UNIVERSITA' VITA-SALUTE SAN RAFFAELE

CORSO DI DOTTORATO DI RICERCA IN NEUROSCIENZE COGNITIVE

Biological signatures of cognitive impairment in mood disorders

DoS: Prof. Francesco Benedetti

Tesi di DOTTORATO di RICERCA di Beatrice Bravi

matr. 019546

Ciclo di dottorato XXXVII

SSD MED/25

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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.

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

1) Bio-plex and PsychArray experiments were performed by Dr. Cristina Lorenzi and Dr. Sara Spadini, Psychiatry and Clinical Psychobiology Unit, Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy.
2) HPLC and LC-MS/MS experiments were performed by Prof. Stefano Comai, Dr. Stefania Sut, and Dr. Stefano Dall'Acqua, Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy.
3) MRI scans were performed by Valentina Novati, in collaboration with CERMAC (Centro Eccellenza Risonanza Magnetica ad Alto Campo), Scientific Institute Ospedale San Raffaele, Milan.

I declare that throughout the text, we reported some of the results of our previously published manuscript. In detail, the following manuscripts were repeatedly cited:

- Bravi B, Melloni EMT, Paolini M, Palladini M, Calesella F, Servidio L, Agnoletto E, Poletti S, Lorenzi C, Colombo C, Benedetti F. Choroid plexus volume is increased in mood disorders and associates with circulating inflammatory cytokines. Brain Behav Immun. 2024 Feb;116:52-61. doi: 10.1016/j.bbi.2023.11.036. Epub 2023 Nov 27. PMID: 38030049.

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ABSTRACT

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), are among the leading causes of disability worldwide, characterized by a high rate of non-responsiveness to canonical treatments. One of the most life-affecting conditions is represented by cognitive impairments, which worsen across illness duration and persist in euthymic phases. The kynurenine pathway (KP), a major metabolic route for tryptophan, could be a compelling candidate to be investigated due to its multifaceted role in modulating neuroinflammation, glutamatergic neurotransmission, and its implication in cardiovascular diseases, possibly providing novel insights into the pathophysiology of mood disorders. We conducted a comprehensive investigation KP in mood disorders, focusing on its relationship with inflammation, its effects on neurovascular mechanisms, and how these interactions contribute to cognitive dysfunction in patients with MDD and BD. We first explored the impact of peripheral analytes on KP activity, highlighting that pro-inflammatory cytokines and growth factors were significantly linked to indoleamine 2,3-dioxygenase (IDO) activation. The association between KP metabolites and choroid plexus (ChP) volume was then examined, revealing an opposite effect of quinolinic acid (QA) and kynurenic acid (KynA) on ChP volume, suggesting a potential impact on cerebrospinal fluid-blood-brain barrier permeability. We then explored how KP metabolites modulate neurovascular coupling within the default mode network (DMN), as measured by fractional amplitude of low-frequency fluctuations (fALFF) and hemodynamic response function (HRF) parameters. We found that metabolites affecting DMN dynamics predicted cognitive performance, with time to peak (TTP) and full width at half maximum (FWHM) mediating the impact of KP metabolites on cognition. We then examined the genetic contribution to KP activity: the polygenic risk score (PRS) for Kynurenine significantly predicted plasma Kyn levels and was associated with white matter hyperintensities (WMHs) and microstructural integrity, affecting in the end cognitive functioning. The influence of the SH2B3 rs3184504 SNP on the relationship between Kyn PRS and WMHs further highlighted the shared genetic underpinnings between mood disorders and cardiometabolic conditions. Overall, this study underscores the complex interplay between inflammation, genetic predisposition, and neurovascular processes mediated by the KP, offering new insights into the mechanisms underlying cognitive dysfunction in mood disorders.

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ACRONYMS AND ABBREVIATIONS

3-HK: 3-hydroxykynurenine

5-HIAA: 5-hydroxy indoleacetic acid

5-HT: 5-hydroxytryptamine/serotonin

ACC: anterior cingulate cortex

AD: axial diffusivity

AFNI: Analysis of Functional NeuroImages

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

ANK3: ankyrin 3

AQP4: aquaporin 4

ATR: anterior thalamic radiation

BACS: Brief Assessment of Cognition in Schizophrenia

basic FGF: basic fibroblast growth factor

BBB: blood-brain barrier

BCSFB: blood cerebrospinal fluid barrier

BD: bipolar disorder

BDNF: brain-derived neurotrophic factor

BET: brain extraction tool

BOLD: blood oxygenation level dependent

Ca2: calcium

CACNA1C: Calcium Voltage-Gated Channel Subunit Alpha1 C

CAD: coronary artery disease

CB: cingulum bundle

CBF: cerebral blood flow

CC: corpus callosum

CCL: C-C motif ligand

ChP: choroid plexus

COMT: Catechol-O-methyltransferase

CR: corona radiata

CRP: C-reactive protein

CSF: cerebrospinal fluid

CVD: cardiovascular disease

CXCL: C-X-C motif chemokine ligand

dACC: dorsal anterior cingulate cortex

dlPFC: dorsolateral prefrontal cortex

DMN: default mode network

DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th edition)

DTI: diffusion tensor imaging

FA: fractional anisotropy

fALFF: fractional amplitude of low-frequency fluctuations

FC: functional connectivity

FDR: false discovery rate

FGF: fibroblast growth factor

FLAIR: Fluid Attenuated Inversion Recovery

fMRI: functional magnetic resonance imaging

FSL: FMRIB Software Library

FWHM: full width at half maximum

FX: fornix

G-CSF: granulocyte colony stimulating factor

GLZM: generalized linear model

GM: grey matter

GM-CSF: granulocyte macrophage colony stimulating factor

GWAS: genome-wide association studies

HC: healthy controls

HDRS-21: 21-Hamilton Depression Rating Scale

HGF: hepatocyte growth factor

HPA: hypothalamic–pituitary–adrenal axis

HPLC: high-performance liquid chromatography

HRF: hemodynamic response function

HTR2A: 5-Hydroxytryptamine Receptor 2A

HTTLPR: serotonin transporter promoter polymorphism

ICV: intracranial volume

IDO: indoleamine-2,3-dioxygenase

IFN: interferon

IFOF: inferior fronto-occipital fasciculus

IL: interleukin

IL-1Ra: interleukin-1 receptor antagonist

ILF: inferior longitudinal fasciculus

K: potassium

KP: kynurenine pathway

Kyn: kynurenine

KynA: kynurenic acid

LC-MS: liquid chromatography–mass spectrometry

LIF: leukemia Inhibitory Factor

LR: likelihood ratio

LST: Lesion Segmentation Tool

MAF: minor allele frequency

M-CSF: macrophage colony stimulating factor

MCP: monocyte chemoattractant protein

MD: mean diffusivity

MDD: major depressive disorder

MIF: macrophage migration inhibitory factor

MIG: monokine Induced by Gamma interferon

MIP: macrophage inflammatory protein

ML: machine learning

MLR: monocyte to lymphocytes ratio

MNI: Montreal Neurological Institute

MRI: magnetic resonance imaging

NIPALS: Nonlinear Iterative Partial Least Squares

NK: natural killer

NLR: neutrophils to lymphocytes ratio

NMDA: N-methyl-D-aspartate

NO: nitric oxide

NVU: neurovascular unit

PDGF-BB: platelet-derived growth factor-BB

PET: positron emission tomography

PFC: prefrontal cortex

PGC: Psychiatric Genomics Consortium

PLR: platelets to lymphocytes ratio

PLS: partial least square

PRS: polygenic risk score

QA: quinolinic acid

QC: quality control

RCT: randomised control trial

RD: radial diffusivity

RDoC: Research Domain Criteria

RH: response height

ROI: region of interest

ROS: reactive oxygen species

rsFC: resting-state functional connectivity

rs-fMRI: resting-state functional magnetic resonance imaging

SCF: stem cell factor

SCGF-β: stem cell growth factor β

SII: systemic immuno-inflammatory index

SLF: superior longitudinal fasciculus

SNP: single nucleotide polymorphism

SPM: Statistical Parametric Mapping

TBSS: tract-based spatial statistics

TDO: tryptophan-2,3-dioxygenase

TFCE: threshold-free cluster enhancement

Th: T-helper

TIV: total intracranial volume

TNF: tumor necrosis factor

Trp: tryptophan

TRAIL: TNF-related apoptosis-inducing ligand

TSPO: translocator protein

TTP: time to peak

UF: uncinate fasciculus

VEGF: vascular endothelial growth factor

VIF: variance inflation factor

VIP: variable importance in projection

vPFC: ventral prefrontal cortex

vlPFC: ventrolateral prefrontal cortex

WM: white matter

WMHs: white matter hyperintensities

β-NGF: β-nerve growth factor

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INTRODUCTION

Mood disorders are defined as mental health conditions characterized by pervasive and marked disruptions in emotional states that persist across time and situations. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), classifies mood disorders mainly as Major Depressive Disorder (MDD) and Bipolar Disorder (BD) (American Psychiatric Association, 2013). MDD is characterized by persistent feelings of sadness and melancholy, whereas BD involves intense mood swings between depressive lows and hyperthymic highs.

Mood disorders are considered among the major sources of disabilities worldwide. The global burden associated with psychiatric disorders is rising, with depressive disorders accounting for 40% of it (Whiteford *et al*, 2013) occupying the sixth place for life-affecting disabilities (Diseases & Injuries, 2020).

The disability associated with these psychopathological conditions is also given by the high rate of unresponsiveness to treatment and suicidality, both having a relevant weight on patients' quality of life (Ferrari *et al*, 2016). This is also due to an initial misdiagnosis of the disorder, specifically for BD. Indeed, data report that a third of patients with MDD do not respond to treatment (Al-Harbi, 2012; Fekadu *et al*, 2009; Kurian *et al*, 2009; Pandarakalam, 2018) and that up to 40% of patients with BD are resistant to treatment with lithium (Post, 1990), with 37% of them relapsing into depression or mania within 12 months (Grande *et al*, 2016; Radua *et al*, 2017).

In this frame, the search for biomarkers of the diseases becomes then a fundamental priority (Zarate *et al*, 2013) to enrich the multifaceted etiopathological picture of BD and MDD and to identify new targets for therapeutic interventions.

Mood disorders

Major depressive disorder

MDD is the most commonly diagnosed depressive disorder and ranks among the top ten causes of lifelong disability worldwide (Diseases & Injuries, 2020). According to the World Mental Health Survey, MDD has a global prevalence of approximately 6% with variation observed among different age groups. The typical age of onset is around 25 years, with women being twice as likely as men to develop

MDD, a disparity attributed to a combination of biological, hormonal, and social factors (Bromet *et al*, 2011; Kuehner, 2017).

MDD is defined by at least one major depressive episodes (MDE) lasting a minimum of two weeks, marked by enduring sadness, profound emotional distress, and overwhelming feelings of hopelessness. Another key symptom is anhedonia, or the inability to find pleasure in daily activities. Individuals often experience exhaustion and reduced energy, making even simple tasks feel overwhelming. Cognitive difficulties indeed, such as problems with concentration, memory, and thought processes, are also common, and in severe cases, significant memory issues may occur (American Psychiatric Association, 2013; Goodwin & Jamison, 2007). In severe cases, cognitive impairments can mimic those seen in neurodegenerative conditions (Conradi *et al*, 2011). Sleep disturbances, appetite changes, and psychomotor agitation or retardation are other key symptoms (Lam *et al*, 2014; Nutt *et al*, 2008).

Depressive episodes typically last between three to seven months, with most patients recovering within a year. However, only one-quarter of patients achieve remission within six months, and over half continue to experience MDD for two years or longer (Otte *et al*, 2016). Furthermore, the risk of relapse remains high, with some studies indicating that up to 80% of individuals who have had a major depressive episode will face another recurrence at some point in their lives (Monroe & Harkness, 2011).

Bipolar disorder

BD is characterised by the presence of cycles of depressive and hypomanic or manic episodes. In these conditions the mood is alternately between two poles: it can be high and euphoric or depressed (American Psychiatric Association, 2013).

BD is divided into two types: type I (BD-I) and type II (BD-II). BD-I is defined by the occurrence of manic episodes, with the eventual presence of hypomanic or major depressive episodes. In contrast, BD-II is characterized by recurring hypomanic and depressive episodes, without any history of manic episodes and with the predominance of depressive phases (American Psychiatric Association, 2013; Goodwin & Jamison, 2007). Manic episodes consist of the presence of a euphoric and excited mood, or irritability. Other symptoms included in manic episodes are

(American Psychiatric Association, 2013; King *et al*, 2013): hypertrophic self-esteem, often accompanied by delusions of grandeur, where abilities are unrealistically high; reduced need for sleep with the feeling of increased energy to carry out his activities even with a few hours of sleep, (an aspect that differentiates the symptom from insomnia); increased loquacity and pressure to keep talking accompanied by subjective experience that racing thoughts; distractibility and difficulty maintaining attention that is easily diverted to irrelevant objects; increased targeted activity (work, sex, or school) or psychomotor agitation; involvement in potentially risky activities or activities with harmful consequences such as uncontrolled shopping, inappropriate sexual behaviour, or reckless financial investment.

Hypomania is a less severe form of mania, characterized by milder symptoms that do not significantly impair daily functioning. Although there is a striking qualitative resemblance in symptoms with mania, the fundamental difference that characterises hypomania is that it does not typically lead to hospitalization, does not present psychotic manifestations, and tends to have a shorter duration (Benazzi, 2007). The burden of the disease is the severe emotional symptomatology associated with early mortality due to a high suicide rate (Pompili *et al*, 2009). About 50% of BD patients indeed attempt suicide during their lifetime and 11% of such attempts result in premature death (Jamison, 2000).

BD-I's worldwide incidence is estimated to be around 0.5%, disproportionally affecting males compared with women, while BD-II affects approximately 0.3% of the population and is more common in females. BD-I tends to have an earlier onset, with a mean age of 18.4 years, whereas BD-II typically begins around age 20 (Merikangas *et al*, 2011). However, there may be an underestimation of the prevalence of BDs because of the difficulty of diagnosis, often due to the late onset of manic and hypomanic episodes, leading to a unipolar diagnosis (Fagiolini *et al*, 2013). Indeed, about 60% of people with BD receive an initial misdiagnosis of MDD (Hirschfeld *et al*, 2003).

Symptoms affect about half of the illness course of both BD-I and BD-II, with depressive phases being significantly more frequent than manic or hypomanic ones (Judd *et al*, 2002). Consequently, the prevalence of bipolar II disorder is predominantly

female, as women are more prone to major depressive episodes (Leibenluft, 1996; Piccinelli & Wilkinson, 2000).

Biological correlates of mood disorders

Genetics

Research has uncovered numerous genetic, neural, and inflammatory alterations in both bipolar disorder (BD) and major depressive disorder (MDD), with significant heritability indicated for both conditions. Twin studies estimate the heritability of BD to be around 60–85%, pointing to a strong genetic influence (Barnett & Smoller, 2009; Smoller & Finn, 2003), while MDD shows a more moderate heritability of about 35% (Sullivan *et al*, 2000). Early genetic investigations into BD, largely focused on linkage analysis, struggled to capture the complexity of its inheritance patterns (Prathikanti & McMahon, 2001). Although some candidate genes, such as SLC6A4 and DAOA, were highlighted as relevant in BD (Allen *et al*, 2008; Detera-Wadleigh *et al*, 2007), these studies yielded inconsistent results. Similarly, candidate gene studies in MDD, focusing on genes like BDNF, COMT, HTR2A, and HTTLPR were largely inconclusive (Border *et al*, 2019), highlighting the challenges in identifying key loci, suggesting that both mood disorders are polygenic conditions (McIntosh *et al*, 2019), paving the way to the development of Polygenic Risk Scores (PRS).

Genome-wide association studies (GWAS) have significantly advanced the understanding of the genetic basis of both BD and MDD. The largest GWAS for BD, identified ANK3 and CACNA1C as key genes linked to the disorder (Mullins *et al*, 2021). These genes are implicated in crucial neural processes, such as axonal myelination and synaptic signalling (Belmonte Mahon *et al*, 2011; Hayashi *et al*, 2015). On the other hand, TRANK1 has also been identified as a gene associated with BD that encodes a protein that may be involved in maintaining the integrity of the BBB (Schiavone *et al*, 2017). The most extensive GWAS to date, encompassing over a million participants, identified 223 significant single-nucleotide polymorphisms (SNPs) which represent only a small fraction of the genetic risk for the disorder, emphasizing its polygenic nature (Levey *et al*, 2021; McIntosh *et al.*, 2019).

Despite these advances, SNP-based heritability estimates for BD are much lower (~20%) than those reported by twin studies, suggesting that many genetic factors remain undiscovered (Mullins *et al.*, 2021). This gap is also present in MDD, where large-scale studies have found that common genetic variants explain only a fraction of the disorder's overall heritability (Major Depressive Disorder Working Group of the Psychiatric *et al*, 2013). Both BD and MDD are highly heterogeneous conditions, with genetic studies indicating overlap between BD and schizophrenia, as well as a closer genetic relationship between BD-II and MDD compared to BD-I (Brainstorm *et al*, 2018; Mullins *et al.*, 2021). Additionally, several genes associated with circadian regulation, including CLOCK and PER3, have been linked to mood disorders, influencing the onset and relapse of both BD and MDD (Etain *et al*, 2017; Larsen *et al*, 2012). Interestingly, research showed that CACNA1C and ANK3 are key genes involved in both BD and cardiometabolic regulation, while MDD shares genetic loci with cardiometabolic traits linked to insulin regulation and inflammation (Torgersen *et al*, 2022). GWAS have revealed a strong genetic overlap between mood disorders and cardiometabolic diseases, with PRS of MDD and BD increasing the risk for type 2 diabetes and coronary artery disease (CAD) (Amare *et al*, 2017). Despite this, large cohort studies have been essential for uncovering numerous risk loci, contributing to a better understanding of the genetic architecture of mood disorders.

MRI studies

Neurobiological underpinnings of mood disorders have been widely studied using magnetic resonance imaging (MRI), revealing impairments in both structural and functional connectivity in depressed patients. The emotional instability and cognitive dysfunctions observed in both MDD and BD may result from abnormalities primarily affecting the cortico-limbic system (Price & Drevets, 2010), which governs emotional regulation. This system integrates emotion with cognition, leading to the behavioural manifestations characteristic observed in mood disorders (Chen *et al*, 2018b). Several MRI studies have focused on examining these areas from both a structural and functional connectivity perspective.

Functional connectivity

In terms of functional connectivity, both MDD and BD patients display abnormal patterns in resting-state functional connectivity (rsFC) and during task-based functional MRI (fMRI). Both disorders exhibit increased activation in key emotional processing regions such as the amygdala, dorsal anterior cingulate cortex (dACC), and insula, coupled with reduced activity when processing negative stimuli of the dorsal system including the dorsolateral prefrontal cortex (dlPFC) involved in cognitive control (Frodl *et al*, 2010; Matthews *et al*, 2008). This imbalance between heightened emotional reactivity and impaired cognitive couples with the reduced integrity of WM tracts part of the system better described below.

BD, in particular, shows a marked imbalance between overactivity in the ventral emotional system and underactivity in the dorsal cognitive system (Vai *et al*, 2019). This imbalance leads to mood instability and emotional dysregulation characteristic of BD, but similar patterns of hyperactive emotional regions and hypoactive cognitive regions are also seen in MDD. Meta-analyses have reported reduced activation in the ventrolateral prefrontal cortex (vlPFC), along with increased limbic activation in both disorders (Chen *et al*, 2011; Delvecchio *et al*, 2012).

Furthermore, both disorders exhibit weakened task-based functional connectivity between the dlPFC and amygdala during emotion regulation tasks (Anticevic *et al*, 2013). MDD and BD patients showed abnormal connectivity patterns within the default mode network (DMN) (Doucet *et al*, 2017; Wang *et al*, 2017), which is involved in self-referential thinking and emotional regulation (Fransson, 2005). The DMN is thought to facilitate intrinsic, task-independent thinking rather than processing external stimuli. Studies have shown that the greater the suppression of DMN activity, the better individuals perform on tasks that require attention to external stimuli. In a healthy brain, stronger DMN suppression is also linked to improved memory formation, indicating its role in balancing internal thought with task-related focus (Daselaar *et al*, 2004; Daselaar *et al*, 2009). In both MDD and BD, an increased global signal representation within the DMN has been found, reflecting abnormal connectivity within and between networks (Kaiser *et al*, 2015; Scalabrini *et al*, 2020). Hyperactivation of the DMN in mood disorders contributes to cognitive and emotional symptoms, such as difficulty disengaging from introspective thought patterns like

rumination (Whitfield-Gabrieli & Ford, 2012). This overactivity prevents individuals from shifting their focus to sensory-based external stimuli, further exacerbating their inability to regulate attention and emotions effectively. This persistent inward focus is a hallmark of depressive symptoms, limiting their capacity to engage with the external environment. For example, instead of the typical anticorrelation seen in HCs, a positive association between DMN and executive network occurs (Chai *et al*, 2011a). This dysregulation is further evident in patients with MDD and BD, who display a failure to suppress DMN activity during goal-oriented tasks. This failure is linked to poorer task performance, as efficient task engagement normally requires DMN deactivation (Eichele *et al*, 2008; Grimm *et al*, 2011; Sheline *et al*, 2010; Zarp Petersen *et al*, 2022).

Indeed, beyond traditional cortico-limbic circuits, altered connectivity in fronto-parietal networks, which are involved in executive function and attention, further contributes to cognitive deficits in mood disorders (Schultz *et al*, 2018; Zweerings *et al*, 2019).

New insights from functional connectivity alterations in mood disorders also came from studies evaluating spontaneous neural activity in patients. In particular, the fractional amplitude of low-frequency fluctuation (fALFF) derived from resting state fMRI (rs-fMRI) seemed to be an effective measure to capture the intensity of regional spontaneous brain activity, less susceptible to physiological noise signals than ALFF (Zou *et al*, 2008). More specifically, fALFF is calculated as the ratio of the power spectrum in the low-frequency range (0.01–0.08 Hz) to that of the entire frequency range. In brain disease, a decreased fALFF in resting state fMRI predicts variations in hemodynamic response at rest (Bailes *et al*, 2023), and may mark lesion-induced neurovascular uncoupling (Agarwal *et al*, 2017; Agarwal *et al*, 2021). Indeed, fALFF also associates with cerebral blood flow (CBF) in healthy subjects (Hu *et al*, 2019). During resting state, fALFF within regions part of the DMN showed to be increased, as the network activity emerged when the brain is not involved in goal-oriented tasks (Greicius *et al*, 2003; Zou *et al.*, 2008). Interestingly, and in line with previous findings, patients with mood disorders exhibit higher fALFF levels in areas part of the DMN compared to controls (Gao *et al*, 2021; Long *et al*, 2020; Marino *et al*, 2021; Runia *et al*, 2022). This suggests hyperactivity within the DMN, which may drive excessive neural activity in these regions, possibly contributing to the imbalance

between networks observed in depressive symptomatology (Martino *et al*, 2016; Seeley, 2019).

