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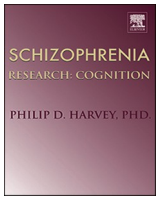

# Neuroinflammation and kynurenines in schizophrenia: Impact on cognition depending on cognitive functioning and modulatory properties in relation to cognitive remediation and aerobic exercise

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ABSTRACT

*Background:* In the last decade, the kynurenine pathway (KP) has gained attention in the pathogenesis of cognitive impairment in schizophrenia being at the croassroad between neuroinflammation and glutamatergic and cholinergic neurotransmission. However, clinical findings are scarse and conflicting, and the specific contributions of these two systems to the neurobiology of cognitive symptoms are far from being elucidated. Furthermore, little is known about the molecular underpinnings of non-pharmacological interventions for cognitive improvement, including rehabilitation strategies.

*Methods:* The current study examined 72 patients with schizophrenia, divided in two clusters depending on the severity of the cognitive impairment, with the aim to evaluate the impact of inflammatory biomarkers and KP metabolites depending on cognitive functioning. Moreover, we studied their possible link to the cognitive outcome in relation to sessions of cognitive remediation therapy (CRT) and aerobic exercise (AE) in a longitudinal arm of 42 patients.

*Results:* Neuroinflammation appeared to exert a more pronounced influence on cognition in patients exhibiting a higher cognitive functioning, contrasting with the activation of the KP, which had a greater impact on individuals with a lower cognitive profile. Cognitive improvements after the treatments were negatively predicted by levels of TNF-α and positively predicted by the 3-hydroxykynurenine (3−HK)/kynurenine (KYN) ratio, an index of the kynurenine-3-monooxygenase (KMO) enzyme activity.

*Conclusion:* Overall, these findings add novel evidence on the biological underpinnings of cognitive impairment in schizophrenia pointing at a differential role of neuroinflammation and KP metabolites in inducing cognitive deficits depending on the cognitive reserve and predicting outcomes after rehabilitation.

## 1. Introduction

Schizophrenia is a severe mental illness characterized by high heterogeneity in terms of symptoms, biological underpinnings and clinical course (Tandon et al., 2009; Bosia et al., 2022). Cognitive impairments continue to pose a significant challenge in schizophrenia as its

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underlying neurobiology is multifaceted, encompassing complex interactions between several molecules which might help to explain the heterogeneity of cognitive profiles (Bechi et al., 2019; Harvey et al., 2022; Sapienza et al., 2023b).

### 1.1. Cognitive impairment and neurotransmission: the role of the kynurenine pathway

The dopaminergic system was the first to be investigated with regards to cognition, and several pieces of evidence pointed at frontal and pre-frontal dopamine levels as one of the crucial determinants of the cognitive outcome (Braver et al., 1999; Bosia et al., 2007). Other robust findings were then reported on the relationship between *N*-methyl-D-aspartate (NMDA) neurotransmission and the cholinergic system and cognitive functioning (Spangaro et al., 2012; Moghaddam and Javitt, 2012). Indeed, it was observed that compounds which stimulate cholinergic receptors improve cognitive performances (Gibbons and Dean, 2016). Differently, molecules that block NMDA receptors cause cognitive impairment (Verma and Moghaddam, 1996; Moghaddam et al., 1997). However the glutamatergic system still remains an open issue, as glutamatergic neurotransmission improve the cognitive functioning but at the same time high levels of glutamate can induce excitotoxicity, which causes loss of neurons and damage to oligodendrocytes, thus white matter (WM) disruption (Wang and Qin, 2010; Domercq et al., 2005; Matute et al., 2007).

Notably, the kynurenine (KYN) pathway (KP) of tryptophan (Trp) is of interest in schizophrenia being at the croassroad between neuroinflammation and neurotransmission, as two of the main enzymes of the pathway, the indolamine-2,3-dioxygenases 1 and 2 (IDO1 and IDO2), are inducted by pro-inflammatory cytokines (Comai et al., 2020; Messaoud et al., 2022), and some downstream metabolites can modulate cholinergic and glutamatergic neurotransmission (Sapienza et al., 2024b). IDO1, IDO2 and tryptophan-2,3-dioxygenase (TDO) convert Trp into KYN which is then metabolized either by the kynurenine aminotransferase (KATs) enzymes into kynurenic acid (KYNA) or by the kynurenine 3-monooxygenase (KMO) enzyme into 3-hydroxykynurenine (3-HK) (Comai et al., 2020). 3-HK showed neurotoxic properties in several studies, however some findings on its neuroprotective effect are also described (Colín-González et al., 2013). 3-HK can be transformed either in xanthurenic acid (XA) by KATs or to 3-hydroxyanthranilic acid (3-HANA) by the enzyme kynureninase. 3-HANA, following some enzymatic and nonenzymatic steps is then converted into either picolinic acid or quinolinic acid (QUIN) which spontaneously converts into nicotinic acid, an intermediate in NAD+ synthesis (Comai et al., 2020). During infammatory conditions, cytokines can increase the amount of Trp catabolised along the KP inducing an unbalance between neuroactive, neurotoxic and neuroprotective metabolites depending on the activity of specific enzymes of the pathway (Comai et al., 2020; Kindler et al., 2020). Overall, it is important to note that both neuroinflammation and KP metabolites can impact cognitive function (Kindler et al., 2020; Sapienza et al., 2023b).

### 1.2. Cognitive impairment and the role of the immune system

Besides neurotransmitter dysregulation impacting cognition in schizophrenia, the role of neuroinflammation in cognitive impairment is gaining attention (Khandaker et al., 2015; Kindler et al., 2020; North et al., 2021; Patlola et al., 2023). Indeed, several studies identified the activation of microglia and increased levels of pro-infammatory cytokines as pivotal pathogenic mechanisms of the disease (van Berckel et al., 2008; Howes and McCutcheon, 2017). The cytokines which play a major role in the pathophysiology of schizophrenia are Interleukin (IL)-1β, Tumor Necrosis Factor (TNF)-α, IL 6, IL-17, but also many other chemokines (Potvin et al., 2008; Miller et al., 2011). Notably, also systemic inflammation/sub-inflammtion is able to impact cognition as widely reported by several studies on metabolic health in patients with schizophrenia that pointed out a crosstalk of the immune system between the brain and the periphery (Yaffe et al., 2004; Boyer et al., 2014; Bosia et al., 2021). Indeed, Metabolic Syndrome (MetS) is a frequent comorbidity of schizophrenia and it is associated to an increased peripheral levels of cytokines and chemokines due to insulin resistance, which cause the secretion of resistine by the adipose tissue, and dyslipidemia in a vicious circle (Strassnig et al., 2014; Grover et al., 2019; Cuoco et al., 2022). The systemic sub-inflammation and neuroinflammation trigger a wide range of cognitive deficits due to the induction of high oxidative stress, cytotoxicity, enhanced synaptic pruning due to microglia activation, and white matter (WM) disruption (Howes and McCutcheon, 2017; Upthegrove and Khandaker, 2020; North et al., 2021; Sapienza et al., 2023a; Patlola et al., 2023; Howes and Onwordi, 2023; Sapienza et al., 2024a).

