interaction was significant ($b=-3.13$, $p=0.002$): The intensity and direction of the PRS effect is moderated by the level of ERS, with a positive slope for low ERS (i.e., low environmental risk), and a negative slope for high ERS. In predicting positive schizotypy, the direct effects of PRS ($b=0.116$, $p=0.477$) and ERS ($b=0.006$, $p=0.068$) were not significant. However, we demonstrated an indirect effect through brain structural variation, showing a significant mediation ($index=0.223$, bootstrapped confidence interval 0.094–0.542). Cluster variation had a significant main effect on positive schizotypy ($b=-0.277$, $p=0.049$), but was modulated by the level of cognitive function, with a positive slope for low CF, and a negative slope for high CF, showing a second significant interaction ($b=-0.070$, $p=0.027$).

**Discussion:** Our finding is the first to integrate polygenic and poly-environmental markers with MRI parameters to demonstrate that the interaction of these cumulative risk factors leads to the emergence of subclinical symptoms through changes in brain structure. Furthermore, our model confirms cognition as a protective factor, indicating that above-average levels of cognitive function can compensate for dysfunctional processes that arise from altered neurodevelopment. Such compensatory mechanisms are crucial for understanding resilience, explaining high (positive) symptom load in unaffected individuals. Conventional diathesis-stress models propose increased vulnerability specifically to adverse events—our model extends this to suggest an inverted effect for high PRS and low ERS subjects. Under favorable environmental conditions, an increased genetic load might paradoxically result in low psychopathology outcomes or gain in function, supporting the notion of genes associated with schizophrenia as “plasticity genes” rather than simple risk factors. In sum, the present study provides proof for a multivariate model predicting the impact of genetic and environmental risk on a psychosis risk phenotype, extendable to other clinical spectra.

### S14. ANALYSIS OF METHYLATION AGE AND BLOOD CELL COMPOSITION IN SUBJECTS WITH CURRENT SUICIDE IDEATION

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**Background:** Suicidal Ideation (SI) remain an important and common risk factor affecting people with SCZ, who eventually attempt or complete suicide. Then the question is, what if factors (such as stressful life events and related molecular biomarkers) known to be involved in the aetiology of SCZ could help in predicting SI in this population? The accelerated aging hypothesis of SCZ posits that physiological changes associated with normal aging occur at an earlier age in individuals with SCZ than in the general population. Importantly, epigenetic changes may constitute an important component of aging process. Based on this, the chronological age can be predicted by the epigenetic clock in a highly consistent manner. The aims of this research were to determine the effect of cellular blood composition on current SI.

**Methods:** A total of 103 participants with a DSM-IV diagnosis of schizophrenia spectrum and other psychotic disorders were recruited from the Center of Addiction and Mental Health. The SI was assessed by the Columbia-Suicide Severity Rating Scale. Genome-wide DNA methylation analysis was generated from whole blood cells. The DNA methylation was assessed using the Illumina Infinium HumanMethylation450 Bead Chip while the DNA methylation-based age prediction and white blood cell composition was performed using the statistical pipeline developed by Horvath.

**Results:** Out of 103 participants, 18 had current SI (17%) while 85 had NSI. The DNAm age correlated with chronological age in the overall sample ($r=0.814$, $p<0.0001$), NSI ($r=0.823$, $p<0.0001$) and SI subjects ($r=0.734$, $p=0.001$). The strong linear relationship between DNAm age and chronological age showed a high accuracy of the epigenetic clock. However, DNAm age acceleration residuals did not differ between NSI and SI groups ($t=1.532$, $p=0.129$). Comparison of the cellular blood composition between the NSI and SI groups indicated no significant differences between the NSI and SI groups (lymphocytes ($t= -0.338$, $p=0.736$), monocytes ($t=-1.405$, $p=0.163$) and granulocytes ($t=0.924$, $p=0.358$)). Furthermore, there were no significant differences between the SI and NSI groups in the analysis of the plasmablast ($t=0.138$, $p=0.890$), CD4 naïve ($t=0.010$, $p=0.992$) and CD8 naïve ($t=0.681$, $p=0.497$)

**Discussion:** Stressful life events may change DNA methylation, which in turn can affect suicide ideation and suicidal behavior. Although SCZ is associated with age-related physiological factors, we were unable to find accelerated aging in our study. Nevertheless, we cannot rule out the possibility of other aging mechanism independent of epigenetic aging in SCZ patients. Conclusion: Further studies aimed at investigating the accelerated aging hypothesis in peripheral tissue are warranted to identify individuals with SCZ at risk for suicide. This will permit a tailored treatment and will prevent suicide in SCZ individuals.

