple general linear regression were then performed in order to individuate significant predictors of FA in the tracts of interest, including TNF-α or KYNA as continuous predictors (according to the correlations reported above), ad MetS, age, CPZeq, duration of illness and sex as covariates. Results of the regressions are reported in Table 15. TNF-α resulted to widely negatively affect white matter integrity (mean FA β=-0.46), whereas absence of MetS and KYNA were positively correlated with FA of IFO-L.

Table 15. GRMs results: significant predictors of FA

White matter tract (FA)	Adj R^2	F	p	Regressors	β	p
Mean FA	0.19	9.80	.003	TNF-α	-0.46	.003
ACR	0.19	9.56	.004	TNF-α	-0.46	.004
CR	-	-	-	-	-	-
EC-L	0.17	8.66	.006	TNF-α	-0.44	.006
FX-ST	0.08	4.55	.04	TNF-α	-0.34	.04
RLIC	0.21	10.61	.002	TNF-α	-0.48	.002
SLF-L	0.08	4.2	.048	TNF-α	-0.32	.048
SS-L	0.12	6.16	.018	TNF-α	-0.38	.018
IFO-L	0.31	6.73	.001	KYNA	0.36	.04
				MetS-	0.49	.012
				AGE	-0.32	.004

4. DISCUSSION

This study aimed at disentangling the complex relationship between Metabolic Syndrome, inflammation, and cognition in schizophrenia, also investigating possible influences of MetS and related inflammatory biomarkers on white matter integrity and DLPFC neurometabolites. Overall, we reported that, among patients with schizophrenia, MetS and its components are associated with higher levels of proinflammatory cytokines and greater activation of the Kynurenine Pathway. Our results also revealed that the interplay between MetS and related inflammatory biomarkers significantly influences patients' cognitive functioning, with MetS moderating the effects of TNF-α and KYNA on Verbal Memory and overall cognitive outcome. Finally, MRI analyses evidenced that MetS and altered levels of TNF-α and KP metabolites predict reduced white matter integrity and neurometabolic alteration associated with neurodegenerative processes in the DLPFC.

Taken together, results of this study confirm previous preliminary evidence indicating an association between metabolic disturbances, inflammation, and cognitive functioning in schizophrenia, thus contributing to better understand the great clinical variability of the disease. Moreover, these data further indicate the need of combined treatment strategies including interventions aimed at improving metabolic status, in order to improve both health and cognitive outcome of patients with Schizophrenia.

In the following paragraphs, main findings of this study will be discussed.

MetS is associated with peripheral proinflammatory biomarkers

Our data showed higher peripheral levels of inflammatory cytokines and KP metabolites among patients with schizophrenia affected by MetS. Specifically, among the different cytokines of interest included in this study, we observed increased plasmatic concentrations of IL-1β, IL-1ra, and TNF-α. IL-1 pathway is of the main determinant of inflammatory processes, with IL-1β acting as IL-1r agonist and being thus associated with inflammation and microglial activation (Momtazmanesh et al, 2019). Although IL-1ra acts as endogenous antagonist to IL-1r, its elevations are directly correlated with IL-1 activation, and despite its anti-inflammatory activity it is currently used as marker of IL-1 activation and inflammation (Lind et al, 2021). Higher IL-1β and IL-1ra have been

previously associated with both MetS and schizophrenia, consistently with our result. Of note, higher IL-1ra was found to be correlated to all the MetS components in general population, as well as with dysmetabolic processes associated with olanzapine treatment among patients with schizophrenia (Lin et al, 2018). Similarly to IL-1, TNF-α represents one of the main central and peripheral inflammatory mediators, involved in several crucial functions such as cell proliferation, microglial activation, and apoptosis. TNF-α induces production of both pro-inflammatory and anti-inflammatory cytokines, being highly implicated in immune regulation. TNF-α is produced and secreted by several cells including microglia and adipocytes (Bortolato et al, 2015). Consistently with our result, elevated peripheral levels of TNF-α have been previously associated with both MetS and schizophrenia, as well as with other psychiatric disorders such as Bipolar Disorder and Depression (Maslov et al, 2019, Frydecka et al, 2018).

Concerning KP metabolites, in this study we observed higher Kyn and lower KYNA peripheral levels among patients with MetS. Moreover, MetS patients resulted also associated with increased Kyn/Trp and lower KYNA/Kyn ratios, respectively representing indirect indexes of IDO-TDO and KAT activity (Simonato et al, 2021). Consistently with results concerning cytokines, KP is known to be induced by proinflammatory cytokines, such as IL-1β and TNF-α. KYNA and KAT are associated with neuroprotection and anti-inflammatory processes, and their reduction has been recently suggested as trait marker of psychotic illness (De Picker et al, 2020). However, meta-analytic studies concerning plasmatic KP metabolites report conflicting results. Still, studies concerning metabolic disturbances consistently reported higher Kyn levels among MetS and obese subjects (Mangge et al, 2014). Moreover, a recent study of Zhang and colleagues conducted among patients with schizophrenia showed an association between MetS and higher QUIN/Kyn levels, indirect index of low KAT activity (Zhang et al, 2021).

