Received: 15 February 2018 | Revised: 5 April 2018 | Accepted: 16 April 2018

DOI: 10.1002/ajmg.b.32639

RESEARCH ARTICLE

WILEY American Journal of Medical Genetics Part B: Neuropsychiatric Genetics

A longitudinal approach to biological psychiatric research: The PsyCourse study

Monika Budde[1] | Heike Anderson-Schmidt[1,2] | Katrin Gade[1,2] | Daniela Reich-Erkelenz[1] | Kristina Adorjan[1,3] | Janos L. Kalman[1,3,4] | Fanny Senner[1,3] | Sergi Papiol[1,3] | Till F. M. Andlauer[5] | Ashley L. Comes[1,4] | Eva C. Schulte[1,3] | Farah Klöhn-Saghatolislam[1,3] | Anna Gryaznova[1] | Maria Hake[1] | Kim Bartholdi[1] | Laura Flatau[1] | Markus Reitt[2] | Silke Quast[2] | Sophia Stegmaier[6] | Milena Meyers[7] | Barbara Emons[7] | Ida Sybille Haußleiter[7] | Georg Juckel[7] | Vanessa Nieratschker[6] | Udo Dannlowski[8] | Sabrina K. Schaupp[1,9] | Max Schmauß[9] | Jörg Zimmermann[10] | Jens Reimer[11] | Sybille Schulz[11] | Jens Wiltfang[2,12,13] | Eva Reininghaus[14] | Ion-George Anghelescu[15] | Volker Arolt[8] | Bernhard T. Baune[16] | Carsten Konrad[17] | Andreas Thiel[17] | Andreas J. Fallgatter[6] | Christian Figge[18] | Martin von Hagen[19] | Manfred Koller[20] | Fabian U. Lang[21] | Moritz E. Wigand[21] | Thomas Becker[21] | Markus Jäger[21] | Detlef E. Dietrich[22,23] | Sebastian Stierl[24] | Harald Scherk[25] | Carsten Spitzer[26] | Here Folkerts[27] | Stephanie H. Witt[28] | Franziska Degenhardt[29,30] | Andreas J. Forstner[29,30,31,32] | Marcella Rietschel[28] | Markus M. Nöthen[29,30] | Peter Falkai[3*] | Thomas G. Schulze[1,2*] | Urs Heilbronner[1*]

[1]Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany

[2]Department of Psychiatry and Psychotherapy, University Medical Center Goettingen, Goettingen, Germany

[3]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany

[4]International Max Planck Research School for Translational Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany

[5]Department of Translational Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany

[6]Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany

[7]Department of Psychiatry, Ruhr University Bochum, LWL University Hospital, Bochum, Germany

[8]Department of Psychiatry, University of Münster, Münster, Germany

[9]Department of Psychiatry and Psychotherapy, Bezirkskrankenhaus Augsburg, Augsburg, Germany

[10]Psychiatrieverbund Oldenburger Land gGmbH, Karl-Jaspers-Klinik, Bad Zwischenahn, Germany

[11]Department of Psychiatry, Klinikum Bremen-Ost, Bremen, Germany

*Peter Falkai, Thomas G. Schulze and Urs Heilbronner have contributed equally to this work.

[12]German Center for Neurodegenerative Diseases (DZNE), Goettingen, Germany

[13]iBiMED, Medical Sciences Department, University of Aveiro, Aveiro, Portugal

[14]Department of Psychiatry and Psychotherapeutic Medicine, Research Unit for Bipolar Affective Disorder, Medical University of Graz, Graz, Austria

[15]Department of Psychiatry, Dr. Fontheim—Mental Health, Liebenburg, Germany

[16]Discipline of Psychiatry, Royal Adelaide Hospital, Adelaide Medical School, The University of Adelaide, Adelaide, Australia

[17]Department of Psychiatry and Psychotherapy, Agaplesion Diakonieklinikum, Rotenburg, Germany

[18]Karl-Jaspers Clinic, European Medical School Oldenburg-Groningen, Oldenburg, Germany

[19]Clinic for Psychiatry and Psychotherapy, Clinical Center Werra-Meißner, Eschwege, Germany

[20]Asklepios Specialized Hospital, Göttingen, Germany

[21]Department of Psychiatry II, Ulm University, Bezirkskrankenhaus Günzburg, Günzburg, Germany

[22]AMEOS Clinical Center Hildesheim, Hildesheim, Germany

[23]Center for Systems Neuroscience (ZSN), Hannover, Germany

[24]Psychiatric Hospital Lüneburg, Lüneburg, Germany

[25]AMEOS Clinical Center Osnabrück, Osnabrück, Germany

[26]ASKLEPIOS Specialized Hospital Tiefenbrunn, Rosdorf, Germany

[27]Department of Psychiatry, Psychotherapy and Psychosomatics, Clinical Center Wilhelmshaven, Wilhelmshaven, Germany

[28]Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

[29]Institute of Human Genetics, University of Bonn School of Medicine & University Hospital Bonn, Bonn, Germany

[30]Department of Genomics, Life & Brain Center, University of Bonn, Bonn, Germany

[31]Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, Switzerland

[32]Department of Psychiatry (UPK), University of Basel, Basel, Switzerland

Correspondence
Urs Heilbronner, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Nußbaumstr. 7, Munich D-80336, Germany.
Email: urs.heilbronner@med.uni-muenchen.de

Present address
Detlef E. Dietrich, Burghof-Klinik Rinteln, Rinteln, Germany

Funding information
German Research Foundation (Deutsche Forschungsgemeinschaft; DFG), Grant/Award Numbers SCHU 1603/4-1, 5-1, 7-1, FA241/16-1; German Federal Ministry of Education and Research (BMBF), Grant/Award Numbers: Integrated Network IntegraMent 01ZX1614K, 01ZX1614G, and 01ZX1614A; German Federal Ministry of Education and Research (BMBF), BipoLife Network; Dr. Lisa Oehler Foundation BONFOR Programme of the University of Bonn; Ilídio Pinho professorship; iBiMED, Grant/Award Number: UID/BIM/04501/2013; German Research Foundation (DFG), Grant/Award Number: FOR2107 DA1151/5-1, SFB-TRR58, Project C09; Interdisciplinary Center for Clinical Research (IZKF) of the medical faculty of Münster, Grant/Award Number: Dan3/012/17

In current diagnostic systems, schizophrenia and bipolar disorder are still conceptualized as distinct categorical entities. Recently, both clinical and genomic evidence have challenged this Kraepelinian dichotomy. There are only few longitudinal studies addressing potential overlaps between these conditions. Here, we present design and first results of the PsyCourse study ($N = 891$ individuals at baseline), 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. To provide an initial characterization of the PsyCourse study sample, we compare two broad diagnostic groups defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) classification system, that is, predominantly affective ($n = 367$ individuals) versus predominantly psychotic disorders ($n = 524$ individuals). Depressive, manic, and psychotic symptoms as well as global functioning over time were contrasted using linear mixed models. Furthermore, we explored the effects of polygenic risk scores for schizophrenia on diagnostic group membership and addressed their effects on nonparticipation in follow-up visits. While phenotypic results confirmed expected differences in current psychotic symptoms and global functioning, both manic and depressive symptoms did not vary between both groups after correction for multiple testing. Polygenic risk scores for schizophrenia significantly explained part of the variability of diagnostic group. The PsyCourse study presents a unique resource to research the complex relationships of psychopathology and biology in severe mental disorders not confined to traditional diagnostic boundaries and is open for collaborations.

