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Table of Contents

List of abbreviations **1**
List of gene names **2**
Summary **3**
Summary (English) 3
Zusammenfassung (German) 5
Introduction **7**
The polygenic architecture of schizophrenia and bipolar disorder 7
Psychiatric diagnoses: categorical vs. dimensional approaches 12
The course of psychiatric disorders 13
References **17**
Publications **22**
Publication #1: A longitudinal approach to biological psychiatric research: The PsyCourse study 22
Main publication 23
Supplementary information 37
Publication #2: Efficient region-based test strategy uncovers genetic risk factors for functional outcome in bipolar disorder 50
Main publication 51
Supplementary table 66
Appendix
Publication list I
Acknowledgements II

List of abbreviations

BD	bipolar disorder
BD-PRS	bipolar disorder polygenic risk score
DFG	Deutsche Forschungsgemeinschaft
DGPPN	German Association for Psychiatry, Psychotherapy and Psychosomatics
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FIERS	functionally-informed efficient region-based test strategy
GAF	Global Assessment of Functioning
GWAS	genome-wide association study
hiTOP	Hierarchical Taxonomy of Psychopathology
ICD-10	International Statistical Classification of Diseases and Related Health Problems
IDS-C_{30}	30 Item Inventory of Depressive Symptomatology
ISPG	International Society of Psychiatric Genetics
MAF	minor allele frequency
NIMH	National Institute of Mental Health
OR	odds ratio
PANSS	Positive and Negative Syndrome Scale
PGC	Psychiatric Genomics Consortium
PRS	polygenic risk score
RDoC	NIMH Research Domain Criteria
SNP	single nucleotide polymorphism
SZ	schizophrenia
SZ-PRS	schizophrenia polygenic risk score
WTCCC	Wellcome Trust Case Control Consortium
YMRS	Young Mania Rating Scale

List of gene names

COPS2	COP9 signalosome subunit 2
CTCF	CCCTC-binding factor
CYP2D6	cytochrome P450 family 2 subfamily D member 6
DTWD1	DTW domain containing 1
EID1	EP300 interacting inhibitor of differentiation 1
HLA-B	major histocompatibility complex, class I, B
SHC4	SHC adaptor protein 4

Summary (English)

Schizophrenia and bipolar disorder often have devastating impacts on the lives of affected individuals. The etiology of these disorders has yet to be fully understood. Heritability estimates from twin studies are high for schizophrenia and bipolar disorder (> 80 % (Bienvenu et al., 2011)), highlighting potentially large genetic influences. Findings from genome-wide association studies (GWAS) support the highly polygenic architecture of both disorders. Extraordinarily large samples are required in GWAS, owing to the small effect sizes of the individual genetic variants, and a large multiple testing burden.

Although represented as different categorical entities in current diagnostic systems, both genetic and phenotypic overlap has been shown for schizophrenia and bipolar disorder. These findings constitute the rationale for transdiagnostic studies with hierarchically (Kotov et al., 2017) and dimensionally (Cuthbert and Insel, 2010; Insel et al., 2010) measured phenotypes. Furthermore, both disorders are characterized by a heterogeneous course of illness. The combination of illness course and genetic background may provide insights to define more homogeneous, treatment-specific subgroups (“stratified medicine”, (Kapur et al., 2012)).

In the presented work, two strategies were applied to investigate the genetic underpinnings of quantitative indicators of the course of illness in patients with severe mental disorders. In the first publication, our prospective transdiagnostic longitudinal PsyCourse study is introduced in terms of study design and a first symptom-specific characterization of the sample. Over an 18 months period data were collected from patients with disorders from the affective-to-psychotic continuum. These data included a comprehensive dimensional assessment of psychopathology and general functioning combined with the collection of peripheral blood samples, providing a unique resource to research the complex relationship between psychopathology and biology. As expected, predominantly psychotic patients showed more pronounced psychotic symptoms and a lower general functioning over time as well as a higher polygenic load with schizophrenia risk alleles compared to predominantly

affective patients. The level of depressive as well as manic symptoms, however, did not differ significantly between groups over time. These findings support a dimensional rather than a categorical model of psychiatric disorders.

- ***Budde M, Anderson-Schmidt H, Gade K,[…], Falkai P, Schulze TG, Heilbronner U. 2019a. A longitudinal approach to biological psychiatric research: The PsyCourse study. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 180: 89–102.***

From both ethical as well as economic perspectives it is important to make optimal use of already existing data. Although large from a clinical perspective, the size of available data on quantitative phenotypes in psychiatric research is often limited from a genetic point of view. Consequently, there is a need for data analysis methods with reduced multiple testing burden in order to successfully use samples moderate in size. In the second publication, we did just that by combining powerful statistical methods using prior knowledge on biological function and dependence of genotypes. Specifically, we investigated functional outcome as an important cross-sectional indicator of course of illness in bipolar disorder patients in two independent samples and identified a significantly associated locus on chromosome 15. This study confirms the ability of cross-sectional data of moderate sample size to provide important contributions to psychiatric genetic research.

- ***Budde M, Friedrichs S, Alliey-Rodriguez N, […], Rietschel M, Schulze TG, Malzahn D. 2019b. Efficient region-based test strategy uncovers genetic risk factors for functional outcome in bipolar disorder. Eur. Neuropsychopharmacol. 29: 156–170.***

Zusammenfassung (German)

Schizophrenie und bipolare Störungen haben oft verheerende Folgen für das Leben der Betroffenen. Die Ätiologie dieser Erkrankungen ist bisher nicht vollständig aufgeklärt. Zwillingsstudien haben Heritabilitätsschätzungen von über 80 % für Schizophrenie und bipolare Störungen ergeben (Bienvenu et al., 2011) und sprechen somit für einen deutlichen Einfluss genetischer Faktoren. Die Ergebnisse genomweiter Assoziationsstudien (GWAS) legen einen hoch polygenen Charakter dieser Erkrankungen nahe. Für ebendiese GWAS werden aufgrund der kleinen Effekte der einzelnen genetischen Varianten sowie des multiplen statistischen Testens außerordentlich große Stichproben benötigt.

Auch wenn Schizophrenie und bipolare Erkrankungen in aktuellen Diagnosesystemen als unterschiedliche kategoriale Einheiten abgebildet sind, konnten Überschneidungen sowohl auf genetischer als auch auf phänotypischer Ebene gezeigt werden. Diese Befunde bilden die Basis für diagnoseübergreifende Studien mit hierarchischen (Kotov et al., 2017) und dimensionalen (Cuthbert and Insel, 2010; Insel et al., 2010) Phänotypen. Darüber hinaus weisen Patienten mit beiden Erkrankungen sehr heterogene Krankheitsverläufe auf. Die Kombination von Verlauf und genetischem Hintergrund könnte daher ein Schlüssel sein, um homogenere, behandlungsrelevante Subgruppen zu finden (“stratified medicine”, (Kapur et al., 2012)).

In dieser Arbeit wurden zwei verschiedene Strategien angewendet, um die genetischen Grundlagen von Indikatoren des Krankheitsverlaufs bei Patienten mit schweren psychischen Erkrankungen zu untersuchen. In der ersten Publikation wird unsere prospektive diagnoseübergeifende longitudinale PsyCourse Studie vorgestellt und eine symptomspezifische Charakterisierung der Stichprobe vorgenommen. Über einen Zeitraum von 18 Monaten wurden bei Patienten aus einem Kontinuum von affektiven hin zu psychotischen Erkrankungen Daten erhoben. Diese Datenerhebung beinhaltete eine umfassende dimensionale Erfassung der Psychopathologie sowie des allgemeinen Funktionsniveaus und die Entnahme von Blutproben. Somit wurde eine bedeutsame

Ressource geschaffen, um komplexe Beziehungen zwischen Psychopathologie und ihren biologischen Grundlagen zu erforschen. Wie erwartet zeigten Patienten mit überwiegend psychotischen Erkrankungen im Vergleich zu denen mit überwiegend affektiven Erkrankungen im Studienverlauf stärker ausgeprägte psychotische Symptome, ein niedrigeres Funktionsniveau und eine höhere polygene Belastung mit Risikoallelen für Schizophrenie. Die Belastung mit depressiven sowie manischen Symptomen unterschied sich dagegen im Studienverlauf nicht zwischen den Gruppen. Diese Ergebnisse stützen eher ein dimensionales als ein kategoriales Modell für psychiatrische Erkrankungen.

- ***Budde M, Anderson-Schmidt H, Gade K,[…], Falkai P, Schulze TG, Heilbronner U. 2019a. A longitudinal approach to biological psychiatric research: The PsyCourse study. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. 180: 89–102.***

Sowohl aus ethischen als auch aus ökonomischen Gesichtspunkten ist es wichtig, bereits existierende Daten optimal zu nutzen. Auch wenn sie aus klinischer Perspektive groß erscheinen, sind die Datensätze zu quantitativen Phänotypen für psychiatrisch-genetische Analysen oft verhältnismäßig klein. Daher werden statistische Methoden benötigt, bei denen das Problem des multiplen Testens verringert wird, um auch kleinere Stichproben erfolgreich nutzen zu können. In der zweiten Publikation haben wir statistische Methoden so kombiniert, dass vorhandenes Wissen zu biologischen Funktionen von genetischen Varianten sowie zur Abhängigkeit zwischen Genotypen optimal genutzt werden konnte. Konkret haben wir das Funktionsniveau als wichtigen Querschnittsindikator für den Krankheitsverlauf bei Patienten mit bipolaren Störungen in zwei unabhängigen Stichproben untersucht und dabei einen signifikant assoziierten Locus auf Chromosom 15 identifiziert. Diese Studie bestätigt, dass auch Querschnittsdaten aus weniger großen Stichproben wichtige Beiträge zur psychiatrisch-genetischen Forschung liefern können.

- ***Budde M, Friedrichs S, Alliey-Rodriguez N, […], Rietschel M, Schulze TG, Malzahn D. 2019b. Efficient region-based test strategy uncovers genetic risk factors for functional outcome in bipolar disorder. Eur. Neuropsychopharmacol. 29: 156–170.***

Introduction

The polygenic architecture of schizophrenia and bipolar disorder

Schizophrenia (SZ) and bipolar disorder (BD) are severe mental illnesses with devastating impact on the lives of affected individuals. Currently the lifetime prevalence is estimated at 1 % for SZ (Kahn et al., 2015) and up to 2.4 % for BD (Merikangas et al., 2011). In the Global Burden of Disease Study 2016, SZ was ranked among the top 20 and BD among the top 30 causes for years lived with disability, a measurement for the burden of a disease (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Despite considerable progress in research, the etiology of these disorders has yet to be fully understood.

Biological-psychiatric research seeks a better understanding of disease mechanisms with the ultimate goal of developing more effective treatments and tailoring treatments to the specific needs of an individual. However, a truly “personalized medicine” still seems far off. As psychiatric disorders are characterized by heterogeneous phenotypes, it would be immensely helpful to have biomarkers or other indicators to broadly stratify patients into treatment-specific subgroups (Kapur et al., 2012). Given the wealth of studies in the field of biological psychiatry, this approach of “stratified medicine” seems achievable (Kapur et al., 2012). Naturally, pharmacogenetics is the branch of psychiatric genetics currently receiving most attention in clinical practice (Moreno-De-Luca et al., 2018). The goal of pharmacogenetics is to find genetic variants that can predict the therapeutic response and/or adverse reactions of an individual to a specific medication (Moreno-De-Luca et al., 2018). Despite great research efforts, e.g. into genetics of lithium response in BD patients (for a review see (Budde et al., 2017a)), a task force of the International Society of Psychiatric Genetics (ISPG) stated recently that the evidence to support widespread use of pharmacogenetic tests is still inconclusive (International Society of Psychiatric Genetics, 2019). Likewise, to this day, only two clinical implementations are supported by the German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN): (1) testing of

CYP2D6 prior to prescription of tricyclic antidepressants and (2) determining the *HLA-B*1502* genotype in patients of Asian origin before using carbamazepine (Müller et al., 2018).

Severe psychiatric disorders like SZ and BD aggregate within families (Gottesman et al., 2010; Lichtenstein et al., 2009). The heritability of both disorders, i.e. the proportion of phenotypic variation that is accounted for by genetic variation, is estimated at over 80% in twin studies (Bienvenu et al., 2011). To characterize these genetic components, early molecular genetic studies like linkage studies and candidate gene association studies were conducted, albeit with modest success owing to the complex genetic architecture of psychiatric traits. Technical progress has led to genome-wide association studies (GWAS) which use hypothesis-free analysis methods usually carried out in a sample of unrelated individuals. The first GWAS in the field of psychiatry was published by the Wellcome Trust Case Control Consortium (WTCCC) in 2007 (Wellcome Trust Case Control Consortium, 2007). In psychiatric genetics, mostly qualitative binary outcome phenotypes, particularly case-control comparisons, have been analyzed (Andlauer et al., 2018). In case-control GWAS, minor allele frequencies (MAF), i.e. the frequency at which the second most frequent allele occurs in a given sample, of millions of single nucleotide polymorphisms (SNPs) are compared between cases and controls. These studies require large sample sizes, for two main reasons. Firstly, SNPs explored in GWAS are common SNPs with a minor allele frequency of usually $\geq 1\%$. These common SNPs are likely to stem from ancient mutations (Sham and Cherny, 2011) and are expected to have relatively small individual effects. If an allele had large negative effects on individuals' fitness, allele frequency would have been reduced by natural selection throughout evolution (Wray et al., 2013). In fact, the individual effects of common SNPs have been empirically found to be relatively small. More precisely, almost all variants associated with SZ or BD on a genome wide-significant level show odds ratios (OR) < 1.2 (Pardiñas et al., 2018; Stahl et al., 2019). The only exception is the top finding of the SZ GWAS, a locus within the major histocompatibility complex ($OR = 1.28$ (Pardiñas et al., 2018)). Therefore, large samples are needed to achieve sufficient statistical

power to detect the small effects of individual SNPs. Secondly, simultaneous statistical analysis of millions of SNPs in a GWAS makes stringent adjustment of significance level necessary in order to avoid an excess of false-positive SNPs (Type-I error cumulation). Therefore, in samples of European descent, only associations with corresponding *p*-values of $p \leq 5 \times 10^{-8}$ are considered genome-wide significant (Andlauer et al., 2018; Sham and Purcell, 2014). The latter equals a Bonferroni correction for 1 million tests and reflects the number of statistically independent genetic loci (Andlauer et al., 2018; Sham and Purcell, 2014).

