NAME OF PRESENTING AUTHOR: Petra Rupert

EMAIL ADDRESS OF PRESENTING AUTHOR: per29@pitt.edu

LOCATION OF PRESENTING AUTHOR: North America

TIME ZONE OF PRESENTING AUTHOR: USA Eastern Daylight Time

TITLE: Genetic variation in cognitive flexibility brain activation in schizophrenia: A multiplex extended pedigree study

FULL AUTHOR LIST: Petra E. Rupert[1], David R. Roalf[2], Konasale Prasad[3], Susan Kuo[1,4], Christie W. Musket[1], Joel Wood[3], Ruben C. Gur[2], Laura Almasy[5], Raquel E. Gur[2], Vishwajit L. Nimgaonkar[3], & Michael F. Pogue-Geile[1,3]

AFFILIATIONS: [1]Department of Psychology, University of Pittsburgh, Pittsburgh, PA, USA; [2]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; [3]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA; [4]Department of Psychiatry, University of California Los Angeles, Los Angeles, CA, USA; [5]Department of Genetics, University of Pennsylvania, Philadelphia, PA, USA

KEYWORDS: schizophrenia; fMRI; cognitive flexibility; genetic correlation

ABSTRACT: On executive tasks of cognitive flexibility, individuals with schizophrenia have poorer performance and often differing patterns of brain activation. The present study sought to compare the degree to which cognitive flexibility performance and its related brain activation may reflect effects of schizophrenia genetic risk using an extended pedigree design. A total of 521 participants, 30 schizophrenia probands, 202 of their relatives (1st to 4th degree), and 289 unrelated controls completed similar versions of a computerized cognitive flexibility task (Penn Conditional Exclusion Test) both out of and in an MRI scanner. Both behavioral performances and brain activation during the task in five ROIs were analyzed. In order to examine diagnostic specificity, we also investigated genetic correlations between diagnosed depression and PCET performance and brain activation. Cognitive flexibility performance was significantly genetically correlated with schizophrenia both out of (R_g=-0.65, p=0.005) and in the scanner (R_g=-0.56, p<0.001) after false discovery rate (FDR) correction. In contrast, genetic correlations between schizophrenia and ROI brain activation in the Frontal Pole (right

Rg=0.30, p=0.30, left Rg=1.00, p=0.01), Anterior Cingulate Gyrus (bilateral Rg=0.39, p=0.18), and Middle Frontal Gyrus (right Rg=1.00, p=0.04, left Rg=0.60, p=0.12) were either not nominally significant or were not significant after FDR correction. Neither behavioral performance or brain activation measures were significantly genetically correlated with depression. In contrast to some hypotheses, these results suggest that behavioral performance on this measure of cognitive flexibility (PCET) is more sensitive (and also more specific compared with depression) to schizophrenia genetic risk effects than fMRI measures of its regional brain activation.