Once identified the inflammatory biomarkers associated with MetS, we subsequently analyzed which of the different individual MetS components was involved in proinflammatory processes. GRMs showed that abdominal obesity was the most influencing factor, predicting higher levels of IL-1ra, Kyn, and Kyn/Trp ratio, as well as lower KYNA/Kyn ratio. Moreover, hypertriglyceridemia resulted to be positively correlated with IL-1β plasmatic concentrations. Involvement of these two specific criteria

is in line with literature, as abdominal obesity has been previously described as the main trigger of metabolic inflammation, associated with IR, FFA, and higher production of both cytokines and adipokines. Hypertriglyceridemia may represent one of the consequences of abdominal obesity, but is also able to directly determine higher FFA levels, associated with inflammation and IR (Boden, 2008).

Interactions of MetS with TNF-α and KP metabolites on cognition in schizophrenia

SSMs and moderation analyses showed that TNF-α, Kyn and KYNA peripheral levels predicted cognitive outcome of patients with schizophrenia according to the presence of MetS. Specifically, among subjects without MetS, SSMs reported a positive correlation between KYNA and Verbal Memory, and between KYNA\Kyn and Working Memory; negative correlations between Kyn and Kyn/Trp and Working Memory, and between TNF-α and global Cognitive Index. Conversely, a positive correlation between Verbal Memory and TNF-α levels was reported among patients with MetS. Taken together, these results suggest that presence of MetS is on one side associated with inflammatory processes, as previously reported and confirmed by the observation of higher CRP levels, but on the other this metabolic proinflammatory state may lead to differential effects of TNF-α and KP metabolites on cognition. Similar inferences may also arise from the observation of moderation analyses results, that showed moderating effects of MetS on the influence of TNF-α and KYNA on Verbal Memory, and of TNF-α on Cognitive Index. Of note, moderations also reported a direct positive effect of KYNA on Verbal Memory, and negative direct influences of MetS on Verbal Memory, and of TNF-α and MetS on Cognitive Index. Previous meta-analytic evidence also showed associations between MetS and cognitive deficit in schizophrenia, although studies reported conflicting results, also due to the huge number of possible influencing and confounding factors. In this study, ANOVA did not reveal any significant association between MetS and cognitive outcome, but moderation analyses accounting for duration of illness and MetS inflammatory biomarkers (TNF-α, KYNA) showed a negative direct effect of MetS on Verbal Memory and Cognitive Index of patients with schizophrenia. As previously discussed, TNF-α is one of the main mediators of central and peripheral immune response, as well as a physiological regulator of homeostatic cell proliferation, differentiation and apoptosis. Increased plasmatic levels of TNF-α induce positive

feedback in the CNS through a peripheral-central immune cross-talk that further increases microglial TNF-α production, thus inducing activation of microglia and central KP. Beside immune modulation, several preclinical and clinical studies previously evidenced neuroactive effects of TNF-α, mostly involving the glutamatergic system. Indeed, TNF-α lead to increased expression of glutaminase in astrocytes, thus raising glutamate production and enhancing NMDAr transmission. Moreover, TNF-α also inhibits activity of the family of excitatory amino acid transporters (EAATs), responsible for synaptic glutamate reuptake and highly implicated in cognitive functioning (Spangaro et al, 2012, 2014, 2018). Indeed, our group previously demonstrated that genetic variability of EAAT2, accounting for >90% of cerebral glutamate reuptake, influences working memory and executive functions in schizophrenia, with lower transporter expression associated with worse cognitive functioning. These results have been subsequently replicated also in large samples of both healthy and schizophrenic populations, suggesting that adequate glutamate uptake is a crucial mechanism for physiological cognitive functioning (Zhang et al, 2015).

It is however important to underline that relationship between TNF-α and neuroinflammation is not linear, as this cytokine acts as a modulator of immune response, and its activity is crucial for both inflammatory and anti-inflammatory processes. Indeed, inhibition of TNF-α underlies several immune diseases such as tuberculosis, vasculitis, Multiple Sclerosis and encephalomyelitis. This dual pro/anti-inflammatory activity of TNF-α is due to the presence of two different TNF receptors, TNFR1 and TNFR2. In details, TNFR1 is expressed in all cell types and its effects are associated with inflammatory and apoptotic processes; TNFR2 is mainly expressed on neurons and immune cells, activating anti-inflammatory and neural repair pathways (Kemanetzoglou et al, 2017).

Consistently with these divergent effects, previous studies concerning the relationship between TNF-α and cognition in schizophrenia reported conflicting results (Misiak et al, 2018), showing associations of cognitive deficit with both elevated and reduced TNF-α levels. Interestingly, Goldsmith and colleagues recently showed meta-analytic evidence of higher TNF-α in schizophrenia, as well as a direct correlation between TNF-α and deficit syndrome and negative symptoms of schizophrenia (Goldsmith et al, 2018).

In this study, we reported that among patients with schizophrenia TNF-α effects on cognition are moderated by the presence of MetS. Specifically, we observed that TNF-α correlated with worse Cognitive Index among patients without MetS, and with better verbal Memory performance among patients with MetS. These divergent TNF-α effects may be due the biological mechanisms discussed above. Here we observed, consistently with literature, that MetS resulted associated with inflammation and higher levels of peripheral proinflammatory cytokines, including TNF-α. Moreover, beside chronic inflammation, MetS also determines a wide range of neurobiological alterations that together synergically affect cognition, such as adipokines production, oxidative stress, HPA disturbances and IR. We can hypothesize that in the context of this altered and inflammatory state induced by MetS, TNF-α mainly acts as anti-inflammatory cytokine, thus positively influencing Verbal Memory, whereas under physiological conditions without MetS could negatively affect patients' cognitive functioning.