### 1.3. Cognitive remediation and aerobic exercise

Cognitive Remediation therapy (CRT) is a behavioral training-based intervention mainly delivered through electronic devices, which is effective in improving and preventing cognitive decline in multiple cognitive domains, with persistent effects on both cognition and functional outcome even 10 years later (Cavallaro et al., 2009; Buonocore et al., 2022). It mainly induces molecular changes at central level (Spangaro et al., 2018; Penadés et al., 2018; Matsuda et al., 2019) and the most recent European guidelines for schizophrenia treatment identified CRT as the best option to improve cognition in schizophrenia despite the moderate effect size (Vita et al., 2022; Wykes et al., 2011). Therefore, other non-pharmacological treatments should be explored in augmentation to CRT to further improve cognition, and, given that the comorbidity with metabolic syndrome affects over 40 % of people with schizophrenia and it is proven to affect the degree of response to CRT, aerobic exercise (AE) has gained attention. Indeed, several metanalyses demonstrated the efficacy of AE in improving global cognition, attention/vigilance, working memory, verbal learning, reasoning and problem solving in patients with schizophrenia (Firth et al., 2017; Shimada et al., 2022; Xu et al., 2022). Interestingly, it was demonstrated that AE is able to reduce systemic sub-inflammation, thus the peripheral activation of the KP which leads to accumulation of KP metabolites in the brain with possible positive implications for cognition (Cervenka et al., 2017; Martin et al., 2020).

### 1.4. Aims

The specific contribution of the kynurenine pathway (KP) and neuroinflammation to the observed cognitive impairment in schizophrenia remains unclear. Therefore, there is an urgent need to thoroughly investigate and unravel the biological foundations of cognitive impairment, considering the varying levels of cognitive functioning, as distinct performances may align with different molecular substrates (Kindler et al., 2020; Sapienza et al., 2023b). In this study, our primary objective was thus to investigate the relationship between inflammatory markers, kynurenine pathway (KP) metabolites, and cognitive performance in patients with schizophrenia, considering their cognitive profiles. The secondary aim was to examine the interplay between CRT, AE, and inflammatory/KP markers to identify reliable indicators of cognitive improvement associated with rehabilitative interventions. We hypothesized that a proinflammatory state and elevated levels of neurotoxic KP metabolites might impede cognitive improvement following interventions. Regarding neuroactive KP metabolites, their impact was anticipated to be contingent on their ability to either support or hinder glutamatergic or cholinergic neurotransmission.

## 2. Materials and methods

### 2.1. Participants

The sample is derived from a multicenter Randomized Controlled Trial (RCT) including 93 patients, which took place from 2019 to 2023 at the Schizophrenia Research and Clinical Unit, IRCCS San Raffaele Scientific Institute of Milan and at the Department of Mental Health, Spedali Civili Hospital of Brescia. Patients were diagnosed with schizophrenia according to the DSM-5 criteria. The inclusion criteria were age between 18 and 65 years and diagnosis of schizophrenia according to the DSM-5 criteria. Exclusion criteria were hospitalization due to psychotic exacerbation, psychiatric and cardiac comorbidities, intellectual disability (IQ < 70), substance or alcohol abuse, neurological disorders and brain injury, concomitant infectious\inflammatory diseases or cancer. The sample consisted of patients in the chronic phase of the illness with no acute exacerbation requiring hospitalization or changes in antipsychotic treatment in the previous two months and through the duration of the study, with an overall mild to moderate severity of illness (symptom dimension detailed in 3.1). First-line responder patients were treated with haloperidol, risperidone or paliperidone, resistant patients (Treatment-Resistant Schizophrenia, TRS) were treated with clozapine as indicated for TRS (Zanardi et al., 2022), whereas ultra-treatment-resistant patients were treated with clozapine + one of the first line antipsychotics in augmentation.

### 2.2. Study design

After a complete description of the study protocol, informed consent to participation was obtained from 93 patients. The protocol followed the principles of the Declaration of Helsinki and was approved by the local ethics committee. Then, 60 patients were randomly assigned 1: 1: 1 to 3 treatment-arms: 1) 1 h CRT twice a week for 3 months; 2) 1 h-session of AE twice a week for 3 months, or 3) both CRT + AE. For this this study, the analysis included a cross sectional sample of 72 patients and a longitudinal arm of 42 patients. Among the 60 patients who initially constituted the 3 longitudinal arms, only 16 patients in the CRT + AE group, 15 in the AE group and 11 in the CRT group completed the program as shown in Fig. 1. In the longitudinal arm, cognitive functioning and psychopathology were assessed pre and post interventions while plasma levels of inflammatory and KP biomarkers were assessed at baseline. Details on the study protocol are shown in Fig. 1. Demographic, cognitive and clinical data of the longitudinal sample are reported in Table 2 and levels of biomarkers at baseline are reported in Table 3.

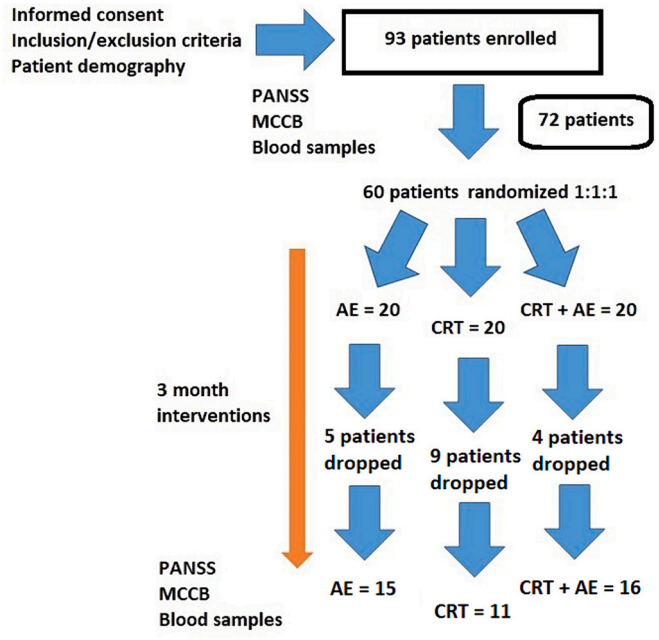


**Fig. 1.** Study design and flowchart.

### 2.3. Cognitive assessment

The Italian version of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) was administered by trained psychologists and was used to assess 6 cognitive domains: Processing speed, Attention, Working memory, Verbal learning, Visual learning and Reasoning. Specifically, the Symbol Coding, the Animal Naming and the Trail Making tests were used to assess Processing speed. The Continuous Performance Test (CPT) and the Neuropsychological Assessment Battery were used to assess Attention and Reasoning respectively, whereas Working Memory was assessed through the Spatial Span and Letter-Number Span tests. Finally, the Hopkins Verbal Learning Test and the Brief Visuospatial Memory Test were used to estimate Verbal learning and Visual learning respectively (Nuechterlein et al., 2008).

