Peer-reviewed version available at *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **2018**; doi:10.1002/ajmg.b.32639

Article

A Longitudinal Approach to Biological Psychiatric Research: The PsyCourse Study

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Abstract: In current diagnostic systems, schizophrenia and bipolar disorder are still conceptualized as distinct categorical entities. Recently, both clinical and genetic evidence have challenged this Kraepelinian dichotomy. There are only few longitudinal studies addressing the potential overlaps between these conditions. Here, we present design and first results of the PsyCourse study, an ongoing transdiagnostic study of the affective-to-psychotic continuum that combines longitudinal deep phenotyping and dimensional assessment of psychopathology with an extensive collection of biomaterial. Within the DSM-IV framework, we compare two broad diagnostic groups: one consisting of predominantly affective and one of predominantly psychotic disorders. Depressive, manic, and psychotic symptoms as well as global functioning over time were analyzed. Furthermore, we explore the effects of polygenic risk scores for schizophrenia on diagnostic group membership and address their effects on non-participation in follow-up visits. While phenotypic results show differences in both current psychotic and manic symptoms, depressive symptoms did not vary between both groups. Polygenic risk scores for schizophrenia significantly explained part of the variability of the diagnostic group. Furthermore, there was a trend that a higher polygenic loading for schizophrenia was associated with attrition. Because of its unique properties, the PsyCourse study presents a prime resource for the interrogation of complex genotype-phenotype relationships.

Keywords: schizophrenia; bipolar; psychosis; depression; polygenic risk score; diagnosis; RDoC

1. Introduction

The Kraepelinian dichotomy, which postulates adult affective and psychotic disorders to be separate categorical entities, still has a major influence on Western psychiatry. It therefore remains in current diagnostic systems such as the DSM-5. This dichotomous view has recently been questioned by biological researchers [1]. Moreover, there is extensive overlap of symptoms between schizophrenia

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(SZ) and bipolar disorder (BD) as observed in clinical reality [2]. Traditional categorical nosological systems have therefore been fundamentally challenged during the past years. Alternative concepts of hierarchically and dimensionally measured phenotypes have been put forward by the NIMH Research Domain Criteria (RDoC; [3] [4]) and the Hierarchical Taxonomy of Psychopathology (HiTOP; [5]), the former emphasizing the need for biologically informed domains early on. To this end, genetics have often played an important role in redefining psychiatric diagnoses [6]. More recently, findings regarding an overlapping but distinct genetic basis of SZ and BD in both family [7] and molecular genetic studies [8] [10], have accelerated the momentum towards dimensionally defined diagnosis [11] of severe mental disorders. Even though spectrum phenotypes have been introduced in the DSM-5 in the areas of autism and substance use, this modern diagnostic approach has not been applied to SZ and BD. However, as outlined above, there are several compelling reasons for the introduction of a psychosis spectrum disorder (for a detailed discussion see [12]). There is thus a pressing need to incorporate this biological information into future diagnostic systems.

In our opinion, successful research into the matter requires addressing two important issues: Firstly, longitudinal research is necessary to capture variation over time. Pronounced heterogeneity in the longitudinal course of both SZ (e.g. [13] [14]) and BD (e.g. [15]) exists. Overlap of symptoms, comorbidity and instability of diagnoses over time occur frequently in everyday clinical practice. Thus, just as subtypes of traditionally defined nosological categories emerged by examining their clinical course (e.g. [16]), similarities and differences between traditionally defined SZ and BD may emerge when a combination of biological information and clinical course is considered. While only few modern longitudinal studies for severe mental illnesses exist, the longitudinal course of affective disorders, such as BD, has received particularly little attention to date [17]. Second, a major emphasis on phenomics is needed, "the systematic study of phenotypes on a genome-wide scale" [18]. In an age in which genomic and other high-throughput data can be obtained relatively inexpensively and rapidly, a major challenge is to obtain extensive high-quality phenotype data. Such data is required establish meaningful genotype-phenotype relationships, and will ultimately lead to biologically informed patient stratification [19].

The aim of this communication is to introduce the PsyCourse study, a longitudinal study of severe mental disorders on the affective-to-psychotic continuum, which aims to address these issues. Deep phenotyping is combined with an extensive collection of biological material at every measurement point, enabling the combination of multi-level omics and longitudinal clinical data. Specifically, current symptomatology, cognitive status and self-report measures are assessed at every measurement point, interspersed with the collection of relevant cross-sectional data (see Table 1).
Here, we report analyses on both cross-diagnostic and longitudinal aspects of the PsyCourse study. First, we present longitudinal data on positive, depressive and manic symptoms as well as data on global psychosocial functioning of the clinical participants of the PsyCourse study. We compare these variables between two broad diagnostic groups within the DSM-IV framework, defined as psychotic and affective, by their predominant symptoms. In addition, we use polygenic risk scores for SZ (SZ-PRS) for a first biological characterization of these diagnostic groups. PRS are a method for estimation of the polygenic load of common risk alleles an individual carries for a certain trait or disorder ([8]; for overview see [20]), in this case for SZ. Findings from PRS analyses support the notion of both overlapping [8] and specific [21] genetic backgrounds of SZ and BD as well as the continuum model of psychosis [22]. To study genetic overlap between disorders by means of PRS, it is usually analyzed whether PRS for one disorder, e.g. SZ, can successfully predict case-control status for other traits, for example BD [8] [9]. Another approach, focusing on the specific genetic backgrounds of SZ and BD, was used by Ruderfer and colleagues [21] who created a PRS for the discrimination between SZ and BD. Here, we present a novel way to use PRS to study the genetic background of two disorders. We directly explore to what extent SZ-PRS can differentiate between two groups of patients in the PsyCourse study, predominantly psychotic and affective participants. As longitudinal research inevitably leads to attrition, selective dropout of subgroups of study participants is a major challenge.

This is especially important as it is well-known that demographic variables like age, sex, socioeconomic status as well as emotional and behavioral problems are associated with attrition [23] [24]. Notably, a recent study found a higher SZ-PRS to be associated with nonparticipation over time in a population-based cohort study [25]. Therefore, we present analyses on possible demographic and illness-related predictors of dropout and further explore the association of SZ-PRS and dropout in our patient sample. A selective dropout of participants with a specific biological profile would have important implications for longitudinal biological research in psychiatry.

2. Materials and Methods

2.1 Properties of the PsyCourse study

PsyCourse is an ongoing multi-center study, conducted by a network of clinical sites in Germany and Austria. The study protocol was approved by the respective ethics committee at each study center. At the time of writing, 18 different clinical centers participated in data collection of clinical participants, two of which additionally collect data from non-clinical (control) individuals. Study participants are assessed at four points in time, in intervals of six months, hereafter referred to as study visits 1 (T1; baseline), 2 (T2; +6months), 3 (T3; +12 months) and 4 (T4; +18 months). Additional visits should be conducted for clinical participants if they are re-admitted for inpatient treatment during the study period. At each measurement, venous blood samples are collected, permitting extraction of biomaterials such as DNA and RNA. Moreover, a comprehensive set of phenotype data is collected, assessing symptom dimensions, cognitive function and self-report measures (Table 1).

Table 1. Phenotypes collected in the PsyCourse study. Abbreviations: ALDA-Scale – Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder [44]; ASRM - Altman Self Rating Mania Scale [45]; BDI-II - Beck Depression Inventory II [46]; BFI-10 - Big Five Inventory [47]; CAPE – Community Assessment of Psychic Experiences [48] [49]; CGI - Clinical Global Impression [50]; CTS - Childhood Trauma Screener [51]; DSM-IV-TR - Diagnostic and statistical manual of mental disorders (4th edition) [52]; F/U - follow-up; GAF - Global Assessment of Functioning Scale [52]; IDS-C30 - Inventory of Depressive Symptomatology (30 items, clinician rated) [53]; LEQ - Life Events Questionnaire [54]; MINI-DIPS - Diagnostisches Kurzinterview bei psychischen Störungen [26]; MSS - Manie-Selbstbeurteilungsskala [55]; MWT-B - Mehrfachwahl-Wortschatz-Intelligenztest [56]; OPCRIT - Operational Criteria Checklist for Psychotic Illness [57]; PANSS - Positive and Negative Syndrome Scale [58]; SCID I - Structured Clinical Interview for DSM-IV (Axis I Disorders) [59]; SF-12 - SF-12 Health Survey [60]; VLMT - Verbaler Lern- und Merkfähigkeitstest [61]; WHOQOL-BREF - World Health Organization Quality of Life questionnaire [62]; YMRS - Young Mania Rating Scale [63].

Participants			***Clinical***		***Non-clinical[a]***	
a) Clinician ratings			Timepoint		Timepoint	
Section	***Instrument***	***Focusing on***	***Baseline***	***F/U***	***Baseline***	***F/U***
General						
	Demographics		X	X	X	X
	Family history of psychiatric illness		X		X	
	Psychiatric history of illness		X		X	
	Medical data and physical impairments		X	(X[b])	X	(X[b])
	Medication		X	X	X	X

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	ALDA-Scale	Response to Lithium		X		
	Tobacco and Alcohol		X	X	X	X
	Substance abuse/dependence		X	X	X	X
Diagnosis						
	SCID-I (Sections A, B, X, C, D)	Life-time clinical diagnosis according to DSM-IV-TR criteria	X			
	Parts of MINI-DIPS	Screening for psychiatric illness			X	
General Psychopathology						
	CGI	Current severity of illness (also compared to previous ratings)	X	X		
	OPCRIT item 90	Course of disorder		X		
Clinical Symptomatology						
	PANSS	Positive and negative symptoms	X	X	X	X
	IDS-C_{30}	Depressive symptoms	X	X	X	X
	YMRS	Manic symptoms	X	X	X	X
Level of functioning						
	GAF	Psychosocial functioning	X	X	X	X
Neuropsychological assessments						
	Trail Making Test	Executive functioning	X	X	X	X

Digit-Symbol-Test	Processing speed	X	X	X	X
Digit-Span	Verbal working memory	X	X	X	X
MWT-B	Intelligence screening	X		X	
VLMT	Verbal learning and memory		X		X
b) Self-ratings					
Clinical Symptomatology					
BDI–II	Depressive symptoms	X	X	X	X
MSS	Manic symptoms	X	X	X	X
ASRM	Manic symptoms	X	X	X	X
CAPE	Psychotic-like experiences			X	
Quality of life					
WHOQOL-BREF	Subjective quality of life	X	X	X	X
SF-12	Health related quality of life			X	X
Environmental factors					
LEQ	Life events within the last 6 months	X	X	X	X
Personality					
BFI-10	Big Five personality traits	X		X	
Other					
Religiousness		X		X	

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	Medication adherence	Medication adherence over last 7 days and last 6 months	X	X	
	CTS	Exposure to traumatic experiences as a child		X	X

[a]*scales used to assess non-clinical (control) subjects*

[b]*weight is assessed at each time point*

2.1.1 Clinical participants and broad diagnostic groups

Adult patients (≥18 years), with an ICD-10 life-time diagnosis of SZ (F20.x), brief psychotic disorder (F23.x), schizo-affective disorder (SZA; F25.x), BD (F31.x), manic episode (F30.x), or recurrent major depression (reMDD; F33.x) are identified based on recommendations of the clinical staff or by querying patient registries of the participating clinical centers. Eligible individuals are invited to participate in the first study visit (T1), where, after giving informed consent (see below), their diagnosis is re-assessed within the DSM-IV framework using an adapted version of the Structured Clinical Interview for DSM-IV; Axis I Disorders (SCID-I). Participants with a life-time DSM-IV diagnosis of SZ (295.10/295.20/295.30/295.60/295.90) or schizophreniform disorder (295.40), brief psychotic disorder (298.8), or SZA (295.70) constitute the group with predominantly psychotic symptoms, whereas those with a life-time DSM-IV diagnosis of BD (296.0x/296.4x/296.5x/296.6x/296.8x) or reMDD (296.3x) constitute the predominantly affective group. If none of the above DSM-IV diagnoses can be ascertained, clinical participants are excluded from the study, as are those without sufficient language or intellectual capacities.

2.1.2 Non-clinical (control) participants

Inhabitants of the catchment areas of Göttingen and Munich are contacted either by mail, based on address lists acquired from the local Residents' Registration Office, or by advertisements in public areas and are invited to participate in the study. Individuals without sufficient language or intellectual capacities are excluded from study participation. Those included in the study follow a similar protocol as the clinical participants (see Table 1). History of affective or psychotic illness is assessed using a short diagnostic interview for mental disorders [26].

2.1.3 Broad informed consent

Before study participation, written informed consent is obtained from study participants. A special broad informed consent is required from participants, as the exact research objectives are not specified and both phenotypic data and biomaterial are to be stored until they are no longer useful for research [27]. According to European and German law, such broad informed consent is only possible if special data protection measures are taken to shield personal data from unauthorized access (see section 2.1.5 on data protection). Participating individuals must explicitly agree to these measures, if they want to participate in the study. Moreover, potential participants must decide whether they want to be informed about possible incidental findings that the study may uncover. Collaboration with non-psychiatric research disciplines and the possibility to jointly analyze data together with other researchers or research consortia is explicitly allowed, albeit only using pseudonymized data. Furthermore, participants are asked to release medical facilities involved in their prior treatment from doctor-patient confidentiality, so that information on their past medical records can be obtained. This serves as an additional source of information on their medical history.

2.1.4 Opt-out

If a participant decides to opt-out after enrolling in the study, two options exist:

1. Disposition of the participant's biomaterial and permanent deletion of all phenotypic data, or

2. All information collected until that point in time will be retained but irreversibly anonymized.

Data that are already part of scientific analyses at the time of the opt-out may be used further, regardless of the opt-out, albeit only in anonymized form.

2.1.5 Data protection

As we collect sensitive phenotypic data and biomaterials, a data protection concept was developed [28]. Briefly, it includes an array of organizational measures such as pseudonymization to minimize the risk of participant identification and unauthorized transmission of personal data to third parties. Four different IT components have been established by the Department of Medical Informatics at the University Medical Center, Göttingen, Germany (see Figure 1):

1. The identity tool, responsible for storing the identifying data and for generating two different pseudonyms.

2. The administrative tool, for managing study organization, informed consent, and communication with the study participants (linked to the identity tool).

3. The phenotype database, containing information collected using rating scales, questionnaires and cognitive tests.

4. The biomaterial database for administering the collected biological samples.

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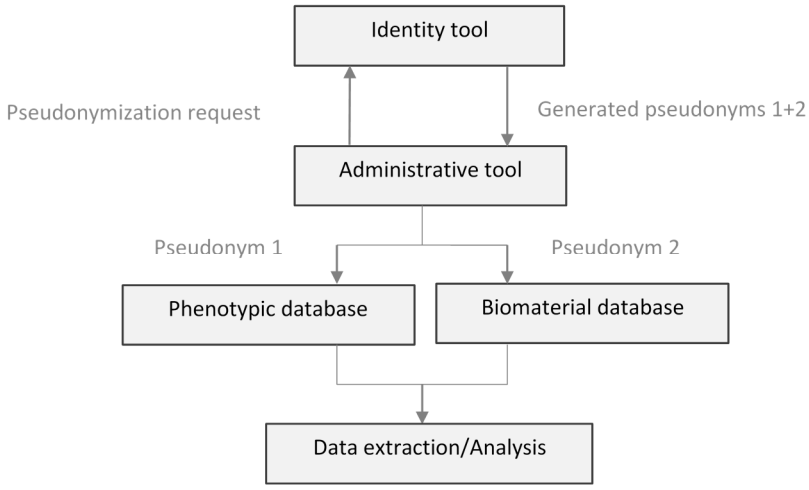

Figure 1. IT components of the PsyCourse study responsible for identifying, managing and storing phenotype data and biological samples.

2.1.6 Interviewers

Interviewers are provided with instructions in written form for all instruments and each new interviewer is extensively trained in administering the phenotyping battery by an experienced interviewer. Depending on interviewer experience, training includes discussing the instructions in detail, watching an experienced investigator conducting a visit and performing a visit under supervision of the latter. In addition, trainings for all investigators are held on a regular basis.

2.2 Biological-psychiatric analyses in the PsyCourse resource

Clinical data presented herein are from a snapshot of the phenotype database taken on the 19th of September 2016 and include a total of 891 clinical participants. Regarding biomaterial, venous blood samples were collected at each study visit. Briefly, DNA, RNA and plasma and serum samples were prepared using standard methods. Data were analyzed using R (www.r-project.org, version 3.3.2), and SPSS (IBM, version 24). Files describing statistical analysis steps are contained in the Supplementary Materials. Descriptions of the content of these files can be found in Appendix A.

2.2.1 Phenotype analyses

Cross-sectional phenotype data were analyzed with Pearson's chi-squared and t-tests, depending on the type of data (see Table 2). Longitudinal data were analyzed using linear mixed-effect regression (R package lme4; [29]). The variables age at first study visit, psychiatric treatment at first study visit (ordinal variable with levels "outpatient/no psychiatric treatment" and "in- or day patient"), sex, group and time as well as interactions between sex, group and time entered the model as fixed effects. Subject and clinical center of the first study visit were modeled as random intercept effects. To fulfill the requirement of normally distributed residuals, we transformed data of the Inventory of Depressive Symptomatology (IDS-C_{30}), the Young Mania Rating Scale (YMRS) and the Positive and Negative Syndrome Scale (PANSS) Positive Score using the natural logarithm. Subsequent visual inspection of the residuals of each model did not show any obvious deviation from normality. The anova function in the R lmerTest package [30] was used to obtain P-values for

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fixed effects using Satterthwaite's approximation of degrees of freedom. We did not correct for the cumulative type-I error rate in the phenotype analyses because of the inherent mutual dependency of depressive, manic, and psychotic symptoms.

2.2.2 Genotyping and imputation of genetic data

DNA samples of 825 clinical participants were genotyped using the Illumina Infinium PsychArray (Illumina, USA), yielding information for approximately 590,000 genetic markers. More than 10% of these markers are in genetic loci previously associated with neuropsychiatric disorders. After standard quality control procedures, genotype imputation was performed using SHAPEIT2 (https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html) and IMPUTE2 (http://mathgen.stats.ox.ac.uk/impute/impute_v2.html) [31] [32] [33]. The 1000 Genomes project dataset (http://www.internationalgenome.org/; Phase 3 integrated variant set) was used as reference panel. Genetic variants with a poor imputation quality (INFO <0.8) were not included in downstream analyses.

2.2.3 Population structure

The EIGENSOFT package (smartPCA [34]) was used to model ancestry differences between the study participants. It uses a principal component analysis based on a pruned subset of approximately 50,000 autosomal SNPs, after excluding regions with high linkage disequilibrium.

2.2.4 Calculation of polygenic risk scores

SZ-PRS were calculated with PLINK 1.07 (http://zzz.bwh.harvard.edu/plink/) using the imputed genotypes. Briefly, summary statistics from the SZ GWAS of the Psychiatric Genomics Consortium (http://www.med.unc.edu/pgc; Discovery Sample) were used to ascertain risk variants, their p values, and associated odds ratios [35]. In the sample of the present study (Target Sample), the number of risk alleles carried by an individual (0, 1, or 2) for each SNP contributing to the PRS, was multiplied by the logarithm of the odds ratio for that particular variant according to the results from the Discovery Sample. The resulting values were summed up in an additive fashion to obtain an estimate of the SZ genetic burden for each individual at eleven different p-value thresholds ($p \leq 5*10\text{-}8$; $p \leq 0.0001$; $p \leq 0.001$; $p \leq 0.01$; $p \leq 0.05$; $p \leq 0.1$; $p \leq 0.2$; $p \leq 0.3$; $p \leq 0.4$; $p \leq 0.5$; $p \leq 1$). SZ-PRS do not significantly deviate from normality and were standardized using z-score transformation.

2.2.5 Polygenic risk score analyses of diagnostic group

Ancestry principal components were calculated specifically for the subsample entering these analyses (for methods see 2.2.3) to be able to correct for potential effects of population substructure. Blockwise logistic regression analyses were used to estimate the amount of variation of diagnostic group (predominantly affective versus psychotic symptoms) explained by z-standardized SZ-PRS at eleven different p-value thresholds. Potential confounding variables, namely sex, age at baseline, age^2, sex x age interaction as well as the first five ancestry principal components, were entered in the first block. In the second block, the predictor of interest, the respective z-standardized SZ-PRS, was added. The reported estimates of change in R^2 represent the gain in Nagelkerke's R^2 by adding SZ-PRS to the model.

311 2.2.6 Analyses of follow-up study participation

312 To address the question of selective dropouts in the PsyCourse study, subjects with baseline data
313 only, hereafter referred to as the dropout group, were compared to subjects with follow-up data for
314 at least one timepoint within the 18-month study period, hereafter referred to as the follow-up
315 group. To assure a valid assignment to these groups in the ongoing project, the study period of 18
316 months plus an additional time of five months for data entry were considered. Since the export
317 from the database was carried out on 19th of September 2016, only subjects with a T1 before 19th of
318 October 2014 were selected for these analyses (N=678).

319 Logistic regression (forced entry method) was used to test the effects of the following phenotypic
320 predictors on group-membership (dropout group vs. follow-up group): sex, age at baseline, age2,
321 age x sex interaction, center, diagnosis, educational status, psychiatric treatment at baseline,
322 duration of illness, PANSS positive score, PANSS negative score, PANSS general score, IDS-C_{30} sum
323 score, YMRS sum score and Global Assessment of Functioning (GAF). In a second step, blockwise
324 logistic regression analyses were performed to estimate the effects of SZ-PRS for eleven different p-
325 value thresholds, as explained above. Ancestry principal components were calculated specifically
326 for the subsample entering these analyses (for methods see 2.2.3) in order to be able to correct for
327 potential effects of population substructure. The significant phenotypic predictors from the
328 previous analyses, namely sex, sex x age interaction and psychiatric treatment at baseline, as well as
329 the first five ancestry principal components were entered as covariates in the first block. In the
330 second block, the respective z-standardized SZ-PRS was added as a predictor. Estimates of change
331 in Nagelkerke's R^2 relative to the SZ-PRS are reported.

332

3. Results

We report data of N=891 clinical individuals, 526 (59.0%), 415 (46.6%) and 351 (39.4%) of whom completed the second, third and fourth study visit, respectively. We compare clinical groups with predominantly affective symptoms (n=367 individuals [41.2% of total sample]; 294 with Bipolar-I Disorder, 68 with Bipolar-II Disorder and 5 with reMDD) to those suffering from predominantly psychotic symptoms (n=524 individuals [58.8% of total sample]; 424 with SZ, 83 with SZA, 11 with schizophreniform disorder and 6 with brief psychotic disorder). Approximately half of the sample (n=440, 49.8%) was treated as in- or daypatient at baseline.

3.1 Phenotypic analyses

Cross-sectional comparisons on demographic variables between the two groups are reported in Table 2. Participants in the predominantly psychotic group were characterized by a lower proportion of females, a lower age at baseline, a lower age at illness onset, a higher proportion of single (never married) individuals and were more frequently treated as in- or daypatients compared to the predominantly affective group. Moreover, fewer participants in the predominantly psychotic group reported a family history of psychiatric illness. Descriptive cross-sectional differences between sexes are shown in Table 3. Figures 2 - 5 show the longitudinal course of acute depressive (IDS-C_{30}), manic (YMRS) and psychotic (PANSS Positive Scale) symptoms as well as psychosocial functioning (GAF) over the study period.

Table 2. Comparisons between patient groups with predominantly affective versus predominantly psychotic disorders on demographic variables. Abbreviations: DF – degrees of freedom.

	Affective	Psychotic	Test statistic	DF	P
Female sex, n (%)	178 (48.5)	210 (40.1)	5.89 (X^2)	1	0.015
Age at first interview, mean (range)	45.4 (18-78)	40.8 (18-73)	5.27 (t)	741.43	<0.001
Age at illness onset, mean (range)	33.6 (11-73)	27.9 (7-73)	6.94 (t)	592.21	<0.001
Marital status single (never married), n (%)	158 (43.1)	336 (64.1)	37.35 (X^2)	1	<0.001
Family history of psychiatric illness, n (%)	268 (77.7)	334 (67.1)	10.73 (X^2)	1	0.001
In- or day patient at first study visit, n (%)	128 (34.9)	312 (59.5)	48.16 (X^2)	1	<0.001

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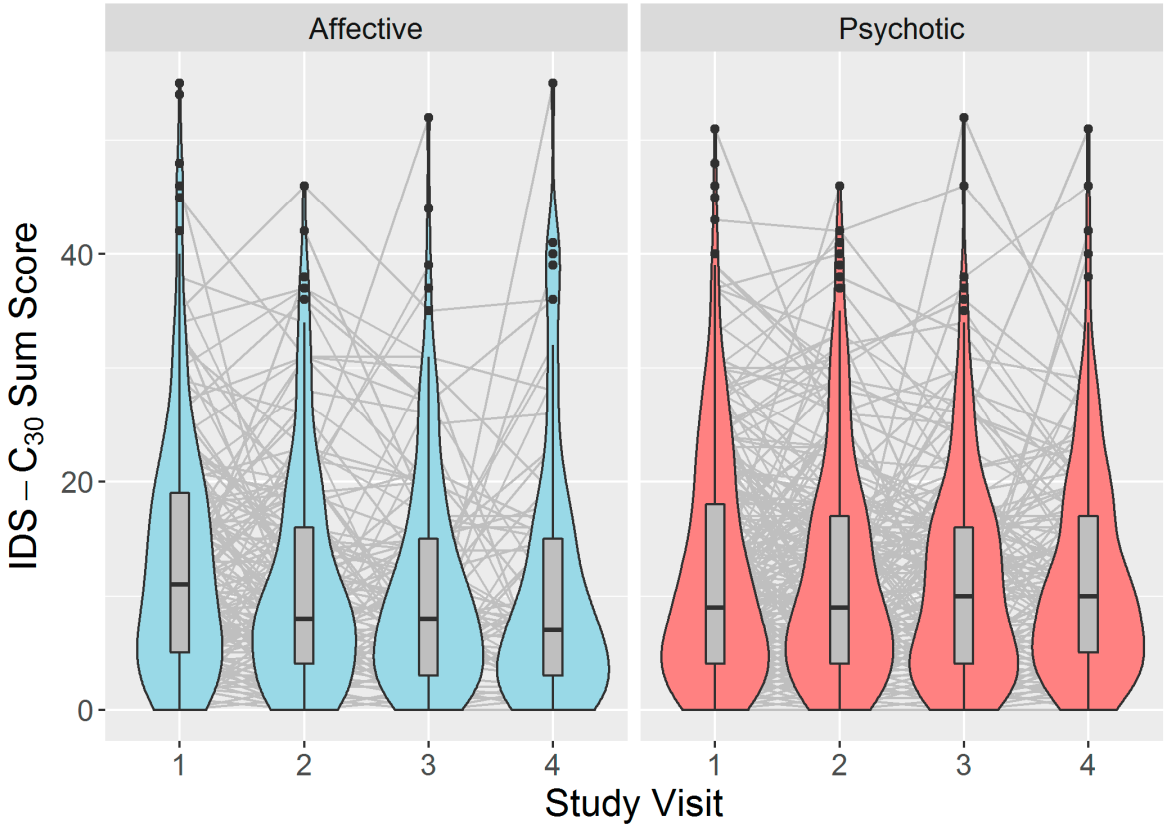
358 **Table 3.** Sex-specific descriptive statistics of both clinical groups.

	Female	Male
Affective group		
n	178	189
Age at first visit, mean (range)	45.2 (21-78)	45.6 (18-76)
Age at illness onset, mean (range)	33.7 (12-73)	33.5 (11-73)
Marital status single (never married), n (%)	70 (39.5)	88 (47.1)
Family history of psychiatric illness, n (%)	137 (80.6)	131 (75.3)
In- or day patient at first visit, n (%)	59 (33.5)	69 (37.5)
Psychotic group		
n	210	314
Age at first visit, mean (range)	43.8 (19-73)	38.9 (18-72)
Age at illness onset, mean (range)	29.0 (12-73)	27.1 (7-65)
Marital status single (never married), n (%)	100 (47.8)	236 (75.4)
Family history of psychiatric illness, n (%)	140 (72.5)	194 (65.5)
In- or day patient at first visit, n (%)	118 (56.2)	194 (61.8)



359

360 **Figure 2.** Violin plots of the course of depressive symptoms, separately for both patient groups.
361 Individual trajectories are plotted in gray color.

362

363 Linear mixed model analyses of depressive symptoms (Table 4) reveal effects of in- or daypatient
364 status at study inclusion (mean IDS-C_{30} scores at T1-T4 for in- or daypatients: 14.5, 12.2, 13.5, 12.1

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and outpatients/no psychiatric treatment: 10.7, 11.3, 9.8, 11.0) and sex (mean IDS-C_{30} scores at T1-T4 for females: 13.3, 12.2, 12.3, 12.4; males: 12.1, 11.2, 10.2, 10.6). No other variables were significant.

Table 4. Longitudinal analysis of depressive symptoms (IDS-C_{30}). Abbreviations: DenDF – denominator degrees of freedom, Dx – Diagnostic, MS - mean square, NumDF – numerator degrees of freedom, SS - sum of squares, Sign. – Significance.

	SS	MS	NumDF	DenDF	F	P	Sign.
Main effects							
Age at first visit	0.09	0.09	1	823.91	0.21	0.648	
In- or day patient at first visit	16.81	16.81	1	792.37	38.41	<0.001	***
Sex	2.71	2.71	1	888.67	6.19	0.013	*
Dx group	1.52	1.52	1	812.12	3.47	0.063	
Time (Visit)	1.72	0.57	3	1295.28	1.31	0.269	
Interaction effects							
Sex × Dx group	1.11	1.11	1	883.85	2.53	0.112	
Sex × Time (Visit)	0.76	0.25	3	1308.10	0.58	0.630	
Dx group × Time (Visit)	3.08	1.03	3	1304.03	2.34	0.072	
Sex × Dx group × Time (Visit)	2.04	0.68	3	1307.70	1.55	0.199	

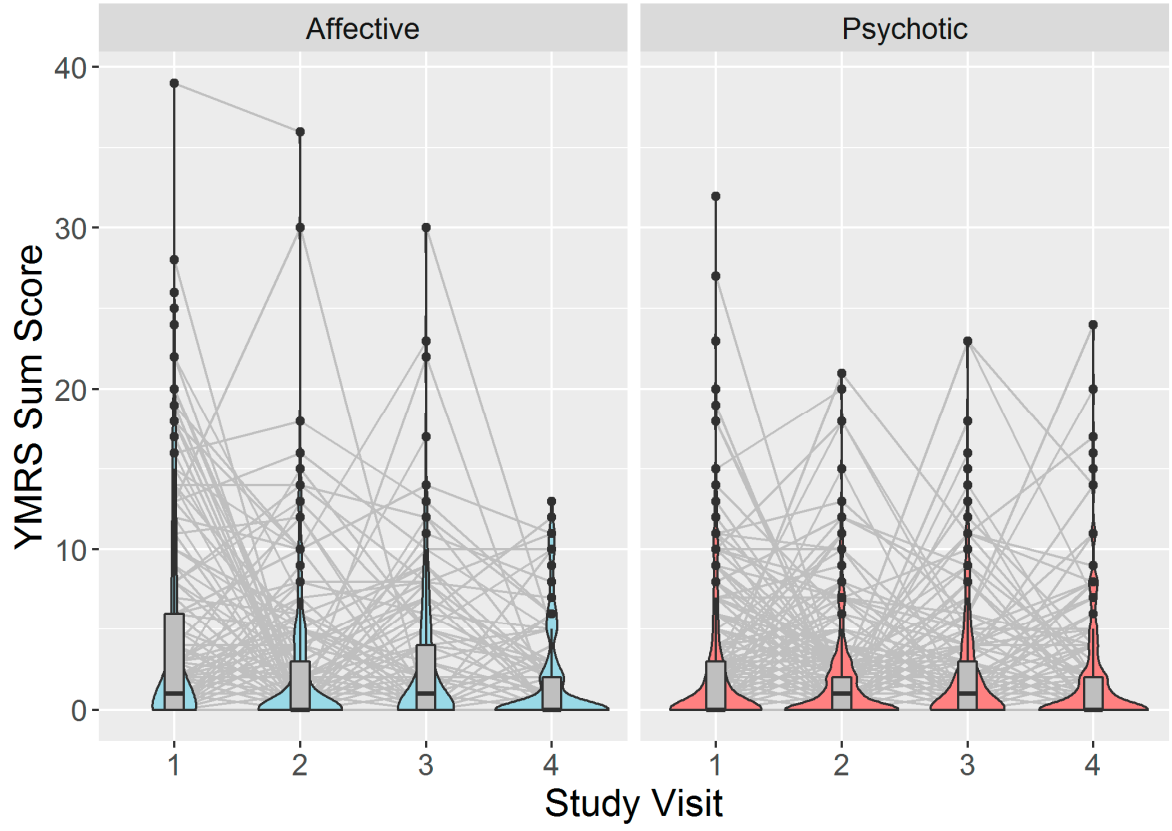

Figure 3. Violin plots of the course of manic symptoms, separately for both patient groups. Individual trajectories are plotted in gray color.

While depressive symptoms were thus not different between the patient groups, both manic (Tables 5 and 6) and psychotic (Tables 7 and 8) symptoms differ both over time (mean YMRS

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scores at T1-T4: 3.0, 2.1, 2.5, 2.1; mean PANSS Positive Scale scores at T1-T4: 12.3, 10.3, 10.4, 10.1) as well as between diagnostic groups [mean YMRS scores at T1-T4: 4.0, 2.5, 2.8, 1.9 (affective group) and 2.4, 1.9, 2.3, 2.1 (psychotic group); mean PANSS Positive Scale scores at T1-T4: 9.5, 8.5, 8.6, 8.3 (affective group) and 14.2, 11.5, 11.6, 11.1, (psychotic group)].

Table 5. Longitudinal analysis of manic symptoms (YMRS). For abbreviations see Table 4.

	SS	MS	NumDF	DenDF	F	P	Sign.
Main effects							
Age at first visit	0.79	0.79	1	774.58	1.50	0.222	
In- or day patient at first visit	1.11	1.11	1	771.85	2.10	0.148	
Sex	2.39	2.39	1	822.08	4.50	0.034	*
Dx group	2.59	2.59	1	748.24	4.88	0.028	*
Time (Visit)	11.50	3.83	3	1454.76	7.22	<0.001	***
Interaction effects							
Sex × Dx group	0.02	0.02	1	814.37	0.03	0.856	
Sex × Time (Visit)	1.63	0.54	3	1471.93	1.03	0.380	
Dx × Time (Visit)	8.98	2.99	3	1466.84	5.64	0.001	***
Sex × Dx group × Time (Visit)	2.84	0.95	3	1471.75	1.79	0.148	

Table 6. YMRS: Post-hoc tests between levels of the Time (Visit) and Diagnostic group factors. Abbreviation: CI – 95% confidence interval.

	Estimate	Lower CI	Upper CI	P
T1 versus T2	1.18	1.09	1.29	<0.001
T1 versus T3	1.07	0.97	1.18	0.156
T1 versus T4	1.21	1.10	1.34	<0.001
T2 versus T3	0.90	0.82	1.00	0.052
T2 versus T4	1.02	0.92	1.14	0.663
T3 versus T4	1.13	1.01	1.27	0.031
Affective T1 vs. Psychotic T1	1.41	1.23	1.62	<0.001
Affective T1 vs. Affective T2	1.34	1.18	1.53	<0.001
Affective T1 vs. Psychotic T2	1.47	1.27	1.71	<0.001
Affective T1 vs. Affective T3	1.19	1.03	1.37	0.020
Affective T1 vs. Psychotic T3	1.36	1.16	1.60	<0.001
Affective T1 vs. Affective T4	1.47	1.25	1.72	<0.001
Affective T1 vs. Psychotic T4	1.41	1.20	1.66	<0.001
Psychotic T1 vs. Affective T2	0.95	0.81	1.11	0.523
Psychotic T1 vs. Psychotic T2	1.04	0.94	1.17	0.435
Psychotic T1 vs. Affective T3	0.84	0.71	0.99	0.042
Psychotic T1 vs. Psychotic T3	0.97	0.86	1.09	0.584
Psychotic T1 vs. Affective T4	1.04	0.87	1.25	0.662
Psychotic T1 vs. Psychotic T4	1.00	0.88	1.13	0.987

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Affective T2 vs. Psychotic T2	1.10	0.93	1.30	0.259
Affective T2 vs. Affective T3	0.88	0.76	1.03	0.122
Affective T2 vs. Psychotic T3	1.02	0.86	1.21	0.851
Affective T2 vs. Affective T4	1.09	0.92	1.30	0.292
Affective T2 vs. Psychotic T4	1.05	0.88	1.25	0.562
Psychotic T2 vs. Affective T3	0.80	0.68	0.96	0.015
Psychotic T2 vs. Psychotic T3	0.92	0.81	1.05	0.237
Psychotic T2 vs. Affective T4	1.00	0.83	1.20	0.967
Psychotic T2 vs. Psychotic T4	0.96	0.84	1.09	0.527
Affective T3 vs. Psychotic T3	1.15	0.96	1.38	0.135
Affective T3 vs. Affective T4	1.24	1.04	1.48	0.018
Affective T3 vs. Psychotic T4	1.19	0.99	1.43	0.064
Psychotic T3 vs. Affective T4	1.08	0.89	1.31	0.452
Psychotic T3 vs. Psychotic T4	1.04	0.90	1.19	0.624
Affective T4 vs. Psychotic T4	0.96	0.79	1.17	0.696

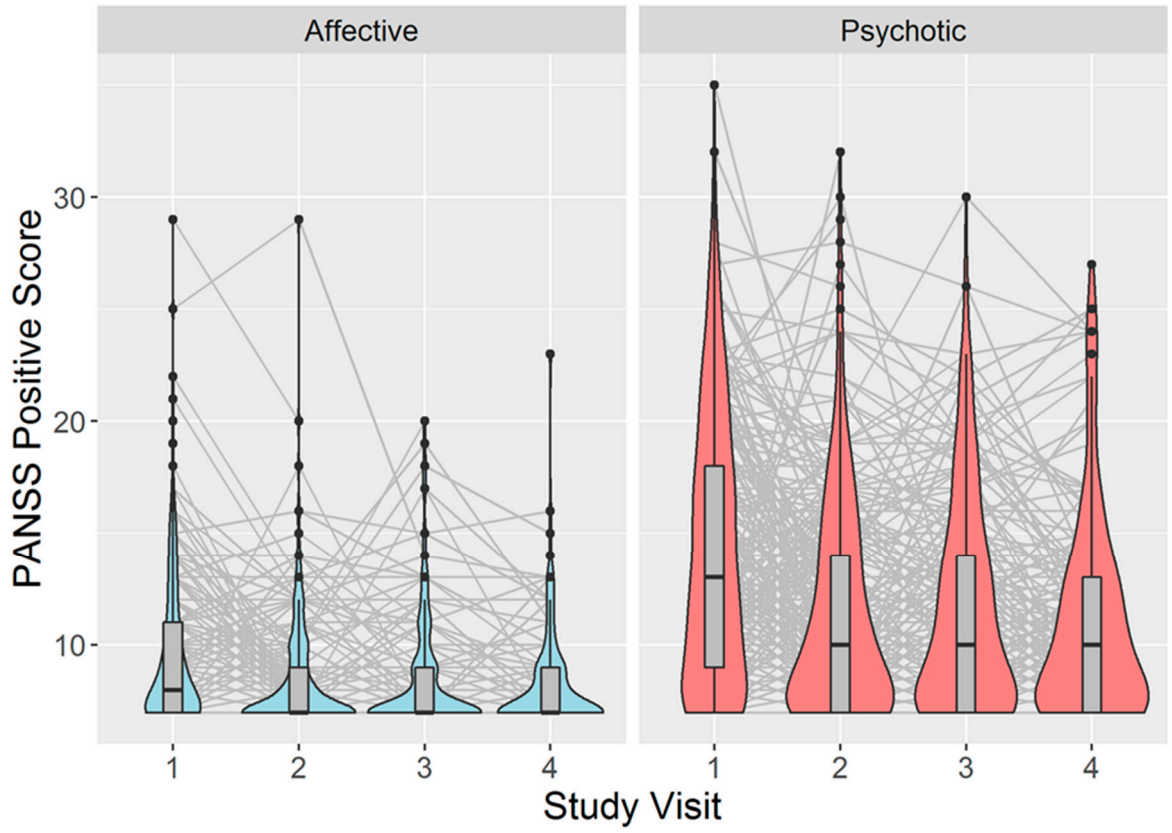

Figure 4. Violin plots of the course of psychotic symptoms, separately for both patient groups. Individual trajectories are plotted in gray color.

Symptoms of mania (Figure 3) also behaved differently in diagnostic groups over time and are independent of in- or daypatient status at the baseline assessment. Regarding symptoms, the most prominent difference between both diagnostic groups is the magnitude of psychotic symptoms (Figure 4). In both groups, there is a decrease of impairment after the baseline assessment and towards the end of the study period.

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Table 7. Longitudinal analysis of psychotic symptoms (PANSS Positive Score). For abbreviations see Table 4.

	SS	MS	NumDF	DenDF	F	P	Sign.
Main effects							
Age at first visit	0.07	0.07	1	848.74	1.24	0.267	
In- or day patient at first visit	0.57	0.57	1	791.26	10.70	0.001	**
Sex	0.16	0.16	1	923.94	3.04	0.082	
Dx group	3.46	3.46	1	847.05	65.50	<0.001	***
Time (Visit)	6.70	2.23	3	1424.64	42.26	<0.001	***
Interaction effects							
Sex × Dx group	0.07	0.07	1	919.44	1.28	0.258	
Sex × Time (Visit)	0.16	0.05	3	1437.95	0.99	0.398	
Dx group × Time (Visit)	0.20	0.07	3	1434.62	1.28	0.281	
Sex × Dx group × Time (Visit)	0.07	0.02	3	1437.35	0.44	0.723	

Table 8. PANSS Positive Score: Post-hoc tests between levels of the Time (Visit) factor. Abbreviation: CI – 95% confidence interval.

	Estimate	Lower CI	Upper CI	P
T1 vs. T2	1.13	1.10	1.16	<0.001
T1 vs. T3	1.12	1.09	1.15	<0.001
T1 vs. T4	1.17	1.13	1.21	<0.001
T2 vs. T3	0.99	0.96	1.03	0.728
T2 vs. T4	1.04	1.00	1.07	0.031
T3 vs. T4	1.04	1.01	1.08	0.017

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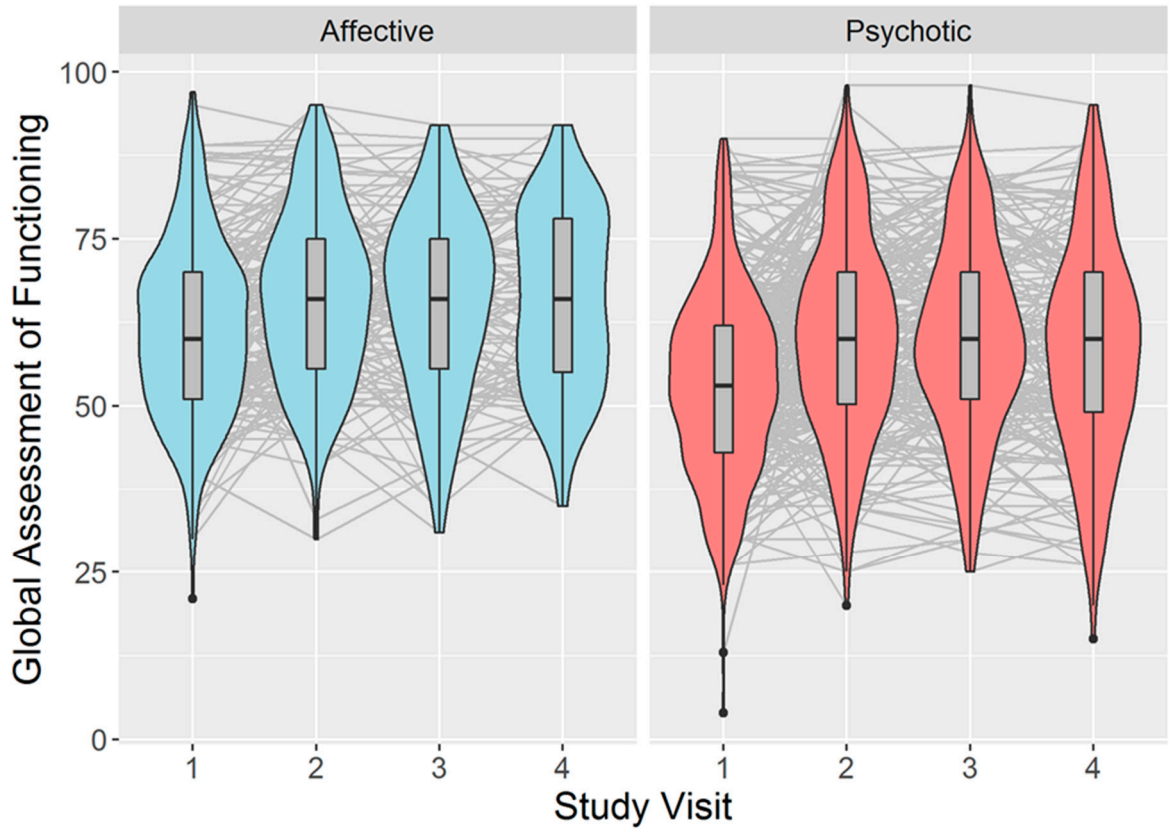

Figure 5. Violin plots of the course of psychosocial functioning, separately for both patient groups. Individual trajectories are plotted in gray color.

Analyses of GAF values over time (Tables 9 and 10) revealed effects of in- or daypatient status, diagnostic group, time and the sex x diagnostic group interaction. Mean GAF values at T1-T4, were: 61.5, 65.9, 65.1, 64.8 (affective group, females); 61.6, 66.5, 65.5, 66.6 (affective group, males); 54.5, 61.5, 61.6, 60.5 (psychotic group, females) and 52.3, 59.8, 58.8, 56.2 (psychotic group, males).

Table 9. Longitudinal analysis of GAF values. For abbreviations see Table 4.

	SS	MS	NumDF	DenDF	F	P	Sign.
Main effects							
Age at first visit	249.8	249.8	1	861.39	2.86	0.091	
In- or day patient at first visit	6357.0	6357.0	1	215.18	72.83	<0.001	***
Sex	207.2	207.2	1	947.67	2.37	0.124	
Dx group	2820.6	2820.6	1	387.57	32.31	<0.001	***
Time (Visit)	8941.0	2980.3	3	1435.55	34.14	<0.001	***
Interaction effects							
Sex × Dx group	466.7	466.7	1	939.32	5.35	0.021	*
Sex × Time (Visit)	74.6	24.9	3	1446.20	0.29	0.837	
Dx group × Time (Visit)	203.1	67.7	3	1444.13	0.78	0.508	
Sex × Dx group × Time (Visit)	130.7	43.6	3	1445.69	0.50	0.683	

Table 10. GAF: Post-hoc tests between levels of the Time (Visit) factor. Abbreviation: CI – 95% confidence interval.

	Estimate	Lower CI	Upper CI	P
T1 vs. T2	-5.18	-6.29	-4.07	<0.001
T1 vs. T3	-4.41	-5.63	-3.19	<0.001
T1 vs. T4	-4.03	-5.34	-2.72	<0.001
T2 vs. T3	0.77	-0.53	2.07	0.245
T2 vs. T4	1.15	-0.23	2.54	0.101
T3 vs. T4	0.38	-1.05	1.82	0.600

3.2 Population structure

Figure 6 shows the PsyCourse subjects and all 1000 genomes super-populations based on the first two ancestry principal components and highlights the European origin of most of the subjects of thePsyCourse study.

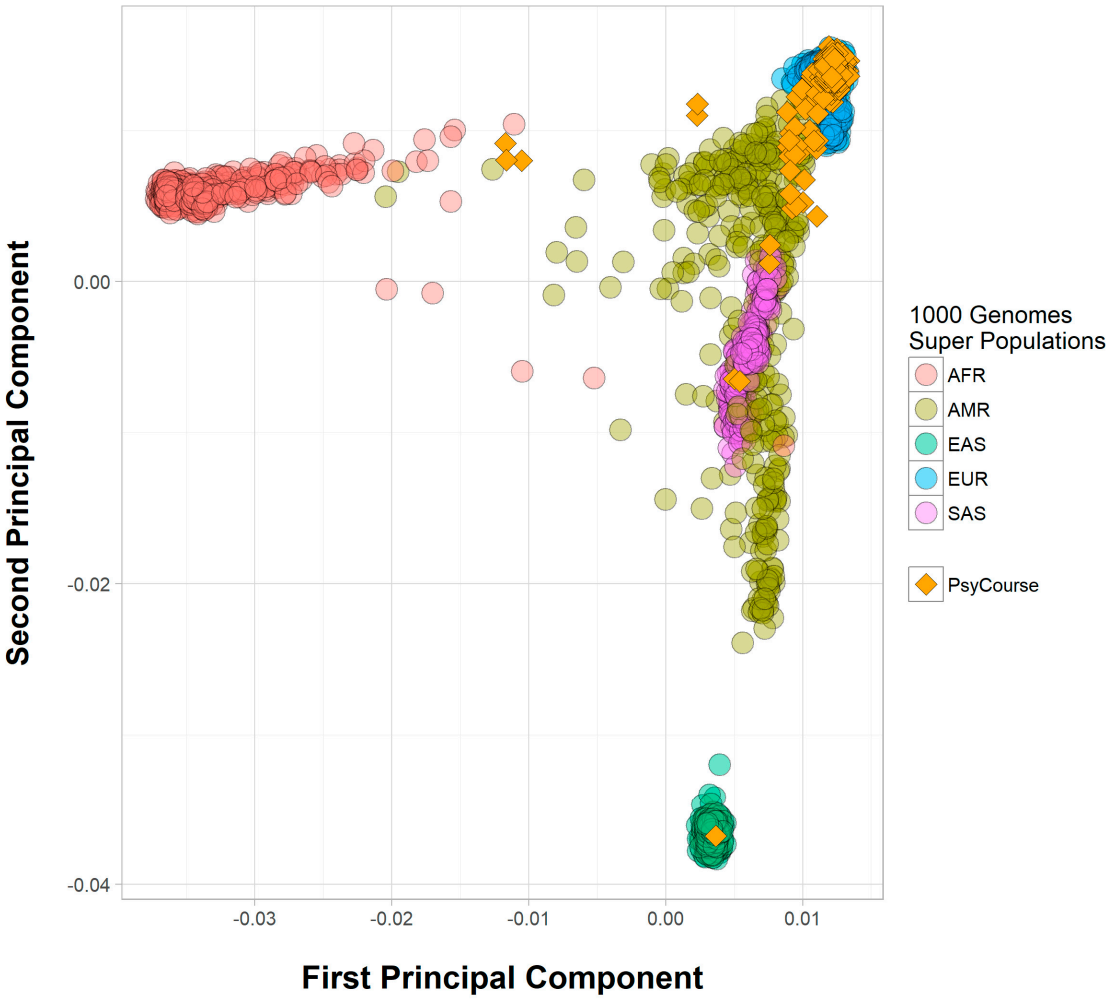

Figure 6. Principal Components Analysis of PsyCourse participants and European 1000 genomes project populations (Legend: AFR: African; AMR: American; EAS: East Asian; EUR: European; SAS: South Asian).

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3.3 SZ-PRS analyses of the diagnostic group

A subset of 771 participants with available SZ-PRS and without missing data in any of the covariates was analyzed. Approximately 57.3% suffered from predominantly psychotic symptoms while 42.7% suffered from predominately affective symptoms. Figure 7 shows changes in Nagelkerke's R^2 due to effects of the SZ-PRS at eleven different p-value thresholds. Along with the increase of the SZ-PRS, the odds of being in the predominantly psychotic group increase. The largest effect was observed for the SZ-PRS at the p-value threshold of 0.05 [Odds Ratio (OR)=1.28; 95% CI: 1.10-1.50].

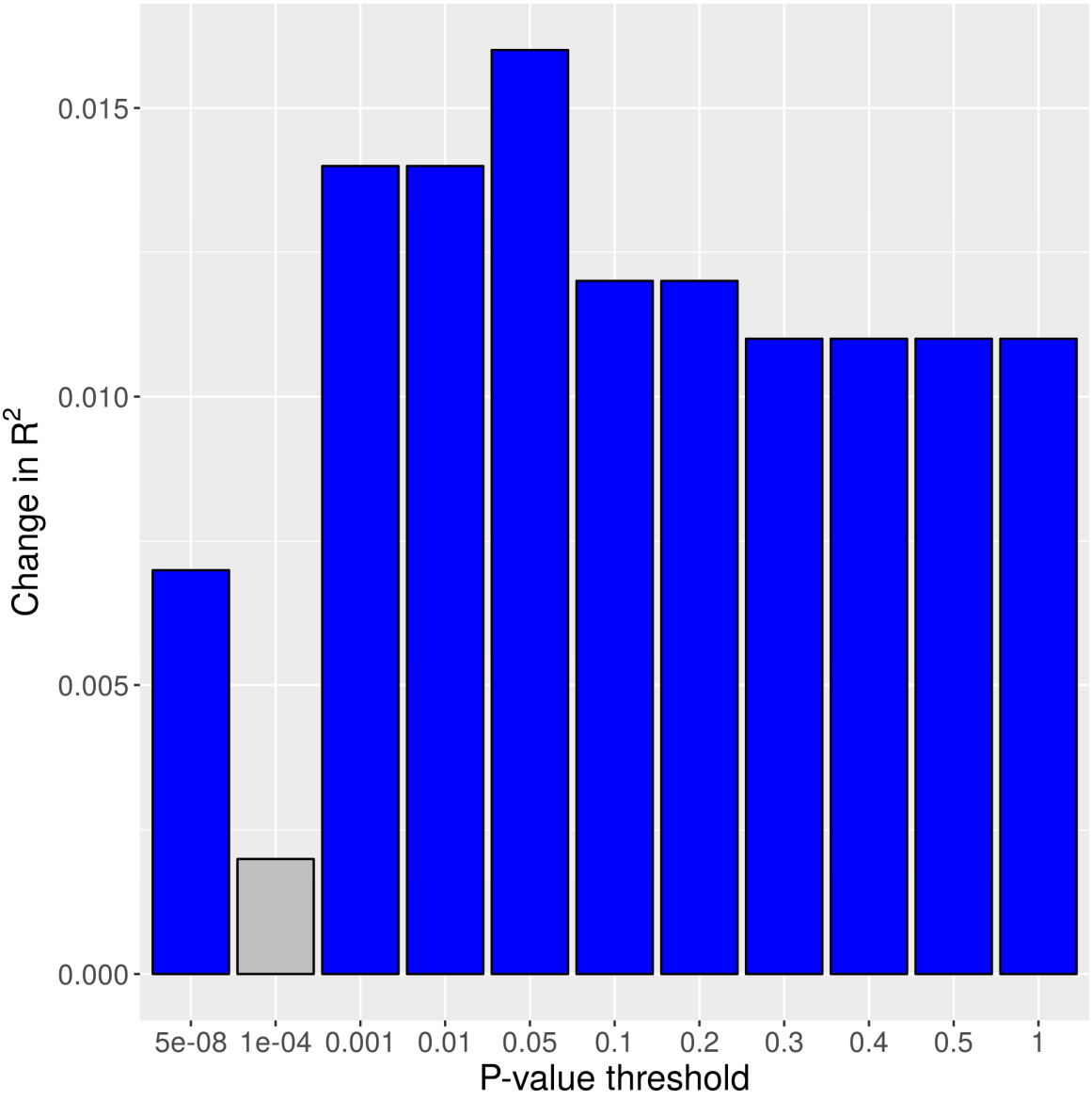


Figure 7. Effects of SZ-PRS on diagnostic group. Nominally significant P-values in blue color (baseline model with covariates only: R^2=0.091; all nominally significant effects of SZ-PRS survive FDR correction).

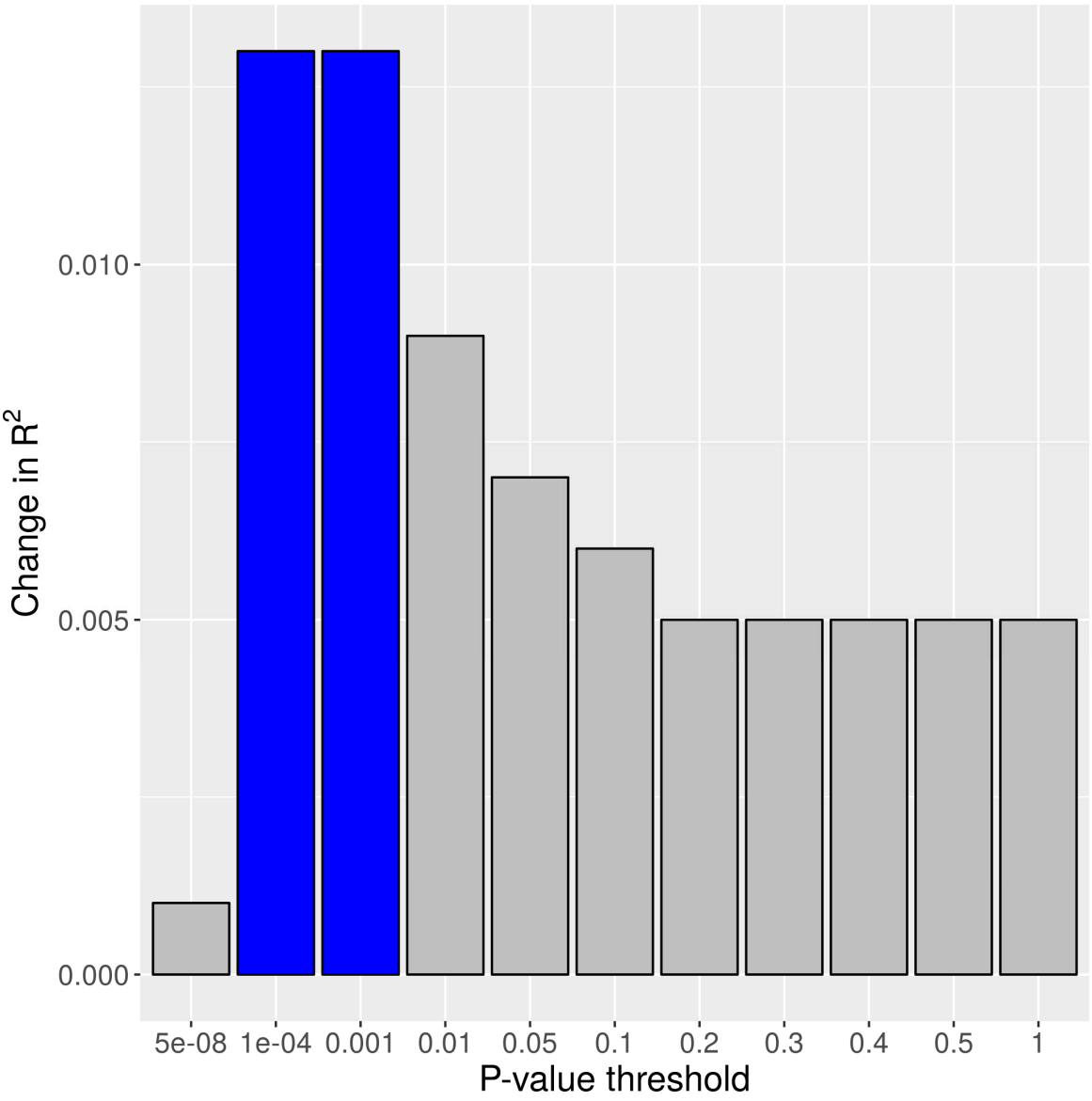
3.4 Analyses of follow-up study participation

Logistic regression was performed in 498 participants without missing data in the phenotypic predictors, 69.5% of whom had follow-up data from at least one additional study visit. Results are shown in Table 11. In the baseline model, i.e. without any information from phenotypic predictors,

69.5% of the subjects were correctly classified. This rate increased to 73.5% when demographic and disease related variables (for details see 2.2.7) were entered in the regression model. Male sex and outpatient treatment at baseline were significantly associated with increasing odds of having follow-up data.

Table 11. Logistic regression of follow-up status on phenotypic variables. B=regression coefficient; SE=standard error; coding of dichotomous variables: sex: 0=male, 1=female; treatment at baseline: 0=outpatient, 1=in/daypatient at first study visit; diagnostic group: 0=predominantly psychotic, 1=predominantly affective; outcome: 0=dropout, 1=follow up. *p<0.05; **p<0.01; Nagelkerke´s R^2 = 0.282.

		95% CI for odds ratio		
Included	B (SE)	Lower	Odds Ratio	Upper
Constant	18.774 (11440.497)			
Center				
Augsburg	1.851 (21967.782)		6.369	
Bad Zwischenahn	-19.389 (11440.497)		0.000	
Bochum	-19.958 (11440.497)		0.000	
Bremen Ost	-19.063 (11440.497)		0.000	
Eschwege	0.554 (22526.837)		1.740	
Göttingen	-20.575 (11440.497)		0.000	
Günzburg	-20.216 (11440.497)		0.000	
Graz	-19.891 (11440.497)		0.000	
Hildesheim	-20.439 (11440.497)		0.000	
Lüneburg	-20.005 (11440.497)		0.000	
Liebenburg	-0.074 (18877.144)		0.929	
München	-19.930 (11440.497)		0.000	
Osnabrück	-20.145 (11440.497)		0.000	
Rotenburg	-18.140 (11440.497)		0.000	
Tiefenbrunn	-19.065 (11440.497)		0.000	
UMG Göttingen	-18.847 (11440.497)		0.000	
Other variables				
Sex (female)	-2.089 (0.845)*	0.024	0.124	0.648
Age at baseline	0.076 (0.058)	0.963	1.079	1.209
Age^2	-0.001 (0.001)	0.998	0.999	1.001
Age*Sex	0.038 (0.019)*	1.000	1.038	1.078
Diagnostic group (affective)	0.222 (0.320)	0.667	1.249	2.338
Educational status	0.022 (0.080)	0.874	1.022	1.196
In- or day patient at first study visit	-1.136 (0.319)**	0.172	0.321	0.600
Duration of illness	0.012 (0.014)	0.985	1.012	1.040
PANSS positive score	0.004 (0.035)	0.937	1.004	1.076
PANSS negative score	0.045 (0.028)	0.990	1.046	1.105
PANSS general score	-0.004 (0.026)	0.946	0.996	1.049
IDS-C_{30} sum score	-0.010 (0.015)	0.961	0.990	1.019
YMRS sum score	-0.012 (0.026)	0.939	0.988	1.041
GAF	-0.001 (0.012)	0.976	0.999	1.022



For the SZ-PRS analyses, a subsample of 613 subjects with SZ-PRS and completely available covariates was analyzed, 71.9% of whom had follow-up data. Figure 8 shows changes in Nagelkerke's R^2 due to effects of the SZ-PRS at eleven different p-value thresholds. As the SZ-PRSs increase, the odds of being in the follow-up group decrease. This trend was nominally significant for risk scores at two different p-value thresholds. Effect sizes at these two p-value thresholds were similar (p-value threshold of 0.0001: OR=0.79; 95% CI: 0.65-0.95; p-value threshold of 0.001: OR=0.78; 95% CI: 0.64-0.95).

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4. Discussion

Here, we present the PsyCourse study, a transdiagnostic study of the affective-to-psychotic continuum that combines longitudinal deep phenotyping and dimensional assessment of psychopathology with an extensive collection of biomaterial. Broad informed consent by the participants allows this study to serve as a unique resource for the interrogation of complex genotype-phenotype relationships. The combination of both longitudinal and cross-sectional phenotype assessments expands the horizon of genetic association studies beyond case-control phenotypes. Data collected in this study will enable researchers to find variants related to disease phenotypes within clinical groups, not confined to traditional diagnostic boundaries, and serve as starting point for the elucidation of disease mechanisms which are urgently needed to develop new therapeutics (see [36] for a review).

4.1 Phenotype analysis of symptom dimensions over time

4.1.1 IDS-C_{30}, YMRS and PANSS Positive scores

Dimensional assessment of depressive, manic and psychotic symptoms as well as psychosocial functioning were compared between predominantly affective and predominantly psychotic disorders over time to identify hallmarks of the short-term course of severe mental disorders [2]. Our analyses highlight mild depressive symptoms in both clinical groups that do not vary over time or show different patterns over time according to diagnostic group. Overall, females had slightly higher depression scores than men at baseline, an effect also observed in samples containing individuals suffering from either BD [37] or SZ [38]. Psychotic symptoms, the symptom dimension that, predictably, showed the largest difference between diagnostic groups, decreased in both groups after the first study visit. This may be interpreted as common treatment effect, as many clinical participants were treated as in- or day patients at the beginning of the study. Manic symptom ratings, were higher in the affective group, albeit generally at very low levels, and showed a different fluctuating pattern than in the psychotic group. As with psychotic symptoms, differences over time are interpreted to mainly reflect treatment effects in both diagnostic groups. It should be noted that the difference of manic symptoms between diagnostic groups does not appear as clear-cut as that of psychotic symptoms and, similarly to symptoms of depression, symptoms of mania were clearly observed in both diagnostic groups. The different behavior over time in the diagnostic groups is thought to reflect the episodic characteristics of BD [39]. The sex effect across diagnostic groups (higher mean YMRS scores in males) appears to be an interesting finding and of opposite direction than the sex effect observed across diagnostic groups with depression scores (higher IDS-C30 scores in females). This finding highlights the advantages of assessing symptom dimensions across diagnoses.

In summary, mild depressive symptoms were comparable between diagnostic groups, whereas large differences in psychotic symptoms were the primary characteristic separating both diagnostic groups. We highlight a sex-specific pattern of more severe symptoms of depression in women and more severe mania symptoms in men suffering from severe mental disorders.

4.1.2 Effects on psychosocial functioning

GAF values covary with symptom status by definition, a strong effect of in- or day patient status is therefore not surprising. Moreover, the pronounced difference in GAF values between diagnostic groups may be attributed to a more severe load of psychotic symptoms in the predominantly psychotic group. Analogous to the improvement of psychotic and manic symptoms, we also interpret

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the GAF improvement over time in both diagnostic subgroups as treatment effect. The finding of a statistical interaction between sex and diagnostic group has been observed before when comparing psychotic and affective illnesses [13] [40], reflecting psychotic females to have higher GAF scores than psychotic males, whereas no such sex difference exists in BD.

4.2 SZ-PRS analyses of diagnostic group

We explored whether SZ-PRS are able to differentiate between predominantly psychotic versus affective participants in the PsyCourse study. The results are in line with knowledge of not only an overlapping [8] but also a specific [21] polygenic background of SZ and BD. Ten of eleven SZ-PRS with different p-value thresholds significantly explained variability of diagnostic group. As expected, a higher SZ-PRS increased the odds of being in the "predominantly psychotic" group. Across the range of SZ-PRS, the explained variation is at about 1% towards a p-value threshold of 1. To put that in context, when comparing patients and controls, SZ-PRS explain about 7% of case-control status in SZ [35] and about 2% in BD [8] [9] [41]. Our results implicate that SZ-PRS can discriminate between predominantly psychotic versus affective subjects at a population level. However, because of the common genetic background of the two groups [8], the amount of explained variability is not as high as the effects usually observed when comparing cases and controls. To our knowledge, this is the first study that directly investigated to what extent SZ-PRS discriminates between predominantly psychotic and predominantly affective patients.

4.3 SZ-PRS analyses of follow-up participation

In the current snapshot of the database, about 70% of the study participants have follow-up data for at least one study visit during the entire 18 months study period. Gender and the treatment at baseline were predictors of dropout. More precisely, being male as well as being treated as an outpatient increased the odds of having follow-up data. Although effect sizes of the significant predictors are small and the rate of correctly classified subjects only improved by 4% in comparison to the baseline model, the selective dropout of hospitalized, hence more severely impaired, participants must be considered when interpreting longitudinal data from the PsyCourse study.

In the present study, associations between SZ-PRS and dropout were lower compared to the findings from Martin and colleagues (2016) in the population-based Avon Longitudinal Study of Parents and Children (ALSPAC). However, a trend in the expected direction with nominally significant effects for risk scores at two different p-value thresholds was observed. Since the current sample of the PsyCourse study is considerably smaller than the ALSPAC sample with nearly 8,000 subjects, the main reason for the lack of significant findings is presumably lower statistical power. Nevertheless, nominally significant results in the present study appear promising and, as recruitment is ongoing, analyses may be repeated using a larger sample in the future. It also needs to be considered that, while the ALSPAC cohort is population-based, the data analyzed here are from psychiatric patients. Therefore, the average polygenic loading for SZ is expected to be higher compared to the general population, which likely made it more difficult to detect significant effects of the SZ-PRS between groups. To our knowledge, there is no comparable investigation in a clinical sample yet.

4.4 Resource for collaborations

The PsyCourse study constitutes a unique resource on different levels. Firstly, the project already created a wealth of phenotypic and biological data. With recruitment still ongoing, the sample size

will increase over time. The project constitutes a major contributor to the DGPPN cohort, a budding initiative spearheaded by the German Association for Psychiatry and Psychotherapy with the aim of establishing a prospective national cohort of patients with major psychiatric disorders [42]. While not in the public domain, the PsyCourse study is meant to be available to bona fide researchers all over the world based on mutually agreed memoranda of understanding. Appendix B contains a brief outline of our Data Sharing Policy. Secondly, the project is accompanied by continuous development of a methodological and logistical framework for longitudinal research in biological psychiatry dealing with issues of practical implementation as well as ethical and legal aspects [43].

Supplementary Materials: The following files documenting our statistical analyses are available online at www.mdpi.com/link/XXX (see Appendix A): S1_R_Markdown_Phenotype_Analyses.html, S2_SPSS_Output_ Polygenic_Risk_Score_Analyses.pdf and S3_R_Code_ Ancestry_PCA_Plot.docx.

Acknowledgments: Thomas G. Schulze and Peter Falkai are supported by the Deutsche Forschungsgemeinschaft (DFG) within the framework of the projects www.kfo241.de and www.PsyCourse.de (SCHU 1603/4-1, 5-1, 7-1; FA241/16-1). The genotyping was in part funded by the German Federal Ministry of Education and Research (BMBF) through the Integrated Network IntegraMent (Integrated Understanding of Causes and Mechanisms in Mental Disorders), under the auspices of the e:Med Programme with grants awarded to Thomas G. Schulze (01ZX1614K), Marcella Rietschel (01ZX1614G), and Markus M. Nöthen (01ZX1614A). Thomas G. Schulze received additional support from the German Federal Ministry of Education and Research (BMBF) within the framework of the BipoLife network and the Dr. Lisa Oehler Foundation, Kassel (Germany). Franziska Degenhardt received support from the BONFOR Programme of the University of Bonn, Germany. Jens Wiltfang is supported by an Ilídio Pinho professorship and iBiMED (UID/BIM/04501/2013), at the University of Aveiro. Udo Dannlowski was funded by the German Research Foundation (DFG, grant FOR2107 DA1151/5-1; SFB-TRR58, Project C09) and the Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster (grant Dan3/012/17 to Udo Dannlowski).

We would like to express our profound gratitude to all study participants without whom this work would not have been possible. We also thank the interviewers Chadiga Aly, Katharina Bachmann, Marianne Bärhold, Jessica Baumgärtner, Susanne Bengesser, Armin Birner, Tina Bittel, Cosima Bitter, Christian Bürger, Nina Dalkner, Katharina Dohm, Daniel Feldhaus, Frederike Fellendorf, Laura Filser, Katharina Förster, Linda Gebel, Nicole Große, Lena Grüber, Michael Hamerle, Silke Jörgens, Nora Kainzbauer, Sophie Kirchner, Marina Krause, Anna Lehmann, Sarah Liebl, Sandra Lorek, Anita von Lünen, Svenja Mattausch, Daniela Meile, Susanne Meinert, Laura Mühlich, Katharina Niamkovich, Barbara Nierste, Jana Nolden, Jaqueline Ohle, Malenna Pieper, René Pilz, Martina Platzer, Robert Queissner, Sabrina Röbbel, Sabrina Schaupp, Jelka Schillmöller, Markus Schott, Judith Stöckel, Mariana Varga, Thomas Vogl, Lara Wieland, Linus Wittmann and Dario Zaremba and our lab team Stefanie Behrens, Birgit Burde, Uta Engelhardt, Verena Gullatz and Anke Jahn-Brodmann.

Author Contributions: Monika Budde and Urs Heilbronner interviewed study participants, analyzed and interpreted data and wrote the manuscript. Sergi Papiol and Till Andlauer analyzed genotype data. Thomas G. Schulze and Peter Falkai designed the study. All other authors contributed to planning, recruitment or interviewing of study participants. All authors critically revised the manuscript and approved the final version.

Conflicts of Interest: The authors declare no conflict of interest. The funding agencies had no role in the design of the study; in the collection, analysis, or interpretation of data. Neither were they involved in the writing of the manuscript or in the decision to publish the results.

Peer-reviewed version available at American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 2018; doi:10.1002/ajmg.b.32639

Appendix A: Files Describing Statistical Analyses

Here, we provide an overview of the files contained in the Supplementary Materials:

Phenotype analyses: " S1_R_Markdown_Phenotype_Analyses.html"
This is an RMarkdown document that contains annotated R code and can thus be used to retrace our analysis steps. Upon appropriate request (see Appendix B), we will share the R data object "var_df.RData" (created under the subheading 6.3: "Create object potentially to be shared with other researchers for reproducibility purposes").

Polygenic risk score analyses: "S2_SPSS_Output_ Polygenic_Risk_Score_Analyses.pdf"
Polygenic risk score data were analyzed using SPSS. This file contains a detailed description of the analysis steps. A starting point is the file "170721_Items_for_MB.csv" that was created using the phenotype data (step 5.1 "Export file for polygenic risk score analyses" in "S1_R_Markdown_Phenotype_Analyses.html"). Polygenic risk scores will be provided upon appropriate request (see Appendix B).

Ancestry principal components plot: "S3_R_Code_ Ancestry_PCA_Plot.docx"
This file provides the code to create Figure 6. Files necessary to reproduce the analysis will be provided upon appropriate request (see Appendix B).

Appendix B: Data Sharing Policy

We are bound by the consent agreement between participants of the PsyCourse study and us. While we may share pseudonymized data with other researchers, this does not extend to making our data available to the public without restrictions.

PsyCourse data can be made available to bona fide researchers collaborating with us. As we are committed to reproducible research, we are also willing to share data analyzed in this publication with researchers aiming to reproduce our analyses.

In any case, a mutually agreed written memorandum of understanding must be signed before data can be obtained from us.

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