In this view, KP metabolites may play a determinant role. In this study we observed that MetS is associated with activation of KP, in term of higher Kyn and Kyn/Trp ratio (indexes of higher inflammation), and reduced KYNA and KYNA/Kyn ratio (indexes of reduced immunosuppression).

SSMs and moderation analyses showed that correlations of KP with cognition were detectable only in absence of MetS, consistently with the results observed for TNF-α. Among KP metabolites, KYNA effect on Verbal Memory resulted moderated by MetS. KYNA presents anti-inflammatory and neuroactive properties, being antagonist at NMDAr and reducing glutamate transmission, thus preventing excitotoxicity. We previously discussed the importance of a fine-tuning of the glutamatergic pathway for cognition, particularly in schizophrenia. However, literature concerning the relationship between KYNA and cognition in schizophrenia reported conflicting results, also depending on the significant difference between central and peripheral KYNA levels, due to the poor ability of the metabolite to cross the BBB (De Picker et al, 2020; Cathomas et al, 2021). Specific involvement of Verbal Memory may be secondary to the different regional specific expressions of KP metabolite. Preclinical studies showed higher QUIN/KYNA ratio in dorsal hippocampus (Parrott et al, 2016). Hippocampus shows high density of NMDAr, and is highly implicated in Verbal Memory abilities among both healthy and psychiatric populations. Meta-analytic evidence indicates that poor Verbal

Memory performance is associated with lower hippocampal volumes in schizophrenia (Antoniades et al, 2018). Of note, hippocampus is also one of the brain regions that present high BBB permeability, being thus more exposed to peripheral immune alterations. Based on this preliminary evidence we could speculate that lower peripheral KYNA levels correlate with NMDAr hyperactivity and poor hippocampal verbal memory abilities. In patients with MetS, we did not observe any significant effect of KYNA, possibly due to the presence of other concomitant detrimental neurobiological processes induced by MetS contrasting procognitive and anti-inflammatory activities of KYNA.

MetS inflammatory biomarkers influence N-acetylaspartate and Glutamatergic levels in the DLPFC

Preliminary 1H-MRS analyses in the MRI subsample showed that patients with MetS were characterized by increased Ins and lower NAA in the DFLPC. GRMs, including socio-demographic influencing factors and MetS inflammatory biomarkers, showed that higher TNF-α predicted lower NAA levels, whereas no effects of MetS, KP metabolites or cytokines were observed for Ins, predicted only by duration of illness. Although not associated with MetS, Glx (glutamate + glutamine) levels resulted positively correlated with KYNA/Kyn ratio.

NAA is one of the main neurometabolites, considered as marker of neuronal density and integrity. It is mainly produced by neurons and contributes to glutamatergic brain energy production. Moreover, NAA is also involved in brain lipid homeostasis, and results thus involved in myelination processes (Langer et al, 2021). Reduced frontal NAA has been recently correlated with higher TNF-α levels among healthy subjects, and studies focused on schizophrenia reported lower NAA levels associated with the disease (Pillinger et al, 2019). To our knowledge, this is the first study correlating peripheral TNF-α concentrations with DLPFC-NAA in schizophrenia. This result suggests a detrimental effect of the cytokine on brain density and integrity, that however needs to be correlated with other MRI measures in larger samples, also considering the reduced MetS prevalence of the MRI subsample (25,6%).

Concerning Glx, a recent large-scale meta-analysis reported lower glutamate concentrations among patients with schizophrenia, although the study included also different VOIs such as Anterior Cingulate Cortex (ACC). Godlewska and colleagues

(2021) showed that reduced glutamate concentrations in the ACC correlated with poor cognitive performance. In this study, given the small size of the subsample, we did not investigate correlations between cognition and MRI. However, given this evidence and our previous results concerning cognition, we could hypothesize that higher KAT activity could positively influence cognition also by modulating cerebral Glx levels (Godlewska et al, 2021).

White matter integrity is influenced by MetS, TNF-α and KYNA

GRMs showed significant effects of MetS, KYNA, and TNF-α on FA. In details, MetS resulted associated with lower FA of left Inferior Fronto-Occipital fasciculus (IFO-L), whereas KYNA (previously found to be reduced in MetS) positively correlated with white matter integrity of the same tract. Results concerning MetS are consistent with data observed in general populations, as well as with our previous study reporting an association between obesity and reduced FA and Axial Diffusivity in schizophrenia (Spangaro et al, 2018).

Concerning KYNA, no previous report associated this KP metabolite with FA in schizophrenia, but a positive correlation between KYNA and white matter integrity has been observed among patients affected by Bipolar Disorder, further supporting its role in mechanisms of neuroprotection. This result is also consistent with our previous data concerning the procognitive effect of KYNA on Verbal Memory among schizophrenic patients without MetS.

Finally, we reported a widespread negative correlation between peripheral TNF-α and FA, interesting several white matter tracts such as anterior corona radiata, external capsule, and superior longitudinal fasciculus. Again, to our knowledge, no study has previously reported a detrimental effect of TNF-α on white matter integrity in schizophrenia, but similar results have been observed among bipolar patients during depressive episodes (Benedetti et al, 2018).

Taken together, DTI data indicate that factors associated with inflammatory processes (MetS, high TNF-α, and low KYNA) could negatively affect whiter matter integrity of patients with schizophrenia, thus potentially further impairing cognitive functioning.