Structural connectivity

White matter (WM) abnormalities have been largely found in both MDD and BD, with WM integrity alterations affecting critical pathways involved in emotional regulation, cognition, and interhemispheric communication (Favre *et al*, 2019; Masuda *et al*, 2020; van Velzen *et al*, 2020). DTI (Diffusion Tensor Imaging) is the primary technique for investigating white matter integrity bundles by measuring the diffusion properties of water molecules in the brain (Assaf & Pasternak, 2008; Le Bihan *et al*, 2001). Key WM tracts such as the anterior thalamic radiation (ATR) and cingulum bundle (CB) show significant reductions in integrity (Bracht *et al*, 2014; Favre *et al.*, 2019; Wang *et al*, 2008a; Wise *et al*, 2016), disrupting the communication between limbic regions (e.g., amygdala, hippocampus) and the prefrontal cortex (PFC), which is critical for cognitive control and emotional processing (Bubb *et al*, 2018). These tracts are essential for relaying emotional and cognitive information, and their impairment contributes to the emotional instability and cognitive deficits commonly observed in both disorders (Schermuly *et al*, 2010). In addition, the uncinate fasciculus (UF), which connects the anterior temporal lobe to the PFC, is another key tract affected in both MDD and BD (Chaddock *et al*, 2009; Favre *et al.*, 2019; van Velzen *et al.*, 2020). Damage to the UF, frequently linked to emotional regulation difficulties, has been consistently observed in these disorders, suggesting that impaired communication between these regions plays a role in mood dysregulation, being coherently correlated with the decrease in rs-FC between the anterior cingulate cortex and the amygdala (Wang *et al*, 2009). The superior longitudinal fasciculus (SLF), which connects the frontal and parietal lobes, is also affected, (Benedetti *et al*, 2011; Chaddock *et al.*, 2009; Liao *et al*, 2013; Mahon *et al*, 2009; Zeng *et al*, 2021), contributing to attentional and executive function deficits (Wang *et al*, 2024). Both MDD and BD also exhibit alterations in corpus callosum (CC) and corona radiata (CR) (Benedetti *et al.*, 2011; Chaddock *et al.*, 2009; Favre *et al.*, 2019; van Velzen *et al.*, 2020; Wang *et al*, 2008b; Wise *et al.*, 2016). Moreover, recent studies have highlighted the inferior fronto-occipital fasciculus (IFOF) and inferior longitudinal

fasciculus (ILF) as additional WM tracts showing reduced integrity in MDD and BD (Chaddock *et al.*, 2009; Mahon *et al.*, 2009). These tracts, which connect visual and emotional processing regions, are disrupted, affecting sensory information processing (Rollans *et al*, 2017) and its integration with emotional responses, further contributing to mood instability (Lai & Wu, 2013). Other interesting results concern unaffected first-degree relatives of patients with BD. It has been observed that there is a reduction in fractional anisotropy in the uncinate fasciculus and superior longitudinal fasciculus in these subjects (Emsell *et al*, 2014). This indicates a genetic variability that could underline the presence of an endophenotype of BD that concerns the integrity of WM as a variable of a hereditary trait (Vai *et al*, 2014).

Immunity/Inflammation

Sickness behaviour

In the last decades, there has been an increasing amount of research dedicated to investigating the immune system's role in psychiatric disorders (Blume *et al*, 2011; Maes, 1999; Maes *et al*, 1995a). The initial advancements were made through the observation of "sickness behaviour", a psychophysiological condition characterized by symptoms like fatigue, anhedonia, and social withdrawal, suppressed libido and sexual behaviour, body weight loss, which arises in response to inflammatory processes (Benedetti *et al*, 2020; Dantzer, 2001; Fu *et al*, 2010; Yirmiya *et al*, 1999). All these symptoms are linked to the inflammatory body reaction and share different phenomenological aspects with depression (Connor & Leonard, 1998; Dantzer *et al*, 1999; Leonard, 2001; Maes, 1999; Maes *et al.*, 1995a). These findings align with the fact that depression prevalence ranges from 5% to 40% among patients with medical conditions, with higher rates observed in those with inflammatory diseases, reaching 50% in patients with autoimmune diseases (Hosaka *et al*, 1999; Pryce & Fontana, 2017). Together with evidence from the administration of pro-inflammatory cytokines such as interferon-α (IFN-α) and tumour necrosis factor-α (TNF-α) as immunotherapies in patients with hepatitis B and cancer with subsequent onset of depressive symptoms (Anisman & Merali, 2003; Meyers, 1999; Pestka *et al*, 2004; Pollak & Yirmiya, 2002), and the antidepressant effects of antibody treatment such as anti-TNF therapies in patients with autoimmune diseases, fMRI studies in individuals

vaccinated against typhoid have provided further evidence of the inflammatory component in depression pathophysiology. Following vaccination increases in IL-6 correlate with depression-like symptoms and alterations in brain circuits, including heightened activity in the subgenual anterior cingulate cortex (sACC) and reduced connectivity between the sACC and the amygdala, medial prefrontal cortex, and nucleus accumbens (Harrison *et al*, 2009). These changes, modulated by peripheral IL-6, suggested a direct link between peripheral inflammation and neural pathways involved in emotional regulation, highlighting the role of cytokines in depressive symptoms.

Markers of inflammation

The investigation of immune-inflammatory abnormalities in mood disorders has been shown to influence key processes related to mood, emotion, and cognition because of the strong spillover effects on neurotransmission, microglial activation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and alterations in brain plasticity (Dantzer, 2018; Najjar *et al*, 2013a). A plethora of research highlighted the presence of an alteration of immune-inflammatory setpoints in mood disorders.

C-reactive protein (CRP) is an acute-phase protein that increases during acute and chronic inflammatory conditions, playing a key role in the innate immune response as an early defence mechanism (Sproston & Ashworth, 2018). Its elevated levels were consistently reported to be abnormal compared with healthy controls in both MDD and BD (Fernandes *et al*, 2016; Haapakoski *et al*, 2015; Halaris *et al*, 2022), being also associated with poorer cognitive performance in these patients (Dickerson *et al*, 2013; Hope *et al*, 2015). Both conditions exhibit heightened inflammatory markers such as IL-1β, IL-6, TNF-α, and IFN-γ key cytokines involved in managing the body's response to infection and stress (Barbosa *et al*, 2011; Kim *et al*, 2007; Kohler *et al*, 2017; Munkholm *et al*, 2013; O'Brien *et al*, 2006; Spoelma *et al*, 2023). In MDD, elevated levels of these pro-inflammatory cytokines have been linked to symptom severity, including sleep disturbances and anhedonia (Motivala *et al*, 2005; Thomas *et al*, 2005). Depressive disorders often occur after early-life immunological insults with increases in cytokines levels, suggesting causality between inflammation and MDD (Au *et al*, 2015; Khandaker *et al*, 2014). A recent meta-analysis reported also elevated

levels of other peripheral cytokines in MDD compared to healthy controls: IL-10, soluble IL-2 receptor, IL-13, IL-18, IL-12, the IL-1 receptor antagonist, and the soluble TNF receptor 2 (Kohler *et al.*, 2017). For BD patients during a depressive phase, results are more inconclusive, but cytokines more reported to be associated with the disease were soluble IL-2, IL-6, and TNF receptors (Goldsmith *et al*, 2016).

Furthermore, both MDD and BD patients showed higher levels of anti-inflammatory cytokines such as IL-10 and IL-4 compared with healthy people (Kohler *et al.*, 2017; Mora *et al*, 2019; Munkholm *et al.*, 2013). This could represent the immune system's effort to antagonize the proinflammatory activity abnormally present in these populations of disease (Mao *et al*, 2018).

Interestingly lithium therapy in BD patients in euthymia has been shown to downregulate cytokine levels, possibly through the inhibition of glycogen synthase kinase-3 (GSK-3), a key regulator of cytokine synthesis and immune reactions (van den Ameele *et al*, 2016). Similarly, antidepressants like venlafaxine and paroxetine were shown to downregulate cytokines like TNF-α, IL-6, IL-1β, and COX-2 in MDD patients (Chen *et al*, 2018a; Patel *et al*, 2023).

Despite common findings, more frequently reported, results in literature are not all in agreement, probably due to the heterogeneity of the disease and to the availability of different assay techniques used to detect plasma analytes (Poletti *et al*, 2024a). Moreover, altered levels of expression of different chemokines were detected in BD: increase of CCL3, CCL4, CCL5, CCL8, CCL11, CCL24, CXCL10 (Barbosa *et al*, 2013; Brietzke *et al*, 2009; Munkholm *et al.*, 2013; Poletti *et al*, 2021b). In MDD research studies mainly report CCL2, CCL8, CCL20, CCL21, and CXCL8 to be associated with the disease (Milenkovic *et al*, 2019; Poletti *et al.*, 2021b).

These proteins are a family of chemotactic cytokines related to the recruitment of immune cells such as leukocytes and monocytes (CCL3, CCL4, CCL5, CCL8), but also natural killer cells (CXCL10), promoting their chemotactic migration into the brain (Arima *et al*, 2012; Ge *et al*, 2008) and within the CNS modulating the activity of microglia (Engelhardt & Ransohoff, 2012; Rostène *et al*, 2011).

Focusing on cell populations, both MDD and BD are characterised by innate and adaptive immune dysfunction (Haapakoski *et al*, 2016; Medina-Rodriguez *et al*, 2018). These include T-cell deficiencies and elevated markers of inflammation driven

by macrophage and monocyte activation (Simon *et al*, 2021). T cells play a central role in adaptive immunity and, along with natural killer (NK) cells, contribute to and regulate the cell-mediated immune response, while monocytes/macrophages are the main actors of the innate response with direct activity of phagocytosis of cellular debris and circulating pathogens and release of cytokines, dampening inflammatory responses in general (Chaintreuil *et al*, 2023). Meta-analytic findings suggest that MDD is associated also with reduced NK cell cytotoxicity and lower NK and T helper (Th) cell counts (Grosse *et al*, 2016; Miller, 2010; Zorrilla *et al*, 2001), though some studies have reported contradictory results (Hosseini *et al*, 2007).

In BD patients, hyperactivity of the Th1 and Th2 systems, which regulate pro-inflammatory and anti-inflammatory responses, has been established (Kim *et al*, 2004; Liu *et al*, 2004). Th1 cells promote cellular immunity by activating macrophages and cytotoxic T cells, while Th2 cells stimulate antibody production. Additionally, abnormalities in the Th17 system, involved in macrophage activation through IL-17 and IL-22 production, suggest that inflammation in BD is driven by Th1 and Th17 hyperactivity. The Th2 system and regulatory T cells counterbalance this to maintain immune balance (Poletti *et al*, 2017).

To translate these results into an easy-to-assess method for investigating immune-related changes in diseases, comparing blood count ratios like Neutrophil/Lymphocyte ratio (NLR), Platelet/Lymphocyte ratio (PLR), and Monocyte/Lymphocyte ratio (MLR), has proven to be an effective tool (Cheng *et al*, 2022). More interestingly, the systemic immune-inflammation index (SII) is a comprehensive measure of all cell counts ((neutrophils x platelets)/lymphocytes), proven to capture the presence of inflammatory states in various diseases like cancer, COVID-19, cardiovascular disease, but also depression (Cui *et al*, 2023; Mangoni & Zinellu, 2023; Wei *et al*, 2022; Ye *et al*, 2022; Zhong *et al*, 2017).

The evidence that systemic inflammatory phenomena are accompanied by neuroinflammation is given through post-mortem and in vivo positron emission tomography (PET) studies. Post-mortem brains of patients who died by suicide had a significant increase of activated microglia compared to healthy controls (Naggan *et al*, 2023; Torres-Platas *et al*, 2014), even if results are contrasting (Schnieder *et al*, 2014; Sneeboer *et al*, 2019). On the other hand, PET studies targeting the 18-kDA

translocator protein (TSPO) in the mitochondrial membrane of microglia, whose expression increases as part of neuroinflammatory reactions, revealed that mood disorder patients showed increased ligand uptake compared with healthy controls mainly in ACC, PFC, hippocampus, and insula, results confirmed also by meta-analyses (Eggerstorfer *et al*, 2022; Gritti *et al*, 2021; Haarman *et al*, 2016). Interestingly, the rate of microglia activation has been associated with peripheral inflammatory cytokines (Drake *et al*, 2011).

Activated microglia and astrocytes, in turn, produce cytokines, nitric oxide (NO), reactive oxygen species (ROS), and proteases, further contributing to neuroinflammation and triggering microglial priming (Perry & Holmes, 2014; Torres-Platas *et al.*, 2014) with a detrimental effect on brain integrity (Stephenson *et al*, 2018; Tang & Le, 2016).

A growing literature has now been rising focusing on choroid plexus (ChP), a key structure involved in the CNS-periphery neuroimmune crosstalk. ChP consists of an epithelial cells monolayer surrounding vascularized connective tissue with permeable capillaries, located at the base of each brain ventricle, forming the blood-cerebrospinal fluid barrier (BCSFB) through tight junctions, which regulates the exchange between blood and cerebrospinal fluid (CSF).

Research indicates that increased peripheral immune activation can reduce the permeability of both the blood-brain barrier (BBB) and BCSFB (Turkheimer *et al*, 2021). Animal models suggest the ChP plays a key role in immune cell trafficking to the brain, acting as a neuro-immunological interface between the brain and circulating immune signals (Schwartz & Baruch, 2014), regulating clearance processes and immune cell trafficking (Lun *et al*, 2015). Notably, its enlargement was recently found in different inflammatory pathologies and psychiatric frames (Althubaity *et al*, 2022; Cao *et al*, 2023; Lizano *et al*, 2019; Yang *et al*, 2021). Also mood disorders exhibit enlarged ChP volumes compared to healthy controls, and it was also associated with higher circulating levels of inflammatory cytokines, microglial activation and duration of illness (Althubaity *et al.*, 2022; Bravi *et al*, 2024; Lizano *et al.*, 2019). Reduced barriers' permeability results in preventing homeostasis mechanisms over time such as the clearance of metabolic products and debris, fostering detrimental effects on the

brain (Enache *et al*, 2019). Indeed, ChP enlargement was associated also with WM disruption in depressed patients (Bravi *et al*, 2023).

Kyn pathway

The presence of a chronic inflammatory state facilitates a strict influence among immune factors and neurotransmitter systems through molecules and enzymes involved in serotoninergic and glutamatergic metabolism (Comai *et al*, 2020; Haroon *et al*, 2012).

Indeed, a chronic inflammatory state, and particularly cytokines such as IFN-γ, TNF-α, IL-1β and IL-6, released by the activated microglia or produced by systemic inflammation, convert the serotonin production chain, alternatively promoting the synthesis of kynurenine (Kyn) by activating the major enzymes that metabolize TRP, indoleamine 2,3 dioxygenase (IDO) and tryptophan-2,3 dioxygenase (TDO) (Dantzer *et al*, 2008; Maes *et al*, 1997; Mastorakos & Ilias, 2006; Pemberton *et al*, 1997; Sellgren *et al*, 2016). TRP breakdown can take place in astrocytes, microglia, and neurons, but about 60% of brain Kyn is transported across the BBB from the periphery and is then circulated into the brain via volume transmission. It has been shown that during immunotherapy, serum levels of tryptophan (but not CSF) are lowered and that the degree to which this occurs correlates with increased concentration of Kyn, measured in CSF and blood, and with the emergence of depressive symptoms (Capuron *et al*, 2002b; Raison *et al*, 2010). Even in animal samples, it has already been seen how the administration of LPS, able to induce an immune response, causes depressive symptoms, whereas it does not occur in mice genetically deficient in IDO, showing resistance to the humoral response due to inflammation (O'Connor *et al*, 2009). (Fuxe *et al*, 2013). Activation of IDO results in depletion of 5-HT (Muller & Schwarz, 2007; Myint & Kim, 2003) and then the kynurenine-3-monooxygenase can then convert Kyn into 3-hydroxy-kynurenine (3HK), 3HK, which can cross the blood-brain barrier (BBB) from peripheral sources, serves as a precursor to both quinolinic acid (QA) and xanthurenic acid. In an alternative pathway, Kyn aminotransferases can convert Kyn into kynurenic acid (KynA). Neither KynA nor QA can cross the BBB, and both are active at the glutamatergic N-methyl-D-aspartate receptor (NMDAR): QA is a direct agonist, while KynA acts as an antagonist. The conversion from Kyn to

QA in the brain takes mainly place in microglia, while Kyn is mainly converted to KynA in astrocytes. TRY breakdown by IDO results then in serotonin depletion, and in perturbing NMDAR neurotransmission, both effects being associated with depressive psychopathology (Khandaker *et al*, 2021; Schwarcz *et al*, 2012). Notably, possibly as a consequence of the persistently altered immune-inflammatory setpoints, increased activity of IDO with heightened rate of TRP breakdown, higher levels of KynA, and higher conversion to QA (QA/KynA) were found in depressed patients compared with healthy controls (Leonard, 2001; Myint *et al*, 2007; Steiner *et al*, 2011), with IDO correlated with immune markers in both MDD and BD (Marx *et al*, 2021). However, results in the literature are inconclusive about the metabolite-specific levels in unipolar or bipolar depression, reporting both increases and decreases of QA, KynA, and 3-HK in MDD and BD patients (Gigante *et al*, 2012; Hashimoto *et al*, 2007; Luykx *et al*, 2012; Moriguchi *et al*, 2019; Steiner *et al.*, 2011). Moreover, the rate of TRP to Kyn breakdown, and the QA/KynA ratio associated with lower cortical thickness (Meier *et al*, 2016; Poletti *et al*, 2019a) and higher circulating KynA influence MRI measures of better myelin sheaths integrity (Poletti *et al*, 2016), probably due to NMDAR and AMPA high expression in the myelinating processes of oligodendrocytes (Gautier *et al*, 2015; Káradóttir *et al*, 2005).

Interestingly, NMDAR is prominently expressed on the ventricular side of neuroepithelial cells in the ChP (Sharp *et al*, 2003) and on neuroendothelial and arteriolar smooth muscle cells, where it participates in neurovascular coupling—a mechanism that matches cerebral blood flow with neuronal energy demands (Anfray *et al*, 2020; Hogan-Cann *et al*, 2019; Zhang *et al*, 2024). Activation of NMDAR is known to dilate cerebral arteries and modulate BBB permeability. Disruption of these processes could lead to BBB leakage and increased cellular trafficking, with pathological NMDAR activation contributing to compromised barrier integrity (Macrez *et al*, 2016). Mood disorder patients show enlarged ChP volumes, associated with age, illness duration, and heightened levels of circulating pro-inflammatory compounds (Bravi *et al.*, 2024), which may reflect alterations in BBB dynamics (Althubaity *et al.*, 2022). Human monoclonal anti-NMDAR antibodies can block the receptor and disrupt the signaling pathway (Kreye *et al*, 2016), and in patients with schizophrenia the ChP volumes were enlarged proportional to the peripheral levels of

anti-NMDAR antibodies (Li *et al*, 2021). It can then be hypothesized that factors affecting NMDAR function, like circulating Kyn pathway (KP) metabolites, could influence ChP volumes by acting on BBB permeability.

Moreover, KP metabolites, such as Kyn, play a role in regulating vascular tone (Wang *et al*, 2010) by dilating blood vessels and exerting antihypertensive effects in various conditions (Worton *et al*, 2021). In mood disorders, cerebral blood flow abnormalities, primarily characterized by hypoperfusion, were found (Toma *et al*, 2018), together with possible neurovascular uncoupling proportional to the severity of depressive symptoms (Dunn *et al*, 2005). In brain diseases resting-state fMRI studies have reported reduced fALFF, a marker for spontaneous neuronal activity and predictor of variations in hemodynamic response at rest (Bailes *et al.*, 2023), suggesting disrupted neurovascular coupling in these patients (Agarwal *et al.*, 2017; Agarwal *et al.*, 2021). Notably, fALFF hypoactivation was observed in mood disorder patients, proportional to metabolic impairment and positively correlated with circulating Kyn levels in MDD (Kamishikiryo *et al*, 2022; Mazza *et al*, 2023; Meda *et al*, 2015).

At the core of neurovascular coupling, the hemodynamic response function (HRF) reflects the brain's capability to dynamically adjust oxygen supply to meet neuronal activity, measurable via blood oxygen level-dependent (BOLD) signals in fMRI, both in response to tasks and to spontaneous events during resting state (Wu *et al*, 2021a). NMDAR-mediated mechanisms have been implicated in synchronizing the oxygen supply with the metabolic needs of neurons through synaptic-like transmission (Zhang *et al.*, 2024). In mood disorders, altered HRF parameters, observed in hubs of the DMN, could suggest deviations in neurovascular coupling (Yan *et al*, 2022). Indeed, these regions are characterised by inter- and intra-network abnormal connectivity in these diseases (Scalabrini *et al.*, 2020). However, a possible interference of KP metabolites on these mechanisms was never explored.

Taking into account previous considerations, activation of the KP can then be considered as a link between low-grade inflammation and abnormal neurotransmission in mood disorders. Interestingly, genetic factors increasing circulating levels of Kyn proportionally increase the risk of depression (Zong *et al*, 2024). Furthermore, beyond neurotransmitters, studies in the general population suggest that the genetic

architecture of plasma Kyn includes cardiometabolic disease mechanisms (Bagheri *et al*, 2021). Notably, patients with mood disorders are at higher risk for the subsequent onset of several medical conditions, including cardiovascular diseases (Momen *et al*, 2020), with lifetime disease trajectories suggesting a direct link between psychiatric disorders and cardiovascular diseases (Shen *et al*, 2023). Moreover, low-grade systemic inflammation is associated with both the development and progression of cardiometabolic disease (Furman *et al*, 2019; Mainous III *et al*, 2024; Pearson *et al*, 2003) and with the presence of MDD and BD (Poletti *et al.*, 2024a). Genetic factors may play a role in the overlap of heightened pro-inflammatory and altered cardiometabolic phenotypes observed in mood disorders. Meta-analyses of genome-wide and candidate gene association studies suggest that mood disorders and cardiometabolic diseases share biological mechanisms, with pleiotropic genes and common biological pathways linking these two groups of conditions. (Amare *et al.*, 2017). Following this perspective, the kynurenine pathway appears a good candidate to study the genetic overlap between inflammation and cardiometabolic risk in mood disorders. Interestingly, among several single nucleotide polymorphisms (SNPs) linked to circulating Kyn levels and included in the Kyn PRS, the *SH2B3* rs3184504 C>T nonsynonymous SNP stands out as a genetic determinant of both plasma Kyn levels and cardiovascular diseases. The missense T variant has been associated with conditions such as hypertension, atherosclerosis, and myocardial infarction, according to phenome-wide association studies (Bagheri *et al.*, 2021).

Given that the activation of IDO and the breakdown ratio of tryptophan to kynurenine was previously associated with detrimental effects in the brain of patients with mood disorders, including disrupted WM microstructure (Poletti *et al*, 2019b), genetic factors affecting the Kyn pathway may influence neurovascular risk and WM integrity in patients affected by mood disorders.

Cognitive deficits in mood disorders

In addition to disruptions in emotional processing, mood disorders significantly impact cognitive functioning (Douglas et al., 2018), which has been recognised as a core feature by the Research Domain Criteria (RDoC, Pan et al., 2019). Individuals with mood disorders frequently exhibit deficits across various cognitive domains,

including attention, memory, executive functioning, processing speed, psychomotor speed, and verbal fluency (Bortolato *et al*, 2016; Bourne *et al*, 2013; Hammar *et al*, 2022; Lee *et al*, 2012; Rock *et al*, 2014). Moreover, the likelihood to struggle with cognitive dysfunction is more pronounced in depressive patients, as demonstrated by longitudinal studies, with this risk increasing in relation to the frequency of depressive episodes (Kessing & Andersen, 2017; Varghese *et al*, 2022). The urgency of focusing on cognitive impairment represented by its persistence during remission and euthymic states, and the progressive worsening of cognitive symptoms with the occurrence of new episodes of diseases (Cullen *et al*, 2010; Fountoulakis, 2020). This trend is indicative of the failure of first-line treatments to target the neurobiological underpinnings of cognitive dysfunction. This leads to longer episode duration, which has been shown to have detrimental effects on both brain structure and function and cognition (Melloni *et al*, 2019). Indeed, cognitive impairment is a predictor of poor treatment response in mood disorders (Roiser *et al*, 2012), and consequently also a predictor of occupational and social functional deficits (Douglas *et al*, 2018; Poletti *et al*, 2021a; Rock *et al.*, 2014). These latter findings suggest that cognitive dysfunction could be considered a core feature of depression rather than an epiphenomenon of MDD and BD.

