UNIVERSITA’ VITA-SALUTE SAN RAFFAELE

CORSO DI DOTTORATO DI RICERCA IN NEUROSCIENZE COGNITIVE

# PRAGMATIC LANGUAGE DISORDER IN SCHIZOPHRENIA: ASSESSMENT AND EEG-BASED NEURAL CORRELATES

DoS: Dott.ssa Marta Bosia

Tesi di DOTTORATO di RICERCA di Giulia Agostoni

matr. 015723

Ciclo di dottorato XXXV

SSD MED/25

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# DECLARATION

This thesis has been composed by myself and has not been used in any previous application for a degree. Throughout the text I use both ‘I’ and ‘We’ interchangeably. This thesis has been written according to the editing guidelines approved by the University.

All the data and results presented here were obtained by myself. The following contributions should be acknowledged:

- Heathy subjects were enrolled in collaboration with Prof. Valentina Bambini, Dr. Luca Bischetti and Dr. Federico Frau, IUSS Pavia;
- EEG machine and tasks’ set-up was performed in collaboration with Dr. Giorgio Arcara and Dr. Sara Zago, IRCCS San Camillo, Venice;
- APACS Brief was developed in collaboration with Prof. Valentina Bambini, Dr. Luca Bischetti and Dr. Federico Frau, IUSS Pavia, and Dr. Giorgio Arcara and Dr. Sara Zago, IRCCS San Camillo, Venice;
- Figures 1, 2, and 3 were performed in collaboration with Dr. Paolo Rebolini, UniSR;
- Figure 15 (APACS Brief structure) was performed in collaboration with Prof. Valentina Bambini, Dr. Luca Bischetti and Dr. Federico Frau, IUSS Pavia.

All sources of information are acknowledged by means of reference.

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"*The strength of the team is each individual member.*

*The strength of each member is the team*"

(Phil Jackson)

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## ABSTRACT

Pragmatic disruption is a main feature in schizophrenia, which affects around 80% of patients and contributes to the functional disability associated with the illness. Despite its relevance, pragmatic impairment is seldom considered in assessment, as the available tests share the limitation of a significantly long administration time, thus making them unfeasible into routine evaluation. Moreover, the neurophysiological underpinnings of pragmatic disruption are still understudied, thus restraining the comprehension of the underlying neural mechanisms and limiting the identification of treatment targets, as well as of possible markers for early diagnosis and treatment outcome evaluations.

Based on these premises, this study aims at testing a novel and brief tool for pragmatics (APACS Brief) in 56 patients with schizophrenia and 56 matched healthy controls, and at characterizing the EEG-based neural correlates of pragmatic language disorder in people with schizophrenia, focusing on both widely explored electrophysiological indexes, such as Mismatch Negativity (MMN) and alpha activity, as well as novel ones, namely aperiodic activity.

Results showed significant differences between patients and controls in all APACS Brief scores, and highlighted the efficacy of this novel task in discriminating between the two groups. Significant correlations between APACS long and brief versions, as well as between the latter and both cognitive and sociocognitive data, were found, further confirming the validity of the tool. Results from electrophysiological data showed significant correlations between: 1) MMN and both cognition and pragmatics, in particular the comprehension of a text containing figurative expressions; 2) alpha activity and both the severity of psychopathology (especially negative symptoms) and pragmatics, in particular irony understanding; 3) aperiodic activity and both cognition and pragmatics, in particular figurative language interpretation.

Overall, results suggest the efficacy of APACS Brief in evaluating pragmatic disruption in schizophrenia, highlighting its equivalence with a validated tool and the feasibility in the National Health System services. EEG results show the relationship between different electrophysiological indexes and pragmatics, thus paving the way for increasing the knowledge on the neurocognitive architecture of the mind, as well as for the identification of possible treatment targets and markers for more refined prediction of diagnosis and treatment outcome.

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**ACRONYMS AND ABBREVIATIONS**

ADHD = Attention Deficit Hyperactivity disorder

ASD = Autism Spectrum Disorder

DSM 5 = Diagnostic and Statistical Manual of Mental Disorders - fifth edition

E/I = excitatory/inhibitory

EEG = Electroencephalogram

EF = Executive Functions

ERPs = Event related potentials

FOOOF = Fitting Oscillations and One Over F

FTD = formal thought disorder

ICA = Independent Component Analysis

MMF = Mismatch field

MMN = Mismatch negativity

NHS = National Health System

PSD = Power Spectral Density

RoI = Region of Interest

TBI = Traumatic Brain Disorder

ToM = Theory of Mind

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# 1. INTRODUCTION

## 1.1 Schizophrenia

Schizophrenia, a severe psychiatric disorder characterized by symptoms such as delusions, hallucinations, and disorganized thinking and behaviour, is considered among the leading causes of disability worldwide. According to a 2019 report from the Global Health Data Exchange (Institute of health Metrics and Evaluation, 2019), schizophrenia affects around 24 million people globally, approximately the population of Australia, and around 245.000 people in Italy. The disorder is associated with significant healthcare costs, both direct and indirect. In the U.S. it is estimated that the economic burden of schizophrenia is more than 261.6 billion $/year (2020) (Lin et al., 2022), while in Italy it is estimated around 8.5 billion €/year (2020) (Latorre et al., 2022), with the 49% of the costs due to rehabilitation, and 30% attributable to disability and loss of productivity. Schizophrenia is also associated with a significant reduction of life expectancy, which is estimated to be around 15 years shorter than in healthy people, and is often related to physical illnesses, such as cardiovascular and metabolic diseases (Jauhar et al., 2022). In addition, the suicide rate in schizophrenia is estimated around 352.2/100000 person-years, highlighting the severity of the problem as well as the harshness of the issues experienced by people affected by the disorder (Fu et al., 2021).

People with schizophrenia usually show pervasive difficulties in social, educational, personal, occupational, and other important areas of life, with widespread consequences on people's well-being and quality of life (Bechi et al., 2017; Green, 2016). The recovery from schizophrenia, defined as the presence of mild symptoms and the reach of a good social functioning, is the ultimate goal in the treatment of the disorder, but to date only around 13.5% of people can achieve recovery (Jääskeläinen et al., 2013). Indeed, functional disability is still one of the major issues, as pharmacological treatments have limited effects on the long-term impairments associated with the illness (Stępnicki et al., 2018). Thus, the identification of functional predictors is of main relevance in order to pinpoint those factors that can improve people with schizophrenia's functional outcome.

In the last decades, cognitive and sociocognitive impairments have been suggested as major predictors of functional impairment, thus representing significant targets for rehabilitative interventions, which may have subsequent effects on people’s functioning (Bechi et al., 2017; Harvey et al., 2022). Recently, communicative-pragmatic abilities have also gained attention, as they proved to be significant predictors of daily functioning, with an effect that encompasses interpersonal and personal domains, and they can be restored by a specific trainings, with a consequent improvement of functional outcome (Bambini et al., 2022).

In this framework, the exploration of pragmatic abilities represent a fertile field of research, however numerous aspect should be addressed by research. Firstly, a significant issue is represented by the assessment. A number of tests are available to assess pragmatics, but, besides the pros of these tasks, the duration of administration time of all the available tests is significantly long (40 minutes or more). Thus, given the time constraints in the National Health System (NHS) services, pragmatic assessment tools can hardly be incorporated into routine assessment of patients with schizophrenia. This highlights the necessity of providing clinicians with a tool for a rapid screening of pragmatic skills. Second, besides the impact of pragmatic impairment, to date the exploration of the related neural mechanisms is still poorly addressed. A better understanding of underlying neural mechanisms associated with cognition, and in particular pragmatics, would provide new targets for treatment and may have potential application for a more refined prediction of diagnosis and treatment outcomes.

## 1.2 Pragmatics

Sam and John are having a walk, when suddenly it starts raining heavily. John says “What a wonderful day for a walk!”. Sam laughs and opens the umbrella. Sam is able to understand John’s sentence because of his pragmatic abilities that allow him to understand that the statement is an ironic way to say that the weather is adverse and rainy.

The term *pragmatics* has been coined by Charles Morris in the 1930s (Nerlich, 1995), however throughout the years multiple definitions, encompassing philosophical and linguistic traditions, have been proposed. Nowadays, there is a large consensus on the definition of pragmatics as a sophisticated communicative ability that allows to appropriately use and interpret language in a wide range of contexts and situations (Cummings, 2014). In everyday life, pragmatics allows to understand an utterance beyond its literal meaning and, as in Sam and John example, to fill the gap between what someone had literally said (e.g., “Such a wonderful day for a walk!”) and what is meant (e.g., the weather is poor and rainy) (Grice & Grice, 1989). This sophisticated interpretation of language relies on an inferential process of the speaker’s “real” communicative intentions, as well as on the integration of contextual knowledge that the interlocutors are supposed to share. In the broader perspective, pragmatics is a communicative tool to communicate and understand each other in real-world situations, taking into account the social, cultural, and situational factors that influence language use (Cummings, 2017).

Figurative language encompasses a variety of linguistic expressions with specific communicative purposes within a given context. These language types differ from their literal counterparts and may be used in preference to them due to their unique ability to achieve specific discursive goals. Among different figurative language types, the most noteworthy are metaphors, irony, proverbs, and idioms. Metaphor is a figure of speech that describes something or someone based on its likening to something else with similar characteristics (e.g., “That lawyer is a shark”). This comparison allows for the transfer of meaning from the vehicle (i.e., the term used metaphorically, for example the shark) to the topic of the metaphor (i.e., the subject of the metaphor, for example the lawyer), based on the recognition of the resemblance between them (in the example, both the lawyer and the shark are supposed to be aggressive) (Gardner & Winner, 1978). Metaphors can be classified based on their level of conventionality (i.e., how widely they are used in a given culture) and salience (i.e., how familiar they are to an individual) (Bowdle & Gentner, 2005; Giora, 2002). Irony is figurative form of speech that allows to express something indirectly and in a different way from what is actually meant (e.g., “Oh, that’s wonderful” when something bad happens) (Rapp et al., 2013). To understand irony, the listener must interpret the speaker's intentions and context, and grasp the ironic nuances of an utterance, thus realizing that the words are not meant to be taken literally. A proverb is a short, common saying that reflects practical wisdom and conveys a moral or lesson (e.g., "Don't judge a book by its cover" is a proverb meaning that one should not make assumptions about something or someone based on appearances alone and should consider other factors, such as character and abilities, before making a judgment) (Cummings, 2009). An idiom is a fixed expression whose meaning is determined by its widespread usage and culture (e.g., “break a leg” is a common idiom used to wish someone luck before a performance) (Cummings, 2009). The understanding of figurative language expressions, besides the specific characteristic of each type, is based on the interpretation of the true meaning of the message, and involves an integration of contextual knowledges and an inferential process based on the interlocutor’s communicative intentions. Figurative language expressions constitute a relevant part of everyday communication, with an estimated frequency of non-literal language of around six per minute of speech (Barlow et al., 1977) and an 8% of ironic exchanges between university students (Gibbs, 2000).

A successful communication is fundamental for everyday life. The maintenance of social relationships, the obtainment and maintenance of vocational and leisure activities, the engagement in community operations, with consequences for psychosocial wellbeing, all rely on a broad set of cognitive abilities, which include pragmatics of communication (Agostoni et al., 2021). Pragmatic breakdowns may occur in everyday life, and may have disruptive consequences on people’s life, leading to the avoidance of social contexts, difficulties in the maintenance of relationships, struggles in academic, social and vocational functioning. In this framework, the disruption of pragmatic abilities, give the main role played in everyday life and communication, is of particular relevance (Agostoni et al., 2021; Cummings, 2017).

Pragmatic breakdowns are documented in a wide range of neurodevelopmental, neurological, and psychiatric conditions. Among neurodevelopmental conditions, autism spectrum disorder (ASD) is well known to be characterized by difficulties in social communication and interaction (Cummings, 2017; Parsons et al., 2017), which constitutes criteria for the diagnosis in the Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM 5) (American Psychiatric Association, 2013). People with ASD are likely to show pragmatic difficulties, ranging from difficulties in producing novel language, narrower ranges of communication acts, to struggles in initiating and effective communication. As for neurological disorders, impairments in pragmatics and social communication are common in people with traumatic brain disorder (TBI), with a disruption that encompasses several aspects of pragmatic communication, such as pragmatic language comprehension and the maintenance of the topic in connected speech

(Giorgio Arcara et al., 2020; Cummings, 2017; Struchen et al., 2011). Among clinical conditions, schizophrenia is worthy of consideration, given the huge and profound impairment of pragmatics, which will be better addressed in the next paragraph.

### *1.2.1 Pragmatics in schizophrenia*

Language has been extensively investigated in schizophrenia, as alterations of language and communication, which have been referred to as formal thought disorder (FTD), have been described since the first nosological description of the illness by Bleuler (Bleuler, 1911). Language disturbances can occur at both semantic and syntactic levels and include a large set of features, such as abnormal semantic associations, neologisms, word approximation, reduced speech frequency and complexity, syntactic errors (Cummings, 2017). However, even when syntax and semantics are preserved, people with schizophrenia may still experience difficulties in the area of pragmatics.

People with schizophrenia struggle to communicate and understand language in relation to the context it is used in, and to interpret the effective meaning an utterance beyond its literal meaning. These difficulties have long been recognized as a manifestation of a breakdown in abstract thinking, referred to as "concretism" (Harrow et al., 1974). Studies have shown that around 77-92% of people with schizophrenia experience severe and pervasive pragmatic disturbances (Angeleri et al., 2012; Bambini et al., 2016), both in their ability to produce as well as to comprehend pragmatic language, which suggests a widespread Pragmatic Language Disorder in schizophrenia.

Let's consider the case of Anne, a person with schizophrenia, who is excited about her first day at work, but when her new colleague at the reception welcomes her with “You must be the new one, break a leg!”, she felt physically threatened and immediately left, losing the job. Healthy subjects are able to understand figurative language, and thus to make an inference on the speaker’s words by using contextually relevant information. By contrast, people with schizophrenia struggle with the understanding of non-literal sentences, thus providing unusual and concrete interpretations (Bambini et al., 2020). In this example, Anne is not able to understand the intended pragmatic meaning of the idiom used, and instead she took the words literally. While the colleague was trying to make a wish to Anne, she didn't grasp the real meaning of the words, thus literally interpreting them. As shown by the example, the inability to understand figurative language in everyday communication can have significant impacts not only on the outcome of the conversation, but also on the relationship with others, the chance to obtain and maintain a job, as well as on the achievement of a satisfactory life (Adamczyk et al., 2016; Agostoni et al., 2021).

Difficulties in the understanding of non-literal language in schizophrenia affects the interpretation of different figurative language types. A large body of literature showed the tendency of individuals with schizophrenia to interpret metaphors literally instead of metaphorically (Parola et al., 2018; Pesciarelli et al., 2014; Tavano et al., 2008). This breakdown of metaphor understanding affects the interpretation of both conventional and novel metaphors and has been found to be a significant predictor of functional outcome, especially employment status (Adamczyk et al., 2016). The understanding of irony can be also particularly challenging for people with schizophrenia, as they show a tendency to take ironic statements literally, instead of recognizing the ambiguity and the hidden meaning behind the concrete words (Gavilán & García-Albea, 2011; Langdon et al., 2002). Moreover, pragmatic difficulties also affect the violation of Grice's maxims (i.e., maxim of quantity, quality, relation, and manner), thus affecting the pragmatic production of language (Mazza et al., 2008; Tényi et al., 2002).

Pragmatic communication relies on a complex interaction among various cognitive functions, such as Theory of Mind (ToM) and Executive Functions (EF), however it is still unclear which specific cognitive domain contributes to the pragmatic disruption (Parola et al., 2020). ToM has been suggested as crucial for pragmatics; as a matter of fact the Relevance Theory posit that pragmatics is a submodule of ToM (Happé, 1993) and several studies found a link between ToM deficits and difficulties in communication tasks (Bosco et al., 2018; Sperber & Wilson, 2002). Moreover, the impairment of EF was related to pragmatic deficit (Mossaheb et al., 2014; Pesciarelli et al., 2014). Conversely, other studies have found no significant association between neither ToM nor EF and pragmatic abilities in schizophrenia (Champagne-Lavau & Stip, 2010; Langdon & Davies, 2002; Mo et al., 2008; Parola et al., 2018). Noteworthy, recent evidence suggested that pragmatic abilities and both cognitive and sociocognitive abilities are related but independent, highlighting that it is not correct to attribute pragmatic breakdown solely to cognitive or ToM impairments (Bambini et al., 2016; Parola et al., 2020).