4.1 Perspectives of the study

In this study, we reported that MetS in schizophrenia is associated with inflammatory processes that are correlated with worse cognitive functioning and altered brain structure and functioning. Moreover, MetS resulted also independently associated with greater cognitive deficit and disrupted white matter integrity of left IFO. Taken together, these data highlight the main detrimental role of MetS in schizophrenia that is also known to lead to decreased longevity and higher rates of comorbid medical conditions. Nonetheless, if on one side metabolic alterations negatively affect prognosis of patients with schizophrenia, on the other its substantial influence on cognitive functioning and altered neurobiological pathways also suggest the adoption of new treatment strategies aimed to improve both cognition and physical health.

In this view, accumulating evidence from clinical and preclinical studies shows that physical exercise, including both aerobic and resistance training, besides improving metabolic status is also able to directly elicit different neurotrophic mechanisms such as neurogenesis, angiogenesis, and dendritic arborization, thus contrasting cognitive decline in neurodegenerative diseases and causing significant measurable improvement in cognitive performance (Schmitt et al, 2018). In line with these findings, several studies on healthy and other clinical populations also proved that exercise has positive effects on neuropsychological domains, especially executive functions and processing speed, by increasing BDNF and enhancing hippocampal plasticity.

Moreover, among healthy subjects physical exercise was found to reduce inflammatory processes, also by lowering TNF-α circulating levels (Paolucci et al, 2018; Bortolato et al, 2015). Over the last decade, different studies investigate effects of exercise in schizophrenia, reporting significant cognitive improvements and neurotrophic changes of hippocampal and frontal regions. More recently, preliminary studies have been conducted in order to evaluate the effect of combined Cognitive Remediation Therapy + physical exercise interventions, based on the hypothesis of a synergic effect on brain plasticity that could lead greater improvements. Among these, Nuechterlein and colleagues directly compared the effects of a 10-weeks combined cognitive remediation and exercise intervention with cognitive remediation alone in patients with recent onset of schizophrenia (Nuechterlein et al, 2016). Results showed greater improvements of global cognitive and socio-cognitive performance, as well as improvements of functional

outcomes among patients assigned to the combined intervention. Moreover, in the aerobic exercise group, additional benefits were reported on muscular endurance, cardiovascular fitness, and diastolic blood pressure as well.

Overall, from available studies aerobic exercise appears to be a promising non-pharmacological intervention to treat both metabolic status and cognitive deficits in schizophrenia, also improving some symptoms domains and general functioning.

Nowadays, new treatment strategies in schizophrenia are moving fast toward personalized approaches that, based on this evidence and on results of this study, should carefully take into account patients' metabolic and inflammatory status, providing integrated interventions that combine antipsychotic therapy, cognitive remediation, and physical exercise.

4.2 Limits and conclusion

The results of our study have to be interpreted in the context of some limitations. Results must be indeed considered as preliminary, because of the small sample size and the lack of a healthy controls group, that should be included in future developments of this project in order to understand if the neurobiological interactions here discussed are specific to schizophrenia or rather generalizable to general population. Recruitment was in a single center, raising the possibility of population stratification and limiting the generalizability of the findings. Moreover, our findings may be influenced by several other unexplored factors, such as environmental elements, specific effects of medications, and other inflammatory and neurobiological pathways. Among these, smoking may play a major role, given its high prevalence in schizophrenia and its previous association with low-grade peripheral chronic inflammation (Fond et al, 2017). Here we only evaluated smoking as a categorical predicting variable, but future studies should also include a quantitative evaluation of smoking and nicotine dependence.

Concerning neuroimaging data, developments of this project should include also analyses of grey matter cortical areas, DTI voxel-wise approaches, fMRI correlates (both resting state and cognitive tasks), and 1H-MRS evaluation also of other VOIs critical for cognition and schizophrenia such as ACC, striatum and hippocampus. In particular, given the hippocampal altered BBB permeability, its high density of NMDAr and its central role for cognition, hippocampus represents an area of main interest for future studies.

Lastly, for a better understanding of the directionality of the effects here reported, longitudinal evaluations should be conducted.

Despite these limitations, this is the first study conducted among patients with schizophrenia that analyzed the effects of the interplay between Metabolic Syndrome and inflammatory state on cognition, also evaluating possible influences on brain structure and DLPFC neurometabolites. In line with previous convergent preliminary evidence, here we confirmed that the interaction between inflammatory and metabolic pathway significantly influence cognition and brain structural integrity. Our findings further indicate for clinical practice the need of combined treatment strategies also including interventions aimed at improving metabolic status, in order to improve both health and cognitive outcome of patients with schizophrenia.