Major technical advances that led to decreasing costs for genotyping have shaped the field of psychiatric genetics since the first GWAS by the WTCCC. Big consortia like the Psychiatric Genomics Consortium (PGC) have been formed, allowing for the large sample sizes required. This development has yielded great successes. The latest GWAS reported 145 genome-wide significant loci associated with SZ (Pardiñas et al., 2018) and 30 loci associated with BD susceptibility (Stahl et al., 2019). While early GWAS were unable to produce replicable findings, the last years have seen more success with loci replicating across multiple GWAS of different cohorts. (see e.g. (Budde et al., 2017b) for a review of GWAS results in BD). This development towards more robust findings will continue as sample sizes grow.

It is important to note that results from GWAS can be utilized for far more than just loci identification (Maier et al., 2018). Equally important, GWAS can help us to unravel the genetic architecture of complex diseases. As noted earlier, overall heritability estimates of SZ and BD from twin studies are high (>80 % (Bienvenu et al., 2011)). Only a small fraction of this variation is explained by the accumulated effects of genome-wide significant loci, e.g. 3.4 % for SZ (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). This phenomenon is called “missing heritability” (Maher, 2008). However, by means of GWAS data, so called SNP-heritabilities for certain traits can be estimated i.e. the proportion of phenotypic variance explained by genotyped SNPs (Maier et al., 2018). A recent publication reported SNP-heritabilities of 20 % for BD and 25 % for SZ (Brainstorm

Consortium et al., 2018). SNP-heritability estimates are typically lower than heritability estimates from twin and family studies for several reasons (Maier et al., 2018). For example, genetic effects might be explained by influences of rare variants with large effects not covered by genotyping chips, non-additive genetic effects or epigenetic mechanisms. However, SNP-heritability estimates are larger than the heritability that can be explained so far by genome-wide significant SNPs alone, suggesting that the "missing heritability" is actually in part "hidden heritability" and that the number of genome-wide significant loci will continue to increase with even bigger samples (Wray et al., 2014). Indeed a linear relationship between the increase of sample size and the increase in the number of loci reaching genome-wide significance was observed for complex traits in sample sizes above a critical number ("inflection point", (Panagiotou et al., 2013)). For example, in SZ with each 1,000 additional cases added beyond a base sample size of approximately 13-18,000 cases (inflection point), one would expect to find approximately four new genome-wide significant markers (Levinson et al., 2014). This implicates that these traits are highly polygenic. Thus, the overall genetic influence consists of small effects of thousands of genetic variants.

GWAS can also reveal shared genetic factors between traits by enabling the calculation of genetic correlations (r_g) between traits. "Two traits are genetically correlated, if there is a correlation between the true effect sizes of SNPs affecting the two traits, or in other words, when, on average, SNPs have directionally similar effects on two traits" (Maier et al., 2018). Severe mental illnesses are significantly genetically correlated (Selzam et al., 2018). The highest correlations were observed between SZ and BD with r_g estimates of up to 0.74 (Consortium Cross-Disorder Group of the Psychiatric Genomics et al., 2019; Selzam et al., 2018), highlighting the genetic overlap between these disorders.

Additionally, GWAS summary statistics allow for the calculation of polygenic risk scores (PRS). PRS are a robust estimate of the polygenic load an individual carries for a certain trait, for example SZ or BD (Purcell et al., 2009; Wray et al., 2014). A PRS is the sum of independent risk and protective minor alleles an individual carries weighted by their

respective effect sizes. Here it is important to note that the information regarding genetic marker selection, effect sizes and direction of effects of alleles comes from an independent discovery GWAS. This means that the sample in which PRS are calculated must not be part of the GWAS that provides the summary statistics used for PRS calculation. While heritability is estimated on the population level and does not allow for inference of individual genetic risks, PRS represent the polygenic load of individuals for a certain phenotype. PRS are often applied in research to study the genetic overlap between diseases. Results support the notion of a partially overlapping (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Purcell et al., 2009), yet also specific (Ruderfer et al., 2014) polygenic basis of SZ and BD. Furthermore, the association of PRS with disease-relevant quantitative phenotypes in patients and the general population can be explored. For example, some studies report a negative association between schizophrenia polygenic risk scores (SZ-PRS) and cognitive impairment (for a review, see (Schaupp et al., 2018)), which is a core feature of severe psychiatric illnesses. Interestingly, SZ-PRS have also been associated with important indicators of severity of illness, namely chronicity (Meier et al., 2016), treatment resistance (Frank et al., 2015), hard to treat symptoms like increased negative symptoms (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018) and religious delusions (Anderson-Schmidt et al., 2019) in SZ. Furthermore, SZ-PRS has been associated with psychotic features in BD (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018). These findings indicate a dose-response relationship between polygenic load and illness severity.

Accuracy of PRS highly depends on the statistical power of the respective discovery GWAS (Dudbridge, 2013). Even though PRS are a robust estimate of a person's genetic load of common SNPs, they are not yet suitable for individual risk prediction in a clinical context owing to their limited predictive accuracy. The two biggest studies to date report that ~7% (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) or rather 5.7% (Pardiñas et al., 2018) of the variation on the liability scale to SZ across samples could

be explained by SZ-PRS. Comparably, bipolar disorder polygenic risk scores (BD-PRS) based on the latest GWAS on BD, explain ~4% of the variation on the liability scale to BD across samples (Stahl et al., 2019). Since GWAS in the field of psychiatry have been mostly case-control comparisons, PRS for important quantitative phenotypes are still warranted.

Psychiatric diagnoses: categorical vs. dimensional approaches

In 1899, the German psychiatrist Emil Kraepelin divided affective and psychotic disorders in adulthood into manic-depressive illness and dementia praecox (Kraepelin, 1899). The latter was characterized by deficits in intellectual functioning as well as deterioration and a poorer prognosis. To this day, BD and SZ are represented as separate categorical entities in common diagnostic systems like the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). However, robust findings of a shared genetic overlap between SZ and BD have challenged this dichotomous view from a biological perspective. In addition, a phenotypic overlap between these disorders exists. Individuals suffering from SZ often experience affective symptoms and affective episodes in BD patients can be accompanied by psychotic symptoms. Both groups of patients suffer from stable cognitive impairment outside of acute illness episodes (Budde and Schulze, 2014; Heilbronner et al., 2016) albeit – as already observed by Kraepelin – to a different degree (Stefanopoulou et al., 2009; Vöhringer et al., 2013).

To this day, there are no biomarkers of psychiatric disease. Hence psychiatric diagnoses are based on phenotypic syndromes and therefore do not necessarily represent biologically distinct entities. Both biological and phenotypic overlap indicate that dimensionally defined diagnoses might map the nature of psychiatric diseases more precisely than categorical ones (Craddock and Owen, 2010; Guloksuz and van Os, 2018). Spectrum phenotypes have been included in the DSM 5 for autism and substance abuse, but not yet for SZ and BD. Along this

line, alternative concepts of hierarchically and dimensionally measured phenotypes have been established by the National Institute of Mental Health (NIMH) Research Domain Criteria framework (RDoC; (Cuthbert and Insel, 2010; Insel et al., 2010)) and the Hierarchical Taxonomy of Psychopathology system (hiTOP; (Kotov et al., 2017)).

The course of psychiatric disorders

Like all severe psychiatric disorders, SZ (an der Heiden and Häfner, 2000; Carpenter and Kirkpatrick, 1988; Heilbronner et al., 2016) and BD (Angst and Sellaro, 2000; Marneros and Brieger, 2002) show a heterogeneous course of illness. Even instability of diagnoses over time is a common phenomenon in everyday clinical practice. In both disorders, there is a spectrum of courses ranging from mild forms with few acute episodes and full remission in between to chronic, treatment resistant conditions. The disease course is of utmost importance to the patient and the clinician. Therefore, studying its determinants is clinically highly relevant. As described earlier, already Kraepelin's categorization of adult psychiatric illnesses was based on his observations of the course of disease.

So far, little is known about biological differences between types of disease courses. However, some indicators of a poorer course have been found to be familial including substance abuse, alcoholism, psychosis, history of suicide attempt, and the level of social functioning in BD (Schulze et al., 2006) and negative symptoms, mania and the deficit syndrome of SZ in psychotic disorders (Peralta et al., 2016). Moreover, as highlighted above, there seems to be a dose-response-relationship between SZ polygenic load and indicators of a poorer disease course. Therefore it seems reasonable that course might be a key to find more homogeneous subgroups of patients for "stratified medicine".

Combining biological information and clinical course may reveal fundamental similarities and differences between SZ and BD. An obvious way to investigate the course of an illness is to conduct a prospective longitudinal study (own contribution publication #1: (Budde et al.,

2019a)). Complementary, indicators of disease course can be assessed retrospectively (own contribution publication #2: (Budde et al., 2019b)).

Studies on transdiagnostically measured quantitative psychiatric phenotypes in general and longitudinal studies in particular are very valuable, yet still limited in number and sample sizes since they are complex and expensive. Therefore, the PsyCourse study by our group (publication #1: (Budde et al., 2019a)) provides an especially valuable resource for studying the biological underpinnings of the course of severe psychiatric disorders. So far, the PsyCourse resource has given rise to several publications, including research on age at onset in BD (Kalman et al., 2019), religious delusions in SZ (Anderson-Schmidt et al., 2019), the genetic relationship between educational attainment and cognition in mental illnesses (Comes et al., 2019) and on the interplay of Hdac1 variants with early life stress (Bahari-Javan et al., 2017). Moreover PsyCourse has contributed data to larger consortia (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Consortium Cross-Disorder Group of the Psychiatric Genomics et al., 2019; Drange et al., 2019; Mullins et al., 2019), and will continue to do so.

Unfortunately, so far there is no agreement on, nor harmonization of, assessment scales that should preferably be used across studies. This complicates the search for replication samples for biologically important quantitative phenotypes beyond case-control status (Kapur et al., 2012). Nevertheless, as previously discussed, sample size is crucial in psychiatric genetics. Therefore, in parallel to setting up transdiagnostic projects with dimensional phenotypes, it is highly desirable to find new ways to make the best use of already existing data (publication #2: (Budde et al., 2019b)). The latter is important both from ethical as well as economic perspectives.

This dissertation combines two publications that apply different strategies to explore phenotypic and genetic correlates of the course of SZ and BD via quantitative phenotypes.

Publication #1: A longitudinal approach to biological psychiatric research: The PsyCourse study (Budde et al., 2019a)

The PsyCourse Study is a multicenter, longitudinal, transdiagnostic study on the course of severe mental illnesses funded by the Deutsche Forschungsgemeinschaft (DFG) led by Prof. Thomas G. Schulze and Prof. Peter Falkai. A dimensional assessment of psychopathology over a time span of 18 months was combined with the collection of biomaterials in patients from the affective-to-psychotic continuum, providing a unique resource to research the complex relationship between psychopathology and biology. From the beginning of the project on, I have contributed in many ways: to the data protection concept (Demiroglu et al., 2012), in the development of the phenotype database, by recruitment of study participants and managing cooperations with other study centers, including database maintenance and quality control of the data. In Budde et al. (2019a), the design of the PsyCourse study as well as a first characterization of the sample is presented. Patients were grouped into those with predominantly affective (n = 367 individuals; diagnoses: BD and recurrent major depressive disorder) vs. those with predominantly psychotic (n = 524 individuals; diagnoses: SZ, schizoaffective disorder, schizophreniform disorder and brief psychotic disorder) symptoms. Depressive (30 Item Inventory of Depressive Symptomatology, IDS-C_{30}), manic (Young Mania Rating Scale, YMRS) and psychotic (Positive and Negative Syndrome Scale, PANSS, positive scale) symptoms as well as global functioning (Global Assessment of Functioning score, GAF) were then analyzed over time in these two groups of patients using linear mixed models. While the degree of psychotic symptoms and global functioning differed between groups, there were no significant differences in both manic and depressive symptoms. These findings support a dimensional rather than a categorical model of psychiatric diseases on a phenotypic level. Diagnostic groups also differed regarding their SZ-PRS. SZ-PRS significantly explained variability between these two diagnostic groups (Nagelkerke's $R^2 \sim 1\%$). As expected, higher SZ-PRS increased the odds of being in the "predominantly psychotic" group.