Another relevant aspect that should be acknowledged is the impact of pragmatics on daily functioning. As previously stated, communicative-pragmatic impairment significantly affects daily living and quality of life in people with schizophrenia, jeopardizing the ability to interact appropriately with others and to fit in with social groups, damaging relationships and the ability to comprehend the requests of the loved ones, and also affecting an individual's chance to succeed in his/her career (Adamczyk et al., 2016; Agostoni et al., 2021). In a previous study of our research group (Agostoni et al., 2021), we confirmed that pragmatics plays a significant role in contributing to the cognitive structure of functional outcome in schizophrenia. We found that cognitive and sociocognitive abilities serve as the platform for pragmatic competence, and that all these neuropsychological skills are the breeding ground for daily functioning, as well as for specific functional domains, such as interpersonal relations and personal autonomy.

Literature has also suggested that the widespread and profound pragmatic impairment can be detected in the early stages of development, even before the onset of schizophrenia. Noteworthy, studies highlighted the subtle pragmatic alteration also in first degree relatives who did not develop the illness (Pawełczyk et al., 2018). Thus, pragmatic impairment has been suggested as a potential endophenotype and vulnerability marker of schizophrenia, which should be better addressed by research, as the identification of disease’s markers has relevant prognostic and diagnostic implications, and it would increase the knowledge on the illness aetiology.

### 1.3 Assessment of pragmatic abilities in schizophrenia

The evaluation of pragmatic abilities has gained significant attention in the field of neuropsychology, with various organizations and studies, such as the American Speech-Language-Hearing Association (Turkstra et al., 2017) and the multinational and multidisciplinary Delphi study (Bishop et al., 2016), providing recommendations for its assessment in both children and adults.

As a result, a number of tools for evaluating pragmatics have been developed, including the Batteria sul Linguaggio dell'Emisfero Destro (BLED) (Rinaldi et al., 2008), the Assessment Battery for Communication (ABaCo) (Angeleri et al., 2012), the Italian version of the Protocole Montréal d'Évaluation de la Communication (MEC) (Tavano et al., 2013), and the Assessment of Pragmatic Abilities and Cognitive Substrates (APACS) (Arcara & Bambini, 2016). Among the available tasks, the ABaCo and the APACS are the most used in Italian people with schizophrenia.

ABaCo is a tool measuring the effectiveness of communication through linguistic and nonverbal means, taking into consideration factors such as paralinguistic features, adherence to social norms and fluid integration within a conversation (Angeleri et al., 2012). ABaCo evaluates five domains through both production and comprehension tasks, namely Linguistic, Extralinguistic, Paralinguistic, Context, and Conversation subtasks. The Linguistic and Extralinguistic scales assess the understanding and use of spoken language and gestures, respectively. The Paralinguistic scale looks at the comprehension and production of communication elements such as facial expressions and prosody. The Context scale evaluates the appropriateness of a communication related to discourse and social customs. The Conversation scale assesses the ability to participate in a conversation properly, including the ability to maintain the topic, to introduce new topics, and to adhere to turn-taking rules. ABaCo proved to be a reliable tool with high internal consistency among its scales (ranging from $\alpha = .52$ to $\alpha = .91$) and factor analysis confirmed that a single factors, accounting for 63% of variance, underlining all domains. Normative data are available for individuals aged 15 to 75.

The APACS focuses on evaluating two primary pragmatic areas, specifically production skills and the comprehension of different figurative language types (Arcara & Bambini, 2016). The production tasks (i.e., Interview and Description) measure the engagement in a semi-structured interview, centred on personal topics, as well as the capacity to provide explanatory descriptions and information about everyday life situations. The comprehension tasks (i.e., Narratives, Figurative Language 1, Humor, and Figurative Language 2) evaluate the understanding of discourse and figurative language features included in a narrative text, as well as the ability to interpret metaphors, idioms, proverbs, and irony through multiple choice questions or verbal explanations. The task provides three global scores, evaluating pragmatic production, pragmatic comprehension, and overall pragmatics. These APACS composite scores allow for the rough categorization of an individual's pragmatic performance, thus giving information on the global pragmatic profile as well as on specific difficulties that can be useful for clinicians. APACS has acceptable internal consistency (ranging from $\alpha = .60$ to $\alpha = .70$), and good test-retest reliability for nearly each task, showing significant coherence and consistency over time. Factor analysis revealed two factors potentially underlying pragmatic abilities (i.e., production and comprehension). Normative data are available for individuals aged 19 to 89.

Despite the pros of all available tests, they all share the limitation of being considerably long, exceeding 40 minutes (BLED: 50 minutes; APACS: 40 minutes; ABaCo: 90 minutes; MEC: two sessions of 45 minutes), which can be a limitation in clinical practice given the time constraints in the NHS services. Also, given the tasks' duration, people with schizophrenia performance may be influence by the well-known cognitive deficits (e.g., in attention domain) that could potentially impact on the results.

To date, there are no rapid assessment tools available for evaluating pragmatics, making it difficult to incorporate into routine assessment of people with schizophrenia with suspected pragmatic language disorder. The lack of a valid and rapid test for pragmatics assessment has multiple implications: 1) from a clinical perspective, it does not allow the routine evaluation in the NHS of people with schizophrenia, with an effect on the possibility of including patients with communication difficulties into rehabilitation programs, which would also improve their functioning and quality of life (Bambini et al., 2022); 2) from the research point of view, the availability of a rapid and valid test could favour the advancement of knowledge regarding the deficit, its impact, and possible neural correlates; 3) in a broader perspective, a rapid test could be used as a screening tool in at-risk populations, such as people at high-risk for psychosis, in which an early evaluation of the onset risk could influence the disorder prognosis.

### 1.4 Neural correlates of pragmatics in schizophrenia

"*Language is like a window into the mind*" said the neuroscientist Dr. D. Titone (Noonan, 2014), highlighting the striking importance of studying language and its underlying neural mechanisms. Over the past four decades, the exploration of language has gained significant attention, as showed by the accumulated results on syntactic and semantic processing. However, the exploration of pragmatic competence has gained little consideration not only in the healthy population but also in clinical one. The identification of underlying mechanisms of language dysfunction in people affected by schizophrenia may help to understand the neural basis of the disorder, thus leading to earlier diagnosis, more effective treatments and rehabilitative interventions, with significant consequents on illness outcome and people's life (Noonan, 2014).

Among different techniques adopted to investigate language, Electroencephalogram (EEG) proved to be a useful methodology in studying brain processing activity. EEG is a non-invasive tool, with a millisecond-range temporal resolution, that can measure the electrical activity of the brain in real time. EEG registers electrical brain activity using electrodes placed on the scalp, which captures the summed post-synaptic potentials across space and time by combining the inhibitory and excitatory activity of neurons, primarily pyramidal cells in the neocortex of the brain (Luck, 2014). The signal collected by electrodes is sent to bio-amplifiers, which transform the electrical signal into a digital one, creating the EEG track that reflects the electrical activity of the whole brain (Niedermeyer & da Silva, 2005).

Although limited, research tried to explore the electrophysiological indexes related to pragmatics, which have shown to be useful to better comprehend neural correlates of language (Canal & Bambini, 2021). The next paragraphs will explore Event related potentials (ERPs), in particular Mismatch negativity (MMN), alpha activity and aperiodic activity.

### *1.4.1 Event related potentials: Mismatch negativity*

Event related potentials (ERPs) are post-synaptic potentials reflecting the neural activity that is temporally associated to a given stimulus or event (Blackwood & Muir, 1990; Kubicki & Shenton, 2020; Luck, 2014). To accurately measure the neural activity in response to a stimulus, it is necessary to precisely track the neurophysiological response with the exact moment in which the stimulus is presented. Thus, a large number of EEG segments that correspond to the response to the stimulus must be analyzed in order to eliminate unrelated background activity. The event of interest is often so small (measured in just a few microvolts) that it can be difficult to distinguish from other signals.

ERPs have been used to explore brain functioning, as they reflect time-locked neuronal activation associated with several cognitive processes such as sensory processing, attention, memory, language, and emotion, as well as to track changes in cognitive functioning over the course of the illness (Kubicki & Shenton, 2020). ERPs methodology, before the development of functional magnetic resonance imaging, has been used to investigate the relationship between disrupted cognition and abnormal brain functioning in different clinical conditions, such as schizophrenia (Bressler & Ding, 2006). In addition, ERP studies, providing insights into the underlying cognitive mechanisms of schizophrenia, have also supported a number of theories about the nature of this disorder, ranging from schizophrenia as a result of pre-attentive and attentional impairments, to the conceptualization of a disorder of higher-order cognitive processing, such as language, to the idea of schizophrenia as the result of abnormal brain connectivity. In this framework, ERPs have been useful to investigate mental chronometry of language processing at large (Canal & Bambini, 2021). Relationship between several ERPs and pragmatic abilities have been demonstrated, however the paucity of results did not allow for stronger conclusions.

Among different ERPs evaluated in schizophrenia, Mismatch negativity (MMN) is one of the most frequently explored and worthy of consideration. MMN is negative potential passively evoked when a series of repetitive, identical stimuli is broken up by a deviant stimulus (Salisbury et al., 2017; Salisbury & Mccathern, 2016). The MMN peak usually appears around 170-250 milliseconds after the stimulus presentation. While many MMN studies in schizophrenia have focused on the auditory presentation of the stimulus, other modalities (e.g., visual modality) can also be used. In MMN experiments, individuals are usually asked to listen to tones without actively paying attention to them, when, randomly, a deviant stimulus is occasionally presented.

A large body of studies have consistently demonstrated that individuals with schizophrenia tend to have a decreased MMN compared to controls (Kim et al., 2019;

Lee & Kim, 2022; Shelley et al., 1991). These findings are consistent throughout various stages of the disease, as MMN reduction has been found in both first episode (Brockhaus-Dumke et al., 2005; Hay et al., 2015; Hermens et al., 2010) and chronic schizophrenia patients (Hamilton et al., 2018; Kiang et al., 2009). It has been suggested that the MMN is sensitive to sensory context and the related expectations (Schmidt et al., 2012). As a result, the difficulties in processing deviant stimuli in schizophrenia, which leads to a reduced MMN, have been connected to impaired detection of prediction errors. It is hypothesized that MMN alteration can be linked to structural abnormalities (e.g., cortical thinning in the frontal and temporal regions) (Kim et al., 2019) and neurochemical alteration (e.g., abnormalities of glutamatergic and GABA-ergic systems) (Javitt et al., 2018).

MMN is one of the neurophysiological indicators that researchers are considering as potential endophenotype in the illness (Light & Swerdlow, 2015; Michie et al., 2016). As a matter of fact, a decrease in MMN amplitude was found in the non-affected relatives of patients with schizophrenia (Earls et al., 2016; Erickson et al., 2016), and MMN has been suggested to be a predictor of conversion to psychosis (Erickson et al., 2016) as its alteration has been detected also in people at high-risk for developing psychosis (Lepock et al., 2018).

Several studies have revealed a relationship between MMN and the severity of symptoms in schizophrenia, particularly auditory hallucinations and negative symptoms (Kärgel et al., 2014; Perrin et al., 2018). It has also been consistently demonstrated that MMN correlates with various cognitive processes (Friedman et al., 2012; Rissling et al., 2014). It is thought that sensory abnormalities related to MMN may contribute to higher-order cognitive abnormalities in schizophrenia, as MMN amplitude was linked to executive functioning (Toyomaki et al., 2008), verbal executive function and verbal IQ (Brockhaus-Dumke et al., 2005), verbal memory (Kärgel et al., 2014; Kawakubo et al., 2006), and overall memory (Minami & Kirino, 2005). The relationship between disrupted cognition and MMN abnormalities in schizophrenia seem to have an impact also on daily functioning. Poor psychosocial functioning has consistently been found to be associated with lower MMN amplitude in schizophrenia (Kawakubo et al., 2007; Kawakubo et al., 2006; Lee et al., 2014; Rissling et al., 2014; Wynn et al., 2010). A reduction in MMN amplitude has also been linked to difficulties in independent living, as well as social and occupational functioning (Wynn et al., 2010).

Nowadays, only a limited number of studies have used MMN as a neurophysiological measure to study abnormal language processing. MMN has been proposed as a tool to assess auditory sensory memory, which is essential for language acquisition and linguistic and auditory memory processing. Abnormalities in sensory memory trace and diminished MMN have been observed in various patient groups with language impairments, as well as in Alzheimer's disease and schizophrenia (Näätänen et al., 2012). As for schizophrenia, Yamasue and co-authors (2004) found that a reduced phonemic MMF (i.e., Mismatch field; the magnetic counterpart of auditory MMN) in the left hemisphere was associated with the volume of the left planum temporale, which is a brain structure involved in the polymodal association cortical network in which has been found a loss of grey matter volume in schizophrenia (Hirano et al., 2020). These findings suggest that abnormalities in language processing in schizophrenia patients may also occur at lower levels of auditory processing, such as phoneme processing, and may be related to structural brain abnormalities.

As for pragmatics, scattered studies have examined the interplay with MMN. Zhao and colleagues (Zhao et al., 2018) suggested that the brain is able to automatically process pragmatic information in the early stages of language comprehension, with a greater MMN amplitude evoked in response to a pragmatic violation compared to a literal sentence. It is possible that MMN amplitude may be related to the processing of figurative language, as both involve the processing of unexpected stimuli. In schizophrenia, the available studies suggest an association between MMN amplitude and both figurative language interpretation and abstract thinking. For example, a correlation has been found between deficits in proverb interpretation and decreased MMN amplitude (Kiang et al., 2007). It has been proposed that impairment in auditory sensory memory encoding may reduce the capacity for short-term storage of verbal information, leading to difficulties in proverb interpretation and linguistic processing. Additionally, decreased MMN amplitude and proverb interpretation difficulties in schizophrenia have been both linked to generalized frontal cortical abnormalities (Baldeweg et al., 2002; Kiang et al., 2007; Näätänen, 2003; Sato et al., 2003).

These studies on MMN in schizophrenia highlight its potential use as neurophysiological correlate strictly related to the disorder, also in the light of the well-documented relationship with cognition and psychopathology. However, the relationship with language, and in particular pragmatics, represent a field that needs further investigations.

### *1.4.2 Alpha activity*

The study of rhythmic brain dynamics, known as oscillatory activity, has gained significant attention in recent years within the field of neuroscience. Advancements in measuring oscillatory activity have seen a rapid growth in clinical applications since the 90s. Neural oscillations are characterized by multiple, rhythmic patterns appearing as distinct peaks in frequency, as observed in EEG recordings. These oscillations are generally grouped into different frequency bands, including delta (1–3 Hz), theta (4–7 Hz), alpha (8–14 Hz), beta (14–30 Hz), and gamma (>30 Hz) (He, 2014). Brain oscillations have a crucial role in neural communication, integration, and computation, as well as in supporting various brain functions such as perception, attention, and cognition (Gupta & Chen, 2016; Robert & Sirel, 2016). This makes them an exceptional tool for understanding healthy and altered brain functioning. Recently, research has focused on uncovering the role of coherence and synchronization of oscillations in assessing functional connections between different neural populations.

Alpha activity is the most common type of spontaneous oscillation that can be found in an adult human's EEG. Typically, alpha is defined by its peak, or central frequency, within the standard alpha frequency range, which is around 7-14 Hz (Yordanova et al., 2013) (see Figure 1). Alpha power can be is higher when a person's eyes are closed, but it can be also appreciated during open eyes paradigms (Kwon et al., 1999), and originates from the parietal-occipital regions of the brain. Alpha activity is often used as a measure of cortical arousal and synchronization between different areas of the brain (Nunez & Srinivasan, 2006), and it has been considered a useful method for evaluating the overall integrity of brain networks. As a matter of fact, alpha synchronization is associated with a state of healthy wakefulness and the ability to process salient information. Alpha activity play a significant role in cognitive functions, such as memory and attention, as well as language and semantic memory (Hanslmayr et al., 2013; Klimesch, 1997). Alteration in alpha activity have been linked to various illnesses, such as bipolar disorder and schizophrenia.

