Conclusion: A wide range of psychotic experiences are predictors of later suicidal behavior, whereas a narrower range of psychotic experiences are predictors of later substance use disorder. These risk markers should be carefully assessed in mental health clinics and can inform about risk of future poor outcomes.

6.4 STRUCTURAL AND FUNCTIONAL BRAIN ABNORMALITIES ASSOCIATED WITH DISTINCT DIMENSIONS OF SUBTHRESHOLD PSYCHOSIS IN YOUTH

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Background: Neuroimaging in population-based studies of youth can help identify neurodevelopmental abnormalities associated with psychosis-spectrum symptoms and risk. To date, little work has examined specific dimensions of psychosis spectrum symptoms in this population, a gap we sought to address here in the large Philadelphia Neurodevelopmental Cohort (PNC).

Methods: In the PNC, ~20% of youth were categorized as psychosis spectrum (PS) based on elevations in positive or negative/disorganized symptoms. Baseline multimodal imaging data were acquired from 1601 youth from the PNC, aged 8–23 years, 452 of whom were identified as PS. Dimensional subclinical positive and negative/disorganized were derived from factor analysis of a structured clinical interview; cognition was measured with the Penn Computerized Neurocognitive Battery.

Results: Subthreshold positive and negative symptom severity was moderately correlated ($r = .37$); reduced cognitive performance was modestly associated with both positive ($r = -.14$) and negative ($r = -.17$) domains. These 3 domains showed distinctive associations with functional and structural imaging. In the working memory fMRI task, PS showed reduced activation in executive control circuitry, which correlated with cognitive deficits ($r = .32$) but not positive or negative symptoms. During emotion identification fMRI, PS demonstrated elevated amygdala responses to threatening facial expressions, which correlated selectively with positive symptom severity ($r = -.16$). Structural imaging revealed gray matter volume reductions in hippocampus associated with positive symptom severity ($r = -.15$). In contrast, unmodulated gray matter density was selectively reduced in the bilateral nucleus accumbens in association with negative symptom severity ($r = -.16$).

Conclusion: These findings extend support for the continuum view of psychosis by demonstrating that specific circuit–symptom correlations are tightly correlated ($r = .37$); reduced cognitive performance was modestly associated with both positive ($r = -.14$) and negative ($r = -.17$) domains. These 3 domains showed distinctive associations with functional and structural imaging. In the working memory fMRI task, PS showed reduced activation in executive control circuitry, which correlated with cognitive deficits ($r = .32$) but not positive or negative symptoms. During emotion identification fMRI, PS demonstrated elevated amygdala responses to threatening facial expressions, which correlated selectively with positive symptom severity ($r = -.16$). Structural imaging revealed gray matter volume reductions in hippocampus associated with positive symptom severity ($r = -.15$). In contrast, unmodulated gray matter density was selectively reduced in the bilateral nucleus accumbens in association with negative symptom severity ($r = -.16$).

8. ALLOSTATIC LOAD IS ASSOCIATED WITH POSITIVE SYMPTOMS IN SCHIZOPHRENIA AND FIRST-Episode PSYCHOSIS AND DECREASES WITH ANTIPSYCHOTIC THERAPY

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Background: Current pathophysiological models of schizophrenia suggest that stress contributes to the etiology and trajectory of the disorder. We investigated whether cumulative exposure to stress, quantified by allostatic load (AL), an integrative index of immune, metabolic, and neuroendocrine dysregulation, is elevated in patients with schizophrenia (SCZ) and first-episode psychosis (FEP) and related to psychotic symptoms and social and occupational functioning and assessed the temporal dynamics of AL in response to treatment with second-generation antipsychotics.

Methods: We assessed AL in a naturalistic study of unmedicated patients with SCZ (n = 28), FEP (n = 28), and healthy controls matched for age and gender (n = 53) at baseline and 6 and 12 weeks after commencement of antipsychotic therapy. Biomarkers for the AL index were selected based on (1) representation of several physiological systems including the cardiovascular, neuroendocrine, immune, and metabolic systems; (2) use in previous AL research; and (3) associations with disease risk. We adopted a scaled AL algorithm whereby each marker proportionally contributes to the overall AL index. Unadjusted and adjusted differences between patients with SCZ, FEP, and controls in AL were tested with ANCOVA, and partial correlations were used to test associations of AL with psychometric variables.

Results: AL was higher in patients with SCZ compared to controls (4.91 ± 1.89 vs. 2.87 ± 1.62, $P = .020$) but not different between patients with SCZ and patients with FEP ($P = .302$). Adjusting for age and smoking, we found that positive symptoms were positively correlated with AL across all patients with a psychotic disorder (adjusted $R = .520$, $P < .001$) and Global Assessment of Functioning (GAF) scores were negatively
correlated with AL at trend level (adjusted R = −.251, P = .070). No significant associations were found for negative symptoms (P = .582). AL decreased after treatment with olanzapine, risperidone, or quetiapine was commenced in patients with SCz and FEP between the baseline assessment and the 6- and 12-week follow-up.

Conclusion: Our data provide evidence for cumulative physiological dysregulation in patients with SCz and FEP that is linked to the experience of current positive psychotic symptoms. AL could be a useful model that takes stress, long-term adaptation, and its failures into account to further understand the pathophysiology of schizophrenia.