The search for pathophysiological underpinnings of the disorders then becomes a fundamental priority (Zarate *et al.*, 2013) to enrich the etiopathological picture of BD and MDD and to identify new targets for treatment.

A complete picture of the neurobiological underpinnings of cognitive impairment in depression is still lacking; however, evidence from various domains—including genetics, molecular pathways, and neural circuits—suggests a complex and multifaceted phenomenon (Pan *et al*, 2019). The predominant theory suggests that disturbances in the structure, function, and connectivity of brain networks linked to cognitive control are central to the cognitive deficits in MDD. Alterations in fronto-temporal and fronto-subcortical circuits, particularly within regions such as the hippocampus, amygdala, and ACC, have been strongly associated with depression (Jiao *et al*, 2011; Pizzagalli, 2011).

Cognitive processes rely on the interplay between interconnected and segregated brain systems, requiring a balance between integrated and independent

functional networks. A critical aspect of this balance involves the coordinated activation and deactivation of certain brain regions, a phenomenon known as anti-correlation, which is essential for optimal cognitive functioning (Cha *et al*, 2014). When the hubs of different networks are disrupted, the resulting imbalance within key structures of the DMN may contribute to the cognitive impairments and decreased cognitive performance observed in individuals with depression (Hamilton *et al*, 2011).

Among new biomarker candidates, peripheral inflammatory markers have been associated with cognitive performance in BD (Poletti *et al.*, 2021a). A possible strategy would be the stratification of patients based on their peripheral markers of inflammation to identify a subpopulation of subjects who could benefit from immunotherapy (Raison *et al*, 2013). Indeed, inflammatory profiles for BD and MDD have been extensively described in the literature at all stages of the disease, identifying a core neurobiological substrate (Benedetti *et al.*, 2020; Brown *et al*, 2018; Enache *et al.*, 2019). The presence of a chronic inflammatory state facilitates a strict influence among immune factors and neurotransmitter systems linked to the treatment response and cognitive functioning acting on molecules and enzymes involved in serotoninergic and glutamatergic metabolism through the kynurenine pathway (Comai *et al.*, 2020; Haroon *et al.*, 2012). Interestingly, cognitive deficits seem to be not due to serotonin depletion but to activation of the KP, given the significant correlation of cognitive impairment with lower levels of neuroprotective KynA, and not with 5-HIAA, the major metabolite of 5HT degradation (Hebbrecht *et al*, 2021). The relevance of focusing on Kyn when dealing with cognition is given by both its impact on the glutamatergic transmission at the NMDAR level and its modulation effect on endothelium-derived vasodilation, possibly affecting the neurovascular unit (NVU) inefficiency showed in depression (Dantzer *et al.*, 2008; Rajkumar, 2024; Wang *et al.*, 2010). NVU is the physio-anatomical substrate of a homeostatic process essential for neuronal function, regulating both global and regional blood flow to ensure an adequate supply of oxygen and nutrients to the active neurons. In this context, increased neuronal demand is “coupled” with enhanced microvascular blood flow (Muoio *et al*, 2014). Najjar and colleagues first hypothesized the involvement of NVU dysfunction in depression through inflammatory-induced BBB disruption (Najjar *et al*, 2013b). In animal models of diabetes, glutamatergic dysfunction was associated

with altered hippocampal NVU (Liu *et al*, 2019). Moreover, as conditions with affected coupling mechanisms, cerebrovascular diseases are associated with both depression and cognitive impairment (Göthe *et al*, 2012; Hedges *et al*, 2019; Momen *et al.*, 2020). In both MDD and BD patients, reduced natural frequencies have been detected compared with healthy controls (Canali *et al*, 2015), possibly as a correlate of NVU inefficiency. Natural frequencies are rhythmic cycles of excitation and inhibition that lead to the synchronized firing rate of brain cells, allowing a specific region to operate with maximum efficiency during a task (Capilla *et al*, 2022). The impossibility of reaching such high-frequency oscillations of glutamatergic pyramidal neurons during cognitive tasks could explain the impairment observed in mood disorders. Altered neurovascular coupling could be considered a critical risk factor for cognitive impairments, as in other human clinical conditions and healthy ageing (Mogi & Horiuchi, 2011; Toth *et al*, 2017), and in animal models (Tarantini *et al*, 2015). Moreover, neurovascular coupling indices like fALFF and HRF were shown to be altered in mood disorder patients, as mentioned above, particularly within the DMN's hubs. This could support the hypothesis that KP metabolites may influence fALFF and HRF parameters through NMDAR-mediated vasodilation and vasoconstriction mechanisms involved in neurovascular coupling in patients with mood disorders, potentially impacting demanding cortical activities like cognitive functioning, as reported for subjective cognitive decline (Lu *et al*, 2022). In particular, through their effect on the NVU, KP metabolites could foster alterations in fALFF and HRF, fostering DMN dysfunction in mood disorder patients, affecting inter-cortical balance and cognitive performance.

Then, considerations about the role of the genetic predisposition to Kyn on cognition and WM integrity have to be made. Indeed, as previously mentioned, given the association between mood disorders and cardiometabolic diseases, their common inflammatory-based signature, and that genetic factors increasing circulating levels of Kyn proportionally increase the risk of depression (Zong *et al.*, 2024), it is tempting to focus on the genetic predisposition to Kyn levels, as a good candidate to evaluate its influence on neurovascular risk and WM integrity in patients affected by mood disorders. Focusing on the impact on WM integrity is well-founded, given that the Kyn/Trp ratio has been linked to white matter disruption (Poletti *et al.*, 2019b).

Additionally, Kyn's role in modulating vascular permeability and tone could contribute to WM damage, manifesting as white matter hyperintensities (WMHs), which are consistently associated with mood disorders (Wang *et al*, 2014). Indeed, WMHs are considered outcomes of presumed microvascular distress (Wardlaw *et al*, 2013) and interestingly, have already been shown to have a detrimental effect on cognition (Hu *et al*, 2021; Wang *et al*, 2022). Furthermore, since WM integrity is closely related to cognitive function in mood disorders (Melloni *et al.*, 2019), it is plausible that this Kyn-related genetic predisposition may affect cognitive performance by impacting structural connectivity.

Overall, it appears conceivable that the KP may shape brain function and connectivity by influencing complex, multifaceted mechanisms, thereby impacting cognitive performance in individuals with mood disorders.

AIM OF THE WORK

This work aims to explore the multifaceted role of the KP in modulating key brain processes, including brain barrier integrity, neural activity, brain connectivity and cognitive outcomes in mood disorders, specifically MDD and bipolar disorder BD. The KP is a particularly suitable candidate to be the focus of this study due to its links with inflammation, the glutamatergic system, and cardiovascular diseases. Inflammation plays a significant role in the pathophysiology of mood disorders, while the glutamatergic system is crucial for cognitive processes. Additionally, the high comorbidity of cardiovascular diseases with depression further underscores the relevance of KP in understanding these disorders.

In this study, we first examine the influence of peripheral analytes on KP metabolites, highlighting how systemic inflammatory processes might affect KP activity. Next, we assess the impact of KP metabolites on ChP volume, a critical regulator of cerebrospinal fluid-blood-brain barrier (CSF-BBB) permeability, to explore potential mechanisms by which KP could influence centre-periphery dynamics. Following this, we investigate the effects of KP metabolites on spontaneous neural activity and hemodynamic response function (HRF) within the DMN, providing insight into how KP may modulate neurovascular coupling and affect a core network altered in depression.

Subsequently, the predictive role of the SII on peripheral Kyn levels was explored, as an indicator of both systemic inflammation and a marker of cardiovascular disorders, to further confirm the involvement of Kyn in vascular permeability modulation and its connection to a state of systemic inflammation. Then, considering the strict link between cardiometabolic disease and mood disorders and their common inflammatory signature, we delved into examining the genetic load of Kyn, as a good candidate to study the genetic overlap between inflammation and cardiometabolic risk in mood disorders.

We first assessed the association between kynurenine polygenic risk score (Kyn PRS) and KP metabolite levels. The impact of Kyn PRS on WM integrity is then evaluated, focusing on both white matter hyperintensities (WMH) and microstructural integrity and investigating the role of SH2B3 rs3184504 C>T nonsynonymous SNP on Kyn PRS. These assessments aim to clarify the role of the genetic load of Kyn on

brain structural connectivity, already linked to cognitive dysfunction in depressed patients.

Finally, we assess how functional and structural connectivity may mediate the relationship between cognitive performance and KP metabolites and Kyn PRS respectively. This step allows us to explore the potential neurobiological mechanisms through which KP might contribute to cognitive deficits in mood disorders. By integrating these diverse analyses, this work aims to provide a comprehensive understanding of how KP activity, influenced by inflammation, genetic factors, and neurovascular dynamics, may shape cognitive outcomes in mood disorders, potentially guiding targeted therapeutic approaches.

METHODS

Sample/Participants

We enrolled 138 depressed patients (84 MDD and 54 BD) recruited at the IRCCS San Raffaele Hospital, Milan, Italy.

Patients with complete KP including both HPLC and LC-MS/MS processing, MRI data, and in the course of a depressive episode of illness included 42 MDD and 36 BD patients (DSM-5 criteria). Patients scored higher than 8 on 21-Hamilton Depression Rating Scale (HDRS-21) (Hamilton, 1986).

Inclusion criteria were: age between 18-65 years old; willingness to participate; absence of other diagnoses on Axis I, pregnancy, history of epilepsy, major medical and neurological disorders; intellectual disabilities; absence of a history of drug or alcohol dependency; absence of inflammation-related diseases or symptoms, including fever and infections; no autoimmune diseases; no uncontrolled systemic, metabolic or other significant somatic disorders known to affect mood; somatic medications known to affect mood or the immune system, such as corticosteroids, non-steroid anti-inflammatory drugs and statins.

Clinical data were collected through structured psychiatric interviews. No patient had received electroconvulsive therapy within 6 months prior to study enrolment. Fasting blood samples were taken in the morning (between 7:00 to 9:00 a.m.). Patients' ongoing drug treatments were calculated as equivalent doses of chlorpromazine, imipramine, lorazepam, and months of lithium treatment.

After the subjects were fully informed about the study, written informed consent was obtained. The local ethical committee (IRCCS Ospedale San Raffaele) approved all the research activities and complied with the Helsinki Declaration of 1975, as revised in 2013.

Cognitive Assessment

Cognitive functions were assessed using the Brief Assessment of Cognition in Schizophrenia (Keefe *et al*, 2004) a widely used neuropsychological battery known for its speed, cost-effectiveness, and ability to evaluate cognitive function comprehensively. Originally developed for use in schizophrenia, the BACS has

become a standard tool in clinical trials due to its reliability and ease of administration (Bakkour *et al*, 2014). It assesses six cognitive domains: verbal memory, working memory, psychomotor speed, selective attention, verbal fluency, and executive functions. Verbal memory is tested through a list-learning task, where individuals recall words from a list before mentioned. Working memory is measured using a digit sequencing task, requiring patients to arrange numbers in ascending order as the sequence length increases. Psychomotor speed is evaluated through a token motor task, where patients place tokens into a container within a time limit. Verbal fluency includes tasks that assess both category and letter fluency, requiring patients to generate as many words as possible within a given time frame. Attention and processing speed are tested using a symbol coding task, while executive functions are assessed through the Tower of London task, which involves problem-solving to match arrangements of colored balls.

The BACS is typically completed in about 30 minutes, offering a reliable and comprehensive assessment of cognitive abilities (Keefe *et al.*, 2004). It was initially validated using a standard neuropsychological battery on a sample of 150 patients with schizophrenia and 50 healthy controls (HC), demonstrating high completion rates and test-retest reliability (intraclass correlation coefficient > 0.79). Its sensitivity is comparable to other cognitive batteries, and its scores show strong correlations with standard neuropsychological tests, confirming its accuracy. The Italian version of the BACS, validated in 204 healthy adults, highlighted demographic influences like age and education, which were used to adjust scores (Anselmetti *et al*, 2008).

While initially focused on schizophrenia, the BACS has been effectively applied to mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), identifying cognitive impairments that span a continuum between healthy controls and schizophrenia patients (Cholet *et al*, 2014; Huang *et al*, 2020; Keefe *et al*, 2014).

Scoring procedure

Patient performance was recorded as raw scores, which were then adjusted for demographic variables based on their influence on specific cognitive domains, using corrections derived from the Italian normative sample (Anselmetti *et al.*, 2008).

All assessments were conducted by a trained psychologist. Normative Italian-adjusted scores (Anselmetti *et al.*, 2008) were utilized for the BACS subtests. To obtain a global cognitive performance score, each subtest was assigned an equivalent score ranging from 0 to 4 and the average score was calculated (Palladini *et al*, 2023) and considered in the analyses.

Laboratory determinations

Systemic Immune-Inflammation Index

The Systemic Immune-Inflammation Index (SII) was calculated from samples collected at the moment of the MRI scan. SII represents a marker of immune response and systemic inflammation derived from peripheral lymphocyte, neutrophil, and platelet counts. Particularly, it has been recently associated with cardiovascular disease (Zhou *et al*, 2022) and general endothelial damage (Yang *et al*, 2020). SII was calculated as follows:

$$SII = \frac{platelets \times neutrophils}{lymphocytes}$$

KP metabolites

KP metabolites were assessed with a standard methodological procedure in the laboratory (Comai *et al*, 2022; Simonato *et al*, 2021). 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 and the plasma was divided into small aliquots and then stored at −80 °C. First, the analysis of Trp and Kyn was performed with a high-performance liquid chromatography (HPLC) system coupled with a fluorometric detector for Trp (excitation at 285 nm, emission at 345 nm) and UV–Vis detector for Kyn (absorbance at 360 nm). The mobile phase was composed of 10 % acetonitrile/90 % phosphate buffer 0.004 M at pH 3.5. Separation was obtained by isocratic elution at 0.8 mL/min along a Synergi Fusion-RP 80A column. Second, 3-hydroxykynurenine (3-HK), KynA and QA were determined using an 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 modes for all the molecules in positive ion mode, except for QA which was quantified 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/min72. The quantification of 3-HK, QA, and KynA was calculated using alfa-methyl tryptophan 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) and Tryptophan 2,3-dioxygenase, KynA/Kyn of Kyn aminotransferase II and 3-HK/Kyn of kynurenine-3-monooxygenase, and 3-HK/Kyn of kynurenine 3-monooxygenase (KMO). Finally, the ratio KynA/QA was determined as an index of antagonistic/agonistic properties elicited on NMDAR.

Plasma analytes

Plasma analyte levels were quantified using the Bio-Plex Pro™ Human Cytokine 48-Plex assays (BIO-RAD). Luminex system based on xMAP technology (Luminex 200™ system, Merck Millipore) following a pre-optimized protocol provided by the manufacturer. The 48-Plex assays included: interleukin (IL)-1β, IL-1 receptor antagonist (ra), IL-1α, IL-2 receptor α (Rα), IL-2,IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p40), IL-12 (p70), IL-13, IL-15, IL-16, IL-17A, IL-18, Interferon (IFN)-γ, IFN-α2, Tumor Necrosis Factor (TNF)-α, TNF-β, Macrophage Migration Inhibitory Factor (MIF), TNF-related apoptosis-inducing ligand (TRAIL); b) chemokines: Eotaxin (CCL11), Growth-Regulated Oncogene (GRO)-α/CXCL1, Interferon gamma-induced protein (IP)-10/CXCL10, Monocyte Chemoattractant Protein (MCP)-1/CCL2, Monocyte Chemoattractant Protein (MCP)-3/CCL7, Monokine Induced by Gamma interferon (MIG)/CXCL9, Macrophage Inflammatory Protein (MIP)-1α/CCL3, MIP-1β/CCL4, Regulated upon Activation Normal T cell Expressed and Secreted (RANTES)/CCL5, Stromal Cell-Derived Factor (SDF)-1α/CXCL12, Cutaneous T-Cell-Attracting Chemokine (CTACK)/CCL27; c) growth factors: Fibroblast Growth Factor (FGF) basic, Hepatocyte Growth Factor (HGF), Beta Nerve Growth Factor (NGF)-β, Platelet-Derived Growth Factor (PDGF)-BB,

Stem Cell Factor (SCF), Vascular Endothelial Growth Factor (VEGF), Granulocyte-Colony Stimulating Factor (G-CSF), Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), Stem Cell Growth Factor (SCGF)-β, Macrophage Colony-Stimulating Factor (M-CSF), and Leukemia Inhibitory Factor (LIF).

These multiplexed sandwich immunoassays utilized commercially available capture and detection antibodies and standard proteins, validated and approved by EDI-GMBH according to established methods (Schmohl *et al*, 2012). Measurements were performed using the Luminex 200 detection platform (Luminex Corporation, Austin, TX, USA), and samples were processed according to the manufacturer's instructions. Mean Fluorescence Intensities (MFI) were used for quantification of each analyte. The use of MFI is preferred to avoid inaccuracies based on possible non-linear fitting of standard curves and to quantify analytes on data points over the limits of the curve (Breen *et al*, 2015).

Genetic data

Genotyping

Genotyping, quality control (QC), and imputation of genetic data were performed in a larger cohort including 192 patients with MDD and 265 BD patients, of which the present sample represents a subset. Participant's blood samples were genotyped through Infinium PsychArray 24 BeadChip (Illumina, Inc., San Diego), which is a cost-effective, high-density microarray specifically developed in collaboration with the Psychiatric Genomics Consortium for large-scale genetic studies focused on psychiatric predisposition and risk. Indeed, this microarray allows extracting information on almost 600,000 genetic variants, including ~271,000 proven tag single nucleotide polymorphisms (SNPs) found on the Infinium Core-24 BeadChip, ~277,000 markers from the Infinium Exome-24 v1.1 BeadChip, and ~50,000 markers associated with common psychiatric disorders, such as schizophrenia, BD, attention deficit hyperactivity disorder, MDD, obsessive-compulsive disorder, and anorexia nervosa (https://www.illumina.com/products/by-type/microarray-kits/infinium-psycharray.html).

Quality control

Quality control (QC) of genotyped data was performed following the guidelines provided by Anderson et colleagues (Anderson *et al*, 2010) and by using the software PLINK 1.9 (Purcell *et al*, 2007). Specifically, the QC process consisted of two different steps: QC per individual and QC per genetic variant. First, individuals whose genotyped sex was different from the phenotypical one, individuals with a genotyping rate lower than 95%, and people with an outlying autosomal heterozygosity (Fhet > ±0.2), were removed. After removing subjects, removal of genetic variants was done if their call rate was lower than 98%, if they were rare, that is if the minor allele frequency (MAF) was lower than 1%, and if they were extremely deviant from Hardy-Weinberg equilibrium ($p<10\text{-}8$). Lastly, relatedness and population ancestry of the sample were checked: individuals were removed if they had a degree of recent shared ancestry (i.e., identity by descendent, IBD) higher than 0.1875, which is the threshold corresponding to the halfway between third- and second-degree relatives, and if their genotype distribution was deviant from the current population, that is if the first two components resulting from a principal components analyses (PCA) were outlying more than 5 standard deviations from the mean. After QC, genotype frequencies of SH2B3 rs3184504 were extracted.

Imputation

Genotype Imputation was computed via the Michigan Imputation Server using Minimac4, version 1.7.1 (https://imputationserver.sph.umich.edu), selecting the following options: (1) the latest version of Haplotype Reference Consortium panel (i.e., HRC r1.1 2016) was selected, (2) the array build was GRCh37/hg19, (3) rsq Filter was set to 0.003, (4) the algorithm Eagle (version 2.4) was chosen for phasing, (5) European population was selected as the reference one. Post-imputation files contained approximately 14 million variants.

PRS calculation

PRS for Kynurenine (Chen *et al*, 2023) was computed as the sum of the number of effect alleles at each SNP position, weighted for their effect size derived from the largest GWAS meta-analyses available at the time of conducting the analyses (see

Table 1). Specifically, PRS for each individual were calculated with the –score function of PLINK 1.9 as follows:

$$PRS_j = \sum_{i}^{N} \beta_i * dosage_{ij}$$

where j is the individual, N is the number of variants considered for the score of the metabolite of interest, i is the genetic variant, dosage consists of the allele counts of variants associated with the metabolite of interest, and β is the weight reflecting the magnitude of association between variant alleles and the levels of kynurenine derived from the latest GWAS. As far as weights are concerned, they were estimated with LDpred2-auto, an R-based tool that allows the estimate of the posterior mean causal effect sizes of each GWAS-included variant solely relying on the original GWAS summary statistics and an external Linkage Disequilibrium (LD) reference panel (Prive *et al*, 2021). Moreover, all GWAS-included variants underwent a QC procedure excluding those markers whose standard deviation exceeded the one derived from the reference panel (Prive *et al*, 2022).

Metabolite of interest	Authors	Year of publication	Number of cases	Number of controls	Ethnicity	PubMed ID
Kynurenine	Chen et al.	2023	8,299	-	European	36635386

Table 1. *Main information from the GWAS studies used as references for calculating effect sizes of variants associated with Kyn.*

MRI acquisition

All MRI scan were performed at C.E.R.M.A.C. (Centro d'Eccellenza di Risonanza Magnetica ad Alto Campo) in San Raffaele Hospital in Milan. Philips Ingenia CX (Philips, Netherlands) 3T scan with a 32-channel SENSE head coil with a standard quadrature was used.

The T1-weighted MPRAGE and Coronal fluid-attenuated inversion recovery (FLAIR) sequences were acquired. T1-w sequence had the following parameters: TR = 8.00 ms, TE = 3.7 ms, FOV = 256 mm, matrix = 256×256, and an in-plane resolution of 1×1 mm, resulting in 182 transversal slices with a thickness of 1 mm. Coronal fluid-

attenuated inversion recovery (FLAIR) images. T1 and T2-weighted FLAIR images were visually inspected as part of the quality check procedure.

For rsfMRI, gradient-echo EPI sequences were used. These sessions involved 200 sequential T2*-weighted volumes, acquired using an EPI pulse sequence with TR = 2000 ms, TE = 30 ms, flip angle = 85°, FOV = 192 mm, 38 slices with a thickness of 3.7 mm, and a matrix size of 64×62 reconstructed up to 96×96 pixels. The slices were tilted 30° downward relative to the bicommissural line to reduce susceptibility artefacts in the orbitofrontal region. Six dummy scans were performed before the fMRI acquisition to ensure longitudinal magnetization equilibrium. The total acquisition time for this sequence was 6 minutes and 56 seconds. Throughout the rs-fMRI acquisition, subjects were instructed to keep their eyes closed.

For DWI acquisitions, the following parameters were used: TR/TE=5900/78 ms, FoV (mm) 240 (ap), 129 (fh), 232 (rl); acquisition matrix 2.14×2.73×2.30; 56 contiguous, 2.3mm thick axial slices reconstructed with in-plane pixel size 1.88×1.88x2.30 mm; SENSE acceleration factor=2; 1 b0 and 40 non-collinear directions of the diffusion gradients; b value=1000 s/mm2. Fat saturation was performed to avoid chemical shift artefacts.

Imaging processing

T1w - Freesurfer

Volumetric brain segmentation was performed using the fully automated and validated FreeSurfer image analysis suite v7.2 (http://surfer.nmr.mgh.harvard.edu/). Standard reconstruction procedures, which delineate brain anatomy into cortical and subcortical labels, were used. The processing includes motion correction (Reuter *et al*, 2010), automated Talairach transformation, segmentation of the subcortical deep gray matter volumetric structures (Fischl *et al*, 2002; Fischl *et al*, 2004), intensity normalization (Sled *et al*, 1998), tessellation of the gray matter-white matter boundary, and automated topology correction (Fischl *et al*, 2001; Segonne *et al*, 2007).

Segmentation of ChP and total ICV were obtained with the FreeSurfer “recon-all” function (Fischl et al., 2002). Volumes of structures were automatically acquired in voxel (voxel size 0.9 mm3). All segmented structures were visually inspected for

accuracy by a neuroimaging expert, who examined each image segmentation by overlaying the segmentation label of each structure on the T1-weighted brain scan.

Volume of ChPs was per mille (‰) normalized for ICV before being entered in the analyses with the formula (ROI*1000)/ICV, as previously suggested, and proved effective for detecting group differences in mood disorders (Bravi *et al.*, 2024; Ricigliano *et al*, 2021).

FLAIR - Lesion Segmentation Tool

Lesions were segmented by the lesion growth algorithm (Schmidt *et al*, 2012) as implemented in the Lesion Segmentation Tool (LST) toolbox version 3.0.0 (www.statistical-modelling.de/lst.html) for SPM. The algorithm first segments the T1-weighted images into the three primary tissue classes: cerebrospinal fluid (CSF), gray matter (GM), and white matter (WM). This segmentation is then integrated with the coregistered FLAIR image intensities to generate lesion belief maps. These maps are thresholded using a predefined initial value (κ) to produce an initial binary lesion map, which is then expanded by including voxels that exhibit hyperintensity on the FLAIR images. The final output is a lesion probability map. For each subject number of lesions were quantified and used for further analyses.

Resting-state fMRI-CONN & AFNI

Standard pre-processing of resting-state fMRI data was conducted using CONN toolbox (www.nitrc.org/projects/conn) of Statistical Parametric Mapping (SPM12).

This included slice timing correction (accounting for the multiband sequence acquisition), realignment and unwrapping, co-registration to anatomical images, de-spiking, normalization to MNI space, and spatial smoothing with an 8-mm full-width at half-maximum isotropic Gaussian kernel. Nuisance covariates were regressed out including 6 head motion parameters, Legendre polynomials up to the 2nd order, and the top 5 principal components of subject-specific white matter (WM) and cerebrospinal fluid (CSF) signals. Outlier scans were identified and removed (scrubbing) (Nieto-Castanon, 2020). Finally, band-pass filtering was applied in the range of 0.01–0.1 Hz.

Preprocessed and denoised images were then entered as inputs in the rsHRF SPM's toolbox (https://www.nitrc.org/projects/rshrf); (Wu *et al*, 2013) in order to estimate and deconvolve HRF for resting state data. Response Height (RH), Time To Peak (TTP), and Full Width at Half Maximum (FWHM) maps were extracted and smoothed using a 6 mm Gaussian kernel, as suggested (Wu *et al*, 2021b).

Then, after resampling, the parameters' maps were masked for the Default Mode Network included in the Functional Connectivity Atlas 7 Networks (Yeo *et al*, 2011). Average values of the HRF parameters for the DMN were calculated for each subject thereafter.

fALFF measures were estimated using AFNI (https://afni.nimh.nih.gov/). The fractional amplitude of low-frequency fluctuations (fALFF) was calculated with AFNI's 3dRSFC tool (Zou *et al.*, 2008) on preprocessed images. Linear and quadratic trends were removed from the preprocessed and denoised fMRI time-series, which were then converted to a power spectrum using a Fourier transform. fALFF was calculated as the average power in the range of 0.01–0.1 Hz relative to the entire frequency spectrum. The fALFF for each voxel was then normalized by dividing by the mean fALFF within the whole brain. Average normalized fALFF values were extracted from the DMN similarly to the HRF parameters.

Diffusion Weighted Images-FSL

The "Oxford Center for Functional Magnetic Resonance Imaging of the Brain Software Library" (FSL 6.0; www.fmrib.ox.ac.uk/fsl/index.html) was used for DTI analyses and preprocessing (Smith *et al*, 2004).

Brain extraction tool (BET) was used for the removal of nonbrain tissue providing a subject-specific brain mask. Then the FSL eddy tool was used, which handles a Gaussian process to predict undistorted data, to which the actual volumes can be aligned (Andersson & Sotiropoulos, 2015). It can estimate and correct for volume-to-volume movement and off-resonance fields, signal dropout due to movement during diffusion encoding, and intra-volume movement (Andersson *et al*, 2018). After, tensor fitting with least-square fit was performed to estimate the fractional anisotropy (FA), eigenvector, and eigenvalue maps. Mean diffusivity (MD) is calculated as the mean of all three eigenvalues ($\lambda 1 + \lambda 2 + \lambda 3)/3$, radial diffusivity

(RD) as the mean of the second and third eigenvalues ($\lambda 2 + \lambda 3)/2$, and axial diffusivity (AD) as the principal diffusion eigenvalue ($\lambda 1$).

Next, all subjects' volumes were skeletonized and transformed into a common space as used in Tract-Based Spatial Statistics (TBSS) (Smith *et al*, 2006). Briefly, all volumes were nonlinearly warped to the FMRIB58_FA template supplied with FSL (http://www.fmrib.ox.ac.uk/fsl/tbss/FMRIB58_FA.html) and normalized to the Montreal Neurological Institute space, by use of local deformation procedures performed by FMRIB's Non-Linear Image Registration Tool (FNIRT). Next, a mean FA image of all subjects was calculated and thinned to create a mean FA skeleton representing the centres of all common tracts. In order to reduce the likelihood of partial voluming in the borders between tissue classes, we applied a threshold (FA > 0.20) and binarized the mean FA skeleton. Individual FA values were warped onto this mean skeleton mask. The resulting tract invariant skeletons for each participant were fed into voxel-wise permutation-based cross-subject statistics. Similar warping and analyses were performed also on MD, AD, and RD data.

Statistical analyses

Data were analysed with commercially available software (StatSoft Statistica 12, Tulsa, OK, USA).

First, clinical-demographic features were compared between MDD and BD subjects. T-test and χ^2 were used for the comparison of continuous and categorical variables respectively.

The normality of the distributions of biological variables was tested with the Shapiro-Wilk W test, and the homogeneity of variances for group effects with Levene test. Biological variables were compared between groups with non-parametric Mann-Whitney U Test.

To assess the effect of pharmacological treatments on KP metabolites, MRI-related measures, and plasma analytes, partial correlations with equivalents of imipramine, chlorpromazine, and lorazepam and months of lithium treatment were performed correcting for age and sex.

When appropriate, multiple comparison correction of levels of significance was applied through adaptive linear step-up procedures, providing final FDR and q-values (FDR-adjusted p-value) (Benjamini & Hochberg, 2000).

We employed a combination of statistical methods to address the expected non-normal distribution of biological variables, the presence of multiple covariates, and the expected significant interactions and multicollinearity among several independent factors. Specifically, we utilized a stepwise approach that integrated linear machine-learning (ML) multiple regression techniques for feature reduction and prediction of effects, followed by an explanatory non-parametric Generalized Linear Model (GLZM) multiple regression. This strategy has been demonstrated to effectively elucidate the complex interactions between immunological variables, clinical phenotypes, and outcomes in mood disorders research (Benedetti *et al*, 2021; Benedetti & Vai, 2023; Mazza *et al*, 2021; Poletti *et al.*, 2021b; Poletti *et al*, 2024b).

To perform a feature reduction by selecting the factors of interest in predicting the variables of interest, we used partial least squares regression (PLS), a ML technique that models the relationships between sets of observed variables with latent variables, to define a linear regression model by projecting the predicted variables and the observable variables to a new space. Like principal component analysis (PCA), PLS creates composite variables of X data, but unlike PCA, it directly maximizes the covariance between predictor variables and the outcome variable (Liu *et al*, 2022). This implies that PLS is specifically designed to find components that are most relevant for predicting the outcome, handling high-dimensional data by simultaneously projecting both predictor and response variables into a lower-dimensional space, thereby improving the predictive power and interpretability of results (Abdi & Williams, 2013).

Moreover, when dealing with both peripheral analytes and metabolites alongside brain-based variables, PLS regression is particularly suitable because peripheral metabolites may have total variance that includes noise or unrelated peripheral phenomena. By focusing on the components most strongly associated with brain features, PLS regression helps to filter out irrelevant variance that does not contribute to the brain-metabolite relationship (Krishnan *et al*, 2011).

Different separate analyses were performed for selecting IDO (Kyn/Trp ratio), ChP volumes, DMN fALFF, and DMN HRF parameters' maximized predictors.

Partial Least Square Regressions on IDO, ChP volume, and fALFF

In the first model, IDO was entered as Y dependent variable, setting plasma 48-plex analytes as X predictors. For the following models, ChP volumes, DMN fALFF, and DMN HRF parameters were entered as dependent variables separately, while plasma KP metabolites as predictors.

Indeed, PLS is particularly well-suited for situations where there is a large number of explanatory variables relative to the number of observations, as well as in cases of severe multicollinearity as in the case of plasma analytes (Wehrens & Mevik, 2007).

In all PLS models, accuracy of the predictive value of the model was assessed by using the Nonlinear Iterative Partial Least Squares (NIPALS) algorithm (Wold, 1966) and optimizing by cross-validation the number of PLS components to extract (A), then calculating R^2X (a A-dimensional vector, to record the explained variance of the data matrix of predictors by each PLS component), R^2Y (a A-dimensional vector, to record the explained variance of response variables by each PLS component); and for each variable predictive weights (w), and the variable importance in projection (VIP) values, to estimate the contribute of each variable to the explanation of the Y variance and the direction of effect. The significance of variable contributions was defined by VIP>1 (Akarachantachote *et al*, 2014; Chong & Jun, 2005; Hill & Lewicki, 2006; Palermo *et al*, 2009). This approach was proved effective in selecting predictors in an RCT with multiple biological and clinical predictors and outcomes (Poletti *et al.*, 2024b).

To confirm the significance of the effects of the variables selected in the PLS, the individual PLS component scores for predictors (48-plex analytes or KP metabolites) were then entered as independent variable into GLZM regressions on ChP volumes, and on DMN fALFF values, with age and sex as covariates (McCullagh & Nelder, 1989). Parameter estimates were obtained with iterative re-weighted least squares maximum likelihood procedures. The significance of the effects was calculated with the likelihood ratio (LR) statistic, thus providing a test of the increment

in the log-likelihood attributable to each current estimated effect (Agresti, 1996; Dobson, 1990). In the presence of a significant effect of the PLS component scores for KP metabolites, simple correlations were then tested for the association of the raw values of the single variables selected by the ML PLS procedure as significant, and the predicted outcomes of interest (ChP volumes and fALFF values) adjusted for age and sex.

Analyses on HRF parameters

Then, in order to test voxel-wise differences in HRF parameter maps between MDD and BD, the multivariate analysis tool 3dMVM in AFNI (Chen *et al*, 2015) was used. The analysis employed 3dMVM on smoothed HRF parameters, applying a 6 mm Gaussian kernel. Within-subject factors included HRF parameters such as RH, FWHM, and time to peak TTP, while between-subject factors comprised diagnostic groups (BD and MDD), with age and gender as nuisance covariates. To control for Type I error across multiple voxel-wise comparisons, a false discovery rate (FDR) correction was applied, maintaining statistical significance for group comparisons at a threshold of $pFDR < 0.05$.

PLS multivariate regression was at this point used setting HRF parameters (RH, FWHM, and TTP) as dependent variables, and plasma KP metabolites as independent factors.

Then, Multivariate Analysis of Variance were used to assess associations among HRF parameters and corrected BACS cognitive scores.

Finally, mediation models were tested entering Kyn, Kyna, and 3-HK as independent variables, TTP and FWHM as mediators, and each BACS domain significantly associated with HRF parameters as dependent variables. PROCESS macro for SPSS version 3.0 (Hayes, 2017), with 5.000 bootstrap resamples to generate Bonferroni-adjusted 99% confidence intervals was used for mediation analyses.

Effect of genetic load for Kyn on WMHs

Afterwards, given results from previous analyses suggesting a vascular modulation role of Kyn, affecting rs-fMRI measures, we explored the relation between

Kyn and SII as a marker of both inflammation and endothelial sufferance, in the context of GLZM, correcting for the effect of age and sex.

Then, analyses focused on possible genetic predisposition to circulating Kyn levels, exploring the association between Kyn and PRS of Kyn, the effect of SH2B3 rs3184504 C>T SNP on Kyn PRS, and subsequently the PRS effects on both brain-based neurovascular risk, as proxied by WMHs, and white matter integrity. Lastly, mediation models predicting cognition were performed.

First, the genotype frequencies of SH2B3 rs3184504 were tested for Hardy-Weinberg equilibrium with a χ^2 test for goodness of fit.

Then, differences between MDD and BD in Kyn PRS were tested through Mann–Whitney U tests.

Afterwards, we tested whether Kyn PRS significantly predicted plasma Kyn levels in our sample in the context of GLZM, entering the variables as independent and dependent variables respectively.

Subsequently, we explored the effect of Kyn PRS on brain white matter structure.

We first tested through GLZM whether the Kyn PRS could predict WMHs volume and number, entering the first variable as predictor and WMHs as dependent variables, with age and sex as nuisance covariates. Same analyses were performed considering plasma levels of Kyn as independent variable.

Then, to test the effect of SH2B3 rs3184504 C>T SNP on PRS for Kyn ANOVA was carried out; when significant effects were found, post-hoc Fisher LSD tests were performed. Similarly, to explore whether SH2B3 rs3184504 C>T SNP influenced plasma Kyn and Kyn/Trp index non-parametric Kruskal-Wallis H tests were carried out; when significant effects were found, post-hoc multiple comparisons of mean ranks were performed.

Then, given the influence of SH2B3 rs3184504 C>T SNP on Kyn PRS, we tested the interaction between the SNP and Kyn PRS in predicting WMHs.

Kyn PRS effect on WM microstructure and cognition

Afterwards, to explore in more detail the effect of PRS on white matter integrity, voxel-wise DTI analyses were performed using nonparametric permutation-

based testing as implemented in Randomise in FSL. We tested for linear effect of Kynurenine PRS on WM integrity, specifically on FA, MD, AD, and RD across the WM skeleton with general linear models (GLM). We accounted for the effects of nuisance covariates which could influence WM microstructure: age (P. *et al*, 2007), sex (M. *et al*, 2011), diagnosis (Koshiyama *et al*, 2020), and whether or not to had been on lithium treatment for at least 6 months at the time of the MRI (Benedetti *et al*, 2013). Threshold-free cluster enhancement (TFCE) was used to avoid defining arbitrary cluster-forming thresholds and smoothing levels. The data were tested against an empirical null distribution generated by 5000 permutations for each contrast, thus providing statistical maps fully corrected for multiple comparisons across space. TFCE-corrected $p < 0.05$ were considered significant.

Afterwards, we extracted mean DTI parameters that significantly affected WM microstructure integrity in the previous analysis. Specifically, skeletonised maps of each participant were masked including only voxels part of significant clusters of TBSS analyses.

Then, MANOVA was performed entering extracted DTI parameters as independent factors and cognitive scores as dependent variables.

Finally, mediation models were performed using DTI measures that were significantly associated with cognitive scores as mediators of the relationship between Kyn PRS and cognition. All models were run through PROCESS macro for SPSS version 3.0 (Hayes, 2017), with 5.000 bootstrap resamples to generate Bonferroni-adjusted 99% confidence intervals, similar to previous mediation models.

RESULTS

The clinical and demographic features of the sample are summarised in Table2.

	MDD (n=42)	BD (n=36)	X^2/t	p	q
Age (years)	51.186 ± 10.292	50.056 ± 12.264	0.446	0.657	0.848
Sex (M/F)	17/25	15/21	0.037	0.848	0.848
Education (years)	13.023 ± 3.738	12.833 ± 3.517	0.230	0.818	0.848
BMI	24.674 ± 3.596	25.752 ± 5.044	-1.105	0.272	0.848
Illness duration (years)	18.861 ± 10.685	20.667 ± 12.506	-0.692	0.491	0.848
Depressive episodes	5.721 ± 5.288	7.306 ± 6.467	-1.198	0.234	0.848
HDRS score	21.878 ± 6.034	21.344 ± 5.326	0.395	0.694	0.848
BACS verbal memory	1.974 ± 1.423	1.794 ± 1.493	0.522	0.603	0.848
BACS verbal fluency	1.838 ± 1.537	1.576 ± 1.324	0.760	0.450	0.848
BACS working memory	1.263 ± 1.201	1.424 ± 1.501	-0.502	0.617	0.848
BACS executive functions	2.000 ± 1.673	1.903 ± 1.620	0.240	0.811	0.848
BACS selective attention	0.658 ± 1.122	0.710 ± 1.006	-0.200	0.842	0.848
BACS psychomotor speed and coordination	1.111 ± 1.237	0.710 ± 1.101	1.393	0.168	0.848
BACS global score	1.470 ± 0.826	1.366 ± 0.926	0.506	0.614	0.848

Table 2. *Clinical-demographic variables. BACS scores are equivalent scores. Means ± standard deviations are reported. Both p and q (FDR-corrected p-values) values are reported for each test.*

MDD and BD patients did not significantly differ in any features, including the neurobiological variables, as reported in Table 3.

	MDD (n=42)	**BD (n=36)**	**U**	**p**	**q**
Trp (mg/mL)	11.688 (3.507)	10.222 (4.337)	598.000	0.114	0.374
Kyn (mg/mL)	0.073 (0.059)	0.081 (0.064)	672.000	0.403	0.820
Kyn/Trp ratio *1000	6.440 (3.632)	8.594 (5.199)	565.000	0.056	0.334
3-hydroxykynurenine (3-HK) (ng/mL)	34.925 (6.180)	34.200 (7.610)	719.500	0.718	0.944
Quinolinic acid (QA) (ng/mL)	131.800 (10.150)	131.225 (9.595)	752.000	0.972	0.988
Kynurenic acid (KYNA) (ng/mL)	7.340 (4.280)	6.570 (3.165)	746.500	0.928	0.988
QA/KYNA ratio	10.650 (1.770)	10.285 (1.405)	743.500	0.904	0.988
KYNA/KYN ratio *1000	18.320 (9.632)	19.483 (8.873)	743.000	0.900	0.988
3-HK/KYN ratio	94.881 (81.800)	97.703 (74.819)	726.500	0.771	0.968
Left ChP volume (mm^3)	0.548 (0.366)	0.460 (0.415)	754.000	0.988	0.988
Right ChP volume (mm^3)	495.350 (217.100)	505.400 (173.350)	688.500	0.502	0.898
IL-1β	20.750 (5.000)	18.000 (6.000)	546.000	0.157	0.488
IL-1ra	10.750 (3.750)	10.000 (6.000)	557.000	0.196	0.578
IL-1α	18.000 (4.875)	17.000 (4.500)	661.500	0.875	0.988
IL-2Rα	49.250 (27.500)	61.000 (25.500)	513.000	0.076	0.334
IL-2	16.250 (6.000)	16.000 (7.000)	622.000	0.557	0.933
IL-3	19.875 (2.750)	20.000 (3.500)	617.500	0.525	0.911
IL-4	14.000 (3.750)	14.000 (10.000)	634.500	0.652	0.933

IL-5	38.500 (32.000)	42.000 (20.500)	582.000	0.307	0.758
IL-6	31.250 (26.250)	32.000 (13.500)	611.000	0.480	0.885
IL-7	21.750 (7.250)	21.250 (6.000)	635.000	0.656	0.933
IL-8	20.375 (8.250)	21.500 (8.000)	509.000	0.070	0.334
IL-9	353.500 (388.750)	199.000 (130.750)	510.500	0.072	0.334
IL-10	15.250 (2.750)	15.000 (4.500)	627.000	0.594	0.933
IL-12 (p40)	14.000 (3.250)	15.000 (4.000)	501.000	0.057	0.334
IL-12 (p70)	17.000 (3.000)	17.500 (7.000)	655.500	0.824	0.988
IL-13	17.000 (5.750)	16.500 (9.000)	592.500	0.364	0.767
IL-15	26.500 (18.750)	30.000 (19.500)	528.000	0.108	0.374
IL-16	35.500 (25.000)	36.000 (11.000)	656.500	0.832	0.988
IL-17	17.000 (3.000)	17.000 (4.750)	642.500	0.716	0.944
IL-18	75.250 (69.625)	73.000 (34.500)	648.500	0.765	0.968
IFN-γ	36.000 (14.250)	33.000 (11.500)	588.500	0.341	0.758
IFN-α2	16.000 (2.000)	15.000 (5.000)	563.000	0.219	0.587
TNF-α	37.000 (22.000)	42.000 (15.000)	501.500	0.058	0.334
TNF-β	769.750 (680.000)	335.500 (422.000)	521.500	0.093	0.343
MIF	683.500 (322.125)	651.000 (223.500)	507.000	0.066	0.334
TRAIL	69.000 (52.000)	61.000 (33.000)	674.000	0.983	0.988
Eotaxin/CCL11	199.000 (136.625)	175.000 (92.500)	589.500	0.347	0.758
GRO-α/CXCL1	135.000 (122.750)	150.000 (128.000)	465.000	0.022	0.325

IP-10/CXCL10	147.250 (87.750)	91.000 (116.500)	454.000	0.016	0.315
MCP-1/CCL2	32.500 (12.750)	29.000 (16.000)	517.500	0.085	0.334
MCP-3/CCL7	14.750 (2.750)	14.000 (4.000)	562.000	0.215	0.587
MIG/CXCL9	66.250 (65.000)	65.000 (45.500)	667.500	0.926	0.988
MIP-1α/CCL3	16.250 (5.500)	17.000 (9.000)	512.000	0.075	0.334
MIP-1β/CCL4	793.500 (1273.000)	772 (943.000)	589.500	0.347	0.758
RANTES/CCL5	5854.000 (5779.250)	5945.500 (2884.500)	628.000	0.602	0.933
SDF-1α/CXCL12	219.375 (132.500)	175.500 (137.000)	517.000	0.084	0.334
CTACK/CCL27	244.500 (300.500)	251.000 (167.000)	668.000	0.931	0.988
FGF basic	21.500 (4.750)	19.000 (6.000)	476.000	0.030	0.334
HGF	37.000 (23.500)	40.000 (15.500)	583.000	0.312	0.758
NGF-β	40.500 (50.500)	50.500 (39.000)	635.000	0.656	0.933
PDGF-BB	88.000 (95.500)	99.000 (144.250)	672.000	0.965	0.988
SCF	40.000 (15.125)	41.500 (8.500)	636.000	0.664	0.933
VEGF	56.500 (56.000)	47.000 (18.500)	608.500	0.463	0.885
G-CSF	23.500 (7.375)	28.000 (18.500	409.500	0.004	0.177
GM-CSF	25.250 (9.000)	24.000 (6.500)	628.000	0.602	0.933
SCGF-β	329.750 (121.500)	266.000 (85.000)	422.500	0.006	0.177
M-CSF	44.000 (25.250)	46.000 (15.000)	609.500	0.470	0.885
LIF	16.000 (2.875)	16.000 (3.250)	643.000	0.720	0.944

Table 3. *Comparison of biological variables between the two samples. Median (IQR) are reported. Both p and q (FDR-corrected p-values) values are reported for each test.*

Moreover, comparing the total sample with the subsample used for MRI analysis, the two do not differ in either clinical-demographic or biological variables, as shown in Table 4.

	Whole sample (n=137)	**Subsample (n=78)**	**X^2/t/U**	**p**	**q**
Age (years)	49.533 ± 10.986	50.641 ± 11.242	-0.705	0.481	0.949
Sex (M/F)	54/83	32/46	0.054	0.817	0.949
Education (years)	12.919 ± 3.389	13.000 ± 3.597	-0.164	0.870	0.949
BMI	25.071 ± 4.480	25.211 ± 4.330	-0.223	0.824	0.949
Illness duration (years)	18.400 ± 11.468	19.487 ± 11.450	-0.662	0.509	0.949
Depressive episodes	5.374 ± 5.076	6.487 ± 5.895	-1.422	0.156	0.949
HDRS score	21.235 ± 5.684	21.542 ± 5.674	-0.319	0.750	0.949
Diagnosis (BD/MDD)	53/84	36/42	1.1425	0.285	0.949
Trp (mg/mL)	11.260 (4.207)	11.153 (4.206)	5172.000	0.697	0.949
Kyn (mg/mL)	0.078 (0.071)	0.078 (0.057)	5258.000	0.847	0.949
Kyn/Trp ratio *1000	7.404 (5.938)	6.899 (5.404)	5323.500	0.965	0.965
Kynurenine PRS	0.150 (0.195)	0.169 (0.221)	4433.500	0.469	0.949

Table 4. *Comparison of demographic and clinical variables between the two samples. Mean ± standard deviations and median (IQR) are reported for normal and non-normal variables respectively. Both p and q (FDR-corrected p-values) values are reported for each test.*

Considering the possible influence of treatments on levels of KP metabolites, MRI-related measures, and plasma analytes, no significant associations were observed after correcting for multiple comparisons.

Normality tests

The distribution of variables was not normal for both ChP volumes (Left: Shapiro-Wilk W=0.96, p=0.013; Right: W=0.95, p=0.006), Kyn (W=0.83, p<0.001),

Kyn/TRY ratio (W=0.78, p<0.001), KynA (W=0.94, p=0.008), KynA/Kyn ratio (W=0.82, p<0.001), QA/KynA ratio (W=0.97, p=0.033), and 3-HK/Kyn ratio (W=0.92, p<0.001). Similar results were reported also for 48-plex analytes: IL-1β (W=0. 59, p<0.001), IL-1ra (W=0.92, p<0.001), IL-1α (W=0.62, p<0.001), IL-2Rα (W=0.69, p<0.001), IL-2 (W=0.34, p<0.001), IL-3 (W=0.68, p<0.001), IL-4 (W=0.76, p<0.001), IL-5 (W=0.88, p<0.001), IL-6 (W=0.74, p<0.001), IL-7 (W=0.93, p<0.001), IL-8 (W=0.68, p<0.001), IL-9 (W=0.83, p<0.001), IL-10 (W=0.67, p<0.001), IL-12 (p40) (W=0.54, p<0.001), IL-12 (p70) (W=0.46, p<0.001), IL-13 (W=0.66, p<0.001), IL-15 (W=0.78, p<0.001), IL-16 (W=0.80, p<0.001), IL-17 (W=0.31, p<0.001), IL-18 (W=0.97, p<0.001), IFN-γ (W=0.32, p<0.001), IFN-α2 (W=0.51, p<0.001), TNF-α (W=0.80, p<0.001), TNF-β (W=0.86, p<0.001), MIF (W=0.99, p=0.049), TRAIL (W=0.96, p<0.001), Eotaxin/CCL11 (W=0.87, p<0.001), GRO-α/CXCL1 (W=0.95, p<0.001), IP-10/CXCL10 (W=0.63, p<0.001), MCP-1/CCL2 (W=0.77, p<0.001), MCP-3/CCL7 (W=0.77, p<0.001), MIG/CXCL9 (W=0.27, p<0.001), MIP-1α/CCL3 (W=0.48, p<0.001), MIP-1β/CCL4 (W=0.87, p<0.001), RANTES/CCL5 (W=0.94, p<0.001), SDF-1α/CXCL12 (W=0.84, p<0.001), CTACK/CCL27 (W=0.95, p<0.001), FGF basic (W=0.20, p<0.001), HGF (W=0.28, p<0.001), NGF-β (W=0.82, p<0.001), PDGF-BB (W=0.74, p<0.001), SCF (W=0.79, p<0.001), VEGF (W=0.91, p<0.001), G-CSF (W=0.71, p<0.001), GM-CSF (W=0.51, p<0.001), SCGF-β (W=0.84, p<0.001), M-CSF (W=0.71, p<0.001), LIF (W=0.58, p<0.001). Also MRI-based measures had non-normal distributions: HRF Height (W=0.78, p<0.001), HRF FWHM (W=0.96, p=0.014), MD (W=0.96, p=0.014), number of WMHs (W=0.93, p<0.001), and mean volume of WMHs (W=0.59, p<0.001), except for HRF TTP (W=0.98, p=0.539) and AD (W=0.99, p=0.340). The PRSs did not differ significantly from a normal distribution.

Effect of plasma analytes on IDO

Several analytes significantly associated with IDO. In the PLS model including as factors the 48-plex analytes, one significant component in the prediction was extracted explaining 6,42% of variance of Kyn/Trp ratio (coefficient of the model=0.066, R^2X=0.379; R^2Y=0.064). Factors significantly contributing to predict Kyn/Trp ratio were: IP-10/CXCL10 (w=0.276, VIP=1.909), IL-1α (w=0.270,

VIP=1.869), GRO-α/CXCL1 (w=0.221, VIP=1.531), RANTES/CCL5 (w=0.212, VIP=1.466), IL-8 (w=0.206, VIP=1.429), IL-16 (w=0.201, VIP=1.389), IL-15 (w=0.195, VIP=1.350), VEGF (w=0.194, VIP=1.347), TRAIL (w=0.188, VIP=1.301), IL-3 (w=0.187, VIP=1.296), IL-7 (w=0.185, VIP=1.284), IL-18 (w=0.182, VIP=1.262), LIF (w=0.171, VIP=1.182), IL-10 (w=0.165, VIP=1.141), TNF-α (w=0.160, VIP=1.110), NGF-β (w=0.159, VIP=1.102), FGF basic (w=0.157, VIP=1.091), IL-6 (w=, VIP=1.090), IFN-γ (w=0.155, VIP=1.075), IL-2Rα (w=0.149, VIP=1.032) (Figure 1).

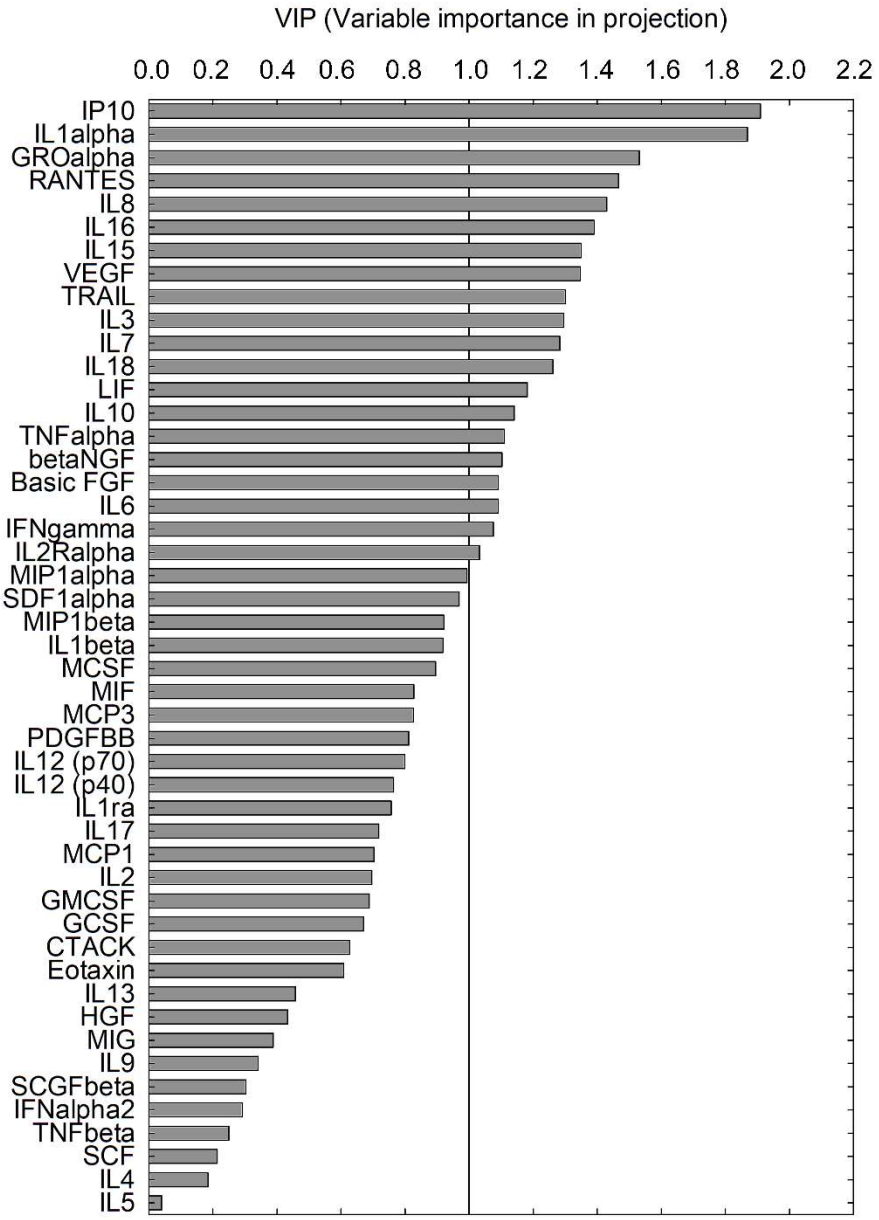

Figure 1. *PLS on plasma analytes predicting IDO. Variables predicting IDO, listed according to their relative VIP values at ML PLS regression*

From the explanatory GLZM assessing the predictive value of the PLS component scores for plasma analytes on IDO showed a significant contribution of the component (LR $\chi2$=5.098, p=0.023), correcting for the effect of age and sex. Factors extracted from PLS component with VIP>1 significantly correlated with IDO values adjusted for age and sex: IP-10/CXCL10 (ρ=0.233, t=2.038, p=0.045), IL-1α (ρ=0.594, t=6.269, p<0.001), GRO-α/CXCL1 (ρ=0.585, t=6.119, p<0.001), RANTES/CCL5 (ρ=0.587, t=6.145, p<0.001), IL-8 (ρ=0.606, t=6.465, p<0.001), IL-16 (ρ=0.665, t=7.551, p<0.001), IL-15 (ρ=0.624, t=6.778, p<0.001), VEGF (ρ=0.711, t=8.578, p<0.001), TRAIL (ρ=0.630, t=6.884, p<0.001), IL-3 (ρ=0.468, t=4.490, p<0.001), IL-7 (ρ=0.549, t=5.570, p<0.001), IL-18 (ρ=0.583, t=6.097, p<0.001), LIF (ρ=0.445, t=4.215, p<0.001), IL-10 (ρ=0.331, t=2.976, p=0.004), TNF-α (ρ=0.613, t=6.584, p<0.001), NGF-β (ρ=0.667, t=7.606, p<0.001), FGF basic (ρ=0.439, t=4.147, p<0.001), IL-6 (ρ=0.671, t=7.685, p<0.001), IFN-γ (ρ=0.415, t=3.866, p<0.001), IL-2Rα (ρ=0.560, t=5.740, p<0.001).

Effects of KP metabolites on ChP volume

KP metabolites influenced ChP volumes. Using a ML multivariate PLS regression modelling (Figure 2), including levels of Trp, Kyn, Kyn/Trpratio, KynA, KynA/Kyn ratio, 3-HK, 3-HK/Kynratio, QA, QA/KynA ratio as factors, a model with one component explained 5.1% of variance in bilateral choroid plexus ‰ volumes (coefficient for the whole model=0.227, Y loading for predicting Left ChP=0.880; Right ChP=0.447; R^2X=0.260; R^2Y=0.051). The variables significantly contributing to predict bigger ChP volumes were lower QA/KynA ratio (w=-0.671, VIP=2.012), lower QA (w=-0.340, VIP=1.021), and higher KynA (w=0.432, VIP=1.297).

With explanatory GLZM regression modelling, the PLS component scores for KP metabolites, as derived by the ML PLS analysis, significantly predicted Left ChP ‰ volumes (LR $\chi2$=7.931, p=0.0049), with a significant positive effect of age (LR $\chi2$=4.596, p=0.0321), and no effect of sex. Both QA/KynA ratio, and QA and KynA concentrations, significantly correlated with the predicted ChP ‰ volumes, adjusted for age and sex (ρ=-0.693, t=-8.372, p<0.001; ρ=-0.326, t=-3.011, p=0.004; and

ρ=0.675, t=7.976, p<0.001; respectively) (Figure 2). Effects were not significant for the Right ChP.

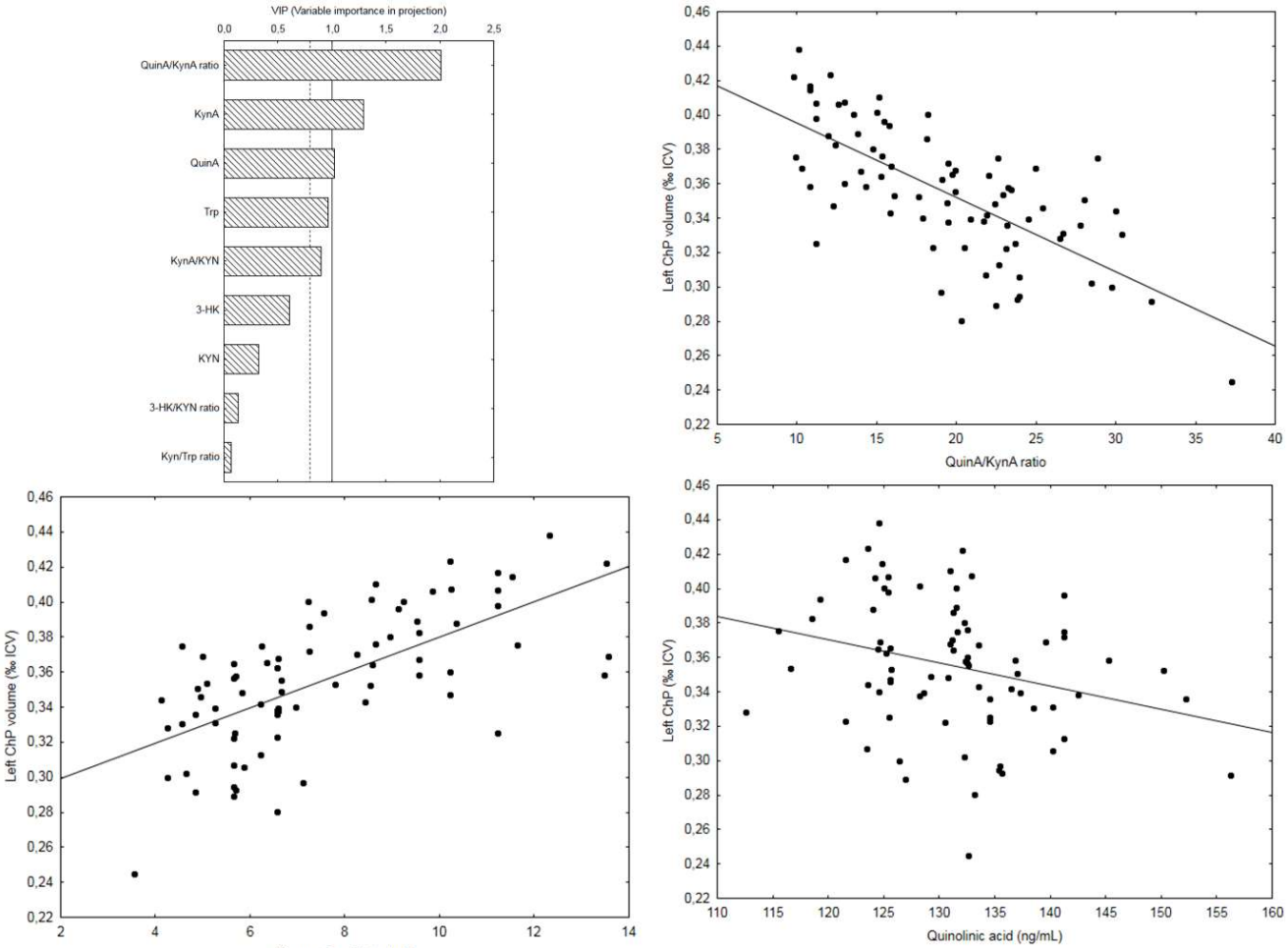

Figure 2. *Choroid plexus volume and KP metabolites analyses. Variables predicting ChP ‰ volumes, listed according to their relative VIP values at ML PLS regression (top left); and correlation between the three significant variables and ChP ‰ volumes, adjusted for age and sex at GLZM regression.*

Effects of KP metabolites on fALFF

KP metabolites influenced fALFF in the DMN. Using a ML multivariate PLS regression modelling (Figure 3), including levels of Trp, Kyn, Kyn/Trp ratio, KynA, KynA/Kyn ratio, 3-HK, 3-HK/Kyn ratio, QA, QA/KynA ratio as factors, a model with one component explained 7.1% of variance in DMN fALFF values (coefficient for the whole model=0.225, R^2X=0.219; R^2Y=0.071). The variables significantly contributing to predict higher fALFF were higher Kyn (w=0.466, VIP=1.398), higher 3-HK (w=0.555, VIP=1.664), and lower KynA (w=-0.342, VIP=1.027). With explanatory GLZM regression modelling, the PLS component scores for KP metabolites, as

derived by the ML PLS analysis, significantly predicted DMN fALFF values (LR $\chi 2$=5.191, p=0.023), with non-significant effects of sex and age. Both Kyn, 3-HK, and KynA concentrations significantly correlated with the predicted DMN fALFF values, adjusted for age and sex (ρ=0.633, t=6.798, p<0.001; ρ=0.378, t=3.388, p=0.001; and ρ=-0.270, t=-2.326, p=0.023; respectively) (Figure 3).

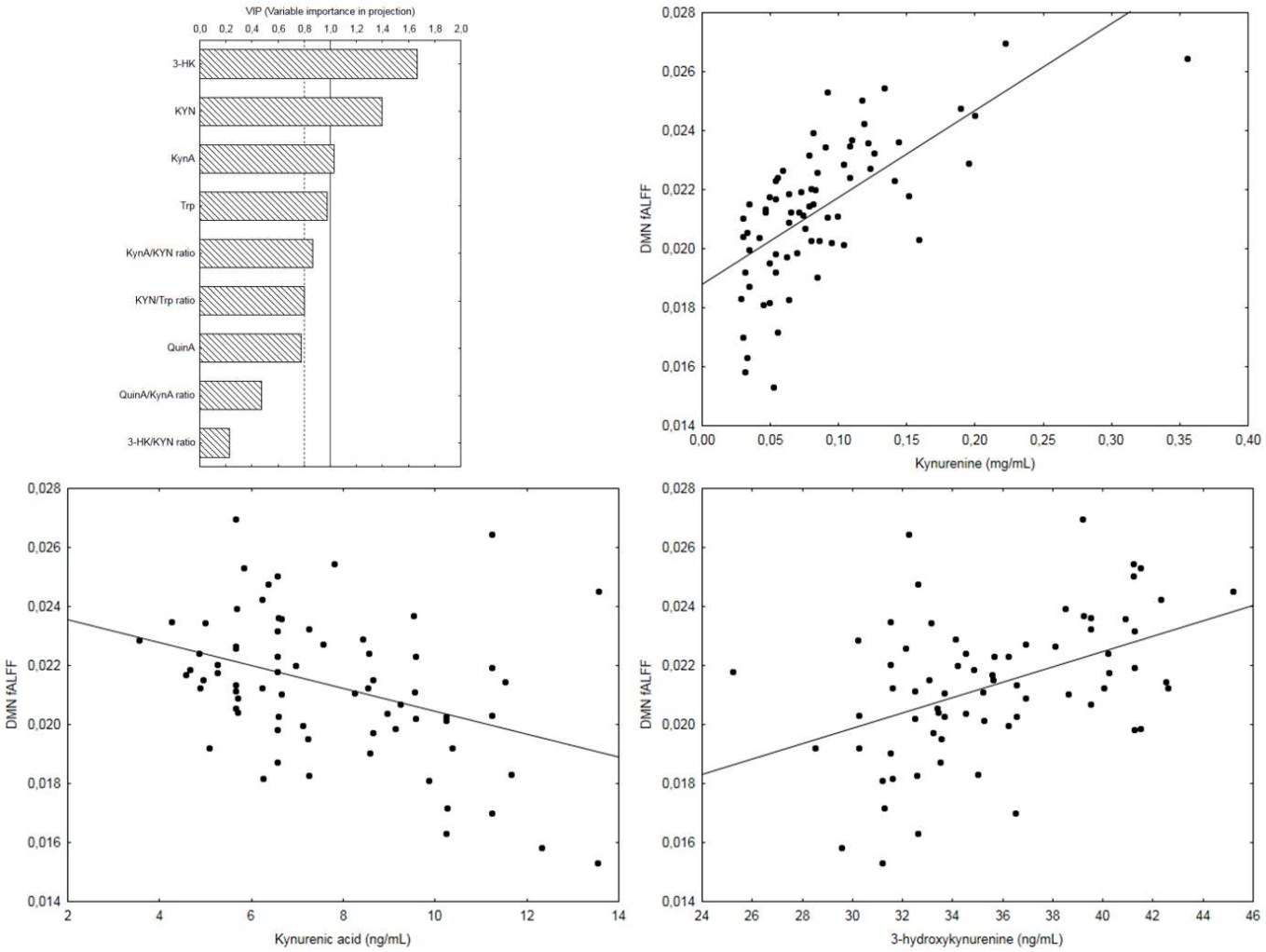

Figure 3. *Relations between fALFF and KP metabolites. Variables predicting fALFF in the DMN, listed according to their relative VIP values at ML PLS regression (top left); and correlation between the three significant variables and DMN fALFF values, adjusted for age and sex at GLZM regression.*

Effect of KP metabolites on HRF parameters

We conducted a between-subjects analysis on HRF parameters' voxel-based images to assess potential differences between the BD and MDD groups. No significant differences emerged in the HRF parameters across the groups from

3dMVM model, so we proceeded in considering the whole sample for HRF-based analyses.

KP metabolites influenced HRF temporal properties. TTP and FHWM highly correlated among themselves (shorter TTP, wider FHWM: $r=-0.911$, $p<0.001$), but not with RH. Using a ML multivariate PLS regression modelling (Figure 4), including levels of Trp, Kyn, Kyn/Trp ratio, KynA, KynA/Kyn ratio, 3-HK, 3-HK/Kyn ratio, QA, QA/KynA ratio as factors; and TTP, FWHM, and RH as dependent variables; a model with one component explained 9.3% of variance HRF temporal parameters (coefficient for the whole model=0.328, $R^2X=0.299$; $R^2Y=0.094$), with stronger effects on TTP and FWHM than on RH (coefficients: TTP= -0.690, FWHM=0.704, RH=0.168). The variables significantly contributing to predict shorter TTP and larger FWHM were higher Kyn (w=0.505, VIP=1.514), higher Kyn/Trp ratio (w=0.382, VIP=1.145), lower KynA/Kyn ratio (w= -0.449, VIP=1.346), and lower 3-HK/Kyn ratio (w= -0.508, VIP=1.524). With explanatory GLZM regression modelling, including age and sex as covariates, individual levels of these four KP metabolites showed significant effects on TTP (Kyn: LR $\chi2=5.191$, $p=0.0227$; Kyn/Trp ratio: LR $\chi2=4.055$, $p=0.044$; KynA/Kyn ratio: LR $\chi2=4.406$, $p=0.036$; 3-HK/Kyn ratio: LR $\chi2=6.071$, $p=0.014$) and FWHM (Kyn: LR $\chi2=6.275$, $p=0.012$; Kyn/Trp ratio: NS; KynA/Kyn ratio: LR $\chi2=4.967$, $p=0.026$; 3-HK/Kyn ratio: LR $\chi2=6.391$, $p=0.012$), but not on RH.

