S175. CLINICAL OUTCOMES IN PEOPLE AT HIGH RISK FOR PSYCHOSIS RELATED TO INTERACTIONS BETWEEN POLYGENIC RISK SCORES AND CHILDHOOD ADVERSITY

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Background: Genetic vulnerability to psychosis is polygenic, involving multiple genes with small individual effects (Psychiatric Genomics Consortium (PGC), 2014). The risk of psychosis is also related to environmental factors, such as childhood trauma (Lardinois et al, 2011). Although the onset of psychosis is thought to result from the interaction of genetic and environmental risk factors (Walker & Diforio, 1997), the extent to which the influence of childhood trauma depends on genetic susceptibility remains unclear. We sought to address this issue in a large prospective study of people at clinical high risk (CHR) for psychosis. These individuals present with psychotic and affective symptoms, and are at increased risk of developing both schizophreniform and affective psychoses.
Methods: We studied subjects of European ancestry, drawn from EU-GEI, a large multi-centre prospective study of people at CHR for psychosis. At baseline, DNA was obtained from subjects who met the CAARMS criteria for the CHR state (n=266) and healthy controls (HC; n=42). Childhood trauma was assessed using the childhood trauma questionnaire (CTQ), which comprises 5 subdomains: emotional abuse, physical abuse, sexual abuse, physical neglect, and emotional neglect. Polygenic risk scores (PRSs) for schizophrenia (SCZ), bipolar disorder (BD) and major depressive disorder (MDD) were constructed separately, using results from meta-analyses by the corresponding Disorder Working Groups of the PGC. The CHR subjects were clinically monitored for up to 5 years and clinical outcomes were assessed in terms of transition to psychosis (as defined by the CAARMS), remission from the CHR state (subject no longer meets CAARMS inclusion criteria) and level of functioning (GAF Disability Scale). Logistic regression models were used to investigate the association between each PRSs and childhood trauma as predictors of transition and remission, adjusted by population stratification using the first 10 principal components, age, sex and site. All findings are reported at p<0.017, Bonferroni-corrected for the 3 PRSs.
Results: Within the CHR sample, the onset of psychosis during follow up was related to interactions between the BD PRS and the total childhood trauma score (OR=0.959, 95% CI 0.930–0.988, p=0.006), and between the BD PRS and physical abuse (OR=0.787, 95% CI 0.689–0.900, p<0.001). Remission from the CHR state was related to an interaction between the SCZ PRS and childhood sexual abuse (OR: 1.110, 95% CI 1.004–1.226, p=0.041).
Discussion: These data indicate that clinical outcomes in CHR subjects are related to interactions between the polygenic risk for psychotic disorders and childhood adversity. The measurement of interactions between genomic and environmental risk factors may help to predict individual outcomes in people at high risk in a clinical setting.

S176. A PRELIMINARY INVESTIGATION OF COMT GENE INVOLVEMENT IN COGNITIVE FLEXIBILITY AND ATTENTION IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Background: Schizophrenia spectrum disorders (SSD) are often characterised by a plateau or decline in cognitive abilities early in the prodrome. The cause of developmental alteration remains unknown, and investigation of genetic involvement in cognitive function in these disorders may assist the understanding of the underlying neurobiological mechanisms involved. Variation at two single nucleotide polymorphisms (SNPs) of the catechol-O-methyltransferase (COMT) gene have previously shown an influence on COMT protein levels and cognition; rs4680 and rs4818. Here we investigate the influence of the nonsynonymous "Val/Met" SNP rs4680 and a second functional SNP, rs4818, on tasks of cognitive flexibility and attention.
Methods: The sample comprised 48 healthy controls (HC; age = 31.95 ± 12.80; 25 males, 23 females), and 43 with a diagnosis of SSD (age = 41.64 ± 10.36; 26 males, 17 females). Measures of cognitive flexibility and attention included the Wisconsin Card Sorting Test (WCST), Continuous Performance Test-Identical Pairs version (CPT-IP), Trail Making Test (TMT), and the D-KEFS Colour Word Interference Test (CWIT). Due to small cohort sizes, in our preliminary analyses we chose to compare people who should be most severely affected because of inheriting COMT haplotypes associated with poor cognitive functioning (GG rs4818 / GG rs4680: G-G haplotype) to those with haplotypes associated with better cognitive functioning (CC rs4818 / AA rs4680: C-A haplotype). Multivariate analysis of variance factors included COMT haplotype, diagnosis (HC and SSD), and gender, with Bonferroni correction for multiple comparisons; age was included as a covariate. Analyses were also conducted based on a non-functional SNP of the COMT gene; rs165599, as a negative control.
Results: SSD exhibited reduced cognitive performance compared to HC; $F(4, 75) = 8.810$, $p < .001$. Investigation of C-A haplotype revealed an interaction with diagnosis on cognitive performance; $F(8, 154) = 2.075$, $p = .041$; SSD had reduced performance compared to HC for the WCST, CPT-IP, and TMT in C-A haplotypes (all $p < .05$). COMT haplotype also interacted with gender on cognitive performance (C-A haplotype; $F(8, 154) = 2.315$, $p = .023$, G-G haplotype; $F(8, 154) = 2.706$, $p = .008$). Males who were C-A non-carriers and /or G-G haplotype (high COMT activity groups) performed better on CPT-IP (both $p < .05$) and worse on CWIT (both $p < .05$) compared to females. Control SNP rs165599 revealed no main effects or significant interactions (all $p > .05$).
Discussion: The role of the COMT gene in the cognitive abilities of SSD remains contentious as gene expression does not differ from a healthy population. This preliminary analysis revealed an interaction between diagnosis and COMT haplotype, however, this only reached statistical significance for the C-A haplotype, where SSD with C-A haplotype and C-A non-carriers had reduced performance compared to HC on most tasks except TMT. The different effects found across the tasks, which probed various elements of cognitive flexibility and attention, supports a nuanced role of COMT in cognitive function. Further, high COMT activity was beneficial for males on CPT-IP but not CWIT compared to females. Gender interaction remains a