5. MATERIALS AND METHODS

5.1 Sample

A sample of 75 biologically unrelated outpatients with schizophrenia was recruited at the IRCCS San Raffaele Scientific Institute of Milan (Italy), Psychotic Disorders Unit.
After a complete description of the study, informed consent to participation was obtained. The protocol followed the principles of the Declaration of Helsinki.
Inclusion criteria were:

- Age included between 18-65 years
- diagnosis of schizophrenia meeting DSM-5 criteria

Exclusion criteria were:

- psychotic exacerbation
- psychiatric comorbidities
- substance abuse
- neurological disorders and brain injury
- concomitant infectious\inflammatory diseases

5.2 Assessment

Basic clinical and demographic data were collected from clinical reports.
Psychopathology was assessed by means of Positive and Negative Syndrome Scale for Schizophrenia - PANSS (Kay et al, 1987).
Data on metabolic parameters (Glycaemia, Hemoglobin Glycosylate, HDL Cholesterol, and Triglycerides, measured from blood tests; systolic and diastolic blood pressure, measured in sitting position; waist circumference measured in cm) and CRP were collected from clinical records of patients. The presence of Metabolic Syndrome has been identified based on measurements according to the most commonly used criteria: ATPIIIA criteria.
Cognitive performance was assessed as in Spangaro et al (Spangaro et al, 2021), with the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al, 2004), Italian version (Anselmetti et al., 2008), a broad neuropsychological battery evaluating core cognitive domains that are typically impaired in schizophrenia. BACS was administered

by trained psychologists, assessing the following neurocognitive functions: Verbal Memory (Words Recall), Working Memory (Digit Sequencing), Psychomotor Speed and Coordination (Token Motor Task), Speed of Processing (Symbol Coding), Verbal Fluency (Semantic and Letter Production) and Executive Functions (Tower of London). Raw scores of each subtest were adjusted for sex, age and education. planning) (Keefe et al, 2004). Equivalent score (ES) were calculated according to the Italian normative data in Anselmetti et al. (Anselmetti et al, 2008), following the method described in detail in Capitani and Laiacona (Capitani & Laiacona, 1997). Specifically, the raw scores of each BACS subtest were adjusted for sex, age and education. Adjusted scores were then fitted into a 5-point interval scale to obtain equivalent scores, in which 0 sets the limit for pathological performance and 4 is equal or better than the median value (Anselmetti et al, 2008). The fraction of subjects ranking over 0 and under 4 was partitioned into three regions that have the same interval on the z axis: equivalent score 1 could be considered as a borderline value while equivalent scores 2 and 3 are intermediate (Capitani & Laiacona, 1997). A Cognitive Index, which is considered a measure of global cognition, was also obtained using equivalent scores, according to the normative data for the Italian population (Anselmetti et al, 2008). Specifically, Cognitive Index has 5-point range (0–4), in which scores<1 are considered as pathological cognitive performance (Spangaro et al, 2021).

5.2.1 Markers of inflammation: cytokines and KP metabolites

Peripheral inflammatory biomarkers were measured and collected following methodological procedure described in Comai et al. (Comai et al, 2021) and Simonato et al. (Simonato et al, 2021).

Blood was collected by venipuncture in Vacutainer tubes containing EDTA in the morning after a fasting overnight period. Blood was then centrifuged at 2000 × g for 15 min at 4 °C and the plasma divided in small aliquots and then stored at −80 °C. Plasma concentrations of immune analytes were determined using the bead-based Luminex system based on xMAP technology (Human Cytokines 27 plex - Bio-Rad Laboratory, Hercules, CA, USA). Cytokines: Interleukin (IL)−1β, IL-1rα, IL-2, IL-4, IL-6, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, Interferon (IFN)γ, Tumor Necrosis Factor (TNF)α; Chemokines: C–C motif ligand 1 (CCL1), CCL2, CCL3, CCL4, CCL5, CCL11; C-X-C

motif chemokine (CXCL)10; Growth factors: fibroblast growth factor (FGF) basic, Granulocyte Colony Stimulating Factor (G-CSF), Granulocyte Macrophage Colony Stimulating Factor, (GM-CSF), Platelet-Derived Growth Factor Beta (PDGF-B), Vascular Endothelial Growth Factor (VEGF). Assays were performed on Magpix (Bio-Rad) system. Samples were analyzed according to manufacturer's instructions (Comai et al, 2021). The concentrations of each specific molecule are calculated based on the fit with a standard curve that shows the typical expected concentration for that particular analyte based on the dilution carried out. If the biological material is insufficient, or if methodological errors are made, or if the protein is not quantifiable due to its scarce presence, the machine is not able to read the values, so they must be attributed by the experimenter according to the control curve and will be called Out Of Range (OOR). In case of cytokine OOR>20% of the total sample the analyte was excluded from the analyses, assuming that systematic errors occurred during its measurement.

After quality check, the following metabolites were excluded from the study due to higher rates of OOR: IL-2, IL-4, IL-5, IL-7, IL-12, IL,15,GM-CSF, VEGF. Among the other, the following cytokines and chemokines have been selected for analyses of this study, according to literature concerning the role of inflammation in schizophrenia: IL-1β, IL-1ra, IL6, IL-8, IL-10, IFN-γ, CCL-1 and TNF-α.

