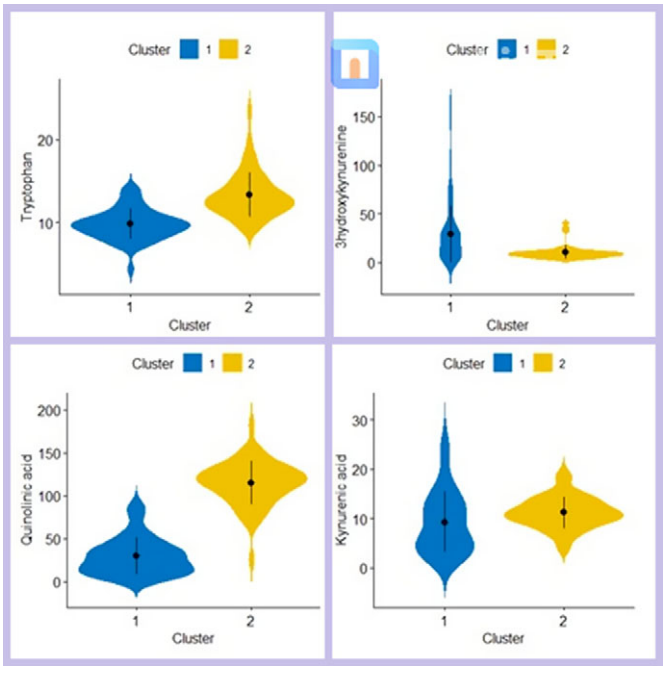
Introduction: Neuroinflammation and the Kynurenine Pathway (KP) have gained attention in the last decades in the pathogenesis of cognitive impairment in schizophrenia. Pro-inflammatory cytokines and microglia activation induce oxidative stress, neurodegeneration, white matter (WM) disruption and increased synaptic pruning and, importantly, activate the KP, whose metabolites have neurotoxic/neuroprotective and neuromodulatory properties on cholinergic and glutamatergic neurotransmission, two pivotal systems in cognitive processes.
Objectives: This study aims to investigate the relationship between levels of inflammatory markers and KP metabolites and cognition in schizophrenia with a focus on the differential impact of these biomarkers on the different phases of the illness.
Methods: Associations between levels of biomarkers and cognitive domains in the wholw sample of 120 patients with schizophrenia were firstly assessed. Then, patients were divided in two subsamples depending on the duration of illness, with the aim to evaluate the impact of inflammatory biomarkers and kynurenines on cognition depending on disease progression. Finally, we performed cluster analysis to investigate kynurenines as possible clustering variables with the final aim to attribute a different cognitive profile to each cluster.
Results: In the whole sample we found negative correlations between multiple inflammatory markers including IL-1β, IL-6, TNF-α, and cognitive functions, particularly verbal memory. Negative associations between verbal memory and TNF-a, IFNg and IL-5 were found in early-phase patients compared to late-phase patients, who showed a less strong associations. Interestingly, kynurenines showed significant associations with cognition in multiple areas regardless of the duration of illness. Regarding clustering, Cluster 1 included patients with lower levels of Tryptophan, Quinolinic Acid, and Kynurenic Acid, as well as higher levels of 3-hydroxykynurenine, compared to Cluster 2 (Fig. 1). Interestingly the two clusters showed different cognitive profiles. Verbal memory, psychomotor speed and attention significantly differed between the two clusters, with Cluster 1 showing the most impaired cognition in all these domains (Fig. 2).

Image 1:



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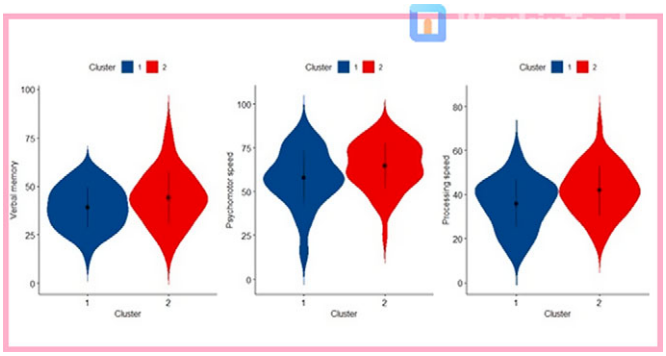

Conclusions: These results stress the primary importance of inflammation and KP abnormalities in cognitive impairment. The effects of inflammation on cognition seems to decline over time, while metabolites of the kynurenine pathway continue to have an impact. Probably, pro-inflammatory cytokines impact cognition more in patients with a shorter duration of illness as the biological bases of cognitive functions are more preserved (cortical volumes, synapses, WM integrity), whilw the neuromodulation of KP metabolites combined with their neurotoxic/neuroprotective profile can explain the diferential effect.