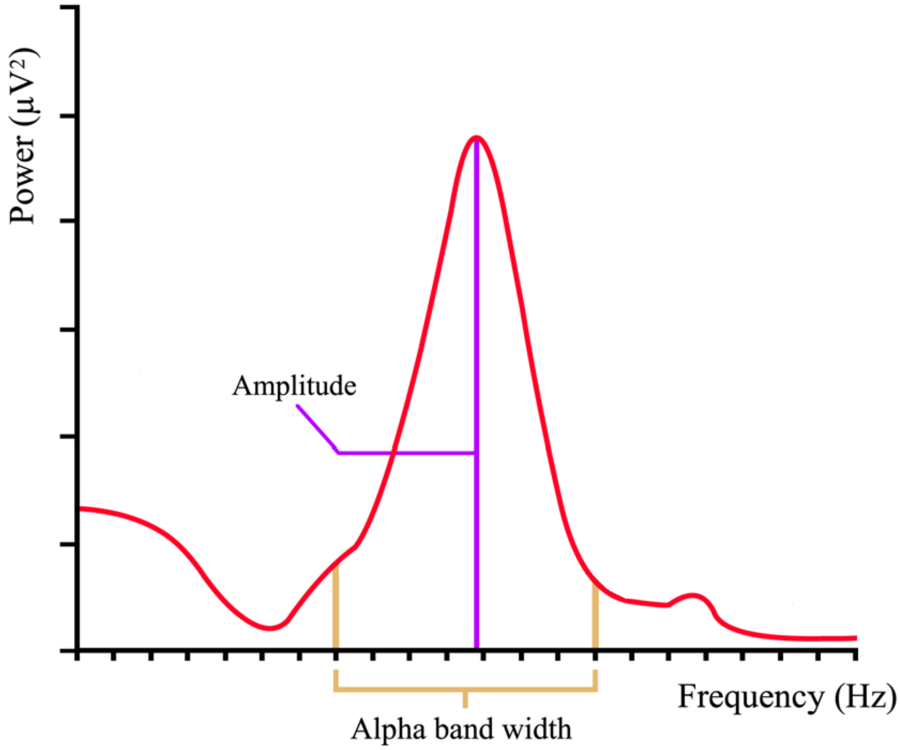


*Figure 1. EEG spectral power of alpha wave*

As early as 1936, EEG researcher Lemere noted that the lack of emotion and apathy characterizing people with schizophrenia was linked to a weak or missing alpha rhythm. Early EEG studies on schizophrenia revealed lower alpha activity, compared to healthy subjects (Lemere, 1936). Research in schizophrenia have repeatedly found a decrease in alpha activity during resting-state recordings (Newson & Thiagarajan, 2019; Vignapiano et al., 2019) as well as during sensory stimulation and cognitive tasks (Başar & Güntekin, 2013). Also, a reduced alpha activity was found in both closed and open eye conditions (Newson & Thiagarajan, 2019). Moreover, people with schizophrenia showed altered alpha activity compared to healthy control subjects, in both occipital and frontal areas (Goldstein et al., 2015). It has been hypothesized that the increased desynchronization of alpha activity in psychosis may be related to altered cortical arousal and promptness to process internal and external information (Marton et al., 2021).

Multiple studies have shown that a reduced alpha activity can be found not only in individuals with chronic schizophrenia, but also in those who are at their first psychotic episode, in prodromal schizophrenia, as well as in non-affected relatives (Catalan et al., 2021; Glenthøj et al., 2020; Mucci et al., 2018; Zhang et al., 2019). These alterations can also be found during remission, and studies suggested that higher alpha activity may be a predictor of better treatment outcome (Boutros et al., 2014; Javitt et al., 2008; Luck et al., 2011). However, there is ongoing debate about whether the peak of alpha activity is at a lower frequency in people with schizophrenia (Harris et al., 2006) or if the alteration in alpha activity indicates a reduced capacity to produce oscillations in this frequency range (Danos et al., 2001; Mathiak et al., 2011).

Studies have found an association between alpha and cognitive abilities, suggesting that a decrease in alpha peak frequency in individuals with schizophrenia may indicate cognitive decline (Karson et al., 1990). However, studies investigating the association between resting-state alpha activity and cognitive domains lead to contrasting results. On the one hand, it has been suggested an association between decreased alpha activity and worse performance at tasks measuring working, visual, and verbal memory (Cavanagh & Frank, 2014; Güntekin & Başar, 2016), as well as emotion recognition (Gica et al., 2019). On the other, there are studies reporting no association between altered alpha and neither cognitive nor sociocognitive abilities (Koshiyama et al., 2021; Vignapiano et al., 2019; Vohs et al., 2016). Interestingly, a study by Castelluccio and co-authors (2020) showed a positive correlation between baseline individual alpha peak frequency and improvements in cognition after cognitive remediation. Also, as for evoked alpha activity, studies reported an association with speed of processing (Prieto et al., 2021) and working memory (Johannesen et al., 2016), which however was not found with memory (Billeke et al., 2015; Qu et al., 2020) and social cognition skills (Martínez et al., 2019).

Concerning psychopathology, studies showed an association between alpha activity and the severity of symptomatology, especially negative symptoms (Scott et al., 2000), which was found in particular in the anterior brain regions (Knyazeva et al., 2008). Moreover, altered alpha activity was found to be related to negative symptoms especially in the right hemisphere (Green & Walker, 1985; McCarley et al., 1989; Merrin & Floyd, 1992), as well as to positive symptoms in left hemisphere (Green & Walker, 1985; McCarley et al., 1989).

As for language, a decrease of alpha oscillations has been observed across several domains, such as the processing of syntactic and semantic violations, irony, and it was related to increased cognitive demands (Prystauka & Lewis, 2019). Furthermore, the storage of syntactic phrases in verbal working memory for the creation of dependencies with other phrases resulted in an increase in alpha power (Bonhage et al., 2017; Canal & Bambini, 2021; Weiss et al., 2005). Studies on young children confirmed the association between alpha band power at rest and language abilities (Kwok et al., 2019). Additionally, Wang and colleagues (2022) confirmed the association between alpha and language processing, highlighting that the decrease of alpha power, indicating an increase in cognitive load, was more evident during language comprehension task instead of a resting state paradigm. This effect was localized in both left and right temporal-parietal regions. Taken together, these studies point out the interplay between language and alpha activity. Although never investigated before, alpha activity might be related to pragmatic language disorder in schizophrenia.

An intriguing aspect of the brain that has been suggested as a potential marker of schizophrenia is hemisphere asymmetry. Human hemispheres have different structures and functions, and various cognitive abilities are lateralized. Typically, the left hemisphere is in charge of logical and linguistic processing in healthy individuals. However, research has shown that people with schizophrenia tend to have reduced dominance of the left hemisphere (Ribolsi et al., 2009). Additionally, studies suggested that the right hemisphere integrity seems to be significant for pragmatic communication (Champagne-Lavau & Joanette, 2009), however contrasting results suggest the need for further research on this topic. Mitchell and Crow (2005) suggested that a reduction of the right-hemisphere lateralization may be a key factor in the communicative difficulties seen in schizophrenia, as language processes requires a full access to the right hemisphere. In line with these results, Champagne-Lavau and co-authors (2007) suggested that psychosis is linked to a breakdown in the separation of functions between the right and left hemispheres of the brain. Furthermore, studies have found that structural reductions in several white matter tracts, such as the corpus callosum, are prevalent in schizophrenia and likely play a significant role in abnormal intra-hemispheric connectivity and the transfer of information between the two hemispheres (Olejarczyk & Jernajczyk, 2017). The cause of reduced left-hemisphere dominance is yet to be fully understood, but it may be linked to disturbances in neuronal development during early stages (Moore & Haynes, 1980).

Recently, scientists are exploring the use of alpha-asymmetry as a potential biomarker for psychiatric conditions such as depression and schizophrenia (Jang et al., 2020; Kaiser et al., 2018; van der Vinne et al., 2017). Studies showed changes in hemispheric asymmetry related to alpha activity in schizophrenia (Olejarczyk & Jernajczyk, 2017). An increase in cortical arousal, which is shown by a decrease in alpha amplitude, is seen during verbal and cognitive tasks (Başar & Güntekin, 2012). This increase in arousal and decrease in alpha amplitude displays an asymmetrical pattern (Merrin & Floyd, 1997), being most prominent in the left hemisphere in patients with severe schizophrenia, due to the left hemisphere being more actively involved in task processing. Additionally, it has been found an inverse relationship between negative symptoms and alpha power (Ribolsi et al., 2009).

Cortical arousal, reflected by a reduction in alpha amplitude, is induced during verbal task activity, and cognitive activities (Başar & Güntekin, 2012). This arousal, with the consequent reduction in alpha amplitude, demonstrated an asymmetrical pattern, being predominantly located in the left hemisphere in more seriously ill patients with schizophrenia, as a result of a more pronounced involvement of the left hemisphere in task processing (Merrin & Floyd, 1997). Moreover, an inverse correlation seems to subsist between negative symptoms and alpha power in the left hemisphere (Green & Walker, 1985; McCarley et al., 1989; Merrin & Floyd, 1992).

The exploration of alpha activity in schizophrenia, also taking into account hemispheric differences, seems to have potential implications, as it can be used as biomarker for schizophrenia, linked to cognitive substrates. Moreover, the exploration of the interplay between altered alpha activity and pragmatic impairment need to be addressed in people with schizophrenia.

### *1.4.2 Aperiodic activity*

The majority of the electrical activity recorded by EEG is not periodic, as brain oscillations, and lacks a predominant temporal scale. This type of brain activity is known as aperiodic (or arrhythmic) activity (He, 2014). Through the years, the large part of research on EEG has focused on specific frequency bands in both healthy and clinical populations, however, less attention has been given to studying the aperiodic activity.

Aperiodic activity is a scale-free activity that shows a decrease in power as frequencies increase, following a 1/f distribution (Freeman & Zhai, 2008; He, 2014). Aperiodic activity is represented in terms of slope, characterized by the exponential decrease of power across increasing frequencies, and offset of the broadband power of the signal (see Figure 2). Oscillatory activity, as alpha activity, is characterized by fluctuations appearing as "bumps" at specific frequencies where exceeds that of the aperiodic signal (Freeman & Zhai, 2008; He, 2014).

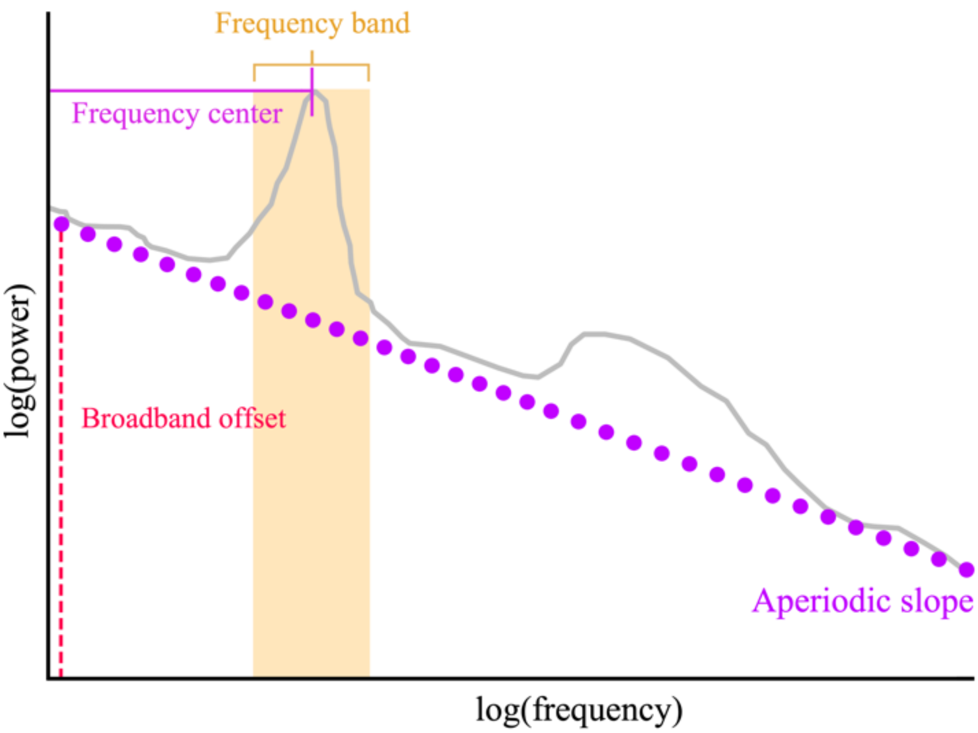


*Figure 2. Periodic and aperiodic spectral features of EEG signal*

*Note. The yellow stripe represents the peak in one of the canonical frequency bands (e.g., alpha activity); the red dotted line indicates the broadband offset, while the purple dotted line depicts the exponent, which is the steepness of the slope characterizing the aperiodic component of the power spectra.*

Aperiodic activity can be thus characterized by two parameters:

1. **Offset:** a parameter that reflects the uniform shift of power across frequencies (see Figure 3, Panel A). The offset valued indicates the shift on vertical axis. An increased offset value results in a higher slope, while a decreased offset generates a lower slope.
2. **Exponent:** a parameter that delineates the steepness of the aperiodic slope (see Figure 3, Panel B). The value of exponent influences the steepness of the slope: a lower exponent determines a flatter slope, while a higher exponent results in a steeper one.

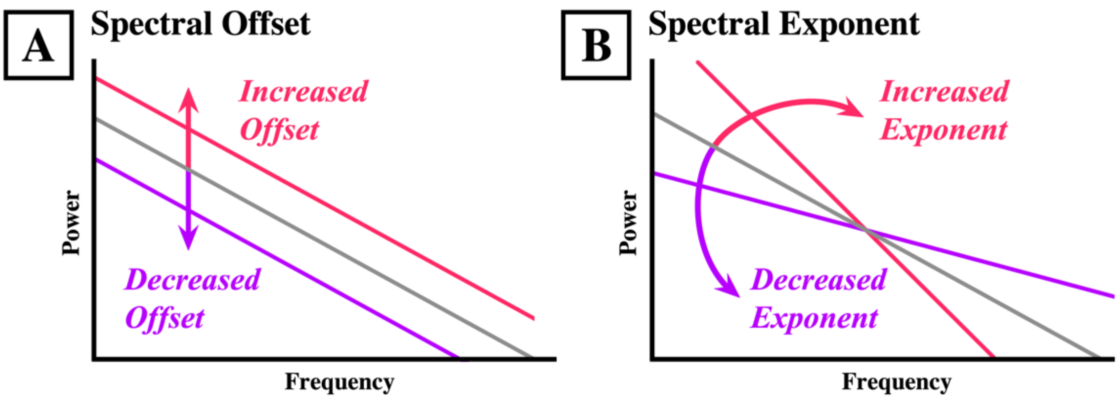


*Figure 3. Effects of the offset and the exponent values on the aperiodic slope*

*Note. Panel A. The effects of the offset value in the aperiodic slope. An increased offset results in a higher slope, while a decreased offset generates a lower slop; Panel 3B. The impact of the exponent on the aperiodic slope. While an increased exponent produces a steeper slope, a decreased one generates a flatter slope.*

To determine the slope, several methodologies have been used. One approach is to use linear regression to fit a straight line to the Power Spectral Density (PSD, displays how the signal power varies in accordance with frequency), which can be seen as an approximation of the underlying aperiodic slope (Gao et al., 2017); however, this method does not account for the presence of both an aperiodic and periodic components in the PSD. This approach can be unreliable, as larger periodic peaks can skew the linear regression fit. A different methodology, the "Fitting Oscillations and One Over F" algorithm (FOOOF) (Donoghue et al., 2020; Haller et al., 2018), which was developed to address the limitations of the first approach. The FOOOF algorithm enables the separation of the periodic and aperiodic components, and provides a new, more direct and non-invasive way of extracting the aperiodic slope of the PSD of EEG data (Haller et al., 2018; Molina et al., 2020). The algorithm focuses on modelling the periodic components by repeatedly applying Gaussian fits to all periodic components, resulting in a model of the periodic feature. This model is then subtracted from the spectrum to obtain an ideally pure aperiodic component (Gerster et al., 2022).

Currently, a growing body of research is focusing on excitation and inhibition (E/I) balance, as its alteration, well known in schizophrenia and other psychiatric conditions, is thought to be related to cognition disruption and perceptual symptoms. Excitability reflects the readiness of individual neurons, or larger neural networks, to fire and can be determined by the level of response (Ly et al., 2016). E/I balance arises from the relationship between (excitatory) glutamatergic signalling and (inhibitory) GABA-ergic input (Xue et al., 2014). E/I balance plays a crucial role in neural networks functioning, allowing for optimal excitability through a steady level of spontaneous background activity (Alvarez & Destexhe, 2004). The E/I equilibrium is vital for efficient neural coding and the optimal transmission of information (Zhou & Yu, 2018). Besides the promising results on the study of E/I imbalance in clinical conditions, to date this field of research is in its early stages as the traditional measures require invasive methodologies (e.g., single-unit or voltage-clamp recordings) making them difficult to apply to human studies (Molina et al., 2020). Recent findings suggest that non-invasive methods, such as EEG, may be used to study the E/I balance, and aperiodic activity has emerged as a candidate biomarker. As a matter of fact, aperiodic activity seems to indicate the level of synchronization within neural networks, as well as the spatial and temporal characteristics of excitatory and inhibitory inputs onto groups of neurons. Thus, the evaluation of aperiodic activity can be considered a proxy measure for E/I balance (or imbalance).