The plasma concentration of serotonin, tryptophan and tryptophan metabolites pertaining to the KP (kynurenine, 3-hydroxykynurenine, kynurenic acid, quinolinic acid) were assessed following the methods described in Simonato et al (Simonato et al, 2021). Tryptophan, serotonin, and kynurenine were determined using a an HPLC system coupled with fluorometric and UV-Vis detectors. 3-hydroxykynurenine, kynurenic acid, quinolinic acid, and melatonin were quantified by LC-MS/MS on a Varian system composed of a binary Prostar pump, 410 autosampler, and MS320 triple quadrupole mass spectrometer equipped with Electro Spray ion source. The instrument was operating in multiple reaction monitoring modes, working in positive ion mode except for the quinolinic acid that was analyzed in negative mode. LC analysis was performed using an Agilent Eclipse XDB C8 column (3 × 150 mm, 3.5 µm) and a gradient elution with (A) water 1% formic acid and (B) Acetonitrile (0 min: 95% A; 5 min: 30% A; 8.3 min: 10% A; 10 min: 10% A; 11 min: 95% A; 15 min: 95% A) at a flow rate of 400 µL/min. The quantification of the kynurenines was computed using alfa-methyl tryptophan as an

internal standard. The following ratios were used as indirect indexes of the activity of the enzymes involved in the different metabolic steps of the kynurenine pathway: kynurenine/tryptophan as an index of tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) activity; kynurenic acid/kynurenine as an index of the kynurenine aminotransferase (KAT) activity. Finally, the ratio kynurenic acid/quinolinic acid was calculated as an index of neuroprotection.

5.2.2 MRI acquisition

All MRI acquisition were performed as in Spangaro et al. (Spangaro et al, 2018) and Poletti et al. (Poletti et al, 2020), at C.E.R.M.A.C. (Centro d'Eccellenza di Risonanza Magnetica ad Alto Campo), IRCCS San Raffaele Scientific Insititute (Milan). A structural MRI study was initially performed to exclude brain lesions and to localize the Volumes of interest (VOIs) for the spectroscopy study, acquiring sagittal T1 images, axial T2 fast spin-echo (FSE) images parallel to the bicomessural line, and coronal fluid-attenuated inversion recovery (FLAIR) images orthogonal to the axial ones.

1H-MRS data were acquired using a point resolved spectroscopy (PRESS) sequence (repetition time [TR] 2,000 ms, echo time [TE] 42 ms, 128 acquisitions) from VOIs of 30 × 20 × 15-mm size positioned at the level of the left DLPFC (Figure 8). Unsuppressed water reference spectra were acquired from the same VOIs (Poletti et al, 2020).

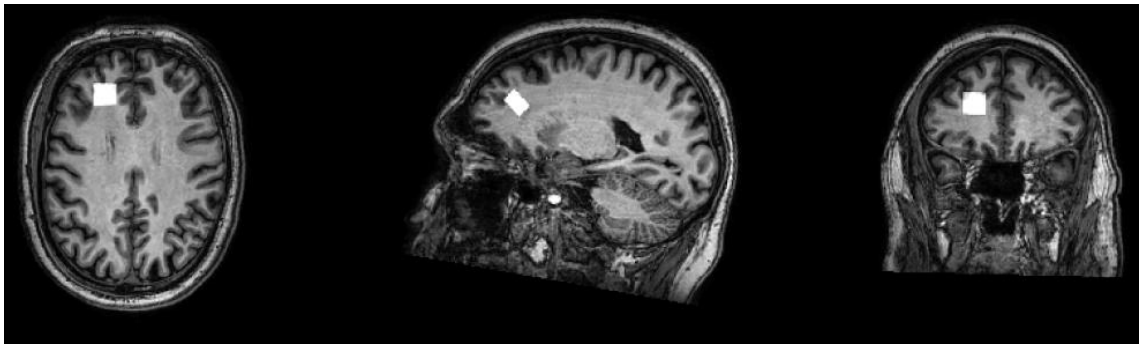

Figure 8. 1H-MRS voxel, Left DLPFC

For 1H-MRS spectra analysis it was used LCModel version 6.3.0. This approach analyzes an in vivo spectrum composed by a linear combination of Model in vitro spectra from individual metabolite solutions. In this way it is possible to maximize the information inside the spectra of the complete model for analysis, rather than using individual

resonances. LCModel is considered a nearly model-free constrained regularization method, which automatically represents the lineshape of spectrum without imposing a restrictive parameterized form on it. The maximum probability of concentration of each individual metabolite and its uncertainty (Cramér-Rao lower bounds) is therefore approximately estimated. As a reference for the quantifications, water signal unsuppressed measured from the same specific VOI was used, assuming that brain water content is about 80%. LCModel calculates the best fit to the experimental spectrum, which is a linear combination of the model spectra, using raw data as standard data input (Figure 9). Finally, the analysis in the frequency domain is done. Tissue segmentation was performed in order to estimate the proportion of gray matter, white matter, and CSF in the voxel. Brain tissue in the three-dimensional T1-weighted brain images was segmented using the Gannet Co Register and Gannet Segment functions in the Gannet 2.0 toolbox in SPM12. The CSF brain tissue fraction was calculated for each voxel [fCSF = %CSF/(%GM + %WM + %CSF)]. Concentrations were then corrected for CSF fraction with the following formula: Corrected concentration = metabolite concentration ∗ (1/[1 – fCSF]) To ensure the accuracy of the measurements obtained, only metabolite results with values of Cramér–Rao lower bound <20% were considered. Metabolites concentrations were then scaled to individual Creatinine+Phosophocreatinine (Cr) concentrations.