KEYWORDS
affective disorder, diagnosis, polygenic risk score, psychosis, 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 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). This dichotomous view has recently been questioned by biological research (O'Donovan & Owen, 2016).

In addition, there is extensive overlap of symptoms between schizophrenia (SZ) and bipolar disorder (BD) as observed in clinical day-to-day reality (Murray et al., 2004). 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; Cuthbert & Insel, 2010; Insel et al., 2010) and the Hierarchical Taxonomy of Psychopathology (HiTOP; Kotov et al., 2017), 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 (Robins & Guze, 1970). More recently, findings regarding an overlapping but distinct genetic basis of SZ and BD in both family (Lichtenstein et al., 2009) and molecular genetic studies (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Forstner et al., 2017; Purcell et al., 2009), have accelerated the momentum toward dimensionally defined diagnosis (Craddock & Owen, 2010) 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 Guloksuz & van Os, 2017). There is thus a pressing need to incorporate this biological information into future diagnostic systems.

Against this background, addressing two important issues might pave the way for a successful research into this matter: First, longitudinal research is necessary to capture variation over time. Pronounced heterogeneity in the longitudinal course of both SZ (e.g., Carpenter & Kirkpatrick, 1988; Heilbronner, Samara, Leucht, Falkai, & Schulze, 2016) and BD (e.g., Angst, 1978) 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., Bleuler, 1968), 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 of severe mental illnesses exist, the longitudinal course of affective disorders, such as BD, has received particularly little attention to date (Pfennig et al., 2017). Second, a major emphasis on phenomics is needed, "the systematic study of phenotypes on a genome-wide scale" (Bilder et al., 2009). 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 are required to establish meaningful genotype–phenotype relationships, and will ultimately lead to biologically informed patient stratification (Kapur, Phillips, & Insel, 2012).

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 multilevel 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 Supporting Information Table 1).

Here, we provide an initial characterization of the PsyCourse study sample. 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 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) framework, defined as psychotic and affective, by their predominant symptoms. In addition, as proof of principle of the PsyCourse sample's potential for genomic analyses, we use polygenic risk scores (PRS) 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 (Purcell et al., 2009); for overview see Wray et al. (2014; in this case for SZ). Findings from PRS analyses support the notion of both overlapping (Purcell et al., 2009) and specific (Ruderfer et al., 2014) genetic backgrounds of SZ and BD as well as the continuum model of psychosis (Tesli et al., 2014). To study genetic overlap between disorders by means of PRS, it is usually analyzed whether PRS for one disorder, for example, SZ, can successfully predict case–control status for other traits, for example BD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Purcell et al., 2009). Another approach, focusing on the specific genetic backgrounds of SZ and BD, was used by Ruderfer et al. (2014) who created a PRS for the discrimination between SZ and BD. Here, we used SZ-PRS because the available discovery genome-wide association study (GWAS) comparing SZ patients and controls is based on a substantially larger sample ($N = 36{,}989$ patients vs. $N = 113{,}075$ controls; Ripke et al., 2014) than the largest published GWAS comparing BD and controls ($N = 13{,}902$ patients vs. $N = 19{,}279$ controls; Charney et al., 2017). Unlike the studies described above, 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 (de Graaf, van Dorsselaer, Tuithof, & ten Have, 2013; Wolke et al., 2009). Notably, a recent study found higher SZ-PRS to be associated with nonparticipation over time in a population-based cohort study (Martin et al., 2016). Therefore, we also 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 multicenter study, conducted by a network of clinical sites in Germany and Austria. At the time of writing, 18

different clinical centers participated in data collection of clinical participants, two of which additionally collect data from nonclinical (control) individuals. The study protocol was approved by the respective ethics committee for each study center and was carried out following the rules of the Declaration of Helsinki of 1975, revised in 2008. Initially, the project was approved by the Ethics Committee of the University Medical Center Goettingen. Some clinical centers were teaching hospitals of the University Medical Center Goettingen, and were thus covered by this initial approval. For those clinical sites that were not covered, we obtained additional approval from the respective Ethics Committees. For all centers, these were (clinical centers in parentheses): Ethics Committees of the University Medical Center Goettingen (UMG Goettingen, Bad Zwischenahn, Eschwege, Asklepios Specialized Hospital Goettingen, Hildesheim, Lüneburg, Liebenburg, Osnabrück, Rotenburg, Tiefenbrunn, Wilhemshaven), Medical Faculty of the LMU Munich (Munich and Augsburg), Medical Faculty of the RU Bochum (Bochum), Medical Association Bremen (Bremen Ost), Medical University of Graz (Graz), Ulm University (Günzburg) and Medical Association Westfalen-Lippe and Medical Faculty University of Münster (Münster).

Study participants are assessed at four points in time, in intervals of 6 months, hereafter referred to as study visits 1 (T1; baseline), 2 (T2; +6 months), 3 (T3; +12 months), and 4 (T4; +18 months). Additional visits should be conducted for clinical participants if they are readmitted for inpatient treatment during the study period. Importantly, participating individuals are allowed to miss one or more follow-up study visits without being excluded from the study. At each study visit, venous blood samples are collected, permitting extraction of biomaterials such as DNA, RNA, plasma, and serum. In addition, a comprehensive set of phenotype data is collected, assessing symptom dimensions, cognitive function, and self-report measures (Supporting Information Table 1; Altman, Hedeker, Peterson, & Davis, 1997; American Psychiatric Association, 2002; Angermeyer, Kilian, & Matschinger, 2000; Army Individual Test Battery, 1944; Aster, Neubauer & Horn, 2006; McGuffin, Farmer, & Harvey, 1991; Grabe et al., 2012; Grof et al., 2002; Hautzinger, Keller, & Kühner, 2006; Helmstaedter, Lendt, & Lux, 2001; Kay, Fiszbein, & Opler, 1987; Konings, Bak, Hanssen, van Os, & Krabbendam, 2006; Krüger, Bräunig, & Shugar, 1997; Lehrl, 2005; Margraf, 1994; McGuffin, Farmer, & Harvey, 1991; National Institute of Mental Health, 1976; Norbeck, 1984; Rammstedt & John, 2007; Rush, Carmody, & Reimitz, 2000; Stefanis et al., 2002; Ware, Kosinski, & Keller, 1996; Wittchen & Fydrich, 1997; Young, Biggs, Ziegler, & Meyer, 1978).

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 reassessed within the DSM-IV framework using an adapted version of the Structured Clinical Interview for DSM-IV; Axis I Disorders (SCID-I; Wittchen & Fydrich, 1997). 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. Participants must be proficient in German language to enroll in the study.

2.1.2 | Nonclinical (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 must be proficient in German language to enroll in the study. Those included in the study follow a similar protocol as the clinical participants (see Supporting Information Table 1). History of affective or psychotic illness is assessed using a short diagnostic interview for mental disorders (Margraf, 1994).

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 (German National Ethics Council, 2004). 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. In addition, potential participants must decide whether they want to be informed about possible incidental findings that the study may uncover. Collaboration with nonpsychiatric 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. Disposal 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.

TABLE 1 Comparisons between patient groups with predominantly affective versus predominantly psychotic disorders on demographic variables at the first study visit (T1)

	Affective	Psychotic	Test statistic	DF	*P*
Female sex, *n* (%)	178 (48.5)	210 (40.1)	5.89 (χ^2)	1	.015
Age at first interview, mean (range)	45.4 (18–78)	40.8 (18–73)	5.27 (*t*)	741.43	<.001
Age at illness onset, mean (range)	33.6 (11–73)	27.9 (7–73)	6.94 (*t*)	592.21	<.001
Marital status single (never married), *n* (%)	158 (43.1)	336 (64.1)	37.35 (χ^2)	1	<.001
Family history of psychiatric illness, *n* (%)	268 (77.7)	334 (67.1)	10.73 (χ^2)	1	.001
In- or day patient at first study visit, *n* (%)	128 (34.9)	312 (59.5)	48.16 (χ^2)	1	<.001

DF = degrees of freedom.

2.1.5 | Data protection

As we collect sensitive phenotypic data and biomaterials, a data protection concept was developed (Demiroglu et al., 2012). 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 Supporting Information 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.

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 September 19th, 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).

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 1). Longitudinal data were analyzed using linear mixed-effect regression (R package lme4; Bates, Maechler, Bolker, & Walker, 2014). 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 ($IDS\text{-}C_{30}$), 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 (Kuznetsova, Brockhoff, & Christensen, 2016) was used to obtain *p*-values for fixed effects using Satterthwaite's approximation of degrees of freedom. *p*-Values of the four linear mixed-effect models were false discovery rate (FDR) corrected to account for Type-I error cumulation resulting from multiple comparisons. A coefficient of determination (R^2) was calculated for each model with the R r2glmm package (https://github.com/bcjaeger/r2glmm) using the Nakagawa and Schielzeth (2013) method.

2.2.2 | Genotyping and imputation of genetic data

DNA samples of 825 clinical participants were genotyped using the Illumina Infinium PsychArray (Illumina), 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; Andlauer et al., 2016; Delaneau, Zagury, & Marchini, 2012; Howie, Donnelly, & Marchini, 2009). 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 | Genomic analysis of population structure

The EIGENSOFT package (smartPCA; Patterson, Price, & Reich, 2006) 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 | Polygenic risk scores

SZ-PRS were calculated with PLINK 1.90 (https://www.cog-genomics.org/plink/1.9) 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 (ORs; Ripke et al., 2014). For this purpose a clumped training dataset of 102,636 independent SNPs available in the aforementioned website (Psychiatric Genomics Consortium) was used for SZ-PRS calculations. Our imputed genotyped set had a substantial overlap with the training set (93,700 SNPs; 91.3% overlap). 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 OR 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 11 different *p*-value thresholds ($p \leq 5$*10-8; $p \leq .0001$; $p \leq .001$; $p \leq .01$; $p \leq .05$; $p \leq .1$; $p \leq .2$; $p \leq .3$; $p \leq .4$; $p \leq .5$; $p \leq 1$). SZ-PRS do not significantly deviate from normality and were standardized using z-score transformation. Since two phenotypes (diagnostic group, see Section 2.2.5, and follow-up study participation, see Section 2.2.6) were tested for association with SZ-PRS, all *p*-values from these logistic regression models were FDR corrected to account for Type-I error cumulation resulting from multiple comparisons.

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 Section 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 11 different *p*-value thresholds. Potential confounding variables, namely sex, age at baseline, age^2, sex × 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.

2.2.6 | Analyses of follow-up study participation

As described in Section 2.1, study participants are allowed to miss one or more follow-up study visits without being excluded from the study. To address the question of selective dropouts in the PsyCourse study, subjects with baseline data only, hereafter referred to as the dropout group, were compared to subjects with follow-up data for at least one timepoint within the 18-month study period, hereafter referred to as the follow-up group. To assure a valid assignment to these groups in the ongoing project, the study period of 18 months plus an additional time of 5 months for data entry were considered. Since the export from the database was carried out on September 19th, 2016, only subjects with a T1 before October 19th, 2014 were selected for these analyses ($N = 678$).

Logistic regression (forced entry method) was used to test the effects of the following phenotypic predictors on group-membership (dropout group vs. follow-up group): sex, age at baseline, age2, age × sex interaction, center, diagnosis, educational status, psychiatric treatment at baseline, duration of illness, PANSS positive score, PANSS negative score, PANSS general score, IDS-C_{30} sum score, YMRS sum score and global assessment of functioning (GAF). In a second step, blockwise logistic regression analyses were performed to estimate the effects of SZ-PRS for 11 different *p*-value thresholds, as explained above. Ancestry principal components were calculated specifically for the subsample entering these analyses (for methods see Section 2.2.3) in order to be able to correct for potential effects of population substructure. The significant phenotypic predictors from the previous analyses, namely sex, sex × age interaction and psychiatric treatment at baseline, as well as the first five ancestry principal components were entered as covariates in the first block. In the second block, the respective z-standardized SZ-PRS was added as a predictor. Estimates of change in Nagelkerke's R^2 relative to the SZ-PRS are reported.

3 | RESULTS

Here, we report data of a total of $N = 891$ clinical individuals that were included in the study at baseline (first study visit; T1). Of these $N = 891$ individuals, 526 (59.0%), 415 (46.6%), and 351 (39.4%) completed the second, third, and fourth study visit, respectively. Importantly, individuals can miss one or more follow-up study visits without being excluded from the study. In such cases, individuals were re-contacted again before the next scheduled appointment and invited to continue to participate in the study. Also the numbers above represent a snapshot of the phenotype database taken on the September 19th, 2016. This means that study participants might still be enrolled in the study at that time and complete further study visits.

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. Information on recruitment numbers from single study centers is displayed in Supporting Information Table 2.

3.1 | Phenotypic analyses

Cross-sectional comparisons on demographic variables between the two groups are summarized in Table 1. 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

TABLE 2 Sex-specific descriptive statistics of both clinical groups at the first study visit (T1)

	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, *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, *n* (%)	118 (56.2)	194 (61.8)

single (never married) individuals and were more frequently treated as in- or daypatients compared to the predominantly affective group. In addition, fewer participants in the predominantly psychotic group reported a family history of psychiatric illness. Descriptive cross-sectional differences between sexes are summarized in Table 2. Exemplary, the longitudinal course of acute depressive (IDS-C_{30}) symptoms over the study period is shown in Figure 1. Analogously, courses of manic (YMRS) and psychotic (PANSS Positive Scale) symptoms as well as psychosocial functioning (GAF) are displayed in Supporting Information Figures 2–4.

Linear mixed model analyses of depressive symptoms (Table 3) reveal effects of in- or daypatient status at study inclusion (mean IDS-C_{30} scores at T1-T4 for in- or daypatients: 14.5, 12.2, 13.5, 12.1 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.

Manic symptoms (Table 4; for post hoc tests see Supporting Information Table 3) were not different between the patient groups after correcting for multiple comparisons (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]). However, symptoms of mania (Supporting Information Figure 2) differed over time (mean YMRS scores at T1–T4: 3.0, 2.1, 2.5, 2.1), behaved differently in diagnostic groups over time and were independent of in- or daypatient status at baseline. Psychotic symptoms (Table 5; for post hoc tests see Supporting Information Table 4) differed both over time (mean PANSS Positive Scale scores at T1–T4: 12.3, 10.3, 10.4, 10.1) and between diagnostic groups (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]).

Regarding symptoms, the most prominent difference between both diagnostic groups is the magnitude of psychotic symptoms (Supporting Information Figure 3). In both groups, there is a decrease of impairment after the baseline assessment and toward the end of the study period.

Analyses of GAF values over time (Table 6; for post hoc tests see Supporting Information Table 5) revealed effects of in- or daypatient status, diagnostic group, time and the sex × diagnostic group interaction. Mean GAF values at T1–T4 (Supporting Information Figure 4)

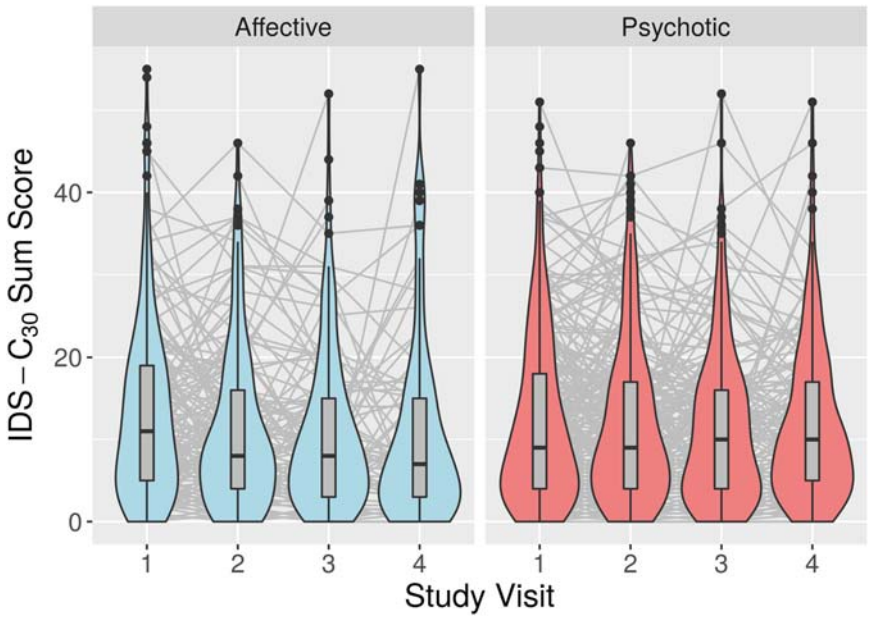

FIGURE 1 Violin plots of the course of depressive symptoms, separately for both patient groups. Individual trajectories are plotted in gray color. The numbers of participants included in this graph (T1–T4, respectively) are: 312, 184, 149, 109 (Affective) and 453, 288, 213, 196 (Psychotic)

TABLE 3 Longitudinal analysis of depressive symptoms (IDS-C_{30})

	SS	MS	NumDF	DenDF	F	*p*	p_{FDR}
Main effects							
Age at first visit	0.09	0.09	1	823.91	0.21	.648	.729
In- or day patient at first visit	16.81	16.81	1	792.37	38.41	<.001	<.001
Sex	2.71	2.71	1	888.67	6.19	.013	.047
Dx group	1.52	1.52	1	812.12	3.47	.063	.162
Time (visit)	1.72	0.57	3	1295.28	1.31	.269	.372
Interaction effects							
Sex × Dx group	1.11	1.11	1	883.85	2.53	.112	.224
Sex × time (visit)	0.76	0.25	3	1308.10	0.58	.630	.729
Dx group × time (visit)	3.08	1.03	3	1304.03	2.34	.072	.172
Sex × Dx group × time (visit)	2.04	0.68	3	1307.70	1.55	.199	.325

R^2 for the model was 5.7%, 95% confidence interval [4.6, 8.7]. DenDF = denominator degrees of freedom; Dx = diagnostic; MS = mean square; NumDF = numerator degrees of freedom; p_{FDR} = false discovery rate-corrected *p*-value; SS = sum of squares.

TABLE 4 Longitudinal analysis of manic symptoms (YMRS)

	SS	MS	NumDF	DenDF	F	*p*	p_{FDR}
Main effects							
Age at first visit	0.79	0.79	1	774.58	1.50	.222	.347
In- or day patient at T1	1.11	1.11	1	771.85	2.10	.148	.253
Sex	2.39	2.39	1	822.08	4.50	.034	.095
Dx group	2.59	2.59	1	748.24	4.88	.028	.083
Time (visit)	11.50	3.83	3	1454.76	7.22	<.001	<.001
Interaction effects							
Sex × Dx group	0.02	0.02	1	814.37	0.03	.856	.856
Sex × time (visit)	1.63	0.54	3	1471.93	1.03	.380	.489
Dx group × time (visit)	8.98	2.99	3	1466.84	5.64	.001	.003
Sex × Dx group × time (visit)	2.84	0.95	3	1471.75	1.79	.148	.253

R^2 for the model was 2.5%, 95% confidence interval [0.2, 4.8]. For abbreviations see Table 4.

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).

3.2 | Genetic analyses of population structure

Supporting Information Figure 5 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 the PsyCourse study.

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 2 shows changes in Nagelkerke's R^2 due to effects of the SZ-PRS at 11 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 .05 (OR = 1.28; 95% CI: 1.10–1.50).

TABLE 5 Longitudinal analysis of psychotic symptoms (PANSS positive score)

	SS	MS	NumDF	DenDF	F	*p*	p_{FDR}
Main effects							
Age at first visit	0.07	0.07	1	848.74	1.24	.267	0.372
In- or day patient at T1	0.57	0.57	1	791.26	10.70	.001	0.004
Sex	0.16	0.16	1	923.94	3.04	.082	0.183
Dx group	3.46	3.46	1	847.05	65.50	<.001	<0.001
Time (visit)	6.70	2.23	3	1424.64	42.26	<.001	<0.001
Interaction effects							
Sex × Dx group	0.07	0.07	1	919.44	1.28	.258	0.372
Sex × time (visit)	0.16	0.05	3	1437.95	0.99	.398	0.493
Dx group × time (visit)	0.20	0.07	3	1434.62	1.28	.281	0.375
Sex × Dx group × time (visit)	0.07	0.02	3	1437.35	0.44	.723	0.766

R^2 for the model was 14.6%, 95% confidence interval [12.5, 17.8]. For abbreviations see Table 4.

TABLE 6 Longitudinal analysis of GAF values

	SS	MS	NumDF	DenDF	F	*p*	p_{FDR}
Main effects							
Age at first visit	249.8	249.8	1	861.39	2.86	.091	.193
In- or day patient at T1	6357.0	6357.0	1	215.18	72.83	<.001	<.001
Sex	207.2	207.2	1	947.67	2.37	.124	.234
Dx group	2820.6	2820.6	1	387.57	32.31	<.001	<.001
Time (visit)	8941.0	2980.3	3	1435.55	34.14	<.001	<.001
Interaction effects							
Sex × Dx group	466.7	466.7	1	939.32	5.35	.021	.069
Sex × time (visit)	74.6	24.9	3	1446.20	0.29	.837	.856
Dx group × time (visit)	203.1	67.7	3	1444.13	0.78	.508	.609
Sex × Dx group × time (visit)	130.7	43.6	3	1445.69	0.50	.683	.745

R^2 for the model was 16%, 95% confidence interval [13.9, 19.3]. For abbreviations see Table 4.

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. Detailed results can be found in Supporting Information Table 6. In the baseline model, that is, 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 Section 2.2.6) were entered in the regression model. Nagelkerke's R^2 for the model was 0.282. Female sex ($p = .01$; OR = 0.12; 95% CI: 0.02–0.65) and inpatient treatment at baseline ($p < .01$; OR = 0.32; 95% CI: 0.17–0.60) were significantly associated with decreasing odds of having follow-up data. The age x sex interaction also had a significant effect in the model ($p = .049$; OR = 1.04; 95% CI: 1.00–1.08). While in both female and male participants older age was associated with increasing odds of having follow-up data, this age effect was slightly stronger in females.

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 3 shows changes in Nagelkerke's R^2 due to effects of the SZ-PRS at 11 different *p*-value thresholds. As the SZ-PRSs increase, the odds of being in the follow-up group decrease. This trend was significant after FDR correction 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 .001: OR = 0.78; 95% CI: 0.64–0.95).

4 | DISCUSSION

Here, we present and provide an initial characterization of the PsyCourse study, a transdiagnostic study of the affective-to-

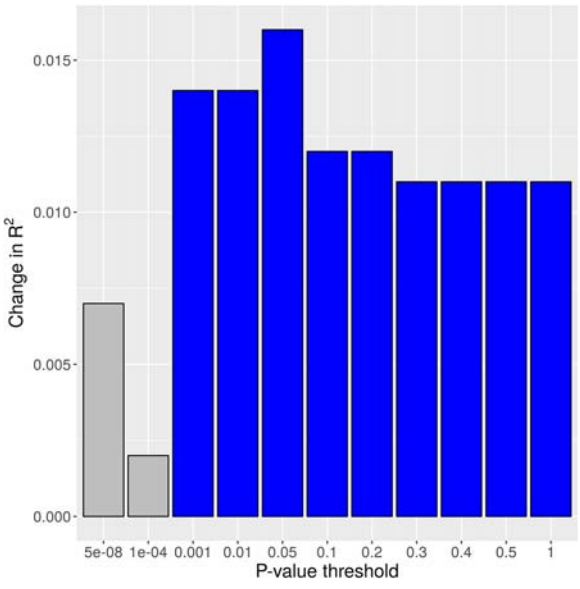

FIGURE 2 Effects of SZ-PRS on diagnostic group. *p*-Values significant after FDR correction in blue color (baseline model with covariates only: Nagelkerke's $R^2 = .091$; FDR corrected *p*-values for the models with *p*-value thresholds from 5e-08 to 1: .059, .29, .022, .022, .022, .022, .022, .024, .022, .022, .022)

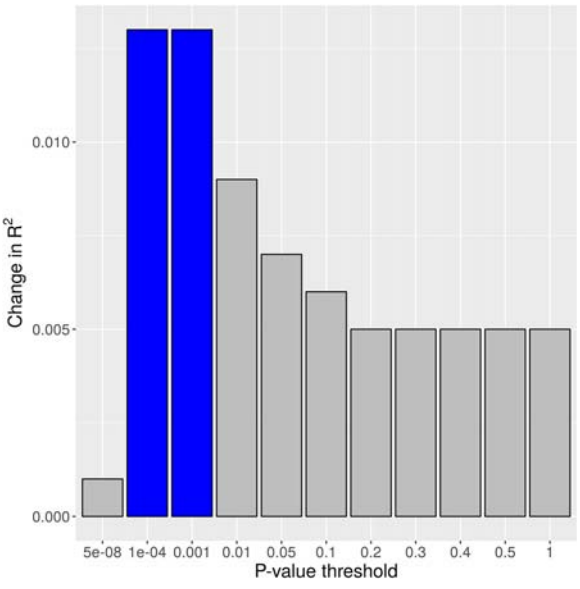

FIGURE 3 Effects of SZ-PRS on dropout. *p*-Values significant after FDR correction in blue color (baseline model with covariates only: Nagelkerke's $R^2 = 0.131$; FDR corrected *p*-values for the models with a *p*-value threshold from 5e-08 to 1: .705, .03, .03, .088, .115, .15, .175, .175, .175, .175, .175)

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 future 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 Wendland & Ehlers, 2016 for a review).

4.1 | Phenotype analyses 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 (Murray et al., 2004). 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 (Parker, Fletcher, Paterson, Anderson, & Hong, 2014) or SZ (Abel, Drake, & Goldstein, 2010). 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 did not vary between diagnostic groups but showed a different fluctuating pattern over time between predominantly psychotic and predominantly affective groups. Similar to symptoms of depression, symptoms of mania were observed in both diagnostic groups and illustrate symptom overlap between diagnostic groups. The different behavior over time of symptoms of mania in the diagnostic groups is thought to reflect the episodic characteristics of BD (Judd et al., 2002). The sex effect observed across diagnostic groups in depression scores (higher IDS-C_{30} scores in females) has neither been reported for SZ (Zisook et al., 1999) nor BD (Diflorio & Jones, 2010) and highlights new findings that may emerge when assessing symptom dimensions across diagnostic boundaries.

In summary, both mild depressive symptoms and symptoms of mania were comparable between diagnostic groups, whereas large differences in psychotic symptoms were the primary characteristic separating both diagnostic groups. Furthermore, we highlight a sex-specific pattern of more severe symptoms of depression in women 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 and does, of course, not imply causality. In addition, 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 symptoms, we also interpret 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 (Gade et al., 2015; Heilbronner et al., 2016), 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 (Purcell et al., 2009) but also a specific (Ruderfer et al., 2014) polygenic background of SZ and BD. Nine of 11 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% toward 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 (Ripke et al., 2014) and about 2% in BD (Charney et al., 2017; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Purcell et al., 2009). The observation that the amount of explained variability in our analysis is not as high as the effects usually observed when comparing cases and controls is probably due to the common genetic background of the two groups (Purcell et al., 2009).

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 associated with dropout. More precisely, being male as well as being treated as an outpatient at baseline increased the odds of having follow-up data. An effect of age was only significant in interaction with sex. While in both female and male participants older age was associated with increasing odds of having follow-up data, this age effect was slightly more pronounced in females. 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. However, the largest effects were observed for in- versus outpatient treatment at baseline. 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 much lower compared to the findings from Martin et al. (2016) in

the population-based Avon Longitudinal Study of Parents and Children (ALSPAC). However, a trend in the expected direction with 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, the results in the present study appear promising and, as recruitment is ongoing, analyses may be repeated using a larger sample in the future. To our knowledge, there is no comparable investigation in a clinical sample yet.

4.4 | Limitations of the present study

Here, we present the PsyCourse study and provide an overall characterization of the clinical study sample to illustrate its usefulness in future biological-psychiatric studies. Therefore, our results are exploratory and should to be treated as such. Furthermore, we did not include medication data in the present analysis. This information will be subject of future studies of the PsyCourse sample. Furthermore, the limited follow-up period of 18 months should be considered. While a longer period of time would be desirable to study the long-term course of severe mental illnesses, prospective samples of chronic patients suitable for biological studies on disease course are scarce. While we think that studies on the short-term course will uncover important mechanisms of severe mental disorders, the PsyCourse study can provide a resource for future longitudinal studies.

4.5 | Resource for collaborations

The PsyCourse study constitutes a unique resource on different levels. First, the project already created a wealth of phenotypic and biological data, such as genomic, small RNAome, and methylation data. With recruitment still ongoing, the sample size will increase over time. The project constitutes a major contributor to a budding initiative spearheaded by the German Association for Psychiatry and Psychotherapy (DGPPN) with the aim of establishing a prospective national cohort of patients with major psychiatric disorders, the so called "DGPPN cohort" (Anderson-Schmidt et al., 2013). 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. The Appendix contains a brief outline of our Data Sharing Policy. Second, 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 (Schwanke, Rienhoff, Schulze, & Nussbeck, 2013).

ACKNOWLEDGMENTS

Thomas G. Schulze and Peter Falkai are supported by the German Research Foundation (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 Program 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.

CONFLICT 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.

AUTHOR CONTRIBUTION

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.

ORCID

Urs Heilbronner http://orcid.org/0000-0001-7135-762X

REFERENCES

Abel, K. M., Drake, R., & Goldstein, J. M. (2010). Sex differences in schizophrenia. *International Review of Psychiatry*, *22*(5), 417–428. https://doi.org/10.3109/09540261.2010.515205

Altman, E. G., Hedeker, D., Peterson, J. L., & Davis, J. M. (1997). The Altman self-rating mania scale. *Biological Psychiatry*, *42*(10), 948–955. https://doi.org/10.1016/S0006-3223(96)00548-3

American Psychiatric Association. (2002). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

Anderson-Schmidt, H., Adler, L., Aly, C., Anghelescu, I.-G., Bauer, M., Baumgärtner, J., … Schulze, T. G. (2013). The "DGPPN-Cohort": A national collaboration initiative by the German Association for Psychiatry and Psychotherapy (DGPPN) for establishing a large-scale cohort of psychiatric patients. *European Archives of Psychiatry and Clinical Neuroscience*, *263*(8), 695–701. https://doi.org/10.1007/s00406-013-0401-8

Andlauer, T. F. M., Buck, D., Antony, G., Bayas, A., Bechmann, L., Berthele, A., … Müller-Myhsok, B. (2016). Novel multiple sclerosis susceptibility loci implicated in epigenetic regulation. *Science Advances*, *2*(6), e1501678–e1501678. https://doi.org/10.1126/sciadv.1501678

Angermeyer, M. C., Kilian, R., & Matschinger, H. (2000). *WHOQOL100 und WHOQOL-BREF. Handbuch für die deutschsprachigen Versionen der WHO Instrumente zur Erfassung von Lebensqualität*. Göttingen, Germany: Hogrefe.

Angst, J. (1978). The course of affective disorders. II. Typology of bipolar manic-depressive illness. *Archiv für Psychiatrie Und Nervenkrankheiten Vereinigt Mit Zeitschrift für Die Gesamte Neurologie Und Psychiatrie*, *226*(1), 65–73.

Army Individual Test Battery. (1944). *Manual of Directions and Scoring*. Washington, DC: War Department, Adjutant General's Office.

Aster, M., Neubauer, A., & Horn, R. (2006). *Wechsler Intelligenztest für Erwachsene. Wechsler Intelligence Test for Adults (German revision and adaptation of the WAIS-III of David Wechsler)*. Frankfurt, Germany: Harcourt Test Services.

Bates, D., Maechler, M., Bolker, B., & Walker, S. (2014). Package "lme4". Retrieved from http://kambing.ui.ac.id/cran/web/packages/lme4/lme4.pdf

Bilder, R. M., Sabb, F. W., Cannon, T. D., London, E. D., Jentsch, J. D., Parker, D. S., … Freimer, N. B. (2009). Phenomics: The systematic study of phenotypes on a genome-wide scale. *Neuroscience*, *164*(1), 30–42. https://doi.org/10.1016/j.neuroscience.2009.01.027

Bleuler, M. (1968). A 23-year longitudinal study of 208 schizophrenics and impressions in regard to the nature of schizophrenia. *Journal of Psychiatric Research*, *6*, 3–12.

Carpenter, W. T., & Kirkpatrick, B. (1988). The heterogeneity of the long-term course of schizophrenia. *Schizophrenia Bulletin*, *14*(4), 645–652.

Charney, A. W., Ruderfer, D. M., Stahl, E. A., Moran, J. L., Chambert, K., Belliveau, R. A., … Sklar, P. (2017). Evidence for genetic heterogeneity between clinical subtypes of bipolar disorder. *Translational Psychiatry*, *7*(1), e993. https://doi.org/10.1038/tp.2016.242

Craddock, N., Owen, M. J. (2010). The Kraepelinian dichotomy – Going, going… but still not gone. *British Journal of Psychiatry*, *196*(02), 92–95. https://doi.org/10.1192/bjp.bp.109.073429

Cross-Disorder Group of the Psychiatric Genomics Consortium. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *The Lancet*, *381*(9875), 1371–1379. https://doi.org/10.1016/S0140-6736(12)62129-1

Cuthbert, B. N., & Insel, T. R. (2010). Toward new approaches to psychotic disorders: The NIMH research domain criteria project. *Schizophrenia Bulletin*, *36*(6), 1061–1062. https://doi.org/10.1093/schbul/sbq108

de Graaf, R., van Dorsselaer, S., Tuithof, M., & ten Have, M. (2013). Sociodemographic and psychiatric predictors of attrition in a prospective psychiatric epidemiological study among the general population. Result of the Netherlands Mental Health Survey and Incidence Study-2. *Comprehensive Psychiatry*, *54*(8), 1131–1139. https://doi.org/10.1016/j.comppsych.2013.05.012

Delaneau, O., Zagury, J.-F., & Marchini, J. (2012). Improved whole-chromosome phasing for disease and population genetic studies. *Nature Methods*, *10*(1), 5–6. https://doi.org/10.1038/nmeth.2307

Demiroglu, S. Y., Skrowny, D., Quade, M., Schwanke, J., Budde, M., Gullatz, V., … Schulze, T. G. (2012). Managing sensitive phenotypic data and biomaterial in large-scale collaborative psychiatric genetic research projects: Practical considerations. *Molecular Psychiatry*, *17*(12), 1180–1185. https://doi.org/10.1038/mp.2012.11

Diflorio, A., & Jones, I. (2010). Is sex important? Gender differences in bipolar disorder. *International Review of Psychiatry*, *22*(5), 437–452. https://doi.org/10.3109/09540261.2010.514601

Forstner, A. J., Hecker, J., Hofmann, A., Maaser, A., Reinbold, C. S., Mühleisen, T. W., … Nöthen, M. M. (2017). Identification of shared risk loci and pathways for bipolar disorder and schizophrenia. *PLoS One*, *12*(2), e0171595. https://doi.org/10.1371/journal.pone.0171595

Gade, K., Malzahn, D., Anderson-Schmidt, H., Strohmaier, J., Meier, S., Frank, J., … Schulze, T. G. (2015). Functional outcome in major psychiatric disorders and associated clinical and psychosocial variables: A potential cross-diagnostic phenotype for further genetic investigations? *The World Journal of Biological Psychiatry*, *16*(4), 237–248. https://doi.org/10.3109/15622975.2014.995221

German National Ethics Council (2004). Human biobanks for research. Retrieved from http://www.ethikrat.org/files/der_opinion_human-biobanks.pdf

Grabe, H., Schulz, A., Schmidt, C., Appel, K., Driessen, M., Wingenfeld, K., … Freyberger, H. (2012). Ein Screeninginstrument für Missbrauch und Vernachlässigung in der Kindheit: Der Childhood Trauma Screener (CTS). *Psychiatrische Praxis*, *39*(03), 109–115. https://doi.org/10.1055/s-0031-1298984

Grof, P., Duffy, A., Cavazzoni, P., Grof, E., Garnham, J., MacDougall, M., … Alda, M. (2002). Is response to prophylactic lithium a familial trait? *The Journal of Clinical Psychiatry*, *63*(10), 942–947.

Guloksuz, S., & van Os, J. (2017). The slow death of the concept of schizophrenia and the painful birth of the psychosis spectrum. *Psychological Medicine*, 1–16. https://doi.org/10.1017/S0033291717001775

Hautzinger, M., Keller, F., & Kühner, C. (2006). *Beck depressionsinventar revision (BDI II)*. Frankfurt, Germany: Harcourt Test services Frankfurt.

Heilbronner, U., Samara, M., Leucht, S., Falkai, P., & Schulze, T. G. (2016). The longitudinal course of schizophrenia across the lifespan: Clinical, cognitive, and neurobiological aspects. *Harvard Review of Psychiatry*, *24*(2), 118–128. https://doi.org/10.1097/HRP.0000000000000092

Helmstaedter, C., Lendt, M., & Lux, S. (2001). *Verbaler Lern- und Merkfähigkeitstest (VLMT)*. Göttingen, Germany: Beltz.

Howie, B. N., Donnelly, P., & Marchini, J. (2009). A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genetics*, *5*(6), e1000529. https://doi.org/10.1371/journal.pgen.1000529

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., … Wang, P. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, *167*(7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379

Judd, L. L., Akiskal, H. S., Schettler, P. J., Endicott, J., Maser, J., Solomon, D. A., … Keller, M. B. (2002). The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Archives of General Psychiatry*, *59*(6), 530–537.

Kapur, S., Phillips, A. G., & Insel, T. R. (2012). Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Molecular Psychiatry*, *17*(12), 1174–1179. https://doi.org/10.1038/mp.2012.105

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276.

Konings, M., Bak, M., Hanssen, M., van Os, J., & Krabbendam, L. (2006). Validity and reliability of the CAPE: A self-report instrument for the measurement of psychotic experiences in the general population. *Acta Psychiatrica Scandinavica*, *114*(1), 55–61. https://doi.org/10.1111/j.1600-0447.2005.00741.x

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., … Zimmerman, M. (2017). The hierarchical taxonomy of psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of Abnormal Psychology*, *126*(4), 454–477. https://doi.org/10.1037/abn0000258

Krüger, S., Bräunig, P., & Shugar, G. (1997). *Manie-Selbstbeurteilungsskala. Deutsche Bearbeitung des Self-Report Manic Inventory (SRMI). Manual*. Göttingen, Germany: Beltz Test GmbH.

Kuznetsova, A., Brockhoff, P. B., & Christensen, R. H. B. (2016). Package 'lmerTest'. Retrieved from http://cran.uib.no/web/packages/lmerTest/lmerTest.pdf

Lehrl, S. (2005). *Mehrfachwahl-Wortschatz-Intelligenztest*. Balingen, Germany: Spitta Verlag.

Lichtenstein, P., Yip, B. H., Bj?Rk, C., Pawitan, Y., Cannon, T. D., Sullivan, P. F., & Hultman, C. M. (2009). Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. *The Lancet*, *373*(9659), 234–239. https://doi.org/10.1016/S0140-6736(09)60072-6

Margraf, J. (1994). *Mini-DIPS*. Berlin, Heidelberg: Springer. https://doi.org/10.1007/978-3-662-08774-9

Martin, J., Tilling, K., Hubbard, L., Stergiakouli, E., Thapar, A., Davey Smith, G., … Zammit, S. (2016). Association of genetic risk for schizophrenia with nonparticipation over time in a population-based cohort study. *American Journal of Epidemiology*, *183*(12), 1149–1158. https://doi.org/10.1093/aje/kww009

McGuffin, P., Farmer, A., & Harvey, I. (1991). A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. *Archives of General Psychiatry*, *48*(8), 764–770.

Murray, R. M., Sham, P., Van Os, J., Zanelli, J., Cannon, M., & McDonald, C. (2004). A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophrenia Research*, *71*(2–3), 405–416. https://doi.org/10.1016/j.schres.2004.03.002

Nakagawa, S., & Schielzeth, H. (2013) A general and simple method for obtaining R2 from generalized linear mixed-effects models. *Methods in Ecology and Evolution*, *4*, 133–142. doi: https://doi.org/10.1111/j.2041-210x.2012.00261.x

National Institute of Mental Health. (1976). Clinical global impressions (CGI). In W. Guy (Ed.), *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service pp. 217–220.