### 2.4. Psychopathology

Psychopathology was assessed with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1987). The clinical interview and evaluation of symptoms were performed by trained psychiatrists. The total score and the scores of the three subscales (Positive Scale, Negative Scale, and General Psychopathology Scale) were then calculated.

### 2.5. Laboratory analysis

Blood was collected by venipuncture in Vacutainer tubes containing EDTA in the morning after a fasting overnight period, then centrifuged at 2000 ×*g* for 15 min at 4 °C, then plasma was divided into 200 μL small aliquots and stored at −80 °C.Plasma concentrations of immune analytes IL-1β, IL-6, IL-1ra, IL-9, IL-10, IL-13, IL-17A, Interferon (IFN)-ɣ, MIP1α, PDGF-BB, RANTES e TNF-α and ANP were determined using an Elisa kit according to manufacturer's instructions (Raybiotech, Atlanta, USA). Plasma levels of the main metabolites of the KP were measured following standard methodological procedures in the lab (Sapienza et al., 2024b) (Comai et al., 2022). The analysis of Trp and KYN was performed with a high performance liquid chromatography (HPLC) system coupled with a fluorometric detector for Trp and UV–Vis detector for KYN. 3-hydroxykynurenine (3-HK), KYNA and QUIN were determined using a LC-MS/MS Varian system composed of a binary Prostar pump, 410 autosampler, and MS320 triple quadrupole mass spectrometer equipped with Electro Spray ion source. The instrument worked in multiple reaction monitoring mode for all the molecules in positive ion mode, except for QUIN that was quantified in negative mode. The quantification of 3-HK, QUIN, and KYNA was calculated using alfa-methyl Trp as an internal standard. The following ratios were calculated as indirect index/proxy of the activity of the following enzymes of the KP: KYN/Trp of Indoleamine 2,3-dioxygenase (IDO), KYNA/KYN of KYN aminotransferase II, and 3-HK/KYN of kynurenine-3-monooxygenase.

### 2.6. Interventions

#### 2.6.1. Cognitive remediation therapy

The CRT protocol consisted of two 1-h sessions per week of domain-specific computerized exercises, over a period of 3 months (12 weeks), for a total of 36 h. Computer-assisted neurocognitive exercises were performed using the Cogpack Software (Marker, 1987–2007) and the cognitive domains targeted by the CRT are those assessed by the

MATRICS scale. Sets of exercises were individually created for each patient based on their performance at the baseline and then the program was set for adaptive exercises, based on subjects' performances during the session. Therefore, for each cognitive domain there are different types of exercises with different degrees of difficulty. For each poor performance (0–1 equivalent score), a domain-specific exercise was included, while, for each good performance (2–4 equivalent score), a non-domain-specific exercise was added. Exercises were administered by trained psychologists, and their role was to support the patients and motivate them during the execution of the CRT without providing the correct answer or solution to the exercises (see Cavallaro et al., 2009).

#### 2.6.2. Aerobic exercise

AE consists of two 1-h sessions of AE per week for 3 months with cycle-ergometer for 40 min at 60 % of the maximum individual oxygen supply and heart rate. Patients performed also 10 min of stretching before and after AE. The choice of cycle-ergometer was made based on the poor feasibility to deliver other types of interventions (walking, jogging) in the hospital setting maintaining the training effect. Similarly, we decided to exclude interventions with a low training potential (low amount of burnt Kcal), such as tai chi, meditation or yoga.

#### 2.6.3. Standard rehabilitation therapy

All patients also received a Standard Rehabilitation Therapy (SRT) consisting of 1-h sessions twice a week to ensure the same intensity and frequency in the three treatment arms. SRT included non-cognitive subprograms of Integrated Psychological Therapy (IPT) (Verbal Communication, Social Skill Training, and Problem-Solving) (Zimmer et al., 2007), social skills training programs for residential, vocational, and recreational functioning (Roder et al., 2002), and psychoeducational interventions (Bechdolf et al., 2004). The social skills training was based on role-playing methodology and selecting daily life activities according to patient needs, to reduce social anxiety, interrupt negative self-reinforcement and to increase social performance. The Problem-Solving module dealt with problem identification, cause-effect reasoning and effective social behavior. Psychoeducational sessions were deputed to the identification of symptoms, relapses and needs, as well as on the use of medication, treatment compliance and the management of side effects elicited by antipsychotics with the goal to increase patient knowledge regarding the illness and to improve treatment compliance.

#### 2.6.4. Cognitive remediation therapy + aerobic exercise

Patients who underwent CRT + AE performed CRT right before or after the two weekly sessions of AE with the cycle-ergometer with a time-break of about 30 min. Therefore, both protocol treatments were applied in the same two days of attendance of our Unit.

### 2.7. Statistical analysis

Statistical analyses were performed with STATISTICA software package for Windows, version 8 and IBM SPSS statistics 27 (Chicago, IL). Figures were made with Rstudio. First, we performed partial correlations to address the relationship between the plasma levels of inflammatory markers, metabolites of the KP and the MCCB cognitive domains in the all sample constituted by 72 patients using age and sex as possible covariates. Then, to achieve a better understanding of the molecular underpinnings underlying cognitive functioning in schizophrenia we decided to split the sample in two subsamples of patients with a high or low cognitive profile. We thus performed a two-step cluster analysis, considering MATRICS scores of neurocognition as clustering variables and then, we re-explored correlations in the two subsamples. Based on these results, we performed multiple stepwise regressions to identify possible predictors of cognitive improvement after treatment, with the Δ(T1-T0) of the MCCB scores as dependent variables, in order to identify the biomarkers of cognitive improvements after all the CRT, AE or CRT + AE interventions. No differences were made among the three interventions due to the relative small number of the longitudinal arm. For the same reason (restricted longitudinal arm), we decided to consider only the ratios as indexes of enzymes activity (KYN/Trp, KYNA/KYN and 3-HK/KYN ratios) and balance of neuromodulatory properties, while cytokines were selected on the basis of both evidence emerged in the literature and exploratory correlations. Indeed, there is evidence that cytokines can induce the kynurenine pathway (Pedraz-Petrozzi et al., 2020). A two-tailed $p$-value $<0.05$ was considered statistically significant.

