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LANGUAGE AS A WINDOW INTO PSYCHOSIS, BETWEEN INFLAMMATORY MARKERS, DRUG-INDUCED EFFECTS AND SUBJECTIVE EXPERIENCE

A Thesis Submitted in Partial Fulfilment of the Requirements
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PH.D. PROGRAM IN THEORETICAL AND EXPERIMENTAL LINGUISTICS

by

Jacopo Sapienza

Supervisor: Prof. Marta Bosia
Co-supervisor: Prof. Valentina Bambini

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“Is schizophrenia the price that Homo sapiens pays for language?”

– Timothy J. Crow

GENERAL ABSTRACT

Language acquisition is a pivotal step in the speciation process, and language represents the most distinctive feature of our species, able to define humankind. It is deeply intertwined with thought and brain organization, thus offering a window into both mind and brain. Being one of the most complex function, language is also highly vulnerable and can be disrupted in several conditions, especially in psychosis, being affected by the underlying pathophysiologic mechanisms and by effects of psychotropic drugs. This project, focused on psychosis with a look toward novel therapeutic avenues, analyzes language, especially pragmatics, a well-known mediator of real-life functioning in schizophrenia, encompassing the biological, pharmacological and subjective inner experiences perspectives. Within this framework, the study integrates behavioral, biomolecular and computational linguistic approaches with the final aim of deepening our understanding of mechanisms underlying psychoses and identifying novel treatment strategies to improve communicative abilities in psychosis.

Study 1 aimed at investigating biological bases of pragmatic impairment in patients with schizophrenia to pave the way for new possible treatment approaches aimed at resizing disability. Specifically, the direct association between inflammatory markers and kynurenines was innovatively investigated with a focus on treatment-resistance. Results showed a significant association between pragmatic impairment and the sub-inflammatory state typical of schizophrenia. Moreover, positive associations between pragmatics and melatonin and quinolic acid emerged in patients with treatment-resistant schizophrenia highlighting clozapine as possible modulator of these positive synergistic effects by facilitating glutamatergic neurotransmission.

Study 2 investigated the acute effects of psychedelics on speech production through a litterature review with the aim of identifying linguistic alterations as possible markers of treatment response or acute intoxication within the context of the growing number of clinical trials on such compounds to treat mental disorders. Several linguistic categories have been shown to be sensitive to psychedelics depending on dosage, the main determinant capable of influencing the underlying biology. Microdoses of psilocybin enhanced verbosity and positive emotions, without hampering discourse organization. Mild doses of psilocybin and LSD led to simplification of syntax and induced an indirect semantic priming effect. Full doses of LSD induced loosening of logical associations, resulting in altered discourse coherence.

Study 3 explored the subjective dimension of auditory hallucinations by computationally analyzing first-person accounts of patients with the aim of identifying linguistic features able to support or guide clinical decisions. Patients still hearing voices experienced higher levels of Sadness but lower levels of Fear. Moreover, antipsychotic response was associated with a reduction of emotional pervasiveness of voices in terms of Fear. Importantly, several linguistic features showed associations with different symptom dimensions in the whole sample suggesting a potential role of NLP in supporting clinicians.

Overall, these studies underscored language as a means to interpret psychosis, a possible marker of treatment response and efficacy, as well as a target of intervention to improve patients' functional outcome and subjective quality of life. Taken together all these findings endorse the importance of continuing to deepen our understanding of the tight relationship between language and psychoses.

GENERAL INTRODUCTION

Language and psychosis

Psychosis represents an altered judgment of reality involving perception, thought, language and self-awareness, inducing disability through a profound impairment of daily functioning. Rather than being limited to a single diagnostic category, psychosis can be understood as a trans-diagnostic phenomenon emerging across different conditions. Schizophrenia is historically considered the prototype of psychosis and represents one of the mental illnesses with the greatest impact in terms of disability worldwide. It shows a myriad of symptoms as possible clinical manifestations, which sometimes are difficult to interpret for clinicians since they are unusual by definition. From an epidemiological point of view, another important category is represented by the substance- or medication-induced psychotic disorder. However, some substances of abuse, such as ketamine, psychedelics and MDMA have been rediscovered in recent years for their therapeutic pot ential in several mental disorders.

Although traditionally studied through clinical symptoms and neurobiological markers, psychosis is fundamentally a disorder of meaning: it affects how individuals interpret reality, construct narratives, and communicate with others. In this sense, language offers a uniquely sensitive and multidimensional window into psychotic phenomena with multiple applications ranging from classification (diagnosis), prognosis and interpretation of symptoms to a possible index of clinical improvement/treatment response or a target of treatment.

Conerning the close relationship between language and schizophrenia, TJ Crow suggested that the nuclear symptoms of schizophrenia represent ‘language at the end of its tether’ or “the price that the homo sapiens species must pay to have language”. In other terms, 1% of individuals affected by schizophrenia worldwide (the prevalence of the disorder) is the price that humanity had paid for its evolution and currently must pay to continue to evolve at a significantly higher speed than other species. The complexity of language is likely to induce psychotic symptoms in 1% of the overall population because language is no longer conceived as one's own. As a matter of fact, patients typically think that thoughts are inserted into or removed from one’s mind by an outside agency, or that thoughts are broadcasted to others or to the surrounding environment. Similarly, auditory hallucinations are hearing one’s thoughts spoken aloud, running commentaries on one’s thoughts or actions or even other kind of voices.

However, language is not merely a symptom domain in psychoses: it is a bridge between biology, brain function, cognition, and lived experience, and it represents a crucial dimension for clinical interventions. By analyzing how individuals with psychotic disorders communicate through language and construct or understand meanings, it is possible to capture alterations that reflect both the underlying biology and the subjective experience of psychosis with possible implications for new tailored treatment strategies.

The three studies composing this thesis are united by a common theoretical thread: psychoses can be investigated through the lens of language, which becomes an investigative tool but also a potential therapeutic target especially if considering pragmatics, the ability to use language appropriately in context, that has been demonstrated as an important predictor of real-life functioning.

Aims and thesis roadmap

The first study aims at demonstrating the independence of pragmatics from neurocognition and then disentangling the biological bases of pragmatic impairment in schizophrenia with a focus on treatment-resistance. In this view, language and specifically pragmatic impairment plays the role of therapeutic target for future combined pharmacological and rehabilitative interventions to resize disability.

The second study is a systematic review on the acute effects of psychedelics on speech production. It develops through a biological framework, and it is aimed at finding possible indicators of adverse events (intoxication) or treatment response within the context of future clinical trials on psychedelics. In this case, language is conceived as a predictor of efficacy or side effects of pharmacological treatments.

The last study investigates the subjective experience of hearing voices through quantitative computational procedures with the aim of better understanding this very complex symptom dimension and its emotional valence and providing tools for clinicians to support their decisions in terms of treatment approaches. In this study language is the real window on psychosis, helps to understand its phenomenology, and for this reason, informs clinicians through symptom interpretation.

STUDY 1

INFLAMMATORY AND KYNURENINE PATHWAYS IN SCHIZOPHRENIA: THE LINK WITH PRAGMATICS, BEYOND COGNITION AND TREATMENT RESISTANCE

ABSTRACT

In the past decades, inflammatory and kynurenine pathways have been extensively studied in schizophrenia, especially for their implications in treatment resistance schizophrenia, for which they currently represent potential treatment targets. Moreover, both have been linked to the severity of the impairment in global cognition that characterizes schizophrenia, including in basic linguistic tasks. However, no evidence is currently available about the relationship between inflammatory and kynurenine pathway (KP) dysregulation and pragmatics, one of the most complex language abilities, whose deficit is a core feature of schizophrenia. This cross-sectional study in a sample of 78 patients with schizophrenia, while addressing the interplay between language and cognition, innovatively investigates the direct association between inflammatory markers and KP metabolites and pragmatic abilities with a focus on treatment resistance schizophrenia. Results support the independence of pragmatics from neurocognition and innovatively show a significant association between pragmatic impairment and the sub-inflammatory state typical of schizophrenia, as well as of a positive association between pragmatic performance and melatonin and quinolic acid in patients with treatment resistant schizophrenia. Overall, these findings bring novel insights on the interplay between pragmatics, inflammation and KP, contributing to increasing knowledge on the biological mechanisms underlying pragmatic abilities and schizophrenia and paving the way for combined therapeutic interventions aimed at resizing pragmatic impairment in people with schizophrenia.

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INTRODUCTION

Schizophrenia and the challenge of treatment-resistance

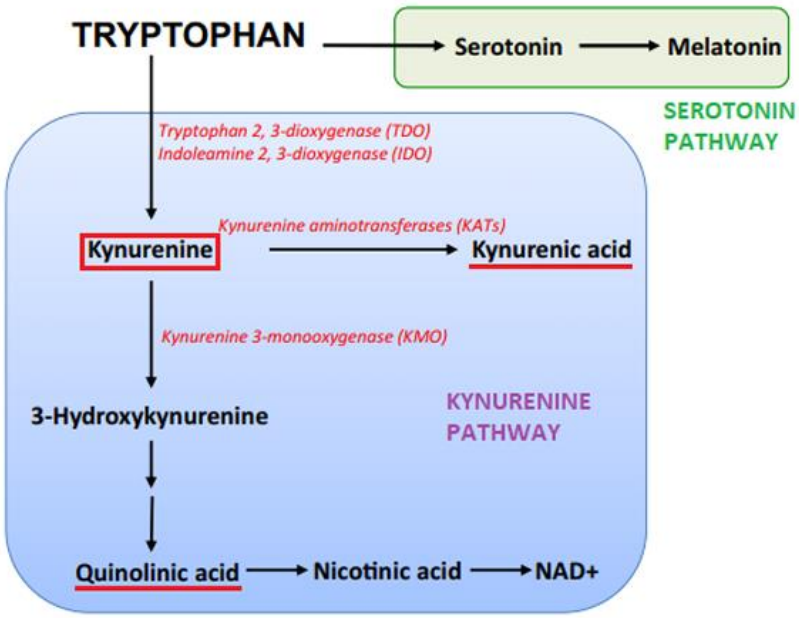
Schizophrenia is a severe and chronic mental disorder characterized by a progressive deterioration that profoundly affects emotional regulation, social functioning, and cognition. One of the most distinctive features of the disorder is its marked heterogeneity, which involves etiopathological mechanisms, symptom dimensions, illness trajectory, and treatment response. Symptomatology is traditionally conceptualized along positive, negative, and cognitive dimensions, with most of the patients presenting a combination of these domains [1]. This clinical heterogeneity reflects underlying biological diversity, involving variations in neurochemical and inflammatory substrates with implications for phrmacoresistance [2]. The treatment of schizophrenia underwent a major transformation with the introduction of antipsychotic medications, beginning with chlorpromazine in the 1950s [3]. However, it soon became evident that a subset of patients showed little or no clinical improvement despite multiple trials with different antipsychotics, with the notable exception of clozapine [4]. In 1988, Kane and colleagues demonstrated the superior efficacy of clozapine in patients unresponsive to other antipsychotic drugs, highlighting its primary therapeutic role in Treatment-Resistant Schizophrenia (TRS) [5]. Although the introduction of antipsychotic medications represented a breakthrough in the treatment of schizophrenia, a substantial proportion of patients continue to show inadequate response to pharmacological interventions. Approximately 30% of individuals meet criteria for treatment-resistant schizophrenia (TRS), defined by the persistence of clinically significant symptoms despite adequate trials of at least two antipsychotics [6]. TRS is associated with poorer premorbid adjustment, more severe symptom burden, increased hospitalization rates, reduced quality of life, and worse functional outcomes [7][8]. Although substantial efforts have been devoted to the definition and management of TRS, considerable heterogeneity persists across studies regarding the criteria used to define treatment resistance. Overall, the concept of TRS is characterized by three pivotal features: (1) confirmed diagnosis of schizophrenia based on validated diagnostic criteria, (2) exposure to adequate pharmacological treatment, and (3) persistence of clinically significant symptoms despite treatment. A widely accepted definition of TRS refers to an inadequate response to at least two consecutive antipsychotic trials administered for an appropriate duration (typically 6–8 weeks) and at adequate dosages within the therapeutic range or at least the minimum effective dose [9]. Furthermore, most clinical guidelines specify that at least one of these trials should involve a second-generation antipsychotic (SGA) [9][10]. Regarding the temporal course of treatment resistance, TRS is present from illness onset in the majority of patients, whereas in others an initial therapeutic response is observed before resistance develops later in the course of the disorder [11]. Only a small proportion of individuals lose responsiveness to antipsychotics over time and after multiple relapses, a condition referred to as secondary TRS, while most patients exhibit treatment resistance from the early stages of illness, defined as primary TRS [12]. Evidence from the past decade suggests that TRS may not simply represent a more severe form of schizophrenia, but rather a neurobiologically distinct subtype, characterized by relatively preserved dopaminergic function, greater glutamatergic dysfunction, and reduced grey matter volumes [13]. More recent data also suggest a role of inflammatory processes to TRS, showing an association with higher levels of pro-inflammatory markers and insufficient compensatory anti-inflammatory response [14]. Interestingly, clozapine, the only antipsychotic medication licensed for TRS with a demonstrated superior efficacy compared to other antipsychotics [10][15] exhibits a distinctive receptor-binding profile, characterized by low affinity for dopamine D2 receptors and, unlike other antipsychotics, enhances glutamatergic

neurotransmission through NMDA receptors, a property that may contribute to its efficacy in TRS [16][17][18]. Moreover, preclinical evidence shows that clozapine reduces pro-inflammatory cytokine production and inhibits the NLRP3 inflammasome in microglia, probably through NMDA receptors modulation [19]. Together, these findings underscore the existence of substantial unmet therapeutic needs and motivate the search for novel biological targets beyond classical dopaminergic mechanisms.

Inflammation and the kynurenine pathway: promising treatment targets

Among the biological systems increasingly implicated in schizophrenia, immune dysregulation and inflammation have received growing attention by the scientific community in the last decades. Notably, converging evidence from meta-analyses and experimental studies indicates that schizophrenia is associated with a state of low-grade systemic and central inflammation, reflected by elevated circulating levels of pro-inflammatory cytokines such as interleukin-6 (IL6), interleukin-1β (IL1β), and tumor necrosis factor-α (TNF α) [20][21][22][23]. This immune activation is thought to be triggered by a combination of genetic vulnerability and environmental risk factors, including perinatal complications and early-life stress, and is sustained by microglial activation (pro-inflammatory M1 phenotype) within the central nervous system (CNS) [50]. In this context, the kynurenine pathway (KP) emerges as a particularly relevant biological system, as it represents the interface between inflammation and neurotransmission [24][25]. Under physiological conditions, tryptophan (Trp), the precursor or serotonin and melatonin, is primarily catabolized through the kynurenine (KYN) pathway (KP) to produce nicotinic acid, a precursor of nicotinamide adenine dinucleotide (NAD+), an essential coenzyme involved in the regulation of multiple metabolic processes [24][25]. During inflammatory states, and of importance in schizophrenia [26], pro-inflammatory cytokines increase the proportion of Trp metabolized along the KYN pathway, leading to an imbalance between neurotoxic and neuroprotective metabolites [27]. In particular, cytokines such as interferon-γ (IFN-γ) and interleukin-6 (IL-6), together with markers of oxidative and nitrosative stress including reactive oxygen species (ROS) and reactive nitrogen species (RNS), as well as lipopolysaccharide (LPS), induce the activity of indoleamine-2,3-dioxygenase (IDO), the limiting enzyme of the pathway, thereby enhancing the conversion of Trp into KYN. This process results in the generation of several bioactive metabolites, some of which are capable of interfering with cholinergic and glutamatergic neurotransmission [25], this ability to modulate neurotransmission places the KP at the crossroads of immune activation and neural function. Figure 1 shows the most important metabolic steps of the KP. Concerning the two main neuroactive metabolites quinolinic acid (QUIN) and kynurenic acid (KYNA), thay modulate NMDA receptor function, acting respectively as a potent agonist of the receptor and a potent antagonist at the glycine allosteric site of the NMDA receptor complex, as illustrated in Figure 2 [26][28]. In turn, this mechanism may contribute to the pathophysiology of positive, negative, and cognitive symptoms of schizophrenia, thereby providing a mechanistic link between inflammation and symptom expression [26][29].

Figure 1. Key metabolic steps of the kynurenine pathway

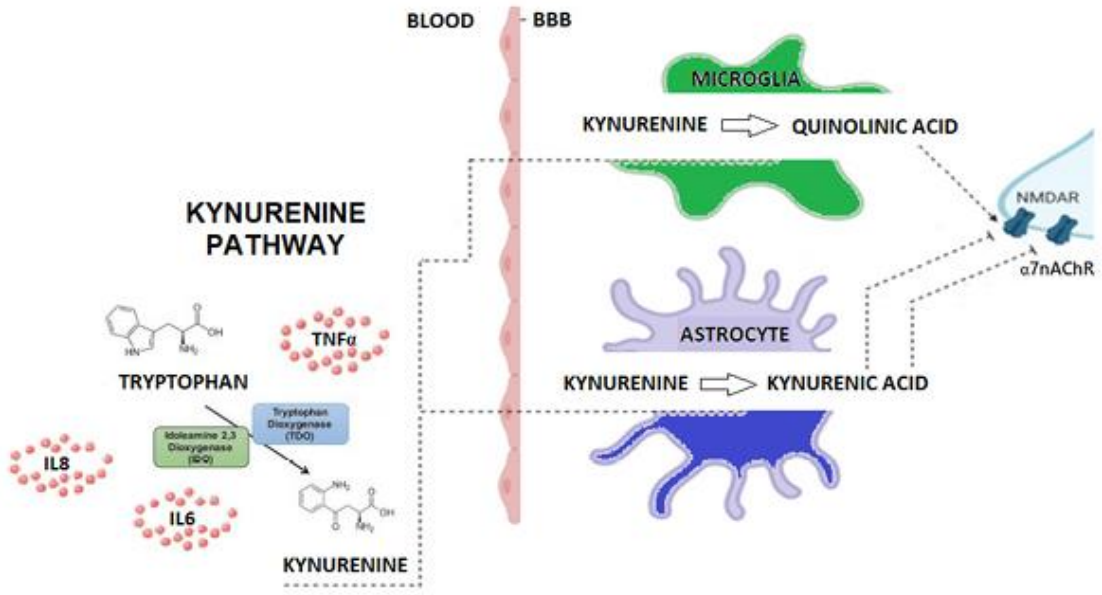


Relevance of inflammation and the kynurenine pathway for treatment resistance and cognitive impairment

Both inflammation and the kynurenine pathway have been extensively reported as overactive in schizophrenia [26][30] with important implications for pharmacoresistance [31] and cognitive impairment [32][33][34][35]. As abovementioned, glutamatergic abnormalities, particularly involving NMDA receptor hypofunction [36], are considered central to the pathophysiology of the disorder [37] and appear to be especially pronounced in TRS [38][39][40]. Elevated glutamate levels have been observed in schizophrenia, with striatal glutamate concentrations negatively predicting response to first-line antipsychotic treatments [38][39]. In this framework, kynurenine metabolites play a crucial modulatory role: QUIN acts as a neurotoxin stimulating NMDA receptors and inducing excitotoxicity, while KYNA being a negative allosteric modulator of NMDA receptors further worsens their functionality making them less prone of binding glutamate and increasing its pre-synaptic release [31]. Although findings regarding KP activation in TRS are not entirely consistent [41][31][42], several studies suggest that increased KYNA levels may contribute more to persistent refractory symptoms in schizophrenia, thus to TRS [31][43][44]. This mechanism is particularly relevant in light of clozapine's unique pharmacological profile. Clozapine enhances NMDA receptor function by increasing synaptic glycine availability, thereby counteracting NMDA receptor antagonism [45][46]. In this sense, KP dysregulation and clozapine may exert opposing effects on glutamatergic neurotransmission, suggesting a complex interaction between inflammation, KP metabolites, and treatment response. Concerning cognition, several lines of research have linked neuroinflammation to cognitive impairment [47][34] and also the dysregulation of the KP has been associated to cognitive deficits in schizophrenia [32]. Of note cognitive impairment appears to be more severe and progressive in TRS, especially in verbal domains [48][49][50]. Deficits have been documented in verbal intelligence, verbal fluency, verbal memory, and susceptibility to verbal interference [48][49][50], with longitudinal evidence indicating a greater cognitive decline over time in treatment-resistant patients [51]. Interestingly, subgroup analyses show a stronger association between elevated inflammation and cognitive impairment in

treatment-resistant populations, with a weaker or absent relationship in first-line responders [52][53][54] suggesting that TRS may mediate the strength of inflammatory effects on cognition.

Figure 2. Main neuroactive metabolites derived from peripheral activation of the pathway



Inflammation, kynurenine pathway and language: limited evidence beyond cognition

The relationship between immune dysregulation, KP and language has so far received limited attention, although sparse evidence suggests that inflammation may underly or exacerbate language dysfunction. Indeed, some studies have reported associations between inflammatory markers or kynurenine metabolites and performance on language-related tasks, such as verbal fluency or verbal memory [47][55], in the context of a broader cognitive assessment. Moreover, results from subgroup analyses pointed to an association between elevated cytokine levels and reduced volume in language-related brain regions (e.g., Broca's area), further supporting a link between peripheral inflammation and language dysfunction in schizophrenia [56]. Such link appears as promising area of investigation, especially in light of the clinical impact of language disturbances in this population, as it may elucidate important pathophysiological mechanisms and guide novel therapeutic strategies.

However, these findings are sparse and inconsistent, and language is typically considered as a component of global cognitive functioning rather than as a multidimensional domain. As a result, potential effects of inflammation and KP dysregulation on language have never been systematically explored, nor differentiated across specific linguistic domains. In particular, higher-order dimensions of language, such as pragmatics, which is one of the most impacted in schizophrenia, remain largely unexplored in biological studies on

schizophrenia. Pragmatics refers to the branch of linguistics that studies how language is used in context and how meaning is constructed beyond the literal content of words and sentences. Unlike structural components of language such as phonology (sound), morphology (word formation), and syntax (sentence structure), pragmatics concerns the ability to adapt communication to social and contextual demands. It includes skills such as interpreting indirect meanings (e.g., irony, metaphors, implicatures), managing conversational rules (e.g., turn-taking, topic maintenance), and integrating contextual and interpersonal cues to produce and comprehend appropriate utterances [57]. Pragmatic competence therefore relies on the integration of linguistic knowledge with cognitive and socio-cognitive processes, including executive functions and theory of mind, making it particularly vulnerable in neuropsychiatric conditions characterized by impairments in these domains [57]. Nowadays, it is well established that pragmatic impairment represents a nuclear feature of schizophrenia. As a matter of fact, individuals with schizophrenia exhibit impairments in the pragmatic use of language, including difficulties in social communication, in generating contextually appropriate speech, and in interpreting meanings that depend on contextual cues [57]. Further evidence indicates that pragmatic deficits are already detectable in prodromal populations [58][59] and in first-degree relatives of patients with schizophrenia [60][61]. Taken together, these findings suggest that impairments in communication [62], and particularly disruptions in pragmatic language use, may serve as potential endophenotype of illness, consistent with the neurodevelopmental hypothesis of the disease [63] that locates the origins of the disorder in early brain development. It is important to note that, pragmatic abilities have been extensively related to both executive functions [64] and theory of mind (ToM) [65][66][67] and both are disrupted in schizophrenia due to cognitive impairment and socio-cognitive deficits. Concerning TRS, there are no studies on pragmatic abilities in this population. However, there is evidence on both cognitive functioning and socio-cognitive abilities, the two main determinants of pragmatic abilities, in TRS patients. Indeed, they have been reported to exhibit more pronounced cognitive impairments in verbal domains, including language abilities, verbal intelligence, verbal fluency, verbal memory, and susceptibility to verbal interference [48][49][50] and, moreover, they are burdened by a more severe cognitive decline over time as shown by longitudinal evidence [51]. Notably, these deficits can be detected as early as the first episode of psychosis [68]. Less consistently, TRS has also been associated with greater impairments in non-verbal cognitive domains, such as performance intelligence, processing speed, visuospatial functioning, and visual memory [48][69][70]. Similarly, Nakata and colleagues reported that the degree of social cognitive dysfunction and autistic traits in TRS patients could be very similar to those patients diagnosed with an autistic spectrum disorder [71]. Overall, these findings provide indirect evidence suggesting that also a more pronounced disruption of pragmatic abilities may be a key feature of TRS.

Aims

The present study further addresses the interplay between language and cognition and innovatively investigates through a systematic evalutation the direct association between inflammatory markers and KP metabolites and pragmatic abilities in schizophrenia, focusing also on the subgroup of patients with TRS.

In detail, we first aimed at identifying profiles of pragmatic and neurocognitive abilities and analyzing their association. Then, we tested whether inflammatory markers and KP metabolites are directly associated with pragmatic performance in the overall sample.

Finally, we explored if the strength of the associations between inflammatory markers and tryptophan KP metabolites may vary depending on TRS status.

METHODS

Sample

A sample of 78 biologically unrelated patients with schizophrenia was recruited at the IRCCS San Raffaele Scientific Institute of Milan (Italy), Schizophrenia Research and Clinical Unit.

After a complete description of the study, informed consent to participation was obtained.

The protocol followed the principles of the Declaration of Helsinki.

Inclusion criteria were:

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

Exclusion criteria were:

- psychotic exacerbation
- psychiatric comorbidities
- substance/alcohol abuse
- neurological disorders and brain injury
- intellectual disability (IQ<70)
- chronic inflammatory diseases
- concomitant infectious\inflammatory diseases.
- use of immunosuppressant or immunomodulant drugs

"Psychotic exacerbation" refers to an acute worsening of psychotic symptoms (delusions, hallucinations, and disorganization) compared to the patient's baseline clinical condition. This was determined based on clinical evaluation conducted by experienced psychiatrists, and, when available, supported by the comparison between previuos standardized clinical rating scales when the patient was in the acute phase of the illness and at the time of recruitment.

Definition of treatment resistance schizophrenia

TRS was defined according to APA guidelines. Patients must have shown a clinical inadequate response to at least two trials of antipsychotics, one of which is a second-generation antipsychotic, and treatments must have been assumed for at least 6 weeks of treatment at therapeutic range [72]. All TRS patients enrolled in the study were treated with clozapine, as indicated by clinical guidelines [9].