E/I balance may change as a byproduct of several factors and across numerous clinical conditions. Hyperexcitability is characterized by an excitation exceed over inhibition (i.e., < GABA signaling and/or > glutamate signaling), which results in a weaker signal-to-noise ratio and leads to more impromptu brain activity (Zhou & Yu, 2018). As for aperiodic activity, hyperexcitability results in a flatter slope (Molina et al., 2020). Conversely, hypoexcitability, which is a condition where the E/I equilibrium is skewed towards inhibition (i.e., > GABA signaling and/or < Glutamate signaling), resulting in diminished signaling, making the neural network unable to function at their best (Shew et al., 2011). As for aperiodic activity, hypoexcitability results in a steeper slope (Molina et al., 2020).

Research has shown that age has a noticeable impact on aperiodic activity, with older individuals typically displaying flatter slopes (Dave et al., 2018). Voytek and colleagues (2015) found a positive correlation between age and aperiodic activity, which seems to play also a role in the decline of visual working memory performance in older individuals (Dave et al., 2018). Age-related changes in aperiodic activity may impact various aspects of cognition, such as metacognitive awareness, memory retrieval speed, cognitive load, and recall accuracy throughout adulthood (Thuwal et al., 2021). Also, recently there has been growing interest in exploring E/I imbalance, as it considered as a marker as well as a candidate underlying mechanism for different clinical conditions. Thus, as previously reported, the exploration of aperiodic activity seems to be promising as it could be a proxy measure for E/I balance. Studies on Attention Deficit Hyperactivity disorder (ADHD) showed a flatter aperiodic slope, which was normalized after the use of medication that increases dopamine and norepinephrine, resulting in a normalization of E/I balance (Pertermann et al., 2019). In contrast, other studies have found that children with ADHD have steeper slopes (Robertson et al., 2019), leading to hypothesize a range of optimal spectral slopes for different developmental stages, and that slopes alteration (i.e., “too flat” or “too steep”) may result in cognitive difficulties. Additionally, it was suggested that individuals who were tested in situations requiring high cognitive control may have developed a compensatory mechanism involving increased GABAergic activity. Moreover, in people with depression, aperiodic slope steepness was correlated with the severity of depressive symptoms and the course of the illness, highlighting the potential utility of evaluating aperiodic slope in assessing the long-term effectiveness of antidepressants combined with deep brain stimulation (Veerakumar et al., 2019).

As previously stated, very scarce literature about aperiodic activity is available as of today. Particularly, research on aperiodic activity in schizophrenia, as a proxy measure for E/I imbalance, is still an uncharted yet promising field. Molina et al (2020) employed the FOOOF algorithm on EEG recordings obtained during early auditory information processing evaluations in both heathy controls and patients with schizophrenia, to investigate E/I balance. Results revealed that patients had a steeper aperiodic slope, which suggested an E/I imbalance, and that a single 20-mg dose of memantine (i.e., a NMDA receptor antagonist drug) can temporarily normalize aperiodic slope and thus restore E/I balance. This study highlighted that the aperiodic slope indexes can be potential biomarkers for cortical E/I balance, easier to evaluate and less invasive than other methodologies currently used. Furthermore, Racz and co-authors (2021) observed altered aperiodic activity (especially in the exponent index) in a small group of adult patients with schizophrenia when compared to healthy individuals, suggesting that the electrophysiological alteration in schizophrenia affect not only oscillatory components, bit also aperiodic ones.

As pragmatics, to date no studies investigated the possible relationship between aperiodic activity and pragmatics in healthy population, nor in schizophrenia. Interestingly, a study by Dave and colleagues (2018) evaluated aperiodic slope across two different language tasks (i.e., a comprehension task where participants had to read single sentences, and a prediction task, where participants had to predict the last word of a two-sentence narrative). Results showed that aperiodic activity influences ERP measures (e.g., N400) related to language processing and in particular accurate lexical prediction. Researchers hypothesized that neural network synchrony plays a crucial role in determining the accuracy of predictions made during the process of anticipating events.

In line with these results, recent research in cognitive neuroscience suggested that the brain utilizes top-down mechanisms to process incoming sensory information and generate predictions for future events based on past experiences (Bastos et al., 2012). Accordingly, the brain is considered a Bayesian "prediction machine" that uses statistical patterns in the environment to make predictions (Bastos et al., 2012; Clark, 2013; Friston, 2010). It is proposed that anticipatory mechanisms are embedded in the temporal relationships between different neural populations and that top-down information can influence the size, strength, and cohesive firing of neural assemblies activated for expected input (Engel et al., 2001). Studies have found that synchronized brain activity is associated with predictable stimuli (Arnal et al., 2011; Doelling et al., 2014; Engel et al., 2001; Samaha et al., 2015) and individuals with more synchronized neuronal networks are believed to have better prediction abilities (Dave et al., 2018).

Language processing seems to be related to neuronal spiking synchrony and to aperiodic activity. Since aperiodic activity is suggested to indicate the level of synchronization within neural networks, and based on these results showing the relationship with the accuracy of lexical prediction in a language task, we may hypothesize that also pragmatics may be relates to aperiodic activity as well as neural synchrony. Indeed, the elaboration of pragmatic language requires a process of prediction of the expected words within an utterance; when an unexpected stimulus (e.g., a metaphor) occurs, language interpretation requires a consequent re-elaboration based on the integration of contextual information as well as an inferring process. We may hypothesize that people with schizophrenia, which show an abnormal neural synchrony, can be also characterized by altered aperiodic activity (as suggested by the scattered studies in the literature), which may be in turn related to pragmatic abilities. The exploration of the interplay between aperiodic activity and pragmatics may support the exploration of neural correlates of the disorder, with clinical and research implications, stemming from the use of EEG indexes as refined predictors of diagnosis and treatment outcome, to the identification of novel targets for treatment.

# 2. AIM OF THE STUDY

Pragmatics allows speakers to use and interpret language in context and to engage in successful communication, allowing people to reach a successful and rich life. The disruption of pragmatic abilities is widespread across numerous clinical conditions, and especially in schizophrenia, affecting more than 70% of people. Pragmatic impairment, given its social features, causes reduced social interactions and lower quality of life. Yet it is seldom considered in assessment and the related neurophysiological correlates are still understudied. Our research group has previously published studies showing not only the significant impact of pragmatics on different facets of daily functioning in schizophrenia (Agostoni et al., 2021), but also the malleability of pragmatics, since it can be restored by a rehabilitative training, with consequent positive effects on functional outcome (Bambini et al., 2022). Based on this background, this project objective is two-fold. First, we tested a brief assessment of pragmatics in patients with schizophrenia, which may be easily implemented in NHS services as assessment tool and treatment outcome measure. In order to reach this goal, a brief version of the APACS test was developed in collaboration with IUSS Pavia, and psychometric properties and normative data were collected and analysed within a partnership with IUSS Pavia and IRCCS San Camillo. Second, we characterized the EEG-base neural correlates of pragmatic language disorder, with possible diagnostic and prognostic value. Specific aims were:

1) AIM 1: to compare performance in APACS Brief between patients with schizophrenia and healthy controls. To confirm the correlation between APACS and APACS Brief, as well as between APACS Brief and clinical, cognitive and functional assessment with tests normally used in clinical routine.

2) AIM 2: to analyse the relationship between pragmatics and MMN, alpha and aperiodic activity. Correlations with clinical and cognitive data were also explored.

We hypothesized that pragmatic language disorder can be captured with a rapid and easy tool, useful for different pathologies, and that it is associated with specific electrophysiological correlates that could predict treatment outcome and guide new interventions.

# 3. RESULTS

## 3.1 Sample

The sample was composed by 56 patients with schizophrenia (M:F = 49:7) and 56 healthy controls (M:F = 21:35). Table 1 shows the demographic and clinical characteristics of the sample. ANOVAs showed no significant differences between patients and controls concerning age (F = 2.02, p = .15) and education (F = 2.91, p = .09).

| | Patients with Schizophrenia (N = 56) | Healthy Controls (N = 56) |
|---|---|---|
| Age | 38.93 (± 12.90) | 43.20 (± 18.37) |
| Education (years) | 11.98 (± 2.74) | 13.02 (± 3.61) |
| Onset | 21.91 (± 5.10) | --- |
| Illness duration (years) | 17.02 (± 11.71) | --- |
| Chlorpromazine equivalent dose (mg) | 390.32 (± 182.6) | --- |
| PANSS – Positive score | 16.45 (± 4.87) | --- |
| PANSS – Negative score | 21.16 (± 5.03) | --- |
| PANSS – General score | 41.94 (± 11.43) | --- |
| PANSS – Total score | 79.55 (± 17.08) | --- |

*Table 1. Demographic and clinical characteristics of the sample*

*Note. Data are reported as mean and (standard deviation)*

Pragmatic abilities, evaluated with the APACS Brief (for both patients and controls) and with the APACS (only for patients), are reported in Table 2.

| | Patients with Schizophrenia (N = 56) | Healthy Controls (N = 56) |
|---|---|---|
| APACS Brief – Interview | 0.78 (± 0.19) | 0.93 (± 0.12) |

| | | |
|---|---|---|
| APACS Brief – Narratives | 0.70 (± 0.21) | 0.79 (± 0.13) |
| APACS Brief – Figurative Language 1 | 0.88 (± 0.19) | 0.97 (± 0.08) |
| APACS Brief – Humor | 0.67 (± 0.32) | 0.88 (± 0.21) |
| APACS Brief – Figurative Language 2 | 0.29 (± 0.27) | 0.54 (± 0.30) |
| APACS Brief – Total score | 0.66 (± 0.13) | 0.82 (± 0.08) |
| APACS – Interview | 0.90 (± 0.05) | --- |
| APACS – Description | 0.95 (± 0.09) | --- |
| APACS – Narratives | 0.81 (± 0.13) | --- |
| APACS – Figurative Language 1 | 0.93 (± 0.10) | --- |
| APACS – Humor | 0.78 (± 0.27) | --- |
| APACS – Figurative Language 2 | 0.64 (± 0.15) | --- |
| APACS – Production score | 0.92 (± 0.06) | --- |
| APACS – Comprehension score | 0.79 (± 0.13) | --- |
| APACS – Total score | 0.86 (± 0.07) | --- |

*Table 2. Pragmatic abilities of the sample*

*Note. Data are reported as mean and (standard deviation)*

Cognitive abilities, evaluated with the BACS, and ToM, evaluated with the PST, in patients group are reported in Table 3.

| | Patients with Schizophrenia (N = 56) |
|---|---|
| BACS – Verbal memory score | 40.43 (± 12.97) |
| BACS – Working memory score | 17.95 (± 4.60) |
| BACS – Psychomotor speed score | 59.79 (± 17.69) |
| BACS – Fluency score | 41.27 (± 10.71) |
| BACS – Attention score | 39.89 (± 12.75) |
| BACS – Executive functions score | 16.54 (± 5.10) |
| BACS – Verbal memory score | 41.67 (± 14.44) |
| BACS – Working memory score | 17.54 (± 5.08) |

| | |
|---|---|
| BACS – Psychomotor speed score | 60.75 (± 19.16) |
| BACS – Fluency score | 48.49 (± 10.80) |
| BACS – Attention score | 40.56 (± 13.03) |
| BACS – Executive functions score | 17.28 (± 6.25) |
| PST – Questionnaire score | 18.45 (± 04.05) |
| PST – Sequencing score | 28.86 (± 6.98) |
| PST – Total score | 47.30 (± 9.92) |

*Table 3. Cognitive and ToM abilities of patients with schizophrenia*

*Note. Data are reported as mean and (standard deviation)*

## 3. 2 APACS Brief

### *3.2.1 Differences between patients and controls*

We performed several ANOVAs to compare APACS Brief between patients with schizophrenia and healthy controls. ANOVAs (see Table 4 and Figure 4) showed significant differences between patients and controls in all APACS Brief subscores as well as in APACS Brief Total score, with patients performing significantly lower than healthy subjects in all pragmatic domains.

| | ANOVA | |
|---|---|---|
| | F | *p* |
| APACS Brief – Interview | 23.33 | <.0001 |
| APACS Brief – Narratives | 7.08 | .009 |
| APACS Brief – Figurative Language 1 | 10.01 | .002 |
| APACS Brief – Humor | 13.96 | <.0001 |
| APACS Brief – Figurative Language 2 | 21.86 | <.0001 |
| APACS Brief – Total score | 55.59 | <.0001 |

*Table 4. ANOVAs between patients and controls on APACS Brief subscores and Total score*

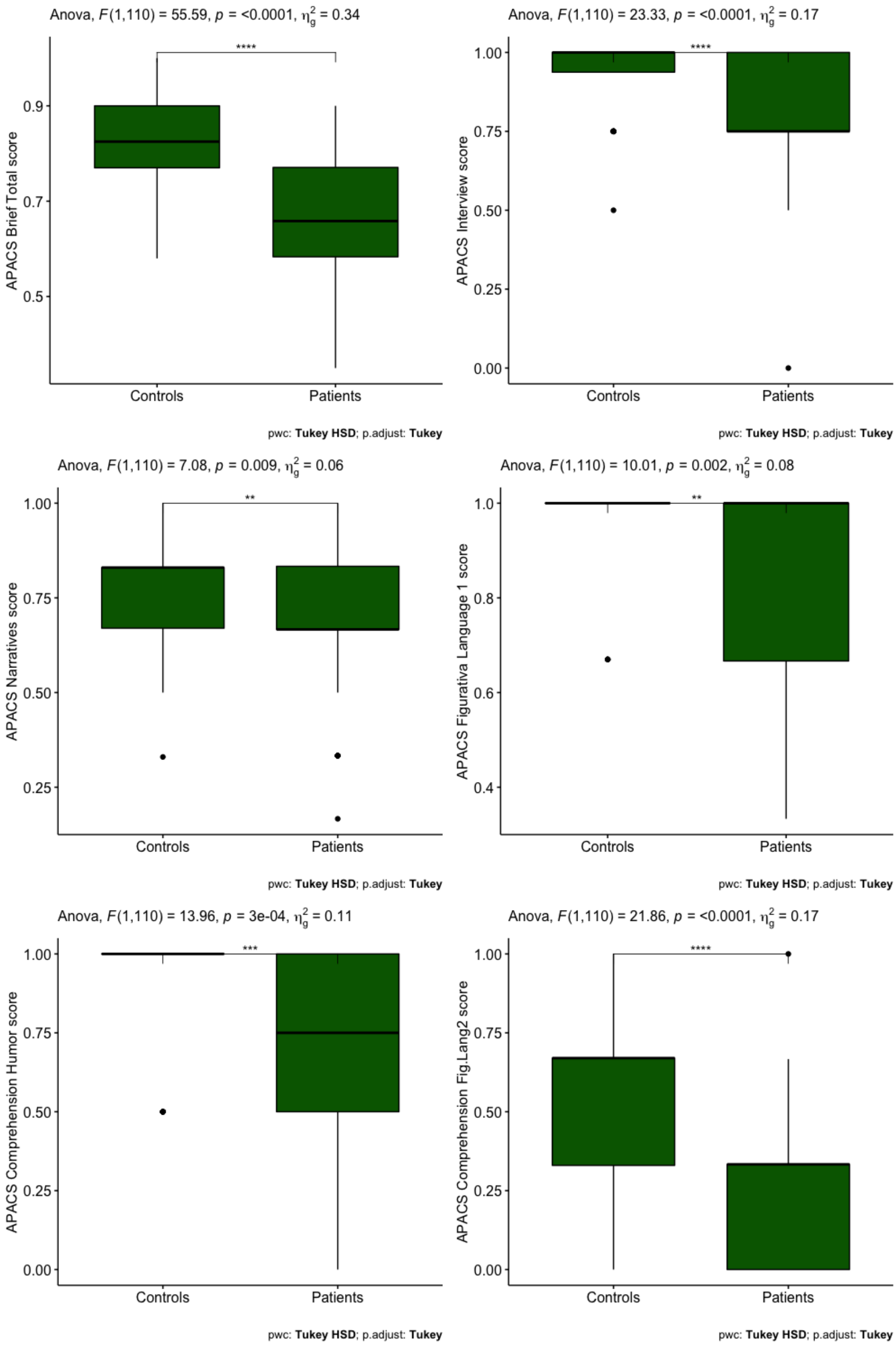


*Figure 4. Differences between patients and controls on APACS Brief subscores and Total score*

To explore the discriminatory power of APACS Brief Total score in differentiating people with schizophrenia from healthy subjects, we run a ROC curve analysis. The ROC curve (see Figure 5) showed that an APACS Brief Total score (AUC = 0.83, $p < 0001$) of 0.89 had the best discriminant validity (sensitivity = 95%, specificity = 69%) in differentiating patients with schizophrenia from healthy controls.