Disclosure of Interest: None Declared

EPP066

Disentangling clinical heterogeneity in schizophrenia through neuropsychophysiological profiles

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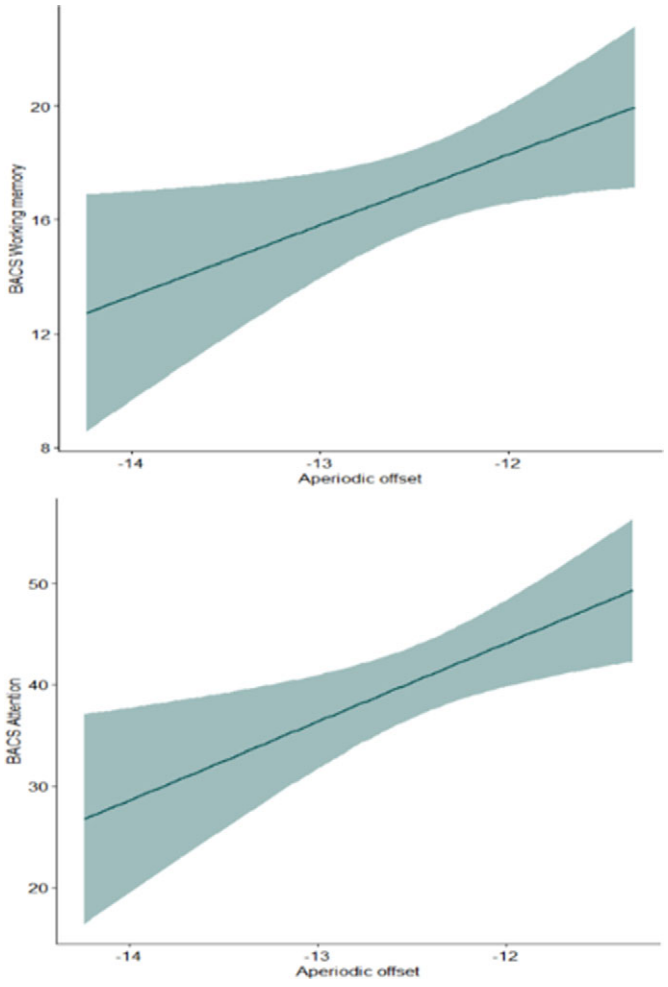
Introduction: Cognitive disruption is a key feature in schizophrenia, and the identification of the neurophysiological underpinnings is of particular interest. One of the most promising markers of cognition is aperiodic activity, which is considered as a proxy measure of excitation inhibition (E/I) balance, stemming from the equilibrium between glutamatergic and GABAergic neurotransmission. E/I alteration has been found in multiple disorders, but its relationship with cognition in schizophrenia has never been explored.
Objectives: This study aims at demonstrating the link between aperiodic activity and cognition in schizophrenia, and at creating neuropsychophysiological profiles, associated with clinical and functional features.
Methods: 48 patients with schizophrenia were assessed for cognition, well-being and the severity of psychopathology and underwent an electroencephalogram (EEG) recording during a resting state. EEG tracks were processed to extract aperiodic parameters (offset and exponent). Pearson correlation analyses between

aperiodic and cognitive measures were performed. Aperiodic indexes and the related cognitive domains were used to create neuropsychophysiological profiles, using a two-step cluster analysis. Analyses of Variance were performed to characterize significant differences in severity of psychopathology and well-being between profiles. Moderation analyses were run to identify the interplay between profiles, psychopathological severity and well-being.