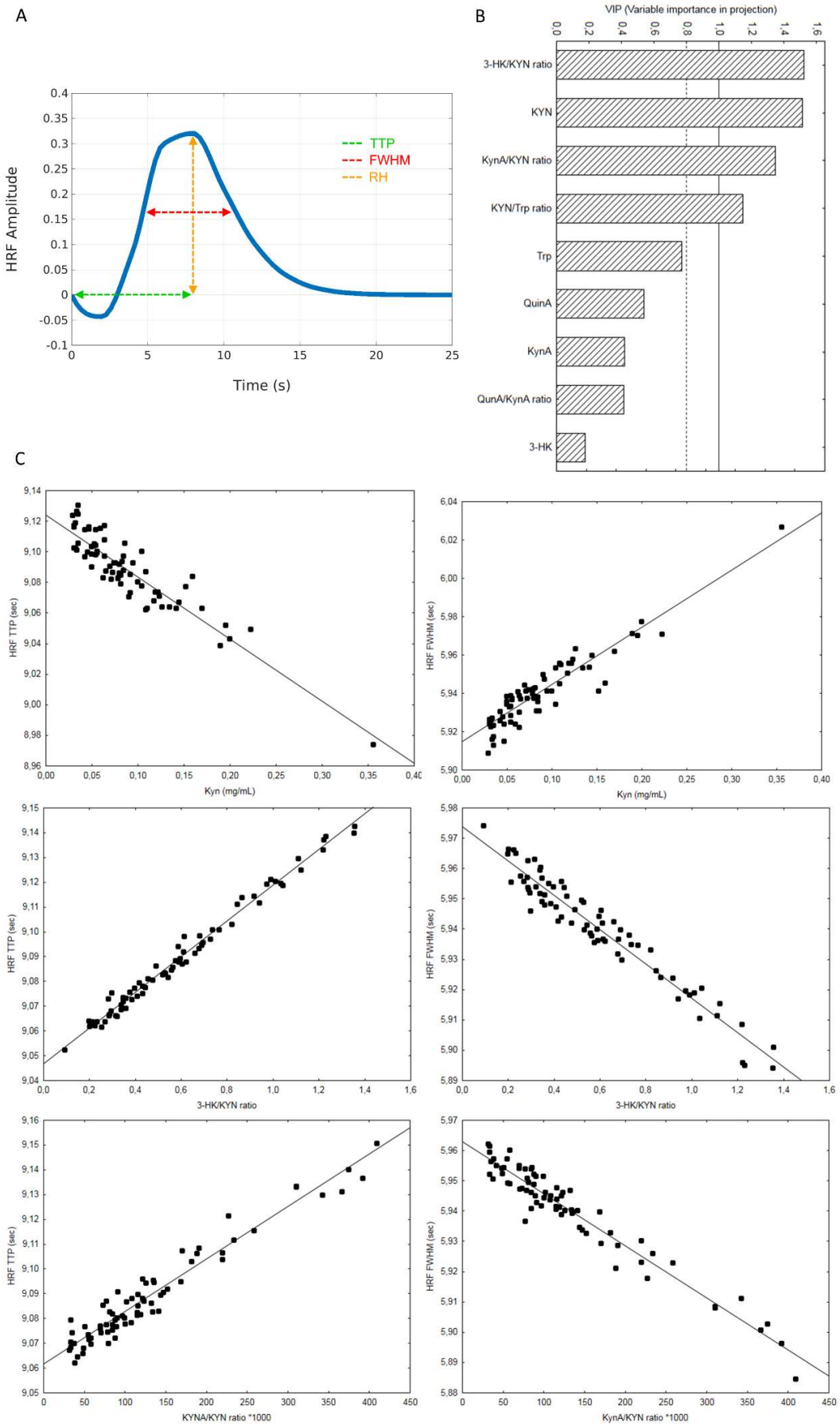

Figure 4. *Effects of KP metabolites on HRF features. In A) Sample-based average HRF function and HRF's parameters; B) PLS results with variables predicting HRF; C) correlation between the significant variables and TTP and FWHM, adjusted for age and sex at GLZM regression.*

Mediation models on metabolites' effect on cognition through HRF parameters

HRF features influenced cognition: TTP and FWHM were entered in separate models because of high multicollinearity (VIF=113.985, tolerance=0.009). Specifically, TTP has a multivariate effect on BACS scores (Wilks=0.771, F=2.464, ηp2=0.229, p=0.028), significantly predicting BACS global score (β=0.301, t=2.529, p=0.014), verbal fluency (β=0.271, t=2.253, p=0.028), working memory (β=0.243, t=2.005, p=0.049), executive functions (β=0.281, t=2.339, p=0.022), processing speed (β=0.355, t=3.041, p=0.003), and psychomotor speed and coordination (β=0.260, t=2.149, p=0.035).

Also, FWHM significantly predicted BACS global score (β=-0.275, t=-2.291, p=0.026), verbal fluency (β=-0.302, t=-2.533, p=0.014), working memory (β=-0.254, t=-2.098, p=0.040), and processing speed (β=-0.267, t=-2.218, p=0.030).

KP metabolites influenced cognitive function by acting on the HRF. Mediation modelling (Figure 5) showed that the effect of Kyn on BACS scores was fully mediated by TTP and FWHM, with no significant direct effect. Specifically: TTP completely mediated the effect of Kyn on verbal fluency (a*b: β=-0.101, CI [-0.238; -0.008]), psychomotor speed and coordination (a*b: β=-0.102, CI [-0.235; -0.018]), and on BACS global score (a*b: β=-0.108, CI [-0.286; -0.007]). FWHM completely mediated the effect of Kyn on verbal fluency (a*b: β=-0.113, CI [-0.266; -0.010]), and on BACS global score (a*b: β=-0.095, CI [-0.267; -0.001]). Also the effect of 3-HK on verbal fluency was completely mediated by FWHM (a*b: β=0.115, CI [0.005; 0.261]), while TTP fully mediated the 3-HK effect on psychomotor speed and coordination (a*b: β=0.134, CI [0.018; 0.293]).



Figure 5. *Mediation models. Effects of KP metabolites on cognition fully mediated by their effects on HRF features.*

Effect of SII on Kyn levels

Considering the analysis of the predictive role of SII on Kynurenine levels, GLZM reported a significant positive prediction (LR $\chi2$= 4.763, p=0.029; Figure 6).

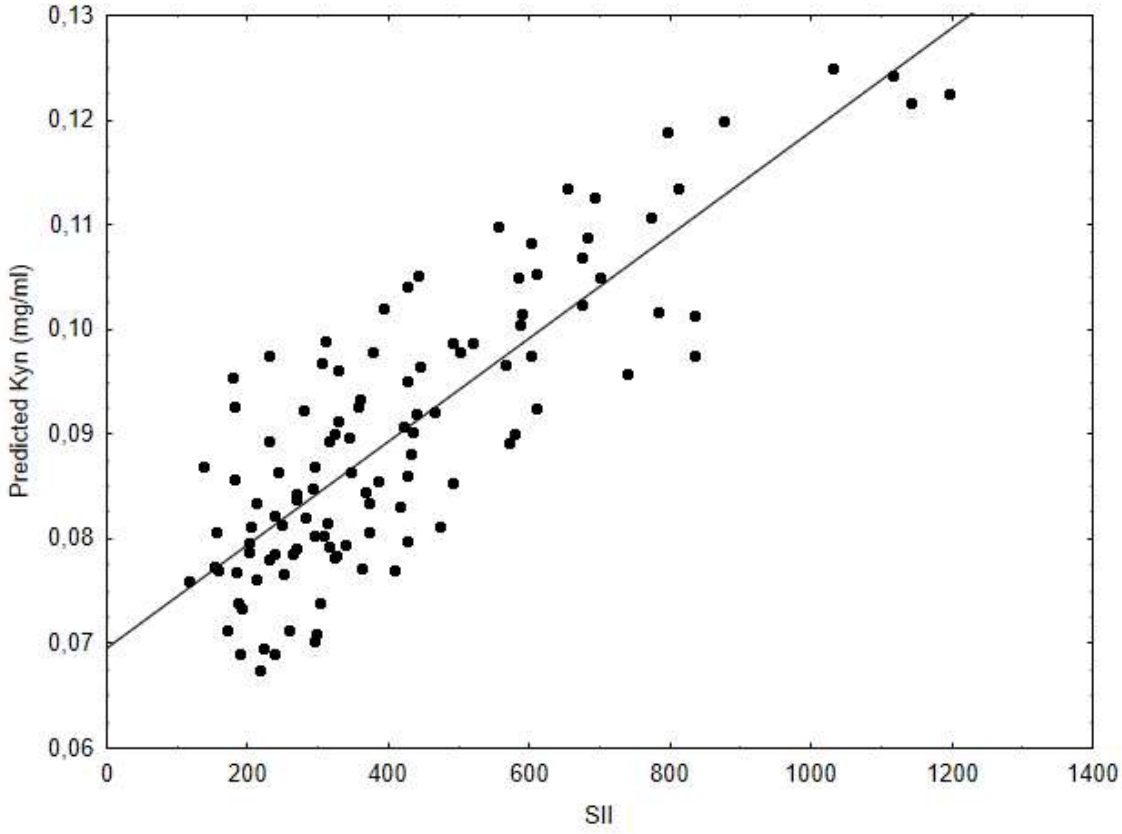

***Figure 6**. SII prediction of Kyn. On the Y axis, Kyn predicted values, corrected for age and sex.*

Genetic-related analyses on Kyn

Frequencies of SH2B3 rs3184504 C>T SNP variants were in Hardy-Weinberg equilibrium (C/C: n=23, 16.78%; C/T: n=77, 56.52%; T/T: n=37, 27.00%; H-W χ^2=2.477, p=0.290). The frequency of the T allele was 55.26%.

MDD and BD patients showed no significant difference in Kyn PRS.

Kyn PRS significantly predicted Kyn levels (LR $\chi2$= 4.320, p=0.037) and Trp breakdown index (LR $\chi2$= 4.452, p=0.034) (Figure 7).

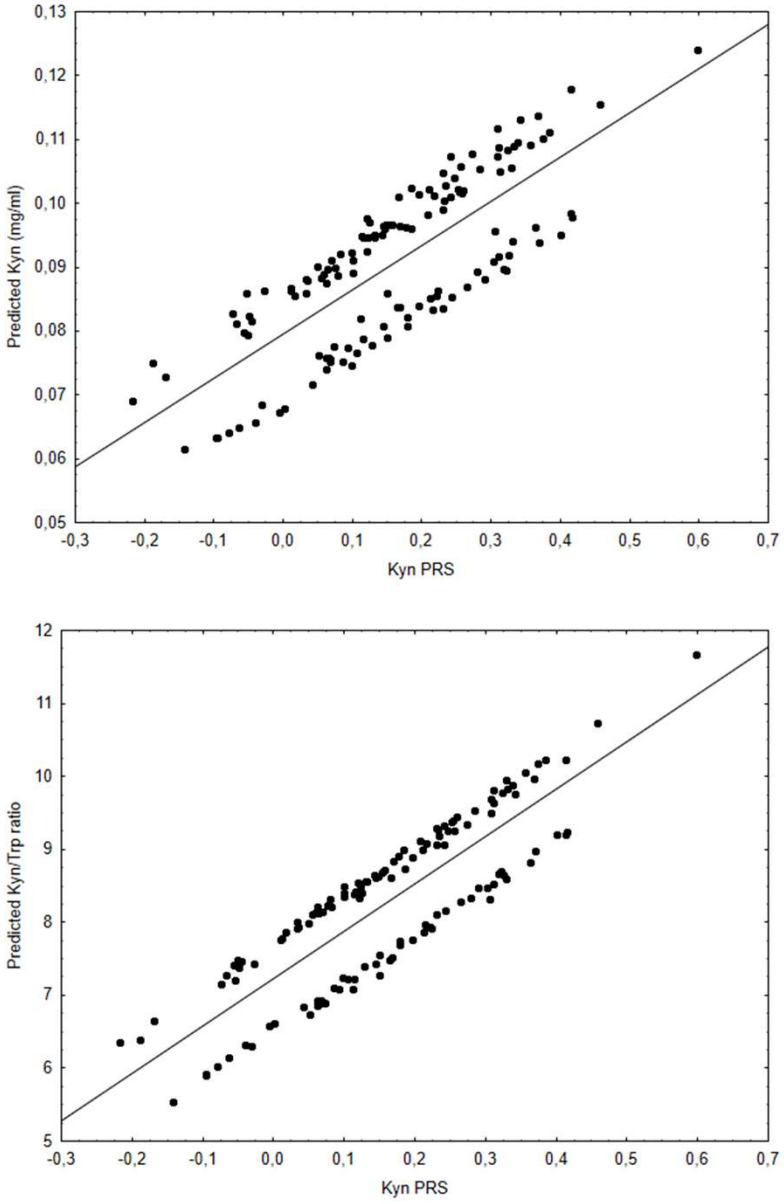

Figure 7. *Kyn PRS predict IDO and Kyn. Top: Kyn PRS predict plasma Kyn levels; Bottom: Kyn PRS predict IDO activation.*

Effects of genetic predisposition to Kyn on WMHs

The PRS for Kyn significantly predicted the number of WMHs number (higher PRS, more WMHs; LR $\chi 2 = 12.014$, $p<0.001$) and the mean volume of WMHs (higher PRS, larger WMHs: LR $\chi 2 = 11.703$, $p<0.001$) in our sample (Figure 8). However, plasma Kyn levels did not show significant effects on WMHs.

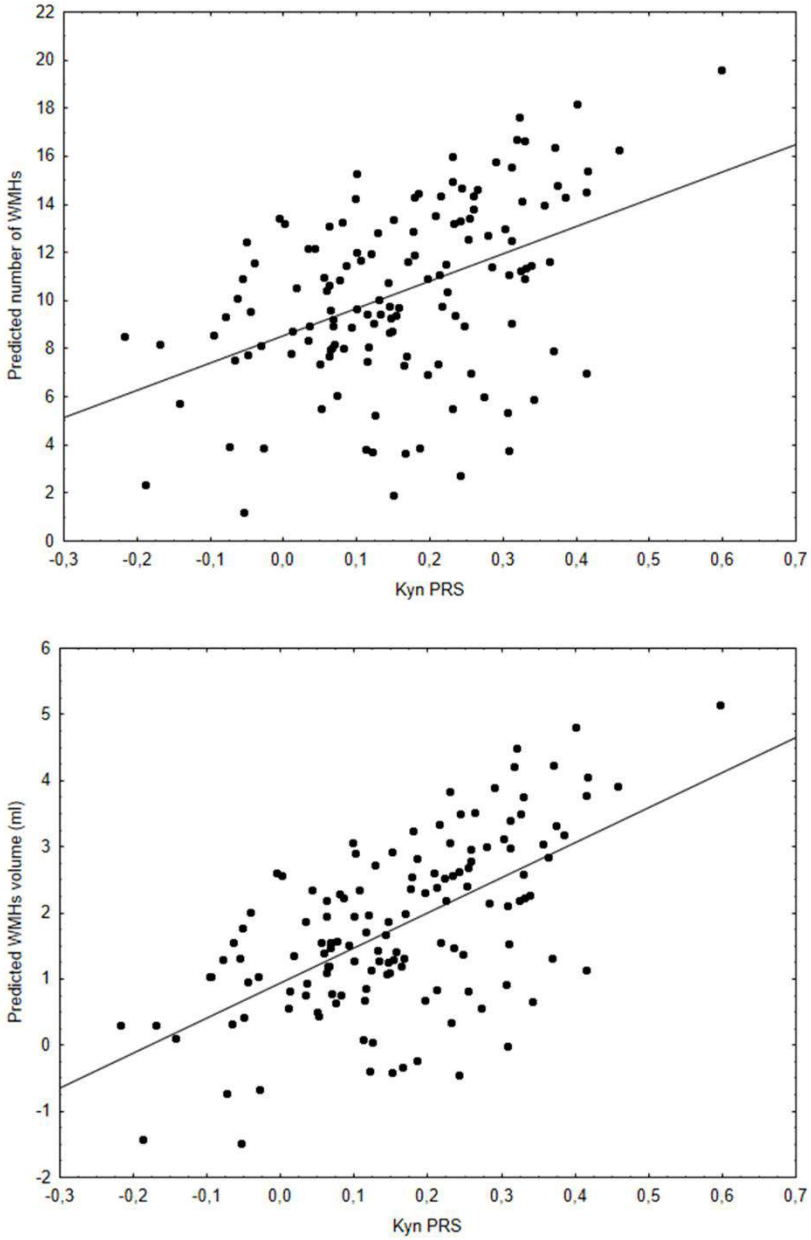

Figure 8. *Kyn PRS predict WMHs. Top: Kyn PRS predict the number of WMHs; Bottom: Kyn PRS predict the mean volume of WMHs. On the Y axis, predicted values are WMHs corrected for age and sex.*

The SH2B3 rs3184504 C>T SNP significantly influenced the PRS for Kyn (F=5.349, p =0.006) with homozygotes for the missense rs3184504*T variant showing higher scores than both T/C heterozygotes (p=0.031), and rs3184504*C homozygotes (p=0.002), with T/T homozygotes having the highest scores, the C/C ones the lowest, and C/T heterozygotes having intermediate values (Figure 9).

However, rs3184504 did not significantly influence neither plasma Kyn levels, nor Trp/Kyn ratio.

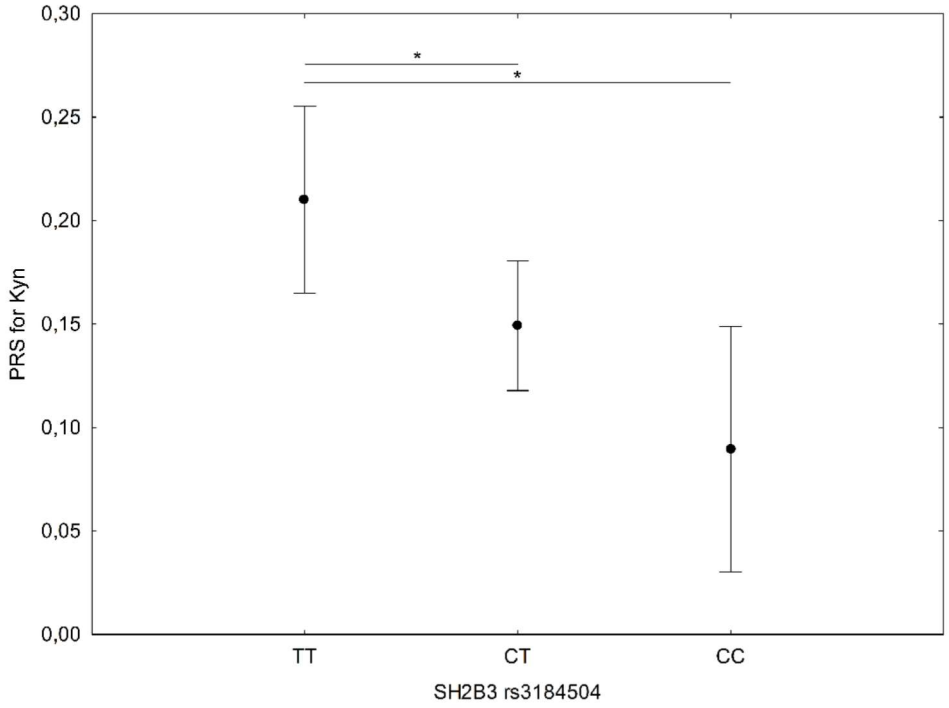

Figure 9. *Effect of SH2B3 rs3184504 C>T SNP on Kyn PRS scores. Mean and standard deviations are reported. T/T carriers have significantly higher scores than C/T and C/C carriers.*

Also, c significantly interact with PRS for Kyn in the prediction of the number of WMHs (LR $\chi 2$= 11.300, p=0.004), with T/T and C/T carriers showing a positive predictive role of the PRS for WMHs, while an opposite effect was present for the C/C carriers with Kyn PRS negatively predict WMHs. Similar effects were observed in predicting the mean volume of WMHs (LR $\chi 2$= 12.570, p=0.002; Figure 10).

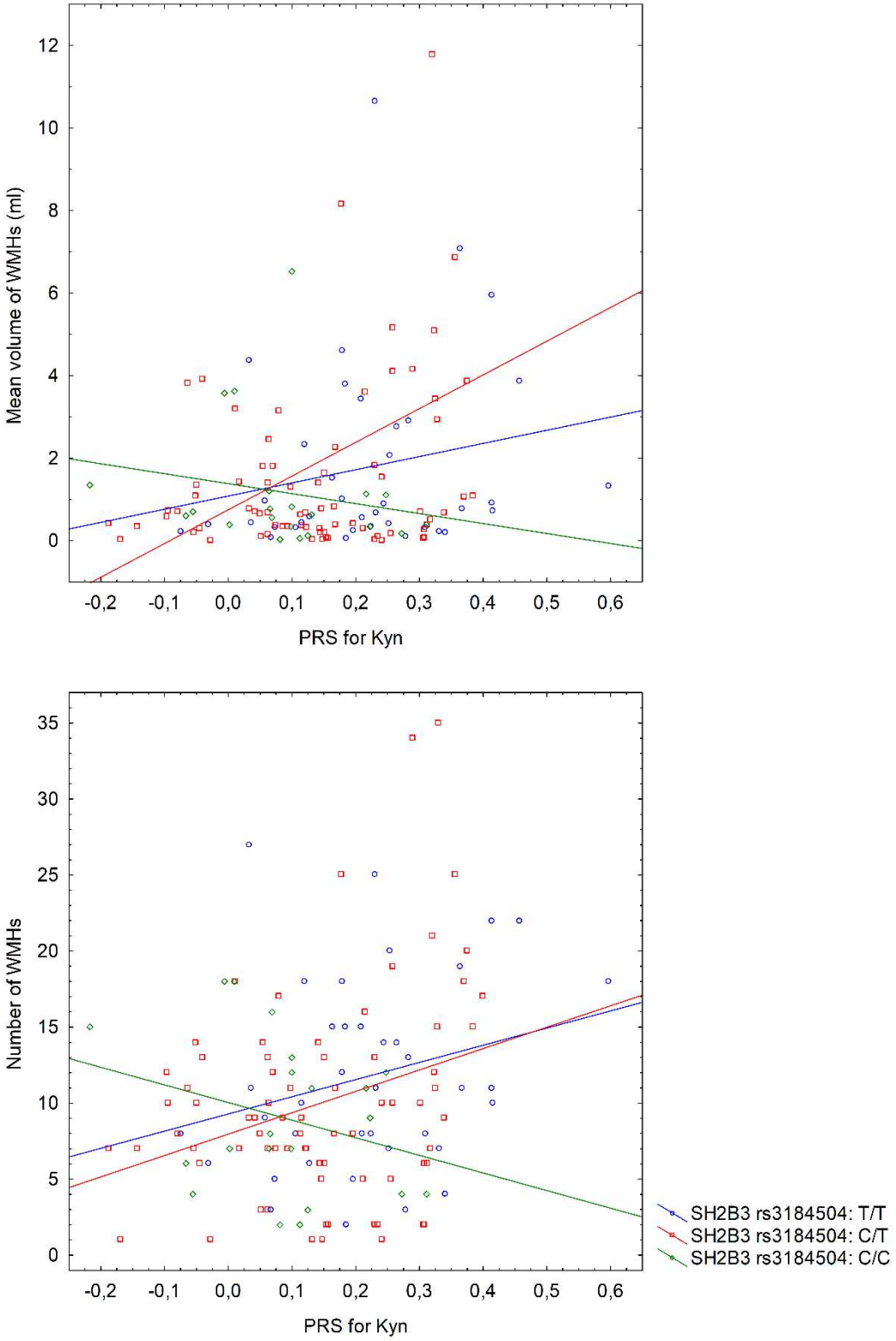

Figure 10. *Moderation of SH2B3 rs3184504 C>T SNP in the prediction of WMHs by Kyn PRS. Top: moderation on the relationship between Kyn PRS and mean volume of WMHs; bottom: moderation on the relationship between Kyn PRS and mean volume of WMHs*

The circulating Kyn and Kyn/Trp ratio levels did not significantly influence WMHs number and volume.

Effects of Kyn PRS on WM microstructure

Dealing with TBSS analyses, Kyn PRS showed to be a significant positive effect on AD (p=0.003), MD (p=0.02) (Figure 11; Table 5), and a trend towards significance for RD (p=0.098).