Publication #2: Efficient region-based test strategy uncovers genetic risk factors for functional outcome in bipolar disorder (Budde et al., 2019b)

Although there is a pressing need for longitudinal studies, it is equally important to make optimal use of already existing data. This work was a joint project in cooperation with Dr. Dörthe Malzahn from the Department of Genetic Epidemiology in Göttingen, who conducted the statistical analyses, and groups from Bonn and Mannheim as well as the Bipolar Genomics Consortium (USA), who contributed data. We explored genetic effects on global functioning (GAF score), which measures the overall psychological, social and occupational functioning of a subject, in two independent samples of BD patients (N = 1,592 in total). The GAF was assessed during outpatient treatment as an indicator of disease course outside of acute episodes. Although large from a clinical perspective, the sample does not provide enough power for a GWAS. To overcome these sample size limitations, we combined powerful statistical methods into a *f*unctionally-*i*nformed *e*fficient *r*egion-based test *s*trategy (FIERS). FIERS uses prior knowledge on biological function and dependence of genotypes to reduce the multiple-testing burden and provides improved sensitivity and specificity to detect consistent effects across studies. With this method, a significantly associated locus on chromosome 15 (hg38: chr15: 48965004-49464789 bp) was identified with consistent effect strength between samples. Haplotype analysis revealed risk and protective haplotypes for functional outcome on the most strongly associated SNPs. Plausible biological candidates related to the associated region are a *CTCF* binding site (regulatory element), the genes *COPS2, EID1 and SHC4,* which are known to be involved in neuronal differentiation and function, as well as *DTWD1*, which is relevant for psychopharmacological side effects. This study demonstrates that an efficient combination of statistical methods and contextual knowledge enables the field to gain mechanistic insight into the biology underlying important quantitative phenotypes.

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RESEARCH ARTICLE

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A longitudinal approach to biological psychiatric research: The PsyCourse study

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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-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)

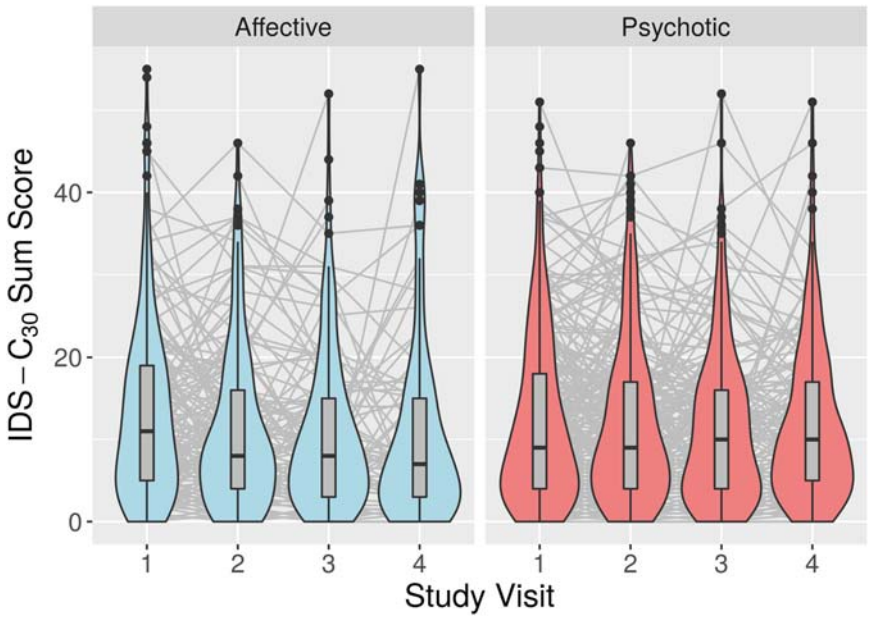

FIGURE 1 Violin plots of the course of depressive symptoms, separately for both patient groups. Individual trajectories are plotted in gray color. The numbers of participants included in this graph (T1–T4, respectively) are: 312, 184, 149, 109 (Affective) and 453, 288, 213, 196 (Psychotic)

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-

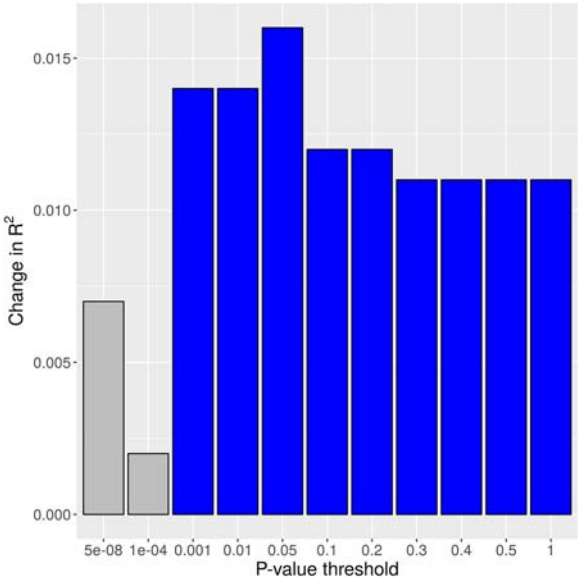

FIGURE 2 Effects of SZ-PRS on diagnostic group. *p*-Values significant after FDR correction in blue color (baseline model with covariates only: Nagelkerke's $R^2 = .091$; FDR corrected *p*-values for the models with *p*-value thresholds from 5e-08 to 1: .059, .29, .022, .022, .022, .022, .022, .024,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

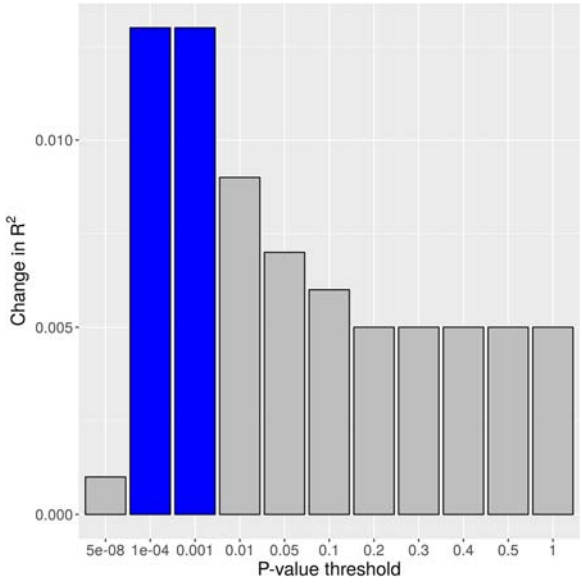

FIGURE 3 Effects of SZ-PRS on dropout. *p*-Values significant after FDR correction in blue color (baseline model with covariates only: Nagelkerke's $R^2 = 0.131$; FDR corrected *p*-values for the models with a *p*-value threshold from 5e-08 to 1: .705, .03, .03, .088, .115, .15, .175, .175, .175, .175,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

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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.

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SUPPORTING INFORMATION

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

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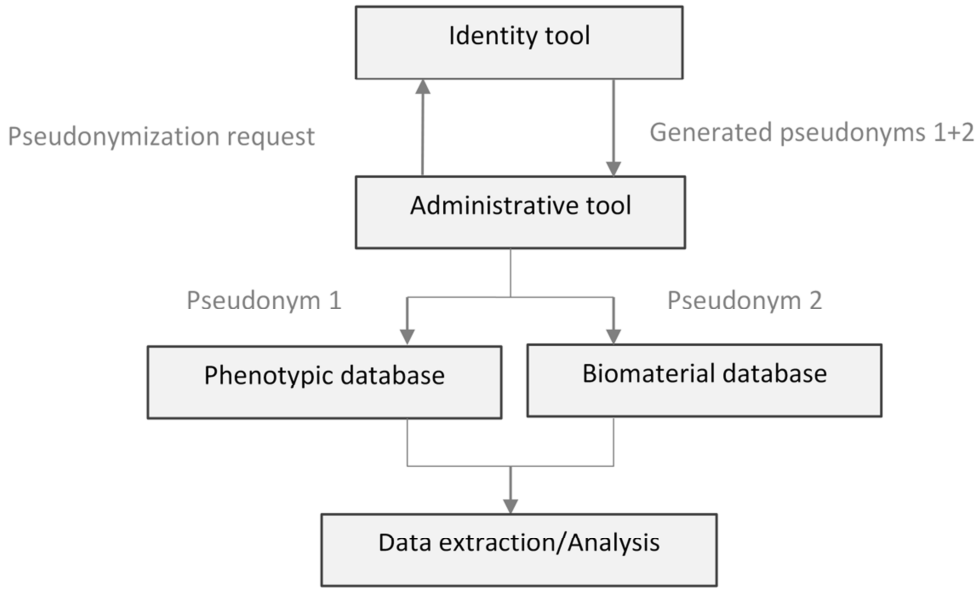
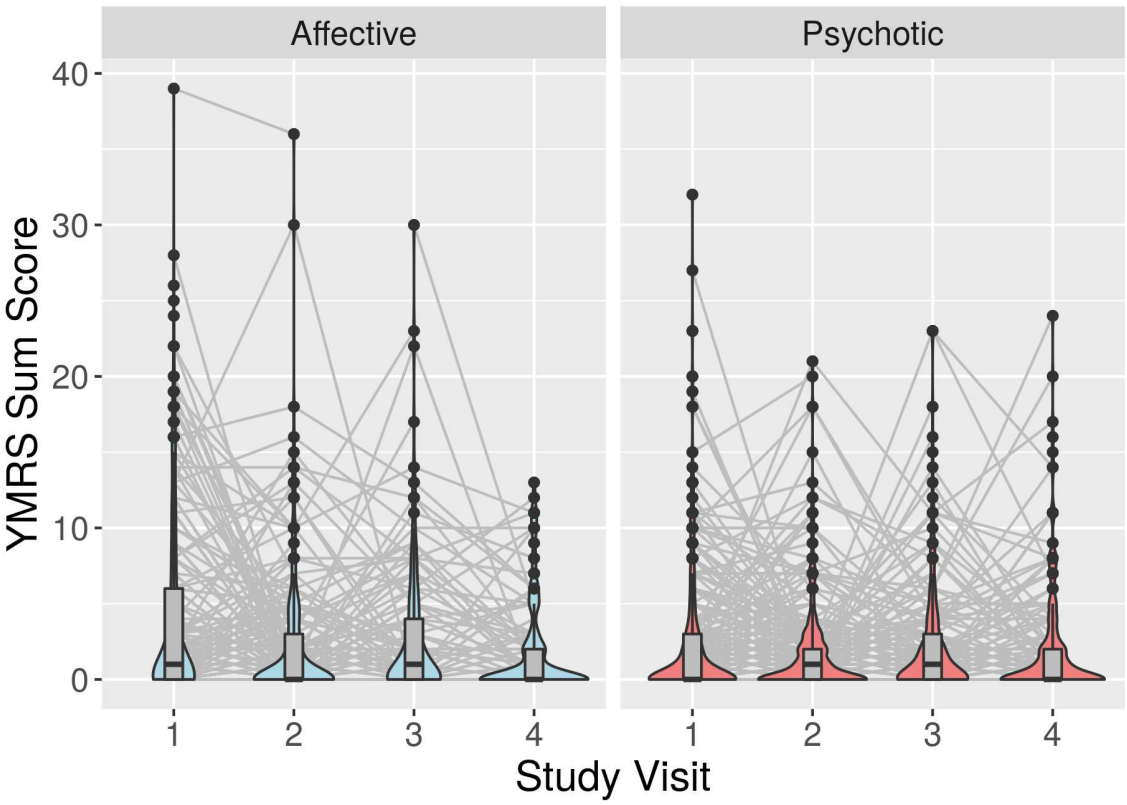
APPENDIX : DATA SHARING POLICY

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.

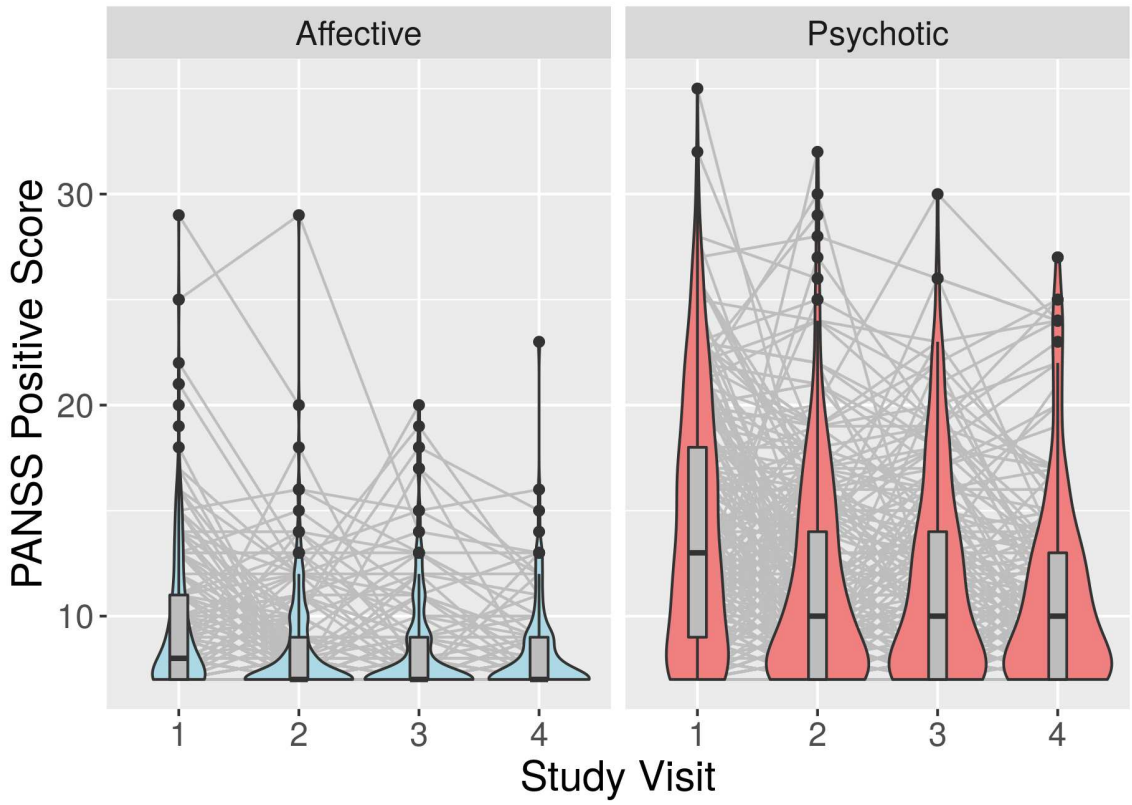
Supplementary Figures



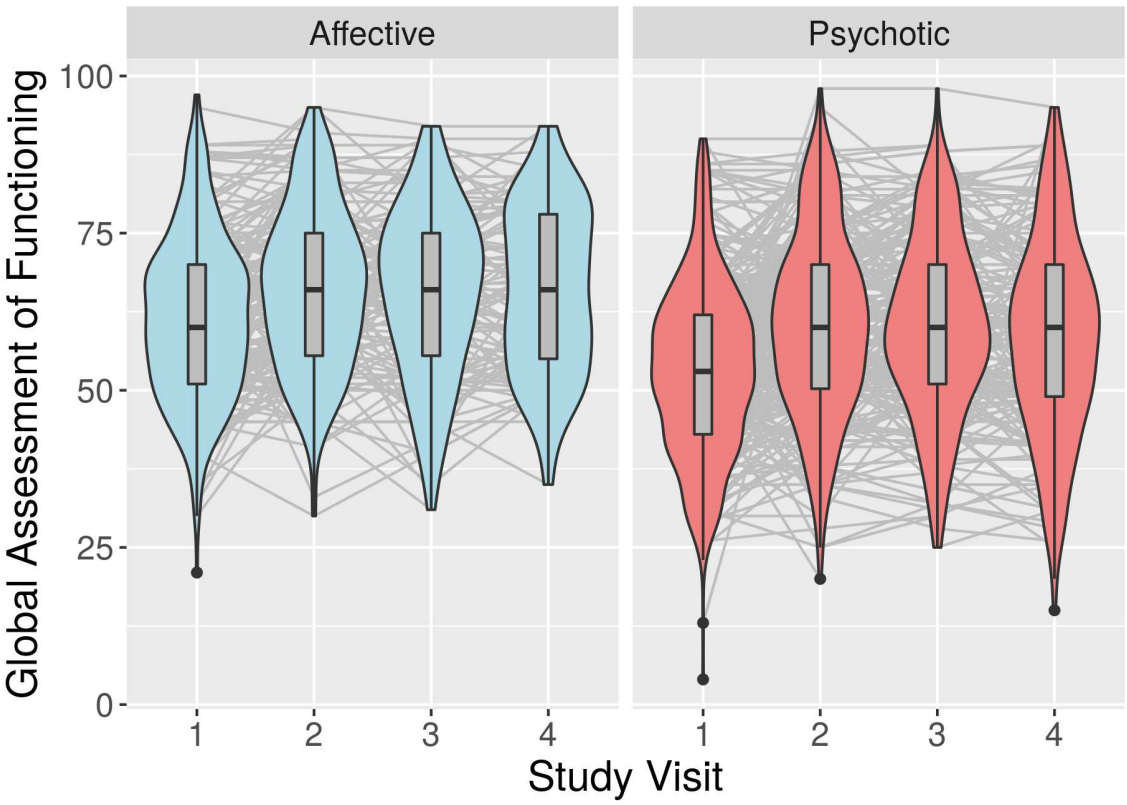
Supplementary Figure 1. IT components of the PsyCourse study responsible for identifying, managing and storing phenotype data and biological samples.



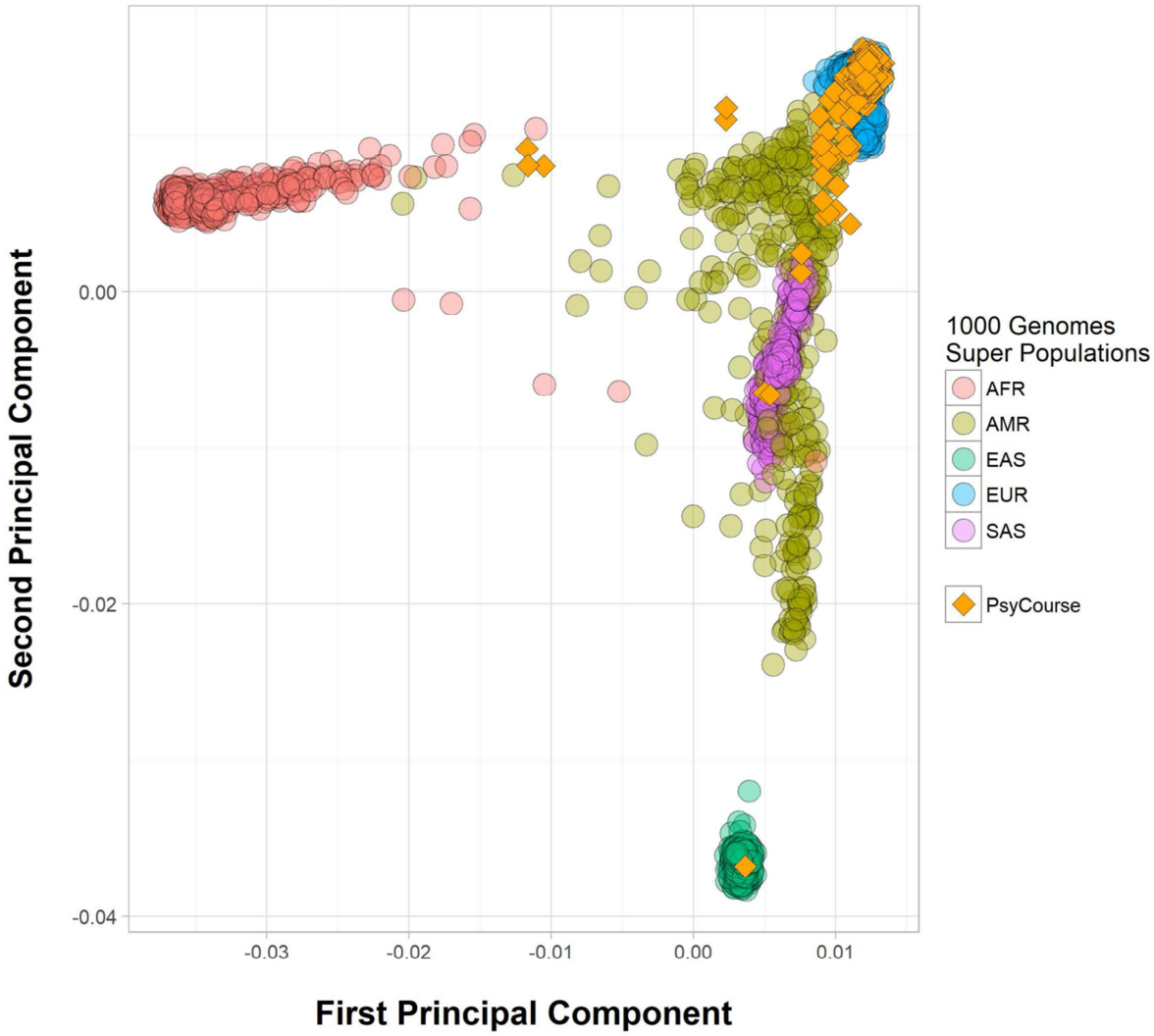
Supplementary Figure 2. Violin plots of the course of manic symptoms, separately for both patient groups. Individual trajectories are plotted in gray color. The numbers of participants included in this graph (T1-T4, respectively) are: 349, 207, 163, 126 (Affective) and 502, 307, 232, 214 (Psychotic).



Supplementary Figure 3. Violin plots of the course of psychotic 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: 355, 210, 168, 130 (Affective) and 518, 309, 243, 221 (Psychotic).



Supplementary Figure 4. Violin plots of the course of psychosocial functioning, separately for both patient groups. Individual trajectories are plotted in gray color. The numbers of participants included in this graph (T1-T4, respectively) are: 358, 207, 167, 129 (Affective) and 517, 310, 242, 220 (Psychotic).



Supplementary Figure 5. 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).

Supplementary Tables

Supplementary Table 1. Phenotypes collected in the PsyCourse study. Abbreviations: ALDA-Scale – Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder (Grof et al., 2002); ASRM - Altman Self Rating Mania Scale (Altman, Hedeker, Peterson, & Davis, 1997); BDI-II - Beck Depression Inventory II (Hautzinger, Keller, & Kühner, 2006); BFI-10 - Big Five Inventory (Rammstedt & John, 2007); CAPE – Community Assessment of Psychic Experiences (Konings, Bak, Hanssen, van Os, & Krabbendam, 2006; Stefanis et al., 2002); CGI - Clinical Global Impression (National Institute of Mental Health, 1976); CTS - Childhood Trauma Screener (Grabe et al., 2012); DSM-IV-TR - Diagnostic and statistical manual of mental disorders (4th edition) (American Psychiatric Association, 2002); F/U - follow-up; GAF - Global Assessment of Functioning Scale (American Psychiatric Association, 2002); IDS-C30 - Inventory of Depressive Symptomatology (30 items, clinician rated; Rush, Carmody, & Reimitz, 2000); LEQ - Life Events Questionnaire (Norbeck, 1984); MINI-DIPS - Diagnostisches Kurzinterview bei psychischen Störungen (Margraf, 1994); MSS - Manie-Selbstbeurteilungsskala (Krüger, Bräunig, & Shugar, 1997); MWT-B - Mehrfachwahl-Wortschatz-Intelligenztest (Lehrl, 2005); OPCRIT - Operational Criteria Checklist for Psychotic Illness (McGuffin, Farmer, & Harvey, 1991); PANSS - Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987); SCID I - Structured Clinical Interview for DSM-IV (Axis I Disorders; Wittchen & Fydrich, 1997); SF-12 - SF-12 Health Survey (Ware, Kosinski, & Keller, 1996); VLMT - Verbaler Lern- und Merkfähigkeitstest (Helmstaedter, Lendt, & Lux, 2001); WHOQOL-BREF - World Health Organization Quality of Life questionnaire (Angermeyer, Kilian, & Matschinger, 2000); YMRS - Young Mania Rating Scale (Young, Biggs, Ziegler, & Meyer, 1978).

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
	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	
	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]self-reported weight is assessed at each time point

Supplementary Table 2. Numbers of participants from each clinical center included in the present analyses.

Clinical center	*Number of included participants*
Augsburg	41
Bad Zwischenahn	57
Bochum	98
Bremen Ost	27
Eschwege	7
Göttingen	11
Graz	123
Günzburg	100
Hildesheim	19
Liebenburg	9
LMU München	95
Lüneburg	36
Münster	6
Osnabrück	39
Rotenburg/Wümme	29
Tiefenbrunn	5
UMG Göttingen	176
Wilhelmshaven	13

Supplementary Table 3. YMRS: Post-hoc tests (least square means) 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
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

Supplementary Table 4. PANSS Positive Score: Post-hoc tests (least square means) 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

Supplementary Table 5. GAF: Post-hoc tests (least square means) 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

Supplementary Table 6. 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. N=498; *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)		<0.001	
Bochum	-19.958 (11440.497)		<0.001	
Bremen Ost	-19.063 (11440.497)		<0.001	
Eschwege	0.554 (22526.837)		1.740	
Göttingen	-20.575 (11440.497)		<0.001	
Günzburg	-20.216 (11440.497)		<0.001	
Graz	-19.891 (11440.497)		<0.001	
Hildesheim	-20.439 (11440.497)		<0.001	
Lüneburg	-20.005 (11440.497)		<0.001	
Liebenburg	-0.074 (18877.144)		0.929	
München	-19.930 (11440.497)		<0.001	
Osnabrück	-20.145 (11440.497)		<0.001	
Rotenburg	-18.140 (11440.497)		<0.001	
Tiefenbrunn	-19.065 (11440.497)		<0.001	
UMG Göttingen	-18.847 (11440.497)		<0.001	
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

Publication #2:

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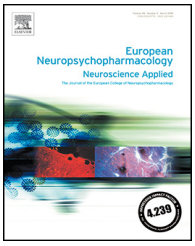

Efficient region-based test strategy uncovers genetic risk factors for functional outcome in bipolar disorder

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Abstract
Genome-wide association studies of case-control status have advanced the understanding of the genetic basis of psychiatric disorders. Further progress may be gained by increasing sample size but also by new analysis strategies that advance the exploitation of existing data, especially for clinically important *quantitative* phenotypes. The *f*unctionally-*i*nformed *e*fficient *r*egion-based test strategy (FIERS) introduced herein uses *prior* knowledge on biological function and dependence of genotypes within a powerful statistical framework with improved sensitivity and specificity for detecting consistent genetic effects across studies. As proof of concept, FIERS was used for the first genome-wide single nucleotide polymorphism (SNP)-based investigation on bipolar disorder (BD) that focuses on an important aspect of disease course, the functional outcome. FIERS identified a significantly associated locus on chromosome 15 (hg38: chr15:48965004 – 49464789 bp) with consistent effect strength between two independent studies (*GAIN*/*TGen*: European Americans, *BOMA*: Germans; $n = 1592$ BD patients in total). Protective and risk haplotypes were found on the most strongly associated SNPs. They contain a *CTCF* binding site (rs586758); *CTCF* sites are known to regulate sets of genes within a chromatin domain. The rs586758 – rs2086256 – rs1904317 haplotype is located in the promoter flanking region of the *COPS2* gene, close to microRNA4716, and the *EID1, SHC4, DTWD1* genes as plausible biological candidates. While implication with BD is novel, *COPS2, EID1*, and *SHC4* are known to be relevant for neuronal differentiation and function and *DTWD1* for psychopharmacological side effects. The test strategy FIERS that enabled this discovery is equally applicable for tag SNPs and sequence data.