Results: The mean aperiodic offset was -12.45 (± 0.65), while the mean exponent was 0.85 (± 0.28). Significant correlations with aperiodic parameters were found for: Working Memory, Processing Speed and Psychomotor Speed (Fig1-2). Cluster analysis identified two profiles (Profile1 N=15, Profile2 N=33): Profile1 had a higher offset, a steeper slope. ANOVAs revealed that Profile1 showed significantly higher scores in Working Memory and Processing speed, and lower levels of General Psychopathology, Anxiety/Depression and Uncontrolled Excitement and Hostility. Lastly, mediation models, showed an interaction between Profiles (R^2=0.21, p=.04) and Anxiety/Depression as well as between Profiles and General psychopathology (R^2=0.30, p=.003) on Self-Acceptance, with significant negative relationship only in Profile2 in both models (Fig 3).

Image 1:



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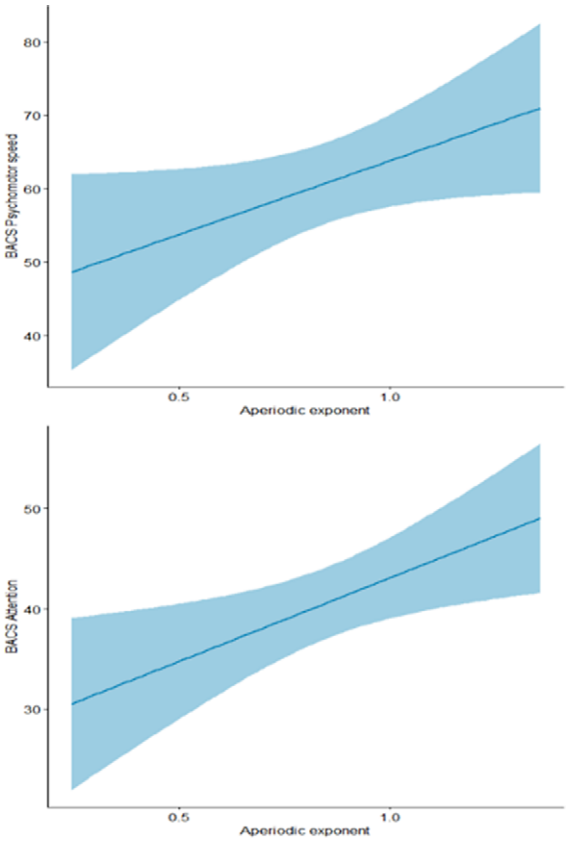
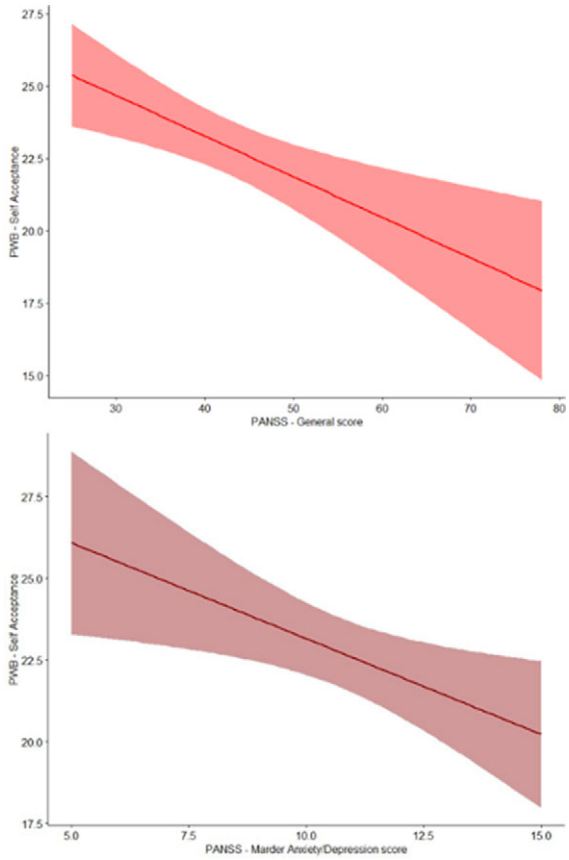


Image 3:



Conclusions: Our data support an altered E/I balance in schizophrenia and innovatively show a direct link between aperiodic activity and the cognitive disruption. This relationship is further confirmed by the identification of two profiles, characterized by distinct neuropsychological and neurophysiological measures, with a flatter aperiodic slope, corresponding to an altered E/I balance, being associated with more severe cognitive impairment and illness severity. The clinical relevance is highlighted by the interplay between symptoms severity and neuropsychophysiological patterns on subjective well-being.