9. ELEVATED TNF-α LEVELS IN CEREBROSPINAL FLUID OF PATIENTS WITH SCHIZOPHRENIA

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Background: Elevated levels of proinflammatory cytokines have provided evidence in support of the inflammatory hypothesis of schizophrenia. Most studies in schizophrenia have reported cytokine levels in peripheral blood, but the number of studies investigating cytokines in CSF in schizophrenia is still very small and those studies typically have small sample sizes. Of the cytokines studied, IL-6 and IL-8 have been most commonly measured and reported while abnormalities in other cytokines, such as TNF-α, have not been reported in CSF of patients with schizophrenia. Therefore, our aim was to study a panel of cytokines in cerebrospinal fluid of a decently large sample of patients with schizophrenia and healthy volunteers. In addition, we examined correlations between these cytokines and psychiatric symptoms.

Methods: Thirty-three patients with schizophrenia-spectrum disorders and 23 healthy volunteers underwent a lumbar puncture. CSF of 15–25 cc was obtained from each subject. CSF cytokine (IL-1β, IL-2, IL-4, IL-6, IL-8, and TNF-α) concentrations were determined in duplicate by enzyme-linked immunosorbent assay (ELISA) and a high-sensitivity MilliplexTM Multiplex kit (HSTCMAG-28SK-06, Millipore, Billerica, MA) per manufacturer's instructions. In patients, psychiatric symptoms were assessed using the Brief Psychiatric Rating Scale–Anchored version (BPRS-A). Comparisons in cytokine levels between groups were performed using either t-tests for normally distributed variables or Wilcoxon rank-sum tests for nonnormally distributed variables. Correlations were computed using the Pearson's coefficient.

Results: The mean age of 36.6 years (SD = 11.7) in patients and 38.1 years (SD = 10.1) in controls. Twenty-four (72.2%) of 33 patients and 14 (60.1%) of the 23 healthy volunteers were male. Mean total BPRS score in patients was 28.6 (SD = 9.0). Mean TNF-α values were elevated in patients (6.47 pg/ml [SD = 3.1]) compared to healthy volunteers (3.76 pg/ml [SD = 2.5], P = .001). There were no statistically significant differences in levels between patients and controls in IL-2 (mean = 5.46 pg/ml [SD = 1.9] vs. 4.82 pg/ml [SD = 2.0], IL-6 (9.31 pg/ml [2.6] vs. 8.9 pg/ml [2.9]) and IL-8 (49.44 pg/ml [11.2] vs. 47.21 pg/ml [12.2]). Levels of IL-1β and IL-4 were not detected in more than 30% of the CSF samples; therefore, these cytokines were not entered in the analysis. Correlational analysis showed that TNF-α was significantly correlated with the conceptual disorganization item on the BPRS-A (r = .39, P = .04). No other correlations were statistically significant.

Conclusion: TNF-α, a pro-inflammatory cytokine and a key participant in the acute phase response of the inflammatory cascade, is elevated in CSF of patients with schizophrenia providing support to the inflammatory hypothesis in schizophrenia. Future studies should focus not only on IL-6 but also on TNF-α to further understand the role of proinflammatory cytokine in schizophrenia.

10. BRAIN STRUCTURE BIOMARKERS AT THE PSYCHOSIS/NONPSYCHOSIS INTERPHASE: FINDINGS FROM THE BIPOLAR–SCHIZOPHRENIA NETWORK FOR INTERMEDIATE PHENOTYPES

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Background: The study presents whole brain and regional gray matter density (GMD) characteristics contrasted along the psychosis/nonpsychosis interface in (1) schizophrenia—schizoaffective—psychotic bipolar—nonpsychotic bipolar probands, and (2) their first-degree relatives organized by lifetime psychosis expression, from the B-SNIP consortium sample.

Methods: A total of 1652 3Tesla T1-weighted MPRAGE or IR-SPGR scans were analyzed using Voxel-Based Morphometry (SPM8/VBM8/DARTEL) with subsequent subject-level regional GMD characterization.

Results: Among probands, individuals with schizophrenia (mean d = 0.66) and schizoaffective disorder (mean d = 0.73) showed overlapping and diffusely distributed GMD reductions spanning cortical and subcortical regions, with the largest effects in the frontotemporal, cingulate, and insular cortices, compared to healthy controls. Proband psychotic bipolar disorder contrasted with controls showed modest GMD reductions (mean d = 0.54), primarily localized to anterior limbic regions. The data for nonpsychotic bipolar probands will also be reported; we predict normal/ near-normal GMD characteristics, relative to controls. Among relatives organized by lifetime psychosis manifestations, relatives with DSM-IV Axis I psychotic disorders and Axis II psychosis spectrum personality disorders (schizoid, paranoid, and schizotypal) showed GMD reductions intermediate in magnitude between the psychosis probands and healthy controls, primarily localized to bilateral frontal regions. In contrast, relatives without lifetime Axis I/II psychotic disorders showed GMD not different from healthy controls. No effect of concurrent medications (antipsychotics, mood stabilizers, antidepressants) on GMD outcomes was detected in probands; the majority of relatives were unmedicated.

Conclusion: Our findings indicate divergent GMD characteristics for psychotic versus nonpsychotic phenotypes among probands with severe mental illness and their biological relatives and suggest that GMD alterations may serve as a biomarker unique to psychosis.

11. EXTENDED ASSOCIATION STUDIES OF SMOOTH PURSUIT AND ANTISACCADE EYE MOVEMENTS: FINDINGS FROM THE B-SNIP STUDY

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