1. Introduction

For years, collaborative consortia have vastly increased sample sizes for genome-wide association studies (GWAS). However, worldwide sample size is finite, and data on clinically important *quantitative* phenotypes is currently limited, largely due to high costs of deep phenotyping and lacking harmonization of assessment scales and conditions across studies. Nevertheless, quantitative phenotypes are especially valuable for understanding underlying biological mechanisms and between-patient heterogeneity. Hence, complementary to increasing sample size, new approaches and strategies that advance the exploitation of existing genome-wide data are highly desirable.

To gain power and identify underlying mechanisms, recently single-marker tests have been replaced by joint statistics on biological units (Subramanian et al., 2005; Wang et al., 2007). Joint statistics greatly reduce the multiple-testing burden and may increase power by aggregating association signals from multiple functionally-related loci. Many pioneering approaches have aggregated single-SNP GWAS *p*-values into enrichment statistics for genes or pathways (Wang et al., 2010). However, unbiased scoring often necessitates time-consuming permutation procedures, since genes and pathways differ in numbers of SNPs, gene length, gene number and linkage disequilibrium (LD)-patterns. Alternatively, SNPs may be aggregated into polygenic risk scores that serve for association testing or trait prediction (Dudbridge, 2013). Risk scores reduce the model space: they collapse multiple SNPs into a single score with *a priori* assumptions on the selection and weighting of contributing SNPs (Dudbridge, 2013). A third set of methods provide actual joint tests of SNPs at the individual-data level. Among them, the kernel score test SKAT (Schaid, 2010) is very powerful for a broad range of genetic architectures, computationally convenient, and yields exact *p*-values.

Whereas LD is a nuisance for most statistics, SKAT can exploit LD to increase power compared to single-marker tests (Schifano et al., 2012) to the extent that testing LD-blocks with SKAT is especially powerful (Malzahn et al., 2016). Since SKAT is a joint test, power increases with cumulative association strength and the ratio between sample size and number of jointly tested SNPs. Therefore, tag SNPs may provide higher power than a denser common SNP panel of the same region (Malzahn et al., 2014). Whereas association strengths and available sample sizes depend on studied phenotypes, sizes of tested SNP sets are the

analysts' choice. Of all 284 human pathways listed in the KEGG (Kanehisa and Goto, 2000) database at the time of download, only 9.5% contained fewer than 500 SNPs of a typical GWAS marker panel, but 47% of the pathways contained more than 2000 SNPs, and the longest pathway contained around 14,500 SNPs. For clinically important phenotypes however, primary studies or even worldwide samples with comparable phenotyping may encompass only a few thousand subjects. In these instances, power likely differs profoundly between short and long pathways, whereas smaller biological units provide stable power. Note also that pathways may share genes and genes may share SNPs, thus yielding partially overlapping test sets. Herein, we leverage the observed enrichment of small *p*-values across GWAS among SNPs linked with specific functional elements (Schork et al., 2013). We *a priori* identify and test only LD-blocks containing specific functional SNPs, considering these regions putatively relevant in a hypothesis-driven GWAS. A variety of classes of putative functionality of SNPs may be used for selecting genomic regions of interest *a priori*. Herein, we chose to use non-synonymous coding SNPs (nsSNPs) and no other functional information, as currently nsSNPs can be most reliably predicted (Li and Wei, 2015; Saunders and Baker, 2002) and many genes implicated with BD susceptibility (Hou et al., 2016), the disorder of interest herein, are protein coding. Hence the presented analysis focused on LD-blocks that overlap with protein-coding sections of the genome, with the extension that exploiting LD putatively may include additional information from SNPs with other functionalities as well. The testing of LD-blocks fully capitalizes on SKAT's advantages. In addition, we improved sensitivity and specificity to detect consistent genetic effects across studies by employing an extension of SKAT (Malzahn et al., 2014) for cross-study analysis of individual-level data (mega-analysis).

As proof of concept, we demonstrate the success of this **f**unctionally-**i**nformed **e**fficient **r**egion-based test **s**trategy (FIERS) to uncover genetic risk factors for functional outcome in bipolar disorder (BD) in two independent studies, *Genetic Information Association Network* (*GAIN)* (Smith et al., 2009)/*Translational Genomics Research Institute (TGen)* study (Smith et al., 2011), United States, and the *Bonn-Mannheim (BOMA)* study (Cichon et al., 2011; Fangerau et al., 2005), Germany, comprising 1592 patients. BD is among the 20 leading causes of disability worldwide (Vos et al., 2012) and genetic factors contribute to BD susceptibility (Bienvenu et al., 2011; Charney et al., 2017). However, functional outcome of BD is highly variable. While some patients with a mild course of BD experience hardly any restrictions in work or personal relationships between illness episodes, an estimated 30–60% suffer from substantial impairment up to the point of disability (Sanchez-Moreno et al., 2009). Apart from severe socio-economic consequences, impaired functional outcome also implies a reduced perceived quality of life of patients (Sum et al., 2015). Several socio-demographic, clinical and cognitive factors associate with impaired functional outcome in BD (for an overview see Gade et al., 2015; Reinares et al., 2013; Solé et al., 2018). The knowledge of these factors and of their interplay is critical for optimizing individualized treatment (Reinares et al., 2013). Along the same line, it is of utmost importance to gain deeper insights into the biological underpinnings of between-patient heterogeneity of functional outcome of BD.

Heritability and familial clustering of reduced global (Savage et al., 2012; Vassos et al., 2008), social (Schulze et al., 2006), and occupational (Potash et al., 2007) functioning in families of patients with schizophrenia (Savage et al., 2012; Vassos et al., 2008) or BD (Potash et al., 2007; Schulze et al., 2006) suggest genetic influences. Furthermore, Global Assessment of Functioning (GAF; DSM-IV Axis V) was lower in healthy carriers of neuropsychiatric copy-number-variants compared to non-carriers (Stefansson et al., 2013). We present here the first genomic study of functional outcome of BD. While BD has an episodic character, most patients experience longer times outside of severe acute manic or depressive episodes than within. Consequently, FIERS was employed to analyze GAF assessed during outpatient treatment, as important cross-diagnostic indicator of overall course and severity of psychiatric disorder.

2. Experimental procedures

2.1. Study participants

Data were provided by the *GAIN*/*TGen* study, United States (Smith et al., 2009, 2011), and the *BOMA* study, Germany (Cichon et al., 2011; Fangerau et al., 2005). All participants gave written informed consent prior to study participation. Study protocols were approved by the respective institutional review boards and in accordance with the 1964 Declaration of Helsinki. For the *BOMA* sample, summary statistics can be accessed via the Psychiatric Genomic Consortium (http://www.med.unc.edu/pgc/) and individual data by contacting the Institute of Psychiatric Phenomics and Genomics, University Hospital, LMU Munich, Germany (Thomas G. Schulze). *GAIN*/*TGen* data can be obtained by contacting the Bipolar Genome Study (John R. Kelsoe). *GAIN* genotypes are also available at the *database of Genotypes and Phenotypes* (phs000017.v3.p1).

From *GAIN*/*TGen*, we analyzed 1081 adults of European American ancestry diagnosed with BD according to DSM-IV criteria who had GAF scores. *GAIN*/*TGen* provided imputed genome-wide genotypes (see Smith et al., 2009, 2011 for details). Patient age ranged from 17 to 77 years (mean $\pm$ sd: 43 $\pm$ 12 years), duration of illness from 0.5 to 64 years (mean $\pm$ sd: 24 $\pm$ 13 years), and 34.9% ($n = 377$) of participants were men. Diagnoses were obtained based on the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) and review of available family history and medical records through a best estimate procedure.

BOMA participants had minimal illness duration of 6 months and were recruited for the purpose of genetic studies (Fangerau et al., 2005) from consecutive hospital admissions at the Central Institute of Mental Health, Mannheim and the Department of Psychiatry, University of Bonn, Germany. Diagnoses were established by the German version of the Structured Clinical interview for DSM-IV-TR Axis I Disorders (Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text revision, SCID-I) (First et al., 2002; Wittchen and Fydrich, 1997). We analyzed 511 adult inpatients with a lifetime-diagnosis of BD according to DSM-IV criteria

and available pre-admission GAF scores and genome-wide genotypes (Illumina: HumanHap550v3, Human610, Human660w) (17). *BOMA* patient age was comparable to *GAIN/TGen* and ranged from 18 to 78 years (mean ± sd: 46 ± 13 years), duration of illness was on average shorter (ranging from 0.5 to 61 years, mean ± sd: 17 ± 12 years), and the proportion of men was higher (45.0%, $n = 230$).

2.2. Phenotype

Functional outcome was assessed by the GAF score (DSM-IV Axis V, American Psychiatric Association, 2002); details on scale development are described elsewhere (Endicott et al., 1976; Luborsky, 1962). GAF rates the overall psychological, social and occupational functioning of a subject on a continuum ranging from 1 to 100 (Luborsky, 1962). Poorer functioning is indicated by lower GAF scores.

We analyzed GAF in BD outpatients to target course of disorder outside acute illness episodes. GAF assessments were performed by board-certified psychiatrists or psychologists or psychiatry/psychology trainees at advanced stages in their postgraduate education. In *GAIN/TGen*, GAF was an average rating over the past (last) month assessed by direct interview of outpatients. Observed scores ranged from 5 to 100 with a median score of 61. In *BOMA*, the GAF score represents a pre-admission state right before the "current" episode for which the patient received clinical treatment at the time of study interview. Observed GAF scores in *BOMA* were higher compared to *GAIN/TGen* and ranged from 25 to 100 with a median score of 80.

2.3. Statistical methods - FIERS

FIERS applied a hypothesis-guided filter on the genome, combining two types of *prior* information: LD structure (from independent reference data) and functional knowledge (from bioinformatic annotation tools). The goal was to *a priori* identify LD-blocks that contain specific functional elements. In a second step, only these LD-blocks were tested for genotype-phenotype association by employing a generalization of SKAT (Malzahn et al., 2014) for cross-study analysis of individual-level data (mega-analysis, details below). This comprised the genotypic information of an LD-block into a single association test, yielding a single *p*-value per LD-block, respectively. The employed generalization of SKAT was especially powerful since it methodically optimally exploited all available information; specifically, genomic correlations and consistency (or lack thereof) of putative genetic effects across samples. Finally, to gain additional insight, the detected significant LD-block was examined in detail by single-SNP and haplotype association analyses.

2.3.1. FIERS - step I: hypothesis-guided LD-based selection of genomic regions

Prior information on nsSNPs and LD were obtained for independent population-based reference data from the International Haplotype Map Project (HapMap phase II CEU sample - northern and western European ancestry; 2591820 SNPs, Sabeti et al., 2003) and matched to *GAIN/TGen* and *BOMA* using hg38 SNP-positions obtained with biomaRt (bioconductor). A listing of nsSNPs was obtained based on SNP rs-identifier numbers from SNPnexus (Dayem Ullah et al., 2013) as predicted by at least one of the widely accepted SIFT (Kumar et al., 2009) or PolyPhen (Adzhubei et al., 2010) bioinformatics tools (Friedrichs et al., 2016), and irrespective of predicted nsSNP impact as this may vary across transcript isoforms. The hg38 start and end positions of LD-blocks that contain these functionally annotated SNPs were determined using the default algorithm of Haploview 4.2 (Barrett et al., 2005) such that within assigned LD-blocks at least 70% of all SNP pairs had D' estimates with lower 95% confidence limits above 0.5. The rationale was to detect reasonably strongly correlated SNP sets for subsequent combined evaluation (Malzahn et al., 2016).

GAIN/TGen and *BOMA* samples were genetically homogeneous and indistinguishable in the four most important principal components (multidimensional scaling analysis, PLINK, data not shown; see Table 1 and Fig. 2 [symbols in bottom panel] for high cross-study similarity of estimated variant frequencies and SNP correlations). Combining external LD information with nsSNP data identified 2957 LD-based blocks for association testing (containing 51,382 SNPs in total) from 410,943 common SNPs available in *GAIN/TGen* and *BOMA* after quality control. SNPs were directly typed (*BOMA*: Hardy-Weinberg equilibrium p-value $\geq 10^{-5}$, call rate $\geq$ 95%) or came from a larger imputed panel (*GAIN/TGen*, see Smith et al., 2009, 2011 for details on genotyping, quality control and imputation). By construction, GWAS marker panels are LD-pruned. Nevertheless, substantial amounts of LD remain and test strategy FIERS exploits this. The two largest tested LD-based blocks contained 430 and 186 SNPs; all other blocks contained fewer than 79 SNPs. With regards to nsSNP content, 72% of the tested LD-based blocks contained a single nsSNP, 28% contained at least two, with a maximum of 26 nsSNPs in a block.