### S15. BIMODAL DISTRIBUTION OF TONE-MATCHING DEFICITS INDICATES DISCRETE PATHOPHYSIOLOGICAL ENTITIES WITHIN THE SYNDROME OF SCHIZOPHRENIA

Abstract not included.

### S16. INDEPENDENT SUPPORT FOR CORTICOPALLIDAL CONTRIBUTIONS TO SCHIZOPHRENIA-RELATED FUNCTIONAL IMPAIRMENT

Abstract not included.

### S17. GLOBAL DNA METHYLATION IN CURRENT AND EMERGENT SUICIDAL IDEATION: ANALYSIS IN SCHIZOPHRENIA

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**Background:** Several lines of evidence have shown that epigenetic mechanisms influence suicidal behavior, but do not indicate specific susceptibility variants. In a recent study, analysis of global methylation levels found that psychiatric patients with a history of suicide attempt (SA) had significantly higher levels of 5-methyl cytosine (5mC), suggesting that patients with a history of SA have global hypermethylation of their genome. However, there is no study investigated the link between global DNA methylation and suicidal ideation (SI) in schizophrenia. In this study, we analyzed global DNA methylation in suicide ideators and non-ideators in a sample of schizophrenia patients to find if global DNA methylation can predict SI in schizophrenia.

**Methods:** There are several methods of detecting total 5-methylcytosine content in the genome. We used Cell Biolabs’ Global DNA Methylation ELISA Kit, which is a competitive enzyme immunoassay developed for rapid detection and quantitation of 5-methyl-2’-deoxycytidine (5MedCyd) in DNA extracted from white blood cells (WBC). We digested the genomic DNA, extracted from WBC, into single nucleotides and the quantity of 5MedCyd was determined by comparing its absorbance with that of a known 5MedCyd standard curve. We measured global DNA methylation in predicting current and emergent suicidal ideation.

**Results:** In the analysis of current SI in our schizophrenia patients, the average quantity of 5MedCyd was 7.56 ± 0.77 ng 5mC/µg DNA for suicide
S18. STRUCTURAL COVARIANCE PREDICTORS OF CLINICAL IMPROVEMENT AT 2-YEAR FOLLOW-UP IN FIRST-EPISTODE PSYCHOSIS

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**Background:** Neural correlates of psychotic disorders encompass multiple brain regions in multiple brain circuits, even at early stages. Previous research has characterized structural brain alterations in first-episode psychosis (FEP), but few studies have focused on the relationship between brain alterations and disease trajectories. First psychotic episodes typically evolve into a chronic course, affecting quality of life of patients and their families, with huge societal costs. Importantly, up to 80% of the patients relapse in the next five years after a first psychotic episode, with a significant risk of developing treatment resistance. Here, we investigated whether disease course may be predicted from brain structural assessments. Specifically, we measured structural covariance, a well-established approach to identify abnormal patterns of volumetric correlation across distant brain regions, which allows to incorporate network-level information to structural assessments. We performed a whole-brain structural covariance assessment of three bilateral regions form to three different cortical networks - dorsolateral prefrontal cortex (dlPFC) for the executive network, posterior cingulate cortex for the default mode network and insulae for the salience network - and subcortical structures (hippocampi, amygdalae and dorsomedial nucleus of the thalamus) that have shown to play a key role in schizophrenia.

**Methods:** We assessed a sample of 74 subjects from a multicentric, naturalistic, prospective and longitudinal study designed to evaluate clinical, neuropsychological, neuroimaging, biochemical, environmental and pharmacogenetic variables in first episode psychotic patients (PEPs project). Magnetic resonance imaging (MRI) scans were acquired at baseline and at 2-year follow-up, as well as clinical assessments. Psychotic symptoms were assessed using the Positive and Negative Symptom Scale (PANSS) due its widespread use in clinical studies and its reliability in assessing psychosis pathology across a range of patient populations. The sample was split in two groups as a function of the clinical improvement at 2-year follow-up: responders (i.e. 40% reduction in PANSS global score from baseline; n=29) and non-responders (n=45).