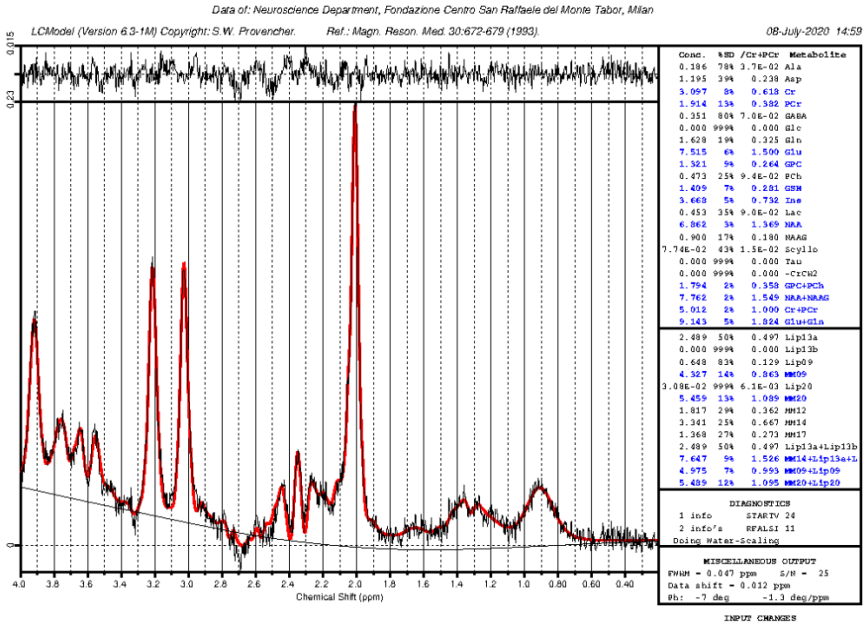

Figure 9. 1H-MRS spectra, LCModel output

After quality check, the following metabolites have been included as1H-MRS values of this study:

- *N-acetylaspartate (NAA):* represents the greater peak of the 1H spectrum, resonating at 2ppm frequency. NAA is a synthesized in healthy neurons' mitochondria that diffuses along axons, and high NAA concentration is considered a mark of well being of cerebral functions, index of high neuronal density (Blüml, 2013).
- *Myo-inositol (Ins):* Ins (3.6 peak) is involved in phosphatidylinositol (a membrane phospholipid) metabolism, and under normal conditions it is expected to be invisible to MRS. Under altered membrane conditions and brain pathological diseases Ins levels increase, and is thus considered an index of neurodegenerative processes (Blüml, 2013).
- *Glutamate + Glutamine (Glx):* Glutamate (2.3 peak) is the most common excitatory neurotransmitter and often it is reported together with glutamine (Glu astrocytic metabolite) as their resonance frequencies are very similar and their contribution to the peak is not always distinguishable (Blüml, 2013). Both reduction and elevation of glutamate levels have been associated with neural alterations, with increased glutamate levels associated with excitotoxicity and impaired prefrontal cognitive functions (Spangaro et al, 2012).
- *Creatine (Cr) and Phosphocreatinine (Pcr):* present in both white and gray matter, detectable in all the brain cells microglia, astrocytes, and neurons). Involved in cellular metabolism and basic functions such as homeostasis. Pathological brain conditions may lead to higher Cr+Pcr concentrations. Given the uniform distribution of Cr and Pcr, their values are used in order to calculate metabolite ratios (Blüml, 2013).

Diffusion tensor imaging (DTI) was performed as in Spangaro et al (2018) on a 3.0 T scanner (GyroscanIntera, Philips, Netherlands) using SE Eco-planar imaging (EPI) and the following parameters: TR/TE = 8753.89/58 msec, FoV (mm) 231.43 (ap), 126.50 (fh), 240.00 (rl); acquisition matrix 2.14 × 2.71 × 2.31; 55 contiguous, 2.3-mm thick axial slices reconstructed with in-plane pixel size 1.88 x 1.87 mm; SENSE acceleration factor = 2; 1 b0 and 35 non-collinear directions of the diffusion gradients; b value = 900 s/mm2. Fat saturation was performed to avoid chemical shift artefacts. It was performed through Spectral Presaturation with Inversion Recovery (SPIR), a hybrid technique that combines

a fat-selective RF-pulse and spoiler gradient together with nulling of the residual longitudinal fat magnetization through an inversion delay mechanism (http://mriquestions.com/spir.html) (Spangaro et al, 2018).

Whole-brain tract-wise average FA values were extracted in the dataset according to ENIGMA-DTI protocols (available online at http://enigma.ini.usc.edu/protocols/dti-protocols/), as in Comai et al (Comai et al, 2021). DTI images were pre-processed using FSL tools (http://www.fmrib.ox.ac.uk/fsl). By FSL's "eddy correct" command, all volumes were corrected for eddy current induced distortions and subjects movements (Horsfield, 1999). A brain mask was then created using FSL's Brain Extraction Tool (BET) (Smith, 2002), which deletes non-brain tissues from the image. Next, by FSL's DTIFIT command, included in FMRIB's Diffusion Toolbox (FDT) (Behrens et al., 2003), a voxel-wise diffusion tensor model was fit to the data in order to obtain parametric maps of FA. Whole brain statistical analyses of all subject's FA images were conducted using FSL's Tract-Based Spatial Statistics (TBSS; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS) analytic method. All subject's FA data were aligned to the Montreal Neurological Institute (MNI) space, by use of local deformation procedures performed by FMRIB's Non-Linear Image Registration Tool (FNIRT) (www.fmrib.ox.ac.uk/fsl/fnirt/index.html). The mean of all aligned FA images was then created and a "thinning" process was applied to create a skeletonised mean FA image representing the centres of all common tracts. A threshold of 0.2 was set to this image in order to control for inter-subject variability and reduce the likelihood of partial volume effect. Quality control, including inspections of data, vector gradients, registration, and average skeleton projection distance, were performed according to the ENIGMA-DTI protocol. Finally, all individual FA image was projected onto the skeleton by searching perpendicular from the skeleton for maximum FA values. Average FA values were calculated from voxels in each subject's white matter skeleton within 46 tract-wise regions of interest (ROIs) (Table 16), derived from the Johns Hopkins University (JHU) white matter parcellation atlas (Mori et al., 2008). All measures were separately calculated for right (R) and left (L) hemispheres in each ROI, except for body of corpus callosum (BCC), corpus callosum (CC), fornix (FX), genu of corpus callosum (GCC) e splenium of corpus callosum (SCC).