2.3.2. FIERS - step II: region-based cross-study analysis of individual-level data

PLINK and R (version 3.2.2) were used for statistical analyses. All p-values reported are two-sided. Genetic association screening was performed for the full sample (*quantitative GAF*). Additionally, subjects who had GAF values in the lowest versus highest sample quartile were compared (*GAF extremes*). All analyses were adjusted for fixed effects of sex and duration of illness (Gade et al., 2015). Putative functional LD-based blocks were tested with SKAT in each study (*GAIN/TGen*, *BOMA*) and in cross-study analyses (mega-analysis of individual-level data; *quantitative GAF*: linear model, adjusting for between-study differences of GAF values by a random effect (Malzahn et al., 2014); *GAF extremes*: logistic model, adjusting for between-study differences of GAF values by the additional covariate *study*). Mega-analysis of individual-level data within SKAT assumed common SNP effects across studies and a linear kernel on minor allele dosages (additive model) with *beta*-density SNP-weights *Beta*(MAF,0.5,0.5) that depend on the minor allele frequency (MAF) of SNPs. This choice of kernel and SNP-weights ensured robust power for detecting genetic main effects (Malzahn et al., 2016). Mega-analysis increased the power (*sensitivity*) for detecting reproducible genetic effects as it combined concordant effects across stud-

Table 1 GAF in BD outpatients associates with an LD-block on chromosome 15 (hg38: chr15:48965004 - 49464789 bp).

		Position	Frequency		Effect on *quantitative GAF*				Effect on *GAF extremes*			
REGION[a]					Single studies			Mega analysis	Single studies			Mega analysis
Chromosome 15		48965004 -	44 SNPs		GER	$P = 4.9 \times 10^{-4}$		$P = 1.3 \times 10^{-5}$	GER	$P = 5.4 \times 10^{-4}$		$P = 5.6 \times 10^{-6}$
		49464789			US	$P = 5.9 \times 10^{-3}$			US	$P = 1.6 \times 10^{-3}$		
Top-ranked SNPs within this region[b] and negatively correlated nsSNP *rs11854184*												
SNP	MA	Position	Frequency		Effect: beta[b]		95%CI[b]	Meta-analysis	Effect: OR[b]		95% CI[b]	Meta-analysis
rs4474633	A	48968404	GER	0.316	GER	−3.72	[−5.63, −1.80]	$P = 4.4 \times 10^{-5}$	GER	2.21	[1.47, 3.42]	$P = 1.3 \times 10^{-5}$
			US	0.329	US	−1.59	[−2.93, −0.25]		US	1.48	[1.14, 1.93]	
rs11854184	A	49000997	GER	0.199	GER	2.84	[0.54, 5.13]	$P = 0.013$	GER	0.56	[0.33, 0.91]	$P = 0.013$
			US	0.188	US	1.34	[−0.32, 3.00]		US	0.75	[0.54, 1.03]	
rs2413930	T	49083018	GER	0.230	GER	−4.12	[−6.28, −1.97]	$P = 1.5 \times 10^{-5}$	GER	2.26	[1.44, 3.63]	$P = 5.8 \times 10^{-6}$
			US	0.285	US	−1.99	[−3.38, −0.61]		US	1.63	[1.23, 2.16]	
rs586758	A	49216375	GER	0.287	GER	−3.81	[−5.80, −1.82]	$P = 2.5 \times 10^{-5}$	GER	2.31	[1.51, 3.62]	$P = 2.0 \times 10^{-6}$
			US	0.297	US	−1.84	[−3.21, −0.47]		US	1.63	[1.23, 2.17]	
rs2086256	T	49265829	GER	0.346	GER	−3.23	[−5.13, −1.33]	$P = 1.1 \times 10^{-5}$	GER	2.06	[1.37, 3.16]	$P = 4.6 \times 10^{-6}$
			US	0.348	US	−2.27	[−3.60, −0.94]		US	1.62	[1.24, 2.13]	
rs1904317	T	49270069	GER	0.289	GER	−3.79	[−5.77, −1.81]	$P = 2.5 \times 10^{-5}$	GER	2.28	[1.49, 3.56]	$P = 2.2 \times 10^{-6}$
			US	0.297	US	−1.84	[−3.22, −0.47]		US	1.63	[1.23, 2.17]	
Six-locus haplotype[c] rs4474633 - rs11854184 - rs2413930 - rs586758 - rs2086256 - rs1904317												
Haplotype group		Position	Frequency		Effect: beta[c]		95%CI[c]	Single studies	Effect: OR[c]		95% CI[c]	Single studies
***GCC		48968404 -	GER	0.654	GER	3.23	[1.33, 5.13]	$P = 9.1 \times 10^{-4}$	GER	0.49	[0.32, 0.73]	$P = 6.6 \times 10^{-4}$
		49270069	US	0.652	US	2.27	[0.94, 3.60]	$P = 8.3 \times 10^{-4}$	US	0.62	[0.47, 0.81]	$P = 4.4 \times 10^{-4}$
***ATT		48968404 -	GER	0.287	GER	−3.81	[−5.80, −1.82]	$P = 2.0 \times 10^{-4}$	GER	2.31	[1.51, 3.62]	$P = 1.8 \times 10^{-4}$
		49270069	US	0.297	US	−1.84	[−3.22, −0.47]	$P = 8.7 \times 10^{-3}$	US	1.63	[1.23, 2.17]	$P = 6.7 \times 10^{-4}$
***GTC		48968404 -	GER	0.058	GER	0.86	[−2.99, 4.72]	$P = 0.661$	GER	0.76	[0.29, 1.93]	$P = 0.567$
		49270069	US	0.051	US	−2.36	[−5.14, 0.42]	$P = 0.097$	US	1.16	[0.68, 1.97]	$P = 0.587$

CI, confidence interval; GER, German (*BOMA* study); MA, minor allele; nsSNP, non-synonymous coding SNP; OR, odds ratio; *P*, *p*-value; US, US American Europeans (*GAIN*/*TGen* study).

[a] SKAT cross-study mega-analysis of individual-level *BOMA* and *GAIN*/*TGen* data on chromosome 15, hg38: chr15:48965004 - 49464789 bp (*quantitative GAF*: linear model, *GAF extremes*: logistic model; adjusted for sex, illness duration, and study; see Methods for details). SKAT-derived *p*-values (*P*) summarize the joint influence of the available 44 SNPs in this LD-block on *quantitative GAF* and *GAF extremes*.

[b] Displayed are single-SNP analyses of additive minor allele effects on functional outcome for the five most strongly associated SNPs and the enclosed nsSNP *rs11854184* in the significant LD-block. Analyses within studies are adjusted for sex and illness duration. Studies were meta-analytically combined by Fisher's *p*-value pooling. A protective minor allele effect is indicated by a positive regression coefficient beta > 0 (*quantitative GAF*, linear model) and odds ratio OR < 1 (contrast between *GAF extremes*, logistic model); beta < 0, OR > 1 for risk minor alleles. Minor allele dosages of all five strongly associated SNPs are pairwise strongly positively correlated, and negatively correlated to the minor allele dosage of putative nsSNP *rs11854184*.

[c] Individual best-estimate haplotypes were nonambiguous on the last three positions and grouped accordingly. The three most frequent haplotype groups had the identifying nucleobase combinations GCC, ATT, GTC at rs586758, rs2086256, rs1904317; nucleotide base combinations at rs4474633, rs11854184, rs2413930 varied (indicated by ***). For haplotype groups, an additive haplotype effect on functional outcome was tested in each study, with adjustment for sex and illness duration. Effects (beta, OR) are specified per haplotype copy. A protective haplotype effect is indicated by a positive regression coefficient beta > 0 (*quantitative GAF*, linear model) and odds ratio OR < 1 (*GAF extremes*, logistic model); beta < 0, OR > 1 for risk haplotypes.

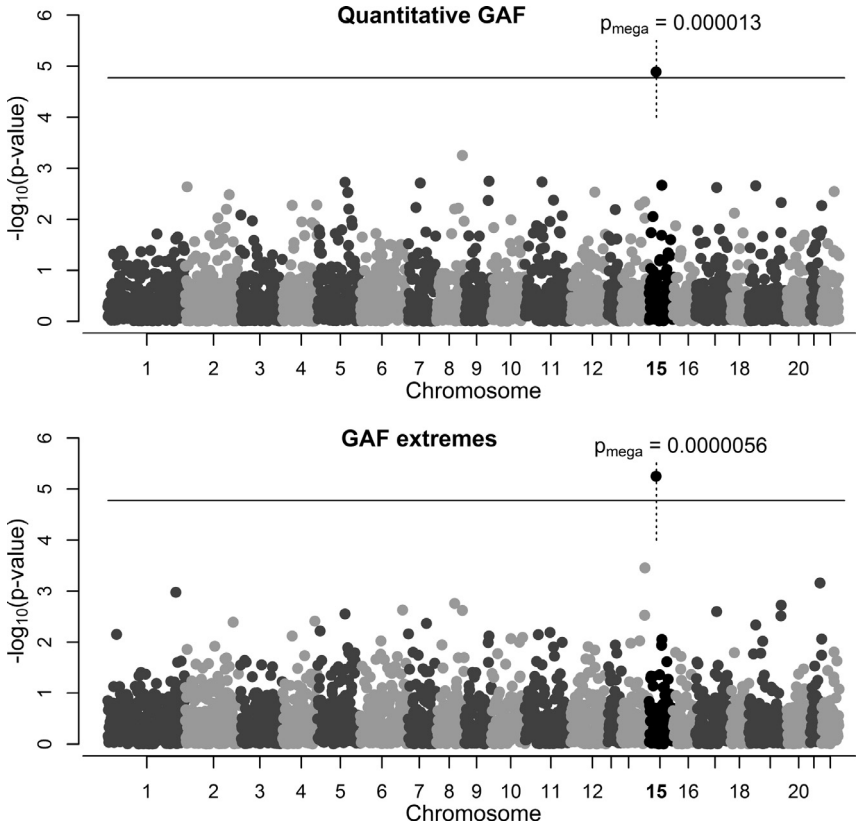

Fig. 1 Mega-analysis of GAF in German and European American BD outpatients, adjusted for sex and duration of illness. Manhattan-like plots display SKAT-derived *p*-values on the 2957 tested putatively functionally relevant LD-based genomic regions (cross-study mega-analysis of individual-level *BOMA* and *GAIN/TGen* data). Significance (horizontal line, Bonferroni $\alpha = 0.05/2{,}957 = 1.7 \times 10^{-5}$) was reached for both *quantitative GAF* and *GAF extremes* for an LD-block on chromosome 15 (hg38: chr15:48965004 - 49464789 bp). The dashed vertical line highlights the coinciding location of significance.

ies into more powerful common effect estimates. Mega-analysis also increased *specificity* since discordant effect directions across studies will (partially) cancel into small(er) average effects, which suppresses their detection. SKAT exact *p*-values were obtained by Davies method (Davies, 1980). For the 2957 SKAT tests performed, the multiple-testing adjusted significance threshold was $\alpha = 1.7 \times 10^{-5}$ (Bonferroni).

2.3.3. FIERS - step III: detailed insight into significant regions

For the 44 SNPs in the detected significant LD-block, single-SNP association tests were performed within studies and meta-analytically combined between studies by Fisher's *p*-value pooling (Fisher, 1925). Furthermore, individual best-estimate haplotypes on the five most strongly associated SNPs and an enclosed nsSNP were determined with PLINK. Haplotype association was analyzed within studies assuming an additive model of the effect of a haplotype or group of haplotypes, combining results meta-analytically across studies by Fisher's *p*-value pooling.

3. Results

FIERS tested 2957 putatively relevant LD-based regions. Fig. 1 displays Manhattan-like plots of SKAT-derived *p*-values from cross-study mega-analysis of individual-level *GAIN/TGen* and *BOMA* data. SNP correlations within LD-based blocks were subsumed by SKAT tests. Hence SKAT tests of LD-based blocks are largely independent of one another. The traits *quantitative GAF* (all subjects) and *GAF extremes* (lowest versus highest study quartile) both identified the same significant LD-block on chromosome 15 (hg38: chr15:48965004 - 49464789 bp; *quantitative GAF* $p_{mega} = 1.3 \times 10^{-5}$, *GAF extremes* $p_{mega} = 5.6 \times 10^{-6}$).