## 3. Results

### 3.1. Clinical and demographic characteristics of the sample

Demographic characteristics, symptomatology and cognitive performances at baseline and the mean dosage of chlorpromazine equivalents are reported in Table 1.

### 3.2. Correlation between cognitive domains and plasma biomarkers

Baseline partial correlations in the whole study sample between plasma levels of inflammatory and ANP with cognition (subscores of the

**Table 1**
Demographic, clinical characteristics and biomarkers of the whole sample.

| Demographic characteristics | Mean (Standard Deviation) |
|---|---|
| Age | 36.30 (12.60) |
| Education | 11.21 (2.80) |
| Sex (M/F, % M) | 75.26 % M |
| Onset | 21.56 (4.82) |
| Duration of illness (years) | 15.49 (11.37) |
| Chlorpromazine equivalents | 448.51 (251.47) |
| | |
| PANSS | |
| PANSS Positive | 18.69 (6.55) |
| PANSS Negative | 21.91 (5.86) |
| PANSS General | 40.40 (10.62) |
| PANSS Total | 81.01 (19.14) |
| | |
| Matrics | |
| Processing Speed | 32.62 (12.20) |
| Attention | 36.22 (10.73) |
| Working Memory | 37.80 (12.71) |
| Verbal Learning | 41.60 (11.65) |
| Visual Learning | 32.19 (10.90) |
| Reasoning | 38.69 (10.10) |
| | |
| Biomarkers | |
| IL-1beta (pg/mL) | 1.30 (1.70) |
| IL-1ra (pg/mL) | 243.11 (222.47) |
| IL-6 (pg/mL) | 5.22 (8.91) |
| IL-9 (pg/mL) | 541.85 (69.39) |
| IL-10 (pg/mL) | 3.99 (2.71) |
| IL-13 (pg/mL) | 2.15 (1.72) |
| IL-17A (pg/mL) | 6.53 (3.70) |
| IFN-gamma (pg/mL) | 2.10 (1.30) |
| MIP-1alfa (pg/mL) | 1.26 (0.46) |
| PDGF-BB (pg/mL) | 667.33 (605.50) |
| RANTES (pg/mL) | 3689.96 (1421.64) |
| TNF-alfa (pg/mL) | 25.33 (6.50) |
| TRP (μg/mL) | 12.18 (2.36) |
| KYN (ng/mL) | 0.22 (0.20) |
| 3HK (ng/mL) | 24.38 (34.40) |
| KYNA (ng/mL) | 8.40 (4.45) |
| QUIN (ng/mL) | 107.92 (41.56) |
| KYN/Trp*1000 ratio | 18.98 (17.58) |
| KYNA/QUIN ratio | 16.59 (11.11) |
| KYNA/KYN*1000 ratio | 88.34 (95.21) |
| 3-HK/KYN ratio | 129.20 (115.51) |

**Table 2**
Demographic and clinical characteristics of the longitudinal arm.

| Demographic characteristics | T0 Mean (Standard Deviation) | T1 Mean (Standard Deviation) |
|---|---|---|
| Age | 36.85 (11.59) | |
| Education | 11.41 (2.82) | |
| Sex (M/F. % M) | 66.66 % M | |
| Onset | 21.16 (4.20) | |
| Duration of illness (years) | 15.82 (11.50) | |
| Chlorpromazine equivalents | 469.76 (277.11) | |
| | | |
| PANSS | | |
| PANSS Positive | 19.38 (6.82) | 18.25 (6.63) |
| PANSS Negative | 22.72 (6.98) | 22.16 (8.57) |
| PANSS General | 42.36 (11.13) | 38.23 (12.08) |
| PANSS Total | 84.46 (21.59) | 78.67 (24.27) |
| | | |
| MATRICS | | |
| Processing Speed | 30.38 (15.13) | 31.57 (15.10) |
| Attention | 36.83 (10.68) | 33.54 (14.85) |
| Working Memory | 35.64 (14.33) | 35.34 (16.56) |
| Verbal Learning | 37.38 (9.93) | 39.18 (10.62) |
| Visual Learning | 31.05 (10.03) | 32.98 (14.29) |
| Reasoning | 36.00 (9.57) | 38.32 (9.67) |

**Table 3**
levels of biomarkers of the longitudinal arm at baseline.

| Biomarkers | T0 Mean (Standard Deviation) |
|---|---|
| IL-1beta (pg/mL) | 1.55 (1.63) |
| IL-1ra (pg/mL) | 239.85 (216.46) |
| IL-6 (pg/mL) | 5.10 (10.10) |
| IL-9 (pg/mL) | 550.32 (72.35) |
| IL-10 (pg/mL) | 3.70 (1.07) |
| IL-13 (pg/mL) | 2.17 (1.82) |
| IL-17 A (pg/mL) | 6.52 (3.71) |
| IFN-gamma (pg/mL) | 2.06 (1.24) |
| MIP-1alfa (pg/mL) | 1.23 (0.35) |
| PDGF-BB (pg/mL) | 666.92 (481.12) |
| RANTES (pg/mL) | 3850.38 (1613.47) |
| TNF-alfa (pg/mL) | 25.14 (5.57) |
| TRP (μg/mL) | 12.61 (3.01) |
| KYN (ng/mL) | 103.52 (34.78) |
| 3HK (ng/mL) | 8.23 (3.39) |
| KYNA (ng/mL) | 10.92 (3.99) |
| QUIN (ng/mL) | 91.00 (49.50) |
| KYN/Trp*1000 ratio | 8.52 (3.15) |
| KYNA/QUIN ratio | 0.36 (0.80) |
| KYNA/KYN*1000 ratio | 130.89 (101.18) |
| 3-HK/KYN ratio | 98.62 (85.46) |
| ANP | 12.88 (10.84) |

MCCB) as well as KP biomarkers and cognition (subscores of the MCCB) using age and sex as control variables are reported in Tables 4 and 5, respectively.

We found significant negative associations between IL-17 A levels and Verbal learning ($r = -0.345$; $p = 0.031$) and Trp levels and Visual learning ($r = -0.265$; $p = 0.048$). A positive association emerged between ANP levels and Processing speed ($r = 0.25$; $p = 0.05$).

### 3.3. Cluster analysis of study population based on the neurocognitive profile

The analysis produced two clusters of patients: Cluster 1 (low neurocognitive profile) and Cluster 2 (high neurocognitive profile) as shown in Fig. 2. The Bayesian information criterion (BIC) was 305.87 for the two-cluster solution, also confirmed by the cohesion index and the separation of the silhouettes. Cluster 1 was formed by 36 patients and Cluster 2 by 28 patients, as only 64 of 72 patients completed all the cognitive subtests of the MATRICS Consensus Cognitive Battery needed for the clustering. The longitudinal arm was composed by 26 patients from Cluster 1 and 14 patients from Cluster 2 (the remaining two patients of the longitudinal arm not classified as Cluster 1 or Cluster 2 pertain to the patients that at baseline did not complete all the cognitive subtests). The demographic clinical and cognitive data of the two clusters are reported in Table 1S, while the levels of biomarkers of the two clusters are reported in Table 2S (Supplementary Materials and Methods).

