

Neuroanatomical Correlates of Psychotic-Like Experiences Assessed in 2,695 Individuals via the ENIGMA Consortium

Mathilde Antoniades¹, Igor Nenadic², Tilo Kircher², Alex Krug², Dominik Grotegerd², Alex Fornito³, Udo Dannlowski⁴, Pamela DeRosse⁵, Bernhard Baune⁶, Melissa Green⁷, Yann Quide⁷, Christos Pantelis⁸, Raymond Chan⁹, Ulrich Ettinger¹⁰, Martin Debbané¹¹, Christian Gaser¹², Bianca Besteher¹², Kelly Diederer¹, Thomas Spencer¹, Wulf Rössler¹³, Veena Kumari¹⁴, Haeme Park¹⁵, Imke Lemmers¹⁶, Paul Allen¹⁷, Jan-Bernard Marsman¹⁸, James Gilleen¹⁷, Matthias Kirschner¹⁹, Alain Dagher¹⁹, Irina Lebedeva²⁰, Stefan Kaiser²¹, Anne Fett²², Iris Sommer¹⁸, Theo G. M. van Erp²³, Jessica A. Turner²⁴, Paul M. Thompson²⁵, André Aleman¹⁸, Gemma Modinos¹, for the ENIGMA Schizotypy Working Group*

*Aurina Arnatkeviciute, Ashley Moyett, Kristina Wiebels, Dominik Grotegerd, Lukasz Smigielski, Melodie Derome, Alexander Tomyshev, Yi Wang, Petya Kozhuharova

(affiliations listed at the bottom of this document)

Background: Recent meta-analytical evidence indicates that cortical thickness abnormalities in schizophrenia are influenced by illness severity and antipsychotic medication exposure. Schizotypy research allows investigating the neuroanatomical correlates of psychotic-like experiences without illness- and treatment-related confounders. Here we present the first large-scale meta-analysis of cortical thickness in schizotypy across 23 datasets worldwide.

Methods: The study involved structural MRI scans from 2,695 healthy individuals (mean [range] age, 29.1 [17-55.8], 46.3% male) who also completed self-report schizotypy questionnaires. Each site used FreeSurfer to extract cortical thickness for 70 Desikan-Killiany atlas regions (34 regions per hemisphere + left and right hemisphere mean thickness), and performed partial correlation analyses with total schizotypy scores in R to predict left, right and mean cortical thickness by region, adjusting by sex and age. Random-effects meta-analyses of partial correlation effect sizes for each region were performed using R's metafor package.

Results: Schizotypy scores were positively associated with mean cortical thickness of the medial orbitofrontal cortex ($r=0.077$; $pFDR=0.006$) and the frontal pole ($r=0.073$; $pFDR=0.006$). By hemisphere, schizotypy was associated with cortical thickness of the left medial orbitofrontal cortex ($r=0.066$; $pFDR=0.044$), and at trend-level with the right medial orbitofrontal cortex and left frontal pole (both $r=0.062$; $pFDR=0.053$).

Conclusion: Worldwide cooperative analyses of neuroimaging data shows that subclinical psychotic-like experiences are associated with greater prefrontal cortical thickness. The directionality of the effects is opposite to that of thinner cortex in schizophrenia. Given that accelerated prefrontal thinning has been associated with progression to psychosis in at-risk individuals, our findings may reflect mechanisms of resilience in schizotypy.

¹ King's College London, London, UK

² University of Marburg, Marburg, Germany

³ Monash University, Melbourne, Australia

- 4 University of Münster, Münster, Germany
- 5 Zucker Hillside Hospital, Glen Oaks, NY, USA
- 6 University of Adelaide, Adelaide, Australia
- 7 University of New South Wales, Sydney, Australia
- 8 Melbourne Neuropsychiatry Centre, University of Melbourne, Melbourne, Australia
- 9 Institute of Psychology, Chinese Academy of Sciences, Beijing, China
- 10 University of Bonn, Bonn, Germany
- 11 University of Geneva, Geneva, Switzerland
- 12 Jena University Hospital, Jena, Germany
- 13 University of Zurich, Zurich, Switzerland
- 14 Brunel University, London, United Kingdom
- 15 University of Auckland, Auckland, New Zealand
- 16 Free University of Amsterdam, Amsterdam, Netherlands
- 17 University of Roehampton, London, United Kingdom
- 18 University of Groningen, Groningen, The Netherlands
- 19 McGill University, Montreal, Canada
- 20 Mental Health Research Center, Moscow, Russian Federation
- 21 Geneva University Hospital, Geneva, Switzerland
- 22 City University London, London, United Kingdom
- 23 Department of Psychiatry and Human Behavior, University of California, Irvine, USA
- 24 Imaging Genetics and Neuroinformatics Lab, Georgia State University, Atlanta, USA
- 25 Imaging Genetics Center, Mark and Mary Stevens Neuroimaging & Informatics Institute, Keck School of Medicine of the University of Southern California, Los Angeles, USA