S13. Symposium: VULNERABILITY FOR SCHIZOPHRENIA: EUROPEAN CLINICAL AND GENETIC HIGH RISK STUDIES

S13.01

Co-aggregation of cognitive, personality and genetic risk indicators of schizophrenia in an ongoing Catalan family study

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Background: Neurocognitive deficits and schizotypal features are elevated in first-degree relatives of schizophrenia patients. However, the co-aggregation of these indicators is not well known. Some studies have found that neurocognitive deficits and schizotypy increase in severity with the density of family history of schizophrenia. Therefore, we studied in affected families a) whether the status of Presumed Carrier (PC) of the genetic risk for schizophrenia is associated with higher levels of neurocognitive deficits and schizotypic features and b) the relationship between schizotypy and neurocognition.

Methods: From an ongoing Catalan Multicentric Family Study on Schizophrenia, 70 families were included in this analysis. 90 non-psychotic parents of schizophrenic patients (age 50.7/8.8; education 10.3/4.04; IQ 96.2/14.6) were defined as PC if they had at least one first (apart of offspring) or second degree relative with schizophrenia spectrum disorders (FIGS), resulting in 17 PC and 73 non-PC. Schizotypic features were assessed with the SCID-II and the SPQ-B. Working memory (WM), executive functioning, sustained attention, verbal fluency and logical memory were also assessed.

Results: PC differed significantly from NPC on verbal working memory, even after controlling for IQ (d=0.8). They did not differ on any of the self-reported or interview measures of schizotypy. The negative schizotypic dimension was associated with more WCST-perseverative errors, and low scores in spatial-WM, verbal fluency and immediate/delayed logical memory.

Discussion: A large association was found between verbal-WM and the familial background of schizophrenia. Only negative features were associated with some neurocognitive functions, supporting the view of multiple independent dimensions or a pleiotropic expression of risk.

S13.02

Cognitive trait and state markers in subjects at genetic high risk

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Background: Prospective studies of young individuals at high genetic risk of schizophrenia allow investigation of whether any neurodevelopmental abnormalities usefully predict the development of the disorder.

Method: 163 high risk subjects with an initial mean age of 21 years were recruited as they had at least two relatives with schizophrenia. Together with 36 control subjects, they were examined at baseline (with developmental, clinical, neuropsychological and structural/functional MRI measures) and at 18 month intervals thereafter. Comparisons were made between those who developed schizophrenia, well controls, a well high risk group and those of the high risk sample with partial or isolated psychotic symptoms.

Results: 21 high risk subjects developed schizophrenia within an average time of two and a half years. A much larger number have shown isolated or partial psychotic symptoms and the whole high risk sample differed from controls on several variables. Those who developed schizophrenia differed from those with psychotic symptoms who did not on several measures including: interview and self-report measures of schizotypy, the AVLT1-5, and fMRI-BOLD responses on three separate tasks.

Conclusions: Schizophrenia is a disorder which has its origins very early in life, but develops over years. Its mode of inheritance affects many more individuals than will develop the illness and partial impairment can be found in them. Highly significant predictors of the development of schizophrenia are detectable years before onset.

S13.03

Childhood victimization and developmental expression of sub-clinical psychosis

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Experiences of childhood trauma and victimization may be associated with adult psychosis. This association will be examined cross-sectionally and longitudinally in an adolescent sample from the general population. In an adolescent sample of 1290 14-year olds, the association between unwanted sexual experiences and being bullied on the one hand and psychotic experiences on the other, was examined. Both sexual trauma (OR: 4.8, 95% CI 2.3-10.1) and being bullied (OR 2.9, 95% CI 1.8-4.8) were strongly and independently associated with psychotic experiences. After a follow-up of 2 years, sexual trauma (OR: 5.7, 95% CI 2.5-12.9) and being bullied (OR: 2.1, 95% CI 1.1-3.9) remained significantly associated with psychosis-like experiences.

These results suggest that reported associations between childhood victimization and adult psychosis can be understood in a developmental framework of onset of at-risk mental states in early adolescence. It will be argued that the mechanism by which trauma is likely to impact on psychosis risk is through cognitive and emotional pathways on the one hand, and biological pathways, possibly involving dopamine sensitisation, on the other.

S13.04

Impact of schizophrenia candidate genes on schizotypy and cognitive endophenotypes at the population level

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Background: Aspects of cognitive function and schizotypy have been proposed as potential endophenotypes for schizophrenia. It is unknown if the expression of these endophenotypes at the population level is modulated by the genetic variability of candidate susceptibility genes for schizophrenia.