Clinical and neuropsychological assessment

Positive and Negative Syndrome Scale

Psychopathology was assessed by means of Positive and Negative Syndrome Scale for Schizophrenia (PANSS), a widely recognized evaluation of the severity of positive, negative

symptoms and general psychopathology in patients with schizophrenia [73]. The clinical interview and evaluation of symptoms were performed by trained psychiatrists. The PANSS scale consists of 30 items divided into three subscales:

PANSS – Positive Scale

- P1. Delusions – Fixed false beliefs not shared by others.
- P2. Conceptual disorganization – Disorganized, illogical thinking and speech.
- P3. Hallucinatory behavior – Perceptual experiences without external stimuli.
- P4. Excitement – Heightened emotional arousal and agitation.
- P5. Grandiosity – Inflated self-worth or exaggerated beliefs about abilities.
- P6. Suspiciousness/Persecution – Distrust or belief of being harmed or targeted.
- P7. Hostility – Verbal or physical aggression, anger.

PANSS – Negative Scale

- N1. Blunted affect – Reduced emotional expression.
- N2. Emotional withdrawal – Lack of emotional engagement with others.
- N3. Poor rapport – Difficulty establishing interpersonal connection.
- N4. Passive/apathetic social withdrawal – Reduced social initiative.
- N5. Difficulty in abstract thinking – Impaired conceptual reasoning.
- N6. Lack of spontaneity and flow of conversation – Reduced speech fluency.
- N7. Stereotyped thinking – Rigid, repetitive thought patterns.

PANSS – General Psychopathology Scale

- G1. Somatic concern – Excessive focus on physical health.
- G2. Anxiety – Feelings of fear, tension, or nervousness.
- G3. Guilt feelings – Self-blame or remorse.
- G4. Tension – Motor or psychological restlessness.
- G5. Mannerisms and posturing – Odd or unnatural movements.
- G6. Depression – Sad mood, hopelessness.
- G7. Motor retardation – Slowed movements and speech.
- G8. Uncooperativeness – Resistance or lack of collaboration.
- G9. Unusual thought content – Odd or bizarre ideas not fully delusional.
- G10. Disorientation – Confusion about time, place, or person.
- G11. Poor attention – Difficulty concentrating.
- G12. Lack of judgment and insight – Poor awareness of illness or consequences.
- G13. Disturbance of volition – Reduced motivation or goal-directed behavior.
- G14. Poor impulse control – Difficulty inhibiting inappropriate behavior.
- G15. Preoccupation – Excessive focus on internal thoughts or themes.

- G16. Active social avoidance – Deliberate avoidance of social interaction.

Brief Assessment of Cognition in Schizophrenia

Cognitive performance was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) [74], Italian version [75]. The BACS is a comprehensive neuropsychological battery designed to evaluate core cognitive domains that are typically impaired in schizophrenia.

The assessment was administered by trained psychologists and included measures of:

- Verbal memory (Word Recall).
- Working memory (Digit Sequencing).
- Psychomotor speed and coordination (Token Motor Task).
- Speed of processing (Symbol Coding).
- Verbal fluency (Semantic and Letter Fluency).
- Executive functioning (Tower of London). [74]

Raw scores for each subtest were adjusted for sex, age, and years of education.

Assessment of Pragmatic Abilities and Cognitive Substrates

The Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) is a neuropsychological instrument developed to evaluate pragmatic language abilities in individuals with acquired communication disorders, including schizophrenia, traumatic brain injury (TBI), dementias, amyotrophic lateral sclerosis (ALS) and other illnesses [76][77]. APACS is a relatively brief assessment, requiring approximately 35–40 minutes to administer, and demonstrates good internal consistency as well as good reliability [76]. The battery primarily includes measures aimed at assessing the comprehension of figurative language and humor, abilities that rely, at least in part, on Theory of Mind [77]. Within the studied samples, the only expected demographic effect concerns age, which has a negative impact on performance across several tasks, particularly those assessing figurative language and humor [78].

The test battery consists of six tasks:

- **Interview.** A semi-structured interview focused on autobiographical topics, scored for fluency, coherence, prosody, and informativeness.
  - Fluency: smoothness and continuity of speech production.
  - Coherence: logical organization and maintenance of topic.
  - Prosody/Intonation: appropriate use of rhythm, stress, and intonation patterns.
  - Informativeness: adequacy and relevance of the information provided.
- **Description.** Description of ten photographs depicting everyday life situations, scored based on the accurate identification of the scene, agents, and actions.
  - Scene identification: correct recognition of the overall situation depicted.
  - Actor identification: accurate identification of people involved.
  - Action identification: correct description of ongoing actions and events.

- **Narratives.** Listening to six short stories followed by comprehension questions assessing global understanding, detail recall, and implicit meaning, as well as the explanation of two non-literal expressions.
- Global comprehension: understanding the overall meaning of the story.
- Detail comprehension: recall and understanding of specific elements.
- Implicit meaning inference: ability to infer unstated intentions or implications.
- Non-literal expression explanation: interpretation of figurative expressions embedded in the narratives.
- **Figurative Language 1.** A multiple-choice task involving 15 expressions, including five idioms, five novel metaphors, and five proverbs.
- Idioms: comprehension of conventional figurative expressions.
- Novel metaphors: interpretation of unfamiliar metaphorical meanings.
- Proverbs: understanding of culturally shared figurative statements.
- **Humor.** Completion of seven short stories by selecting the appropriate ending, either the correct humorous conclusion or an incorrect alternative (literal or non sequitur).
- Incongruity detection: recognition of incongruous or unexpected elements.
- Humorous inference: ability to select the contextually appropriate humorous ending.
- Literal vs non-literal distinction: rejection of literal or illogical alternatives.
- **Figurative Language 2.** Verbal explanation of 15 figurative expressions (idioms, metaphors, and proverbs), scored on a 0–2 scale.
- Interpretive accuracy: correctness of the figurative meaning.
- Abstraction ability: capacity to generalize beyond literal content.
- Verbal formulation: clarity and adequacy of the verbal explanation.

From all these tasks, three composite scores are derived: Pragmatic Production (Interview + Description), Pragmatic Comprehension (Narratives + Figurative Language 1 + Humor + Figurative Language 2), and the Total APACS score [76].

Laboratory procedures

Inflammatory markers

Blood samples were collected by venipuncture into EDTA-containing Vacutainer tubes in the morning after an overnight fasting period. Samples were centrifuged at 2,000 × g for 15 minutes at 4 °C, after which plasma was aliquoted and stored at −80 °C until analysis. Plasma was divided into 200 µL aliquots. Plasma concentrations of immune analytes, including IL-1β, IL-6, IL-1ra, IL-9, IL-10, IL-13, IL-17A, interferon-γ (IFN-γ), macrophage inflammatory protein-1 (MIP-1), platelet-derived growth factor-BB (PDGF-BB), RANTES, tumor necrosis factor-α (TNF-α), and atrial natriuretic peptide (ANP), were measured using

enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions (RayBiotech, Atlanta, USA).

Kynurenine Pathway metabolites

Trp and kynurenine (KYN) concentrations were determined using high-performance liquid chromatography (HPLC) coupled with a fluorometric detector for Trp and a UV–Vis detector for KYN. Levels of 3-hydroxykynurenine (3-HK), kynurenic acid (KYNA), and quinolinic acid (QUIN) were measured using an LC–MS/MS Varian system equipped with a binary ProStar pump, a 410 autosampler, and an MS320 triple-quadrupole mass spectrometer with an electrospray ionization source. The mass spectrometer operated in multiple reaction monitoring mode in positive ionization for all analytes, except for QUIN, which was quantified in negative ion mode. Quantification of 3-HK, KYNA, and QUIN was performed using α-methyl-tryptophan as an internal standard. Finally, the following metabolite ratios were calculated as indirect indices of enzymatic activity within the KP: the KYN/Trp ratio as a proxy for indoleamine-2,3-dioxygenase (IDO) activity, the KYNA/KYN ratio as an index of kynurenine aminotransferase II activity, and the 3-HK/KYN ratio as a proxy for kynurenine-3-monooxygenase activity.

Systemic Inflammatory Index

the Systemic Immune-Inflammation Index (SII) is increasingly used in the clinical practice of inflammatory and internal diseases due to its simplicity, feasibility and greater reliability compared to other inflammatory markers to detect a low-grade inflammatory state. It is easily calculated from routine blood tests using three parameters: neutrophil count (N), platelet count (P), and lymphocyte count (L) and reflects the patient's inflammatory and immune status [79]:

$$SII = \frac{N\ x\ P}{L}$$

Statistical analysis

Descriptive statistics were provided for socio-demographic data, inflammatory state, KP pathway, cognitive and pragmatic abilities in the whole sample.

To identify groups of patients with different profiles of pragmatic abilities, we ran a two-step cluster analysis, considering all APACS scores as clustering variables. Specifically, we used k-means clustering and the number of clusters (k = 2) was selected based on the silhouette score, which reached its maximum value for k = 2, indicating a clear separation between clusters. Additionally, this choice ensures interpretability of the results within the context of the study. We then assessed, by means of Analysis of Variance (ANOVA), differences between the two groups characterized respectively by higher and lower pragmatic performance on symptoms severity, cognitive abilities and levels of peripheral inflammatory markers and KP metabolites. To further analyze the interplay between pragmatic and neurocognitive abilities, we applied the same approach to group patients based on their neurognitive profiles and tested their association. In detail, we used a two-step cluster approach, with BACS scores as clustering variables. We then compared groups based on pragmatic profile vs groups based on neurocognitive ones using Chi-Square tes. Second, to assess the relationship between inflammation, KP and pragmatics, we ran Pearson correlations between APACS subtests and composite scores on the one hand and the panel of inflammatory markers, SII, KP metabolites, serotonin and melatonin on the other. Third,

to explore whether the relationship between inflammation, KP and pragmatics varies depending on the TRS status, we repeated the same correlations separately in the subgroups of TRS patients and FLR. Based on correlations results, to disentangle effects of the correlated variables, we then performed, on the TRS subsample only, a linear stepwise-forward regression model with APACS Total score as dependent variable and melatonin and quinolic acid as regressors. Finally, we conducted a separate slope regression model on the whole sample, to further analyze if the relationship between melatonin and quinolic acid and pragmatic abilities differs across TRS patients and FLR.

RESULTS

Sample description

The sample was composed by 78 participants with schizophrenia, 54 males and 24 females with a mean age of the sample of 37.26 years ± 12.81 years. Regarding pharmacological treatments, 60.26% of participants (n = 47) were treated exclusively with first- or second-generation antipsychotics (FLR), while the remaining 42.3% of patients (n = 30) were treated exclusively with clozapine (TRS), while the remaining 39.74% (n = 31) were receiving clozapine alone or in combination with an additional antipsychotic. Clinical and demographic data of the whole sample are represented in Table 1, while cognitive functioning and pragmatic competence in Table 2. Concerning data extracted from laboratory procedures, pro-inflammatory cytokines or markers of inflammation and metabolites of the kynurenine pathway are reported in Table 3 and Table 4 respectively. Similarly, specific data and discrepancies between FLR and TRS patients are respectively reported in Table 5, 6, 7 and 8.

Table 1. Clinical and demographic data of the whole sample

	Mean	SD
Age	37.26	12.81
Years of education	12.73	2.43
Disease onset	21.68	5.06
Duration of illness	15.58	11.42
PANSS Positive score	17.33	5.52
PANSS Negative score	21.17	4.59
PANSS General Score	40.77	8.00
PANSS Total score	79.28	14.96

Table 2. Cognitive and pragmatic abilities of the sample

BACS (agg scores)	Mean	SD
Verbal Memory	41.57	14.52
Working Memory	17.81	5.22
Psychomotor speed	61.64	17.89
Verbal Fluency	46.74	12.36
Processing Speed	40.92	13.13
Executive functions	16.18	6.70
APACS scores	**Mean**	**SD**
Pragmatic Production	0.91	0.06
Pragmatic Comprehension	0.76	0.14
APACS Total score	0.84	0.09

Table 3. Inflammatory markers in the whole sample

Inflammatory markers	Mean	SD
IL-1a	54.59	156.66
IL-1b	17.83	50.40

IL-2	73.09	136.90
IL-4	345.67	1722.25
IL-5	55.81	87.12
IL-6	124.98	127.92
IL-8	60.01	109.51
IL-10	20.88	43.89
IL-12p70	5.41	17.08
IL-13	7.72	13.66
GM-CSF	60.52	153.13
GRO	135.82	328.02
IFNg	64.15	157.56
MCP-1	288.93	128.16
MIP-1a	8.74	22.68
MIP-1b	42.79	59.28
MMP-9	22703.24	21563.50
RANTES	530.04	119.20
TNFa	1399.33	1924.71
VEGF	119.75	118.65
SII	539.22	394.33

Table 4. Metabolites of the kynurenine pathway in the whole sample

KP metabolites	Mean	SD
Tryptophan (mcg/Ml)	12.11	2.93
kynurenine (mcg/Ml)	0.14	0.07
3-hydroxykynurenine (ng/Ml)	17.88	24.58
Quinolinic acid (ng/Ml)	80.19	50.61
Kynurenic acid (ng/Ml)	10.40	4.50
Serotonin (ng/Ml)	27.56	50.77
Melatonin (pg/Ml)	14.65	11.40
Kyn/Trp ratio *1000	12.28	7.98
3-HK/Kyn ratio	123.14	107.38
KYNA/Kyn ratio	106.29	86.53
QUIN/KYNA ratio	8.13	4.42

Table 5. Clinical and demographic data of FLR and TRS

	Mean FLR	SD FLR	Mean TRS	SD TRS	F	p
Age	34.45	12.58	41.52	12.14	**6.06**	**0.02**
Years of education	13.00	2.23	12.32	2.69	1.46	0.23
Disease onset	21.83	5.35	21.45	4.67	0.10	0.75
Duration of illness	12.62	10.65	20.06	11.24	**8.74**	**<0.01**
PANSS Pos. score	16.48	6.08	18.55	4.43	2.61	0.11
PANSS Neg. score	20.95	4.16	21.48	5.20	0.24	0.63
PANSS Gen. Score	40.41	7.84	41.29	8.32	0.22	0.64
PANSS Total score	77.84	14.22	81.32	15.96	0.98	0.32

Table 6. Cognitive and pragmatic abilities FLR vs TRS patients

BACS (agg scores)	Mean FLR	SD FLR	Mean TRS	SD TRS	F	p
Verbal Memory	42.78	14.72	39.96	14.38	0.58	0.45
Working Memory	17.56	5.01	18.15	5.57	0.20	0.66
Psychomotor speed	62.88	15.99	59.98	20.35	0.40	0.53
Verbal Fluency	46.18	12.97	47.49	11.69	0.17	0.68
Processing Speed	42.17	12.03	39.25	14.54	0.76	0.39
Executive functions	14.99	4.00	17.77	8.99	2.72	0.10
APACS scores	**Mean**	**SD**	**Mean**	**SD**	**F**	**p**
Pragmatic Production	0.91	0.07	0.92	0.04	0.40	0.53
Pragmatic Compr.	0.77	0.14	0.76	0.13	0.02	0.89
APACS Total score	0.84	0.09	0.84	0.08	0.01	0.91

Table 7. Inflammatory markers in FLR and TRS individuals

Inflammatory markers	Mean FLR	SD FLR	Mean TRS	SD TRS	F	p
IL-1a	60.37	188.68	45.83	90.95	0.16	0.69
IL-1b	16.79	47.12	19.40	55.77	0.05	0.82
IL-2	71.59	157.68	75.37	99.85	0.01	0.91
IL-4	379.23	2007.00	294.78	1196.78	0.04	0.83
IL-5	56.48	96.46	54.81	72.20	0.01	0.93
IL-6	111.37	88.35	145.60	171.17	1.34	0.25
IL-8	57.29	105.69	64.13	116.71	0.07	0.79
IL-10	20.80	44.46	20.99	43.75	0.00	0.99
IL-12p70	5.37	18.15	5.46	15.63	0.00	0.98
IL-13	6.55	9.79	9.48	18.08	0.86	0.36
GM-CSF	69.38	184.48	47.10	87.70	0.39	0.53
GRO	139.90	360.30	129.65	277.57	0.02	0.89
IFNg	54.31	140.86	79.08	181.42	0.46	0.50
MCP-1	281.15	125.23	300.73	133.70	0.43	0.51
MIP-1a	8.69	21.71	8.82	24.43	0.00	0.98
MIP-1b	40.56	34.16	46.18	84.92	0.17	0.68
MMP-9	24831.52	24985.00	19476.49	14779.09	1.15	0.29
RANTES	529.83	133.40	530.36	95.82	0.00	0.98
TNFa	1394.04	1926.13	1407.33	1954.35	0.00	0.98
VEGF	132.98	139.84	99.69	73.87	1.48	0.23
SII	496.76	270.42	605.68	334.82	1.07	0.30

Table 8. Metabolites of the kynurenine pathway depending on the treatment-resistance condition

KP metabolites	Mean FLR	SD FLR	Mean TRS	SD TRS	F	p

Tryptophan (mcg/Ml)	11.60	2.66	12.83	3.18	3.05	0.09
kynurenine (mcg/Ml)	0.15	0.08	0.12	0.05	2.25	0.14
3-hydroxykynurenine (ng/Ml)	21.78	30.84	12.50	9.53	2.45	0.12
Quinolinic acid (ng/Ml)	68.39	50.58	96.48	46.73	**5.53**	**0.02**
Kynurenic acid (ng/Ml)	10.34	4.93	10.48	3.93	0.02	0.90
Serotonin (ng/Ml)	33.66	48.63	18.53	53.57	1.22	0.27
Melatonin (pg/Ml)	16.86	13.78	11.61	5.91	3.71	0.06
Kyn/Trp ratio *1000	13.89	9.05	10.07	5.65	**4.02**	**0.05**
3-HK/Kyn ratio	140.80	131.08	97.03	48.82	2.33	0.13
KYNA/Kyn ratio	106.51	100.83	105.99	63.44	0.00	0.98
QUIN/KYNA ratio	7.35	4.71	9.19	3.81	3.00	0.09

Profiles of pragmatic abilities

Cluster analysis (k-clustering with k=2) based on APACS, produced 2 clusters characterized by higher (n=43) and lower (n=35) pragmatic performance. As detailed in table 9, the two clusters significantly differed in all scores, except for Figurative Language 1 Proverbs (Table 9).

Table 9. Significant differences between the two clusters for each APACS sub-item

	CLUSTER 1 ↓ Pragmatics		**CLUSTER 2 ↑ Pragmatics**		**ANOVA**	
	Mean	**SD**	**Mean**	**SD**	**F**	**p**
Interview Production	37.86	3.25	39.88	3.27	**7.45**	**0.01**
Scene Description Production	43.37	4.79	46.37	3.89	**9.32**	**<0.01**
Text Comprehension	37.60	6.32	49.77	3.45	**116.84**	**<0.01**
Stories – Main Sense	4.91	0.98	5.49	1.30	**4.67**	**0.03**
Stories – Secondary Details	3.68	1.30	4.56	1.07	**10.51**	**<0.01**
Stories – Main Inference	3.40	0.81	5.19	1.76	**30.59**	**<0.01**
Stories – Detail Inference	2.83	1.17	4.93	1.97	**30.88**	**<0.01**
Figurative Language Stories 1	6.77	2.34	10.42	1.40	**72.61**	**<0.01**
Figurative Language Stories 2	6.17	2.39	9.88	1.83	**60.25**	**<0.01**
Figurative Language Comprehension 1	12.77	2.17	14.72	0.50	**32.62**	**<0.01**
Figurative Language 1 – Idioms	4.31	0.96	4.95	0.21	**17.91**	**<0.01**
Figurative Language 1 – Metaphors	4.00	1.11	4.84	0.37	**21.47**	**<0.01**
Figurative Language 1 – Proverbs	4.06	0.90	4.32	0.56	2.56	0.11

Humor Comprehension	4.23	1.99	6.02	1.44	**21.36**	**<0.01**
Figurative Language Comprehension 2	14.08	3.60	21.05	3.18	**82.17**	**<0.01**
Figurative Language 2 – Idioms	8.43	3.26	14.00	6.81	**19.72**	**<0.01**
Figurative Language 2 – Metaphors	5.17	2.16	7.93	1.35	**47.34**	**<0.01**
Figurative Language 2 – Proverbs	1.48	1.48	4.09	2.16	**36.87**	**<0.01**
Pragmatic Production	0.88	0.06	0.94	0.06	**17.27**	**<0.01**
Pragmatic Comprehension	0.65	0.12	0.86	0.07	**96.39**	**<0.01**
APACS Total Score	0.76	0.07	0.90	0.04	**101.32**	**<0.01**

When comparing the two groups according to cognitive abilities, no difference emerged

With respect to psychopathology, a significant difference emerged only for PANSS itemN5-Difficulty in abstract thinking (mean Cluster 1 = 3.53±1.13, mean Cluster 2 = 2.90±1.26; F=5.02, p=0.03).

Considering inflammatory markers and molecules associated with the kynurenine pathway, a significant difference between clusters emerged only for SII, as shown in Table 10.

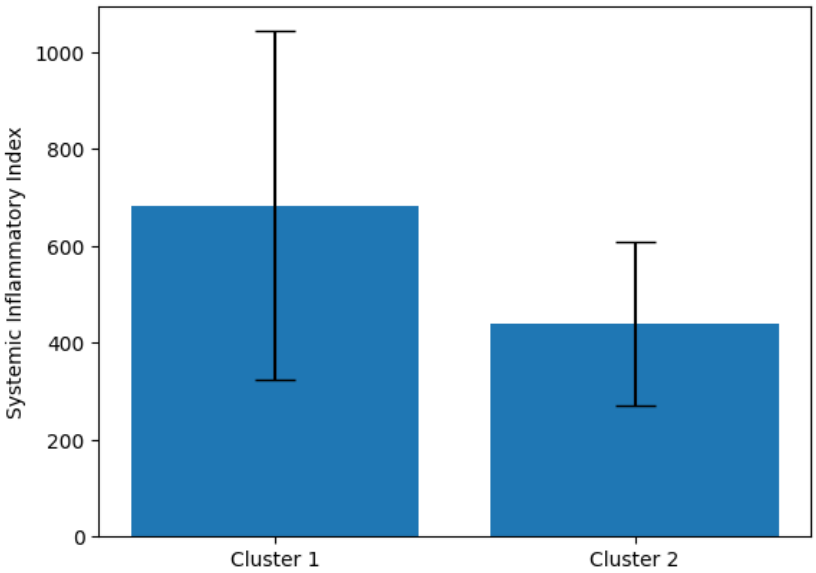
Table 10. Differences in levels of inflammatory markers and kynurenine pathway's molecules between the two clusters

	Mean Cluster 1	**SD Cluster 1**	**Mean Cluster 2**	**SD Cluster 2**	**F**	**p**
IL-8	72.58	134.63	49.77	84.10	0.83	0.36
IL-10	22.57	51.19	19.49	37.50	0.09	0.76
IL-12p70	7.70	23.65	3.54	8.63	1.15	0.29
IL-13	8.06	16.24	7.43	11.34	0.04	0.84
GM-CSF	55.56	108.78	64.56	182.68	0.06	0.80
GRO	107.39	267.54	158.96	371.61	0.47	0.49
IFNg	80.76	205.81	50.64	103.95	0.70	0.40
MCP-1	288.77	105.64	289.06	145.18	<0.01	0.99
MIP-1a	13.19	31.82	5.13	9.65	2.48	0.12
MIP-1b	48.34	82.67	38.28	29.39	0.55	0.46
MMP-9	24184.99	20792.66	21497.17	22342.06	0.30	0.59
RANTES	536.07	105.82	525.13	130.11	0.16	0.69

TNFa	1392.65	1985.25	1404.76	1897.63	<0.01	0.98
VEGF	112.87	114.53	125.35	122.95	0.21	0.65
Tryptophan (mcg/Ml)	12.0	2.4	12.2	3.4	0.05	0.83
kynurenine (mcg/Ml)	0.1	0.1	0.1	0.1	1.99	0.16
3-HK (ng/Ml)	12.4	11.3	22.6	31.3	3.06	0.08
Quinolinic acid (ng/Ml)	75.8	47.9	84.0	53.2	0.44	0.51
Kynurenic acid (ng/Ml)	10.5	4.8	10.3	4.3	0.06	0.81
Serotonin (ng/Ml)	20.8	49.2	34.1	52.2	0.97	0.33
Melatonin (pg/Ml)	16.6	14.8	13.0	7.1	1.67	0.20
Kyn/Trp ratio *1000	11.0	7.2	13.4	8.6	1.49	0.23
3-HK/Kyn ratio	105.6	78.8	140.1	128.3	1.48	0.23
KYNA/Kyn ratio	111.6	87.6	101.7	86.5	0.22	0.64
QUIN/KYNA ratio	7.5	4.0	8.7	4.7	1.27	0.26
SII	684.0	359.6	439.9	168.8	**5.91**	**0.02**

Specifically, SII was significantly higher in Cluster 1 (683.99±359.56), characterized by lower pragmatic abilities, compared to Cluster 2 (439.94±168.83), more efficient in pragmatics, as shown in Figure 1.

Figure 1. Cluster 1 shows higher systemic inflammation (SII) compared to Cluster 2



Association between neurocognitive and pragmatic profiles

Cluster analysis (k-clustering with k=2) based on BACS scores produced 2 clusters characterized by higher (n=45) and lower (n=18) neurocognitive performance. As detailed

in table 11, the two clusters significantly differed in all scores, except for Executive Functions (Table 11).

Table 11. Differences in terms of cognitive scores across BACS domains between the two clusters A and B

	CLUSTER A		CLUSTER B		ANOVA	
	Mean	**SD**	**Mean**	**SD**	**F**	**p**
Verbal Memory	45.75	13.43	31.12	11.85	**16.25**	**<0.01**
Working Memory	19.04	5.00	14.74	4.55	**9.96**	**<0.01**
Psychomotor speed	69.92	10.68	40.93	15.38	**72.97**	**<0.01**
Verbal Fluency	49.08	11.31	40.89	13.23	**6.12**	**0.02**
Processing Speed	45.84	11.44	28.63	8.12	**33.74**	**<0.01**
Executive functions	15.82	4.01	17.08	10.99	0.45	0.51

Considering the distribution of patients across the groups classified according to pragmatic vs neurocognitive abilities, we found no significant overlap (Pearson Chi-square=0.19; p=0.66).

Relationship between inflammation, Kynurenine pathway and pragmatics

As showed in Fig. 2, only few significant correlations emerged between APACS scores and our panel of peripheral inflammatory markers. Specifically, we observed a negative correlation between MIP-1b levels and performance on the Figurative Language 1 Texts item ($r = -0.22$; $p = 0.04$), as well as a between the Systemic Immune-Inflammation Index (SII) and the Figurative Language 2 task and Metaphors items ($r = -0.30$; $p = 0.02$; $r = -0.32$; $p = 0.01$).