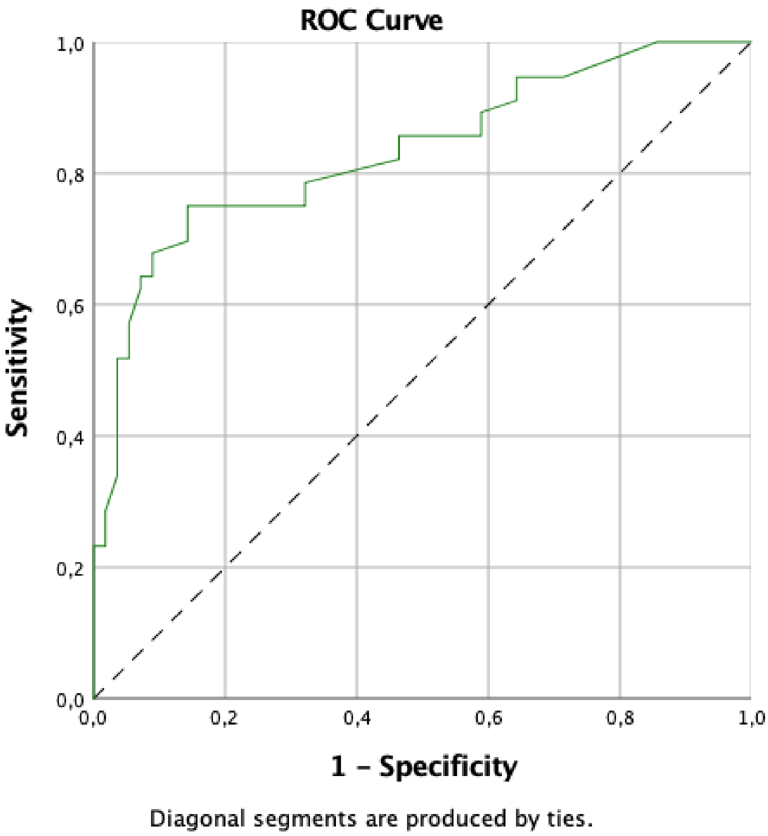


*Figure 5. ROC analysis for APACS Brief Total score in discriminating patients with schizophrenia and healthy controls*

### *3.2.2 Correlations with validated measures*

We run a Pearson correlation analysis between APACS Total score and APACS Brief Total score in the schizophrenia group, to further confirm the correlation between APACS long and short versions. Correlation showed a significant relationship between the two APACS versions (Pearson $r = 0.65$, $p < .0001$) (see Figure 6).

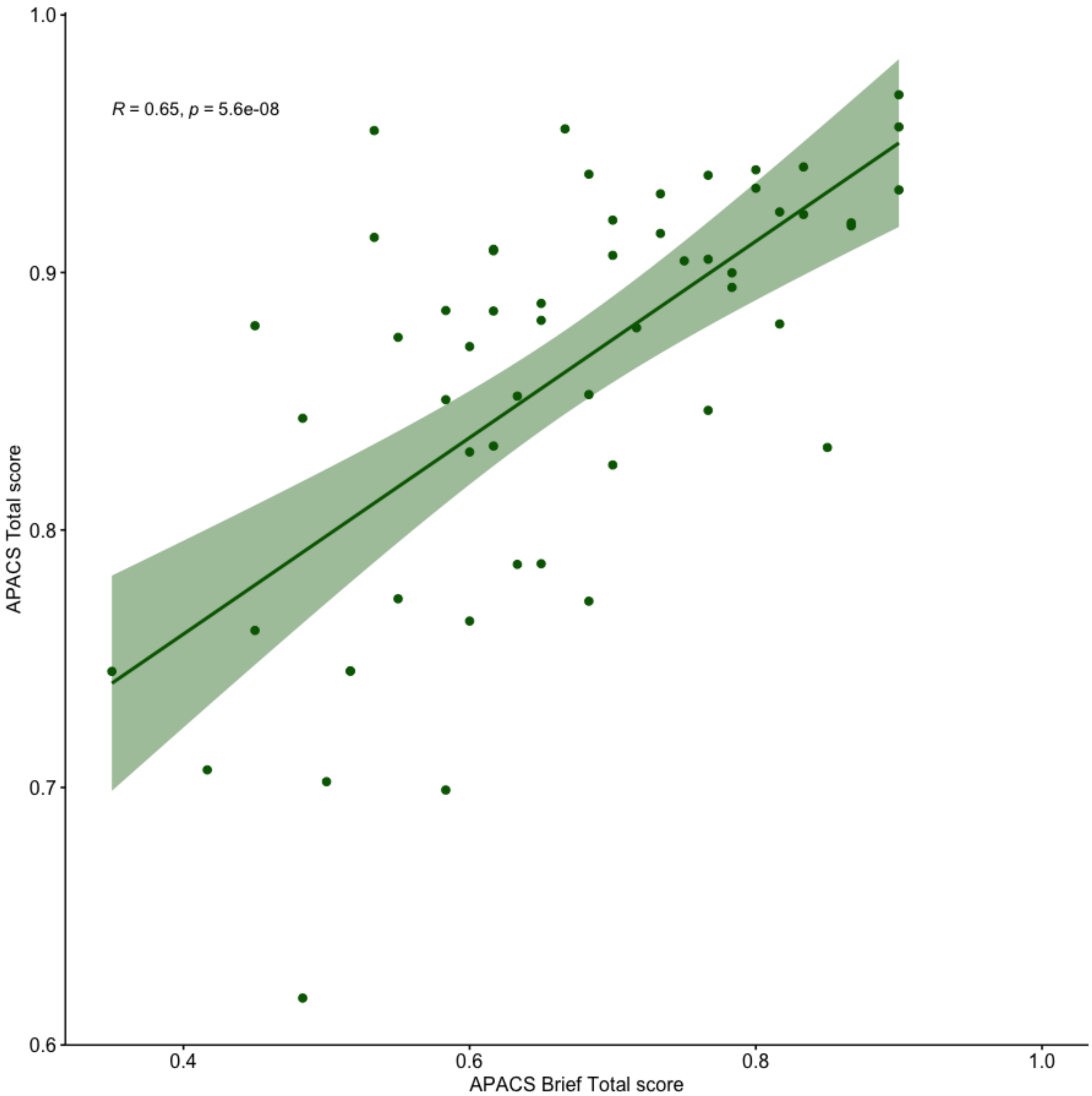


*Figure 6. Correlation between APACS Total score and APACS Brief Total score in patients with schizophrenia*

The interplay between pragmatic abilities (evaluated with the APACS Brief) and cognitive and ToM abilities (evaluated with the BACS and the PST, respectively) was evaluated with Pearson correlations. The correlation matrix (see Figure 7) showed significant correlations between: a) APACS Brief Interview score and PST Questionnaire (Pearson r = 0.27, p = .04); b) APACS Brief Narratives score and PST Questionnaire (Pearson r = 0.27, p = .04), Sequencing (Pearson r = 0.38, p = .003), and Total scores (Pearson r = 0.38, p = .004), and BACS Psychomotor speed (Pearson r = 0.26, p = .04); c) APACS Brief Figurative Language 1 score and PST Questionnaire (Pearson r = 0.53, p < .0001) and Total scores (Pearson r = 0.33, p = .01), and BACS Attention score (Pearson r = 0.32, p = .01); d) APACS Brief Humor score and PST Questionnaire (Pearson r = 0.37, p = .004), Sequencing (Pearson r = 0.28, p = .03), and Total scores (Pearson r = 0.35, p = .08); e) APACS Brief Figurative Language 2 and PST Questionnaire score (Pearson r = 0.27, p = .04); f) APACS Brief Total score and PST Questionnaire (Pearson r = 0.63, p < .0001), Sequencing (Pearson r = 0.39, p = .002), and Total scores (Pearson r = 0.53, p < .0001).

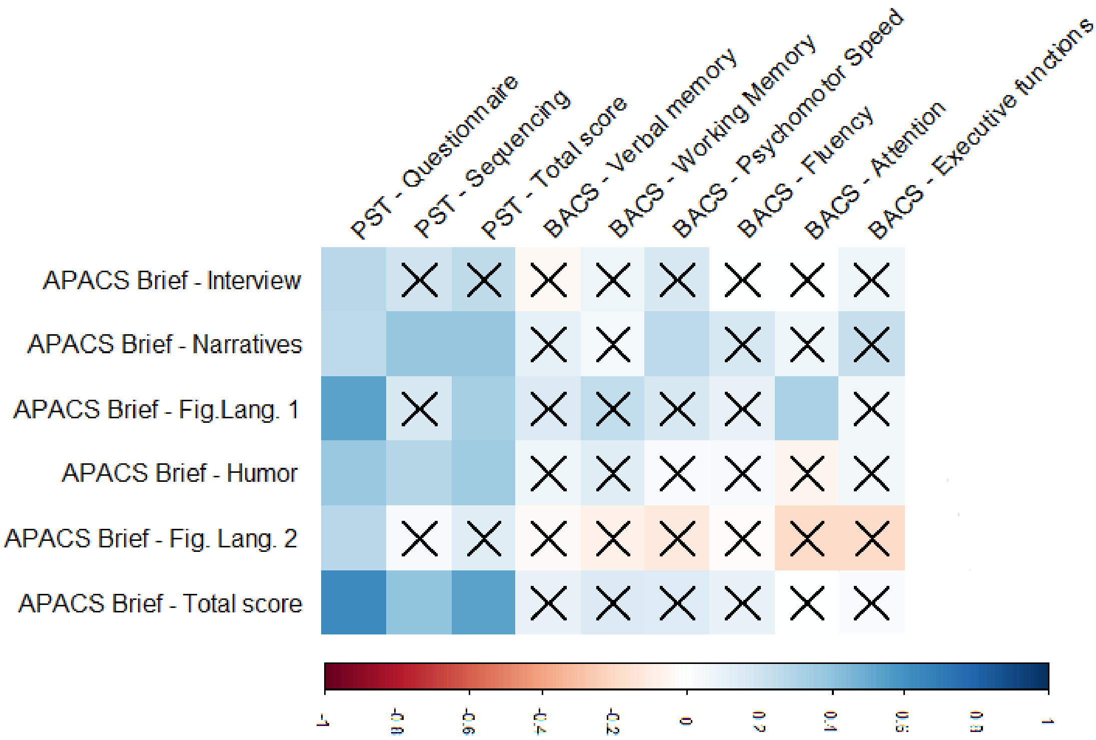


*Figure 7. Correlation matrix between pragmatic and cognitive and ToM abilities in patients with schizophrenia*

## 3.3 EEG data

During the study, six participants dropped out before EEG recording. The remaining sample of patients with schizophrenia (N = 50) underwent a protocol of 5-minutes resting states at opened eyes and a MMN paradigm task.

### *3.3.1 Mismatch negativity*

To characterize MMN, average responses for both the standard and deviant conditions were calculated, and then the average of the standard condition was subtracted from the deviant condition average. The MMN from the whole had a peak at 232 ms, with an occipital localization.

Then we performed a Pearson correlation matrix to analyze the relationship between MMN amplitude and pragmatic (APACS Brief subscores and Total score), cognitive (BACS subscores), ToM (PST subscores and Total score), and clinical (PANSS subscores and Total score) data.

Results showed significant correlations between MMN amplitude and APACS Brief Narratives (Pearson r = 0.34, p = .01), and BACS Verbal memory (Pearson r = 0.41, p = .003) and Attention (Pearson r = 0.42, p = .003) scores (see Figure 8).

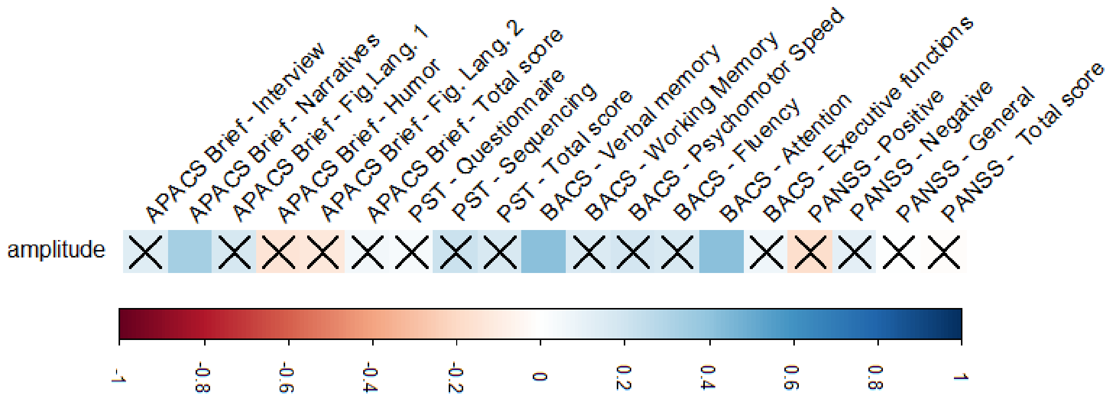


*Figure 8. Correlation matrix between MMN and pragmatic abilities, cognition, ToM, and psychopathology in the whole sample of patients with schizophrenia*

### *3.3.2 Aperiodic and alpha activity*

The Power Spectral Density (PSD), reflecting the power of the different frequencies contributing to the recorded signal, was calculated. Then, we applied the FOOOF algorithm to the PSD. The FOOOF algorithm allows for separation of the periodic and aperiodic components, thus parametrizing the 1/f slope of the PSD as well as alpha activity (Haller et al., 2018; Molina et al., 2020).

The employment of the FOOOF algorithm allowed us to characterize the aperiodic activity, with a mean offset of -12.3 (± 0.74) and a mean exponent of 0.85 (± 0.28). Figure

9 displays the mean aperiodic activity of the sample. The figure shows how signal power (y-axis) varies in accordance with frequency (x-axis) for each electrode. The exponent value influences the slopes' steepness, while the offset value determines the slope's position in the vertical plane, dictating at which point the slope meets the y-axis.

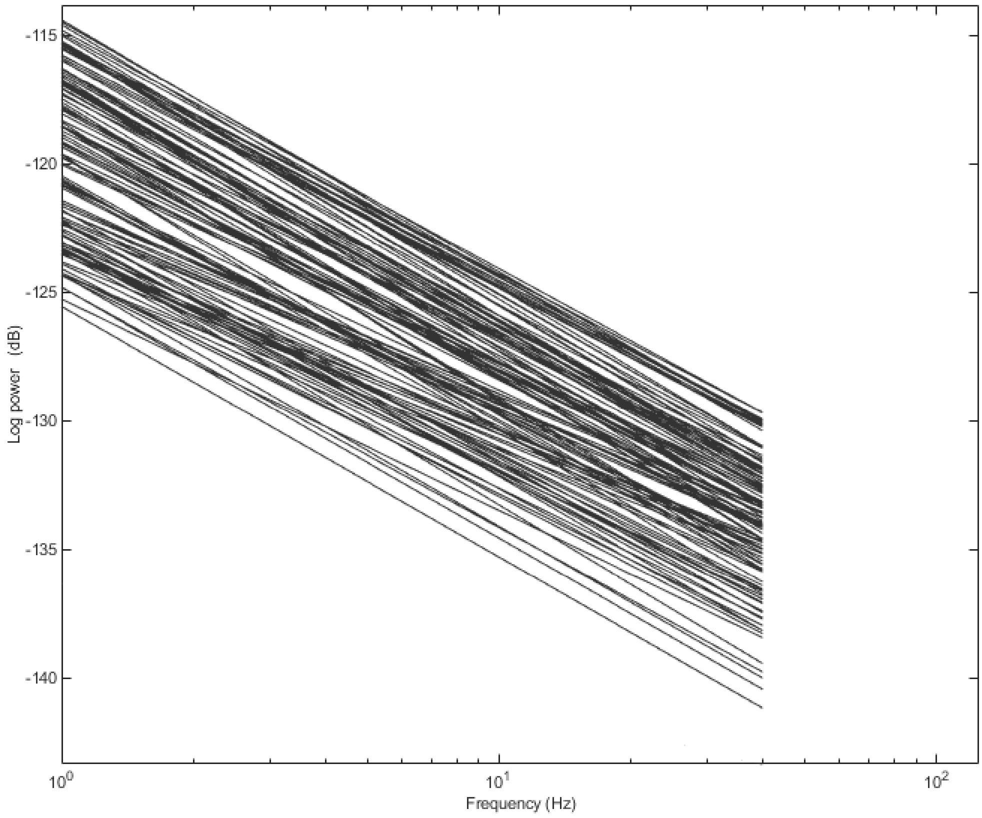


*Figure 9. Graphical representetion of the slope characterizing the Aperiodic activity of the whole sample*

Moreover, the FOOOF algorithm was able to identify the mean alpha peak for the whole sample, which can be estimated at 9.56 Hz (SD= 3.78), with a mean amplitude of 0.64 (SD= 0.18). Figure 10 depicts the mean alpha peak and its topography. As it is described by literature (Yordanova et al., 2013), alpha waves originate from the posterior region of the brain, specifically from the occipital lobe, while the alpha peak is found at 7-14 Hz.

