Synopsis for EU-GEI WP5 Publication

Synopsis no.: *S2.34*

Preliminary title: Shared and non-shared genetic and environmental risks of non-affective and affective psychotic disorders

Contact info for the person(s) proposing the synopsis

Name: Uli Reininghaus
Partner no: 1, 2
e-mail address: u.reininghaus@maastrichtuniversity.nl

Publication category: 3

Working and writing group: Uli Reininghaus, Diego Quattrone Andrei Szoke, Frank Schurhoff, Bathilde Ambroise, James Kirkbride, Bart Rutten, Jim van Os, Alex Richards, Michael O'Donnovan, Marta di Forti, Robin Murray, Craig Morgan

Work Packages involved: WP2

EU-GEI Partners involved from whom candidate co-authors (*additional to working and writing group*) should be nominated: IoP, Faculté de Médecine, Université Paris-Est, Créteil, University College London,

Objectives (scientific background, hypothesis, methods, and expected results):

Scientific background
In recent years, the Kraepelinian dichotomy has been challenged in light of evidence on shared genetic and environmental factors for schizophrenia and bipolar disorder.[1-8] There have also been calls for research cutting across diagnostic boundaries to strengthen the dimensional approach to classification in psychiatry.[9-11] However, empirical efforts to identify a more fundamental phenotype of psychosis at the clinical symptom level remain remarkably limited. Recent evidence for a bifactor model suggests that there is one general psychosis dimension underlying affective and non-affective psychotic symptoms as well as five specific psychosis dimensions of positive symptoms, negative symptoms, disorganization, mania, and depression in schizophrenia spectrum disorder.[12] In a more recent analysis, there was further evidence that the general psychosis dimension cuts across boundaries of the Kraepelinian dichotomy, suggesting that schizophrenia and bipolar disorder lie on a psychosis spectrum with overlapping non-affective and affective symptoms.[13] However,... General and specific psychosis dimensions, if replicated, provide a directly measurable clinical phenotype for cross-disorder investigations into the role of shared genetic and environmental factors of psychosis.

Hypotheses
The aim of this publication is to investigate:

1) a) whether the previously identified general psychosis dimension and the five specific psychosis dimensions (positive symptoms, negative symptoms, disorganization, mania, depression) replicate (and provide the best model fit compared with alternative models[12]) in a new sample of cases with a first episode of (non-affective and affective) psychotic disorder; b) the diagnostic utility of general and specific psychosis dimensions for classifying patients correctly into categorical diagnoses of psychotic disorders (Lead: Quattrone/Reininghaus).
2) whether cannabis use is associated with general and specific psychosis dimensions (Lead: Quattrone/Murray/di Forti)
3) social factors associated with general and specific psychosis dimensions (Lead:

Reininghaus/Morgan)

4) genetic factors associated with general and specific psychosis dimensions (Richards/O' Donnovan).

Method and expected results

Symptom ratings of the OPerational CRITeria (OPCRIT) system in cases with a first episode of (non-affective and affective) psychotic disorder will be used and combined with data on genetic risk and environmental exposures. Data on genetic risk and environmental exposures will only be analysed in relation to OPCRIT data. Multidimensional item response modelling will be conducted on OPCRIT ratings to examine whether there is a general psychosis dimension and, in addition, whether there are 5 specific symptom dimensions of positive symptoms, negative symptoms, disorganization, mania, and depression, compared with alternative item response models[12]. In order to examine the extent to which factor scores of general and specific psychosis dimensions (as predictor variable) allow for accurate classification of patients into diagnostic categories (as outcome variable), multinomial Receiver Operating Characteristic (ROC) analysis[14] will be conducted in Stata version 13.[15] Linear regression will be used to examine genetic and environmental factors associated with, and (more complex) gene-environment interaction effects on general and specific psychosis dimensions. These analyses will generate evidence on shared and non-shared genetic and environmental risks of non-affective and affective psychotic disorders.

Data needed for the study: (please list the EU-GEI WP5 instruments)

- OPerational CRITeria (OPCRIT) items and diagnosis
- MRC Sociodemographic Schedule
- Schedules for the assessment of social contexts and experiences (i.e., Childhood Experience of Care and Abuse (CECA) interview, Social Environment Assessment Tool (SEAT))
- Childhood Trauma Questionnaire (CTQ)
- Cannabis Questionnaire (+alcohol and drugs)
- Polygenic scores (i.e., a) 'shared' score of genes associated with both affective and non-affective psychosis (based on previous research); b) 'non-shared' scores of genes associated either affective or non-affective psychosis (based on previous research))

Plan for statistical analysis (overall strategy):

1) Multidimensional item response modelling will be conducted on OPCRIT ratings to examine whether there is a general psychosis dimension and, in addition, whether there are 5 specific symptom dimensions of positive symptoms, negative symptoms, disorganization, mania, and depression, compared with alternative item response models[12]. In order to examine the extent to which factor scores of general and specific psychosis dimensions (as predictor variable) allow for accurate classification of patients into diagnostic categories (as outcome variable), multinomial Receiver Operating Characteristic (ROC) analysis[14] will be conducted in Stata version 13.[15]
2) …
3) Linear regression will be used to examine social factors associated with general and specific psychosis dimensions.
4) …

We will further conduct more complex modeling of gene-environment interactions and investigate their effects on general and specific psychosis dimensions. We will also explore whether the sample recruited as part of WP6 may be used as a replication sample for findings from these analyses.