Methods: We examined the potential impact of 19 single nucleotide polymorphisms (SNPs) within five susceptibility genes for schizophrenia (COMT, DTNP1, NRG1, DAOA/G32 and DAAO genes) on cognition and self-rated schizotypy, in a representative population of 2,243 young male military conscripts. Single SNP and haplotype associations were evaluated.

Results: Val carriers of the COMT val 158 met polymorphism, were associated with higher scores on the negative schizotypy factor, and a greater variability of response in attention capacity. DTNP1 SNPs rs2619522 and rs760761 exhibited several single marker associations, the minor alleles being associated with lower attention capacity but also a decrease in positive and paranoid schizotypy scores. DTNP1 haplotype load had borderline associations with non verbal IQ, paranoid schizotypy and sustained attention. For individual NRG1 polymorphisms, isolated but weak signals of association were noted with sustained attention and working memory, but not schizotypy. The risk allele of functional SNP8NRG243177 was associated with reduced spatial working memory capacity. An isolated effect of DAAO haplotype variability was noted on negative and disorganization schizotypy. No convincing association of DAOA/G32 variability was detected.

Conclusion: DTNP1 and val 158 met COMT, and less so NRG1 and DAAO variants, may exert gene-specific modulating effects on schizophrenia endophenotypes at the population level.

S13.05

Neurocognitive deficits in clinical high risk subjects: Relationship to symptoms and disease progression

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Background and Aims: Psychosis is preceded by cognitive and physiological alterations. This may be useful in the risk assessment in subjects with putatively prodromal symptoms, and could contribute to better understand the temporal unfolding of the disease.

Methods: The early recognition and intervention program of the German Research Network on schizophrenia defines early and late prodromal stages according to psychopathological criteria. For concurrent and prospective validation of these risk stages, subjects undergo neurocognitive, electrophysiological and oculomotor assessments of putative vulnerability markers. About 125 early prodromal subjects (defined by the presence of basic symptoms, Klosterkoetter et al. 2001), and 90 late prodromal subjects (defined by attenuated positive symptoms or by brief occurrences of psychotic symptoms) have been assessed at inclusion.

Results: As compared to psychiatrically healthy matched controls, late prodromals have significantly inferior verbal memory, verbal fluency, visual motor skills, and working memory. Impairments are qualitatively similar, but less pronounced in subjects in an early prodromal stage, with deficits of immediate verbal memory, verbal fluency and visuomotor performance being significant. Both groups show reduced auditory startle prepulse inhibition. Impairments are not correlated with depression and general distress scores, and are also largely independent of prodromal and attenuated positive symptoms. In early prodromals, global cognitive performance is related to the occurrence of psychotic symptoms during follow-up. Auditory P 300 is reduced in both prodromal groups, and predicts transitions to psychosis.

Conclusions: Neurocognitive and neurophysiological assessments validate and improve psychopathological risk assessment, and allow to disentangle stable vulnerability markers from indicators of imminent risk.

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S14. SYMPOSIUM: NEUROCOGNITIVE AND CLINICAL EFFECTS OF CANNABINOIDS (Organised by the AEP Section on Neuroimaging)

S14.01

Effects of cannabis on memory and response inhibition

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Background: Cannabis has well established effects on cognitive processing but the neural basis of these is unclear. We used functional neuroimaging to investigate this, focusing on tasks that engaged verbal memory and response inhibition.

Methods: Subjects were 15 healthy males who had used cannabis < 25 times in their lifetime. Each subject was studied on 3 occasions, and was given either THC, CBD or placebo 1 hour prior to scanning, in a double-blind design. The order of drug administration was randomised and there was 1 month between each scanning session. During each session, images were acquired on a 1.5T GE camera while subjects performed a verbal paired associates memory task and a Go/No Go task. The modulatory effects of THC and CBD relative to placebo were examined by comparing activation during each task.

Results: During the encoding phase of the memory task THC attenuated activation in the left temporal cortex compared to placebo. During the go-no go task, THC attenuated activation in the right inferior frontal cortex. Neither of these effects were attributable to differences in behavioural performance, sedation, or intoxication. The severity of psychotic symptoms provoked by THC was a function of its effect on right inferior frontal activation during response inhibition.

Conclusions: The effects of cannabis on verbal memory and motor control may be mediated through the influence of THC on left temporal and right inferior frontal activity, respectively. The induction of psychotic symptoms by cannabis may reflect an effect of THC on right inferior frontal activity.

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