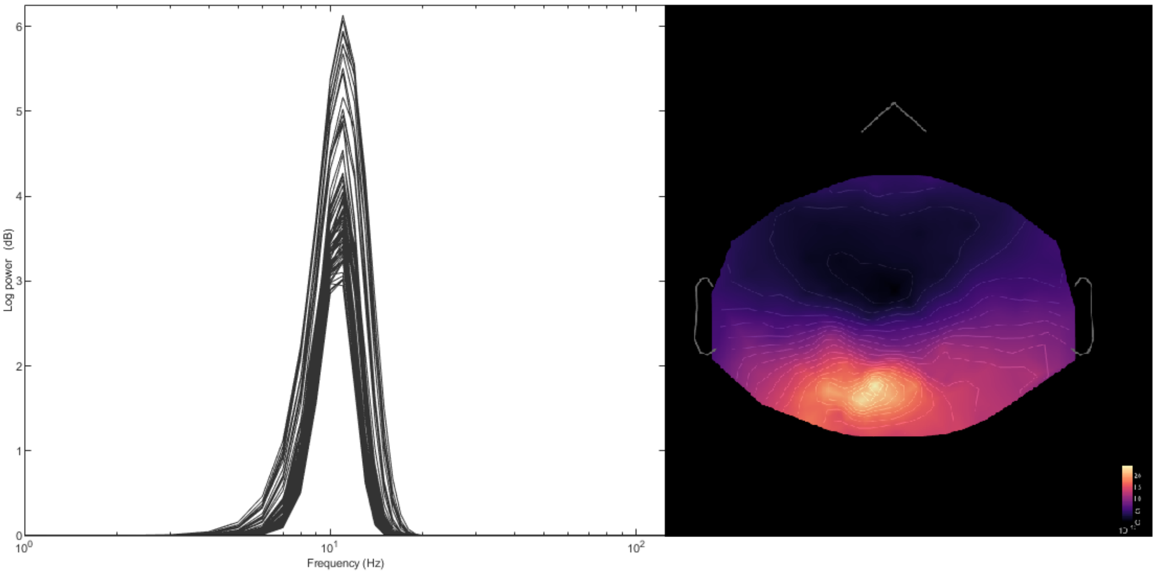


*Figure 10. Alpha activity and its topography of alpha activity across the scalp, where yellow indicates greater activity and purple represents lower activity.*

*Note. The FOOOF algorithm was applied, with a frequency range of 0.5 – 40 Hz and default peak width limits (0.5 – 12 Hz) to characterize the alpha peak, excluding other frequency band*

Then we performed several Pearson correlations, separately run for each Region of Interest (i.e., RoI-1 = all electrodes, RoI-2 = left hemisphere electrodes, and RoI-3 = right hemisphere electrodes), to analyse the relationship between aperiodic and alpha activity and pragmatic, cognitive, ToM, and clinical data. In detail, we included data related to aperiodic (offset and exponent) and alpha activities (center frequency and amplitude) and APACS Brief subscores and Total score, BACS subscores, PST Total score, and PANSS subscores and Total score.

**RoI-1 (whole electrodes)**. As for aperiodic activity we found significant correlations between offset and APACS Brief Figurative Language 1 (Pearson r = 0.29, p = .04), and BACS Working memory (Pearson r = 0.32, p = .02) and Attention (Pearson r = 0.39, p = .006) scores. The exponent value was correlated with BACS Psychomotor speed (Pearson r = 0.29, p = .04) and Attention (Pearson r = 0.36, p = .01) scores. Concerning alpha activity, we found that center frequency was related to PANSS General score (Pearson r = -0.31, p= .04) and PANSS Total score (Pearson r = -0.34, p = .02), while amplitude was related to PANSS Negative score (Pearson r = -0.31, p = .04) (see Figure 11).

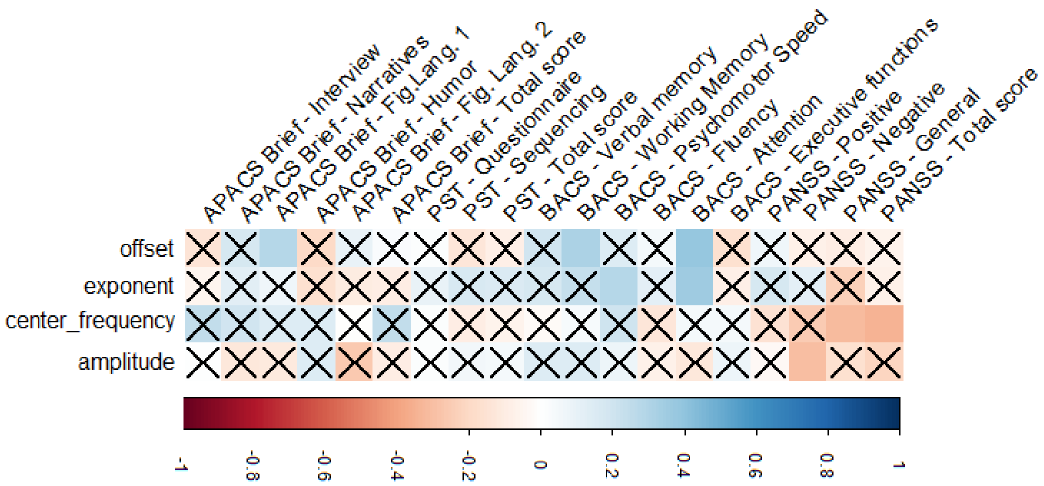


*Figure 11. Correlation matrix between aperiodic and alpha Indexes and pragmatic abilities, cognition, ToM, and psychopathology in RoI-1*

**RoI-2 (left hemisphere electrodes)**. Concerning aperiodic activity we found significant correlations between offset and APACS Brief Figurative Language 1 (Pearson r = 0.38, p = .007), and BACS Working memory (Pearson r = 0.35, p = .01) and Attention (Pearson r = 0.43, p = .002) scores, while the exponent was related to BACS Attention score (Pearson r = 0.37, p = .008). Concerning alpha activity, we found that center frequency was related to APACS Brief Humor score (Pearson r = 0.31, p= .01) and PANSS Negative score (Pearson r = -0.38, p = .043), while we did not find any correlation with amplitude (see Figure 12).

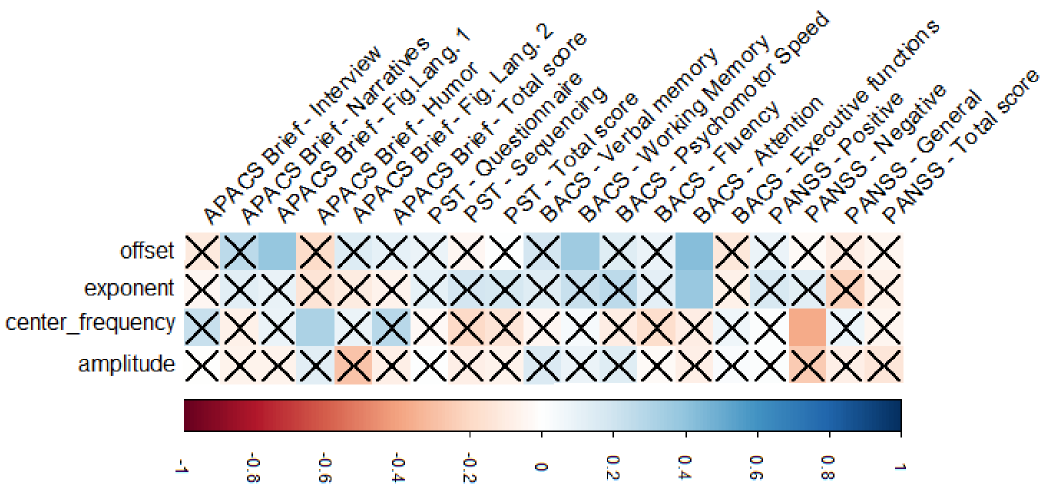


*Figure 12. Correlation matrix between aperiodic and alpha Indexes and pragmatic abilities, cognition, ToM, and psychopathology in RoI-2*

**RoI-3 (right hemisphere electrodes)**. As for aperiodic activity, we found significant correlations between offset and BACS Attention score (Pearson r = 0.34, p = .01), while the exponent was related to BACS Psychomotor speed (Pearson r = 0.30, p = .03) and Attention (Pearson r = 0.33, p = .02) scores. Concerning alpha activity, we found that center frequency was related to APACS Brief Humor score (Pearson r = 0.31, p= .03) and PANSS Negative score (Pearson r = -0.36, p = .01), while we did not find any correlation with amplitude (see Figure 13).

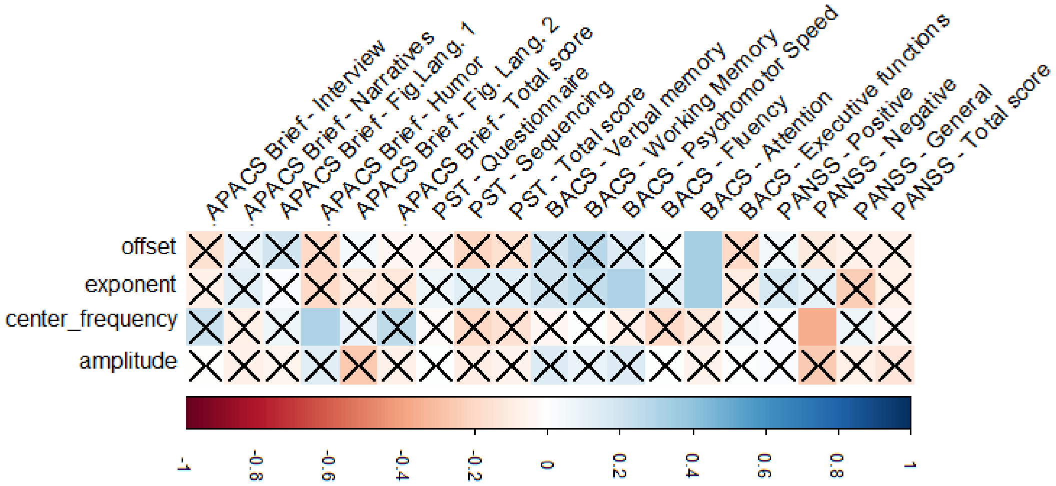


*Figure 13. Correlation matrix between aperiodic and alpha Indexes and pragmatic abilities, cognition, ToM, and psychopathology in RoI-3*

# 4. DISCUSSION

The use of language within a specific context, known as pragmatics, has a vital role in people's interpersonal relationships, educational success, career advancement, and quality of life at large. People with pragmatic difficulties face the other side of the coin, as they might struggle with learning, socializing and finding employment, with an increased risk of social marginalization. Pragmatic disruption is a main challenge in schizophrenia, as it affects around 80% of people with the disorder and further contributes to functional disability and lower quality of life in subjects affected by the disorder. Beside the pivotal impact of pragmatic deficit, to date it is still insufficiently considered in the clinical practice and addressed by rehabilitation. This treatment issue is a result of the lack of feasible and rapid tools that can be incorporated into routine assessment, and of the sparse knowledge on the related neurobiological underpinnings. To fulfil these gaps, this study aims at, firstly, testing a novel brief task for pragmatic evaluation in schizophrenia, secondly, shedding new light on the neural correlates of pragmatic impairment in schizophrenia. The development of feasible tasks and the identification of neurophysiological patterns of pragmatics may provide a better understanding of the impairment, thus identifying new targets for treatment with potential application for a more refined prediction of diagnosis and treatment outcomes.

## *4.1 APACS Brief*

Healthcare services require rapid and feasible assessment tools, and these needs become especially crucial when assessing pragmatic skills, for which few tools exist. Here, we tested APACS Brief, a novel task specifically designed to target pragmatics in around 10/12 minutes, developed in collaboration with IUSS Pavia, in 56 subjects with schizophrenia and 56 matched healthy controls.

ANOVAs showed significant differences in all APACS Brief subtests and Total score between the groups, with significantly lower performance in people affected by schizophrenia across all pragmatic features. Moreover, the ROC analysis showed that APACS Brief Total score was able to effectively discriminate between people with schizophrenia and healthy controls (AUC = 0.83), further supporting the capability of APACS Brief in detecting pragmatic disruption. Additionally, we found significant correlations between APACS Brief Total score and APACS Total score, thus confirming the equivalence between the long and short versions of the APACS test. Also, we found significant correlations between APACS Brief subscores and Total score and BACS Attention and Psychomotor speed scores, as well as PST Questionnaire, Sequencing, and Total score; these results highlight that the relationship between pragmatics and both cognitive and sociocognitive abilities is still captured with this novel and brief task.

These results are in line with a large body of literature arguing that people with schizophrenia show a pervasive pragmatic impairment, which affect both production and comprehension domains (Angeleri et al., 2012; Bambini et al., 2016). Moreover, results suggest that APACS Brief effectively detect pragmatic impairment and allow to discriminate people with schizophrenia from healthy controls. Our data suggest an equivalence between APACS Brief and APACS test, a validated extensive measure for pragmatic evaluation, as supported by the significant correlation between the two APACS versions. This result is in line with the correlation value between the Italian version of the Protocole Montréal d'Évaluation de la Communication (MEC) (Tavano et al., 2013) and its shorter version based on a novel set of items, namely MEC B (Casarin et al., 2020). Similarly, APACS Brief items are not a subset of the items derived from the APACS test, but rather a new set of items, thus further suggesting the equivalence between the APACS long and short versions, which should be confirmed by future studies. Moreover, the efficacy of APACS Brief in detecting pragmatic deficit in schizophrenia is also supported by the correlations with cognitive abilities (especially psychomotor speed and attention skills) and ToM abilities, as previously explored in the literature (Bosco et al., 2018; Parola et al., 2020). Our results did not show a relation between pragmatics and EF. This is a debated issue in literature, with some evidence reporting an association (Mossaheb et al., 2014; Pesciarelli et al., 2014), but also a body of research suggesting the independence between the two domains (Champagne-Lavau & Stip, 2010; Langdon & Davies, 2002; Mo et al., 2008; Parola et al., 2018).

All together, these data suggest that APACS Brief is a tool able to evaluate pragmatics in schizophrenia and that, if supported by other studies, it could be considered equal to a long and validated task such as the APACS test. The brief administration time makes

APACS Brief a useful and adaptable task for numerous contexts, including the NHS services, where the time constraints do not allow for longer evaluations. The identification of people with schizophrenia showing a pragmatic deficit could maximize the application of the available rehabilitative interventions, such as PragmaCom (Bambini et al., 2022), with significant consequence on people's daily functioning and quality of life. As functional disruption is still a major issue in schizophrenia, contributing to the economic burden associated with the disorder (Latorre et al., 2022), the identification of treatment targets and the availability of tools to assess them is crucial. Clinical implications of APACS Brief also include its use for refined diagnosis and treatment outcome prediction, as well as for monitoring the course of the disorder in chronic patients. Furthermore, in a broader perspective, APACS Brief can have transdiagnostic implications, as it could be a feasible tool in other populations characterized by pragmatic impairment, including both neurological and psychiatric conditions, such as TBI and ASD (Arcara et al., 2020; Parsons et al., 2017), as well as in the general population, especially in the healthy aging, in which a mild decay has been found (Bischetti et al., 2019; Messer, 2015). APACS Brief may contribute to promoting awareness of difficulties in communication as well as to implement effective intervention strategies in schizophrenia and in other clinical and non-clinical populations that are still underserved.

### *4.2 EEG*

Neurobiological correlates of altered cognitive and pragmatic abilities in schizophrenia are, to this day, still relatively unexplored. The current neglect of research on cognitive neural patterns may contribute to the lack of effective treatments in schizophrenia. Here, we explored neurophysiological correlates of pragmatics, adopting an EEG approach, which allows for a precise, real-time, millisecond resolution of normal and pathological brain processing that underlie key aspects of human cognition. In detail, we focused on EEG features that are well-explored in literature, such as auditory MMN and alpha activity, as well as features that have received attention only in the recent few years, such as aperiodic activity.

MMN is thought to measure the brain's automatic and pre-attentive processing of information, by computing the difference in brain activity between a standard stimulus and a deviant stimulus within a series of stimuli (Salisbury et al., 2017). A large body of studies have consistently demonstrated an altered MMN in schizophrenia (Kim et al., 2019; Lee & Kim, 2022; Shelley et al., 1991), which has been related to the severity of psychopathology (especially negative symptoms) (Kärgel et al., 2014; Perrin et al., 2018), as well as to cognitive impairment (Brockhaus-Dumke et al., 2005; Kärgel et al., 2014; Minami & Kirino, 2005; Toyomaki et al., 2008) and functional outcome (Lee et al., 2014; Rissling et al., 2014).