Figure 2. Correlations between inflammatory markers and APACS sub-items

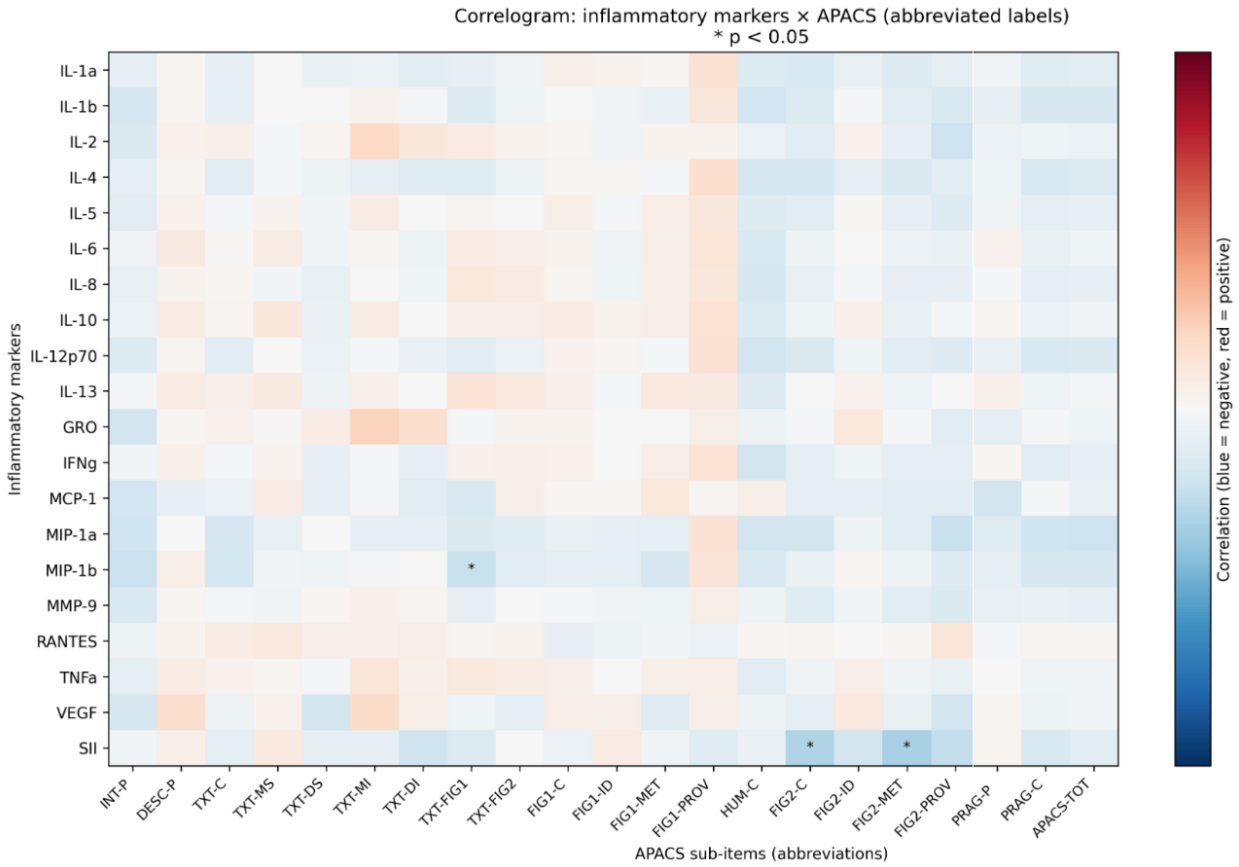


Figure 3. Correlations between KP metabolites, serotonin and melatonin and APACS sub-items

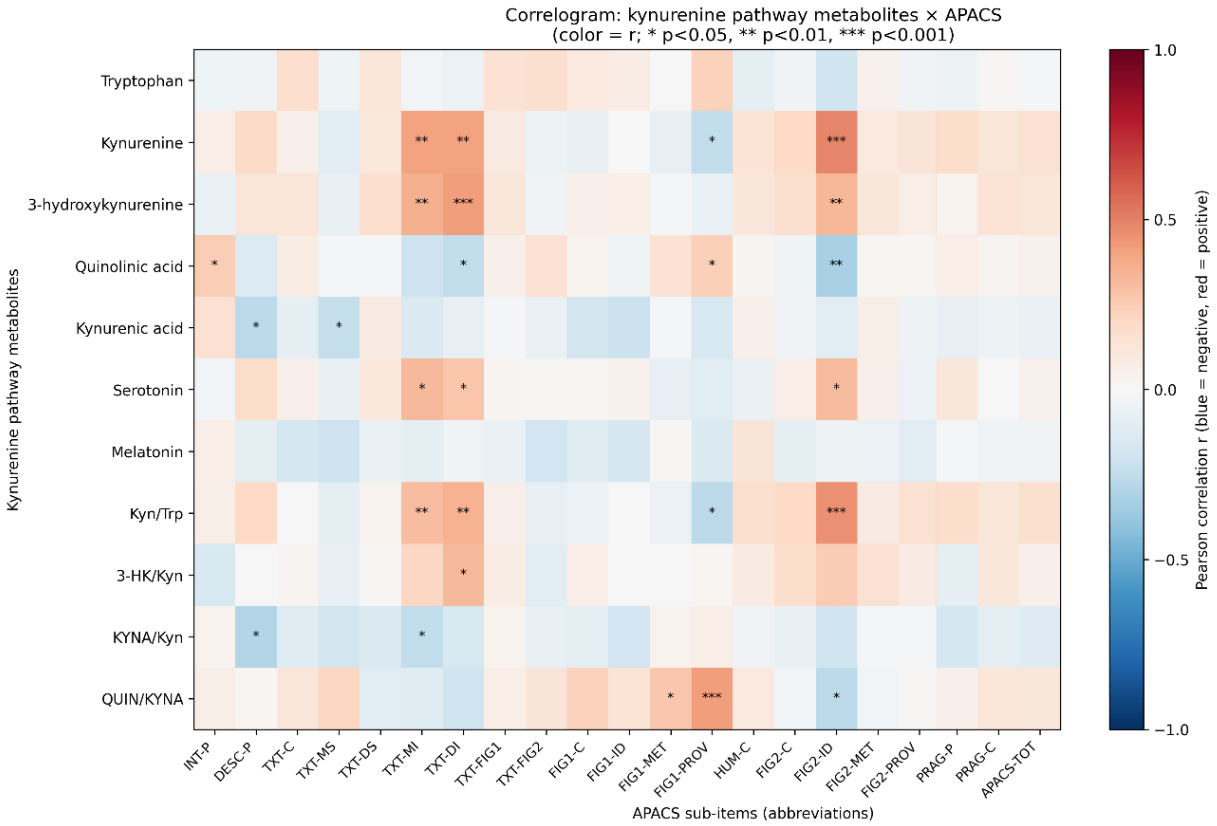


Figure 3 shows correlations between pragmatics and KP metabolites, serotonin and melatonin. In production tasks, Interview Production showed a positive correlation with QUIN ($r = 0.25$; $p = 0.04$). Scene Description Production showed a negative correlation with both KYNA ($r = -0.26$; $p = 0.03$) and the KYNA/Kyn ratio ($r = -0.29$; $p = 0.01$).

Within the comprehension domain, MS Texts negatively correlated with kynurenic acid ($r = -0.242$, $p = 0.045$), and MI Texts and DI Texts showed a similar pattern, both correlating positively with KYN ($r = 0.40$, $p < 0.01$ and $r = 0.40$, $p < 0.01$, respectively), with 3-HK ($r = 0.35$, $p < 0.01$ and $r = 0.42$, $p < 0.01$, respectively), with serotonin ($r = 0.32$, $p = 0.01$ and $r = 0.28$, $p = 0.03$), and with the Kyn/Trp ratio ($r = 0.31$, $p = 0.01$ and $r = 0.35$, $p < 0.01$, respectively).

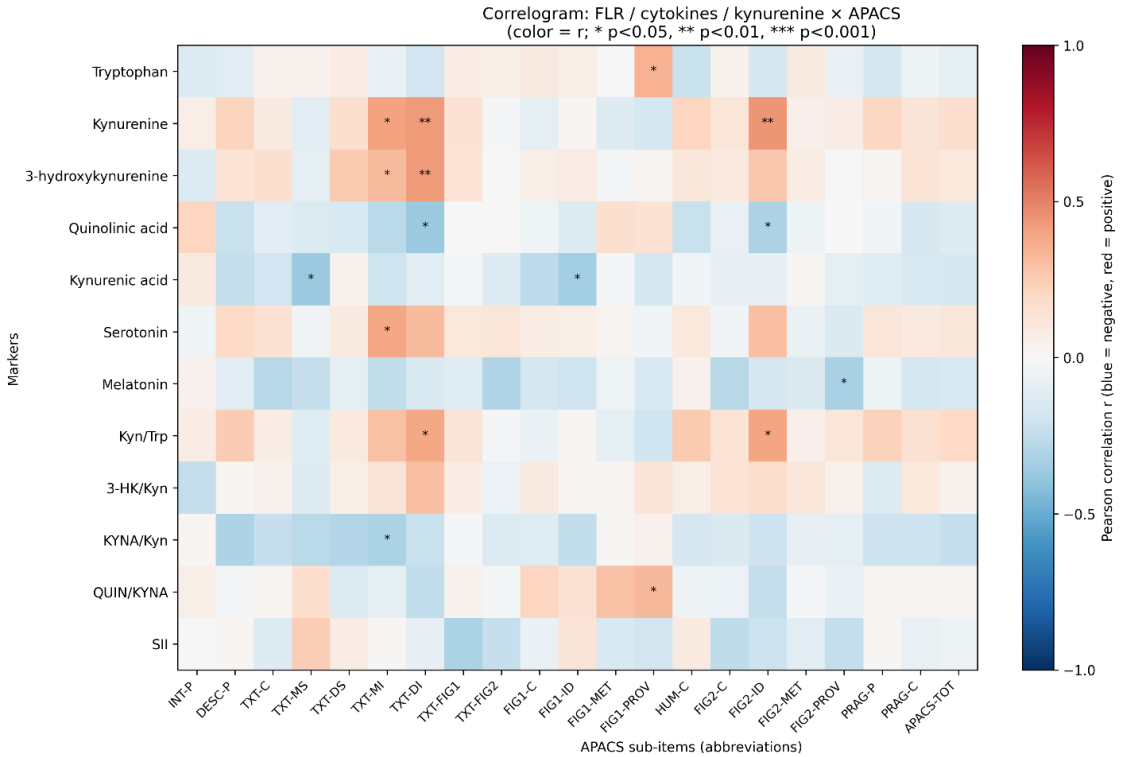
Regarding figurative language, Fig Lang 1 – Metaphors positively correlated with the QUIN/KYNA ratio ($r = 0.27$; $p = 0.02$). Fig Lang 1 – Proverbs negatively correlated with KYN ($r = -0.24$; $p = 0.04$) and with the Kyn/Trp ratio ($r = -0.26$; $p = 0.03$), and positively with QUIN ($r = 0.24$; $p = 0.05$) and with the QUIN/KYNA ratio ($r = 0.41$; $p < 0.01$). In contrast, the Fig Lang 2 – Idioms subscale positively correlated with KYN ($r = 0.48$; $p < 0.01$), 3-hydroxykynurenine ($r = 0.34$; $p = 0.01$), serotonin ($r = 0.32$; $p = 0.02$), and the Kyn/Trp ratio ($r = 0.46$; $p < 0.01$), while it was negatively associated with QUIN ($r = -0.32$; $p = 0.01$) and with the QUIN/KYNA ratio ($r = -0.26$; $p = 0.32$).

Different effects of inflammation and kynurenine pathway on pragmatic abilities depending on pharmacoresistance

Given the lack of substantial associations in the whole sample between cytokines and proinflammatory markers and pragmatics except for SII, separate correlations in the sub-samples of FLR and TRS patients were analyzed only between KP metabolites and SII and pragmatics.

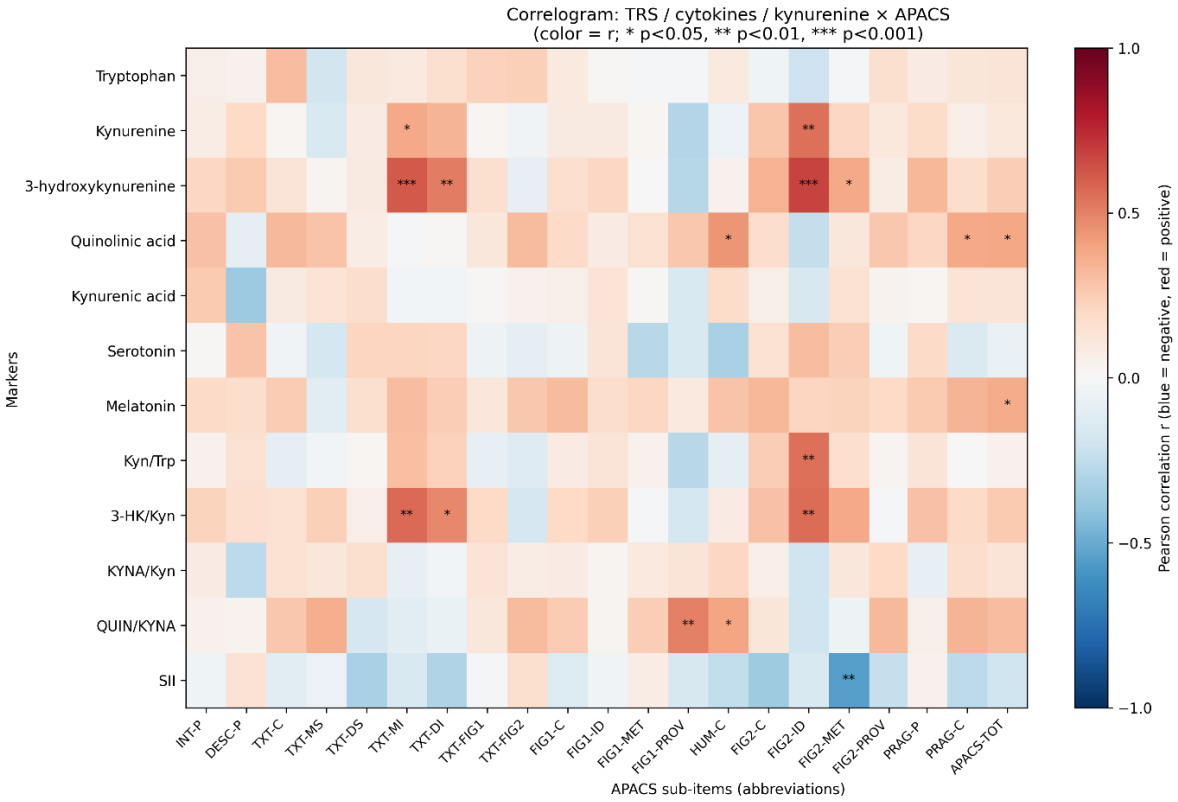
In FLR, as reported in Figure 4, several significant correlations were observed between kynurenine pathway metabolites and specific pragmatic–linguistic measures. Specifically, Trp levels were positively correlated with performance on the Figurative Language 1 Proverbs ($r = 0.35$; $p = 0.03$). KYN showed consistent positive associations with narrative comprehension tasks, correlating with both Texts MI ($r = 0.40$; $p = 0.01$) and Texts DI ($r = 0.43$; $p = 0.01$). In addition, kynurenine levels were positively associated with Figurative Language 2 Idioms ($r = 0.44$; $p = 0.01$). Similarly, 3-HK was positively correlated with Texts MI ($r = 0.31$; $p = 0.05$) and Texts DI ($r = 0.43$; $p = 0.01$), indicating a relationship with inferential aspects of text comprehension. In contrast, quinolinic acid exhibited significant negative correlations with Texts DI ($r = −0.37$; $p = 0.02$) and with Figurative Language 2 Idioms ($r = −0.31$; $p = 0.05$), suggesting that higher QUIN levels were associated with poorer performance in these pragmatic domains. Negative associations were also observed for KYNA, which was inversely correlated with Texts MS ($r = −0.37$; $p = 0.02$) and with Figurative Language 1 Idioms ($r = −0.34$; $p = 0.03$). With regard to the serotonin pathway, serotonin levels were positively correlated with Texts MI ($r = 0.38$, $p = 0.02$), whereas melatonin showed a negative association with Figurative Language 2 Proverbs ($r = −0.32$; $p = 0.04$). Considering kynurenine pathway ratios, the Kyn/Trp ratio was positively correlated with Brani DI ($r = 0.39$; $p = 0.01$) and with Figurative Language 2 Idioms ($r = 0.40$; $p = 0.01$). Conversely, the KYNA/Kyn ratio showed a modest but significant negative correlation with Texts MI ($r = −0.31$; $p = 0.05$). Finally, the QUIN/KYNA ratio was positively associated with Figurative Language 1 Proverbs ($r = 0.33$; $p = 0.04$).

Figure 4. Associations between kynurenines, serotonin and melatonin in first-line responders



In the TRS subsample, as detailed in Fig. 5, several significant associations emerged between kynurenine pathway metabolites, melatonin and SII, and pragmatic performances. Specifically, KYN levels were positively correlated with performance on the Texts MI item ($r = 0.38$; $p = 0.04$) and showed a strong positive association with the Figurative Language 2 Idioms sub-item ($r = 0.55$; $p < 0.01$). Similarly, 3-HK exhibited robust positive correlations with Texts MI ($r = 0.61$; $p < 0.01$) and Texts DI ($r = 0.51$; $p = 0.01$), as well as with Figurative Language 2 – Idioms ($r = 0.68$; $p < 0.01$). A weaker but still significant association was also observed with Figurative Language 2 Metaphors ($r = 0.38$; $p = 0.05$). With respect to downstream metabolites, QUIN was positively associated with Humor Comprehension ($r = 0.44$; $p = 0.02$). Additionally, QUIN levels correlated with Pragmatic Comprehension ($r = 0.38$; $p = 0.04$) and with the APACS Total score ($r = 0.39$; $p = 0.04$). A positive association was also found between melatonin levels and overall pragmatic performance, as indexed by the APACS Total score ($r = 0.37$; $p = 0.05$). Regarding kynurenine pathway ratios, the Kyn/Trp ratio was positively correlated with Figurative Language 2 Idioms ($r = 0.55$; $p < 0.01$). The 3-HK/Kyn ratio showed significant positive correlations with Texts MI ($r = 0.57$; $p = 0.01$), Texts DI ($r = 0.48$; $p = 0.02$), and Figurative Language 2 Idioms ($r = 0.56$; $p = 0.01$). Moreover, the QUIN/KYNA ratio was positively associated with Figurative Language 1 – Proverbs ($r = 0.51$; $p = 0.01$) and with Humor Comprehension ($r = 0.39$; $p = 0.04$). Finally, SII showed a significant negative correlation with Figurative Language 2 Metaphors ($r = -0.55$; $p = 0.01$), indicating that higher systemic inflammatory load was associated with poorer performance on this specific pragmatic subcomponent.

Figure 5. Associations between kynurenines, serotonin and melatonin in patients treated with clozapine (TRS)

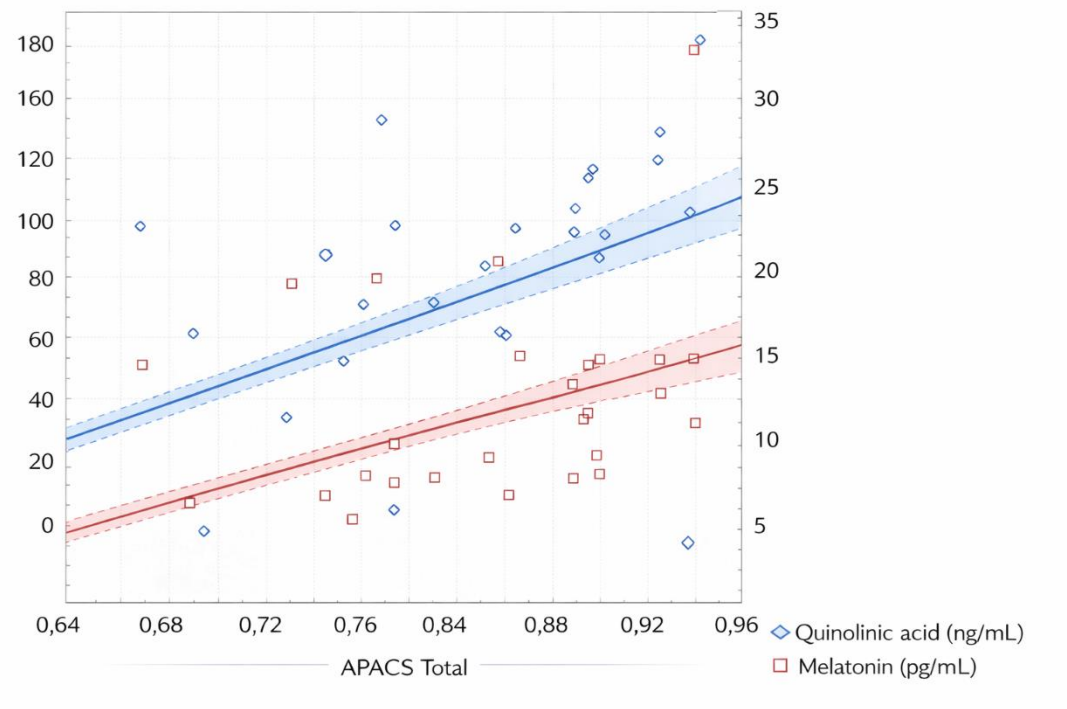


Given the significant correlations emerged in TRS patients between QUIN and melatonin and APACS total score we performed a stepwise-forward regression model to assess the ability of QUIN and melatonin of predicting the overall pragmatic performance. APACS Total score was selected as dependent variable, while QUIN and melatonin levels were entered as predictors. Coefficients of the regression model are reported in Table 12, while Figure 6 provides a graphical representation.

Table 12. Stepwise forward regression coefficients

R= 0.54; R^2= 0.29; Adjusted R^2= 0.24; p=0.01		
	β	p
QUIN (ng/Ml)	0.39	0.03
Melatonin (pg/Ml)	0.37	0.03

Figure 6. Quinolinic acid and melatonin



Finally, Separate Slope Model showed a trend for differentiated effects of QUIN and Melatonin on APACS according to TRS status. As reported in table 13, both QUIN and melatonin showed marginal positive effects on pragmatic performance in the TRS group, while no significnat effects emerged in FLR.

Table 13. Differential effects of QUIN and melatonin depending on the condition of pharmacoresistance

Dep. Variable	Separate slope	F	p	Effect	β	p
APACS Total	QUIN*TRS	2.37	0.1	QUIN (TRS)	0.42	0.06
APACS Total	QUIN*TRS	2.37	0.1	QUIN (FLR)	-0.17	0.29
APACS Total	melatonin*TRS	2.38	0.1	melatonin (TRS)	0.39	0.07
APACS Total	melatonin*TRS	2.38	0.1	melatonin (FLR)	-0.18	0.23

DISCUSSION

This study stems from a growing body of evidence highlighting a key role of pro-inflammatory processes and KP disregulation in the pathophysiology of schizophrenia. These two systems, strictly intertwined, have so far being studied especially with respect to TRS, a condition observed in over 30% of patients, where they appear as promising novel treatment targets [14][31][42][43]. Inflammation and, to a more limited extent, also the KP, have further been linked to cognitive performance, which is typically impaired in schizophrenia and refractory to currently avaible treatments [35][47]. Moreover, few data suggest that the negative impact of pro-inflammatory status on cognition is more pronounced in TRS patients, compared to treatment responders [14][52]. Interestingly, some of these studies assessed cognition with broad batteries encompassing language tasks, reporting negative associations between proinflammatory markers and linguistic abilities [47][56]. The link between inflammation and language function is further supported by neuroimaging data showing chronic inflammation, through microglial activation and impaired synaptic pruning, disrupts neurotransmission and brain structure in regions critical for language processing [80]. However, clinical evidence is so far limited to basic language tasks, such as verbal fluency, naming and repetition, while no study examined the effects of inflammation and KP disregulation on higher order language functions, such as pragmatics, whose impairment is a core feature of schizophrenia and a relevant treatment target to improve functional outcome [57][81]. Based on these premises, this work aims at investigating if the effects of inflammation and KP in schizophrenia extend to the most sophisticated language ability, namely pragmatics, beyond cognition and treatment-resistance. Given the interplay between pragmatics and neurcognitive functions, expecially executive ones, we first further analyzed their relationship before specifically addressing the association between pragmatics and inflammatory and KP markers, also distinguishing between TRS and FLR.

Profiles of pragmatic abilities and relation with cognition

We identified, through cluster analysis, two groups of patients characterized by higher and lower pragamtic abilities. The two profiles were highly homogenous within groups, showing significant differents across all the assessed pragmatic tasks, except for proverb interpretation, which is one of the most challenging [82]. Looking at differences between these two groups, for symptoms severity, we found a significantly higher score of PANSS item N5-Difficulty in abstract thinking in patients with lower pragmatic abilities, compared to those with higher performance, further supporting that pragmatics is the linguistic counterpart of clinical “concretism” [82][83]. On the contrary, when looking at cognition, no differences emerged between the two groups on neurocognitive task scores. Similarly, when we grouped patients according to their neurocognitive profile, we did not find a significant overlap in the distribution of patients across pragmatic and neurocognitive profiles. These negative findings support previous evidence that pragmatics and neurocognition, although with some moderate relations, represent two distinct and not interchangeable constructs [67][77].