Norbeck, J. S. (1984). Modification of life event questionnaires for use with female respondents. *Research in Nursing & Health*, *7*(1), 61–71. https://doi.org/10.1002/nur.4770070110

O'Donovan, M. C., & Owen, M. J. (2016). The implications of the shared genetics of psychiatric disorders. *Nature Medicine*, *22*(11), 1214–1219. https://doi.org/10.1038/nm.4196

Parker, G., Fletcher, K., Paterson, A., Anderson, J., & Hong, M. (2014). Gender differences in depression severity and symptoms across depressive sub-types. *Journal of Affective Disorders*, *167*, 351–357. https://doi.org/10.1016/j.jad.2014.06.018

Patterson, N., Price, A. L., & Reich, D. (2006). Population structure and eigenanalysis. *PLoS Genetics*, *2*(12), e190. https://doi.org/10.1371/journal.pgen.0020190

Pfennig, A., Leopold, K., Ritter, P., Böhme, A., Severus, E., & Bauer, M. (2017). Longitudinal changes in the antecedent and early manifest course of bipolar disorder—A narrative review of prospective studies. *Australian & New Zealand Journal of Psychiatry*, *51*(5), 509–523. https://doi.org/10.1177/0004867417700730

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., … Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, *460*(7256), 748–752. https://doi.org/10.1038/nature08185

Rammstedt, B., & John, O. P. (2007). Measuring personality in one minute or less: A 10-item short version of the big five inventory in English and German. *Journal of Research in Personality*, *41*(1), 203–212. https://doi.org/10.1016/j.jrp.2006.02.001

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K.-H., Holmans, P. A., … O'Donovan, M. C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*(7510), 421–427. https://doi.org/10.1038/nature13595

Robins, E., & Guze, S. B. (1970). Establishment of diagnostic validity in psychiatric illness: Its application to schizophrenia. *American Journal of Psychiatry*, *126*(7), 983–987. https://doi.org/10.1176/ajp.126.7.983

Ruderfer, D. M., Fanous, A. H., Ripke, S., McQuillin, A., Amdur, R. L., Gejman, P. V., … Kendler, K. S. (2014). Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Molecular Psychiatry*, *19*(9), 1017–1024. https://doi.org/10.1038/mp.2013.138

Rush, A. J., Carmody, T., & Reimitz, P.-E. (2000). The inventory of depressive symptomatology (IDS): Clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. *International Journal of Methods in Psychiatric Research*, *9*(2), 45–59. https://doi.org/10.1002/mpr.79

Schwanke, J., Rienhoff, O., Schulze, T. G., & Nussbeck, S. Y. (2013). Suitability of customer relationship management systems for the management of study participants in biomedical research. *Methods of Information in Medicine*, *52*(4), 340–350. https://doi.org/10.3414/ME12-02-0012

Stefanis, N. C., Hanssen, M., Smirnis, N. K., Avramopoulos, D. A., Evdokimidis, I. K., Stefanis, C. N., … Van Os, J. (2002). Evidence that three dimensions of psychosis have a distribution in the general population. *Psychological Medicine*, *32*(02), 347–358.

Tesli, M., Espeseth, T., Bettella, F., Mattingsdal, M., Aas, M., Melle, I., … Andreassen, O. A. (2014). Polygenic risk score and the psychosis continuum model. *Acta Psychiatrica Scandinavica*, *130*(4), 311–317. https://doi.org/10.1111/acps.12307

Ware, J., Kosinski, M., & Keller, S. D. (1996). A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. *Medical Care*, *34*(3), 220–233.

Wendland, J. R., & Ehlers, M. D. (2016). Translating neurogenomics into new medicines. *Biological Psychiatry*, *79*(8), 650–656. https://doi.org/10.1016/j.biopsych.2015.04.027

Wittchen, H.-U., & Fydrich, T. (1997). *Strukturiertes Klinisches Interview für DSM-IV (SKID-I und SKID-II)*. Göttingen, Germany: Hogrefe.

Wolke, D., Waylen, A., Samara, M., Steer, C., Goodman, R., Ford, T., & Lamberts, K. (2009). Selective drop-out in longitudinal studies and

non-biased prediction of behaviour disorders. *British Journal of Psychiatry*, *195*(03), 249–256. https://doi.org/10.1192/bjp.bp.108.053751

Wray, N. R., Lee, S. H., Mehta, D., Vinkhuyzen, A. A. E., Dudbridge, F., & Middeldorp, C. M. (2014). Research review: Polygenic methods and their application to psychiatric traits. *Journal of Child Psychology and Psychiatry*, *55*(10), 1068–1087. https://doi.org/10.1111/jcpp.12295

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity and sensitivity. *The British Journal of Psychiatry: The Journal of Mental Science*, *133*(5), 429–435.

Zisook, S., McAdams, L. A., Kuck, J., Harris, M. J., Bailey, A., Patterson, T. L., … Jeste, D. V. (1999). Depressive symptoms in schizophrenia. *The American Journal of Psychiatry*, *156*(11), 1736–1743. https://doi.org/10.1176/ajp.156.11.1736

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Budde M, Anderson-Schmidt H, Gade K, et al. A longitudinal approach to biological psychiatric research: The PsyCourse study. *Am J Med Genet Part B*. 2019;180B:89–102. https://doi.org/10.1002/ajmg.b.32639

APPENDIX : DATA SHARING POLICY

Participants of the PsyCourse study have consented to us sharing their pseudonymized data with other researchers and research consortia. Thus, PsyCourse data will 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. However, in any case, a mutually agreed written memorandum of understanding must be signed before data can be obtained from us.

Author/s:
Budde, M;Anderson-Schmidt, H;Gade, K;Reich-Erkelenz, D;Adorjan, K;Kalman, JL;Senner, F;Papiol, S;Andlauer, TFM;Comes, AL;Schulte, EC;Kloehn-Saghatolislam, F;Gryaznova, A;Hake, M;Bartholdi, K;Flatau, L;Reitt, M;Quast, S;Stegmaier, S;Meyers, M;Emons, B;Haussleiter, IS;Juckel, G;Nieratschker, V;Dannlowski, U;Schaupp, SK;Schmauss, M;Zimmermann, J;Reimer, J;Schulz, S;Wiltfang, J;Reininghaus, E;Anghelescu, I-G;Arolt, V;Baune, BT;Konrad, C;Thiel, A;Fallgatter, AJ;Figge, C;von Hagen, M;Koller, M;Lang, FU;Wigand, ME;Becker, T;Jaeger, M;Dietrich, DE;Stierl, S;Scherk, H;Spitzer, C;Folkerts, H;Witt, SH;Degenhardt, F;Forstner, AJ;Rietschel, M;Noethen, MM;Falkai, P;Schulze, TG;Heilbronner, U

Title:
A longitudinal approach to biological psychiatric research: The PsyCourse study

Date:
2019-03-01

Citation:
Budde, M., Anderson-Schmidt, H., Gade, K., Reich-Erkelenz, D., Adorjan, K., Kalman, J. L., Senner, F., Papiol, S., Andlauer, T. F. M., Comes, A. L., Schulte, E. C., Kloehn-Saghatolislam, F., Gryaznova, A., Hake, M., Bartholdi, K., Flatau, L., Reitt, M., Quast, S., Stegmaier, S. ,... Heilbronner, U. (2019). A longitudinal approach to biological psychiatric research: The PsyCourse study. AMERICAN JOURNAL OF MEDICAL GENETICS PART B-NEUROPSYCHIATRIC GENETICS, 180 (2), pp.89-102. https://doi.org/10.1002/ajmg.b.32639.

Persistent Link:
http://hdl.handle.net/11343/248153