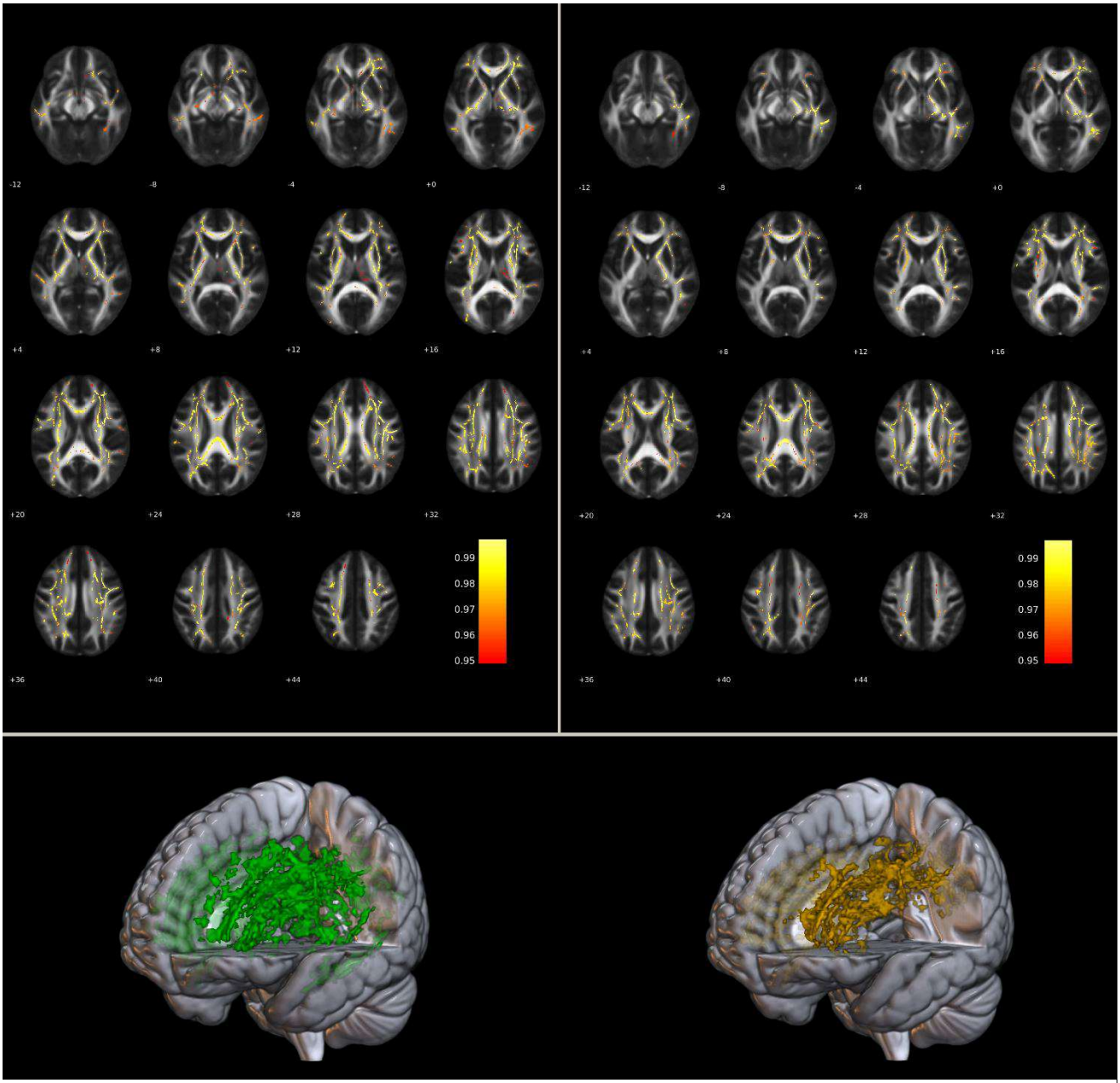

Figure 11. *TBSS analyses on Kyn PRS effect on WM microstructure. Top left: tracts where Kyn PRS positively correlated with AD; top right: tracts where Kyn PRS positively correlated with MD; bottom: in green 3D rendering of WM bundles where AD associates with Kyn PRS, in orange tracts where MD associates with MD.*

DTI Measure (mean ± SD)	No. voxels & signal peaks (*x*, *y*, *z*)	White matter tracts
L1 0.122 ± 0.003	32259 34; 6; 20 (Superior longitudinal fasciculus R.)	Anterior thalamic radiation L Anterior thalamic radiation R Corticospinal tract L Corticospinal tract R Cingulum (cingulate gyrus) L Cingulum (cingulate gyrus) R Forceps major Forceps minor Inferior fronto-occipital fasciculus L Inferior fronto-occipital fasciculus R Inferior longitudinal fasciculus L Inferior longitudinal fasciculus R Superior longitudinal fasciculus L Superior longitudinal fasciculus R Uncinate fasciculus L Uncinate fasciculus R
MD 0.076 ± 0.003	25079 41; 6; 18 (Superior longitudinal fasciculus R.)	Anterior thalamic radiation L Anterior thalamic radiation R Corticospinal tract L Corticospinal tract R Cingulum (cingulate gyrus) L Cingulum (cingulate gyrus) R Forceps major Forceps minor Inferior fronto-occipital fasciculus L Inferior fronto-occipital fasciculus R Inferior longitudinal fasciculus L Inferior longitudinal fasciculus R Superior longitudinal fasciculus L Superior longitudinal fasciculus R Uncinate fasciculus L Uncinate fasciculus R

Table 5 *WM tracts significantly associated with Kyn PRS according to DTI measure.*

Multivariate analyses revealed that MD significantly affected cognitive scores (Wilks=0.861, F=2.446, ηp2=0.134, p=0.031). Post-hoc univariate results highlighted a significant effect on verbal memory (β=-0.519, t=-3.189, p=0.002) and processing speed (β=-0.344, t=-2.052, p=0.043).

When running mediation models, MD totally mediated the predictive effect of Kyn PRS on verbal memory scores (a*b: β=-0.087, CI [-0.164; -0.025]; Figure 12).

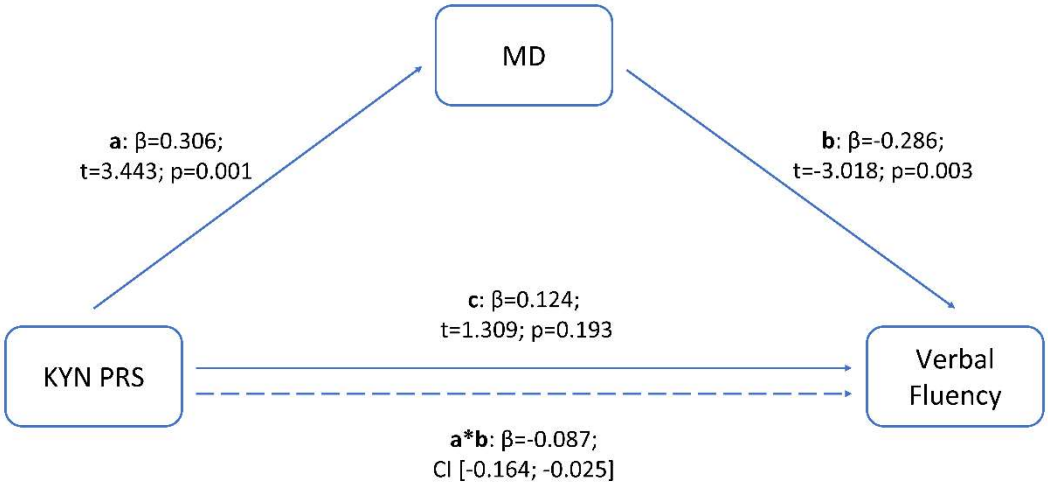

Figure 12. *Mediation model for Kyn PRS. MD fully mediated the effect of Kyn PRS on verbal fluency*

DISCUSSION

In this study, we explored the complex influence of the KP on the brain, examining its relationship with inflammation, its effects on brain barriers, neural activity, and brain connectivity, and how these factors impact cognitive functions in MDD and BD.

First, the role of inflammation in Trp degradation was assessed, showing that a range of pro-inflammatory cytokines and chemokines already noted in the literature to significantly affect the Trp degradation were associated with IDO activity, but also of growth factors and analytes whose receptors are present on important membranes regulating centre-periphery communication and on vascular endothelial cells (Changsirivathanathamrong *et al*, 2011; Wang *et al*, 2015).

We then investigated the association between KP metabolites and ChP volume. The ChP, located at the interface between the brain and the periphery, was of interest due to the presence of NMDARs on its ventricular side. Notably, QA and KynA, which act as an agonist and antagonist on NMDARs respectively, were revealed to have opposite effects on ChP volume: QA reduced volume while KynA increased it.

Given the modulatory effect of metabolites on barrier dynamics and the expression of NMDA receptors also by neuroendothelial and arteriolar smooth muscle cells (Sharp *et al.*, 2003), which mediate dilation of cerebral arteries, an involvement of KP in modulating neurovascular coupling mechanisms was hypothesised.

We further examined KP metabolites' effect on brain function, particularly on spontaneous neuronal activity in the DMN as measured by fALFF. While Kyn and 3-HK correlated positively with fALFF, KynA had a negative impact. KP metabolites also influenced HRF parameters, such as TTP and FWHM, with Kyn and Kyn/Trp positively associated with TTP, and KynA/Kyn and 3-HK/Kyn showing the opposite.

We then explored how these KP-related changes in HRF parameters affected cognition. TTP was a positive predictor of global cognitive function, verbal fluency, working memory, and psychomotor speed, while higher FWHM predicted poorer performance in these areas. Mediation analyses confirmed that KP metabolites influenced cognition indirectly via HRF parameters. This suggests that these compounds could modulate the reactivity and sustained activation of the DMN,

possibly resulting in unbalanced dynamics with other networks fostering cognitive dysfunction in mood disorder patients.

We then focused on the neurovascular effect of Kyn. Interestingly, we found a positive predictive effect of SII on Kyn levels in our sample, a result in line with literature mentioning KP metabolites to be associated with cardiovascular diseases (Zuo *et al*, 2016) and SII to be a marker of neurovascular sufferance (Ye *et al.*, 2022).

We investigated the genetic contribution to Kyn levels and its potential influence on neurovascular and cognitive outcomes using PRS for Kyn. Our findings revealed that PRS for kynurenine significantly predicted plasma Kyn levels, demonstrating that genetic variation contributes to the regulation of the kynurenine pathway in patients with mood disorders. This genetic influence extended beyond Kyn levels, as PRS for Kyn also predicted both numbers and mean volume of WMHs, but also WM microstructure integrity, being positively associated with AD and MD, indicating an impact on outcomes of presumed microvascular distress (WMHs) and on axonal integrity, conditions already observed in patients with cardiovascular and cardiometabolic diseases (Kumar *et al*, 2011; McBride *et al*, 2022; Moroni *et al*, 2018), and cognitive performance (Power *et al*, 2019; Wang *et al.*, 2022; Zanon Zotin *et al*, 2022).

Also, we focused on the genetic load related to circulating levels of Kyn considering that PRS for Kyn is associated with the risk of cardiometabolic diseases in the general population (Bagheri *et al.*, 2021).

Our first finding regarded that PRS for Kyn significantly predicted plasma Kyn levels in our patients. Also, PRS for Kyn significantly predict both numbers and mean volume of WMHs, but also WM microstructure integrity, being positively associated with AD and MD, indicating an impact on outcomes of presumed microvascular distress (WMHs) and on axonal integrity, conditions already observed in patients with cardiovascular and cardiometabolic diseases (Kumar *et al.*, 2011; McBride *et al.*, 2022; Moroni *et al.*, 2018), and cognitive performance (Power *et al.*, 2019; Wang *et al.*, 2022; Zanon Zotin *et al.*, 2022). We found that MD negatively predicted verbal fluency and processing speed, and fully mediated the effect of Kyn PRS on verbal fluency in mediation models, highlighting the role of Kyn PRS in affecting cognitive functions through its effect on structural connectivity integrity.

Effect of plasma analytes on IDO

Kyn to Trp ratio is widely used to quantify IDO activity and Trp catabolism into Kyn (Badawy & Guillemin, 2019). Mood disorder patients had a higher rate of Kyn synthesis starting from Trp compared with HCs (Leonard, 2001), given by higher activation of both TDO and IDO, promoted by stress-related and immune-related factors respectively (Dantzer, 2018). Notably, MDD and BD patients are characterised by altered inflammatory set-points and abnormal reactivity to stress, as highlighted by dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Murphy *et al*, 2022). Moreover, cytokines sensitise the HPA axis, disrupting the negative feedback loop and leading to further propagation of the inflammatory response, both at the peripheral and central level, through the activation of microglia (Hassamal, 2023).

In this context, we did not observe significant differences in KP or cytokine levels between MDD and BD, which may be attributed to shared underlying mechanisms of inflammation and stress reactivity that characterize both disorders. Additionally, literature findings on KP metabolites and peripheral cytokines do not show a consistent pattern that would confirm higher levels in BD over MDD, suggesting a lack of absolute convergence on this aspect (Goldsmith *et al.*, 2016; Marx *et al.*, 2021; Rosenblat *et al*, 2014; Savitz, 2020). Mood disorders in general are marked by a heightened inflammatory response and HPA axis dysregulation, leading to a common biochemical and inflammatory profile in both MDD and BD.

Considering inflammation, different plasma analytes have already been associated with IDO activity in several kinds of conditions, like chronic inflammatory disorders (Schroecksnadel *et al*, 2006; Wolf *et al*, 2004), neurological conditions (Lovelace *et al*, 2017), psychiatric diseases (Qin *et al*, 2018), and in patients with ongoing cellular immune activation in general (Fuchs *et al*, 1990). In particular, IDO activity is known to be induced by pro-inflammatory cytokines such as IL-1, IL-6, IL-18, TNF-α, and IFN-γ (Anderson & Maes, 2017). Our results aligned with existing literature, finding that IL-1α, IL-16, IL-18, TNF-α, and IFN-γ positively predicted IDO activation. Increases of these cytokines were also found in depression (Chang *et al*, 2024). Indeed, altered immune-inflammatory set-points in patients with depression are characterised by an increase in the number of circulating lymphocytes and phagocytic

cells with upregulation of serum levels of mentioned stimulatory analytes (Schiepers *et al*, 2005). Moreover, we enriched this pool of proinflammatory analytes that stimulate IDO activity finding also positive associations with IL-16, and IL-15, acting as chemoattractant for different types of cells including T CD4+ lymphocytes, eosinophils, dendritic cells and monocytes, and maintaining long-lasting, high-avidity CD8+ memory T cells, respectively (Nolz & Richer, 2020), and raising following inflammatory challenges. A previous study observed that IL-16 was correlated with Kyn/Trp ratio in systemic lupus erythematosus (Akesson *et al*, 2018), and higher levels of IL-16 were found in MDD patients (Almulla *et al*, 2024; Powell *et al*, 2018; Strawbridge *et al*, 2019) and were associated with deficits in cognitive performance (Peilstocker *et al*, 2023). Interestingly, IL-15 was found to induce sickness behaviour (Kubota *et al*, 2001) and IL-15 genes resulted in being upregulated after TNF treatment, serving as an amplifier of TNF signaling (Pan *et al*, 2009). Coherently, higher IL-15 levels were found in depressed adults and adolescents (Perez-Sanchez *et al*, 2018; Simon *et al*, 2008). Another cytokine found to positively predict IDO activity was TRAIL, implicated as a pathogenic or protective factor in various pulmonary diseases, particularly pulmonary arterial hypertension, but also found to be overexpressed in individuals with MDD reporting childhood trauma (Lu *et al*, 2013). Interestingly, TRAIL receptors when binding to the ligand can induce apoptosis in many cells via the receptors DR4 and DR5 (Voss *et al*, 2021). TRAIL also can activate signaling pathways that increase the production of pro-inflammatory cytokines, leading to the activation of IDO (Jiang *et al*, 2017).

Similar results emerged also considering regulatory interleukins such as IL-3, IL-7, and IL-2ra. IL-3 is known to stimulate the proliferation of different kinds of immune cells including myeloid lineage cells in conjunction with IL-7 and IL-6 (Dougan *et al*, 2019).

Meta-analytic analyses revealed higher levels of IL-3 in depressed patients compared with HCs (Osimo *et al*, 2020), and similar results for IL-7 even if evidence in the literature is scarce (Simon *et al.*, 2008). As regards IL-2ra, it represents the soluble receptor antagonist for IL-2 and its higher levels have already been observed in depression (Maes *et al*, 1995b), while low-dose IL-2 administration showed promising antidepressant effects (Poletti *et al.*, 2024b). Interestingly, an association

between IL-2ra and IDO activity has already been reported in panic disorder (Quagliato *et al*, 2019), along with Kyn levels correlating with defective IL-2 signaling in HIV-infected subjects through the production of reactive oxygen species (Dagenais-Lussier *et al*, 2016).

Furthermore, among the analytes associated with the Kyn/Trp ratio, several chemokines—including CXCL1, CXCL8, CXCL10, and CCL5—were identified, suggesting that IDO activation and subsequent KP activity may play a role in cell trafficking (Yeung *et al*, 2015). These analytes are involved in processes such as T cell recruitment, NK cell activation, and monocyte/macrophage chemotaxis, and have been found to be associated with depression (Kohler *et al.*, 2017; Oglodek, 2022), with CXCL10 and CCL5 predicting poor cognitive performance in BD patients (Poletti *et al.*, 2021a). Indeed, in the brain microglia actively release CXCL10 in Alzheimer's disease and Multiple Sclerosis (Xia *et al*, 2000).

Both CXCL8 and CXCL1 share similar functions, as they promote inflammation and are highly expressed in patients with chronic inflammatory diseases as well as depression. Similarly, CCL5 is recognised as a pro-inflammatory chemokine that recruits NK cells and leukocytes to inflammation sites. Interestingly, its receptor, CCR5, is found on the surface of T cells, smooth muscle endothelial cells, epithelial cells, and parenchymal cells (Nakano *et al*, 2012).

Interestingly, CXCL10 shares functional similarities with CCL5, being both induced by IFN- γ (Hardaker *et al*, 2004; Liu *et al*, 2005; Nakano *et al.*, 2012; Oslund *et al*, 2014) and promoting T cell recruitment by enhancing T cell adhesion to endothelial cells. In addition, both CXCL10 and CCL5 influence angiogenesis, suggesting a common modulatory action on vascular dilation (Cole *et al*, 1998).

Following this line, our results raised interesting points about a more complex and polyhedric role of IDO and Kyn rather than solely inducer of 5-HT depletion and a marker and modulator of inflammation in depression. Indeed, we found that different growth factors were positive predictors of Kyn/Trp ratio in our sample, including VEGF, β-NGF, and Basic-FGF. Together with CXCL10 and CCL5, these factors are involved in the modulation of vascular tone and permeability. VEGF is a vasodilator and enhances the vascular permeability (Senger *et al*, 1986). After inflammatory challenges, VEGF increases, probably facilitating increased blood flow to the

inflammation site, and promoting immune cells' transmigration (Dvorak, 2006). Moreover, VEGF production is induced in cells that do not receive a sufficient supply of oxygen: when a cell is hypoxic, it produces HIF (Hypoxia Inducible Factor), a transcription factor that stimulates the release of VEGF that can force the process of angiogenesis (Manalo *et al*, 2005; Zhu & Zhang, 2018). Coherently, Kyn affects endothelial cells during systemic inflammation leading to systemic hypotension through activation of adenylate cyclase and soluble guanylate cyclase pathway and endothelial dysfunction (Changsirivathanathamrong *et al.*, 2011; Wang *et al.*, 2015). Both Kyn and VEGF are elevated in depression, paving the way for the hypothesis of a compensatory mechanism between the activity of the two factors (Castillo *et al*, 2020; Clark-Raymond *et al*, 2014). Similarly, also basic-FGF physiologically involved in cell proliferation, tissue repair, and cell growth, was found to be higher in patients with depression, and specifically, its levels were associated with cognitive dysfunction in BD (Poletti *et al.*, 2021a). Indeed in the brain, damaged neurons can produce basic-FGF to attract immune cells including microglia (Noda *et al*, 2014). Reports about basic-FGF in depression are inconsistent, with studies detecting higher levels and other no significant increased or decreased levels. In line with our results, Kyn was shown to increase NGF synthesis in glial cell cultures (Dong-Ryul *et al*, 1997)

However, our results finding growth factors associated with IDO activity could find support in previous works that mention basic-FGF, VEGF, and β-NGF as neurotrophic factors expressed in depressed patients as compensatory mechanisms to counteract the detrimental effect of inflammation (Wu *et al*, 2016).

Indeed, neutrophines promote cell survival and repair following injury (Snider & Johnson Jr, 1989). Interestingly, FGF and VEGF are emerging as critical biomarkers of cardiovascular diseases (Florek *et al*, 2024), supporting our hypothesis that these factors are associated with vascular suffering and hypoxia, promoting compensation mechanisms. On the other hand, as already considered for cardiovascular diseases, higher levels of these compounds in the long run could be harmful in destabilizing atherosclerotic plaques and causing vascular leakage (Holm *et al*, 2009). Moreover, studies have shown that inflammation-related pathways, including both the KP and pro-angiogenic factors like VEGF and FGF, can be simultaneously activated in response to stress, ischemia, or inflammation (O'Farrell & Harkin, 2017; Yang *et al*,

2009). This results in a complex interplay where angiogenic factors not only contribute to tissue repair and vascular function but also interact with the immune system to regulate IDO activity.

In mood disorders, this association suggests a broader systemic response where neurovascular and immune-inflammatory processes converge and synergically interact, potentially influencing brain structure and function at the central level (Najjar *et al.*, 2013a). A double possible explanation of our result could fit also with the predictive effect of IL-10 and LIF on IDO activity in our sample. Indeed, IL-10 is known as an anti-inflammatory cytokine, promoting Th2 regulatory response, while LIF induces anti-inflammatory signals in various inflammatory states through activation of T reg cells, both analytes trying to maintain immune balance by inhibiting excessive inflammatory damage (Metcalfe, 2011; Mosmann & Moore, 1991). In MDD increased plasma IL-10 was correlated with the intensity of depressive symptoms (Capuron *et al*, 2002a). In line with our results, IL-10 was already associated with IDO activity in HCV-associated chronic hepatitis (Yang *et al*, 2019). In this sense, IL-10 may limit inflammation and injury, but it also contributes to the persistence of a disease condition.

Effect of KP metabolites on ChP volume

After the evaluation of the relatedness of peripheral inflammatory markers and KP, the effect of KP metabolites on ChP was explored. Previous analyses revealed a significant positive impact of a pool of pro-inflammatory cytokines and chemokines already associated with IDO activity in literature, but also of growth factors and of analytes whose receptors are present on important membranes regulating centre-periphery communication, vascular endothelial cells, and immune cells.

One of the main brain structures involved in the CNS-periphery exchanges is ChP. The ChP is formed by a monolayer of epithelial cells surrounding a highly vascularised connective tissue with permeable capillaries and is located at the base of each of the four brain ventricles. These cells are joined by tight junctions forming the BCSFB, which strictly regulates the exchange of substances between the blood and cerebrospinal fluid (CSF). There is evidence of a relationship between heightened peripheral immunity and the reduction of the brain barriers' permeability, with

increased ChP volume in different inflammatory-related diseases, including mood disorders (Althubaity *et al.*, 2022; Bravi *et al.*, 2024; Turkheimer *et al.*, 2021). Representing a unique interface for the immune cross-talk across periphery and CNS, and given that NMDAR is also highly expressed in human neuroepithelial and neuroendothelial cells including ChP (Sharp *et al.*, 2003), it was crucial to investigate the relatedness of KP metabolites and ChP volume in our sample. Indeed, KynA and QA, both neuroactive products of the KP, bind to glutamatergic NMDAR, acting as antagonist and agonist of the receptor respectively (Stone, 1993).

