nature neuroscience

Polygenic risk scores for schizophrenia and bipolar disorder predict creativity

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We tested whether polygenic risk scores for schizophrenia and bipolar disorder would predict creativity. Higher scores were associated with artistic society membership or creative profession in both Icelandic ($P = 5.2 \times 10^{-6}$ and 3.8×10^{-6} for schizophrenia and bipolar disorder scores, respectively) and replication cohorts ($P = 0.0021$ and 0.00086). This could not be accounted for by increased relatedness between creative individuals and those with psychoses, indicating that creativity and psychosis share genetic roots.

Great thinkers of the past from Aristotle to Shakespeare have remarked that creative genius and insanity are often characterized by the same unleashing of thoughts and emotions. This is supported by epidemiological studies demonstrating overlap between psychiatric disorders and creativity[1–7]. In a large Swedish study, Kyaga *et al.* found that individuals with bipolar disorder and healthy siblings of people with schizophrenia and bipolar disorder are over-represented in creative professions but those with major depression and their relatives are not. This overlap appears to be independent of IQ[8]. By contrast, members of the creative professions are not more likely to be diagnosed with psychiatric diseases with two exceptions: writers are more likely to be diagnosed with psychiatric disorders in general and members of all of the creative professions are more likely to be diagnosed with bipolar disorder[9].

Psychological theories propose that the schizophrenic spectrum is accompanied by a decrease in practical reasoning, as schizophrenia patients outperform controls in logical deduction that is in conflict with practical reasoning[8,10]. Furthermore, it has been suggested that those less restrained by practical cognitive styles may have an advantage in artistic occupations[8]. These results provide support for the notion that creativity and psychiatric disorders, particularly schizophrenia and bipolar disorder, share psychological attributes. However, whether and to what degree this is due to shared environment or genetics has not been assessed with modern genomic tools.

Creativity can be viewed in various ways[11,12], and, although it is a difficult concept to define for scientific purposes, the creative person is most often considered one who takes novel approaches requiring cognitive processes that are different from prevailing modes of thought or expression[11]. Thinking differently from others is therefore a prerequisite for creativity[11]. Schizophrenia and bipolar disorder are disorders of thoughts and emotions, which means that those affected show alterations in cognitive and affective processing. Yet it is unclear whether the cognitive deviations of psychiatric patients and of creative individuals can be explained in part by shared genetic variation. We have previously shown that control carriers of copy number variants (CNVs) conferring risk of schizophrenia have cognitive abnormalities that are akin to those encountered in schizophrenia although not as severe[13]. The population controls carrying the neuropsychiatric CNVs did not have schizophrenia, autism, bipolar disorder or a diagnosis of intellectual disability. Hence, variants in the genome that confer modest to high risk of psychiatric diseases affect cognition in controls.

Here we investigated whether common variants that affect the risk of schizophrenia and bipolar disorder, and thus are potentially detrimental to the individuals who carry them, may also underlie cognitive traits that can be advantageous to society. Polygenic risk scores, or cumulative genetic risk profiles from across the genome, were used to explore this question. Based on results from two mega-analyses[14,15], neither of which included Icelandic data, we generated separate polygenic risk scores for schizophrenia and bipolar disorder. These scores were then examined in a sample of 86,292 individuals from the general population of Iceland.

We first tested the ability of these polygenic risk scores to predict their corresponding disorders. Prediction accuracy (variance explained) was assessed throughout the study using Nagelkerke's pseudo-R^2, the likelihood-based measure used in previous work[14,15]. We found that both scores did associate with their matching disorder in Iceland ($n = 583$ and 500 for schizophrenia and bipolar disorder, respectively), with prediction accuracy plateauing at a P-value threshold of around 0.1 to 0.2 (**Fig. 1a**). The maximum variance explained was 5.5% for schizophrenia and 1.2% for bipolar disorder. To consider all polygenic