Disclosure of Interest: None Declared

EPP068

The Influence of Birth Weight on Cognitive Reserve and its impact on one-year Functioning in First-Episode Psychosis patients

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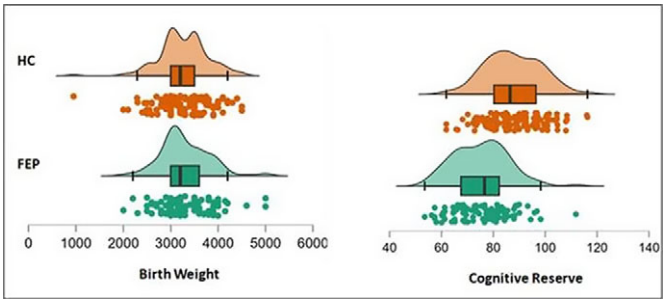
Introduction: Cognition is key to long-term outcomes in first-episode psychosis (FEP). Obstetric complications affect working and verbal memory in schizophrenia (Amoretti *et al.* Psychol Med, 2022;52:2874-2884). Among them, birth weight (BW), an indicator of prenatal development, has been studied in relation to cognition (Krishna *et al.* Int J Geriatr Psychiatry, 2019;34:1139-1169). Higher cognitive reserve (CR) is associated with better cognitive and functional outcomes (Amoretti *et al.* Psychol Med, 2022;52:526-537). It is hypothesized that low BW impacts fetal brain development, reducing CR and later functioning (Krishna *et al.* Int Psychogeriatr, 2021;1-14)

Objectives: To examine the relationship between BW and functioning one year after the onset of psychosis, mediated by CR and cognitive performance

Methods: 117 FEP patients and 224 healthy controls (HC) were recruited. BW was collected as a continuous variable in grams. The Functioning Assessment Short Test (FAST) assessed functioning. CR was quantified via premorbid IQ, educational attainment, and lifetime participation in leisure and social activities. A complete neurocognitive assessment was performed. Correlational analyses explored relationships between BW, CR, and cognition in FEP and HC. Serial mediation analysis (PROCESS Model 6) examined indirect effects of BW on functioning through CR and cognition

Results: No significant differences were found in BW between patients and HC (p=0.719). HC had higher CR than patients (p<0.001) **(Figure 1)**. In patients, BW correlated with CR (r=0.20, p=0.027), though no correlation was found in HC (r=0.10, p=0.216) **(Figure 2)**. The mediation model confirmed that BW was associated with CR (β=0.01, p=0.015), CR was linked to verbal memory (β=2.21, p=0.001) and verbal memory with functioning (β=0.07, p=0.004). The direct and total indirect effects of BW on functioning were non-significant. Among the indirect paths, only the one involving CR and verbal memory was significant (95%CI [0.0001, 0.0016]) **(Figure 3)**.

Image 1:



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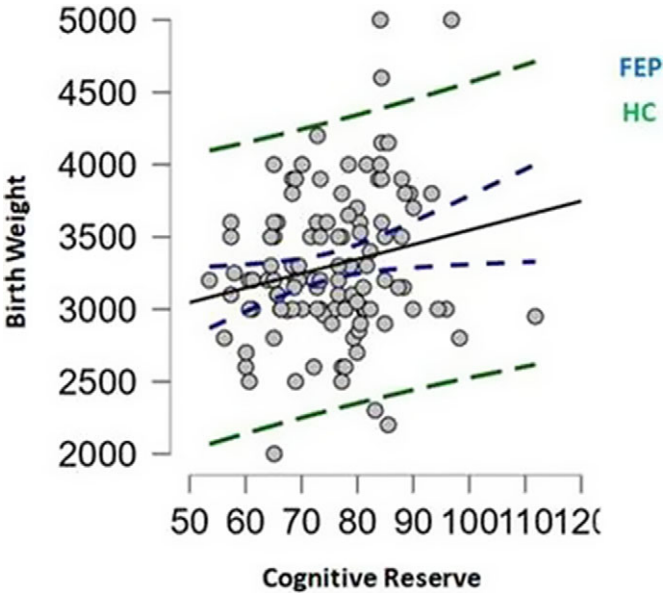

Image 3: