representation, reinforcement learning. Computational models were applied to task data to infer potential mechanisms and network analysis was used to evaluate which reward processing domain was most central for each group.

Results: CHR and SZ groups had similar behavioral and neurophysiological deficits on the domains of reinforcement learning, reward anticipation, effort-cost computation, and value representation. However, CHR youth displayed a self-reported and neurophysiological impairment in hedonic response that was not present in SZ. Actor-critic, Q-learning, and bias models implicated different underlying mechanisms for deficits in reinforcement learning and effort-cost computation across phases of illness. Reinforcement learning and effort-cost computation abnormalities were driven by top-down control abnormalities in SZ and under-valuation of rewards in CHR youth. Network analysis revealed that hedonic response was the most central domain of reward processing in CHR youth, whereas value representation was most central in SZ.

Discussion: Findings suggest that abnormalities in reward processing underlie avolition in CHR and SZ populations; however, the underlying mechanisms are different across phases of illness, with basic hedonic deficits propagating forward and resulting in impairments in higher-order domains in CHR youth and frontally-driven impairments in generating, updating, and maintaining mental representations of value underlying broader deficits in reward processing in adults with SZ. Evidence for equifinality suggest that different treatment approaches are needed for avolition in SZ and CHR youth.

O13.4. GENETIC PREDISPOSITION FOR TYPE 2 DIABETES MELLITUS IS ASSOCIATED WITH ALTERED CHILDHOOD IMMUNE AND METABOLIC FUNCTION WHICH IS LONGITUDINALLY ASSOCIATED WITH RISK OF PSYCHOSIS

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Background: Subclinical metabolic dysfunction and inflammation have been associated with early psychosis and depression, suggesting the possibility of an intrinsic association. This may be due to shared genetic vulnerability. We aimed to test: 1) whether genetic or environmental predisposition for type 2 diabetes mellitus (T2DM) is longitudinally associated with risk of psychotic disorder and/or depression at age 18 years; 2) whether genetic or environmental predisposition for T2DM is associated with an altered childhood (age 9 years) metabolic or immune function present on the longitudinal pathway leading to risk of psychotic disorder or depression.

Methods: We used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. We used regression to first test whether polygenic risk scores (PRS) for T2DM (genetic risk) or cardiometabolic family history (environmental risk) were associated with psychosis risk or depression; before and after adjustments.

We used logistic and linear regression to test whether genetic or environmental risk for T2DM was associated with a range of biochemical measures of metabolic and immune function at age 9 years, before and after adjustments.

We further explored associations by testing mediation by metabolic and immune markers between PRS for T2DM and psychotic disorder/depression, before and after adjustments. We tested for moderation effect of PRS for T2DM on associations between metabolic and immune markers and risk of psychosis.

Results: We included 4,532 participants. Genetic risk for T2DM was significantly associated with psychotic disorder (adjusted OR=1.62 (95% C.I. 1.10–2.40) but not depression. Environmental risk was not associated with psychotic disorder or depression. After adjustments, genetic risk for T2DM was associated with age 9 levels of fasting plasma glucose, C - reactive protein (CRP) and triglycerides. Age 9 levels of interleukin-6 (IL-6), CRP, and fasting insulin were associated with psychosis risk at age 18 years. Age 9 levels of High Density Lipoprotein (HDL), leptin and IL-6 were associated with depression at age 18 years.

We found evidence of an enhancing and association switching interaction effect of PRS for T2DM on the association between IL-6 and psychosis risk. We found evidence that the association between PRS for T2DM and psychosis risk at age 18 years is partially mediated by CRP.

Discussion: This longitudinal study provides evidence that even before birth, a summation of minor genetic variations may predispose to a course of events through childhood and early adolescence involving minor immune and metabolic alterations, leading over time to risk of psychosis and T2DM. The findings may help to explain known cardiovascular disease associations and decreased life-expectancy borne by patients with psychotic disorders.

O13.5. GLUTAMATERGIC METABOLITES ASSOCIATED WITH ALTERED HIPPOCAMPAL AND STRIATAL ACTIVATION DURING NOVELTY SALIENCE IN PEOPLE WITH A CLINICAL HIGH RISK FOR PSYCHOSIS

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Background: Using Magnetic Resonance Spectroscopy (MRS) we have recently shown that, in individuals with a Clinical High Risk (CHR), transition to psychosis is associated with increased left hippocampal glutamate levels at presentation. We have also shown that relative to healthy controls (HC), CHR participants show reduced hippocampal activity during a novelty salience task when processing pure stimulus novelty. However, the extent to which elevated glutamatergic metabolite levels in CHR cohorts are related to reduced hippocampal function has yet to be investigated.

Methods: Seventy-five individuals with a CHR for psychosis and 31 HC completed MRS and functional Magnetic Resonance Imaging during a novelty salience task to measure hippocampal glutamatergic metabolite levels and task-related activity (during pure stimulus novelty) respectively. In the CHR group 13 participants made a transition to psychosis at clinical follow-up (mean = 18.5 months). Three-way interactions were modeled between task-related activity, hippocampal glutamatergic metabolite levels and group (HC vs. CHR) using a Region of Interest (ROI) approach in bilateral hippocampus and striatum (which receives glutamatergic outputs from the hippocampus and is also activated during a novelty salience task).

Results: The CHR group were significantly younger and had received fewer years of education than HC. CHR and HC groups were matched for gender, estimated IQ scores, tobacco and alcohol use. Ten CHR participants were receiving low doses of antipsychotic medication. There was no interaction between left hippocampal glutamate levels, task-related activity and group in either ROI. There was a significant interaction between Glx levels (combined glutamate and glutamine peaks), task related activity and group in the right hippocampus (x = 28, y = -30, z = -6; Z =3.62; p FWE = .02) and the right dorsal striatum (x = 6, y = 16, z =6; Z = 3.67 p FWE = .01). In both hippocampal and striatal ROIs the 3-way interaction was driven by a positive association between hippocampal Glx levels and activity during pure stimulus novelty in the HC group. In the CHR group however, the relationship between Glx and task-related activity was negative and largely driven by CHR participants that had transitioned to psychosis at follow-up.

Discussion: Hippocampal glutamatergic metabolite levels are associated with altered functional activation in the hippocampus and dorsal striatum during a novelty salience task. These findings are consistent with previous clinical and pre-clinical work that posit a role for glutamate in hippocampal dysfunction and associated risk for psychosis.