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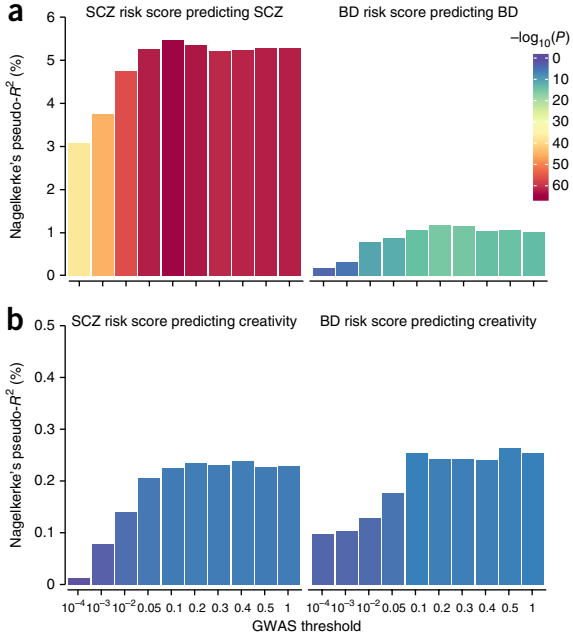
Received 1 March; accepted 11 May; published online 8 June 2015; doi:10.1038/nn.4040

Figure 1 Polygenic risk scores for schizophrenia and bipolar disorder predict their corresponding disorder and creativity. (**a**) Prediction of schizophrenia (SCZ) and bipolar disorder (BD) in Iceland using polygenic risk scores derived from independent GWASs of these disorders[14,15]. Nagelkerke's pseudo-R^2 is shown for scores derived using ten significance thresholds. Variance explained on the liability scale, which is adjusted for case-control ascertainment, is around 8% for schizophrenia and 2% for bipolar disorder, in keeping with previous estimates[14]. (**b**) Prediction of creativity in Iceland using scores derived from independent GWASs of schizophrenia and bipolar disorder[14,15]. Nagelkerke's pseudo-R^2 is shown for scores derived using ten significance thresholds.



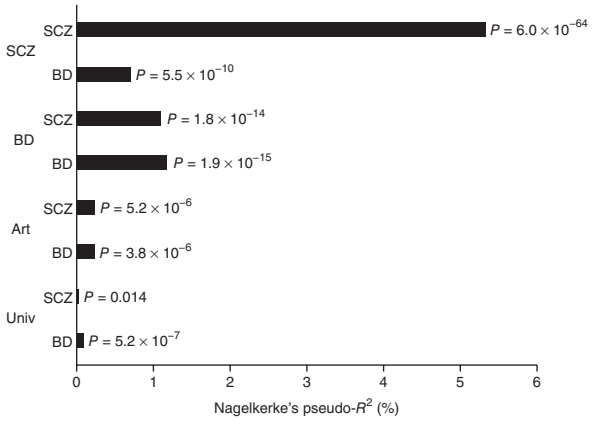
risk scores on the same scale, scores were centered and scaled to have a mean of 0 and a s.d. of 1. Odds ratios (ORs) computed using these scores were 2.22 for schizophrenia and 1.46 for bipolar disorder based on a P value threshold of 0.2.

Next, we tested for an association between the polygenic risk scores and creativity. Creative individuals were defined as those belonging to the national artistic societies of actors, dancers, musicians, visual artists and writers (n = 1,024; **Supplementary Table 1**). We found that both schizophrenia and bipolar disorder polygenic risk scores were associated with creativity, with the schizophrenia and bipolar disorder scores explaining a maximum of 0.24% and 0.26% of the variance of creativity, respectively (**Figs. 1b** and **2**). At a P-value threshold of 0.2, ORs for creativity were 1.17 for both scores ($P = 5.2 \times 10^{-6}$ and 3.8×10^{-6} for the schizophrenia and the bipolar scores, respectively).

In contrast to these results, none of 20 non-psychiatric diseases tested, including three phenotypes affecting cognition, were significantly associated with the psychosis polygenic risk scores (**Supplementary Table 2**). We also found no significant association with the psychosis scores for five other types of profession (**Supplementary Table 3**).

In an analysis including both scores as predictors of creativity, both scores were significantly associated with artist status, together accounting for 0.39% of the variance in creativity ($P = 6.8 \times 10^{-8}$), somewhat less than the sum of their independent scores owing to the positive correlation between them (r = 0.23). ORs were similar for four different classes of artist (actor or dancer, musician, visual artist and writer) using either schizophrenia or bipolar disorder scores (**Supplementary Table 4**).

To determine whether the association with creativity is driven by general cognitive function or educational attainment, we also tested for an association of the polygenic risk scores with the number of years in school or having a university degree. We found that higher bipolar disorder polygenic risk scores were associated with greater educational attainment ($\beta = 0.15$, $P = 4.8 \times 10^{-9}$ and OR = 1.09, $P = 5.2 \times 10^{-7}$ for number of years in school and university degree, respectively) and that higher schizophrenia scores also predicted greater educational attainment,



although less significantly ($\beta = 0.096$, $P = 1.2 \times 10^{-4}$ and OR = 1.04, P = 0.014 for number of years in school and university education, respectively). In the subset of the data with education information, both bipolar disorder and schizophrenia scores remained significant predictors of creativity when educational attainment was included in the model, with little or no attenuation of the effect (OR = 1.18 and 1.10 for the schizophrenia and bipolar scores, respectively; for schizophrenia scores, $P = 1.2 \times 10^{-4}$ and $P = 3.6 \times 10^{-4}$ without and with adjustment for education, respectively, and for bipolar disorder scores, P = 0.0078 and P = 0.038 without and with adjustment for education, respectively), suggesting that the association of the polygenic risk score with creativity cannot be accounted for by differences in educational attainment.

Schizophrenia polygenic risk scores are elevated in relatives of schizophrenia patients, such that scores of first degree relatives are expected to be elevated by half the elevation of schizophrenia patients and those of second degree relatives are expected to be elevated by one quarter. The elevation in the group of creative individuals was 20% of that seen in patients with schizophrenia. It is conceivable that the association we observe between the polygenic schizophrenia risk score and creativity could be driven by having a relative with schizophrenia. In this case the observed elevation in creative people would demand that, on average, they would have a second degree relative with schizophrenia. The actual average meiotic distance between creative individuals and their closest relative with schizophrenia was 6.2 meioses. That would only account for an elevation of the polygenic schizophrenia risk score of 5.03%, which does not explain the observed association with creativity (0.21, compared to 0.045 under the null hypothesis; $P = 3.3 \times 10^{-4}$).

We also examined the association of creativity and psychosis polygenic risk scores conditional on the fraction of first, second and third degree relatives who were schizophrenia or bipolar disorder patients. This resulted in little change to the significance of the association between creativity and psychosis polygenic score (OR = 1.17, $P = 7.1 \times 10^{-6}$ and OR = 1.17, $P = 4.3 \times 10^{-6}$ for schizophrenia and bipolar disorder scores,

Figure 2 Nagelkerke's pseudo-R^2 in Iceland for schizophrenia (SCZ), bipolar disorder (BD), artist (Art) and university degree (Univ) based on schizophrenia and bipolar disorder polygenic risk scores derived at the significance threshold of $P < 0.2$.

Table 1 Prediction of artist status by schizophrenia and bipolar disorder polygenic risk scores in four replication cohorts

Phenotype and study	*n*, artist	*n*, non-artist	Schizophrenia score OR	Schizophrenia score *P*	Bipolar disorder score OR	Bipolar disorder score *P*
Artistic profession						
NTR	118	6,160	1.31	0.022	1.43	0.00015
RS	62	7,819	1.18	0.19	1.10	0.46
STR	65	8,828	1.25	0.096	1.16	0.23
NBS	28	4,265	1.12	0.54	0.95	0.79
Combined	273	27,072	1.23	0.0021	1.23	0.00086
CAQ-Arts score	*n*					
STR	804		1.11	0.11	1.06	0.34

n values for artist and non-artist are shown where applicable. Polygenic risk scores were calculated using a *P*-value threshold of 0.2 and were standardized to have a mean of 0 and a s.d. of 1. Results are from logistic regression except in the case of the CAQ-Arts score, where ordered logistic regression was used. NTR, Netherlands Twin Registry; RS, Rotterdam Study; STR Swedish Twin Registry; NBS, Nijmegen Biomedical Study.

respectively), demonstrating that the association is not solely the result of a closer relationship between creative individuals and psychosis patients.