Of the 44 SNPs contained in this associated LD-block (see Supplement for summary statistics), 26 had consistent single-SNP effects across studies and meta-analysis *p*-values $p_{meta} < 0.05$ for both traits (Fisher's *p*-value pooling of studies). Eighteen of these SNPs even had *p*-values $p_{study} < 0.05$ in both studies and traits (Fig. 2, top and middle panel). The five top-ranked SNPs ($p_{meta} < 5 \times 10^{-5}$, Table 1) have strongly positively correlated minor allele dosages ($r > 0.67$); rs586758 and rs1904317 are nearly synonymous ($r = 0.998$). In the vicinity lies a nsSNP (rs11854184); its minor allele dosage is negatively correlated with that of the five top-ranked SNPs (range $= -0.25 > r > -0.34$). Individual best-estimate haplotypes on these six SNPs (estimated with PLINK) were nonambiguous on the last three positions and grouped accordingly. This revealed a protective haplotype group (***GCC, *quantitative GAF:* $p_{meta} = 1.1 \times 10^{-5}$, *GAF extremes:* $p_{meta} = 4.6 \times 10^{-6}$) and a risk haplotype group (***ATT, *quantitative GAF:* $p_{meta} = 2.4 \times 10^{-5}$, *GAF*

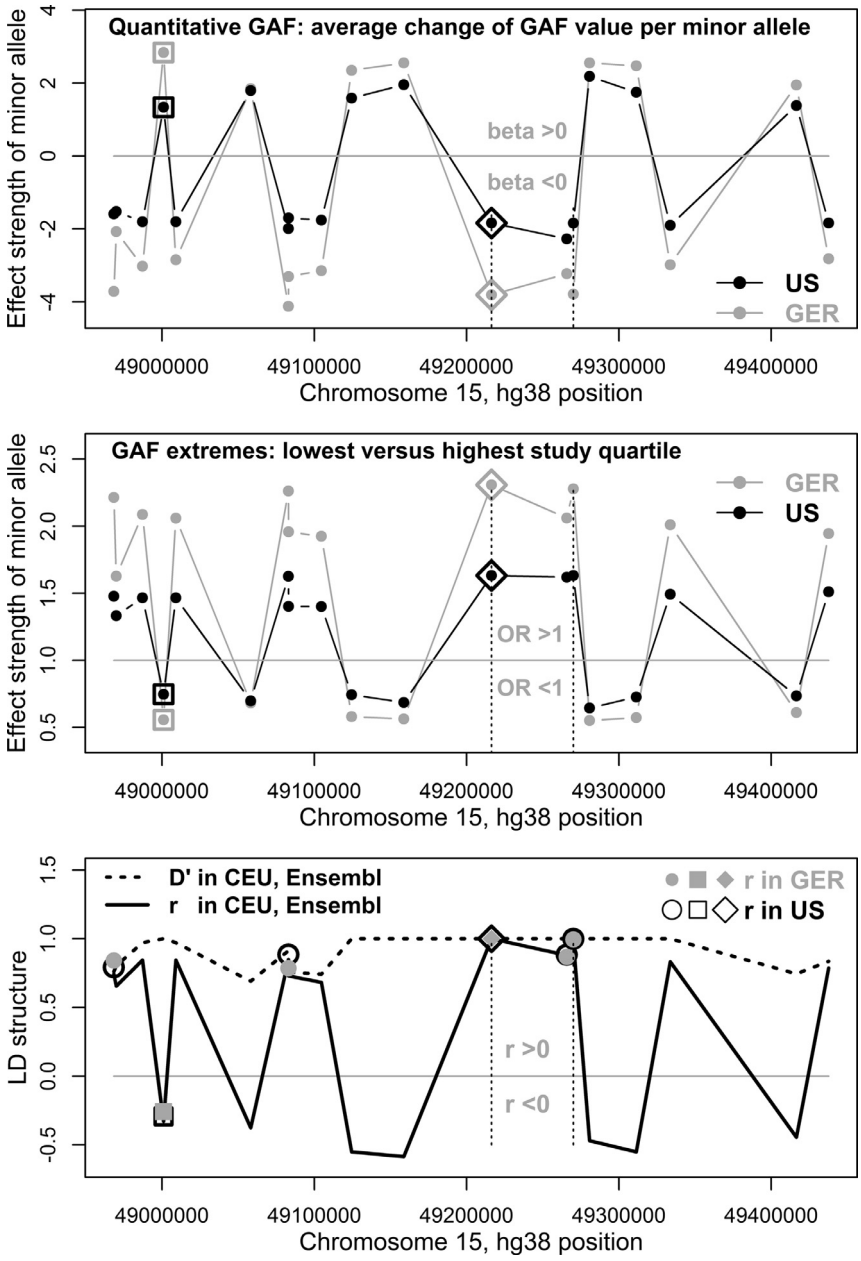

Fig. 2 Consistent effect strength across BD outpatient samples.
In the associated LD-block hg38: chr15:48965004 – 49464789 bp, estimated minor allele effects were consistent across studies (US: *GAIN*/*TGen*, GER: *BOMA*) for *quantitative GAF* (top, additive effect per minor allele) and *GAF extremes* (middle, multiplicative effect per minor allele; within-study single-SNP analyses, adjusted for sex and illness duration). Results are displayed for 18 SNPs that had *p*-values $p_{study} < 0.05$ in each study and for nsSNP rs11854184 (square). Sign of effect estimates (risk: beta < 0, OR > 1; protective: beta > 0, OR < 1) corresponds to the correlation *r* of minor allele dosages (bottom panel, solid line) with *CTCF* binding site rs586758 (diamond). The latter is part of the discovered rs586758 – rs2086256 – rs1904317 haplotype (vertical lines, hg38: chr15:49216375 – 49270069 bp) and yielded the strongest association evidence among the 5 top-ranked SNPs ($p_{meta} < 5 \times 10^{-5}$, Table 1 middle panel). The 5 top-ranked SNPs have strongly positively correlated minor allele dosages ($r > 0.67$ bottom panel, *BOMA*: filled symbols, *GAIN*/*TGen*: open symbols; square: nsSNP rs11854184). Lines (*D'*: dashed, *r*: solid) display the highly similar LD structure of a CEU reference population (1000 Genomes phase 3, northern and western European ancestry, obtained from Ensembl (Cunningham et al., 2015, http://www.ensembl.org/).

extremes: $p_{meta} = 2.0 \times 10^{-6}$, Fisher's *p*-value pooling of studies). Between-study consistency of haplotype association is displayed in Table 1. A consistent reduction or increase of the risk of poor GAF, respectively, was also observed in all members of the two haplotype groups that were frequent enough for separate association testing (data not shown).

4. Discussion

Functional outcome in outpatient care is an important cross-diagnostic indicator for course of psychiatric disorder, clinically highly relevant, and highly variable in BD. To the best of our knowledge, this is the first SNP-based investigation into the genetic basis of GAF in outpatient care. Despite moderate sample size, we identified a significant genomic region by introducing the efficient test strategy FIERS. Plausibility of our finding on chromosome 15 (hg38: chr15:48965004 – 49464789 bp) is supported by consistency of effect strength between independent BD patient samples (Fig. 2) and between genotyped (*BOMA*) and imputed SNPs (*GAIN/TGen*). Moreover, further underlining plausibility, the association evidence centers at a functional SNP, and the associated region overlaps with and lies in the vicinity of genes that are relevant for neuronal differentiation and function (see below).

Single-SNP and haplotype analyses indicate that nsSNP rs11854184 is not likely responsible for the association. The reduced power of rs11854184 compared to the top-ranked SNPs (Table 1) cannot sufficiently be explained by its lower minor allele frequency. In contrast, rs586758 displayed the strongest single-SNP association, was part of the discovered haplotypes (G/A position) and is a *CTCF* binding site (Cunningham et al., 2015). *CTCF* sites regulate groups of genes within a chromatin domain.

GAF is not a measure of cognition and may deteriorate in psychiatric disorder for several reasons as it comprises social, occupational, and psychological functioning into a single score. Nevertheless, functional outcome and degree of cognitive impairment are significantly associated in BD and schizophrenia patients (Bowie et al., 2010). Furthermore, GAF scores and cognitive performance were lower in healthy carriers of neuropsychiatric copy-number-variants compared to non-carriers (Stefansson et al., 2013). The novel associated haplotype reported herein is located in the promoter flanking region of the *COPS2* gene (COP9 signalosome subunit 2, also known as *TRIP15*, *CSN2*, *ALIEN*), near microRNA4716 as plausible biological candidates. *COPS2* is involved in cell cycle regulation and DNA repair, mediates gene silencing, and participates in modulating hormone response and cell proliferation (Papaioannou, 2007). Moreover, functional studies demonstrated that *COPS2* plays crucial roles in neuronal differentiation and development as well as in maintaining neuronal functions (Akiyama et al., 2003; Chaerkady et al., 2011). Adjacent to the significantly associated LD-block, three additional genes are of interest: upstream *EID1* (EP300 interacting inhibitor of differentiation 1) which influences synaptic plasticity and memory function (Liu et al., 2012) and *SHC4* (Src homology 2 domain containing family member 4, also known as *ShcD*) which contributes to the regulation of neuronal function through mediation of the tyrosine kinase receptor TrkB downstream signaling pathway (You et al., 2010). Downstream, gene *DTWD1* (DTW domain containing 1) has previously been implicated in a pharmacogenomics study on side-effects of antidepressant treatment (Clark et al., 2012). Hence it is conceivable that *DTWD1* regulation through *CTCF* binding at rs586758 might alter GAF by altering side-effects of psychopharmacological medication and hence medication adherence.

A particular strength of this study is the test strategy. FIERS contributes to more powerful analyses of existing genome-wide data in general and even enables successful genomic analyses of moderately sized samples. Using general prior knowledge on putative function and LD, FIERS better focused association screening on relevant parts of the genome which greatly reduced the number of statistical tests performed. Across GWAS, small *p*-values are especially enriched among SNPs that are in LD with specific functional elements (Schork et al., 2013). FIERS exploits this by jointly testing SNPs within *LD-based regions* opposed to only testing functionally annotated SNPs. Among the variety of functional annotations that may be used to select LD-blocks *a priori,* nsSNPs have been most extensively validated so far. Currently, SIFT and PolyPhen provide one of the most widely accepted and accurate (Saunders and Baker, 2002) annotations (nsSNPs) whereas it is still difficult to annotate and predict non-coding SNPs (Li and Wei, 2015). Analyzing nsSNP-containing LD-blocks focused this analysis on protein-coding regions of the genome with the extension that exploiting LD putatively included additional information from SNPs with other functionalities as well.

A further strength of this investigation is cross-study mega-analysis, i.e. joint analysis of individual-level data across studies within SKAT. With appropriate covariate-adjustments, mega-analysis uses the data most efficiently and yields the greatest power. Mega-analysis within SKAT assumed concordant SNP effects across studies. This increased sensitivity for detecting replicable genetic effects and increased specificity by suppressing detection of discordant effects. In comparison, meta-analysis by Fisher's *p*-value pooling of separately analyzed covariate-adjusted studies was less sensitive and less specific but confirmed the reported significance on chromosome 15, albeit with lower power (data not shown). If mega-analysis should become infeasible (e.g., because studies have different covariates to accommodate or individual-level data cannot be shared), SKAT score statistics may also meta-analytically, i.e. on the level of summary statistics, account for between-study concordance of SNP effects (Lee et al., 2013).

Mandatory for power of any statistical method is that size of the unit of analysis (LD-block, gene, pathway) and model complexity (main effects, genetic interactions) are appropriate in relation to available sample size. Although large from a clinical perspective, available sample size was a study limitation. We mastered this challenge by testing putatively functionally relevant LD-blocks for main effects. For larger samples, natural extensions are analyzing genes or pathways and allowing for genetic interactions (Liu et al., 2007). In general, summary statistics on biological units either use select representative SNPs (Li et al., 2011, 2012) or aggregate association evidence from *all* contained SNPs. Aggregation is easily, exactly, and powerfully accomplished

by SKAT on individual-level data. In contrast, tedious corrections for SNP correlations are required when aggregating single-SNP *p*-values, e.g. by Fisher combination test (de Leeuw et al., 2016; Li et al., 2011). Other *p*-value based joint tests such as count-based (SNP-ratio or hypergeometric test) and rank-based (Kolmogorov–Smirnov) enrichment statistics suffer similar drawbacks as the Fisher combination test but with lower power (de Leeuw et al., 2016). Using representative SNPs instead of fully aggregating all evidence is more powerful only when causal SNPs are greatly outnumbered within tested SNP sets (Li et al., 2011) or when causal SNPs cannot share association signals well with other SNPs, e.g., due to low minor allele frequency (Li et al., 2012). Analogously, single-SNP tests may be more powerful than aggregate tests if associations are strong but involve very few SNPs only (Chen et al., 2014). Otherwise, SKAT is very often among the most powerful methods, and is robustly powerful for a broad range of genetic architectures (see below) (Chen et al., 2014; Li et al., 2012). Since SKAT tests combine individual-level information of multiple SNPs and their correlations, they exploit most of the information used in genotype imputation – without doing imputation (Howey and Cordell, 2014). SKAT can also analyze sequence and rare variants (Malzahn et al., 2016; Wu et al., 2011). However, LD should always be estimated on sufficiently frequent SNPs to avoid premature division of LD-blocks. As a self-contained test (de Leeuw et al., 2016), SKAT evaluates whether any of the jointly tested SNPs associates with a trait of interest. Aggregation of associations (multiple loci, pathway effects) but also relatively localized yet sufficiently strong associations such as polygenes or minor genes within pathways may make SKAT significant. This consideration hardly makes a difference for the LD-block analyses presented herein. However, it highlights that for correct *data interpretation*, genetic architectures underlying SKAT significances should be examined.

So far, the success of psychiatric genetics is largely based on the strategy of founding large consortia for case-control studies. However, data on clinically important *quantitative* phenotypes is still limited, largely due to high costs of deep phenotyping and lacking harmonization of assessment scales and conditions across studies. Owing to this, a potential limitation of the present investigation is that only two independent studies were available. That significance was reached in the total sample but not in single studies is typical for GWAS which commonly regard consistency of effect estimates across studies (Fig. 2) as additional conclusive evidence. Nevertheless, our consistent finding that rs586758 – rs2086256 – rs1904317 haplotype ATT carriers (*BOMA*: 49.2% ± 4.3%, *GAIN/TGen*: 50.6% ± 3.0%) have lower GAF values would require additional independent validation. Furthermore, no information on medication or medication adherence was available and GAF assessment differed to some extent between studies. GAF was assessed at a *time point* (*BOMA*: pre-admission), or *averaged* over a period (*GAIN/TGen*: past month) during which the state of illness, although sufficiently remitted for outpatient care, may have varied. Statistical analyses were adjusted for between-study differences of GAF values. Nevertheless, differences of GAF assessment might yield phenotypes with slightly different underlying biological mechanisms. This may explain why genetic effects in the associated region (Table 1 and Fig. 2), while consistent across studies, were slightly stronger in the putatively better remitted *BOMA* sample compared to *GAIN/TGen*.