Other analyses/methods: N/A

Involvement of external Parties (non EU-GEI):

IPR check (Intellectual property rights): N/A

Timeframe: Start date: Date of completion of OPCRIT data collection/entry Month 2: Literature search; initial analyses (Milestone 1) Month 4: Completion of statistical analysis and first draft of manuscript (Milestone 2) Month 6: Manuscript submission (Milestone 3)
Additional comments: N/A

References

1. Cardno AG, Rijsdijk FV, Sham PC, Murray RM, McGuffin P. A twin study of genetic relationships between psychotic symptoms. *Am J Psychiatry.* 2002;159(4):539-545.

2. Craddock N, O'Donovan MC, Owen MJ. The genetics of schizophrenia and bipolar disorder: dissecting psychosis. *J Med Genet.* 2005;42(3):193-204.

3. Craddock N, Owen MJ. The Kraepelinian dichotomy - going, going... but still not gone. *Br J Psychiatry.* 2010;196(2):92-95.

4. Cross-Disorder Group of the Psychiatric Genomics C, Lee SH, Ripke S, Neale BM, Faraone SV, Purcell SM, Perlis RH, Mowry BJ, Thapar A, Goddard ME, Witte JS, Absher D, Agartz I, Akil H, Amin F, Andreassen OA, Anjorin A, Anney R, Anttila V, Arking DE, Asherson P, Azevedo MH, Backlund L, Badner JA, Bailey AJ, Banaschewski T, Barchas JD, Barnes MR, Barrett TB, Bass N, Battaglia A, Bauer M, Bayes M, Bellivier F, Bergen SE, Berrettini W, Betancur C, Bettecken T, Biederman J, Binder EB, Black DW, Blackwood DH, Bloss CS, Boehnke M, Boomsma DI, Breen G, Breuer R, Bruggeman R, Cormican P, Buccola NG, Buitelaar JK, Bunney WE, Buxbaum JD, Byerley WF, Byrne EM, Caesar S, Cahn W, Cantor RM, Casas M, Chakravarti A, Chambert K, Choudhury K, Cichon S, Cloninger CR, Collier DA, Cook EH, Coon H, Cormand B, Corvin A, Coryell WH, Craig DW, Craig IW, Crosbie J, Cuccaro ML, Curtis D, Czamara D, Datta S, Dawson G, Day R, De Geus EJ, Degenhardt F, Djurovic S, Donohoe GJ, Doyle AE, Duan J, Dudbridge F, Duketis E, Ebstein RP, Edenberg HJ, Elia J, Ennis S, Etain B, Fanous A, Farmer AE, Ferrier IN, Flickinger M, Fombonne E, Foroud T, Frank J, Franke B, Fraser C, Freedman R, Freimer NB, Freitag CM, Friedl M, Frisen L, Gallagher L, Gejman PV, Georgieva L, Gershon ES, Geschwind DH, Giegling I, Gill M, Gordon SD, Gordon-Smith K, Green EK, Greenwood TA, Grice DE, Gross M, Grozeva D, Guan W, Gurling H, De Haan L, Haines JL, Hakonarson H, Hallmayer J, Hamilton SP, Hamshere ML, Hansen TF, Hartmann AM, Hautzinger M, Heath AC, Henders AK, Herms S, Hickie IB, Hipolito M, Hoefels S, Holmans PA, Holsboer F, Hoogendijk WJ, Hottenga JJ, Hultman CM, Hus V, Ingason A, Ising M, Jamain S, Jones EG, Jones I, Jones L, Tzeng JY, Kahler AK, Kahn RS, Kandaswamy R, Keller MC, Kennedy JL, Kenny E, Kent L, Kim Y, Kirov GK, Klauck SM, Klei L, Knowles JA, Kohli MA, Koller DL, Konte B, Korszun A, Krabbendam L, Krasucki R, Kuntsi J, Kwan P, Landen M, Langstrom N, Lathrop M, Lawrence J, Lawson WB, Leboyer M, Ledbetter DH, Lee PH, Lencz T, Lesch KP, Levinson DF, Lewis CM, Li J, Lichtenstein P, Lieberman JA, Lin DY, Linszen DH, Liu C, Lohoff FW, Loo SK, Lord C, Lowe JK, Lucae S, MacIntyre DJ, Madden PA, Maestrini E, Magnusson PK, Mahon PB, Maier W, Malhotra AK, Mane SM, Martin CL, Martin NG, Mattheisen M, Matthews K, Mattingsdal M, McCarroll SA, McGhee KA, McGough JJ, McGrath PJ, McGuffin P, McInnis MG, McIntosh A, McKinney R, McLean AW, McMahon FJ, McMahon WM, McQuillin A, Medeiros H, Medland SE, Meier S, Melle I, Meng F, Meyer J, Middeldorp CM, Middleton L, Milanova V, Miranda A, Monaco AP, Montgomery GW, Moran JL, Moreno-De-Luca D, Morken G, Morris DW, Morrow EM, Moskvina V, Muglia P, Muhleisen TW, Muir WJ, Muller-Myhsok B, Murtha M, Myers RM, Myin-Germeys I, Neale MC, Nelson SF, Nievergelt CM, Nikolov I, Nimgaonkar V, Nolen WA, Nothen MM, Nurnberger JI, Nwulia EA, Nyholt DR, O'Dushlaine C, Oades RD, Olincy A, Oliveira G, Olsen L, Ophoff RA, Osby U, Owen MJ, Palotie A, Parr JR, Paterson AD, Pato CN, Pato MT, Penninx BW, Pergadia ML, Pericak-Vance MA, Pickard BS, Pimm J, Piven J, Posthuma D, Potash JB, Poustka F, Propping P, Puri V, Quested DJ, Quinn EM, Ramos-Quiroga JA, Rasmussen HB, Raychaudhuri