Finally, we investigated the association between creativity and psychosis polygenic risk scores in four longitudinal studies from the Netherlands ($n = 18{,}452$) and Sweden ($n = 8{,}893$). Two creativity phenotypes were used: artistic profession, which was available for all cohorts, and a quantitative measure of creativity derived from the Creative Achievement Questionnaire (CAQ) and assessing an individual's activities in the fields of visual arts, music, dance, writing and theater (CAQ-Arts) that was available for a subset of one study. For artistic profession, similar ORs as those for artistic society membership in Iceland were observed (in the combined cohorts, OR = 1.23, $P = 0.0021$ and OR = 1.23, $P = 8.6 \times 10^{-4}$ for schizophrenia and bipolar disorder scores, respectively; **Table 1**). The CAQ-Arts measure was associated with both scores in the expected direction (**Table 1**). The power of the replication cohorts to detect an effect of similar magnitude to that in the discovery sample was around 70–80%.

It has been suggested that alleles conferring risk of disorders reducing fecundity, such as schizophrenia, may persist through balancing selection if their negative fitness effects are offset by benefits[16,17]. However, creative individuals in our sample had fewer children than population controls (effect derived from a Poisson log-linear model = 0.92, $P = 6.8 \times 10^{-5}$), making an offset manifested through creativity unlikely.

The study of the association between creativity and psychiatric disorders has in the past primarily been addressed in two types of studies: studies assessing psychiatric disorders in eminent creative individuals and studies assessing creativity in psychiatric patients and their relatives. Our study lends support to direct influences of genetic factors on creativity as opposed to sharing an environment with individuals with psychosis influencing creative aptitude. Thus, the main finding presented here is that creativity, conferred, at least in part, by common genetic variants, comes with an increased risk of psychiatric disorders conferred by the same genetic variants. How this genetic overlap fits into evolutionary models of disease persistence remains to be determined.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Any Supplementary Information and Source Data files are available in the online version of the paper.

ACKNOWLEDGMENTS

The authors are grateful to the participants and thank the staff at the Krókháls recruitment center. We thank P. Arp, M. Jhamai, M. Moorhouse, M. Verkerk and S. Bervoets for their assistance in creating the GWAS database. The authors are very grateful to the participants and staff from the Rotterdam Study, participating general practitioners and the pharmacists. The Netherlands Twin Registry thanks all participants. The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement 115008, resources of which are composed of European Federation of Pharmaceutical Industries and Associations (EFPIA) in-kind contributions and financial contributions from the European Union's Seventh Framework Programme (FP7/2007-2013) and the European Union–funded FP7-People-2011-IAPP grant PsychDPC (GA 286213). This study presents independent research funded in part by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley, NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR or the Department of Health. The Rotterdam Study was funded by the Netherlands Organisation for Scientific Research NWO Investments (175.010.2005.011, 911-03-012), the Research Institute for Diseases in the Elderly (014-93-015; RIDE2) and the Netherlands Genomics Initiative (NGI)/Netherlands Consortium for Healthy Aging (NCHA) project 050-060-810. The Rotterdam Study is funded by the Erasmus Medical Center; Erasmus University, Rotterdam; the Netherlands Organization for the Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly (RIDE); the Ministry of Education, Culture, and Science; the Ministry for Health, Welfare, and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. Funding for the Netherlands Twin Registry was obtained from the Netherlands Organization for Scientific Research (NWO) and MagW/ZonMW, BBMRI-NL (184.021.007), the VU University Institute for Health and Care Research (EMGO+) and Neuroscience Campus Amsterdam, the European Science Council (ERC) Genetics of Mental Illness (230374), Avera Institute for Human Genetics and US National Institute of Mental Health (1RC2MH089951-01 and 1RC2 MH089995). The Swedish Twin Registry was financially supported by the Ragnar Söderberg Foundation (E9/11), the Swedish Research Council (421-2013-1061), the Jan Wallander and Tom Hedelius Foundation (P2012-0002:1), the Sven and Dagmar Salén Foundation, the Bank of Sweden Tercentenary Foundation (M11-0451:1) and the Karolinska Institutet. Some of the statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org/), which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003 PI: Posthuma) along with a supplement from the Dutch Brain Foundation and the VU University Amsterdam.

AUTHOR CONTRIBUTIONS

R.A.P., S.S., D.G., G.B., H.S. and K.S. were involved in study design. G.B., H.S., E.S., S.S., K.S., D.C., P.K.E.M., F.U., C.A.R., H.T., A. Hofman, F.J.A.v.R. and G.W. were involved in cohort ascertainment, phenotypic characterization and recruitment. R.A.P., S.S., G.B., H.S., G.B.W., T.E.T., A.I., M.J., T.E.G. and J.J.H. were involved in informatics and data management. R.A.P., S.S., A.K., D.G., C.A.R., A.A. and M.M.N. carried out statistical analysis. D.C., D.J.B., M.J., A. Helgason, L.A.K., P.K., D.I.B., H.S. and K.S. were involved in planning and supervising the study. R.A.P., S.S., G.B., E.S., D.G., H.S. and K.S. wrote the first draft of the manuscript and all authors contributed to the final version of the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details are available in the online version of the paper.

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ONLINE METHODS

Icelandic study. *Subjects.* The study was approved by the National Bioethics Committee of Iceland and the Icelandic Data Protection Authority. Subjects were recruited to the study by a research clinic overseen by the Icelandic Data Protection Authority. All personal identifiers were removed from samples and data and replaced with encrypted identifiers. Written informed consent was obtained from participants.

Genotyping and imputation. Genotyping was carried out using Illumina HumanHap (300, 370, 610, 1M, 2.5M) and Illumina Omni (670, 1M, 2.5M, Express) arrays[13]. Long-range phasing and imputation based on whole genome sequencing of 2,636 Icelanders was performed as previously described[18].

Scoring. Polygenic scores were constructed using the *P* values and $\log_{10}$ odds ratios from the most recent PGC GWAS of schizophrenia and bipolar disorder[14,15]. The SNPs used were those selected by the analysts of those studies using *P*-value-informed clumping in PLINK[19] with a cutoff of $r^2 = 0.25$ within a 200-kb window, and excluding the MHC region of the genome owing to its complex linkage disequilibrium structure. Of the 102,637 and 108,834 clumped SNPs from the original analyses of schizophrenia and bipolar disorder, 100,996 and 108,161, respectively, existed in the Icelandic data. For each individual, scores were generated using SNPs with *P* values less than 0.0001, 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5 and 1.0.

Statistical analysis. Polygenic risk scores for schizophrenia and bipolar disorder were tested for association with schizophrenia, bipolar disorder, creativity, 20 non-psychiatric disorders and 5 professions using logistic regression. The analyses were corrected for sex, age, age squared, sex-by-age, sex-by-age squared, county of birth and 20 principal components. In the analyses of creativity, individuals diagnosed with schizophrenia or bipolar disorder or classified as disabled were excluded. To account for relatedness, we used genomic control. Simulations showed that the variance inflation of the polygenic score was very similar to that of a single marker. Thus, we used the λ derived from genome-wide single marker association to adjust the chi-squared statistics for the polygenic scores in the same manner as for individual markers. Variance explained by polygenic scores was calculated as the Nagelkerke's pseudo-R^2 of the full model including polygenic scores and covariates minus the Nagelkerke's pseudo-R^2 of the model including only covariates.

Determination of meiotic distance. The average meiotic distance between the creative subjects and the schizophrenia patients was calculated by using the Icelandic genealogy database, Íslendingabók, to find the meiotic distance from each creative person to the closest schizophrenia patient and averaging these distances.

Adjusting for the average distance to the closest relative with schizophrenia. The schizophrenia polygenic risk score is 0.90 higher in those with schizophrenia than in controls. The average meiotic distance between creative individuals and their closest relative with schizophrenia is 6.2 meiosis and the mean kinship between creative individuals and their closest relative with schizophrenia is 5.03%, which moves the expected polygenic risk score in creative individuals to $0.90 \times 0.0503 = 0.045$. To account for this shift, we tested for deviation of a schizophrenia polygenic risk score of 0.21 seen in creative individual from 0.045 rather than 0.

Replication studies. *Phenotypes.* Creative professionals were defined as those having (or ever having had, where lifetime data were available) positions in the fields of dance, film, music, theater, visual arts or writing. Those teaching these subjects at the secondary level or above were also included. The Creative Achievement Questionnaire (CAQ) is a self-report measure of creative achievement that assesses achievement across multiple domains of creativity[20]. For this study, a Swedish adaptation of the questionnaire was used. We defined the CAQ-Arts as the sum of the scores in the visual arts, music, dance, writing and theater domains. CAQ-Arts scores were available for 804 individuals.