We found that ChP volume was negatively associated with QA, and positively with KynA. Current insights into the interplay between BBB permeability, NMDAR signaling, and the ChP may help explain these observations.

QA, which is nearly as potent as glutamate and aspartate in stimulating NMDAR subtypes containing the NR2A and NR2B subunits, is then absorbed and broken down into NAD+ and carbon dioxide via quinolinate phosphoribosyl transferase. However, this enzyme quickly becomes saturated, resulting in more prolonged NMDAR activation by QA compared to glutamate (Lugo-Huitrón *et al*, 2013). These specific NMDAR subunits are also present in the ChP (Brown III *et al*, 1998). In contrast, KynA functions as an antagonist, blocking the allosteric enhancing site of the alpha7 nicotinic cholinergic receptors and the glycine coagonist site of the NMDAR. This prevents the potential formation of an alpha7 nicotinic receptor–NMDAR heteroreceptor complex in the glutamate synapse (Fuxe *et al.*, 2013). The contrasting effects of QA and KynA on ChP volume observed in our study point to NMDAR signaling as a crucial mechanism that may shape ChP structure. As previously noted, the cerebral epithelial barrier on the ventricular side of the ChP contains NMDARs, and it has been suggested that their activation could prompt Ca2+ influx into neuroepithelial cells, which may increase solute permeability (Sharp *et al.*, 2003). However, the exact processes by which NMDA stimulation might alter the neuroepithelial barrier remain unexplored. Neuroendothelial NMDARs are composed of GluN1, GluN2B, and GluN3A subunits, with GluN3A imparting unique properties. Instead of triggering Ca2+ influx, these receptors exhibit non-ionotropic functions, where co-stimulation by NMDA agonists and the serine protease tissue plasminogen activator initiates metabotropic signaling via the Rho/ROCK pathway. This, in turn,

increases permeability by phosphorylating the myosin light chain and causing the shrinkage of human brain endothelial cells (Mehra *et al*, 2020). Increases in ChP volume in mood disorders have been linked to elevated circulating cytokine levels and reduced BBB permeability Our results suggest that the balance between QA and KynA, as resulting from a cascade of events triggered by inflammation, could play a major role in modulating BBB permeability (Althubaity *et al.*, 2022; Bravi *et al.*, 2024), resulting in changes of ChP volume via NMDAR stimulation or antagonism.

These findings could help explain the compensatory mechanism hypothesised in the previous paragraph. Specifically, the increased volume of the ChP observed in mood disorder patients may suggest the influence of KP metabolites on this structure, specifically QA and KynA, leading to reduced barrier permeability. This, in turn, could result in decreased delivery of intravascular substances and essential compounds to central structures, including a possible reduction in oxygen supply (Ueno *et al*, 2019). Such conditions may contribute to cellular distress and hypoxia, triggering compensatory mechanisms mediated by growth factors and mediators stimulating angiogenesis and vascular permeability involving NO as second messanger (Wu *et al*, 1996), as previously described (Fischer *et al*, 1999). At the same time, reduced permeability may result in failure of CSF clearance mechanisms through arachnoid villi and meningeal lymphatic vessels, fostering the accumulation of debris and central inflammatory conditions (Aspelund *et al*, 2015; Goyal *et al*, 2014). In this sense, alteration in the barrier's permeability may affect regional cerebral blood flow (rCBF) with consequent altered blood supply that fails to meet the energy demands of activated neurons (Prager *et al*, 2010).

Effects of KP metabolites on rs-fMRI measures and cognition

KP metabolites indeed, also affected measures of hemodynamic function and spontaneous neural activity. Insights on these results involved again the role of glutamatergic receptors in these two key brain functions and could provide a tentative mechanistic explanation of our results. Indeed, KP metabolites significantly impact cardiovascular function and have been linked to cardiovascular diseases (Ala & Eftekhar, 2022). During inflammation, IDO activation occurs in both endothelial and vascular smooth muscle cells (Worton *et al.*, 2021). Among KP metabolites, Kyn

uniquely induces blood vessel relaxation, promoting hypotension—a response not replicated by KynA, 3-HK, or QA (Wang *et al.*, 2010), but partly mediated by xanthurenic acid (XanA) (Fazio *et al*, 2017a). XanA targets metabotropic glutamate receptors mGLU2 and mGLU3 (Fazio *et al*, 2017b) with the latter receptor involved in slow tonic brain blood flow regulation crucial for neurovascular coupling (Baslow & Guilfoyle, 2016). Additionally, Kyn promotes endothelium-independent vasodilation through K+ channels in vascular smooth muscle (Sakakibara *et al*, 2015; Worton *et al.*, 2021). Though human studies on KP metabolite roles in vascular tone and hemodynamic response regulation remain limited, findings suggest that arterial responses to Kyn remain consistent in normotensive and hypertensive pregnant women (Worton *et al.*, 2021). Moreover, small dietary-induced increases in Kyn, such as from black tea, correlate with blood pressure reduction in healthy humans (Gostner *et al*, 2015), highlighting a sensitive mechanism that may function independently of inflammation.

Current research posits that endothelial NMDAR stimulation facilitates activity-dependent brain hemodynamic responses tied to arterial dilation necessary for neurovascular coupling (Hogan-Cann *et al.*, 2019), with loss of NMDAR function abolishing this effect (Lu *et al*, 2019). Recent optogenetic studies reveal that individual glutamatergic axons dilate their innervating arterioles through synaptic-like NMDAR-mediated signaling at neural-arteriolar junctions (Zhang *et al.*, 2024). Our findings show that KynA, an NMDAR antagonist, reduces fALFF measures of spontaneous neural activity, a defect associated with impaired neurovascular coupling (Agarwal *et al.*, 2021). In contrast, vasodilating Kyn and 3-HK, a precursor to vasodilating XanA and NMDAR agonist QA, enhance fALFF. Notably, the same relationship between KynA and fALFF appears in the left dorsolateral prefrontal cortex of MDD patients before serotonergic treatment, where an increase in both metrics correlates with antidepressant response (Kamishikiryo *et al.*, 2022). These results suggest that KP metabolites modulate crucial hemodynamic responses, potentially sustaining spontaneous neural function via combined endothelium-dependent and independent pathways, thereby influencing the hyperemic response in cerebral blood flow associated with neural activity.

Consistently, KP metabolites such as Kyn, KynA, and 3-HK appear to influence HRF parameters, exerting a similar vascular-mediated effect on TTP and FWHM, corroborating results observed with fALFF. Kyn associates with a reduced TTP and a sustained BOLD response, as indicated by increased FWHM, within the DMN. On the other hand, KynA exhibited the opposite effect, delaying the time to reach the BOLD signal peak and resulting in a more transient response. In line with its fALFF association, Kyn may facilitate potential DMN hyperactivity, a phenomenon documented in mood disorder patients (Ressler & Mayberg, 2007) possibly affecting network interactions (Scalabrini *et al.*, 2020). Conversely, KynA and 3-HK appear to dampen the DMN BOLD signal, reducing its amplitude and increasing response latency. Here, 3-HK aligns with KynA activity rather than its fALFF effects, as it also serves as a precursor to different other metabolites including QA and XanA, as well as neuroprotective picolinic acid, known for its anti-QA properties (Beninger *et al*, 1994; Hughes *et al*, 2022). Notably, KynA may alter neurovascular mechanisms by acting on NMDARs, inhibiting blood vessel dilation in response to locally activated neurons (Busija *et al*, 2007). Moreover, elevated glutamate levels correlate with taller, quicker, and narrower HRFs (Muthukumaraswamy *et al*, 2012). These findings outline neurovascular mechanisms driven by KP metabolites that modulate resting-state activity in mood disorder patients, potentially influencing the dynamic balance between activation and inhibition across cortical networks.

Indeed, the DMN, known for its role in self-referential and introspective mental processes (Fransson, 2005), typically deactivates during cognitive or behavioural tasks compared to resting state (Christoff *et al*, 2016; Esposito *et al*, 2006). In mood disorders, however, the DMN shows an unusual positive correlation with the executive network, diverging from the expected anticorrelation seen in healthy controls (Chai *et al*, 2011b). Consistent with this, MDD and BD patients demonstrate impaired DMN suppression during goal-oriented tasks (Grimm *et al*, 2009; Sheline *et al*, 2009; Zarp Petersen *et al.*, 2022), a phenomenon linked to poorer task performance (Daselaar *et al.*, 2009; Eichele *et al.*, 2008). This aligns with our findings, suggesting that Kyn indirectly negatively affects cognitive functions such as verbal fluency, psychomotor speed, coordination, and overall cognitive performance, possibly promoting DMN hyperreactivity and sustained activity through its impact on DMN HRF. This may

result in DMN interference during cognitive tasks, impairing its deactivation and affecting performance as previously noted (Disner *et al*, 2011).

Supporting this, studies showed abnormal DMN activation during verbal fluency tasks in MDD patients (Backes *et al*, 2014), a commonly affected cognitive domain in mood disorders (Kriesche *et al*, 2023) correlated with depressive symptoms (Talarowska *et al*, 2015). Psychomotor speed deficits in depression are also associated with lower baseline CBF in the primary motor cortex (Yin *et al*, 2018), whose activity in physiological conditions is inversely predicted by the posterior cingulate cortex, a key DMN hub (Uddin *et al*, 2009). Consistent with the hypothesis that Kyn sustains DMN dysfunction, we found that metabolites like 3-HK, which oppose these effects on DMN HRF, are associated with better cognitive performance. This protective role of 3-HK aligns with findings in inflammatory conditions, such as Type II diabetes (Bakker *et al*, 2021). Notably, only Kyn and 3-HK are linked to brain function and cognition, likely due to their capacity to cross the blood-brain barrier.

The cognitive profile observed here supports previous findings that cognitive deficits are a core feature of mood disorders, persisting beyond depressive symptoms and showing limited improvement with pharmacologic treatment (Poletti *et al*, 2014).

Effect of Kyn PRS on WM and cognition

Further evidence of the influence of KP metabolites on vascular modulation mechanisms comes from the observed association between Kyn and the SII. Indeed, under inflammatory conditions, IDO is mainly expressed in vascular endothelial cells converting Trp into Kyn, together with the secretion of vascular endothelial cells synthesize vasodilators like NO (Wang *et al.*, 2010). Notably, independently from NO pathway, Kyn can induce vasodilation by acting directly on oxidized/heme-free soluble guanylate cyclase (sGC), increasing the production of cGMP, the main inducer of vascular smooth muscle relaxation (Sausbier *et al*, 2000; Stasch *et al*, 2006). SII is considered a biomarker of inflammatory-related disease and risk of cardiovascular disease (CVD) (Mori *et al*, 2021; Ye *et al.*, 2022). In particular, platelets – included in SII calculation together with lymphocytes and neutrophil counts – have a central role in regulating vasculature homeostasis, however, they showed to be upregulated during arterial thrombosis and atherosclerotic process, highlighting vascular suffering

(Gawaz *et al*, 2005). Moreover, low lymphocyte count has been positively linked to cardiovascular events and is associated with a worse prognosis in various conditions, including stable coronary artery disease (Ommen *et al*, 1997). Both lymphopenia and comorbidity with cardiovascular diseases are conditions characteristic of mood disorder patients (Demir *et al*, 2015; Hare *et al*, 2014; Nemeroff & Goldschmidt-Clermont, 2012).

Moreover, given that higher markers of inflammation are associated with the development and progression of cardiometabolic medical conditions in the general population (Furman *et al.*, 2019; Mainous III *et al.*, 2024; Pearson *et al.*, 2003), that circulating inflammatory biomarkers are markedly raised both, in MDD and BD (Poletti *et al.*, 2024a), and that in these conditions Kyn levels are elevated (Lovelace *et al.*, 2017), it is not surprising to observe Kyn levels to be predicted by SII in our sample.

Moreover, our results found that Kyn PRS significantly predicted Kyn and Kyn/Trp ratio, both upregulated in mood disorders and cardiometabolic and cardiovascular diseases (Hestad *et al*, 2017; Song *et al*, 2017). Indeed, delving into Kyn's genetic landscape was of particular interest because of its crucial role in CVD, cardiometabolic disease, and depression, all characterized by low-grade inflammatory conditions. In this sense, genetic factors could contribute to this overlap of higher pro-inflammatory and cardiometabolic altered phenotypes in mood disorders, since meta-analyses of genome-wide and candidate gene association studies suggested shared biological mechanisms of mood disorders and cardiometabolic diseases, with pleiotropic genes and biological pathways common to the two categories of diseases (Amare *et al.*, 2017). Moreover, since circulating levels of Kyn pathway metabolites associate with detrimental effects on brain grey and white matter in patients with mood disorders (Poletti *et al.*, 2019b), genetic factors affecting IDO activation could then influence multiple phenotypic traits, to predict clinical outcomes of the disorders, including neuroprogression, the risk of neurovascular insults, and cognition.

Interestingly, PRS for Kyn, but not circulating levels of Kyn or IDO activity, positively predicted WMHs, brain signs of microvascular pathology. In this sense, Kyn role in the regulation of vascular permeability is complex and multifaceted. Indeed, Kyn induces endothelium-independent vasodilation through the activation of

potassium channels in vascular smooth muscle cells (Sakakibara *et al.*, 2015; Worton *et al.*, 2021). This mechanism suggests a potential role for Kyn in modulating vascular tone and influencing hemodynamic responses in human physiology, as indicated by findings that arteries from both normotensive and hypertensive pregnant women exhibit similar responsiveness to Kyn-induced vasodilation (Worton *et al.*, 2021). The involvement of Kyn in cardiovascular regulation is highly complex, with evidence pointing towards a cardioprotective role for certain metabolites within the KP (Yang *et al*, 2024). Furthermore, Kyn is capable of crossing the blood-brain barrier, and animal studies have demonstrated that peripheral administration of Kyn enhances cerebral blood flow under both normal and ischemic conditions (Sas *et al*, 2003).

The PRS for Kyn exhibited a strong association with both the number and volume of WMHs, as did the SH2B3 rs3184504 genotype. Notably, rs3184504 significantly influenced individual PRS for Kyn scores, though it did not affect circulating Kyn levels. Consistent with previous research, this suggests that the genetic architecture of Kyn encompasses gene variants closely linked to inflammatory processes rather than directly to Kyn concentrations (Bagheri *et al.*, 2021). SH2B3 is implicated in infection defence, with the rs3184504*T allele enhancing immune response and increasing sepsis survival (Allenspach *et al*, 2021). During the early stages of sepsis, indoleamine 2,3-dioxygenase (IDO) activation initially triggers a pronounced proinflammatory response, with Kyn subsequently contributing to T-cell response suppression and promoting immunological tolerance through innate immune cells (Gaelings *et al*, 2017; Krupa *et al*, 2022).

In this respect, previous research has demonstrated a link between the composition and activation state of circulating immune cells and WM integrity in mood disorders, with distinct roles played by Th17, natural killer (NK), and CD8+ T cells (Poletti *et al.*, 2024a). Specifically, activated CD8+ T cells were found to correlate negatively with WM microstructure (Aggio *et al*, 2023), and the rs3184504*T allele is associated with enhanced effector functions of these cells. Indeed, carriers of the T allele exhibited a strong positive correlation between higher Kyn PRS and an increased number of WMHs, whereas individuals with the C/C genotype showed a reversed relationship, suggesting a physiological protective effect. Indeed, carriers of the T allele were characterised by a strong and positive association

between higher Kyn PRS scores and more WMHs, while C/C carriers completely reversed the relationship, exerting a protecting role. More interestingly, SH2B3 rs3184504 SNP is also included in the coronary artery disease (CAD) PRS, with T allele being associated with increased risk of CAD (Consortium *et al*, 2013), elevated platelet counts (Gudbjartsson *et al*, 2009), as well as atherosclerosis and thrombosis (Wang *et al*, 2016). Consistent with our results, the CAD PRS - although not yet widely studied - has been associated with WMHs in Alzheimer's disease (de Silva *et al*, 2022).

We also found WM microstructure to be affected by PRS for Kyn in our patients. Specifically, a positive association between Kyn PRS and diffusivity measures, specifically AD, MD, and a trend toward significance for RD was observed across overlapping different tracts, encompassing corpus callosum, bilateral cingulum bundle, inferior fronto-occipital fasciculus, inferior and superior longitudinal fasciculi, and uncinate fasciculus.

Together with the emergence of WMHs, WM microstructure disruption is a neurobiological biomarker of both mood disorders and cardiovascular diseases (Favre *et al.*, 2019; Li *et al*, 2024; Moroni *et al.*, 2018; Silva *et al*, 2024; Thomas *et al*, 2002; van Velzen *et al.*, 2020). In particular, our results showing PRS associated with higher AD and MD along with a trend in the same direction for RD, speak about axonal integrity alterations, myelin disruption with possible vasogenic edema, conditions already observed in patients with cardiovascular and cardiometabolic diseases (Kumar *et al.*, 2011; McBride *et al.*, 2022; Moroni *et al.*, 2018), and cognitive performance (Power *et al.*, 2019; Wang *et al.*, 2022; Zanon Zotin *et al.*, 2022). More specifically, extracellular edema occurs as a typical reaction to inflammation with alterations in BBB, allowing plasma-like fluid to leak from blood vessels into the extracellular space, with water molecules diffusing more freely in all directions, as reflected by higher MD, AD, and RD (Assaf & Pasternak, 2008; Aung *et al*, 2013). Interestingly, aquaporin 4 (AQP4), a specialised water channel that regulates the water flow across the BBB, was found to be positively associated with the rate of IDO and TDO activation (Du *et al*, 2020), possibly promoting edema formation (Ito *et al*, 2005). Coherently, dexamethasone administration with consequent downregulation of TDO expression is used as a medication for the mitigation of brain edema (Kostaras *et al*, 2014; Shannon *et al*, 2015).

Given previous results linking Kyn PRS to WMHs, it is likely that higher genetic predisposition to inflammatory, vascular, and endothelial alterations could lead to neurovascular disruptions, which affect cerebral blood flow and WM structure.

Notably, the pattern of our results overlaps with the widespread pattern of WM tracts affected by inflammatory compounds in MDD and BD (Benedetti *et al*, 2016; Lim *et al*, 2021). Since we speculated about the immune-inflammatory underground of Kyn PRS, this could foster immune dysregulation in depression, thus affecting WM microstructure.

In this respect, a reduction in myelin integrity or bundle coherence could lead to the development of cognitive deficits as observed in mood disorders (Poletti *et al*, 2015).

In particular, we observed higher MD within bundles affected by Kyn PRS to significantly predict lower verbal memory and processing speed performance in our sample, both domains commonly affected in mood disorders (Little *et al*, 2024; Raucher-Chene *et al*, 2017). Research demonstrates that increased MD in key white matter tracts, such as the corpus callosum and cingulum bundle, is associated with poorer performance on tasks requiring verbal memory. The disorganization in these tracts could compromise the connectivity within and between language-related regions, impacting verbal memory recall and encoding abilities, which are foundational in tasks assessing this cognitive domain. Elevated MD is also linked with slower processing speed, a cognitive domain often impacted in both mood disorders and cardiometabolic conditions. This effect can be attributed to compromised signal transmission efficiency due to microstructural disruptions in long-range white matter pathways, such as the inferior fronto-occipital fasciculus and superior longitudinal fasciculus, which are implicated in higher cognitive processes and speed of information processing.

Mediation results, showing the effect of PRS for Kyn on verbal memory mediated by MD in WM tracts significantly affected by the PRS emphasize that the genetic load linked to KP brings to structural vulnerability that ultimately affects behavioural manifestations, such as cognitive functioning.

Limits of the present study

Although our study offers fresh insights into the role of the kynurenine pathway in mood disorders through a comprehensive multimodal approach—integrating genetic, biochemical, neuroimaging, and cognitive assessments to explore the pathway's interactions with inflammation and structural and functional brain measures—some limitations must be acknowledged.

Firstly, the absence of a healthy control group limits our ability to draw definitive conclusions about the specificity of the relationships found to mood disorders. Without a control group for direct comparison, it is challenging to determine whether the observed findings are disease-specific or if they may also be present in individuals without mood disorders. Future studies incorporating a matched healthy control group will be essential to better contextualize these results and enhance the interpretability of our findings. Additionally, the patients included in our study were not drug-naive, which may introduce some bias induced by the effects that lifetime treatments can have on most of the measures used in this work. Future research with drug-naive patients would provide clearer insights into the intrinsic alterations associated with MDD and BD, free from medication-related effects.

Another limitation is the lack of ethnic variability within our sample, which restricts the generalizability of our findings across different populations.

Finally, despite the balanced distribution of samples' clinical-demographic and biological features, the relatively small sample size limits the statistical power of our study, potentially affecting the robustness and generalizability of our findings. A larger sample size could provide more detailed characterizations both within and between diagnostic groups.

Conclusions

In conclusion, this study offers a comprehensive investigation into the multifaceted role of the KP in mood disorders, highlighting its impact on inflammation, neurovascular dynamics, brain structure, and cognitive function. Our findings provide novel insights into how KP metabolites interact with immune and vascular systems, contributing to the pathophysiology of MDD and BD.

Results highlighted that IDO activation associated with a wide array of pro-inflammatory cytokines and chemokines. Importantly, we also identified growth factors, such as VEGF, β-NGF, and basic-FGF, as positive predictors of IDO activity. These growth factors, which are known to modulate vascular tone and permeability, may act as compensatory mechanisms in response to inflammation, supporting vascular and tissue repair but potentially destabilizing the neurovascular environment over time. This highlights a complex interplay where IDO activity is regulated not only by inflammatory stimuli but also by neurotrophic factors that influence vascular homeostasis.

We further explored the impact of KP metabolites on ChP volume, a crucial interface regulating CNS-periphery exchanges. QA and KynA were found to exert opposing effects on ChP volume, likely mediated through NMDA receptor signaling, which may alter BBB permeability and cerebral blood flow regulation. This finding underscores the significant role of KP metabolites in modulating vascular permeability and barrier function, potentially affecting neurovascular integrity.

Furthermore, following previous results on the possible influence on brain barriers, we uncovered that KP metabolites significantly impact spontaneous neuronal activity and HRF parameters within the DMN, suggesting potential disruptions in neurovascular coupling, possibly through modulation of vascular permeability. KP metabolites' effect on DMN activity, with possible downstream effects on network interactions, was linked to cognitive dysfunction, particularly in domains like verbal fluency and processing speed.

Considering the genetic architecture of Kyn, our findings reveal a significant influence of genetic factors, particularly through PRS for Kyn, on plasma Kyn levels but also on neurovascular health, as evidenced by associations with the number and volume of WMHs and alterations in WM microstructure. These structural disruptions align with patterns seen in cardiovascular and cardiometabolic conditions, reinforcing the hypothesis of a common genetic and pathophysiological foundation pointing to immune-inflammatory dysregulation, as suggested by the modulatory effect of SH2B3 rs3184504 SNP on Kyn PRS scores. Indeed, the T allele of rs3184504, which is associated with enhanced immune response and increased risk of CAD, emerged as a key modulator, amplifying the relationship between Kyn PRS and WMHs. This SNP

has been linked to elevated platelet counts, atherosclerosis, and thrombosis, highlighting the overlap between genetic risk factors for cardiovascular conditions and mood disorders.

Moreover, increased AD and MD, were linked to higher Kyn PRS, indicating microvascular distress and axonal integrity compromise. Elevated MD in WM tracts was then found to mediate the relationship between Kyn PRS and impaired cognitive performance, emphasizing the structural vulnerability conferred by genetic variations linked to KP activity.

Overall, our findings underscore the multifaceted role of KP in modulating brain and vascular health, bridging inflammation, neurovascular function, and cognition in mood disorders. These insights provide a deeper understanding of the pathophysiological mechanisms underlying MDD and BD and highlight potential avenues for targeted therapeutic interventions aimed at modulating the KP to improve both brain integrity and cognitive impairments.

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