Pragmatic abilities and inflammatory markers

This is the first study to investigate the relation between pragmatic abilities and inflammation through a systematic assessment. Results showed no direct correlations between pragmatic abilities and our broad panel of peripheral pro-inflammatory markers, except for MIP-1beta. However, significant negative correlations emerged between the systemic inflammatory index and pragmatics, especially in the figurative language domain. The association between higher systemic inflammation and poorer pragmatic performance was also supported by the finding of significantly higher SII in the group of patients with overall low pragmatic abilities. These results appear of particular relevance for treatment implication and align with previous literature on cognition and neuroimaging. SII is a composite inflammatory index easily calculated from hematological parameters derived from the complete blood count and does not represent a direct measure of levels of pro-inflammatory agents such as cytokines [79]. However, it indirectly reflects their downstream effects by capturing their impact on the immune system, and this is why it is frequently associated to levels of C reactive protein (CRP), IL1, IL6 and TNF- α [84][85]. Specifically, it is characterized by a lack of disease specificity and influenced even by other factors as decreased adaptive immunity (reduction of functional lymphocytes) and activation of the coagulation pathways [86]. Overall, it is a proxy of the balance between innate (neutrophils, platelets) and adaptive (lymphocytes) immunity, lacking the specificity of cytokine profiling [79][86][87]. Considering evidence on schizophrenia, several cross-sectional studies [88][89][90][91][92] and a 3-year retrospective study [93] found that SII is consistently elevated in both first episode and chronic patients with schizophrenia, compared to healthy controls and correlates with symptom severity [89][94] and cognitive impairment [95][96][97]. The most important evidence is represented by a prospective cohort study involving 161,968 participants from a UK Biobank, in which longitudinal associations between elevated innate immunity markers such as SII, CRP and incident psychiatric disorders, including schizophrenia, and dementia were demonstrated [98]. Importantly, SII is more aspecific and more related to cardiovascular, metabolic diseases and metabolic syndrome (MetS), which are typically associated to schizophrenia. As a matter of facts MetS represents the most frequent comorbidity of schizophrenia, affecting almost 40% of patients [99]. Considering associations between inflammatory markers involved in innate immunity, such as CRP, a negative correlation with cognitive functioning emerged [100]. Indeed, a recent study from North and colleagues, found that peripheral sub-inflammation measured through CRP levels can play a role in cognitive deterioration of patients with schizophrenia and it is negatively related to cortical thickness at prefrontal and cingulate cortices level [34]. However, there is currently no direct evidence in literature addressing the relationship between inflammatory markers and pragmatic abilities in individuals with schizophrenia. Therefore inferences and possible explanation must be done based on the neurocognitive substrates of pragmatics, and particularly cognition (and its neurobiological bases), especially executive functions, and social cognition/Theory of Mind [66][67]. Concerning peripheral inflammation and cognitive functioning in schizophrenia, two of the most recent meta-analyses confirmed a prominent role of innate immunity (CRP, SII) in determining the cognitive impairment typical of the illness [100][47]. Focusing on executive functions, cross-sectional and longitudinal studies confirmed that increased pro-inflammatory cytokines, particularly IL-6, IL-8, and TNF-α, are associated with deficits in verbal fluency, Stroop, and Wisconsin Card Sorting Test performance, which specifically assess executive functions [101][102][103]. Regarding social cognition, peripheral inflammation, particularly IL-6 and TNF-α, may selectively impact social cognitive functioning in psychoses, being an important determinant of misinterpreting social stimuli, thus developing delusional symptoms and

functional impairment in daily life [104][105][106]. The neurobiological underpinnings of social-cognitive impairment remain poorly understood, however, an abnormal activation of brain areas involved in social cognition and a pattern of dysconnectivity within social-cognitive networks have been identified as possible contributors [107]. Oxidative stress and neuroinflammation are mainly I for neurotoxicity and neurodegeneration (loss of neurons' soma and dendrites/synpses), while enhanced synaptic pruning (loss of dendrites and synapses) and white matter disruption (dysfunctional impulse transmission) are mainly related to dysconnectivity [108]. Overall, it has been proposed that such microscale disconnectivity (cellular and molecular level) can impact macroscale connectivity (Frmi), with the addition of disrupted white matter and myelination, leading to altered functioning of social brain [107][109]. Notably, these pathogenetic mechanisms caused by neuroinflammation and involving neuron loss, impoverishment of dendritic arborization and white matter disruption, underly even cognitive impairment and executive functions deficits [33]. Therefore, it is likely that even pragmatics can be affected as well, relying mostly on these two cognitive (executive functions) and sociocognitive (ToM) dimensions. Considering that Temporo-parietal Junction (TPJ) represents the brain region in which theory of Mind (ToM) is located, disconnectivity can have a more negative impact on pragmatics given the distance between Prefrontal Cortex (PFC) and TPJ and, overall, given the more distributed nature of pragmatics across the brain [110][111]. For this reason, by increasing the complexity of the system organization, the system itself could become more susceptible to detrimental effects of inflammation. Indeed, the meta-analysis performed by Frau and colleagues showed that pragmatic skills in schizophrenia are associated with social cognition (particularly theory of mind) and executive functions, with a stronger correlation with social cognition that acts as moderator of the effects, suggesting a functional hierarchy between these domains [67]. Thus, more complex functions, requiring a greater level of integration, could be more affected by the sub-inflammation typical of schizophrenia and its comorbidity MetS. Overall, these findings represent the first evidence of increased levels of systemic inflammation in patients with schizophrenia burdened by greater pragmatic impairment.

Pragmatic abilities and kynurenine pathway: focus on treatment-resistance

We found significant differences in terms of age and duration of illness between FLR and TRS in line with evidence of a loss of response in a proportion of patients who were initially responsive to treatment [11]. Looking at the KP, we found increased activation of the pathway in FLR (higher KYN/Trp ratio) despite higher levels of QUIN were found in TRS, pointing to an imbalance in the activity of the two branches of the kynurenine pathway, with a predominance of the neurotoxic branch. Bearing in mind that KP is at the crossroad between inflammation and neurotransmission, we interesting found several correlations between metabolites levels and different pragmatic tasks scores. To better disentagle this complex interplay, we separately addressed associations in patients with treatment resistance, undertaking clozapine and first line reponders, treated with antipsychotics, other than clozapine. This choice was motivated both by previous findings showing stronger effects of inflammation on cognition in TRS, compared to treatment respnders [14][52][112], and by the specific pharmacodynamics of clozapine. Indeed, clozapine is able to directly or indirectly modulate the effects of some neuroactive molecules or enzymes through the glutamate system [31][113], which is in turn directly modulated by KP metabolites.

Significant correlations between levels of molecules involved in the KP and pragmatic scores emerged in both groups (FLRs vs TRS), althought with different patterns. Indeed, stronger correlations were observed in patients with TRS, and opposite directions were also detected for main neuroactive metabolites which affect glutamatergic transmission, i.e. QUIN and KYNA. In detail, QUIN and melatonin were positively and significantly associated with APACS Total score in TRS patients. QUIN is produced in high amounts by activated microglia and widely considered a neurotoxic molecule [114] due to its ability to induce excitotoxicity through the overstimulation of NMDA receptors (agonistic activity) and many other mechanisms, such as the production of ROS, impairment of mitochondrial function, activation of apoptotic pathways and neurodegeneration [115]. However, TRS patients are treated with clozapine which is able to indirectly modulate the conformation of NMDA receptors, increasing their functionality, thus resizing the increased compensatory glutamate release at presynaptic level [116] and in turn even excitotoxicity [46][18][45][113][31].

Genetic data [36] and a recent genome-wide association study (GWAS) [117] corroborated empirical evidence derived from drug-models (ketamine, phencyclidine) on NMDA receptor hypofunction as a comprehensive model of schizophrenia. Indeed, Trubetskoy and colleagues found that genetic variants in 287 distinct loci were associated to schizophrenia and many of them participate to the biology of excitatory synapses, including the GRIN2A gene, encoding the glutamate NMDA receptor subunit GluN2A [117]. Notably polymorphisms affecting the conformation of the GluN2A subunit induce a loss of function secondary to dysfunctioanal assembly the different subunits [118][119]. Due to NMDAR hypofunction, an increased compensatory release of glutamate occurs at the presynaptic level [116][120][121], responsible of the so called excitotoxicity [116]. This is probably why there is strong evidence of increased levels of glutamate in schizophrenia [37] and especially TRS [122], being glutamate levels in the striatum negative predictors of antipsychotic response to first-line treatments [39][38]. Evidence from prospective studies has demonstrated that antipsychotic treatment can modulate glutamatergic neurotransmission by reducing levels of glutamate metabolites, thereby contributing to symptom improvement [40]. Notably, significantly higher serum glutamate levels have been observed in clozapine-responsive patients compared with clozapine non-responders, underscoring the involvement of glutamatergic mechanisms in TRS [123]. Furthermore, serum glutamate concentrations have been shown to correlate with the severity of positive symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) [39]. Interestingly, one of the proposed mechanisms underlying clozapine's therapeutic efficacy is the enhancement of glutamatergic neurotransmission at the level of NMDA receptors, which in trun decreases levels of glutamate released at pre-synaptic level. Indeed, clozapine inhibits glycine transport, leading to increased synaptic glycine availability [124]. More specifically, clozapine blocks both the glycine transporter 1 (GlyT1) and system A–mediated transport, which represents an alternative glycine reuptake pathway [46][125]. Additional evidence has suggested a possible direct interaction between clozapine and the allosteric glycine-binding site of NMDA receptors, although these conclusions are based on indirect observations [45]. Notably, glycine acts as a positive allosteric modulator of NMDA receptors and thereby enhances NMDA receptor function, potentially contributing to the normalization of glutamate levels. This effect has been supported by recent prospective 1H-MRS studies examining individuals before and after clozapine treatment [126]. Overall, these findings suggest that clozapine may restore glutamatergic neurotransmission

abnormalities arising from NMDA receptor dysfunction [18][127][128]. In this view, QUIN by stimulating NMDA receptors in the presence of clozapine does not induce excitotoxicity but properly stimulates glutamatergic neurotransmission with a procognitive effect [113]. As for melatonin which was also positively associated with APACS Total score only in TRS patients, a similar mechanism related to a synergistic effect with clozapine may be implicated. Indeed, there have been several lines of research over time converging on the robust evidence on the ability of melatonin to resize excitotoxicity exerted by glutamate on NMDA receptors [129][130][131][132][133][134]. Moreover, there is evidence even on the abiliy of melatonin to directly counteracts and attenuate oxidative stress and neurotoxicity induced by QUIN through glutamatergic excitotoxicity [135][136][137].

Looking jointly, trough regression model, at effects of QUIN and melatonin on pragmatic competence, we found that QUIN and melatonin levels were able to explain 24% of the global pragmatic variance in TRS patients. This result can be explained based on the synergistic effect of clozapine, QUIN and melatonin which induces increased glutamatergic neurotransmission in the brain coupled with a reduction of glutamaergic excitotoxicity. It is essential to consider that glutamate represents the most important and widespread excitatory neurotransmitter, fundamental for supporting cognitive processes and higher-order functions [138], probably more than dopamine which is also involved in excitatory neurotransmission but in specific areas connected to the four main dopaminergic pathways (mesolimbic, mesocortical pathway, nigrostriatal and tuberoinfundibular pathways) such as PFC and striatum [139]. It is important that glutamate levels effectively contribute to glutamatergic neurotransmission through the bond with the active site of the receptor, which in turn must be configured in the proper shape to allow the process [118][113], otherwise higher levels of glutamate in the extracellular space cause excitotoxicity [113] and cognitive decline [140].

The differential effects of QUIN and melatonin on pragmatics depending on TRS status were furter supported the separate slope regression model on the all sample, which showed marginal associations only in TRS, with no effects among FLRs. Overall, despite higher levels of QUIN, typically considered neurotoxic, in TRS, its synergistic effect with clozapine and melatonin results in a pro-pragmatic effect due to the enhancement of glutamatergic neurotransmission in the brain with possible positive implications for connectivity.

Limits of study

The current study presents some limitations that need to be acknowledged. First, the absence of a control group of healthy participants do not allow comparisons with the general population. Second, the lack of longitudinal evaluations prevented us to assess the evolution of pragmatic performance in relation concentrations of melatonin and QUIN. Then, we did not measure CRP levels as a proxy of innate immune response along with hematological parameters used to calculate SII index. Moreover, we did not measure MetS parameters in order to covariate SII, as BMI or parameters needed to diagnose MetS or the presence/absence of MetS coul play a role in differences in SII levels. We had excessively incomplete data regarding weight, height, and metabolic parameters to calculate BMI in an acceptable number of patients; moreover, we did not have information on patients' smoking status. The absence of these factors, which may influence patients' inflammatory status,

represents an additional limitation of the study. Other limitations which reduce the generability of our conclusions and the validity of our explanatory hypotheses are the lack of a ToM assessment which could have been useful in explaining the absence of a significant overlap between cognitive and prgmatic clustrers. Finally, there is no direct neuroimaging evidence (RMI, Frmi, PET) about our conclusions on the detrimental effect of neuroinflammation (SII index) on the biological substrates of pragmatics, and not even about glutamate levels (Magnetic Resonance Spectroscopy) or increased functionality of cerebral networks (fRMI).

Conclusions and clinical perspectives

This study, while further supporting the independency of pragmatics from neurocognition, provides the first evidence of an association between pragmatic impairment and the sub-inflammatory state typical of schizophrenia, as well as of a positive association between pragmatic performance and melatonin and quinolic acid in patients with treatment resistant schizophrenia. Results bring novel insights on the the interplaybetween pragmatics, inflammation and KP, contributing to increase knowledge on the biological mechanism underlying pragmatic abilities and schizophrenia. While preliminary, they might also pave the way for combined therapeutic interventions aimed at resizing pragmatic impairment in people with schizoprenia. Specifically, it has been demonstrated that targeted rehabilitation interventions, such as Pragmacom [81] represents an effective strategy to improve pragmatic abilities in patients with schizophrenia, with benefits extending to daily functioning. However, the degree of improvement varies across individuals, highlighting the need of further potentiating strategies. In this view our findings suggests that the integration of other non-pharmacological interventions reducing inflammation, such as aerobic exercise [33], or pharmacological ones targeting melatonin and QUIN may potentiate the improvement of pragmatic abilities, especially in patients with TRS. Given that the pharmacovigilance monitoring protocol of clozpine has just gone through an extensive revision toward a lower complexity, even by increasing the prescription of clozapine could help patients in improving their functioning and quality of life with positive implications in terms of costs for society.

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STUDY 2

PSYCHEDELIC DISCOURSE: ACUTE EFFECTS ON SPEECH PRODUCTION. A SYSTEMATIC REVIEW OF CLINICAL STUDIES

ABSTRACT

Psychedelics are emerging as a promising treatment for several mental illnesses; however, little is known about their effects on speech production. An in-depth characterization of psychedelic-induced speech alterations might be of paramount importance to gain novel insights on the potential of psychedelics treatment. To evaluate the impact of psychedelics administration on speech, we performed a systematic review of clinical studies in individuals under the acute effect of psychedelic compounds, with a focus on the different linguistic categories affected, and carefully considering dosage as a possible explanatory variable of the results. We searched PubMed/MEDLINE, Scopus, and Embase according to PRISMA guidelines. All studies measuring the acute impact of any psychedelic compound on speech production were included in the review, for a total of 14 studies. Administration was associated with alterations affecting language production across pragmatics, semantics, and syntax, with dosage explaining most of the variability across studies. Microdoses of psilocybin enhanced verbosity and positive emotions conveyed through speech, without hampering discourse organization. Mild doses of psilocybin and LSD led to simplification of syntax and to alterations of semantic content, also inducing an indirect semantic priming effect. Full doses of LSD induced loosening of logical associations, resulting in altered discourse coherence. These findings show the importance of carefully considering linguistic alterations within the context of clinical trials on psychedelics.

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INTRODUCTION

Language and psychedelics

In the last decades, mounting evidence has shown the outstanding potential of psychedelics in the treatment of several psychiatric disorders [1]. These pieces of evidence have revived the interest after the prohibition era that followed the Controlled Substances Act in 1970, laying the foundations for the "psychedelic renaissance" [2][3]. Indeed, a multitude of ongoing clinical trials are trying to demonstrate the therapeutic potential of psychedelics on several symptom dimensions in many mental illnesses [2]. In particular, there is an increasing body of evidence regarding the possible use of psychedelics in the treatment of schizophrenia [4][5], the prototype of formal thought disorders (FTD) [6][7]. Indeed, despite psychedelics have been considered a drug model of schizophrenia for a long time, nowadays emerging evidence on their biological effects, coupled with findings from old clinical trials [4], is pointing at a possible role in resizing negative symptoms and cognitive impairment, thus negative FTD language dimension, such as alogia [6][8]. However, the possibility that such compounds would alter cognitive functioning and language production is still overlooked within the context of clinical trials, where it might serve as an indicator of adverse effects or an indirect measure of clinical efficacy based on the profile of induced alteration. Language impairment is a core clinical feature of several mental diseases, especially in individuals with schizophrenia, where deficits span from speech to higher-level pragmatic skills intersecting cognitive and sociocognitive dysfunctions [9][10][11][12][13][14][15] and deeply impacting daily functioning [16], one of the most unmet clinical needs of the disease. Thus, understanding the impact of psychedelics on the different linguistic dimensions typically impaired in schizophrenia is worthy of investigation. Nonetheless, evidence on the effects in the healthy population is sparse and conflicting due to the heterogeneity of compounds and doses used, routes of administration, and tasks performed during the experiments [17][18][19][20]. The first study on the ability of psychedelics to alter linguistic dimensions dates back to the '60s, and it showed decreased talkativeness and predictability of language under LSD, as well as an inverse relationship between predictability and the number of words spoken per time unit [21]. Lower predictability in language under the effect of psychedelics is supported by recent evidence [22][23], which reported the tendency towards a broader activation of the semantic network. However, the findings are conflicting [17][19]. A decrease in talkativeness was also found in recent studies [17], while others reported an increase in the same linguistic measure [18]. On the other hand, concerning the content of the speech, converging findings reported a shift towards a more concrete use of language [24][25][26]. In addition, most of the studies focused on the semantic content of written retrospective reports, in which participants were asked to describe previous psychedelic experiences, rather than on the acute effect of the drug on different linguistic categories. This limits the reliability of these studies in identifying linguistic categories that can be used within clinical trials to assess the efficacy and possible side effects of psychedelic compounds [20].

Neurobiology of psychedelics

Psychedelics are psychoactive substances able to induce mainly distorted perceptions (e.g., illusions, hyperesthesia, and visual hallucinations) and an altered state of consciousness [27][28]. Most of them are 1) semi-synthetics, such as LSD and N,N-dimethyltryptamine (DMT, the active ingredient in *ayahuasca*) or 2) derived from plants,

such as plant-derived tryptamines like psilocybin (the active compound of *Psilocybe cubensis* dried mushroom) and phenethylamines, such as mescaline (the active compound of the *peyote*) [2][29]. Pharmacodynamics of psychedelics can differ depending on the specific compound, despite all of them acting as agonists or partial agonists at the 5-HT2A receptor level [27]. Psychomimetic effects depend on the pharmacodynamics and the specific dose of the molecule administered.

What is characteristic about psychedelics is the ability to induce long-lasting neuroplasticity by the activation of 5-HT2A receptors within the serotonin receptor family, as demonstrated by in vitro findings [30][31]. Interestingly, new in-vitro findings are pointing at the 5-HT2A intracellular receptors as the key mediators of the enhanced phenomenon of neuroplasticity, as psychedelics can cross the neuronal membrane due to their lipophilicity, as opposed to serotonin itself, which thus cannot induce neuroplasticity [32][33]. In other terms, psychedelics can modify the cytoarchitecture of neurons, triggering specific intracellular pathways (mammalian target of rapamycin, mTOR, and tropomyosin receptor kinase B, TrKB) that lead to the sprouting of newborn, immature, yet enduring dendrites, forming new connections with other neurons [30][34][35]. The macroscopic counterpart of these findings has been provided by fMRI studies, highlighting the ability to induce the rearrangement of brain networks and circuits as one of the cardinal features of psychedelic compounds [36][37][38][39]. Indeed, a whole-brain reduction of direct functional connectivity (FC) and an increase of indirect FC, which are considered hallmarks of increased connections across brain regions, are well-replicated findings in the brains of healthy people under the effect of psychedelic compounds [34][40]. The resulting chaotic exchange of information taking place across the whole brain entails an overall increase in brain entropy, which supports the entropic brain hypothesis, according to which the entropy of spontaneous brain activity elicited by psychedelics influencesthe informational richness of conscious states [34][41]. It should be noted that 5-HT2A receptors are mainly expressed in cortical layers (i.e., layer V), especially in the high-level associative cortex [27][42]. Therefore, the ability to modulate the whole-brain connectivity is likely due to the binding between psychedelics and 5-HT2A receptors in layer V, which modulates the local connections of projecting neurons, increasing excitability, and, in turn, the “long-range” connections represented by the projecting axons [42]. Notably, the increased global connectivity is linked to the typical symptoms of acute intoxication, such as ego dissolution, visual illusions and hallucinations, synesthesia, dream-like status, and mystic experiences [42][43][44].

Beyond this phenomenology, psychedelic effects also result in disrupted or deviant language use related to altered connectivity in language-relevant areas of the brain [45][17]. This particular susceptibility of language network to psychedelics might be explained by the cytoarchitectonic and receptorarchitectonic organization of cortical language areas, characterized by enlarged III and V layers, populated by large pyramidal neurons which also invade the IV granular layer [46], and a high density of 5-HT2A receptors [47][48][20]. The evidence of a direct correspondence between changes in FC and the density of 5-HT2A receptors [49][50], makes language likely to be acutely affected by psychedelics and their ability to rearrange language network connectivity. Moreover, spatial transcriptomics discriminated specific patterns of laminar gene expression across cortical layers in the frontal and temporal language cortex with an upregulated transcription of proteins involved in signal projection in neurons of the III and V layers [51]. This represents another piece of evidence supporting the projecting role of brain areas in the language network. Overall,

given the rapidly increasing number of clinical trials on psychedelics for multiple psychiatric disorders, it is fundamental to understand the real impact that such compounds have on language, and which linguistic categories are affected the most. This would pave the way for characterizing side effects, but also indirect measures of the acute effect of psychedelics.

Aims

The overarching aim of the current review is to systematically gather and examine all the clinical studies that assessed language production under the effect of any psychedelic at any dosage in healthy subjects or patients not affected by a psychotic disorder to identify specific patterns of language alterations linked to the effect of such compounds. This review is expected to provide novel evidence linking specific impairment in some linguistic categories to psychedelic intake, with implications for the clinical trials testing the acute effect of these compounds on cognitive functioning. Our expectation is that the results obtained can allow for a comparative discussion with the evidence of language alterations in schizophrenia, such as psychedelics, and particularly LSD, were historically used to recreate drug models of the disease. Overall, taking the most impaired linguistic categories and considering them in light of the neuroplastic effect of psychedelics could provide interesting insights into the neurobiological underpinnings of language functioning and disorganization in psychiatric conditions.

METHODS

Search methodology

We performed a systematic review using Pubmed/MEDLINE, Embase, and Scopus databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using the following keywords: (LSD OR (lysergic AND acid) psilocybin OR DMT OR dimethyltryptamine OR mescaline OR psychedelic* OR hallucinogen*) AND (language OR linguistic* OR speech OR semantic* OR synta* OR discourse OR vocabulary OR phonem* OR phonology OR pragmatic* OR metaphor* OR irony). Search terms were applied to article titles, abstracts, and keywords without restrictions on the year of publication.

Inclusion and exclusion criteria

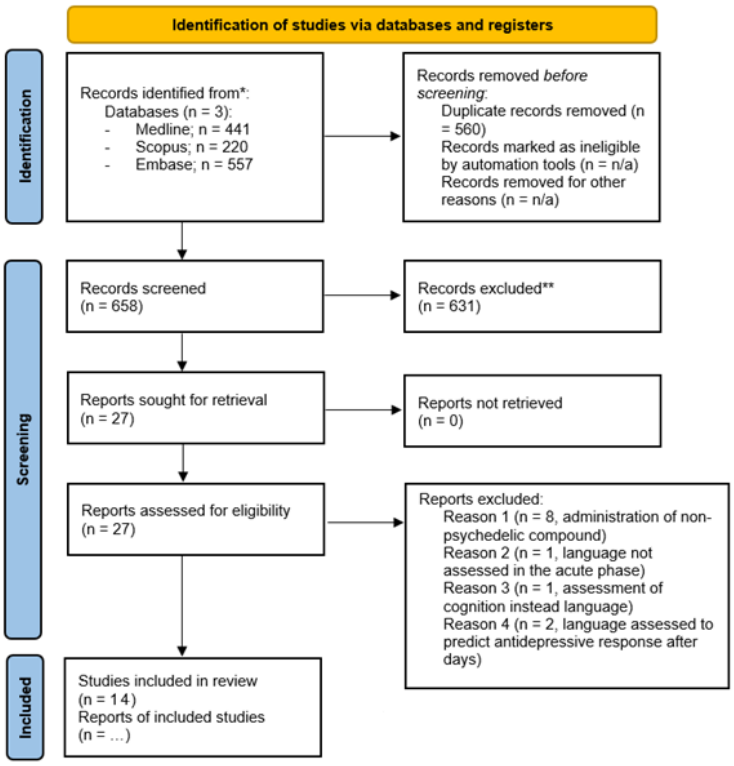
To be included in this review, studies had to: (a) assess language production under the effect of any psychedelic compound; (b) be written in English.

Exclusion criteria: (a) studies on written reports or speech samples collected after the psychedelic experience or on memories related to the experience; (b) intake of other substances (MDMA, ketamine) or other compounds inappropriately called psychedelics.

RESULTS

The literature search returned 1218 records (PubMed/Medline: 441; Scopus: 220; Embase: 557), which were screened for eligibility by two authors (J.S. and F.F.). No disagreement occurred between the two reviewers, and thus, no intervention of a third reviewer to reach a consensus was necessary.
After removing duplicates, 658 records were screened by reading titles and then the abstracts. Of the 27 records initially selected after screening the abstract, only 14 fully met the criteria for eligibility after reading the full article (Figure 1). The included studies are described in Table 1 and can be furtherly divided into two sub-groups: a) semi-anecdotal studies, conducted before 2000 on samples of less than 13 healthy subjects or patients with alcohol abuse or depressive symptoms (N = 11); b) new studies, conducted after 2020 on samples of more than 20 healthy subjects with more sophisticated statistical analysis (N = 3).

Figure 1. PRISMA Flowchart



Linguistic variables included

Linguistic variables in eligible studies included measures assessing speech time composition and fluency, grammar and the lexicon (e.g., lexical richness, sentence composition, and text content), and indices targeting semantic access and pragmatic abilities (discourse organization and figurative language production).

Variables related to speech time composition were limited to pause and vocalization duration as extracted from audio recordings of speech samples elicited via a monologue

production task [52][53], as well as measures of speech rhythm (i.e., the alternation between silences and vocalizations, and interruptions) during a conversation [54]. Regarding fluency, four studies reported the number of spoken words [17][18][21][19].

Lexical richness was addressed in one study only, in which a measure of how many lexical units conveyed information in participants' speech samples was included (Shannon's Information Entropy index; [18]). Three studies evaluated dictionary-based measures – either using manual or automated annotation methods (e.g., the Linguistic Inquiry and Word Count software (LIWC), [17]) – to count the occurrence of units belonging to specific lexical classes or part-of-speech categories [17][24][55]. Martindale & Fisher [24] used the COUNT software [25] to extract words belonging to categories operationalized from psychoanalytic literature and organized in the Regressive Imagery Dictionary, targeting mainly sensorial and psychological processes. Natale et al. [55] focused on words expressing defensive behavior as scored following Weintraub & Aronson (1962), such as non-personal references (e.g., subjects known to the speaker), negators (e.g., negatives), qualifiers (e.g., expressions of uncertainty), retractors (e.g., expressions of detraction), explaining (e.g., expressions clarifying cause-effect relationships), expressions of feeling (e.g., affective words), and evaluators (e.g., judgments). Weißner et al. [17] used the LIWC software to investigate the frequency of words belonging to grammatical categories (i.e., part-of-speech categories, such as verbs and pronouns) and semantic classes (e.g., psychological processes, time, space, etc.).