GAF is an overall rating of a patient's psychological, social and occupational functioning. While clinically highly relevant and commonly used, a single overall score also presents some limitations. Specifically, GAF scores lack information regarding which of the three domains was most impaired and most decisive for individual overall rating. For example, a suicidal person with well-functioning relationships and good performance at his or her job would be assigned a very low GAF score. Hence future research may proceed by operationalizing functional outcome with a more differentiated measure like e.g. the functioning assessment short test (FAST; Rosa et al., 2007). Furthermore, when analyzing GAF scores, it would be of interest to stratify or adjust analyses with respect to concomitant symptom severity. Unfortunately, we did not have sufficient data for this, which is a study limitation.

While low GAF scores may occur in psychiatric patients for clinically different reasons, the generality of the GAF can also be seen as an advantage: GAF is applicable across different psychiatric diagnoses that share a common polygenic background (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Forstner et al., 2017; Purcell et al., 2009) and could be an indicator of a more general resilience/ vulnerability factor. Hence it would be of great interest to analyze GAF or other measures of functional outcome also in other psychiatric disorders, such as schizophrenia, and jointly in patients with different psychiatric disorders.

Conflicts of interests

John I. Nurnberger Jr. is a consultant and investigator for Janssen and an investigator for Assurex. All other authors declare no conflicts of interests.

Author contributions

DM and TGS designed the study. Data (sample collection, phenotyping, genotyping, quality control, linkage disequilibrium boundaries, pathway information) were provided by SF, NA-R, SA, JAB, WHB, CSB, WB, SC, WC, DWC, FD, HJE, TF, AJF, JF, ESG, FSG, TAG, YG, MH, LH, BJK, DLK, WBL, CL, PBM, MGM, FJM, SMM, TWM, SSM, CMN, JIN Jr, EAN, JBP, DQ, JR, JCR, WAS, NJS, TS, PDS, ENS, FS, JS, SS, JT, SHW, PPZ, PZ, SZ, JRK, MMN, MR and TGS. DM conducted the statistical analyses. Data were interpreted by all authors. DM and MB wrote the manuscript. All authors critically reviewed the manuscript and have approved the final version.

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Supplementary material

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Supplementary Table 1: Summary statistics of the 44 SNPs in the significant region

				Effect on *quantitative GAF*					**Effect on *GAF extremes***				
				German BD patients		US European BD patients		Meta-analysis	German BD patients		US European BD patients		Meta-analysis
SNP	CHR	Position	MA	Effect: $beta_{GER}$	$P_{quantitative\ GAF,\ GER}$	Effect: $beta_{US}$	$P_{quantitative\ GAF,\ US}$	$P_{quantitative\ GAF,\ meta}$	Effect: OR_{GER}	$P_{GAF\ extremes,\ GER}$	Effect: OR_{US}	$P_{GAF\ extremes,\ US}$	$P_{GAF\ extremes,\ meta}$
rs12906122	15	48965004	T	-3.41	0.00313	-0.85	0.280	0.00704	1.86	0.00941	1.34	0.0584	0.00468
rs4474633	15	48968404	A	-3.72	0.000162	-1.59	0.0199	0.0000439	2.21	0.000225	1.48	0.00398	0.0000133
rs11631087	15	48969988	G	-2.07	0.0303	-1.52	0.0232	0.00580	1.63	0.0158	1.33	0.0296	0.00404
rs7173509	15	48979887	T	0.35	0.720	0.29	0.681	0.840	0.92	0.670	0.99	0.914	0.913
rs8037958	15	48987209	A	-3.02	0.00153	-1.80	0.00778	0.000147	2.09	0.000495	1.47	0.00399	0.0000279
rs11854184	15	49000997	A	2.84	0.0157	1.34	0.115	0.0132	0.56	0.0217	0.75	0.0801	0.0128
rs7167402	15	49009096	A	-2.85	0.00272	-1.80	0.00778	0.000249	2.06	0.000657	1.47	0.00399	0.0000363
rs4457942	15	49016326	T	-3.26	0.0979	-3.10	0.0135	0.0101	2.17	0.0666	1.68	0.0419	0.0192
rs8029751	15	49031658	A	-2.00	0.0532	-1.19	0.0978	0.0326	1.70	0.0161	1.37	0.0257	0.00364
rs4775798	15	49037239	A	-3.59	0.0330	-1.54	0.167	0.0341	2.41	0.0233	1.22	0.354	0.0479
rs7177541	15	49050433	A	-2.67	0.0153	-1.05	0.163	0.0174	1.92	0.00559	1.44	0.0155	0.000896
rs10519206	15	49058222	T	1.85	0.0460	1.79	0.00740	0.00306	0.68	0.0466	0.70	0.00624	0.00266
rs11070681	15	49066320	G	-3.34	0.00866	-0.81	0.296	0.0179	1.92	0.0125	1.38	0.0393	0.00425
rs2413930	15	49083018	T	-4.12	0.000202	-1.99	0.00488	0.0000146	2.26	0.000513	1.63	0.000715	0.00000580
rs2413931	15	49083128	C	-3.31	0.00126	-1.70	0.0125	0.000190	1.96	0.00215	1.40	0.0112	0.000279
rs2413932	15	49091284	C	0.89	0.408	-0.10	0.894	0.732	0.82	0.364	1.02	0.908	0.696
rs12148348	15	49104667	C	-3.15	0.00217	-1.76	0.0101	0.000258	1.92	0.00268	1.40	0.0122	0.000370
rs11633810	15	49124549	C	2.35	0.0118	1.59	0.0151	0.00172	0.58	0.00631	0.74	0.0233	0.00144
rs3088333	15	49140891	T	0.62	0.595	0.18	0.824	0.840	0.88	0.580	0.91	0.560	0.690
rs12915792	15	49146129	T	0.57	0.730	-1.51	0.270	0.518	0.89	0.739	1.58	0.114	0.292
rs2413935	15	49158747	C	2.55	0.00626	1.95	0.00260	0.000196	0.56	0.00414	0.69	0.00366	0.000183
rs586758	15	49216375	A	-3.81	0.000198	-1.84	0.00881	0.0000249	2.31	0.000177	1.63	0.000670	0.00000201
rs17396612	15	49257746	G	0.56	0.620	0.70	0.363	0.561	0.89	0.618	0.82	0.184	0.361
rs2086256	15	49265829	T	-3.23	0.000905	-2.27	0.000833	0.0000114	2.06	0.000655	1.62	0.000441	0.00000464
rs1904317	15	49270069	T	-3.79	0.000202	-1.84	0.00867	0.0000249	2.28	0.000196	1.63	0.000670	0.00000221
rs16962243	15	49270535	T	-3.17	0.00439	-1.11	0.143	0.00527	1.97	0.00399	1.48	0.0103	0.000456
rs11854557	15	49280763	C	2.55	0.00944	2.19	0.00126	0.000147	0.55	0.00517	0.64	0.00126	0.0000840
rs7177959	15	49293782	A	0.57	0.730	-1.54	0.261	0.507	0.89	0.739	1.58	0.114	0.292
rs11635005	15	49309228	T	0.50	0.673	0.008	0.993	0.938	0.90	0.649	0.93	0.660	0.791
rs7179127	15	49311418	T	2.47	0.00796	1.75	0.00716	0.000614	0.57	0.00501	0.73	0.0130	0.000695
rs2078024	15	49329413	G	0.56	0.622	0.53	0.493	0.669	0.89	0.618	0.84	0.232	0.422
rs10851475	15	49333733	A	-2.99	0.00194	-1.90	0.00512	0.000124	2.01	0.000984	1.49	0.00305	0.0000411
rs16962414	15	49384692	G	1.40	0.460	-1.81	0.209	0.322	0.60	0.222	1.58	0.128	0.130
rs16962418	15	49392588	T	0.30	0.860	-1.88	0.175	0.435	0.84	0.608	1.64	0.0924	0.218
rs12591300	15	49412544	A	1.88	0.0601	0.97	0.154	0.0527	0.69	0.0765	0.78	0.0686	0.0328
rs1904316	15	49416513	C	1.95	0.0381	1.38	0.0332	0.00972	0.61	0.0169	0.73	0.0168	0.00260
rs1429555	15	49419900	A	1.10	0.531	-0.13	0.918	0.838	0.66	0.294	1.03	0.894	0.614
rs12592277	15	49436562	A	0.58	0.599	0.25	0.755	0.811	0.91	0.656	0.93	0.631	0.779
rs4316697	15	49437728	A	-2.82	0.00524	-1.84	0.00933	0.000535	1.94	0.00265	1.51	0.00291	0.0000986
rs7168316	15	49441549	T	0.42	0.705	0.32	0.685	0.834	0.89	0.595	0.92	0.597	0.723
rs4338740	15	49443100	C	0.22	0.836	0.87	0.248	0.533	0.87	0.496	0.84	0.225	0.357
rs11634375	15	49457351	T	0.81	0.424	-0.52	0.444	0.503	0.79	0.240	0.98	0.886	0.542
rs11639111	15	49457538	T	1.96	0.0439	0.24	0.711	0.139	0.77	0.188	0.87	0.299	0.218
rs4480740	15	49463645	A	1.69	0.0871	0.94	0.162	0.0741	0.83	0.346	0.82	0.138	0.194

Abbreviations: CHR, chromosome; GER, German (*BOMA* study); MA, minor allele; OR, odds ratio; P, p-value; Position, hg38 position on chromosome 15; SNP, single nucleotide polymorphism; US, US American Europeans (*GAIN/TGen* study).

Single-SNP analyses of additive minor allele effects on functional outcome in outpatient care (*quantitative GAF* and *GAF extremes*) for the 44 SNPs located in the significant LD-block. Analyses within studies are adjusted for sex and duration of illness. Studies were meta-analytically combined by Fisher's p-value pooling. To aid visual inspection of this table, all p-values were rounded to the first three relevant digits. A protective minor allele effect is indicated by a positive regression coefficient beta>0 (*quantitative GAF*, linear model) and odds ratio OR <1 (contrast between *GAF extremes*, logistic model); beta<0, OR>1 for risk minor alleles. Eighteen SNPs had p-values $p_{study}<0.05$ in both studies (GER: *BOMA*, US: *GAIN/TGen*) and both traits *(quantitative GAF* and *GAF extremes*); the sign of estimated minor allele effect (risk or protective) corresponds to the sign of the correlation of minor allele dosage (positive or negative) with *CTCF* binding site rs586758 (see Figure 2).

Appendix

Publication list

2019

Comes AL, Senner F, **Budde M**, […], Falkai P, Schulze TG, Papiol S. 2019. The genetic relationship between educational attainment and cognitive performance in major psychiatric disorders. Transl Psychiatry. *9*:210.

Mullins N, Bigdeli TB, Børglum AD, […], **Budde M**, […], Kendler KS, McQuillin A, Lewis CM. 2019. GWAS of Suicide Attempt in Psychiatric Disorders and Association With Major Depression Polygenic Risk Scores. Am. J. Psychiatry. *176*:651-660.

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Drange OK, Smeland OB, Shadrin AA, […], Psychiatric Genomics Consortium Bipolar Disorder Working Group, […], Djurovic S, Dale AM, Andreassen OA. 2019. Genetic Overlap Between Alzheimer's Disease and Bipolar Disorder Implicates the MARK2 and VAC14 Genes. Front. Neurosci. *13*: 220.

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Budde M, Friedrichs S, Alliey-Rodriguez N, […], Rietschel M, Schulze TG, Malzahn D. 2019b. Efficient region-based test strategy uncovers genetic risk factors for functional outcome in bipolar disorder. Eur. Neuropsychopharmacol. *29*: 156–170.

Budde M, Anderson-Schmidt H, Gade K,[…], Falkai P, Schulze TG, Heilbronner U. 2019a. A longitudinal approach to biological psychiatric research: The PsyCourse study. Am. J. Med. Genet. Part B Neuropsychiatr. Genet. *180*: 89–102.

Kalman JL, Papiol S, Forstner AJ, […], **Budde M**, […], Nöthen M, Rietschel M, Schulze TG. 2019. Investigating polygenic burden in age at disease onset in bipolar disorder: Findings from an international multicentric study. Bipolar Disord. *21*: 68–75.

2018

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2017

Witt SH, Streit F, Jungkunz M, […], **Budde M**, […],Schmahl C, Bohus M, Rietschel M. 2017. Genome-wide association study of borderline personality disorder reveals genetic overlap with bipolar disorder, major depression and schizophrenia. Transl. Psychiatry *7*: e1155.

Bahari-Javan S, Varbanov H, Halder R,[…], **Budde M**, […], Dityatev A, Sananbenesi F, Fischer A. 2017. HDAC1 links early life stress to schizophrenia-like phenotypes. Proc. Natl. Acad. Sci. U. S. A. *114*: E4686–E4694.

Budde M, Forstner AJ, Adorjan K, Schaupp SK, Nöthen MM, Schulze TG. 2017b. [Genetics of bipolar disorder]. Nervenarzt *88*: 755–759.

Budde M, Degner D, Brockmöller J, Schulze TG. 2017a. Pharmacogenomic aspects of bipolar disorder: An update. Eur. Neuropsychopharmacol. *27*: 599–609.

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Anderson-Schmidt H, Adler L, Aly C, […], **Budde M**, […], Falkai PG, Rietschel M, Schulze TG. 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. Eur. Arch. Psychiatry Clin. Neurosci. *263*: 695–701.

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Demiroglu SY, Skrowny D, Quade M, […], **Budde M**, […], Helbing K, Heilbronner U, Schulze TG. 2012. Managing sensitive phenotypic data and biomaterial in large-scale collaborative psychiatric genetic research projects: practical considerations. Mol. Psychiatry *17*: 1180–1185.

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