**Results:** Responder patients showed increase structural covariance between the left dlPFC and the left middle frontal gyrus, and between the right dlPFC and the right middle and superior gyrus, the left rectus and inferior frontal gyrus, the right hippocampus, and the vermis of the cerebellum. In addition, they showed increased structural covariance between the left anterior hippocampus and the ipsilateral middle occipital gyrus and the contralateral postcentral gyrus. Likewise, the structural covariance of right anterior hippocampus with right superior occipital gyrus and precentral gyrus was also increased in responder patients.

**Discussion:** This study shows, for the first time in the literature, that increased structural covariance at baseline within the executive network and between the hippocampi and posterior brain regions was associated with a superior treatment response at two-year follow-up. These results indicate that the integrity of structural networks should be taken into account to predict treatment outcome in FEP patients.

S19. THE ROLE OF ACE AS POSSIBLE BIOMARKER FOR TREATMENT RESISTANCE TO ANTIIPSYCHOTICS IN FIRST EPISODE OF PSYCHOSIS

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**Background:** Angiotensin I-converting enzyme (ACE) is a peptidase that converts angiotensin I into the vasoactive and aldosterone-stimulating peptide angiotensin II, a key protein in controlling blood pressure. Recently, several evidences have shown a role of ACE in psychosis. However, the role of ACE in psychosis is poorly characterized, and at last unknown. In this study we hypothesized that ACE blood and CSF levels are lower in patients at first episode of psychosis (FEP) compared to controls; that blood ACE levels can predict the response to antipsychotics; that low plasma ACE levels correlate with both severity of symptoms and cognitive performance.

**Methods:** This research used data from a longitudinal cohort study of FEP (N = 138) and controls (N = 115). First of all, we conducted a two-group comparison analyses to assess the differences between patients and controls in terms of ACE levels in both blood and CSF. As a second step, we divided our patients into treatment resistant (TR) and not treatment resistant (non-TR) to investigate ACE blood levels in these two group. Finally, we evaluated the association between ACE blood levels and clinical phenotype and neurocognition.

**Results:** Two-group analyses showed lower levels of ACE in patients than controls, both in blood and CSF (p values< 0.05). The two-group analyses between TR and non-TR showed lower ACE blood levels in TRs compared to non-TRs (p value< 0.05). Finally, multiple regressions showed a continuous relationship between cognitive performance and ACE blood levels (p values < 0.05).

**Discussion:** In conclusion, these findings showed that those FEP with lower ACE blood levels were not only more likely to develop TR conditions, but they also had greater cognitive impairment. These results are very promising, as they suggest that ACE levels can be used as a peripheral biomarker to stratify patients at first episode of psychosis.

S20. LIFETIME PSYCHOPATHOLOGY IN CHILD AND ADOLESCENT OFFSPRING OF PARENTS DIAGNOSED WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

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**Background:** The lifetime prevalence of psychiatric disorders is higher among offspring of parents with schizophrenia or bipolar disorder than among the general population. The aim of this study was to describe the lifetime prevalence of psychiatric disorders in the offspring of parents with schizophrenia or bipolar disorder.

**Methods:** The study population included 100 parents with schizophrenia or bipolar disorder and their 100 offspring. The lifetime prevalence of psychiatric disorders was assessed using the diagnostic interview for genetic studies (DIGS). The DIGS is a semi-structured interview designed to assess the lifetime prevalence of psychiatric disorders and to identify risk factors for the development of these disorders.

**Results:** The lifetime prevalence of psychiatric disorders in the offspring of parents with schizophrenia or bipolar disorder was significantly higher than in the general population. The most common psychiatric disorders were anxiety disorders, affective disorders, and substance use disorders.

**Discussion:** The results of this study suggest that the offspring of parents with schizophrenia or bipolar disorder are at increased risk for the development of psychiatric disorders. These findings highlight the importance of early intervention and the need for targeted prevention programs for these individuals.

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