Regarding sentence composition, one study addressed a measure of syntactic complexity in written texts, namely a measure of the number of coordinate and subordinate clauses in sentences and length of T-units [56], while another study by Weißner et al. [21]focused on verbs by counting their occurrence and analyzing tense .

Moving further, two studies focused on text content: Landon & Frisher [56] assessed the occurrence of concrete and abstract words in participants' speech samples, while Sanz et al. [19] applied a sentiment analysis [57] to investigate whether text content conveyed more positive, negative, or neutral sentiment.

As for the level of semantic and pragmatic skills, two studies [23][58] used measures of semantic access, namely indirect semantic priming (i.e., semantic priming with two indirectly related words, such as *lemon* and *sweet*), taken as an index of semantic knowledge organization [59]. One study used a measure of cloze probability to assess speech predictability based on the semantic context [21], while two studies [18][19] used a measure of semantic variability, operationalized as the semantic distance between consecutive words reflecting speech coherence. Sanz et al. [18] also performed topic modeling using latent semantic analysis [60] to test the semantic distance between the most frequent words in participants' speech (e.g., *mood*, *ego*, *reality*, etc.) and the rest of the words in each speech sample. Weißner et al. [17] adopted a more complex operationalization of semantic distance measures, to measure the global spread of semantic activations (i.e., average distance among all words), the evolution of thoughts over time (i.e., average distance of each word to all predecessors), the length of the "semantic journey" (i.e., the distance of the first word to all subsequent words), and the size of the "journey steps" (i.e., the distance between neighboring words).

Finally, a limited number of studies focused on measures at the pragmatic level, namely variables of discourse organization and figurative language production. In particular, one

study [61] focused on the occurrence of figurative expressions (e.g., metaphors) in participants' speech under the effects of psychedelics, while two studies [17][18] applied speech graph analysis [62] to inspect discourse organization.

Types of psychedelics: molecules and doses used

In the studies included in this review only LSD, psilocybin (active compound of dried mushrooms), and synthesized psilocybin were used at different doses ranging from microdoses to full doses.

Full dose or microdose ranges are reported according to Polito et al. [63]:

1. *Psilocybe cubensis* dried mushroom: full dose range 3–5 g; microdose dose range 0.1–0.5 g.
2. Psilocybin synthetic: full dose range 17–30 mg; microdose dose range 0.8–5 mg.
3. LSD: full dose range 100–200 µg; microdose dose range 6–20 µg.

Importantly, intravenously (iv) administered compounds are recognized to be more potent. However, the conversion regarding iv LSD is not reported.

Linguistic measures under different doses of psychedelics

Here, we summarize the impact of psychedelics on language production across measures. In each paragraph, we focus on specific language dimensions, reporting results from the lowest to the highest dose of psychedelics.

Speech and Fluency, Grammar and the Lexicon

Sanz et al. [19] used microdoses of psilocybin (0,5 g of dried mushrooms) on 34 healthy participants, recording increased verbosity under the effect of the psychedelic compound. Moreover, emotional correlates of speech production inferred by sentiment analysis were more positive. Indeed, participants under microdosing scored higher compared to placebo in all their answers [19].

Different from the other studies, Landon and Fischer [56] and Martindale and Fischer [24] used written texts instead of speech transcripts and mild doses of psilocybin. Specifically, Landon and Fischer administered 80 µg/kg of psilocybin to 2 healthy individuals after repeated administrations of 160 µg/kg at three three-week intervals and asked them to recall and describe previous more intense experiences (160 µg/kg). They reported an increased use of coordinated and a reduced number of embedded clauses with an overall reduction in length of clauses and T-units and an increased use of concrete words compared to the control texts written by the same individuals during non-aroused states. Importantly, measures of statistical significance were not reported in the paper.

Martindale and Fischer [24] administered four mild doses of psilocybin (160 µg, 80 µg, 80 µg, and 200 µg/kg) to one healthy individual in four separate sessions, months apart. The subject was asked to write before (0-60 min after drug ingestion), during (drug peak, 60-120 min after ingestion), and after the hallucinogenic experience (over 120 min after ingestion). Content analysis was performed, and the output was the percentage of words assigned to each category (Drive; Regressive Cognition; Defensive Symbolization; Sensation; Icarian Imagery). Texts produced at the drug peak contained significantly more

words of the primary process content categories (Regressive Cognition $p<0.05$; Icarian Imagery $p<0.05$). No significant differences emerged for the other categories.

Jaffe and colleagues [64][53] analyzed the duration of vocalizations and pauses in a sample of seven individuals during 14 sessions of psychotherapy for each participant (seven under mild doses of LSD 50-100 µg and seven under placebo) in the context of both monologues and dialogues. Interestingly, the average pause duration was lengthened by LSD in monologues ($p<0.05$) and dialogues (p values not reported).

Natale and colleagues [54] used the same speech transcripts of the seven patients enrolled in Jaffe et al. (1972, 1973) [64][53] and found that mild doses of LSD induced increased matching of patient-therapist speech rhythms (p values not reported). Moreover, they scored the transcripts for categories of defensive language (Non-personal reference; Negators; Qualifiers; Retractors; Explaining; Expressions of feeling; Evaluators) and found that LSD caused individuals to make more personal statements ($p<0.01$) and to use explanations ($p<0.05$) and evaluations less often ($p<0.05$) [65].

Natale and colleagues [25], similarly to Martindale and Fischer (1977) [24], also reported differences in words pertaining to certain categories in a sample of four psychoanalytic patients treated with mild doses of LSD (50-100 µg) or placebo in 6-9 separate sessions. The percentage of words belonging to primary-process or secondary-process language categories was calculated. One patient manifested a significant attenuation of secondary-process language ($p<0.05$). Another one showed a significant increase in primary-process language after the intake of LSD ($p <0.05$). No significant differences emerged in the other two patients.

Considering the measures extracted using LIWC software, Wießner and colleagues [17] after having administered mild doses of LSD (50 µg) found a reduced frequency in the use of words of the categories of space, time, ingestion, and numbers, an increased use of assents, words related to physiological processes, and verbs, particularly in the present tense, with an overall reduction of verbs in the past tense.

Semantics and pragmatics

Sanz and colleagues [19] in a sample of 34 healthy participants reported unaltered discourse organization with microdoses of psilocybin (0,5 g of dried mushrooms) compared to placebo, inferred by unchanged semantic variability in response to open-ended questions about the feelings and moods of participants.

Spitzer and colleagues [23] and Gouzoulis-Mayfrank and colleagues [58] performed two experiments to assess the ability of mild doses of psilocybin (0.2 mg/kg body weight) to affect a lexical decision task on the semantic priming, respectively on eight and 12 healthy subjects vs placebo. Interestingly, both experiments found an increased indirect semantic priming effect (Spitzer et al., $p=0,026$; Gouzoulis-Mayfrank et al. p values not reported).

Regarding figurative language production, Natale and colleagues [61] found that the speech transcripts of two of the three males enrolled in the study and recorded during a psychotherapy session presented more novel metaphors under the effect of mild doses of LSD (50-100 µg) compared to their transcripts under placebo. “Novel” was defined as a figure of speech judged to be unique in that context by two raters. Patient 1 significantly increased ($p<0.01$) his use of figurative phrases and novel figurative phrases/1000 words

under the influence of LSD. Patient 2 displayed an LSD-induced increase only in novel figurative phrases/1000 words ($p<0.05$). No significant differences in the use of nonliteral language emerged in patient 3.

Wießner and colleagues [17] performed an RCT in which they randomly and orally administered mild doses of LSD (50 µg) or placebo to 23 healthy volunteers who were asked open-ended questions about their feelings and to perform a storytelling task at different time points. The number of words spoken significantly decreased, as well as local and global parameters in graph analysis (SpeechGraphs) and semantic distances between neighboring words and overall words (FastText).

A similar setting was adopted by Sanz and colleagues in their first experiment in 2021; however they used a different route of administration and administered 75 µg iv of LSD vs placebo in a sample of 20 healthy subjects [18]. Individuals under the effect of full doses of LSD, when asked to report spontaneous thoughts and feelings, showed increased verbosity and increased semantic variability ($p < 0.05$). Speech graph analysis showed increased local and global metrics under LSD, thus LSD increased verbosity but reduced the lexicon.

Amarel and Cheek [21] were the first to describe the effect of LSD on speech production, but they used higher doses compared to other studies. Five minutes of spontaneous speech were recorded from 10 subjects with alcohol use disorder under four different conditions: pre-administration, under full doses of LSD (100 µg-200 µg), and after the acute effect. Predictability and volubility were the two parameters examined, and both ($p<0.01$) were found to decrease under LSD at both doses, and, interestingly, an inverse relationship between predictability and volubility emerged.

Table 1. All studies included

Reference	Participants	Dose	Task	Speech and Fluency		Grammar and the Lexicon			Semantics and Pragmatics		
				Speech Time Composition	Fluency	Lexical Richness	Sentence composition	Text content	Semantic access	Discourse organization	Figurative Language
Sanz et al., 2022	34 healthy participants	Psilocybin microdoses (0.5 g of psilocybin mushrooms)	Open questions on mood and feelings		↑ Verbosity			↑ Positive sentiments		= Variability (compared to placebo)	
Landon and Fischer, 1970 [written texts]	2 university instructors	Psilocybin 80 µg/kg Repeated administration of 160 µg/kg (3 weeks interval)	Under Psilocybin 80 µg/kg subjects were asked to recall and describe previous more intense experiences (160 µg/kg)		↓ Sentence, T-Unit, and clause length		↑ Coordinated syntactic units ↓ Embedded syntactic units	↑ Concrete words			
Jaffe et al., 1972	7 participants in psychotherapy	5-25mg dextroamphetamine. 50-100 µg LSD, and a matching placebo. Each subject received each drug 7 times	Two five-minute monologues (after ingestion and 135 minutes after the first monologue)	↑ Mean pause time (second monologue only) = Mean vocalization time (both monologues)							
Jaffe et al., 1973	7 participants in psychotherapy	5-25mg dextroamphetamine. 50-100 µg LSD, and a matching placebo. Each subject received each drug 7 times	Five-minute monologues before psychotherapy	↑ Mean pause time (LSD) ↓ Mean pause time (DA) = Mean vocalization time (LSD and DA)							

Martindale and Fischer, 1977 [written texts]	1 participant under psilocybin	4 sessions, different doses/kg: -160 µg -80 µg -80 µg -200 µg	2 sessions: to recall and write about a previous 80 µg/kg psilocybin experience	↓ Difference in word length				↑ Words on primary process (more concrete, more imagery, more cognition-oriented)			
Natale et al 1978b	3 male psychoanalitic patients	each patient received each of the three drugs (LSD = 50-100 u; dextroamphetamine = 15 m g; placebo) seven times on a randomized schedule for a total of 21 experimental psychotherapy sessions over a period of 1 and a half year	Transcripts of 40 minutes of psychotherapy sessions								↑ Novel metaphors
Natale, 1979a	7 neurotic depressives participants	Double blind: 5-25mg dextroamphetamine. 50-100 µg LSD, and a matching placebo. Each subject received each drug 7 or 8 times over a 1+1/2-year period; 3-week intertrial interval.	5 minutes to talk about any topic that came to mind Monologues					↓ Non personal reference = Negators = Qualifiers = Retractors ↓ Explaining = Expressions			

								of feeling ↓ Evaluators			
Natale, 1979b	7 neurotic depressives participants	15-25 mg of DA and 50-120 µm of LSD were administered in capsules indistinguishable from PL	Samples of 63 hours of psychotherapy sessions Dialogues	↑ Matching of speech rhythm							
Spitzer et al., 1996	8 healthy participants	0.2 mg/kg body weight of psilocybin or placebo, in random order, on 2 days at least 1 week apart	Semantic priming						↑ Indirect priming effect		
Gouzoulis-Mayfrank et al. 1998	12 healthy physicians	0.2 mg/kg body weight of psilocybin (range: 12.5-17.5 mg) or placebo, on two sessions one to three weeks apart	Lexical decision task						↑ Indirect priming effect		
Wießner et al. 2023	24 healthy volunteers	50 µg LSD Acute and sub-acute effects (time points from 0 to 24 h) in randomized double-blind controlled study 50 µg LSD vs placebo.	- Experience reporting: "how are you feeling today?"					↓ Words on time, past, space, numbers, leisure, relativity (up to 6.5h) ↑ Words on biology (at 6.5h)		= semantic distance[a] ↓ Local connectivity[b] (up to 1.5h) ↓ Global connectivity[c] (up to 1.5h)	
			Storytelling: participants were given 1 min to		↓ Word Count (up to 4h)		↑ Verbs (up to 2h) ↑	↓ Words on time, past, space,		↓ Semantic distance (up to 24h)[a]	

			tell a story about positive, neutral, ambiguous and creative photos				Use of "they" (at 24h)	numbers, assents, ingestion (up to 4h) ↑ Words on present, dictionary, punctuation (up to 6h)		↓ Local connectivity[b] (up to 1.5h) ↓ Global connectivity[c] (up to 4h)	
Sanz et al., 2021	20 healthy participants	LSD 75 µg iv vs placebo fMRI during the peak and MEG during descending phase	Subjects asked to report spontaneous thoughts and feelings during the acquisition of neuroimaging data		↑ Word Count	↑ Shannon's Information Entropy		↑ Words related to perception ↓ Vocabulary density = Semantic similarity in words related to the psychedelic state		↑ Semantic Variability ↑ Recurrent speech	
Amarel et al., 1965	10 alcohol addicted	LSD 100-200 µg	Asked to talk about - themselves - their family - the group		↓ Volubility (i.e. sum of words per speech sample)					↑ Cloze probability	

Footnotes: the colors refer to the dosage used in the specific study according to Polito and Liknaitzky, 2022: green for microdoses, orange for mild doses and red for full doses.

[a] Semantic distance refers to: Semantic Spread (average distance between all words, indicating the spread of semantic activation), Forward Flow (average distance of each word to all predecessors, indicating the evolution of thoughts over time), Flow Distance (average distance of the first word to all subsequent words, indicating the length of the "semantic journey") and Flow Steps (average distance between neighboring words, indicating the size of the "journey steps")

[b] Local connectivity refers to: Repeated edges (number of edges linking the same node pair) and Parallel edges (number of edges linking the same node pair in which the source is the target node of the edge).

[c] Global connectivity refers to: Average Total Degree (sum of all edges normalized by the number of nodes, indicating the degree of connectivity), Largest Connected Component (number of nodes in the largest connected component where all nodes are linked) and Largest Strongly Connected Component (number of nodes in the largest component in which all node pairs are linked and mutually reachable)

DISCUSSION

The current review aimed at elucidating the acute effects of psychedelics on different linguistic dimensions in healthy subjects and patients not affected by psychotic disorders. Results confirmed the ability of LSD and psilocybin to acutely alter several linguistic categories in a dose-dependent manner. Such compounds showed the ability to alter language production in several key domains, ranging from syntax and semantics to pragmatics.

Pragmatics emerged as one of the most affected linguistic dimensions, as denoted by an increased production of metaphors, characterized by greater novelty [61], decreased discourse organization (speech graph analysis) [17][18], and decreased predictability (cloze probability) of discourse [21]. Interestingly, verbosity negatively correlated with predictability (cloze probability) and was positively correlated with increased semantic distances, highlighting that volubility is associated with reduced discourse coherence [17][18][21].

Semantics was largely affected as well. Indeed, an indirect semantic priming effect (semantic priming with two indirectly related words, e.g., *lemon* and *sweet*) was demonstrated by two independent studies [23][58]. Moreover, the use of «concrete» words increased [56][24][25], and the speech was characterized by enhanced positive emotions (sentiment analysis) [19].

Regarding syntax, the number of coordinates increased while the number of subordinates decreased, as well as sentence length and T-units length [25]. Finally, considering speech rhythms, the duration of pauses increased in both monologues and dialogues [52][53], and greater matching of speech rhythms occurred in dialogues [54].

Differential effects of doses

Interestingly, dosage appeared to be the variable able to explain most of the heterogeneity of the results across studies, followed by the specific task administered to the participants, particularly in the range of mild doses (for the dose ranges, refer to recommendations provided by Polito and colleagues [63]). Indeed, full doses of LSD induced loosening of logical associations, resulting in altered discourse coherence and speech disorganization as inferred by increased semantic variability and decreased cloze probability. Interestingly, a reverse correlation between verbosity and cloze probability was demonstrated.

Mild doses of psilocybin or LSD (greater than microdoses but lower than recreational or therapeutic dose range), simplified syntax, and the content of speech in terms of concreteness, tense, reference to time and space, and induced subtle alterations of the semantic network derived by an indirect semantic priming effect. However, they did not affect discourse coherence as shown by unaltered semantic variability.

Finally, microdoses of psilocybin (1-10% of the active dose) did not show the ability to hamper discourse organization, as measured by semantic variability; however, they increased verbosity and induced more positive emotions detectable through sentiment analysis.

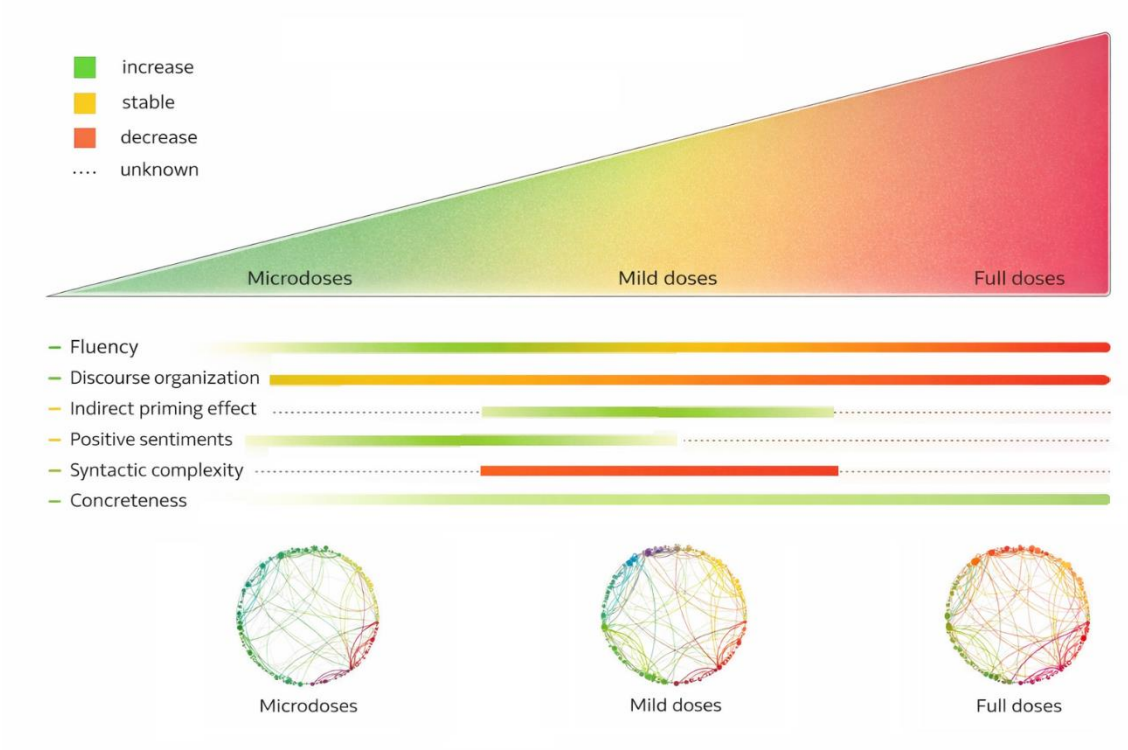
Considering mild doses, the type of task influenced speech in terms of words spoken per time unit. Specifically, storytelling tasks on specific pictures were associated with reduced

semantic variability and fewer words spoken, probably due to the cognitive effort to describe a specific situation depicted in the picture. Indeed, open questions did not elicit such alterations.

Relevance of the dose for connectivity

Regarding the different linguistic categories, semantics appeared to be one of the most affected dimension [17][18][21][58]. Assuming a neurobiological perspective focusing on the susceptibility of projecting pyramidal neurons in the V layer of language network to psychedelics [3], here we propose an explanatory theory for the different patterns of language alterations described under different doses of psychedelics, which is shown in Figure 2.

Figure 2. Linguistic alterations from a dose-effect neurobiological perspective



It is likely that full doses of psychedelics elicit a relevant increase in dendritic arborization and synaptogenesis in the V layer [66], thus increasing neuronal excitability beyond the threshold of action potential [67] and inducing neuronal firing, which propagates along projecting axons. This mechanism should underlie the increased whole-brain connectivity [34][39][40] and be responsible for altered discourse organization (increased semantic distances), which resembles formal thought disorders (FTD) and speech disorganization of patients with schizophrenia [68]. Differently, mild doses can induce sprouting of dendrites and synaptogenesis in the V layer as well [66], with the established pattern of local hyperconnectivity not being enough to increase excitability up to the firing threshold (action potential). Nevertheless, the indirect semantic priming effect encountered with the administration of mild doses [23][58] can be explained by increased dendritic connectivity at the local cortical level, which could sustain the activation of remote semantic

associations, including the activation of one node within a semantic network and its semantic opposite. This explanation is in line with the “Hub and Spoke Theory” [69], a prominent neurocomputation model of semantic memory organization, according to which the temporal parietal lobe and the angular gyrus in the inferior parietal lobe serve as a semantic hub, in which multimodal semantic integration is computed due to the connections with an extremely distributed system at the cortical level [70]. Several modality-specific cortical regions represent the different aspects of conceptual knowledge (e.g. color, shape, name) and all the regions send information to the semantic hub in which multimodal semantic integration occurs, and concepts are represented. The “spokes” represent the connections with the cortical areas in which the relevant information to construct the semantic concept is stored (semantic category and its modalities) [69][71]. Finally, the PFC dynamically monitors and modulates the “Hub and Spoke” semantic representation system constituting the ‘semantic control’ system (controlled semantic cognition)[69]. Mild doses of psychedelics “enlarge” the cortical area activated by a semantic stimulus by inducing cortical hyperconnectivity at the local level (and not long-range hyperconnectivity as full doses), thus the concept of lemon could enclose even opposite modalities (sweet) and the stimulus may have a priming effect even on the presentation of unrelated subsequent words or indirectly related modalities (i.e. sweet and lemon). This happens because the spoke is connected with a cortical area in which boundaries between the representation of different/opposite modalities are nuanced/overlapped due to the pattern of local hyperconnectivity and the integration computed in the semantic hub retains even “unusual” or opposite modalities [30][70]. In other terms, the psychedelic-induced indirect semantic priming effect might be interpreted as “the step before” the disrupted discourse coherence occurring at higher doses, which involves projecting fibers. The hyperassociative state at the cortical level and unusual/remote semantic associations may also explain the increased use of metaphors and their greater novelty described by Natale and colleagues in individuals under psychedelics [61].

Concerning microdoses, it is not possible to establish their association with an indirect priming effect, as it has not been assessed yet. However, the ability to induce positive emotions and talkativeness is probably and strictly related to the primary stimulating action at the 5-HT2A receptor level, as for other recreational drugs such as amphetamines [72]. Interestingly, the ability of psychedelics to improve speech fluency is also endorsed by recent anectodal findings on short-term positive effects on fluency in individuals with stuttering, particularly related to emotional changes and reduced anxiety [73][74].

Similarities with schizophrenia

Altered discourse coherence/speech disorganization is a typical hallmark of formal thought disorder (FTD), a core dimension of schizophrenia. The neurobiology of schizophrenia is characterized by high heterogeneity [75]; however, cortical thinning, dendritic/synaptic pruning, and white matter disruption in language areas may partially explain the FTD dimension [7][76][34][77]. Interestingly, FTD is associated with reduced volumes in the inferior frontal gyrus, superior temporal gyrus, and inferior parietal lobe bilaterally (left greater than right). These regions showed hyperactivity in fMRI studies and both hyper- and hypo-activity in fMRI studies employing semantic processing [7]. Moreover, changes and different patterns of FC were found compared to controls between fronto-temporo-thalamic regions in patients with schizophrenia [78]. Taken together, all these findings point to a pattern of abnormal connectivity in brain regions relevant for language processing in

individuals with schizophrenia showing FTD. Interestingly, the underlying neurobiology of excessive synaptic pruning and white matter disruption is responsible for reduced brain volumes and the rearrangement of brain connectivity through an impoverishment of connections [34]. These mechanisms represent the biological opposite of the flourishing connections occuring under psychedelics due to synaptogenesis and increased firing of pyramidal neurons responsible for cross-cortical connectivity [3][34]. However, it is possible that these two distinct patterns of hypo (schizophrenia) and hyper-connectivity (psychedelics) are both involved through a lack of integration (dis-integration) of information, in aberrant language production [34].

Parallelisms with schizophrenia can be also drawn for the indirect semantic priming effect, as it has also been described in patients with schizophrenia [12][13], probably due to the pattern of disconnection [61][79][80][77], responsible for a parceled and non-homogeneous activation of the cortex during cognitive tasks [81][82]. Indeed, it has been argued that these two models of psychosis (psychedelic-induced psychosis and schizophrenia), despite being opposed in terms of underlying neurobiology (hyperconnectivity and disconnection), similarly result in aberrant associations across the brain [34][77], thus in altered semantic associations. Such opposite pathogenic mechanisms of psychosis have laid the foundation to hypothesize a possible therapeutic role for microdoses of psychedelics in patients with schizophrenia burdened by prominent negative and cognitive symptoms [4][83].

Conclusion and future directions

Taken together all these findings pointed to the susceptibility of language production to the action of psychedelics, depending on the administered dose, which can or cannot affect long-range connectivity through the involvement of projecting fibers. The extent of semantic network distribution is probably the reason why semantic associations represent the most sensitive dimension to psychedelics, even if syntax and lexicon are typically impaired as well, according to dosage.

Considering possible practical implications, positive emotions inferred by sentiment analysis might be used to estimate efficacy (e.g., antidepressant efficacy) of psychedelics within the context of clinical trials on microdoses. Measures of indirect semantic priming or lexicon (word categories) might be considered as an index of efficacy when mild doses are used. These two linguistic categories may reflect enhanced neuroplasticity with positive implications for cognitive flexibility, semantic access and creativity [84] as well as meaningful experiences (altered meaning of percepts and mystical experiences). Finally, disrupted discourse coherence, occurring when full doses are administered, should be interpreted as an index of acute intoxication and related to possible side effects ranging from visual hallucinations to anxiety and ego-dissolution.