In our sample we found a posterior MMN activation. Previous studies showed that MMN is typically observed at fronto-central sites (Fitzgerald & Todd, 2020), thus our finding may be related to the use of Cz as reference. Moreover, our results confirm the relationship between MMN and cognition in schizophrenia, in particular we found significant correlations with BACS Verbal memory and Attention tasks, as previously reported in the literature (Carrión et al., 2015; Kawakubo et al., 2006), highlighting the link between the alteration of early auditory processing and cognitive dysfunction. Innovatively, we found a relationship between MMN and pragmatic abilities, in particular with APACS Brief Narrative task, in people with schizophrenia. To date, literature has suggested that abnormalities in language processing may be related to auditory sensory memory, an essential process for language acquisition and linguistic processing (Näätänen et al., 2012). Moreover, correlations between MMN and the processing of pragmatic language (Zhao et al., 2018) and, in particular, proverb understanding (Kiang et al., 2007) have been found in the general population. However the paucity of the available studies do not allow to draw stronger conclusions, also concerning the explanation of this relationship.

MMN is an index of the readiness of the brain to elaborate a deviant stimulus compared to an expected one. Our results, showing a significant correlation between MMN and pragmatics, confirm our hypothesis that the underlying mechanism may be similar. MMN indicates the ability to process a deviant auditory stimulus compared to the expected one, and, in a similar way, pragmatics can be considered as the ability to process an unexpected stimulus (e.g., a metaphor) when the subject presumes that he will get an expected stimulus (i.e., literal language). It is worthy to note that this relationship was found with the APACS Brief Narrative task. Unlike other tasks, such as Figurative Language 1 and 2 as well as Humor task, in which the subject is asked to interpret figurative expressions without having a general context, in this task the subject is given a story in which literal language (i.e., the expected stimulus) is used and figurative expressions (i.e., the deviant stimulus) are presented in an unexpected way. Then the subject is required to elaborate the unexpected stimulus.

Another EEG index explored in this study, was alpha activity. Alpha activity is a type of spontaneous brain oscillation, characterized by a peak at a frequency of around 7-14 Hz (Yordanova et al., 2013). Alpha activity is considered a measure of cortical arousal and synchronization between different areas of the brain (Nunez & Srinivasan, 2006), and it is associated with a state of healthy wakefulness and cognitive functioning. Reduced alpha activity has been consistently found in schizophrenia since the early EEG studies in the disorder (Lemere, 1936). In our study, we found an alpha peak at 9.56 Hz, leading us to hypothesize its reduction, as previously reported in the literature (Newson & Thiagarajan, 2019; Vignapiano et al., 2019). Given the lack of a control group of healthy subjects, the conclusions that can be drawn are hampered, however a study by Coppola and Chassy (1986) suggested a cut-off of 10.2 Hz, below which a subject is classified as having reduced alpha frequency, as in our sample. Also, a recent study compared first episode patents with healthy controls, showing significant differences in alpha peak (9.72 Hz vs 10.40 Hz, respectively) (Michael & Dost, 2019), in line with the cut-off suggested by Coppola and Chassy as well as with our results.

Taking into account correlation analyses, our data demonstrated a relationship between symptomatology and both alpha amplitude and peak, as previously reported in literature (Knyazeva et al., 2008; Kubicki & Shenton, 2020; Scott et al., 2000). In detail, our results showed significant correlations between alpha center frequency and PANSS General and Total scores, as well as between alpha amplitude and PANSS Negative score. Based on previous studies showing an hemispheric asymmetry related to alpha activity in schizophrenia (Merrin & Floyd, 1997; Olejarczyk & Jernajczyk, 2017), we also evaluated correlations between alpha and pragmatic, cognitive, and clinical data in each hemisphere. Our result showed the same pattern of association in both hemispheric electrodes, with a negative relationship between center frequency and both PANSS Negative symptoms and APACS Brief Humor score. This study confirms the relationship between alpha activity and negative symptomatology, as already reported in the literature (Garakh et al., 2012). Moreover, we did not found correlations between alpha activity and cognitive and sociocognitive abilities. These data can be explained in light of the debate surrounding the relationship between alpha activity and cognitive deficits in schizophrenia. While some studies pointed out the interplay between alpha alterations and cognitive disruption (Gica et al., 2019; Güntekin & Başar, 2016), other studies reported no association between alpha activity and cognitive and sociocognitive abilities in people affected by schizophrenia (Koshiyama et al., 2021; Vignapiano et al., 2019; Vohs et al., 2016).

As for language, only few studies had previously explored the relationship with alpha activity. Research reported an association between alpha oscillations and language-related tasks in the general population (Prystauka & Lewis, 2019), also in healthy children (Kwok et al., 2019). Additionally, research has revealed that alpha activity decreases during language comprehension tasks, indicating an increased cognitive load, whose effect has been found in both the left and right temporal-parietal regions of the brain (Wang et al., 2022). A for pragmatics, and in particular irony comprehension, studies in the literature suggested a relationship with alpha activity. Regel and co-authors (2014) examined the neural responses to sentences that were either literal or ironic, based on the context. They found an alpha decrease in response to ironic sentences compared to literal utterances. Akimoto and colleagues (2017) found a more pronounced alpha desynchronization in the right anterior temporal for ironic sentences, compared to literal ones. Accordingly, it can be hypothesized that irony comprehension may require an increased processing demand, compared to the elaboration of literal sentences, which seems to be related to alpha desynchronization as a result of a more extensive processing for figurative language comprehension. Similarly, ERP studies on N400 and P600 (i.e., a negative and a subsequent positive deflection of the ERPs reaching a maximum at 400 ms and 600 ms from stimulus presentation) confirm an increased cognitive effort in pragmatic language understanding compared to literal one (Brouwer & Hoeks, 2013; Canal & Bambini, 2021; Kuperberg, 2007). These results suggest a complex relationship between alpha activity and pragmatics, although they have been conducted only in the general population, as in schizophrenia no studies have currently explored this relationship. Thus, our study is the first to confirm the interplay between alpha and pragmatic processing in schizophrenia, especially concerning irony. Moreover, our data do not show differences between hemispheric electrodes in the processing of irony, highlighting the importance of hemispheric integration in the interpretation of figurative language.

Oscillatory activity, including alpha activity, has been extensively explored in clinical and non-clinical populations. However, a large part of human electrophysiological activity is represented by its non-periodic component, which is the aperiodic activity, a scale-free component that does not contain a predominant temporal scale (He, 2014). Aperiodic activity is characterized by two parameters, namely offset and exponent. The offset parameter reflects the uniform shift of power across frequencies, while the exponent parameter determines the steepness of the slope. Aperiodic activity has been poorly explored by research, as it has gained attention only recently.

Correlation analyses on aperiodic indexes (i.e., offset and exponent) revealed significant correlations with cognitive abilities in the whole electrodes (i.e., RoI-1), as well as across the two hemispheric electrodes (i.e., RoI-2 = left hemisphere electrodes; RoI-3 = right hemisphere electrodes). Significant correlations also emerged between offset and both BACS Working memory score (in RoI-1 and RoI-2) and BACS Attention score (in all RoIs); as for exponent, we found significant correlations with BACS Attention score (in all RoIs) and BACS Psychomotor speed (in RoI-1 and RoI-3). The relationship between aperiodic activity and cognition is in line with the scattered studies available in the literature. As a matter of fact, aperiodic activity has been proposed as a proxy measure for E/I balance, whose alteration is related to cognitive and perceptual changes (Molina et al., 2020). Accordingly, Voytek and co-authors (2015) suggested that aperiodic activity, in particular the slope flattening, may be considered as an index of cognitive decline related to healthy aging, as they found that aperiodic activity predicts working memory abilities in older adults. These results were confirmed by Donoghue and colleagues (2020), who found that aperiodic parameters were more reliable than alpha indexes in predicting working memory performance in healthy younger and older adults. Similarly, Thuwal and co-authors (2021) suggested a diffuse impact of age-related changes in aperiodic activity on several cognitive processes. Furthermore, Ostlund and colleagues (2021) showed that aperiodic exponent can be considered as a neural correlate of disrupted information processing in adolescents affected by ADHD. All together, these results suggest a significant and complex interplay between aperiodic activity, as a measure of E/I balance (or imbalance), and cognition, however to date no study explored this relationship in people affected by schizophrenia. As previously described in the Introduction, E/I imbalance has been found in schizophrenia and studies showed a link with cognitive disruption. To date, E/I balance can be studied with invasive methodologies, making them difficult to apply to human studies, and thus limiting the exploration of this promising field (Molina et al., 2020; Starc et al., 2017). In this framework, aperiodic activity emerged as a potential proxy measure for E/I balance evaluation. The available data in schizophrenia suggested an alteration of aperiodic activity, which may be linked to the well-known E/I imbalance characterizing the disorder (Molina et al., 2020; Racz et al., 2021). Thus, to our knowledge this is the first study addressing this topic in schizophrenia and confirming the previous results on the interplay between aperiodic indexes and cognition found in other populations.

Concerning pragmatics, results showed significant correlations between aperiodic offset and APACS Brief Figurative Language 1 task in the whole electrodes and in left hemisphere electrodes. To our knowledge, this is the first study exploring the relationship between aperiodic activity and pragmatics. A previous study by Dave and co-authors (2018), on a sample of healthy younger and older subjects, highlighted that aperiodic activity influences ERP measures (e.g., N400) related to language processing. Previous studies showed an association between a larger N400 during metaphor understanding compared to literal items, suggesting the need for a greater effort in accessing and integrating word meaning in figurative language interpretation (Canal & Bambini, 2021). In individuals with schizophrenia, N400 seems to be reduced, and figurative items are processed as literal ones. Thus, these data suggest a relationship between N400 and both aperiodic activity and pragmatics. In this framework, our study add another piece to the puzzle, by showing also the link between aperiodic index and pragmatics. Future studies accounting for all these features are needed to further explore this complex interplay.

Research in cognitive neuroscience suggests a view of the brain as a prediction machine (Bastos et al., 2012), in which improved neural synchronization leads to improved predictive abilities (Dave et al., 2018). Consequently, alterations in this neural synchronization, reflected in an E/I imbalance and the subsequent altered aperiodic activity, would result in difficulties in predictive abilities and coping with unexpected stimuli. Similarly, pragmatics requires a prediction of the expected stimulus (i.e., literal language) and the processing of and unexpected stimuli, which is represented by figurative language. In our study, data suggest that the ability to process figurative language, specifically metaphors, proverbs, and idiomatic expressions, seems to be linked to neural synchronization and balance between inhibition and neural excitation, as represented by aperiodic activity.

Furthermore, we explored the topic of hemispheric differences in understanding figurative language, in light of the wide debate in the literature. Some studies suggest a greater involvement of the right hemisphere (Cutica et al., 2006; Mitchell & Crow, 2005), however other evidence has shown the importance of the left hemisphere in understanding metaphor (Klooster et al., 2020; Save-Pédebos et al., 2016). Reconciling these contrasting data and moving beyond hemispheric segregation, functional imaging research has shown that both hemispheres play a role in understanding metaphors (Bambini et al., 2011; Cardillo et al., 2012; Obert et al., 2014), thus suggesting that the comprehension of metaphors is a bilaterally mediated process (Reyes-Aguilar et al., 2018). In this study, results showed correlation between aperiodic activity and pragmatic in the whole brain with a prevalence for left hemisphere electrodes, supporting the hypothesis of a hemispheric integration related to the interpretation of pragmatic language.

Overall, this study confirms the need for further exploring the electrophysiological underpinnings of cognition in schizophrenia. Our results highlight the importance of EEG indexes in schizophrenia, also as possible markers of the core deficits characterizing the disorder, including pragmatic and cognitive alterations. In detail, results confirm a relationship between indexes already explored in schizophrenia, such as MMN and alpha activity, and both cognitive functions and symptoms. Furthermore, for the first time in schizophrenia, we explored the correlation with aperiodic activity, confirming the relationship recently suggested in healthy individuals and other clinical populations. Innovatively, we delved deeper into the interplay between all these electrophysiological markers and pragmatics, showing how different domains of pragmatic understanding are linked to different electrophysiological correlates. In detail, MMN was related to the comprehension of a text containing figurative expressions, alpha activity was related to irony understanding, while aperiodic activity was related to the interpretation of metaphors, idioms, and proverbs. Furthermore, regarding aperiodic activity, we found whole brain effect with left hemisphere electrodes prevalence, suggesting that hemispheric integration and communication underlies pragmatic abilities. Overall, the exploration of neural correlates of pragmatic and cognitive functioning is crucial, as it will allow for the identification of treatment targets, the clarification of neurobiological underpinnings for the disease, as well as for early diagnosis and risk screening in people at high risk for developing psychosis, and for outcome and disease course prediction.

### *4.3 Limitations*

Limitations should be acknowledged. Firstly, the small sample size could have influenced the statistical power of the analyses and have limited the inclusion of other confounding factors, such as the patients' sex and pharmacological therapy, into the analyses. As a matter of fact, some studies, despite limited, showed a link between antipsychotics, such as clozapine and chlorpromazine, and EEG abnormalities, including epileptiform discharges an EEG slowing (Jackson & Seneviratne, 2019), which should be better explored by future studies. Secondly, the absence of comparison samples of healthy subjects as well as of people affected by other psychiatric disorders, may hamper the strength of the conclusions. Indeed, the aim of this study was to explore a neglected topic in schizophrenia, which is the identification of the neurophysiological underpinnings of pragmatics, which has gained only limited attention in the disorder; future studies should focus also on the comparison between people with schizophrenia and healthy controls concerning the EEG-indexes related to pragmatics. Thirdly, the study did not employ other ERPs that are usually altered in schizophrenia, such auditory steady-state response (ASSR), which should be taken into consideration in order to correlate them to cognition and especially pragmatics. Fourthly, based on the literature showing hemispheric differences related to alpha activity in schizophrenia (Olejarczyk & Jernajczyk, 2017), we decided to focus only on these regions of interest. Future studies should also consider other brain areas, such as the occipital lobe. Fifthly, given the explorative nature of the study, we did not apply a correction for multiple comparisons to correlation analyses. Sixthly, the cross-sectional nature of our study did not enable us to evaluate a causal relationship between EEG indexes and cognitive and clinical data. Moreover, in this study we did not evaluated if the negative association between alpha and severity symptoms was due to a general slowdown of all oscillatory frequencies, or if it was specific to alpha alteration. Future studies should also include other brain oscillation indexes (such as delta, theta, etc frequencies) to better explore the interplay with the severity of psychopathology. Lastly, patients underwent an open eyes resting state paradigm during the EEG recording, which may have hampered the strengths of our conclusions.

### *4.4 Conclusions*

Despite the acknowledged limitations, in this study we: 1) tested APACS Brief, a novel and brief tool, and we showed its effectiveness in the evaluation of pragmatic deficit in schizophrenia; 2) confirmed the relationship between MMN and alpha activity and both cognition and psychopathology, and, innovatively, we explored the link with pragmatics; 3) investigated, for the first time, the interplay between aperiodic activity and pragmatic, cognitive, and clinical data, highlighting the potential utility of evaluating this EEG marker.

Noteworthy, our results have several theoretical and clinical implications. From a theoretical point of view, our data may contribute to increase the current knowledge on neurophysiological correlates of key cognitive and pragmatic processes that are altered in schizophrenia, with relevance also for healthy development and aging, as well as for other neurological and psychiatric conditions. Also, the available tools for the evaluation of E/I balance are invasive and thus non applicable for human studies. The identification of a reliable proxy measure for E/I balance, such as aperiodic activity, may have numerous clinical and research implications, as it may allow to expand the knowledge on the neurocognitive architecture of the mind.

Furthermore, from a clinical point of view, the development and testing of APACS Brief, a task able to detect pragmatic disruption in about 10/12 minutes, will allow for quick and easy screening of pragmatics in clinical routine that can be feasible for the NHS services. The identification of people with pragmatic difficulties, beside the psychiatric diagnosis, has a relevant clinical utility, as it may allow for the proper management of the patients' communicative profile and needs, reducing the costs associated with this disruption. EEG findings may also have potential applications in order to get a more refined prediction of diagnosis and treatment outcome. Most notably, the identification of electrophysiological correlates of pragmatic and cognitive impairments may provide novel targets for treatment, including the use of combined rehabilitative interventions with neuromodulation techniques, such as transcranial magnetic stimulation and neurofeedback, which currently represent a promising therapeutic avenue for cognitive deficits, but still hampered by the lack of reliable markers.

# 5. MATERIALS AND METHODS

## 5. 1 Sample

56 patients affected by schizophrenia according to DSM 5 (American Psychiatric Association, 2013) were recruited at the Schizophrenia Research and Clinical Unit of IRCCS San Raffaele – Ville Turro, Milan, Italy. 56 healthy subjects, matched for age and years of education with the schizophrenia group, were enrolled from the general population. All individuals participating in the study voluntarily agreed to the approved protocol and gave their consent after being informed of the details. This study adheres to the ethical guidelines outlined in the Declaration of Helsinki.

The inclusion criteria for people with schizophrenia were:

- Diagnosis of schizophrenia according to DSM 5 diagnostic criteria;
- Age between 18 and 65 years.