### 3.4. Correlation between cognitive domains and plasma biomarkers depending on cognitive profiles

#### 3.4.1. Patients with lower neurocognitive profile

Partial correlations between plasma levels of inflammatory biomarkers and cognition at baseline in Cluster 1 showed a positive association between ANP levels and Processing speed ($r = 0.566$; $p = 0.003$). Regarding the KP, Processing speed resulted negatively associated to the activation of the pathway (KYN/Trp ratio) ($r = -0.443$; $p = 0.011$) as well as to the levels of KYN (r = −0.4; $p = 0.023$) and 3-HK ($r = -0.428$; $p = 0.015$). Visual learning resulted negatively associated to 3-HK ($r = -0.409$; $p = 0.002$) and KYN levels ($r = -0.408$; p = 0.002). Positive associations emerged between KYNA levels and Processing speed ($r =$ 402; p = 0.023) and 3-HK/KYN ratio and reaction times in the Attention task, thus highlighting a negative association with Attention ($r = 0.528$; $p = 0.012$). Details of partial correlations are reported in Table S3 (Supplementary Materials and Methods).

#### 3.4.2. Patients with higher neurocognitive profile

Partial correlations between inflammatory biomarkers and cognition at baseline in Cluster 2 showed that Working memory is negatively

**Table 4**
Partial correlations between inflammatory biomarkers and cognition.

| | Process. Speed $n = 37$ | | Attention $n = 22$ | | Working Mem. n = 37 | | Verb. Learning n = 37 | | Vis. Learning $n = 23$ | | Reasoning n = 37 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | r | p | r | p | r | p | r | p | r | p | r | p |
| IL-1β | 0.091 | 0.58 | −0.04 | 0.852 | −0.027 | 0.869 | 0.061 | 0.714 | −0.165 | 0.431 | −0.147 | 0.371 |
| IL-1ra | −0.128 | 0.438 | 0.056 | 0.794 | −0.087 | 0.6 | −0.183 | 0.266 | 0.039 | 0.855 | −0.146 | 0.375 |
| IL-6 | 0.128 | 0.438 | −0.033 | 0.877 | 0.056 | 0.733 | −0.08 | 0.629 | 0.384 | 0.058 | 0.098 | 0.554 |
| IL-9 | −0.113 | 0.494 | −0.279 | 0.187 | −0.101 | 0.541 | −0.12 | 0.467 | 0.133 | 0.528 | −0.093 | 0.574 |
| IL-10 | 0.025 | 0.88 | −0.061 | 0.775 | −0.139 | 0.4 | −0.003 | 0.987 | −0.151 | 0.472 | 0.118 | 0.474 |
| IL-13 | 0.101 | 0.54 | 0.206 | 0.335 | 0.225 | 0.168 | 0.168 | 0.307 | −0.125 | 0.551 | 0.123 | 0.456 |
| IL-17 A | −0.106 | 0.521 | 0.041 | 0.848 | −0.304 | 0.06 | **−0.345** | **0.031** | −0.139 | 0.508 | −0.206 | 0.209 |
| IFN-γ | −0.108 | 0.512 | −0.033 | 0.877 | −0.123 | 0.454 | −0.209 | 0.202 | 0.209 | 0.317 | −0.113 | 0.492 |
| MIP-1α | −0.149 | 0.365 | −0.091 | 0.673 | −0.094 | 0.569 | −0.098 | 0.554 | 0.145 | 0.488 | −0.185 | 0.261 |
| PDGF-BB | −0.191 | 0.244 | −0.318 | 0.13 | −0.212 | 0.194 | −0.096 | 0.562 | 0.276 | 0.183 | −0.141 | 0.392 |
| RANTES | 0.051 | 0.757 | −0.179 | 0.404 | −0.055 | 0.74 | 0.022 | 0.895 | −0.048 | 0.822 | −0.106 | 0.519 |
| TNF-α | −0.226 | 0.167 | −0.194 | 0.364 | −0.271 | 0.095 | −0.263 | 0.105 | 0.09 | 0.67 | −0.188 | 0.253 |
| ANP | **0.25** | **0.05** | −0.169 | 0.355 | 0.059 | 0.652 | 0.087 | 0.511 | −0.013 | 0.929 | 0.138 | 0.292 |

**Table 5**
Partial correlations between KP biomarkers and cognition.

| | Process. Speed $n = 72$ | | Attention n = 37 | | Working Mem. n = 72 | | Verb. Learning n = 72 | | Vis. Learning $n = 54$ | | Reasoning n = 72 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | r | p | r | p | r | p | r | p | r | p | r | p |
| TRP | 0.091 | 0.44 | −0.145 | 0.379 | −0.039 | 0.742 | 0.177 | 0.132 | **−0.265** | **0.048** | 0.041 | 0.728 |
| KYN | −0.16 | 0.172 | −0.02 | 0.903 | −0.05 | 0.67 | −0.033 | 0.777 | −0.181 | 0.183 | 0.05 | 0.672 |
| 3HK | −0.149 | 0.205 | −0.034 | 0.838 | −0.069 | 0.557 | −0.166 | 0.156 | −0.175 | 0.196 | −0.08 | 0.499 |
| KYNA | 0.141 | 0.23 | −0.144 | 0.383 | −0.002 | 0.983 | 0.157 | 0.183 | 0.059 | 0.665 | 0.02 | 0.863 |
| QU | −0.001 | 0.993 | 0.048 | 0.771 | 0.11 | 0.349 | 0.107 | 0.363 | 0.079 | 0.564 | 0.017 | 0.888 |
| KYN/Trp | −0.152 | 0.195 | 0.083 | 0.616 | −0.016 | 0.891 | −0.067 | 0.569 | −0.082 | 0.55 | 0.032 | 0.784 |
| QU/KYA | −0.123 | 0.298 | 0.089 | 0.589 | 0.11 | 0.349 | 0.019 | 0.872 | 0.051 | 0.712 | 0.027 | 0.818 |
| KYA/KYA | 0.193 | 0.099 | −0.042 | 0.799 | 0.167 | 0.156 | 0.161 | 0.171 | 0.248 | 0.065 | 0.059 | 0.616 |
| 3HK/KYN | 0.008 | 0.944 | 0.229 | 0.161 | 0.144 | 0.221 | −0.147 | 0.212 | 0.173 | 0.202 | −0.005 | 0.967 |

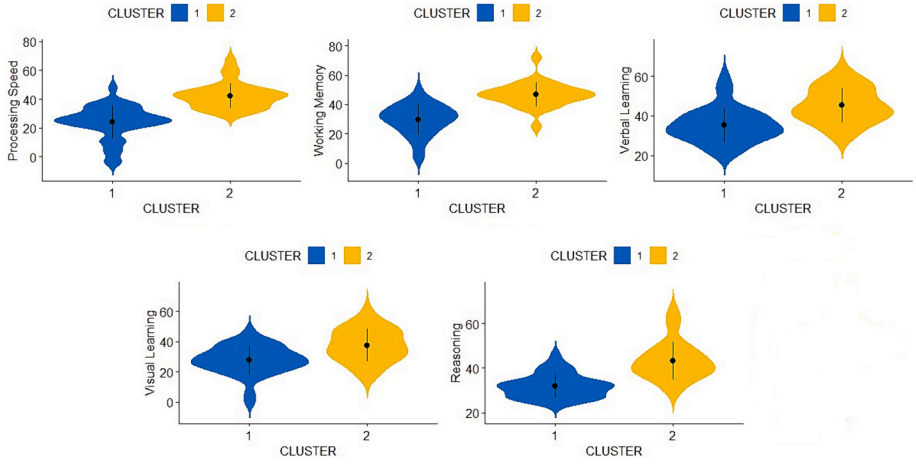


**Fig. 2.** Separation of the silhouettes based on cognition for Cluster 1 and Cluster 2.

associated with IL-17 A ($r = -0.567$; $p = 0.043$), IL-9 ($r = -0.562$; $p = 0.045$), TNF-α ($r = -0.640$; $p = 0.019$), MIP1α ($r = -0.587$; $p = 0.035$), PDGF-BB ($r = -0.693$; $p = 0.009$) and RANTES ($r = -0.623$; p = 0.023). However, MIP1α showed also a negative association with reaction times ($r = -0.581$; $p = 0.048$). With regards to the KP, KYNA levels showed a negative association with Reasoning (r = −0.409; $p = 0.047$) and QUIN a positive correlation with Attention ($r = -0.565$; $p = 0.018$). Details of partial correlations are reported in Table S4 (Supplementary Materials and Methods).

### *3.5. Relationships between basal biomarkers and cognition after the interventions*

To investigate the predictive role of the plasma biomarkers at baseline on the cognitive outcome after the interventions (CRT or AE or CRT + AE) we performed multiple stepwise regressions on the all sample using the Δ(T1-T0) of the MCCB scores as dependent variables. Using the ratios QUIN/KYNA, 3-HK/KYN, KYN/Trp and KYNA/KYN as predictors, 3-HK/KYN explained cognitive improvements in Processing speed (β = 0.349; $R^2 = 0.194$; $p = 0.028$) and Reasoning (β = 0.463; $R^2 = 0.247$; p = 0.002), while QUIN/KYNA negatively predicted the improvement in Reasoning (β = −0.358; $R^2 = 0.247$; $p = 0.014$). Finally, among the pro-inflammatory cytokines, using TNF-α, IL-17 A and ANP as predictors, it was shown that levels of TNF-α hampered improvements in Visual learning (β = −0.487; $R^2 = 0.182$; $p = 0.05$) (See Tables 6 and 7) (See Figs. 3 and 4).

## 4. Discussion

To our knowledge, this is the first study to address the effects of both inflammatory markers and KP metabolites on cognitive performance in schizophrenia, in particular to disentangle their differential impact depending on the cognitive phenotype and to test their predictive role on the cognitive outcome after rehabilitation.

We observed that cognitive functions in patients with a higher cognitive profile are primarily and adversely influenced by levels of cytokines and chemokines, rather than by KP metabolites. Conversely, in patients with a lower cognitive profile, KP metabolites tend to exert a more significant impact on cognitive functions compared to cytokines

**Table 6**
Regression model with QUIN/KYNA. 3-HK/KYN. KYN/Trp and KYNA/KYN as predictors and Δ(T1-T0) Processing Speed as dependent variable; $R^2 = 0.247$.

| | Beta | Std. Err. | B | Std. Err. | t(38) | p-level |
|---|---|---|---|---|---|---|
| Intercept | | | 0.309 | 0.214 | 1.446 | 0.156 |
| T0_3-HK/KYN ratio | 0.463 | 0.140 | 0.003 | 0.001 | 3.330 | 0.002 |
| T0_QA/KYNA ratio | −0.358 | 0.139 | −0.023 | 0.009 | −2.572 | 0.014 |

**Table 7**
Regression model with QUIN/KYNA. 3-HK/KYN. KYN/Trp and KYNA/KYN as predictors and Δ(T1-T0) Reasoning as dependent variable; $R^2 = 0.194$.

| | Beta | Std. Err. | B | Std. Err. | t(37) | p-level |
|---|---|---|---|---|---|---|
| Intercept | | | −0.357 | 0.165 | −2.161 | 0.037 |
| T0_QA/KYNA ratio | 0.248 | 0.161 | 0.01 | 0.006 | 1.534 | 0.133 |
| T0_3-HK/KYN ratio | 0.349 | 0.153 | 0.001 | 0.000 | 2.275 | 0.028 |
| T0_Kyn/Trp*1000 ratio | 0.191 | 0.164 | 0.005 | 0.004 | 1.168 | 0.250 |

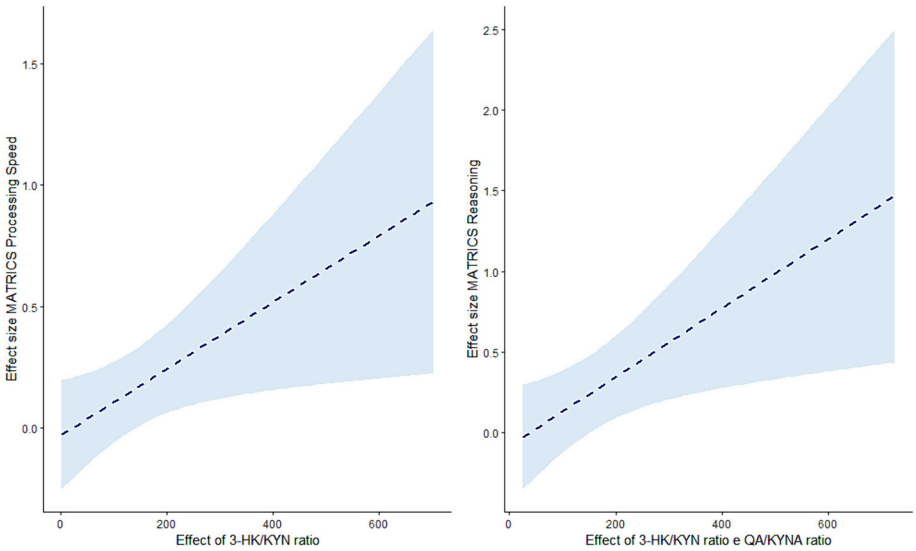


**Fig. 3.** Effect of 3HK/KYN ratio and 3HK/KYN and QUIN/KYNA ratio on Processing Speed.

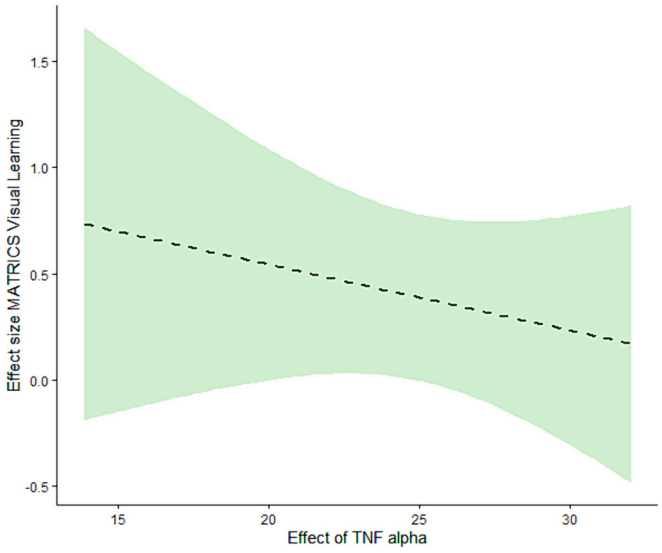


**Fig. 4.** Effect of TNF-α on Visual Learning.

and chemokines.

Our findings align with previous literature reviewed in Sapienza et al. (Sapienza et al., 2023b) demonstrating correlations between both inflammatory and KP measures and cognitive abilities in key domains. However, our results offer new insights into a potential differential impact of the two pathways, suggesting distinct patterns of association based on cognitive profiles.

Moreover, when assessing the influence of baseline markers on cognitive improvement after rehabilitative interventions, we identified significant effects of QUIN/KYNA, 3-HK/KYN, and TNF-α. The QUIN/KYNA ratio, along with TNF-α, negatively predicted cognitive improvements, indicating a detrimental role of QUIN and a positive role of KYNA, consistent with baseline findings. Conversely, 3-HK/KYN predicted favorable cognitive outcomes. Despite the property of the immune system to activate the KP, our mediation models did not show the ability of TNF-α to influence the impact of KP metabolites on cognitive functions. This was probably due to the low sample size.

Regarding the cross-sectional arm, the greater impact of inflammatory biomarkers on working memory in patients with a higher cognitive functioning might be due to a greater susceptibility to the oxidative stress and cytotoxicity exerted by neuroinflammation (Maas et al., 2017; Fourrier et al., 2019; Kindler et al., 2020; Patlola et al., 2023). It is to note that individuals with greater cortical volumes and WM integrity show less cognitive impairment and, for this reason, they might be more exposed to the detrimental effect of inflammation as the biological substrates of cognition are more preserved (Ehrlich et al., 2012; Castro-de-Araujo et al., 2018; Yamada et al., 2022; Kilian et al., 2022; Fan et al., 2022). As a matter of facts, neurons' dendrites and axons contributed to volume composition of the cortex with 30 % and 29 % respectively (Howes et al., 2023) and brain sub-inflammation induces neuron loss, enhanced synaptic pruning and white matter (WM) disruption (Zhang et al., 2016; Uranova et al., 2020; Michalczyk et al., 2022). Among these pathogenic factors, the oxidative stress is mainly involved in myelin disruption and cellular death, thus the loss of both somas and dendritic ramifications, while synaptic pruning is involved in the downsizing of dendritic arborizations and loss of synapses (Howes and McCutcheon, 2017; North et al., 2021). Overall, these pathogenic processes triggered by inflammation damage individuals with greater cognitive reserve the most, through a progressive reduction of cortical volumes (Vita et al., 2012; North et al., 2021; Kindler et al., 2020). The intriguing negative correlations observed between peripheral biomarkers MIP1α, RANTES, and PDGF-BB and working memory underscore the impact of systemic inflammation on cognitive functions. This finding supports the significance of brain-periphery immune crosstalk in determining cognitive impairment, as evidenced by previous studies (Cervenka et al., 2017; North et al., 2021), and the importance to target peripheral subinflammation, typical of the dysmetabolic condition associated to schizophrenia, with AE, to resize cognitive deficits (Della Guardia and Codella, 2021). In essence, it is conceivable that disrupted molecular-level circuits and a reduced number of neuronal somas may impede the retention of “data” in working memory. Considering patients with a lower cognitive profile, we found that the KP plays a prominent role on cognitive performance compared to neuroinflammation. One hypothesis is that the integrity of cortical layers is already compromised in these patients, then the pathogenic processes induced by inflammatory biomarkers cannot induce further significant cognitive impairments. Notably, KP metabolites due to a wide range of neuromodulatory, neurotoxic and neuroprotective properties might impact cognition when the action of inflammatory factors seemed less impactful (Sas et al., 2018; Sapienza et al., 2023b). Overall, in this sub-sample of patients the activation of the KP (as shown by higher KYN levels and KYN/Trp ratio) is detrimental to cognition as also shown by previous findings (Sapienza et al., 2023b), specifically to processing speed and visual learning.

However, implications for other cognitive domains depend on the activity of two of the most important enzymes of the pathway, thus on the metabolic activity along the two branches of the KP. If KYN is metabolized by KMO leading to the production of 3-HK, considering the 3-HK/KYN ratio as a proxy of KMO enzymatic activity, negative effects are observed, particularly in the domains of visual learning and attention. Differently, if KYN is converted into KYNA by KAT, positive effects were shown on Processing speed (Amori et al., 2009). Interestingly, KYNA showed strong antioxidant and neuroprotective properties and the ability to regulate neuronal excitability and plasticity by modulating the expression of cholinergic receptors via the inhibition of alpha 7 nAChR activity, which induces an increased density of non-7 nicotinic receptors (Hilmas et al., 2001; Lugo-Huitrón et al., 2011). Moreover, it elicits a negative allosteric modulation on NMDA receptors which can prevent excitotoxicity and a positive modulatory action at the binding site of the AMPA receptor which can enhance excitatory synaptic transmission (Prescott et al., 2006). Regarding 3-HK, known for its neurotoxic properties causing oxidative damage and cell death (Castellano-Gonzalez et al., 2019), it serves as a precursor to QUIN, an excitotoxin acting on NMDA receptors. There is evidence for a synergistic negative interaction between QUIN and 3-HK (Guidetti and Schwarcz, 1999). Activation of the KMO branch may thus lead to a dual negative impact on cognitive functions.

Regarding the results emerged in the longitudinal arm, the QUIN/KYNA ratio negatively predicted improvements in Reasoning. As abovementioned, several findings reported a neurotoxic effect of QUIN (Guillemin, 2012; Sas et al., 2018; Cathomas et al., 2021). Specifically, QUIN is an agonist at the NMDA receptor and the continuous stimulation of NMDA receptors can cause excitotoxic cell death (Prado De Carvalho et al., 1996; Brown et al., 1998; Shah et al., 2020). In addition to NMDA receptor agonism, it also induces lipid peroxidation (Rodríguez-Martínez et al., 2000), produces Reactive Oxygen Species (ROS), increases the inducible Nitric Oxide Synthase (iNOS) expression, decreases Superoxide dismutase (SOD) activity and causes mitochondrial dysfunction (Sahm et al., 2013). Moreover, it is also toxic to oligodendrocytes (Cammer, 2001), thus can be involved in demyelination processes. Interestingly, Cathomas et al. reported that QUIN levels were inversely related to the composite cognitive score in schizophrenia (Cathomas et al., 2021) and Cogo et al. described a QUIN/KYNA as a reliable biomarker of cognitive decline in individuals after stroke (Cogo et al., 2021). On the contrary, the 3-HK/KYN ratio, an index of KMO activity, showed the ability to predict the improvements in Processing speed and Reasoning. Such discrepancy with respect to the baseline findings might be explained by the dual action of 3-HK. Indeed, despite 3-HK is mainly described as neurotoxic, many findings showed neuroprotective and antioxidant properties of such molecule, highlighting its dual action (Colín-González et al., 2013; Colín-González et al., 2014). Indeed, 3-HK is capable of inducing oxidative damage and cell death but also to exert antioxidant and scavenging properties targeting ROS as nitric oxide (NO), oxygen (O2), hydroxide (HO) and peroxyl radical (ROO) (Goda et al., 1999; Leipnitz et al., 2007; Backhaus et al., 2008). As certain vitamins and metabolites that show this double behavior, the dual action of 3-HK is likely to depend on its concertation and/or the interactions with other molecules in the environment or on the modifications induced by these molecules on the environment (Colín-González et al., 2013). Therefore, the biological/molecular modifications induced by the rehabilitative strategies could enhance the neuroprotective properties of 3-HK in a synergistic manner. For instance, AE showed the ability to induce changes in the redox environment decreasing the glutathione (GSH) to oxidised glutathione (GSSG) ratio, an index of oxidative stress, and increasing malondialdehyde (Chapul et al., 2022). Interestingly, these changes could enhance the antioxidant properties of 3-HK. Overall, the equilibrium between the neurotoxic and neuroprotective attributes of neuroactive metabolites plays a crucial role in influencing processing speed and reasoning. This impact could stem from the balance of such compounds, which is important for the integrity of neural cytoarchitecture and the networks responsible for processing nervous signals, thus processing of the information. Another important finding is that TNF-α levels hamper the effect of rehabilitation strategies on Visual learning. Notably, TNF-α is one of the main pro-inflammatory cytokines involved in the pathogenesis of schizophrenia and several findings reported increased TNF-α levels in patients (Potvin et al., 2008; Miller et al., 2013; Upthegrove et al., 2014; Momtazmanesh et al., 2019). Specifically, a metanalysis by Upthegrove and colleagues including 570 First-episode Psychosis (FEP) patients found increased levels of several pro-inflammatory cytokines, and particularly TNF-α (Upthegrove et al., 2014). Moreover, associations between TNF-α and cognitive decline were also reported in schizophrenia and other populations (McAfoose et al., 2009; Morrens et al., 2022; Morrens et al., 2022), but the more interesting finding supporting the detrimental role of TNF-signaling during AE was reported by Morgan and colleagues, who demonstrated its negative modulatory effect on the cognitive improvements elicited by AE in mice (Morgan et al., 2018). Therefore, the pro-inflammatory state induced by basal TNF- α levels probably sustains the activation of microglia, neurodegeneration, WM disruption and increased synaptic pruning, hampering the cognitive improvements induced by rehabilitation strategies (North et al., 2021).

### 4.1. Limits and future directions

A major limitation of this study is the small sample size, especially in the longitudinal arm, hindering the inclusion of confounding factors and assessment of predictors for each intervention. Hypotheses are at times based on indirect evidence, warranting further validation in larger randomized controlled trials. Moreover, although MCCB is a validated and widely used scale for the cognitive assessment in schizophrenias, particularly in clinical trials (Nuechterlein et al., 2008) (Nuechterlein et al., 2023), it is quite long and complex. Therefore, we cannot rule out that the integrity and objectivity of data acquisition are not affected by such aspect. Another point to acknowledge is that the choice of the type of AE intervention may affect adherence, thus we opted for cycle-ergometer. Future studies should incorporate neuroimaging and a broader panel of biological markers to better understand the complex interactions among multiple biological systems and their potential as cognitive enhancement targets. Thorough clusterization based on specific cognitive functions would likely enhance the relationship between cognitive performance and its molecular underpinnings.

## 5. Conclusion

While preliminary, our findings are noteworthy as they indicate dissociated effects of inflammatory markers and kynurenines on cognitive performance in schizophrenia, depending on the cognitive phenotype of the patients. In particular, a predominant effect of inflammation is observed among patients with relatively preserved cognitive abilities, while the KP plays a major role in patients with more severe deficits. Furthermore, the predictive effects of QUIN/KYNA, 3-HK/KYN, and TNF-α on the extent of cognitive improvement not only support their direct relation to cognition but also suggest these pathways may play a role in the dynamic modulation of cognition. This indicates that they could serve as substrates influenced by ongoing training interventions and as potential targets for future drug discovery programs.

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## CRediT authorship contribution statement

**Jacopo Sapienza:** Writing – original draft, Conceptualization. **Giulia Agostoni:** Software, Formal analysis, Data curation. **Sofia Nasini:** Formal analysis. **Stefano Dall'Acqua:** Formal analysis. **Stefania Sut:** Formal analysis. **Marco Spangaro:** Project administration, Methodology. **Francesca Martini:** Methodology. **Margherita Bechi:** Project administration, Methodology. **Mariachiara Buonocore:** Methodology. **Giorgia Bigai:** Data curation. **Daniela Nocera:** Data curation. **Chiara Ave:** Data curation. **Carmelo Guglielmino:** Project administration. **Federica Cocchi:** Data curation. **Roberto Cavallaro:** Validation, Project administration. **Giacomo Deste:** Project administration. **Marta Bosia:** Writing – review & editing, Validation, Project administration, Methodology, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scog.2024.100328.

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