Overall, all these measures should be considered within the context of future clinical trials on psychedelics to estimate the acute effect of these compounds, and even side effects, in the whole range of doses. It is important to acknowledge that other studies on larger samples are needed to validate/replicate these results, possibly adopting standardized assessments and measures to make them comparable and their findings generalisable.

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STUDY 3

THE LIVED EXPERIENCE OF AUDITORY HALLUCINATIONS: LINGUISTIC, SENTIMENT AND EMOTIONS ANALYSIS TO INFORM CLINICAL DECISIONS

Abstract

Auditory verbal hallucinations (AHs) are a typical symptom of schizophrenia, linked to both perceptual and cognitive dysfunctions, and often causing high emotional distress which is in turn related to the subjective sense of AHs. First-person accounts (FPAs) provide valuable insights into patients' subjective experiences; however, their qualitative nature has traditionally limited their use in clinical practice and research. Recent Natural Language Processing (NLP) techniques allow us to overcome this limit, by capturing the subjective lived experience with a quantitative approach. This study aims at characterizing the subjective dimension of AHs through FPAs automatically analyzed via NLP in a sample of 71 patients with schizophrenia. Specific objectives are: (1) compare linguistic markers, especially emotional and sentiment measures, across patients depending on their history of AHs (never, past, or current); (2) find associations between NLP markers and symptoms, (3) assess the impact of antipsychotic response on negative emotions elicited by AHs. As expected, FPAs of patients still hearing voices were characterized by higher levels of Sadeness but lower levels of Fear. Interestingly, several linguistic markers showed associations with different symptom dimensions suggesting a potential role of NLP in supporting clinical decisions. Finally, antipsychotic response did not seem defined by the disappearance of AHs but by the reduction of their emotional pervasiveness in terms of Fear. These findings suggest that the integration of NLP-based analysis of FPAs with clinical assessments may contribute to a more fine-grained understanding of auditory hallucinations and treatment response.

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INTRODUCTION

First-person accounts

First-person accounts (FPAs) in psychiatric disorders, especially in schizophrenia, have evolved over time from rare anecdotal reports to well recognized qualitative tools to investigate psychopathology. Indeed, FPAs narratives offer a privileged point of view on subjective experience of different symptom dimensions, emotional correlates, the impact of the illness on daily functioning and quality of life, as well as stigma perception. Historically, psychiatry relied mostly on clinician observations and case histories, with limited influence of direct patient narratives. However, descriptions of subjective phenomena such as Schneider's first-rank symptoms (self-disturbances and altered experiences of agency) were often derived from patient reports [1][2]. Interestingly, Schneider's first-rank symptoms had been considered pathognomonic for schizophrenia and nuclear elements of its pathophysiology due to their underivability and absurdity. . A sort of paradigm shift occurred in the late 20th century when FPAs gained visibility with the establishment of dedicated series "First Person Accounts" in *Schizophrenia Bulletin*, which started publishing patient-authored narratives [3][4][5][6][7][8]. This series provided a window into the psychopathology experienced by the patient and provided insights into lived experiences, including hospitalization, medication effects, stigma, and coping strategies, and were intended to inform professionals and support patients and families [9]. Over the past three decades, the role of the FPAs moved beyond being a tool to investigate the subjective symptomatic dimension of the patient to become also a means to disseminate the objective difficulties that patients face every day (lived experiences) and above all the burden of stigma with implications for anti-stigma campaigns. FPAs' use has expanded to include peer support roles and expert patient positions, contributing to more person-centered and holistic care [10][11]. Overall, first-person accounts have provided enduring insights into the subjective experience of schizophrenia, influencing both clinical understanding and service development [9][10][11][12].

The centrality of hallucinations in schizophrenia: the subjective dimension captured through first-person accounts

It is important to bear in mind that FPAs were initially intended to investigate the most unusual and bizarre symptoms experienced by patients: Schneider's first-rank symptoms. Specifically, they include among others 1) **auditory hallucinations**, especially voices commenting on the patient's actions, voices conversing with each other, or voices heard in the third person; 2) thought insertion, the experience that thoughts are being inserted into one's mind by an external force; 3) thought withdrawal, the belief that thoughts are being removed from one's mind by an outside agency; 4) thought broadcasting, the sense that one's thoughts are accessible or being broadcast to others [1]. TJ Crow hypothesized that such unusual and underivable experiences are rooted in one's thoughts/language no longer conceived as one's own. As a matter of fact, patients typically think that thoughts are inserted into or removed from one's mind by an outside agency, or that thoughts are broadcasted to others or to the surrounding environment. Similarly, auditory hallucinations are hearing one's thoughts spoken aloud, running commentaries on one's thoughts or actions or even other kind of voices [13][14]. Interestingly, auditory hallucinations are intrinsically tightly linked to language dimension and, according to many cognitive theories [15], arise from an anomalous system of reference of language to the self (consciousness of the self). Indeed, a frame of reference (coordinates) is needed, and particularly of the 'I' of the speaker/thinker to the present 'now' and to the space 'here', and the failure of this reference system could underlie the nuclear symptoms of schizophrenia [16][17]. Overall, the distinction between the 'I' of the speaker and his interface with the rest of community is lost. Summarizing, Crow suggested that the nuclear symptoms of schizophrenia and particularly auditory hallucinations represent 'language at the end of its tether' [18], providing a window on the transition between speech (language) and thought [16]. He also stated that "schizophrenia is the price that the homo sapiens species must pay to have language [18]", as if polygenic susceptibility for schizophrenia is linked to a predisposition for a reduced self-recognition of own language, interpreted as auditory hallucinations or other first-rank symptoms. Interestingly, a meta-analysis on self-recognition deficits in schizophrenia [15] supported the theories of TJ Crow on auditory hallucinations as a failure in recognizing thoughts, inner speech and mental events as self-generated. All the analyzed 23 studies were included regardless of the different cognitive model being tested as the experimental design always required a judgment regarding whether an action was self-originated or not. They compared healthy controls and individuals with schizophrenia, or individuals with schizophrenia with auditory hallucinations and without auditory hallucinations. Authors found reduced self-recognition performance in patients

hearing voices compared to patients without auditory hallucinations and reduced self-recognition of own mental processes in patients not-hearing voices compared to healthy controls. This meta-analysis by Waters and colleagues [15] underscores impaired self-recognition as a cardinal pathogenic mechanism in schizophrenia, and particularly in those patients with auditory hallucinations, however only studies pertaining to the cognitive model approach were included. As detailed above, the cognitive model, focuses on failures in self-monitoring, source attribution and cognitive control as key factors underlying hallucinatory experiences [19][20]. The 'neurological' model instead emphasizes the role of aberrant brain activity and connectivity and postulates the perceptual nature of auditory hallucinations, which would arise from aberrant activity in brain areas devoted to auditory perception. The main supporting findings to this theory come from auditory phenomena encountered in some patients who suffer from epilepsy [21] or auditory hallucinations induced by neurostimulation of the superior temporal gyrus, typically in individuals undergoing neurosurgery [22]. Moreover, Van de Ven et al showed increased activity in the auditory cortex, including Heschl's gyrus, during hallucination episodes [23]. However, there are also neuroimaging findings in patients with psychosis pointing to a primary involvement of brain areas devoted to language instead of auditory cortex. In particular, Fuentes-Claramonte and colleagues [24] found an activation of language regions and/or regions that are engaged during verbal short term memory but not auditory brain regions when patients experienced voices compared to times when they do not.

Overall, all these premises lay the foundation for understanding why one of the first symptoms investigated through FPAs were precisely auditory hallucinations: to capture their subjective "sense", possible personal explanations, and even the subjective dimension in terms of emotional experiences. These accounts described voices as external autonomous entities, sometimes perceived as external to their own mind, and frequently associated with a sense of being controlled or influenced by an "unseen agency". The voices were described as having distinct identities, sometimes conversational, and often accompanied by emotional distress or fear [1]. More recently, Jason Jepson produced a series of FPAs on several themes related to being an individual suffering from schizophrenia published on *Schizophrenia Bulletin*, however with a preference for auditory hallucinations, coupling the perspectives of the patient and the self-taught clinician, thus describing one of the most disturbing and at the same time fascinating symptom of the disease [25][26][27].

"*A question often asked to me because I am living with schizophrenia is, what do the voices say? I probably hear different voices than other people living with schizophrenia. I am never going to understand them or know where exactly they come from, but I do my best to ignore them*". (Jepson, 2024)[27]

"*I often want to isolate myself, because of the voices inside my head. I am sometimes afraid that the people outside my head know I am hearing voices by the expression in my eyes and on my face. Sometimes it is difficult for me to be neighborly, but I still try*". (Jepson, 2024)

"*I might be in my bathroom brushing my teeth, and then I hear, "He is brushing his teeth. Then he spits." The voices is a running commentary of everyday activities that I might be doing. This voice is heard like a conversation in front of me, only I am alone. I push through or listen to the beat of a song to ignore it. Sometimes I hear voices at night before I go to bed. This voice might be telling me that there is someone outside my front door, or there is someone messing with my car in the parking lot. When this happens, I have learned to check the evidence to reassure myself by looking through my front door's peep hole, or even opening my front door to find nothing and no one is there. I have a balcony that overlooks the parking lot, so I can look out to be sure my car is okay*". (Japson, 2018)[25]

"*These voices are almost always negative in nature and can be very annoying if I get caught up in them. They are cutting, demeaning, and seem to have as their goal to defeat me. These wearisome voices are telling my neighbors terrible things about me*". (Japson, 2022)[26]

"*The voices that I hear often belong to acquaintances and friends from my past life, such as an ex-girlfriend. I may not have spoken to them in years. In my head, they say they do not want to talk to me because my other voices would bother my friends and distract them from their jobs*". (Japson, 2022)[26]

"*Often the voices distract me to the point of causing me to be forgetful. I fear that I will forget to pull up my zipper after using a public restroom. The voices laugh and say they won because they were able to embarrass me. Sometimes when I am driving, I forget where I am going*". (Japson, 2022)[26]

In these fragments of FPAs it is evident how voices can impact the quality of life of patients and induce negative emotions and feelings. Interestingly, there is a large body of evidence regarding emotional correlates of auditory hallucinations

in schizophrenia and their relevance for the quality of life and treatment outcome of patients.

Emotional correlates of the hearing voices condition

The subjective dimension of auditory hallucinations is of paramount importance as beliefs about voice-content have been shown to be even more tightly associated to emotional distress than voice content [28][29]. As a matter of fact, a meta-analysis by Tsang and colleagues [30] confirmed that the interpretation of voices in schizophrenia-spectrum disorders conditions levels of emotional distress experienced by voice-hearers. Positive beliefs/interpretations of auditory hallucinations were associated with small negative effects on voice-related emotional distress, anxiety and depression. Negative voice-content and related emotional distress caused by auditory hallucinations has been shown to be a distinguishing feature between clinical and non-clinical voice hearers (respectively, individuals with schizophrenia spectrum disorders and healthy subjects who hear voices) [31][32][33], and a predictor of need for care and contact with mental health services due to functional impairment [31][32]. The determinants of negative voice-content remains poorly understood, despite adverse life-events, through specific mechanisms like hypervigilance, feelings of shame and self-blame, altered emotional processing, and the association with a lower social class, may play a role [34][35]. Concerning adverse life-events, the phenomenology of voices seems a sort of a “mirror of the past” in the way in which past traumatic events and related post-traumatic processes shape the content of voices and beliefs. Life events experienced as traumatic appeared to be a strong predictor of voices-induced threat, embodied in relational experiences [35]. Considering dynamical interactions between patients’ beliefs and emotions elicited by auditory hallucinations, So and colleagues [36] investigated the bi-directional relationship between negative affect (negative emotions and distress) and voice-content, and the moderating effect of negative beliefs about voices. They found that negative emotions and distress generated by negative appraisals of voices further drive negative voice-content, contributing to the maintenance of auditory hallucinations through a feedback loop.

Overall, cognitive conceptualizations of psychotic disorders started to stress the importance of negative emotions, depression and self-esteem in the development and maintenance of psychosis at the beginning of 21th century [37]. In 2006, Smith and colleagues [38] examined the role of depression, self-

esteem and negative evaluative beliefs in relation to positive symptoms in 100 patients with psychosis. Interestingly, individuals with higher depressive symptoms and lower self-esteem showed greater severity of auditory hallucinations, associated with more negative content and distress. More recently, other studies examining emotional response and adaptation of patients to voices confirmed the pivotal role of negative beliefs and affect in determining anxiety and depressive symptoms in patients with schizophrenia spectrum disorders [39][40]. All these results on the mediating role of malevolent beliefs are in line with what emerges from FPAs of patients. As quite obvious, if a person is worried about the possible harm induced by the voices, the consequence will be a sense of threat, greater anxiety, distress and, chronically, depression [25][26][27]. When adopting a biological approach, interesting findings emerged regarding the emotional correlates of auditory hallucinations. A study by Hjelmervik and colleagues using magnetic resonance spectroscopy showed aberrant glutamatergic signaling and increased NMDA-receptor hypoactivity in patients experiencing voices denoted by negative emotional valence. These results are in line with the glutamate hypothesis of schizophrenia [41] and negative emotional valence of voices as a strong predictor of illness severity [42]. Another study [43] using functional magnetic resonance imaging (fMRI)found reduced emotional processing of external auditory stimuli in patients with schizophrenia suffering from chronic auditory hallucinations compared to patients without auditory hallucinations. Indeed, authors described reduced activation of the left amygdala and hippocampus bilaterally during processing of disturbing sounds. While they might seem counterintuitive, these e results suggest that the distressing and repetitive experience of hearing voices may cause, through long-lasting adaptation mechanism, an increase of the resting-state baseline activity of these regions, thus increasing the emotional threshold for external auditory stimuli. Of relevance is the possibility to get some relief from depressive symptoms secondary to the persistence of voices by weakening the associations between auditory verbal hallucinations and negative self-evaluations. A recent randomized controlled clinical trial (RCT) on competitive memory training (COMET) in patients with persistent auditory hallucinations showed that the positive effects of the intervention on depressive symptoms were mediated by increased self-esteem and acceptance of voices, and even by social rank [44].

Natural Language Processing as a quantitative approach to capture the subjective dimension

FPAs provide a window on the emotional distress and functional impairment of the hearing-voices experience from the point of view of the patient. For this reason, FPAs represent a valuable and powerful tool to explore the psychopathology of schizophrenia but, at the same time, the qualitative approach to their analysis has so far limited their use in clinical practice and research. Several studies have investigated emotions induced by auditory hallucinations in the schizophrenia spectrum disorders through questionnaires, scales and other assessments in order to objectively quantify such experiences and understand their relationship with other psychopathological variables. However, in these studies the quantitative approach is used only to measure the related emotional distress while the more strictly subjective dimension of the patient's experience is left to qualitative interpretation. One way to preserve the subjective dimension of the patient and couple that with quantitative measurements is represented by natuaral language processing (NLP) of patients' records. NLP markers are computationally derived and quantifiable measures of human language production reflecting the underlying biological bases and cognitive processes. NLP is progressively gaining attention from the scientific community given the fact that spoken language is indicative (a window on) of mental states, conveyed through semantic content, form (grammar), and acoustic features. Metrics of speech production can be derived from audio recordings (then transcribed) or written reports. Interestingly, NLP markers might have a useful role for screening, stratification and clinical outcome (eg, prediction of relapse or treatment response) [45]. de Boer and colleagues [46] were the first to apply NLP to analyze transcripts of what the voices said in patients with psychosis (clinical population) compared to subjects who hear voices, without having a psychiatric diagnosis (non-clinical population). Numerous NLP variables were assessed as total words, mean length of utterance, proportion of grammatical utterances, proportion of negations, literal and thematic perseverations, abuses, type-token ratio, embeddings, verb complexity, noun-verb ratio, and open-closed class ratio. They found that the linguistic features of auditory verbal hallucinations differed between the two subgroups. Specifically, psychotic patients had lower syntactic and verb complexity, more verbal abuses and perseverations with a shorter mean length of utterance. Interestingly, some of the same authors [47] replicated previous well-established findings on the negative emotions related to verbal hallucinations with a NLP approach. Again, they compared clinical and non-clinical participants experiencing auditory verbal hallucinations who recorded their verbatim directly upon hearing. The emotional valence of voices in patients was significantly more negative than those of non-clinical voice hearers with a

significant, strong association with the perceived negativity, amount of distress and disruption of life. Thus, patients had a more negative linguistic content of voices, which is associated with the experienced distress. This is a study of paramount importance in the panorama as it demonstrated through objective analyses that patients perceive their voices as more negative. Overall, the few NLP studies on auditory verbal hallucinations confirmed what previous studies demonstrated: the degree of negative content of auditory hallucinations is a distinguish feature between clinical and nonclinical voice hearers [31][32][33] and causes negative emotions.

The relevance of emotions in schizophrenia

The emotional dimension expressed in FPAs (not only focused on auditory hallucinations) of patients with schizophrenia include anxiety, fear, guilt, sadness, shame, and ambivalence, as well as diminished positive affect and anhedonia. These emotions are often described as intense, unstable, and sometimes foreign or perturbing, contributing to an unstable sense of self and significant distress [38][48][49][50]. The severity of psychotic symptoms is closely related to the intensity and quality of these emotions. Higher levels of negative symptoms (such as blunted affect and anhedonia) are associated with diminished positive emotional responses to pleasant stimuli, while higher levels of positive symptoms (such as delusions and hallucinations) are linked to elevated negative emotional responses, including excessive fear and distress [38][50]. Additionally, anxiety and sadness mediate the relationship between positive symptoms and stress and self-esteem on the other hand [51]. Overall, negative emotions in schizophrenia are directly related to the severity of both positive and negative psychotic symptoms. This relationship underscores the importance of assessing emotional experiences in patients with schizophrenia with possible implications for classifying and monitoring treatment response.

Natural Language Processing markers of sentiments and emotions in schizophrenia

So far, NLP has been mainly explored with respect to its ability of NLP to predict the severity of positive symptoms and particularly of disorganized/incoherent speech in schizophrenia which reflects disorganized thinking loosening of associative links between ideas [45]. NLP offers several computational measures to assess speech coherence and, despite incoherence can be conceptualized and quantified in many ways, one of the most used is semantic

similarity obtained measuring cosine between words' vectors in the semantic space. This method also called "semantic distances" can be used to quantify the conceptual connectedness in utterances. Indeed, by using publicly available word2vec language datasets, it is possible to know the specific cosine distance between words [52]. Overall, a large body of evidence showed associations between symptom domains and measures of coherence, despite issues about a lack of reproducibility, due to inconsistency of results across different languages and rating scales [53].

A far less explored field is represented by the emotional dimension of schizophrenia, and particularly, little is known about the capacity of speech content-inferred sentiments and emotions to reflect illness severity or the severity of specific symptom domains. Sentiments in the speech of patients with schizophrenia can be quantified by several NLP measures which infer affective tone of clinical narratives by extracting features such as valence, arousal, dominance, and discrete emotions (e.g., fear, sadness, anger). One of the first studies trying to correlate the affective dimension of the speech with different symptom domains was recently performed by Metha and colleagues [54]. Specifically, sentiment/emotion measures were correlated with the symptom domains of the Brief Psychiatric Rating Scale to assess relationships between emotional expression and symptom severity, and many associations were found between sentiment scores and symptom severity. Another recent study showed that attenuated psychotic symptoms in individuals at clinical high-risk for psychosis (prior onset) are associated with NLP-inferred depressive symptoms and anhedonia in narratives based on emotional pictures [55]. Additionally, sentiment analysis has been applied to social media posts to detect psychosis and monitor symptom trajectories, leveraging the emotional content of freely expressed language to classify psychosis and its severity [56]. Interestingly, all these findings were published in 2025 underscoring the novelty of this approach to psychoses. Concerning treatment response, machine learning models incorporating multimodal features including sentiment analysis can predict outcomes with moderate to high accuracy (up to 80%), but the best predictors remain neurophysiological and combined clinical data with little evidence for sentiment analysis-derived markers, which are not yet validated for guiding specific therapeutic decisions or for monitoring response in routine clinical practice [57]. Overall, sentiment analysis-derived markers provide an objective method to implement traditional clinical assessment by capturing the affective dimension of symptom expression in psychosis and could be considered as complementary tools rather than replacements.

Aims

The primary aim of the current study is to analyze written FPAs of people with schizophrenia who were asked to talk about their condition of psychosis, to find associations between NLP markers, in particular measures of emotional valence and positive and negative sentiments, and PANSS items, especially those pertaining to negative and depressive symptoms. This, in order to understand which of the NLP markers can be useful to estimate specific symptom dimensions, thus, to validate NLP markers as illness and symptom severity predictors, to pave the way for possible clinical implications of NLP in supporting clinical decisions.

Furthermore, written reports about the experience (beliefs, feelings and emotions) of hearing voices in two sub-samples of patients were similarly analyzed in order to compare the different conditions in terms of emotional valence. The first subsample was formed by patients still hearing voices, while the second subsample by patients who heard voices but currently not hearing them anymore.

Moreover, given the evidence of negative emotional valence of voices as a strong predictor of illness severity [42], patients who still hear voices and patients who heard voices were asked to refer the experience of hearing voices to a pre-(effective) treatment condition in order to compare emotions pre and post treatment to assess any changes due to treatment response. Our expectation is that, in line with previous evidence, patients still hearing voices experience more negative emotions and depressive feelings compared to others. In addition, we think that the persistence of voices is the main clinical indicator of a lack of response to pharmacological treatments among patients and that even when voices persist, effective pharmacological treatments can resize their negative emotional valence.

METHODS

Sample

A sample of 71 biologically unrelated outpatients with schizophrenia was recruited at the IRCCS San Raffaele Scientific Institute of Milan (Italy), Schizophrenia Research and Clinical Unit.

After a complete description of the study, informed consent to participation was obtained.

The protocol followed the principles of the Declaration of Helsinki.

Inclusion criteria were:

- Age included between 18-70 years
- diagnosis of schizophrenia meeting DSM-5 criteria
- native italian speakers

Exclusion criteria were:

- psychotic exacerbation
- psychiatric comorbidities
- substance/alcohol abuse
- neurological disorders and brain injury
- intellectual disability (IQ<70)
- Inability to write or illiteracy

“Psychotic exacerbation” refers to an acute worsening of psychotic symptoms (delusions, hallucinations, and disorganization) compared to the patient’s baseline clinical condition. This was determined based on clinical evaluation conducted by experienced psychiatrists, and, when available, supported by the comparison between previuos standardized clinical rating scales when the patient was in the acute phase of the illness and at the time of recruitment.

Stratification according to the hearing-voices condition

Three sub-samples of patients:

1) Never-heard voices group: 19 patients who, according to clinical reports and interviews, never reported auditory hallucinations in their history.
2) Not hearing-voices group: 22 patients who heard voices in the past but currently not hear voices anymore due to antipsychotic treatment.
3) Hearing-voices group: 30 patients who currently still hear voices despite a clinical judgement of at least adequate response to current antipsychotic treatment.

Stratification according to pharmacological treatment

Patients were stratified in three groups: 1) first line responders (FLR): patients treated with antipsychotics other than clozapine and showing adequate response; 2) treatment-resistant (TRS): patients with a history of clinical inadequate response to at least two trials of antipsychotics, one of which is a second-generation antipsychotic, for at least 6 weeks at therapeutic range, currently treated with clozapine and showing adequate response; 3) Ultra-treatment-resistant patients (UTR): patients with TRS who did not showed adequate response to clozapine and are currently treated with clozapine plus another potentiating antipsychotic with mixed (adequate or partial only) clinical response. It is important to note that the definition of “psychotic exacerbation” refers to the acute phase of illness which was successfully treated with the sequential pharmacological approach: at least two first-line AP – clozapine – clozapine + AP. Therefore, the definition of pharmacoresistance (FLR, TRS, UTR) is made “a posteriori” given the antipsychotic therapy.

Assessments

Basic clinical and demographic data were collected from clinical reports and clinical interviews. Psychopathology was assessed by means of Positive and Negative Syndrome Scale for Schizophrenia (PANSS), a widely recognized evaluation of the severity of positive, negative symptoms and general psychopathology in patients with schizophrenia [58]. The clinical interview and evaluation of symptoms were performed by trained psychiatrists.

The PANSS scale consists of 30 items divided into three scales:

- Positive Scale, consisting of seven items, assesses the presence and severity of positive symptoms: P1) Delusions; P2) Conceptual Disorganization; P3)

Hallucinatory behavior; P4) Excitement; P5) Grandiosity; P6) Suspiciousness/Persecution; P7) Hostility.

- Negative Scale, consisting of seven items, assesses the presence and severity of negative

Symptoms: N1) Blunted Affect; N2) Emotional Withdrawal; N3) Poor Rapport; N4) Passive/Apathetic Social Withdrawal; N5) Difficulty in Abstract Thinking; N6) Lack of Spontaneity and Flow of Conversation; N7) Stereotyped Thinking.

- General Psychopathology Scale, consisting of 16 items, assesses the presence of general

psychopathological symptoms: G1) Somatic Concern; G2) Anxiety; G3) Guilt Feelings; G4) Tension; G5) Mannerisms and Posturing; G6) Depression; G7) Motor Retardation; G8) Uncooperativeness; G9) Unusual Thought Content; G10) Disorientation; G11) Poor Attention; G12) Lack of Judgment and Insight; G13) Disturbance of Volition; G14) Poor Impulse Control; G15) Preoccupation; G16) Active Social Avoidance.

Each item is rated on a 7-point scale, from 'absent' (1) to 'extremely severe' (7). The subtotals of the three scales and a total score were calculated.

Cognitive performance was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS) [59], Italian version [60], a broad neuropsychological battery evaluating core cognitive domains that are typically impaired in schizophrenia. BACS was administered by trained psychologists, assessing the following neurocognitive functions: Verbal Memory (Words Recall), Working Memory (Digit Sequencing), Psychomotor Speed and Coordination (Token Motor Task), Speed of Processing (Symbol Coding), Verbal Fluency (Semantic and Letter Production) and Executive Functions (Tower of London). Raw scores of each subtest were adjusted for sex, age and education. planning) [59]. Equivalent scores (ES) were calculated according to the Italian normative data in Anselmetti et al. [60], following the method described in detail in Capitani and Laiacona [61]. Specifically, the raw scores of each BACS subtest were adjusted for sex, age and education. Adjusted scores were then fitted into a 5-point interval scale to obtain equivalent scores, in which 0 sets the limit for pathological performance and 4 is equal or better than the median value [60]. The fraction of subjects ranking over 0 and under 4 was partitioned into three regions that have the same interval on the z axis: equivalent score 1 could be considered as a borderline value while equivalent scores 2 and 3 are intermediate [61]. A Cognitive Index, which is considered a measure of global

cognition, was also obtained using equivalent scores, according to the normative data for the Italian population [60]. Specifically, Cognitive Index has 5-point range (0–4), in which scores<1 are considered as pathological cognitive performance.

First Person Accounts

We developed a short questionnaire, consisting of three sets of questions and a metaphor prompt about beliefs, feelings and emotions related to either: current hallucinations (set A), previous hallucinations (set B) and general experience of living with a psychotic disorder (set C).

Set A, addressing current lived experience of hearing voices, was composed of the following questions:

- *Could you describe your mood, emotions, feelings, fears, and anxieties related to the experience of hearing voices, occasionally or frequently, or in any case perceiving unusual auditory phenomena?*
- *What do you think about these voices/noises/annoyances? Where do they come from? Who is it that's talking sometimes?*
- *Try to explain with an image the sensation/experience of hearing voices as you experience it nowadays.*

Set B was composed of the same questions as in Set A, but referring to the lived experience of hearing voices in the past, before an effective pharmacological treatment ("*before an effective treatment"*).

Set C, addressing the current lived experience of a psychotic disorder in general, was composed of the following questions:

- *Could you describe your current experiences of psychosis? What is it like to live with psychosis?*
- *Try to explain with an image the psychosis as you experience it nowadays.*
- *Could you describe what it means to have lived with psychosis*
- *Try to explain with an image what psychosis has been like*

Patients currently hearing voices were asked to respond to all three sets of questions, while patients who heard voices in the past to Set B and C and patients who never heard voices to set C questions only. A psychiatrist supervised the patient for possible clarifications, but the questionnaire was completely self-administered. No time constraints or specific rules to follow, except that participants were required to write and not draw images to express concepts.

Physical and Mental Metaphor Task

The Physical and Mental Metaphor Task (PMM) was used for the assessment of pragmatic skills and specifically for the evaluation of metaphor comprehension. An adult version of the Physical and Mental Metaphor Task (PMM) was used, as originally the toll was developed for the child population [62]. The task is represented by the oral presentation, by the examiner, of 14 nominal metaphorical expressions. The metaphors are divided into two categories: physical metaphors (e.g., “some singers are nightingales,” indicating that they sing very well) and mental metaphors (e.g., “some friends are anchors,” meaning that they are reliable and a source of support), depending on whether they refer to physical or psychological characteristics. Participants were asked to explain in writing the meaning of the metaphorical expressions. The responses were evaluated in two dimensions:

1) Accuracy: the ability to clearly and relevantly articulate the salient link between the theme and the vehicle of the metaphor, with a score ranging from 0 to 2.

2) Interpretation: aimed at evaluating the type of interpretive process adopted by the subject. The maximum score of 3 corresponds to a psychological type of interpretation, that is, the ability to grasp and articulate the implicit meaning of the metaphor in terms of mental states and complex emotional experiences. For example, a psychological interpretation of the metaphor "Teachers are lanterns" could be: "Teachers, with their knowledge and wisdom, illuminate the path for students."

Linguistic analysis

Written reports were manually transcribed and underwent a pre-processing phase, then, written answers to each question pertaining to the same item were united and analyzed as a single input. A series of variables, usually named

fluency variables when referred to speech transcripts, computed at the word and sentence level, were extracted.

Considering variables usually referred to fluency, Token count is obtained by counting the overall number of tokens per item, N sentences is the number of sentences per utterance, Words per Sentence (WPS) represents the mean length of sentences in each report and the Type/Token Ratio (TTR) is calculated by dividing the number of single tokens by the total number of tokens and it is an important measure of lexical density

Semantic analysis extracted measures of Concreteness and Imageability of words, which were derived from simulated data [63]. Differently, Arousal, Dominance and Valence were identified using the Italian MEmoLon – The Multilingual Emotion Lexicon [64]. Specifically, Arousal measures the intensity of the emotion evoked, Dominance is an index of the degree of control on the experience, and Valence encodes the level of pleasure/displeasure emerginf from the narrative.

Sentiment and Emotion Analysis

Sentiment and Emotion Analysis was carried out at the utterance level. Sentiment analysis identifies the overall emotional polarity of the text (positive and negative sentiment), while emotion analysis estimates the four basic emotions at word level (anger, fear, joy, sadness) using the UmBERTo model fine-tuned on the FEEL-IT corpus [65].

Discourse Coherence

A coherence measure was derived from the patients' texts, which were automatically translated into English to leverage the capabilities of large language models, primarily trained on English data. Sentence embeddings were then extracted using a pre-trained transformer-based model (all-mpnet-base-v2) [see 68], and coherence was quantified by computing the average pairwise cosine similarity between embeddings of consecutive sentences/all the sentences of the texts. Specifically, Consec coherence is a measure of coherence that comes from the similarity between consecutive sentences (e.g., sentence 1 compared to sentence 2, sentence 2 compared to sentence 3, etc.), while All coherence represents a measure of overall coherence computed from the similarity between all pairs of sentences, even non-consecutive ones (e.g., sentence 1 compared to sentence 10, sentence 1 compared to sentence 11, etc.).

Statistical analysis

Descriptive statistics of socio-demographic, clinical and cognitive features as well as pragmatic abilities were provided for the whole sample.

First, we compared the three groups of patients (never-heard voices vs not hearing voices vs hearing voices) with respect to socio-demographic variables, clinical, cognitive and pragmatic scores, as well as the NPL measures extracted from set C questions (general experience of psychotic disorder). We also evaluated differences in treatment status (FLR, TRS, UTRs) across the three groups, as well as differences in severity of hallucinatory behavior between the treatment groups. To this purpose, Analysis of Variance (ANOVA) was used for continuous variables and Chi Squared Test for dichotomous variables, followed by post-hoc analyses.

Then, to identify associations between linguistic measures and symptoms' severity, we performed Pearson's correlations between PANSS scores and both NLP-derived measures and PMM scores. We then classified patients according to their linguistic profiles, through cluster analysis including as clustering variables a set of NPL-derived linguistic measures, selected from correlations' results. We performed ANOVAs to assess differences between the two clusters in terms of symptoms and pragmatic abilities.

Finally, we specifically focused on the emotion of fear, typically related to auditory hallucinations and relevant to the prognostic clinical outcome. To assess if an effective pharmacological treatment was able to reduce fear, we compared by means of t-test the NPL-derived measure of "fear" extracted from set C (current experience of psychotic disorder) with the same measure extracted from set B (past experience of hallucination, prior to adequate response to antipsychotic treatment).

RESULTS

Sample description

The sample was composed of 71 patients, 45 males and 26 females. Regarding antipsychotic treatments, 32.4% of participants (n = 23) were taking first-line antipsychotics (FLR), 42.3% of patients (n = 30) were treated exclusively with clozapine (TRS), while the remaining 25.4% (n = 18) are on a combined therapy of clozapine and a first-line antipsychotic.

Clinical variables and demographic data of the whole sample are represented in Table 1, while cognitive and pragmatic abilities in Table 2.

Table 1. Clinical variables of the sample

	Mean	SD
Age	51.7	16.2
Years of education	11.6	3.0
Disease onset	25.1	7.8
Duration of illness	27.0	11.3
PANSS Positive score	15.6	4.0
PANSS Negative score	21.5	5.3
PANSS General Score	40.3	8.0
PANSS Total score	77.3	14.5

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

BACS (Eq scores)	Mean	SD
Verbal Memory	2.4	1.5
Working Memory	1.2	1.3
Psychomotor speed	1.9	1.5
Verbal Fluency	1.9	1.5
Attention	1.0	1.2
Executive functions	2.1	1.6
PMM scores	**Mean**	**SD**
PMM Accuracy	16.5	7.7
PMM Interpretation	23.8	10.7
PMM total score	40.3	18.3

Differences according to the hearing-voices condition

The whole sample was formed by 19 patients who never-heard voices, 22 patients who didn't hear voices anymore and 30 patients still hearing voices.

Differences among symptoms in the three groups are described in Table 3.

Table 3. Differences among clinical variables depending on the hearing-voices condition

PANSS item	Never heard		Not hearing		Hearing voices		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F	p
P1 Delusions	2.94	1.09	2.42	0.90	3.18	0.90	**3.59**	**0.03**
P2 Conceptual disorganization	2.59	1.84	2.00	0.94	2.25	1.35	0.80	0.46
P3 Hallucinatory behavior	1.65	1.00	2.21	0.92	3.75	0.97	**29.36**	**<0.01**
P4 Excitement	2.12	0.93	2.00	0.67	1.93	0.78	0.31	0.74
P5 Grandiosity	1.71	1.10	1.42	0.69	1.75	1.00	0.73	0.49
P6 Suspiciousness / persecution	2.41	1.12	2.63	1.12	2.82	0.82	0.90	0.41
P7 Hostility	1.29	0.59	1.63	1.16	1.29	0.60	1.21	0.31
PANSS Positive	14.71	5.10	14.05	3.42	16.96	3.06	**3.83**	**0.03**
N1 Blunted affect	3.71	0.92	3.26	0.87	3.32	1.09	1.09	0.34
N2 Emotional withdrawal	3.50	0.82	2.95	1.08	3.29	0.90	1.58	0.22
N3 Poor rapport	2.59	1.18	2.68	1.20	2.79	0.99	0.17	0.84
N4 Passive social withdrawal	3.35	0.93	3.11	1.29	3.39	0.83	0.49	0.61
N5 Difficulty in abstract thinking	3.53	1.33	3.16	1.26	3.18	1.44	0.44	0.65
N6 Lack of Spont. and Flow of Conversation	2.35	1.22	2.58	1.39	2.79	1.34	0.57	0.57
N7 Stereotyped thinking	3.35	1.17	2.84	1.12	2.79	0.79	1.86	0.16
PANSS Negative	22.06	5.08	20.32	5.55	21.68	5.21	0.57	0.57
G1 Somatic concern	2.65	1.00	2.42	1.07	2.29	0.98	0.68	0.51

G2 Anxiety	3.47	0.94	3.37	1.12	3.14	1.04	0.59	0.56
G3 Guilt feelings	2.59	1.06	2.21	0.85	2.64	1.06	1.13	0.33
G4 Tension	2.59	1.18	2.53	0.84	2.64	0.87	0.09	0.92
G5 Mannerisms and posturing	2.59	1.12	2.53	0.96	3.00	0.77	1.82	0.17
G6 Depression	1.88	0.93	2.32	1.06	2.07	1.02	0.85	0.43
G7 Motor retardation	2.29	0.85	2.11	1.10	2.50	0.92	0.97	0.38
G8 Uncooperativeness	1.35	0.70	1.26	0.45	1.43	0.69	0.39	0.68
G9 Unusual thought content	3.18	1.19	2.58	1.02	3.43	1.07	**3.51**	**0.04**
G10 Disorientation	2.06	1.14	1.84	0.76	2.04	1.00	0.29	0.75
G11 Poor attention	2.41	1.12	1.95	0.78	2.43	1.00	1.59	0.21
G12 Lack of judgment and insight	2.82	1.29	2.42	0.77	3.07	1.02	2.25	0.11
G13 Disturbance of volition	2.53	1.01	2.37	0.90	2.89	1.03	1.75	0.18
G14 Poor impulse control	1.47	0.80	1.53	0.90	1.75	1.04	0.57	0.57
G15 Preoccupation	3.53	1.01	3.47	0.90	3.54	1.00	0.03	0.98
G16 Active social avoidance	2.94	1.34	2.84	1.34	2.82	1.22	0.05	0.95
PANSS General	39.50	7.32	38.26	8.89	41.54	7.33	1.04	0.36
PANSS Total	76.00	15.58	72.79	15.09	80.18	12.56	1.59	0.21

Interestingly, significant differences in clinical variables emerged only among the item positive symptoms (F=3.83; p=0.03) and its sub-items Delusions (F=3.59; p=0.03), Hallucinatory behavior (F= 29.36; p<0.01), and also Unusual thought content (F=3.51; p=0.04). Post-hoc analyses revealed significantly higher PANSS scores in these items between the hearing-voices compared to not-hearing voices groups. Specific descriptive data for these symptom dimensions are reported in Table 3. No statistically significant differences emerged for socio-demographic variables, cognitive and pragmatic abilities.

Pragmatic abilities scores and NPL-derived measures stratified by clinical groups are reported in Table 4.

Table 4. Linguistic features and PMM scores across the three groups

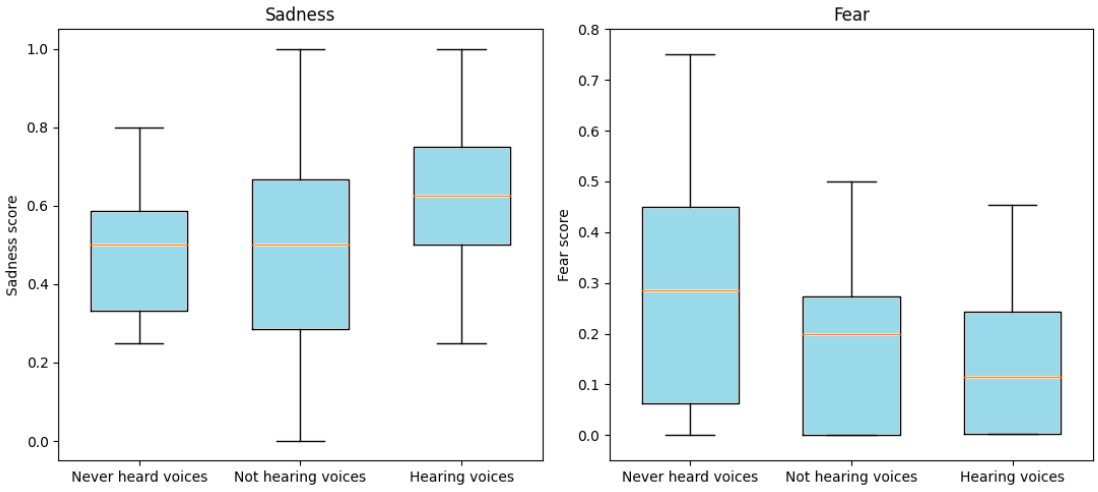
Linguistic markers	Never heard		Not hearing		Hearing voices		ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F	p
PMM Accuracy	16.36	8.97	16.94	7.72	16.20	7.48	0.05	0.95
PMM Interpretation	23.14	11.47	24.61	11.13	23.52	10.58	0.08	0.92
PMM Total	39.50	20.27	41.56	18.65	39.72	17.93	0.06	0.94
Token_count	64.37	81.57	47.95	47.87	48.72	37.07	0.57	0.57
N_sentences	6.74	3.35	5.38	2.54	5.00	2.22	2.54	0.09
Words_per_sentence	7.87	6.30	8.20	4.57	9.30	6.56	0.39	0.68
TTR	0.87	0.23	0.92	0.10	0.86	0.19	0.65	0.53
Concreteness	3.16	0.11	3.16	0.28	3.18	0.25	0.07	0.93
Imageability	3.65	0.08	3.66	0.23	3.69	0.21	0.23	0.80

Valence	5.22	0.32	5.18	0.35	5.19	0.46	0.05	0.95
Arousal	4.13	0.17	4.08	0.13	4.04	0.16	1.99	0.14
Dominance	5.27	0.19	5.28	0.24	5.27	0.30	<0.01	1.00
Sentiment-positive	0.19	0.18	0.17	0.21	0.16	0.19	0.13	0.88
Sentiment-negative	0.81	0.18	0.83	0.21	0.84	0.19	0.13	0.88
Anger_FI	0.11	0.16	0.18	0.17	0.14	0.18	0.81	0.45
Joy_FI	0.13	0.17	0.14	0.16	0.12	0.17	0.09	0.91
Sadness_FI	**0.47**	**0.16**	**0.48**	**0.28**	**0.62**	**0.22**	**3.49**	**0.04**
Fear_FI	**0.29**	**0.24**	**0.20**	**0.18**	**0.11**	**0.18**	**4.74**	**0.01**
Consec coherence	0.24	0.10	0.21	0.09	0.24	0.09	0.75	0.47
All coherence	0.21	0.08	0.21	0.08	0.23	0.06	0.56	0.57

Significant differences emerged among groups in Sadness (F=3.49; p=0.03) and Fear (F=4.74; p=0.01). Post-hoc analyses showed higher scores of Sadness in patients hearing voicescompared to both the two other groups, while the opposite for Fear with lower scores in patients still hearing voicescompared

to patients not hearing voices and patients who never heard voices, as shown in Figure 1.

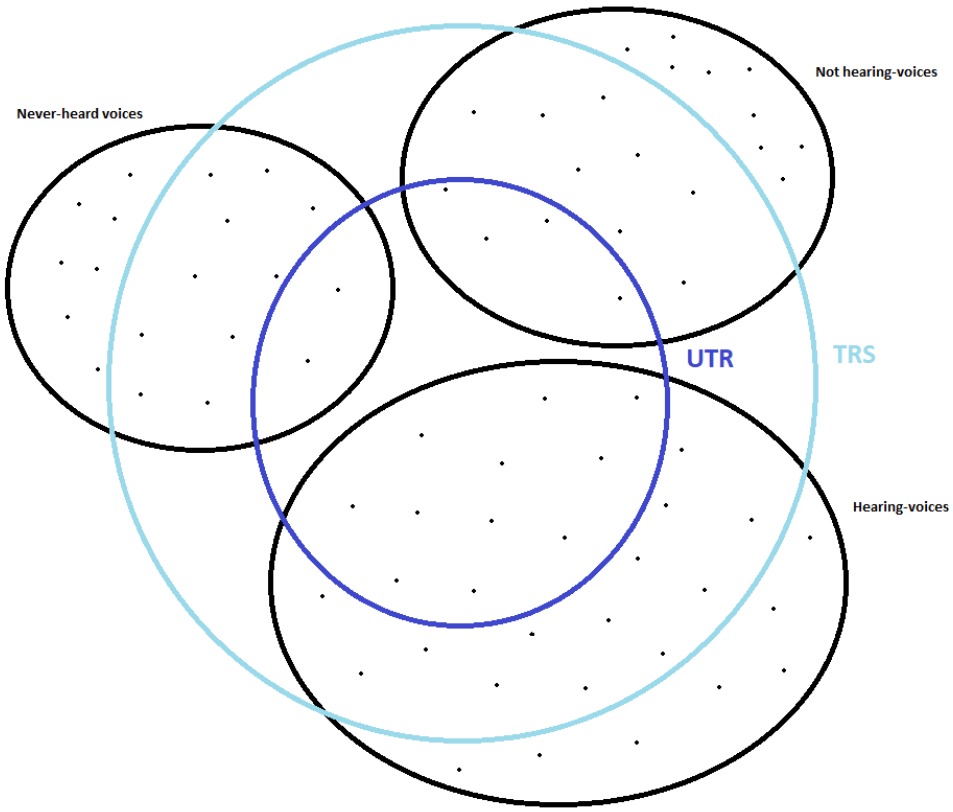
Figure 1. Significant differences in Sadness and Fear depending on the presence of auditory hallucinations



Association between pharmacological treatment status and the hearing-voices condition

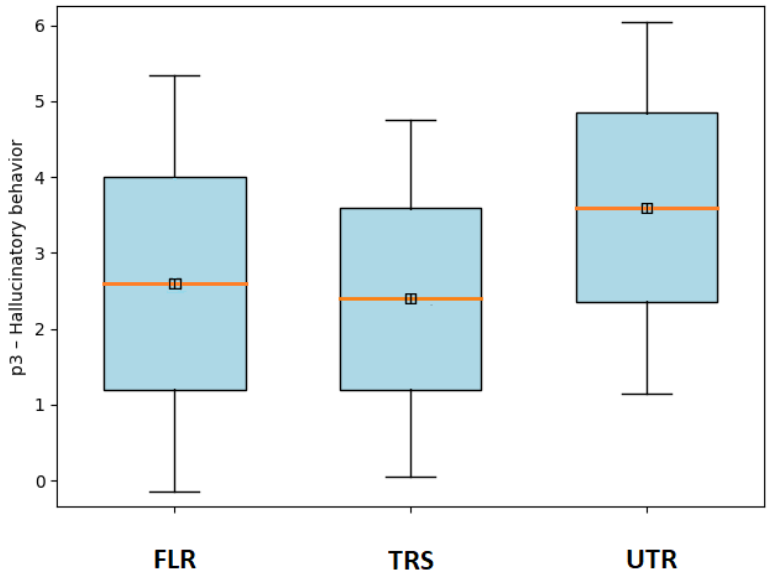
Considering the distribution of patients in the three categories FLR, TRS and UTR we found no significant overlap across samples (Pearson Chi-square=5.76; p=0.22). A schematic representation is provided in Figure 2.

Figure 2. Distribution of patients according to the hearing voices condition and treatment-response status



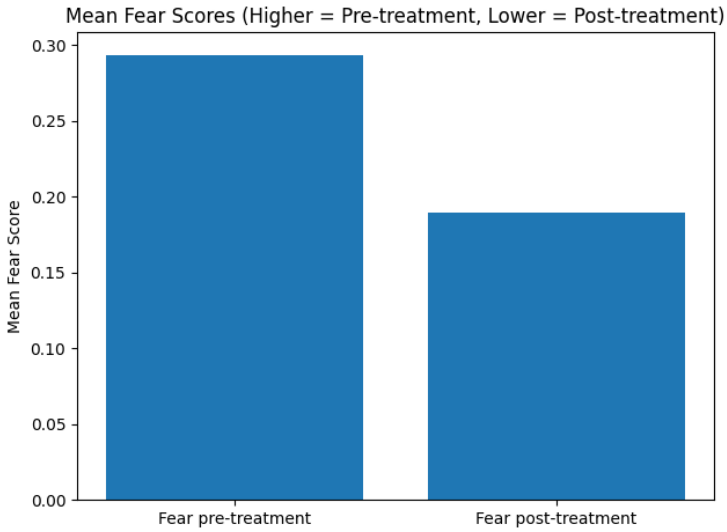
However, UTR patients showed more severe auditory hallucinations compared to FLR and TRS as shown by differences of PANSS-P3 item, Hallucinatory behavior (FLR: mean=2.60, SD=1.38; TRS: mean=2.43, SD=1.17; UTR: mean= 3.62, SD=1.26; F=4.10; p=0.02). Graphical representation of the data is provided in Figure 3.

Figure 3. Differences in Hallucinatory behavior depending on treatment resistance



Finally, the comparison between the emotion Fear extracted from answers to the questions referred to the experience of hearing auditory hallucinations before and effective pharmacological treatment (item B) and Fear referred to the current condition of psychosis (item C) revealed significantly higher levels of such emotion in utterances referred to the past (t=2.38; p=0.02) as shown in Figure 4.

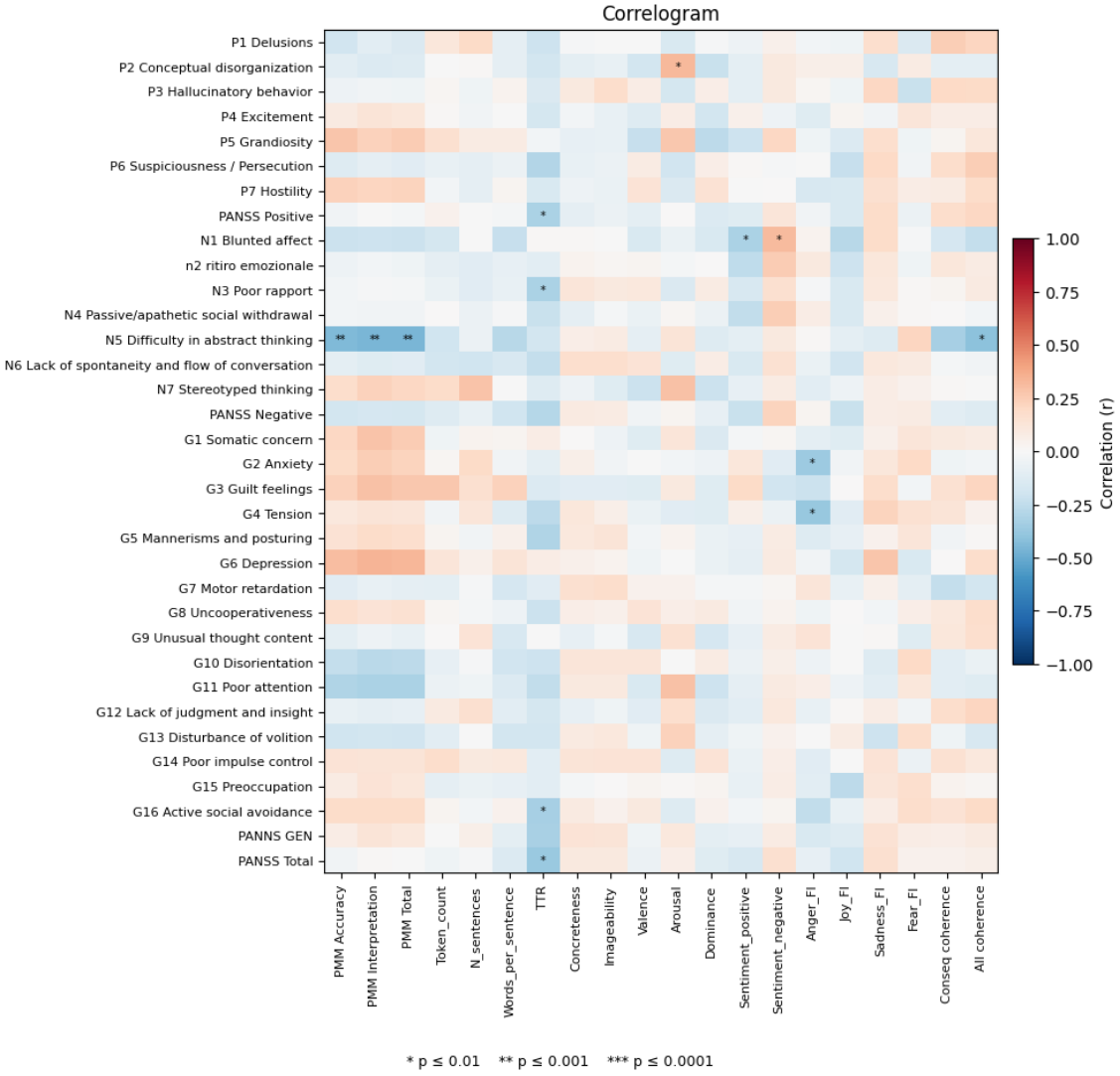
Figure 4. Comparison between levels of reported Fear pre and post an effective pharmacological treatment



Associations between symptom severity and linguistic features

As depicted in Fig.5, we observed several significant correlations between symptoms severity and both NPL-derived linguistic measures and pragmatic performance

Figure 5. Correlations between clinical symptoms, linguistic features and pragmatic abilities



Concerning pragmatic abilities, significant correlations were observed for PMM Accuracy with Grandiosity (r=0.27; p=0.45), Difficulty in abstract thinking (r=-0.44; p<0.01), Depression (r=-0.31; p=0.02) and Poor attention (r=0.30; p=0.03), for PMM Interpretation with Difficulty in abstract things (r=-0.46; p<0.01), Somatic concern (r=0.28; p=0.04), Guilt feelings (r=0.29; p=0.03), Depression (r=0.34; p=0.01), Disorientation (r=-0.27; p=0.05), Poor attention (r=-0.32; p=0.02), and for PMM total score with Difficulty in abstract things (r=-

0.46; p<0.01), Guilt feelings (r=0.27; p=0.05), Depression (r=0.33; p=0.01), Poor attention (r=-0.31; p=0.02).

Significant correlations were observed for Token count with Guilt feelings (r=0.27; p=0.31), Number of sentences with Stereotyped thinking (r =0.28; p=0.23) and Words per sentence with Difficulty in abstract thinking (r=−0.28; p=0.25).

Concerning TTR several significant correlations emerged. TTR correlates with Suspiciousness/persecution (r=−0.30; p=0.17), PANSS Positive score (r=−0.32; p=0.01), Inadequate rapport (r=−0.32; p=0.01), PANSS Negative score (r=−0.28; p=0.24), Tension (r=−0.26; p=0.4), Mannerisms and posturing (r=−0.30; p=0.02), Poor attention (r=−0.25: p=0.05), Active social avoidance (r=−0.34; p=0.01), PANSS General score (r=−0.33; p=0.01) and PANSS total score (r=-0.37 ; p<0.01).

Regarding semantic features, significant correlations were observed for Arousal with Conceptual disorganization (r=0.33; p=0.02), Grandiosity (r = 0.27; p=0.04), Stereotyped thinking (r=0.29; p=0.02), and Poor attention (r=0.29; p=0.02), while Dominance correlates with Grandiosity (r=−0.26; p=0.04).

Concerning sentiment markers, significant correlations were observed for Positive sentiment with Blunted affect (r=−0.32; p=0.01) and Emotional withdrawal (r=−0.25; p=0.05).

Negative sentiment is associated with Blunted affect (r=0.32; p=0.01) and Emotional withdrawal (r=0.25; p=0.05).

Emotional analysis revealed that Anger is associated with Anxiety (r=−0.36; p<0.01) and Tension (r=−0.38; p<0.01), Joy with Blunted affect (r=−0.28; p=0.02) and Preoccupation (r=−0.26; p=0.04), and Sadness with Depression (r=0.28; p=0.02).

Finally significant correlations were observed for Consecutive concreteness with Delusions (r=0.25; p=0.05) and Difficulty in abstract thinking (r=−0.33; p=0.01), and for All coherence with Difficulty in abstract thinking (r=−0.41; p<0.01).

Identification of groups based on linguistic profiles

Cluster analysis (k-clustering with k=2) on computational linguistic features produced 2 clusters characterized by the following differences in terms of semantic, emotional and sentiment markers (Table 5).

Table 5. Characterization of the two clusters based on linuistic featueres

Linguistic features	CLUSTER 1		CLUSTER 2		ANOVA	
	Mean	SD	Mean	SD	F	p
TTR	0.86	0.16	0.96	0.06	**8.27**	**<0.01**
Concreteness	3.19	0.17	3.10	0.22	3.37	0.07
Imageability	3.68	0.14	3.64	0.20	0.97	0.32
Valence	5.30	0.22	4.75	0.25	**97.10**	**<0.01**
Arousal	4.05	0.12	4.15	0.13	**10.19**	**<0.01**
Dominance	5.34	0.13	4.98	0.19	**95.60**	**<0.01**
Sentiment_positive	0.20	0.16	0.05	0.08	**17.44**	**<0.01**
Sentiment_negative	0.80	0.16	0.95	0.08	**17.44**	**<0.01**
Anger_FI	0.13	0.14	0.17	0.16	0.91	0.34
Joy_FI	0.15	0.14	0.05	0.09	**9.50**	**<0.01**
Sadness_FI	0.51	0.18	0.63	0.22	**6.40**	**0.01**
Fear_FI	0.20	0.17	0.15	0.19	1.46	0.23
Consec coherence	0.23	0.08	0.23	0.08	<0.01	0.96
All coherence	0.22	0.06	0.21	0.06	0.53	0.47

Cluster 1 is composed by 51 patients and characterized by lower TTR ($F=8.27$; $p<0.01$), while Cluster 2 (20 patients) showed higher Arousal ($F= 10.19$; $p<0.01$), lower Dominance (95.60; $p<0.01$), higher Negative sentiment ($F=17.44$; $p<0.01$) and Sadness ($F=6.40$; $p=0.01$) and lower Positive sentiment ($F=17.44$; $p<0.01$) and Joy ($F=9.50$; $p<0.01$).

Interestingly, assessing differences in symptom severity and pragmatic abilities between the two clusters only Stereotyped thinking emerged as significant (mean Cluster 1 = 2.80±1.00, mean Cluster 2 = 3.37±0.96; F=4.37; p=0.04), while pragmatic abilities showed a trend of significance for PMM interpretation (mean Cluster 1 = 22.12±11.59, mean Cluster 2 = 27.61±7.37; F=3.40; p=0.07) and PMM total (mean Cluster 1 = 37.62±19.73; mean Cluster 2 = 46.39±13.12; F=2.95; p=0.09) as shown in Table 6.

Table 6. Differences in PANSS scores in the two clusters

PANSS item	Mean Cluster 1	SD Cluster 1	Mean Cluster 2	SD Cluster 2	F	p
P1 Delusions	2.87	0.98	3.00	1.05	0.23	0.63
P2 Conceptual Disorganization	2.33	1.42	2.21	1.40	0.09	0.76
P3 Hallucinatory Behavior	2.87	1.42	2.58	1.26	0.60	0.44
P4 Excitement	1.95	0.81	2.11	0.74	0.49	0.49
P5 Grandiosity	1.57	0.83	1.84	1.17	1.16	0.28
P6 Suspiciousness / Persecution	2.67	0.99	2.58	1.02	0.12	0.73
P7 Hostility	1.37	0.71	1.42	1.02	0.05	0.82
PANSS Positive	15.52	3.88	15.63	4.25	0.01	0.92
N1 Blunted Affect	3.37	1.06	3.47	0.77	0.15	0.70
N2 Emotional Withdrawal	3.27	1.05	3.21	0.63	0.05	0.83
N3 Poor Rapport	2.76	1.20	2.63	0.83	0.18	0.67
N4 Passive/Apathetic Social Withdrawal	3.33	1.10	3.26	0.73	0.05	0.82
N5 Difficulty in Abstract Thinking	3.30	1.28	3.21	1.51	0.06	0.80
N6 Lack of Spont. and Flow of Conv.	2.70	1.31	2.53	1.43	0.21	0.65
N7 Stereotyped Thinking	2.80	1.00	3.37	0.96	**4.37**	**0.04**
PANSS Negative	21.48	5.80	21.47	3.81	<0.01	1.00
G1 Somatic Concern	2.26	0.88	2.74	1.24	3.07	0.08

G2 Anxiety	3.20	0.98	3.53	1.12	1.40	0.24
G3 Guilt Feelings	2.39	1.00	2.74	0.99	1.61	0.21
G4 Tension	2.54	0.96	2.74	0.87	0.57	0.45
G5 Mannerisms and Posturing	2.80	0.96	2.68	0.95	0.21	0.65
G6 Depression	2.02	0.88	2.26	1.24	0.79	0.38
G7 Motor Retardation	2.43	0.96	2.11	0.94	1.61	0.21
G8 Uncooperativeness	1.43	0.69	1.26	0.56	0.92	0.34
G9 Unusual Thought Content	3.13	1.17	3.16	1.12	0.01	0.93
G10 Disorientation	2.13	1.02	1.74	0.87	2.15	0.15
G11 Poor Attention	2.35	1.02	2.21	0.98	0.25	0.62
G12 Lack of Judgment and Insight	2.89	1.12	2.74	0.99	0.27	0.60
G13 Disturbance of Volition	2.72	1.03	2.53	0.96	0.48	0.49
G14 Poor Impulse Control	1.72	1.07	1.47	0.70	0.84	0.36
G15 Preoccupation	3.43	0.89	3.68	1.11	0.92	0.34
G16 Active Social Avoidance	2.91	1.31	2.79	1.18	0.13	0.72
PANSS General	40.00	8.20	40.84	7.57	0.15	0.70
PANSS Total	76.96	15.42	78.00	12.30	0.07	0.79
PMM Accuracy					2.28	0.14
PMM Interpretation	22.12	11.59	27.61	7.37	3.40	0.07
PMM total	37.62	19.73	46.39	13.00	2.95	0.09

Finally, no significant association emerged between the groups based on linguistic profiles and the groups classified according to the experience of hearing voices (Pearson Chi-square=1.51; p=0.47).

DISCUSSION

To our knowledge this is the first study investigating the subjective experience of hearing voices through FPAs computationally analyzed with NLP techniques. The strength of our study relies in coupling a widely used tool to capture the subjective lived experience of patients with a quantitative approach able to return objective data on such narratives. Results overall align with previous qualitative evidence, showing that among NPL-derived features, emotions are those most consistently associated with symptoms severity, especially for hallucinations.

We found that experiencing auditory hallucinations in patients with schizophrenia is associated with greater delusional beliefs and positive symptoms and with lower levels of Fear, but higher levels of Sadness, which in turn are associated to depressive symptoms. Considering the classification based on the degree of pharmacoresistance, we found that is not the presence/absence of auditory hallucinations to be associated with the definition of UTR but their impact on emotions and behaviors (pervasiveness). Interestingly, several associations emerged also between NPL-derived measures and clinical assessments of symptoms severity. In addition, by asking participants to retrospectively describe emotions, beliefs and feelings related to auditory hallucinations before setting an effective pharmacological therapy, we found that levels of Fear significantly decreased with treatments.

Positive symptoms depending on the hearing-voices condition

From a clinical perspective the presence of more severe positive symptoms in patients experiencing auditory hallucinations is well explainable given the fact that patients' wrong beliefs about voices, as previous evidence and FPAs pointed out, mediate false interpretations of them (interpreted as real people speaking), thus delusional thoughts (typically persecutory) inherent the content of auditory hallucinations [7][25][26][27]. These arguments explain greater PANSS P1-scores in the patients still hearing voices as well as a greater overall PANSS positive score, corroborating the hypothesis that positive symptoms are entangled in terms of psychopathology, having a lack of insight as shared underpinning. Similarly, they also explain greater scores in item G9-Unusual thought content. Indeed, a reclassification of PANSS items, made for the first time in 1997, used in several clinical trials and named PANSS Marder factores [67][68], include G9-Unusual thought content in the Positive score.

Emotional valence of auditory hallucinations

Analyzing differences in terms of computational linguistic variables, we found that patients still hearing voices showed significantly higher levels of Sadness and significantly lower levels of Fear. Greater levels of sadness are in line with several previous findings concerning greater depressive symptoms in patients hearing voices inferred through several clinical scales [30][39][40][35][47][38], typically compared to populations of patients affected by psychotic disorders but without auditory hallucinations or non-clinical populations of individuals hearing voices. Indeed, feelings induced by auditory hallucinations have been shown to be a distinguishing feature between clinical and non-clinical voice hearers [31][32][33][34], and a predictor of need for care and contact with mental health services due to functional impairment [31][32]. Moreover, several findings showed that individuals with higher depressive symptoms experienced greater severity of auditory hallucinations, associated with more negative content and distress [38][39][40]. In particular, depressive symptoms and negative self-evaluations (probably due to derogatory voice-contents) induced by voices seem a typical feature of persistent auditory verbal hallucinations, likely related to a treatment-resistant condition [44]. Overall, our findings endorse a key feature of auditory hallucinations in patients with schizophrenia, they are pervasive in terms of negative feelings and emotions, and this is why they are perceived and lived as problematic/annoying/harming by patients as also reported by quantitative studies including clinical scales as assessments and qualitative FPAs [25][26][27]. Concerning lower levels of fear found in the sub-sample of patients still hearing voices, which are not in line with literature, they are probably due to an effective pharmacological treatment, maybe at higher dosage, long duration of illness and mean age of the sample, which are constituted by chronic and stabilized outpatients with schizophrenia. Indeed, as discussed later, the linguistic emotion variable which significantly differed between pre- and post-effective is Fear and, its reduction along the course of the illness, associated with antipsychotic treatment, could be thus interpreted as an index of treatment response. Probably, higher dosages of antipsychotics in patients still hearing voices could be another variable able to explain both lower levels of fear and higher levels of sadness. Moreover, longer duration of illness might be related to greater levels of insight about voices (beliefs/interpretation), thus voices resulted (not fully) interpreted as something not completely real and a “product” of patients’ mind.

Antipsychotic response and auditory hallucinations

Regarding the distinction between FLR, TRS and UTR we did not find significant differences in the distribution of patients depending on the hearing voices

condition. This means that the presence of voices despite an antipsychotic treatment is not the only determinant of the clinical judgment of pharmaco-resistance, thus decision to switch to clozapine (TRS) or proceeding with the augmentation strategy with another antipsychotic drug. It is likely that other variables such as delusional beliefs, disorganization and behavioral abnormalities play an important role on clinical decisions. However, concerning auditory hallucinations, we found that FLR, TRS and UTR groups significantly differed in terms of P3-Hallucinatory bahavior. Therefore, the mere presence of auditory hallucinations is not sufficient to define UTR patients, but the emotional or behavioral pervasiveness of voices can represent one of the criteria on which clinicians rely in order to switch to clozapine or augment clozapine with an additional antipsychotic. Given these premises and previous findings pointing at the emotional correlates of positive symptoms and, in particular, of voices in determinining illness severiy [42], antipsychotics may play a pivotal role in resizing emotional involvement [69]. To test the hypothesis that antipsychotics can resize emotional pervasiveness of auditory hallucinations and positive symptoms we compared the emotion marker Fear extracted from item B (emotions, feelings and beliefs referred to voices pre-effective treatment) to item C (emotions, feelings and beliefs referred to the current state of illness). Interestingly, in line with our expectations, fear emerged as statistically different in the two conditions, pre and post efficacious treatment, showing that the frequent threatening nature of auditory hallucinations is resized by antipsychotic and for this reason are probably judjed as effevtive by patietns and, in turn, even clinicians. This can also explain lower levels of fear in patients still hearing voices, whom, being in a stable phase of illness as an inclusion crietrion, the emotional pervasiveness of their auditory hallucinations might be lower as responsive to antipsychotic treatments (even if UTR).

Clinical implications of linguistic markers

Regardless of the hearing voices condition, correlation analyses in the whole sample showed significant associations between several computatioanl linguistic markers, pragmatic abilities measured through PMM scale and multiple symptom domains. In detail, the two PMM sub-items and the PMM total score strongly correlated with Difficulty in abstract things as expected and well established by literature [70][71].

Regarding the computational metrics pertaining to fluency, the fact that narratives were written by the patients on sheets of paper, despite being recorded vocally and then transcribed, constitutes an important limitation in

interpreting both fluency and coherence variables in relation to symptom scores. Methodological limitations are later discussed, especially regarding coherence. Though, a negative correlation between Words per sentence and Difficulty in abstract thinking is meaningful and reflect the poor and concrete content of the typical thought of schizophrenic patients. Concerning TTR several significant correlations emerged between a wide range of symptom domains including positive negative, general and even total PANSS score. These represent pivotal findings as TTR is a measure of lexical diversity, thus it encompasses many different aspects of psychopathology of schizophrenia given that a reduced TTR could indicate greater negative symptoms due to a lack of volition (alogia), thus will to articulate a complex discourse [72][73], but at the same time the perseveration/hyper-focusing on delusional beliefs and auditory hallucinations can be captured as well by a lack of diversity in the themes [46][74]. Overall, the concept of schizophrenia as a pathology of being stuck oncertain content of thoughts and in the daily lived experience of patients is an old but still contemporary conception, first postulated by Eugène Minkowski [75]. This concept will be furhter discussed after regarding cluster analysis. Concerning sentiment markers, significant positive correlations were observed for Negative sentiment with Blunted affect and Emotional, while the opposite occurred between Positive sentiment and the same PANSS items. Similarly, Emotion analysis revealed that Joy was associated with Blunted affect. Notably, the emotion variable Sadness correlated with the item Depression but not with PANSS items pertaining to the negative symptom dimension, as other emotion and variables inferred from sentiment analysis did. This is a cardinal point to highlight as computational linguistic markers seem able to distinguish between negative and depressive symptoms, a distinction a distinction that many clinicians struggle to differentiate rather than recognize [76][77][78]. Another important correlation emerged between Consecutive coherence and All coherence with Difficulty in abstract thinking. In our opinion, this is an important limitation to acknowledge concerning the use of written narratives because, as we described before, Difficult in abstract thinking neagatively correlated with Words per sentence, and the length of phrases produced by patients may influence the way in which coherence is computed as patients thinking in a concrete way and experiencing greater negative symptoms use a lower number of words, thus similarity between words used in a telegraphic manner is lower as well. Finally, an expected significant correlation which turned out to be not significant, was between the two variables of Coherence and the item P2-Disorganized thinking, given that Coherence is typically associated with this symptom dimension. Probably, this is due to the written modality of patients'

narratives, as patients with loose logical associations between ideas have time to organize a coherent written language while maybe cannot do the same if speaking. Another important aspect is that patients who used a small number of words provided concepts through words, used in a more telegraphic manner, instead of a full-lenght sentence. This can affect the computation of coherence compared to that computed on speech transcripts.

Phenomenology of linguistic profiles

Several studies found that negative beliefs and emotions conditioned by auditory hallucinations were able to distinguish patients from non-clinical voice hearers [31][32][33] and predict the need for care [31][32]. Moreover, they were even associated to greater illness severity [42]. Based on this evidence, we decided to classify patients based on sentiment, emotion and semantic computational linguistic markers, coherence (typically a proxy of disorganized thinking) and TTR, as TTR showed several significant correlations with PANSS items. We identified two groups of patients, one whose narratives are characterized by lower scores of Joy, Dominance (a proxy of agency) and Valence and higher scores of negative emotions (Fear, Sadness) and Arousal, as well as of TTR and, and another with the opposite features. Interestingly, the distribution of patients in the two clusters did not show a significant degree of overlap with other groups based on the presence/absence of auditory hallucinations excluding that patients with greater negative emotional valence are those hearing voices. Moreover, even when looking at symptom severity in different domains, the two clusters did not significantly differ in terms of P3 item-Hallucinatory behavior and not even P1 item-Delusions or PANSS positive score. Therefore, patients with lived experiences of illness denoted by negative feelings and emotions do not experience greater positive symptoms as expected based on previous findings [40][48]. However, patients differed in terms of item N7-Stereotyped thinking and, specifically, patients showing a negative emotional involvement (Cluster 2) experienced greater scores, indicating that they were less prone to change the topic of the conversation and shifting to other themes during the PANSS interview and/or they tended to talk often about the same topics. An interesting consideration is that these patients showed even greater TTR, thus higher lexical variability. Therefore, a possible interpretation of these findings is that patients experiencing negative emotions and feelings, who seem tense, agitated with low degree of control on symptoms (lower dominance), tend to be more focused on the same themes about which they speak in a more detailed way. In other words, patients showing a greater negative emotional involvement despite being more rigid and persistent on the

same prevalent topics, which probably cause tension/agitation and anxiety as well as negative emotions and a sense of being not in control of the situation, use a broader vocabulary to describe their feelings and emotions related to living with a psychotic disorder. They repeat similar concepts/ideas (perseveration) in different ways with words denoted by negative emotional valence. Interestingly, de Boer and colleagues analyzing voice content and related emotions through NLP techniques found that negative emotions and perseverations are typical of patients' voices compared to non clinical populations [46][47]. Thus, despite the two clusters did not significantly differ in terms of number patients hearing voices or in terms of severity of auditory hallucinations, the presence of voices may at least influence a bit cluster differentiation. Resuming the Minkowsi's conception of schizophrenia, as a disturbance of lived temporality, Minkowski argued that people with schizophrenia experience time as static, frozen, blocked. Thought becomes overly abstract, rigid, and detached from real life, losing its grounding in lived experience and focusing on illness experiences. Emotions and affect are thus referred to inner experiences and a loss of vital/emotional contact with reality occurs. Overall, clustering based on linguistic NLP variables seems to capture this dimension of schizophrenia of being stuck in illness experiences and negative emotions and anguish related to this. As Ritunnano and colleagues have pointed out [79][80], investigating the linguistic dimension of schizophrenia through NLP can lead to a more fine-grained psychopathological approach able to better gasp the phenomenology of the disease. Concluding, fine-tuned clustering into two clusters based on NLP markers failed to reflect different illness severity, however it caught distinctions on the role of ruminative thinking on predominant/prevalent thoughts or inner experiences (distressing themes), the loss of agency on them, and secondary negative emotional valence and sadness. Given the relevance of such experiences, patients tended to describe them in detail using a wide vocabulary.

Limits of study

The results must be interpreted in the context of some limitations mostly due to the cross-sectional nature of the study thus the lack of longitudinal assessments. Indeed, the fact that patients when wrote FPAs referred some of their lived experiences to the past, to a hypothetical pre-effective treatment T0, and did not actually produce narratives at T0, represents an importany limitation to aknowledge. In addition, the written nature of narratives places other limits

concerning the interpretability on data related to markers of fluency and coherence. Moreover, the lack of dosages of antipsychotic treatments didn't allow us to explore the hypothesis that patients still-hearing voices were treated with higher dosages of clorpromazine equivalents. Another limit is the lack of a healthy control group or a non-clinical population included by previous similar studies that hamper a comparison between voices in patients and healthy controls in terms of emotional valce, feelings and beliefs. Recruitment was performed in a single center, and patients were outpatients in a stable phase and long duration of illnees. Finally, an important methodological limitation concerns the use of clustering techniques. By design, clustering algorithms impose a discrete structure on the data, assigning individuals to distinct groups even when the underlying distribution may be continuous rather than categorical. In this sense, the identification of two clusters in the present study should not be interpreted as evidence of clearly separable subtypes, but rather as a simplified representation of potentially dimensional variations in linguistic and emotional features. It is plausible that the observed profiles reflect points along a continuum ranging from more positive/neutral to more negatively valenced and emotionally involved narratives. Therefore, the distinction between clusters may partly reflect an analytical artifact of the method, and results should be interpreted with caution. All these aspects limit the generalizability of the findings due to the lack of variability of the enrolled participants that constitute the clinical population.

Conclusion

This is the first studies that computationally analyzed FPAs of patients with schizophrenia on the experience of hearing voices and its emotional correlates and beliefs and on the general conception of illness of patients. In general, NLP markers showed the promising potential to reflect some symptom dimensions of schizophrenia, but further studies are needed to validate the reliability of this tool in predicting the clinical outcome. Sadness emerged as a typical feature of patients still hearing voices in line with several other findings, while fear appeared as an emotion resized by antipsychotic treatments and its reduction could be evaluated as an indicator of treatment response by clinicians. These findings support the need of developing tools to enable patients to get some relief from depressive symptoms secondary to the persistence of voices as some authors already did by increasing self-esteem and acceptance of voices with competitive memory training [44]. Finally, the longitudinal automated

assessment of Fear in speech samples of patients over time can support clinicians in assessing and monitoring treatment response.

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GENERAL CONCLUSION

This dissertation aimed to explore the intersection of language and psychosis with the final goal to find possible useful linguistic markers of psychosis able to inform daily clinical practice and pave the way for future new treatments. The different objectives of each single study have been reached through behavioral, biological, and computational tools that allow us to identify the following key findings.

Biological findings

Pragmatic impairment showed a direct association with the systemic sub-inflammatory state typical of schizophrenia, underscoring the need for integrated interventions to also address immune dysregulation in combination with rehabilitative strategies. Moreover, positive associations between overall pragmatic functioning on the one hand, and melatonin and QUIN on the other hand emerged in TRS patients, highlighting the synergistic role of these two molecules with clozapine on glutamatergic neurotransmission. Given that pragmatics is a complex higher order function highly distributed across the brain and glutamate is the most widespread excitatory neurotransmitter, it is likely that the enhancement of glutamatergic neurotransmission might have a positive impact on brain connectivity and thus on pragmatics in the presence of clozapine. This stresses the importance of addressing the under-prescription of clozapine worldwide, being an effective pharmacological treatment able to resize disability.

Considering the different impact showed by psychedelics on linguistic categories, it is likely that higher doses trigger pyramidal neurons in the V layer of the cortex with implications for cross-cortical connectivity and discourse disorganization, a possible index of acute intoxication due to overdose in the context of clinical trials on psychedelics. Differently, microdoses enhanced positive sentiment and emotions conveyed through speech, probably only acting as an agonist at 5HT2A receptor level. Mild doses induced an indirect semantic priming effect likely mediated by increased neuroplasticity and thus higher local connections between neurons without altering long-range

connectivity (projecting pyramidal neurons). Positive sentiment and emotions or even an indirect semantic priming effect might be used, not to assess adverse events such as intoxication, but as measures of the therapeutic effect of psychedelics. Overall, study 2 provided possible useful linguistic markers of treatment response or intoxication that could be used within the context of new clinical trials aimed at exploring new treatment strategies in individuals with mental disorders.

The importance of considering the subjective dimension of psychosis

FPAs analyzed through NLP techniques allowed us to explore the lived experience of patients with schizophrenia in a quantitative manner. Notably, patients still hearing voices experienced higher levels of sadness and antipsychotic response was associated with a reduction of emotional pervasiveness of voices in terms of Fear. The emotional characterization of the hearing-voices experience emerged as of paramount importance in the subjective dimension of patients rather than the mere presence of voices. In a broader view, more enhanced negative sentiment and emotions inferred through narratives, can define a subgroup of patients not captured by other assessments, more phenomenologically stuck in its psychopathology. Overall, several linguistic features showed associations with different symptom dimensions in the whole sample suggesting a potential role of NLP in informing and supporting clinical decisions.

Final considerations

Overall, these studies highlight the central role of language as a key interpretative framework for psychosis, as well as a potential indicator of treatment response and effectiveness. Importantly, they also support the idea that language, and especially pragmatics, may represent a meaningful target for intervention aimed at improving social adaptation, reducing disability, and enhancing quality of life in individuals with schizophrenia. Taken together, these findings reinforce the importance of continuing to deepen our understanding of the close and multifaceted relationship between language and psychotic disorders.