The exclusion criteria for people with schizophrenia were:

- Intellectual disability;
- Substance dependence or abuse in the preceding 6 months;
- Comorbid psychiatric diagnosis;
- Severe psychotic reacutization in the preceding 3 months.

## 5.2 Assessment

Healthy subjects were tested for pragmatic abilities with the APACS Brief. People with schizophrenia were tested for pragmatics (with both the APACS and the APACS Brief), as well as for cognition, ToM, and psychopathology.

Information about demographic and clinical characteristics was obtained.

Pragmatics was assessed, as in Agostoni and colleagues (2021), with the *APACS* test (Arcara & Bambini, 2016), assessing the patient's ability to communicate effectively as well as to use and interpret non-literal language. It has two sections: a production section, which includes two tasks (Interview, Description), and a comprehension section, containing four tasks (Narratives, Figurative Language 1, Humor, Figurative Language 2). Proportional scores can be derived from each task, as well as composite scores for production, comprehension and global pragmatics domains.

To evaluate pragmatics with a short task, we developed, in collaboration with IUSS Pavia and IRCCS San Camillo (Venice), the *APACS Brief* test, a short measure of receptive and expressive pragmatic skills related to the dimension of discourse and non-literal meaning. It was modelled after the APACS test by maintaining the same structure and introducing a series of modifications based on the following criteria: (i) reducing administration duration to approximately 10 minutes; (ii) creating new items that share the same characteristics of the best items in the APACS; (iii) simplifying the scoring procedure.

As for (i), we decided to reduce the number of items but maintain the same tasks, except for the Description task. This latter task was often associated to almost-ceiling performance also in clinical groups (Carotenuto et al., 2018). Overall, the number of items was reduced by 85% (i.e., from 121 to 18). As for (ii), we decided to create new items, instead of selecting items from the APACS, to reduce practice effects and encourage the joint use of both APACS and APACS Brief tests, for instance in the context where the brief version is used for follow-up, or where the brief version is used for initial screening followed by an extensive assessment. To determine the best items in the APACS, we used an item-total correlation approach and individuated the items in each APACS task that correlated the most with the APACS total score. Then new items that shared the same characteristics in terms of psycholinguistic features (e.g., familiarity and length) with the best APACS items were created. For the Interview task, we selected new autobiographic topics, based on previous works assessing discourse pragmatics aspects (Ruffman et al., 2010; Yin & Peng, 2016). Furthermore, we made sure that none of the new items was included in other tools that might be used together with the APACS brief, namely the Positive And Negative Symptoms Scale (Kay et al., 1987), the Wechsler Adult Intelligence Scale – Revised (WAIS – R) (Wechsler, 1981), and the Pragmatics of Communication (PragmaCom) training program (Bambini et al., 2022; Bambini et al., 2020). As for (iii), the scoring procedure was simplified from the use of 3-point scales to the use of a 2-point scale (0/1) for each item. The final structure of the APACS Brief, together with duration information, is represented in Figure 14.

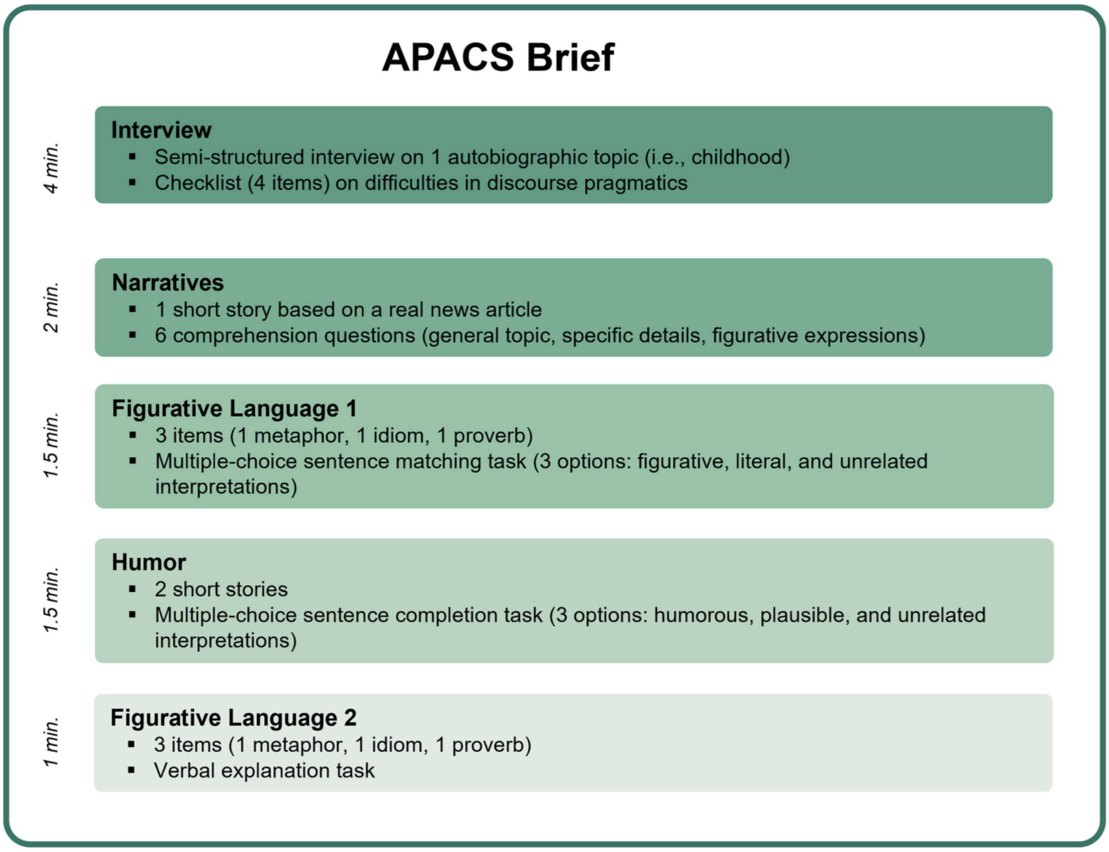


*Figure 14. Structure of the APACS Brief*

Below the description of each task is reported. All tasks are administered orally, and for Figurative Language 1 and Humor tasks there is an additional booklet showing the three options for each item. The order of administration of the tasks is fixed.

**Interview.** It consists of a short structured autobiographic interview about childhood where the examiner offered two prompts (favourite game and friends). Scoring takes into account four communicative difficulties at the pragmatic level (over-informativity, under-informativity, missing reference, abrupt topic shift), rated 0 when present and 1 when not present. Max score 4.

**Narratives.** It consists of one news-like story about a wild boar spotted in the city. The story includes one idiom and one ironic statement. Six questions, four about implicit and explicit aspects of the story and one for each figurative expression are asked. Max score 6.

**Figurative Language 1.** It consists of a multiple-choice figurative language comprehension task, where a figurative expression is presented in a short context (e.g., Italian, “Adoro accarezzare le mie nipotine. Certe guance sono pesche.”; English adaptation, “I love caressing my little nephews. Their cheeks are peaches”) along with three options, one correct (Italian, “Certe guance sono lisce e morbide.”; English adaptation, “Some cheeks are smooth and soft.”), one literal (Italian, “Certe guace sanno di frutta.”; English adaptation, “Some cheeks taste peachy.”) and one unrelated (Italian, “Certe guance sono rugose.”; English adaptation, “Some cheeks are wrinkled.”). It includes one idiom, one metaphor, one familiar proverb, each scored 1 when the correct option is selected and 0 otherwise. Max score 3.

**Humor.** It consists of a multiple-choice story completion task, where a context is presented along with three possible endings: one humorous, one straightforward, and one unrelated. It includes two items, each scored 1 when the humorous ending is selected and 0 otherwise. Max score: 2.

**Figurative Language 2.** It consists of a verbal explanation task, where a figurative expression is presented and the participant is asked to articulate its meaning (e.g., Italian, “L’occasione fa l’uomo ladro”; English adaptation “Opportunity makes the thief”). It includes one metaphor and two proverbs, each scored 1 when the figurative meaning is correctly explained and 0 otherwise. Max score 3.

The APACS Brief Total score is obtained by averaging task scores transformed in proportions (range 0-1).

Cognition was assessed, as in Agostoni and co-authors (2021), with the Italian version of the Brief Assessment of Cognition in Schizophrenia (*BACS*) (Anselmetti et al., 2008; Keefe et al., 2004), evaluating neuropsychological domains that usually impaired in the disease, namely verbal memory, working memory, psychomotor speed and coordination, speed of processing, verbal fluency and executive functions.

Theory of Mind, as in Agostoni and colleagues (2021), was tested using the of Picture Sequencing Task (*PST*) (Brüne, 2003). This task consists of six stories depicted in cartoon images and requires participants to arrange them in a logical order and answer questions about the characters' mental states and motivations. The final score is calculated by combining the results of the sequencing and questionnaire performances, thus deriving a comprehensive measure of ToM abilities.

Psychopathology was assessed with Positive and Negative Syndrome Scale for Schizophrenia (*PANSS*) (Kay et al., 1987). The PANSS tackles the severity of positive, negative, general, and total symptoms in schizophrenia.

### 5.3 EEG acquisition

Patients with schizophrenia also underwent an EEG recording protocol. The EEG data were collected with a BioSemi ActiveTwo amplifier using a Micromed EEG system (Treviso, Italy) consisting of 128 scalp electrodes, using Cz as reference and impedances were maintained below the threshold of 5k. Data were recorded at a 1000 Hz sampling rate, and then were downsampled to 250 Hz prior to analysis. All of the individuals involved had both typical or corrected vision and hearing. The instructions for the recording were given to the participants before the start of the EEG acquisition.

**Resting state**. Patients underwent five minutes of open eyes resting state paradigm, where the participant was instructed to silently look at a fixation point (+) centred on a PC screen. The room in which the experiment took place did not present auditory or visual distractive stimuli.

Data were analysed using Brainstorm (Tadel et al., 2011). Data were down sampled to 250 Hz in order to reduce the computational load, and we applied high-pass (0.5 Hz) and low-pass (45 Hz) filters. Thus, an Independent Component Analysis (ICA) was performed for artifact correction: this technique allows to break up the multivariate signal into independent components, which are identified based on statistical independence of data, in order to isolate the neural signal from interference. For each EEG recording, the identified components have been visually inspected, to remove artefacts that were due to eye blinks, muscular or electrical noise. After this visual inspection of signal quality, for each subject a Power Spectral Density (PSD) was computed, using Welch's method, with a window length of 1s and 50% window overlap. Then a PSD considering all subject was performed in order to obtain a grand average PSD. PSD displays how the signal power varies in accordance with frequency (Hadiyoso et al., 2021), reflecting the power of the different frequencies putatively contributing to the signal (Luck, 2014). PSD was performed because it is less sensitive to the possible presence of fluctuating and extreme power values, among those registered by the different electrodes. Then, the "Fitting Oscillations & One Over F" (FOOOF) algorithm (Donoghue et al., 2020) on PSD has been performed in order to take into account both periodic and aperiodic cortical activity. As illustrated by Donoghue and co-authors (2020), the algorithm operates modelling gaussian curves on peaks of activity, identified over the threshold of noise. Once the model obtained from the original PSD is subtracted, a new one is estimated for the residual aperiodic component that, combined with the utilized gaussian curves, provides the final model, from which the relevant parameters can be extracted. Similarly to the original version of the algorithm, a gaussian distribution has been used for modelling the peaks identified among the spectrum; the ones that were enclosed between 0.5 Hz and 12 Hz were included. All the other process options corresponded to the default settings suggested by the software. The obtained data were then exported in Matlab (MathWorks, 2022) and then in RStudio (PBC, 2022). From each subject's FOOOF models, we extracted data relative to the offset (i.e., the uniform shift of power across the frequencies), the exponent (i.e., the pattern of the aperiodic power across the different bands), the alpha centre frequency (i.e., the frequency of the alpha peak, included between 7 and 14 Hz) and alpha amplitude (i.e., the distance from the centre line to the top of the peak). Based on studies showing an hemispheric asymmetry related to alpha activity in schizophrenia (Merrin & Floyd, 1997; Olejarczyk & Jernajczyk, 2017), we calculated all aperiodic and alpha indexes for three Regions of Interest (RoI): 1) RoI-1 included all 128 electrodes; 2) RoI-2 included electrodes localized on the left hemisphere, excluding electrodes on the sagittal lateral longitudinal line; 3) RoI-3 included electrodes localized on the right hemisphere, excluding electrodes on the sagittal lateral longitudinal line.

**MMN**. A passive odd-ball task using auditory stimuli was used to evoke the Mismatch Negativity response (MMN) in the study. This task involved the presentation of a series of tones, consisting of standard tones (240) intervealed with deviant ones (60). Standard tones were characterised by a 500Hz carrier frequency while deviant ones had 550 Hz frequency. These stimuli were presented to both ears of the participants through ear tubes and were randomly intermixed in a 4:1 ratio of standard to deviant stimuli. There was a 500ms interval between each stimulus (ISI). During the task, participants were asked to focus on a fixation point (+) on a computer screen and press a button when they saw the prompt "press the button" appearing on the screen.

Data from this task we pre-processed and analysed using Brainstorm software. Recordings were downsampled to 250 Hz and band-pass filtered (0.5-40 Hz). Artefacts present in the data were removed using ICA and then data were segmented into epochs (-500 ms to 1000 ms, with a baseline of -100 to 0 ms). Epochs were visually inspected to remove bad epochs. Given the different number of epochs for standard and deviant conditions (240 vs 60), we selected the same number of trials for standard and deviant conditions, based on the uniformity distribution. Average responses for both the standard and deviant conditions were calculated, and then the average of the standard condition was subtracted from the deviant condition average. The obtained data were then exported in Matlab and then in RStudio using erpR package (Arcara & Petrova, 2014). Data relative to the MMN amplitude, set between 170-250 ms, were extracted.

## 5.3 Data analysis

### *5.3.1 APACS Brief*

To test differences between people with schizophrenia and healthy controls on the performance at the APACS Brief, we run several Analyses of Variance (ANOVAs) between subjects with schizophrenia and healthy people, thus confirming efficacy of APACS Brief in detecting pragmatic impairment in schizophrenia. In detail, we performed ANOVAs on APACS Brief subscores and Total score between the two groups.

A Receiver Operating Characteristics (ROC) curve analysis was run, to explore the discriminatory power of each APACS Brief Total score in differentiating people with schizophrenia from healthy subjects. ROC curve analysis is a reliable method for evaluating the diagnostic ability of a task in identifying the accurate condition of subjects (e.g., healthy condition vs illness). The area under the ROC curve (AUC) is a measure of the overall classification power of the task, where a perfect classification has AUC = 1, while a random classification has AUC = 0.5. Sensitivity and specificity of the optimal cut-off were calculated.

Lastly, in the schizophrenia group, we run a Pearson correlation analysis between APACS Total score and APACS Brief Total score, to confirm the equivalence between APACS long and short version. Also, a correlation matrix was run between APACS Brief subscores and BACS subscores, PST subscores and Total score, and PANSS subscores and Total score, to investigate the interplay between pragmatics and cognitive and clinical data.

### *5.3.2 Correlations with EEG data*

To characterize the EEG-based neural correlates of pragmatics and to analyse the relationship between pragmatics and neurophysiological indexes in schizophrenia, we run several correlations.

Concerning MMN, data were exported from Brainstorm to Rstudio, using erpR package (Arcara & Petrova, 2014). We extracted MMN amplitude (MMN peak set between 170 and 250 ms) for each subject. Then, a correlation analysis between MMN amplitude and pragmatic, cognitive, and clinical data was run. In detail, we performed a Pearson correlation analysis, using MMN amplitude, APACS Brief subscores and Total score, BACS subscores, PST subscores and Total score, PANSS subscores and Total score. The p was set at 0.05, given the explorative nature of the analyses.

Concerning resting state paradigm, indexes of aperiodic activity (i.e., offset and exponent) and alpha activity (i.e., centre frequency and amplitude) were imported from Matlab to RStudio, and then averaged for each subject. Then, a correlation matrix was computed to analyse the relationship with pragmatic, cognitive, and clinical data. In detail, we performed a Pearson correlation analysis, entering aperiodic and alpha indexes (offset, exponent, center frequency, amplitude), and APACS Brief subscores and Total score, BACS subscores, PST Total score, PANSS subscores and Total score. All the analyses were separately run for RoI-1 (whole brain), RoI-2 (left hemisphere), and RoI-3 (right hemisphere). The p was set at 0.05, given the explorative nature of the analyses.

Analyses were run using Brainstorm (Tadel et al., 2011), MatLab (MathWorks, 2022), RStudio (PBC, 2022) and SPSS (IBM, 2022). The ERP data export for MMN data was performed the erpR (Arcara & Petrova, 2014).

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