Netherlands Twin Register (NTR). The Netherlands Twin Register carries out longitudinal twin-family studies on health-related behavior. Since 1991, participants have been invited every 2 or 3 years to complete a survey containing questions about demographics, lifestyle, personality and health. All surveys include detailed questions about the participants' occupations (for example, Van der Loos *et al.*[21]). DNA collection took place in several studies, mostly in two biobank projects[22,23]. Genotyping was conducted across Illumina and Affymetrix platforms (see also ref. 24). Platform-specific quality control was performed before imputation. Data were phased using Mach 1.0 and imputed to the 1000 Genomes phase 1 integrated release version 3 (Build 37 HG19) using Minimac[25]. Polygenic scores were based on the pruned, cleaned and publicly available meta-analysis results from the Psychiatric Genomics Consortium for schizophrenia[14] and bipolar disorder[15]. Before statistical analyses, data from ethnic outliers were removed. Prediction analysis (118 artists, 6,160 non-artists) was carried out using generalized estimation equations (GEE) with a logit link function. To account for relatedness, an exchangeable conditional covariance matrix was used (that is, we allowed for correlated residuals between members of the same family) and tests were based on the robust (sandwich-corrected) standard errors[26]. Sex, year of birth and ten principal components were included as covariates.

Rotterdam Study (RS). The Rotterdam Study is a prospective cohort study ongoing since 1990 in the city of Rotterdam in the Netherlands. The study targets cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric, dermatological, oncological and respiratory diseases. As of 2008, 14,926 subjects aged 45 years or over comprise the cohort[27]. Genotyping was performed in the Genetic Laboratory, Department of Internal Medicine, Erasmus MC, Rotterdam (HuGeF) using Illumina HumanHap 550K (RS-I and RS-II) and Illumina 610K Quad (RS-III) chips. Ethnic outliers and individuals with a mismatch between gender and typed X-linked markers, excess autosomal heterozygosity, or within-sample cryptic relatedness were removed. Data were imputed to the 1000 Genomes phase 1 version 3 using MACH. Polygenic scores were computed on the basis of SNPs (best guess data) from the publicly available clumped sets of the PGC analyses having *P* values < 0.2. Analysis was carried out on unrelated individuals ($\hat{\pi} < 0.05$; 62 artists and 7,819 non-artists) using logistic regression and controlling for age, age-squared, sex and four principal components.

Swedish Twin Registry (STR). The Swedish Twin Registry (STR) is a large, population-based twin registry. Between 1998 and 2002, STR administered to twins born in 1958 or earlier a survey called the Screening Across the Lifespan Twin study[28]. A subsample of SALT participants was genotyped using the Illumina HumanOmniExpress BeadChip technology as part of the TwinGene project[29]. TwinGene participants were all born between 1911 and 1958. After data cleaning[29], the data set contained 9,617 individuals. Data were imputed to the 1000 Genomes phase 1 version 3 using MACH. Polygenic scores were computed on the basis of SNPs (best guess data) from the PGC publicly available clumped sets having *P* values < 0.2. Analysis (65 artists, 8,828 non-artists) was carried out using logistic regression, clustering standard errors on the family level and including covariates for age, age-squared, sex and four principal components.

Nijmegen Biomedical Study (NBS). The NBS is a population-based survey conducted by the Department for Health Evidence and the Department of Laboratory Medicine of the Radboud University Medical Center, Nijmegen, the Netherlands. In 2002, 22,451 age- and sex-stratified randomly selected adult inhabitants of Nijmegen, a city located in the eastern part of the Netherlands, received an invitation to fill out a postal questionnaire including questions about lifestyle, health status and medical history, and to donate a blood sample for DNA isolation and biochemical studies. A total of 9,350 (43%) of recipients filled out the questionnaire, of whom 6,468 (69%) donated blood samples. Further details have been given elsewhere[30]. Genotyping was performed at deCODE Genetics using Illumina chips. Following standard quality control, genotype imputation was carried out using SHAPEITv2 and IMPUTE2. Polygenic scores were computed on the basis of the SNPs clumped by the most recent PGC schizophrenia and bipolar disorder GWAS[14,15]. After removing samples likely to be non-European, logistic regression (28 artists, 4,265 non-artists) was carried out controlling for sex, age and four principal components.

A **Supplementary Methods Checklist** is available.

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doi:10.1038/nn.4040