ACR	Anterior corona radiata
ALIC	Anterior limb of internal capsule
BCC	Body of corpus callosum
CC	Corpus callosum
CGC	Cingulate gyrus
CGH	Cingulum (Hippocampal part)
CR	Corona radiata
CST	Cortico-spinal tract
EC	External capsule
FX	Fornix
FX-ST	Fornix stria terminalis
GCC	Genu of corpus callosum
IC	Internal capsule
IFO	Inferior fronto-occipital fasciculus
PCR	Posterior corona radiata
PLIC	Posterior limb of internal capsule
PTR	Posterior thalamic radiation
RLIC	Rentrolenticular part of internal capsule
SCC	Splenium of corpus callosum
SCR	Superior corona radiata
SFO	Superior fronto-occipital fasciculus
SLF	Superior longitudinal fasciculus
SS	Sagittal striatum
UNC	Uncinate fasciculus

Table 16. DTI ROIs derived from JHU white matter parcellation atlas

5.3 Statistical Analysis

First, we investigated socio-demographic, clinical and neuropsychological features of Mets. In details, we analysed with Analysis of Variance (ANOVA) for continuous variables and Chi Squared Test for dichotomous variables, differences between patients meeting ATPIII MetS criteria and patients without MetS on age, sex (socio-demographic variables) duration of illness, antipsychotic load, PANSS total score (clinical variables) and BACS scores. Second, we investigated inflammatory signatures of MetS and their relationship with socio-demographic and clinical variables. To this purpose, differences in inflammatory markers between MetS+ and MetS- patients were analysed by ANOVA, while relationships between inflammatory markers and socio-demographic, smoking and clinical variables were analysed by Pearson's correlations. Then, inflammatory markers that resulted associated with MetS diagnosis were also analysed with respect to each MetS-component (abdominal obesity, hypertriglyceridemia, hyperglycaemia, low HDL and hypertension) by ANOVAs. Moreover, significant results concerning the relationship between MetS components and peripheral markers of inflammation were more thoroughly investigated in the context of multiple general regressions models (GRM) with stepwise backward procedure, considering MetS components as dichotomic predictors, inflammatory markers as dependent variables, and, when previously correlated, age, sex, duration of illness, and antipsychotic load as covariates.

Last, we modeled the interplay between MetS and inflammatory biomarkers on cognition. In details, we performed multiple separate slope models (SSM) with BACS equivalent scores as dependent variables, MetS (+/-) as categorical predictor, inflammatory biomarkers previously associated with Mets as continuous predictors, and duration of illness as covariate, to evaluate differential effect of inflammatory biomarkers on cognition according to the presence of MetS. Significant results of SSMs were then further investigated in the context of regression moderation analyses (Figure 10, Hayes, 2013), to test the hypothesis of MetS moderating the effects of inflammatory markers on cognitive outcome.

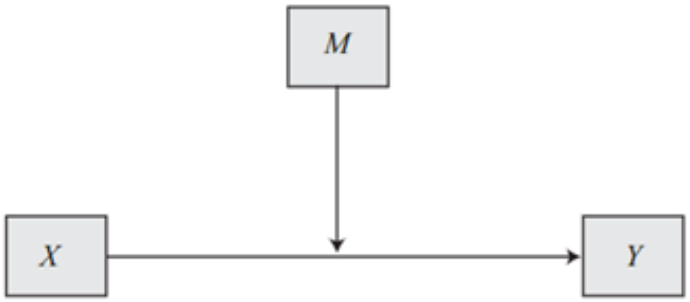

Figure 10. Graphical conceptual representation of moderation model (Hayes, 2013)

The moderation analyses were performed using the significant inflammatory markers as continuous predictors, cognitive performance as continuous dependent variable and MetS as categorical moderating variable (presence\absence of Mets). Moderation analyses were conducted with duration of illness as covariate and using 5.000 bootstrap resamples to generate 95% confidence percentile intervals.

Within the subsample of 39 patients that underwent to MRI acquisition, relationship between MRI parameters (1H-MRS metabolites and FA) with MetS-related inflammatory markers and MetS was initially analyzed through multiple exploratory Pearson's correlation analyses and ANOVAs. 1H-MRS and FA tracts significantly correlated with MetS inflammatory markers were then analyzed as dependent variables in the context of multiple GRMs (stepwise backward), considering MetS as categorical predictor, MetS inflammatory markers as continuous predictor, and, age, sex, duration of illness, and antipsychotic load as covariates.

Moderation regression models were performed with PROCESS macro for SPSS, version 4.0 (Hayes, 2022). All the other statistical analysis were carried out with IBM SPSS Statistic 25 and STATISTICA software package for Windows, version 8.

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