S, Rehnstrom K, Reif A, Ribases M, Rice JP, Rietschel M, Roeder K, Roeyers H, Rossin L, Rothenberger A, Rouleau G, Ruderfer D, Rujescu D, Sanders AR, Sanders SJ, Santangelo SL, Sergeant JA, Schachar R, Schalling M, Schatzberg AF, Scheftner WA, Schellenberg GD, Scherer SW, Schork NJ, Schulze TG, Schumacher J, Schwarz M, Scolnick E, Scott LJ, Shi J, Shilling PD, Shyn SI, Silverman JM, Slager SL, Smalley SL, Smit JH, Smith EN, Sonuga-Barke EJ, St Clair D, State M, Steffens M, Steinhausen HC, Strauss JS, Strohmaier J, Stroup TS, Sutcliffe JS, Szatmari P, Szelinger S, Thirumalai S, Thompson RC, Todorov AA, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Van Os J, Vicente AM, Vieland VJ, Vincent JB, Visscher PM, Walsh CA, Wassink TH, Watson SJ, Weissman MM, Werge T, Wienker TF, Wijsman EM, Willemsen G, Williams N, Willsey AJ, Witt SH, Xu W, Young AH, Yu TW, Zammit S, Zandi PP, Zhang P, Zitman FG, Zollner S, International Inflammatory Bowel Disease Genetics C, Devlin B, Kelsoe JR, Sklar P, Daly MJ, O'Donovan MC, Craddock N, Sullivan PF, Smoller JW, Kendler KS, Wray NR. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet.* 2013;45(9):984-994.

5. Laursen TM, Munk-Olsen T, Nordentoft M, Bo Mortensen P. A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a danish population-based cohort. *J Clin Psychiatry.* 2007;68(11):1673-1681.

6. Lichtenstein P, Yip BH, Bjork C, Pawitan Y, Cannon TD, Sullivan PF, Hultman CM. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet.* 2009;373(9659):234-239.

7. Matheson SL, Shepherd AM, Pinchbeck RM, Laurens KR, Carr VJ. Childhood adversity in schizophrenia: a systematic meta-analysis. *Psychol Med.* 2013;43(2):225-238.

8. Tamminga CA, Ivleva EI, Keshavan MS, Pearlson GD, Clementz BA, Witte B, Morris DW, Bishop J, Thaker GK, Sweeney JA. Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). *Am J Psychiatry.* 2013;170(11):1263-1274.

9. Adam D. Mental health: On the spectrum. *Nature.* 2013;496(7446):416-418.

10. Insel TR. Transforming diagnosis. http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml. Accessed 11.08.2014.

11. Insel TR. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry.* 2014;171(4):395-397.

12. Reininghaus U, Priebe S, Bentall RP. Testing the psychopathology of psychosis: evidence for a general psychosis dimension. *Schizophr Bull.* 2013;39(4):884-895.

13. Reininghaus U, Bohnke JR, Hosang G, Farmer A, Burns T, McGuffin P, Bentall RP. Probing the boundaries of the Kraepelinian dichotomy: Evidence for a bifactor model reveals psychosis spectrum encompassing schizophrenia and bipolar disorder. Submitted. Located at: Schizophr Bull.

14. Peterson LE, Coleman MA. Machine learning-based receiver operating characteristic (ROC) curves for crisp and fuzzy classification of DNA microarrays in cancer research. *Int J Approx Reason.* 2008;47(1):17-36.

15. StataCorp. *Stata Statistical Software: Release 12.* College Station, TX: StataCorp LP; 2011.