

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

significant consideration in studies of the COMT gene, likely involving the catechol-estrogens which are substrates of COMT. As expected there was no significant results with control SNP rs165599, indicating that findings were due to the influence of SNPs rs4680 and rs4818 on COMT activity.

S177. IMPACT OF NOS1AP AND ITS INTERACTION PARTNERS AT THE GLUTAMATERGIC SYNAPSE ON WORKING MEMORY NETWORKS - AN FMRI IMAGING GENETICS STUDY

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Background: N-methyl-D-aspartate receptor (NMDAR) hypofunction is an important pathophysiological mechanism in schizophrenia. At the postsynapse the NMDAR interacts with the post-synaptic density (PSD). Neuronal nitric oxide synthase 1 (NOS1) binds to the PSD scaffolding proteins PSD-93 and PSD-95, enabling NMDAR-mediated release of nitric oxide via NOS1. NOS1AP (adaptor of NOS1) is capable of disrupting the interactions between NOS1, PSD-93, and PSD95. Therefore, NOS1AP is closely involved in both glutamatergic and nitrinergic neurotransmission. NOS1AP has been implicated as a risk gene for schizophrenia and cognitive dysfunction. Its increased expression has been observed in dorsolateral prefrontal post-mortem brain tissue of patients with schizophrenia, and NOS1AP SNPs have been associated with established schizophrenia endophenotypes. These findings suggest that the influence of NOS1AP variants should be observable in neural systems implicated in schizophrenia. In the present study, we investigate the impact of NOS1AP and its interaction partners at the glutamatergic synapse on the cortical working memory (WM) networks using fMRI and a gene set analysis approach.

Methods: 97 right-handed individuals with no personal or family history of psychiatric disorders underwent fMRI in a 3T Siemens Trio scanner during the performance of a visuospatial change detection WM task. Data analysis in Brain Voyager QX 2.8 included standard data preprocessing. Additionally, a multiscale curvature driven cortex based alignment procedure was used to minimize macro-anatomical variability between subjects. Subsequently, data were analyzed using a random-effects multi-subject general linear model. We investigated 19 regions of interest (ROIs) within the core fronto-parietal WM network. We studied all phases of our WM paradigm (encoding, maintenance, retrieval), which were modeled by a total of 5 regressors (encoding, delays 1–3, retrieval). Genetic data was quality controlled and imputed using the RICOPILI pipeline. Gene-set analyses of the 19 ROIs were performed using MAGMA. Two gene sets were selected: 1) NOS1AP/NOS1; 2) NOS1AP/glutamatergic synapse. We applied a Bonferroni correction for the total of 19 ROIs and 5 regressors (95 tests) to both analyses.

Results: Both gene set analyses revealed multiple associations between brain activation in core fronto-parietal WM areas. For the NOS1/NOS1AP set, most associations were observed during the late maintenance phase (Delay 3) of our WM paradigm. One association was significant Bonferroni correction: a cluster in the left intraparietal sulcus during the late maintenance phase (Delay 3; $\beta=2.2459$, $SD=0.0239$, $SE=0.6451$, $p=0.00025$). For NOS1AP / glutamatergic synapse interaction partners, two associations were significant after Bonferroni correction: a cluster in the right IPS during the early maintenance phase (Delay 1; $\beta=0.8525$, $SD=0.0257$, $SE=0.2127$, $p=0.0000308$) and a cluster in a different part of the right IPS during the late maintenance phase (Delay 3; $\beta=0.7186$, $SD=0.0216$, $SE=0.2119$, $p=0.000348$).

Discussion: In our gene set analyses we observed multiple associations between brain activation during WM and NOS1AP and its interaction partners, which were most pronounced during the late maintenance phase of our WM task in bilateral areas within the IPS. Both the more constrained NOS1AP / NOS1 gene set and the NOS1AP / glutamatergic synapse gene set showed similar association patterns. Our results implicate the NOS1AP interactome and the glutamatergic system in information processing and brain function in a cognitive domain strongly impaired in schizophrenia. They also indicate that altered activation of parietal WM areas during the maintenance phase is most strongly affected.

S178. SHOULD SCHIZOAFFECTIVE DISORDER DEPRESSED-TYPE BE DISTINCT FROM SCHIZOPHRENIA? ANALYSIS OF GENETIC LIABILITY AND LIFETIME CLINICAL CHARACTERISTICS.

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Background: Schizoaffective disorder depressed type (SAD) has been considered a distinct diagnostic entity since 1987, yet it is rarely recognised in clinical and research settings as it is considered analogous to schizophrenia with comorbid depression. However, these assumptions are often based on anecdotal evidence, as little research has attempted to examine differences between the two disorders. We aimed to establish the validity of SAD as a diagnosis, by investigating phenotypic and genotypic differences between schizophrenia and SAD.

Methods: Participants were from the Cardiff Cognition study and included if they met ICD-10 criteria for schizophrenia ($n=713$) or SAD ($n=151$). Diagnosis was determined via consensus assessment by trained researchers using lifetime symptom data from the SCAN interview alongside patient medical records. Polygenic risk scores were derived for schizophrenia and major depressive disorder using PRSice. Logistic regressions were used to measure the association between diagnosis and lifetime clinical characteristics across five categories: demographics, premorbid functioning, illness progression, psychosis, and depression. Sex and age at interview were included as covariates. Logistic regressions were used to measure the association between diagnosis and polygenic risk scores for schizophrenia and depression at a threshold of $p<.05$, covarying for sex and principal components.

Results: Compared to schizophrenia, SAD was significantly associated with female sex ($OR=3.19$, 95% $CI=2.23-4.59$, $p=5.0 \times 10^{-9}$), lower global assessment score in worst episode of depression ($OR=0.47$, 95% $CI=0.37-0.59$, $p=5.0 \times 10^{-9}$), higher global assessment score in worst episode of psychosis ($OR=1.44$, 95% $CI=1.20-1.72$, $p=6.8 \times 10^{-4}$), a greater likelihood of an admission for depression ($OR=2.24$, 95% $CI=1.48-3.40$, $p=1.2 \times 10^{-3}$), greater alcohol abuse or dependence ($OR=2.12$, 95% $CI=1.41-3.20$, $p=2.3 \times 10^{-3}$), longer duration of depression ($OR=1.46$, 95% $CI=1.19-1.84$, $p=3.5 \times 10^{-3}$), experiencing childhood abuse ($OR=2.07$, 95% $CI=1.35-3.17$, $p=3.9 \times 10^{-3}$), a reduced likelihood of an involuntary admission for psychosis ($OR=0.40$, 95% $CI=0.22-0.75$, $p=0.01$), depression onset occurring prior to psychosis onset ($OR=2.40$, 95% $CI=1.37-4.43$, $p=0.01$), having a higher number of children ($OR=1.34$, 95% $CI=1.08-1.67$, $p=0.03$), and better cognitive functioning ($OR=1.20$, 95% $CI=1.04-1.40$, $p=0.05$).

Depression polygenic risk score was higher in participants with SAD ($OR=1.33$, 95% $CI=1.06-1.66$, $R^2=0.015$, $p=0.01$); schizophrenia polygenic risk score was not associated with diagnosis ($OR=0.94$, 95% $CI=0.75-1.17$, $R^2=0.001$, $p=0.58$). Secondary analyses were conducted to