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ORIGINAL PAPER

Neurobiology of the major psychoses: a translational perspective on brain structure and function—the FOR2107 consortium

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Abstract

Genetic (G) and environmental (E) factors are involved in the etiology and course of the major psychoses (MP), i.e. major depressive disorder (MDD), bipolar disorder (BD), schizoaffective disorder (SZA) and schizophrenia (SZ). The neurobiological correlates by which these predispositions exert their influence on brain structure, function and course of illness are poorly understood. In the FOR2107 consortium, animal models and humans are investigated. A human cohort of MP patients, healthy subjects at genetic and/or environmental risk, and control subjects ($N=2500$) has been established. Participants are followed up after 2 years and twice underwent extensive deep phenotyping (MR imaging, clinical course, neuropsychology, personality, risk/protective factors, biomaterials: blood, stool, urine, hair, saliva). Methods for data reduction, quality assurance for longitudinal MRI data, and (deep) machine learning techniques are employed. In the parallelised animal cluster, genetic risk was introduced by a rodent model (Cacna1c deficiency) and its interactions with environmental risk and protective factors are studied. The animals are deeply phenotyped regarding cognition, emotion, and social function, paralleling the variables assessed in humans. A set of innovative experimental projects connect and integrate data from the human and animal parts, investigating the role of microRNA, neuroplasticity, immune signatures, (epi-)genetics and gene expression. Biomaterial from humans and animals are analyzed in parallel. The FOR2107 consortium will delineate pathophysiological entities with common neurobiological underpinnings ("biotypes") and pave the way for an etiologic understanding of the MP, potentially leading to their prevention, the prediction of individual disease courses, and novel therapies in the future.

Keywords Cohort study · Animal model · Mental disorder · Etiology · Course of illness

Introduction

The major psychoses (MP), i.e. major depressive disorder (MDD), bipolar disorder (BD), schizoaffective disorder (SZA) and schizophrenia (SZ) are common, chronic, costly and debilitating disorders. Their etiology and pathophysiology remain largely elusive. They are caused by a complex interplay of genetic susceptibility and environmental factors. The MP share a familial risk, with genetic correlations estimated around 0.4–0.7 using molecular genetic methods [1, 2]. Similarly, brain structural studies have reported convergence of effects across the MP [3–6]. Beneficial environmental factors (such as social support) may interact with risk genes in the development of resilience [7, 8]. Little is known about the neurobiological correlates (humans) and causal processes (animal models) of these protective as compared to risk factors.

The mechanisms by which epidemiologically validated risk factors exert their influence on neurobiology, the onset and course of illness remain largely elusive. Understanding these pathways is inevitable for improving prognosis and developing new treatment approaches for modifying or even reversing the detrimental effects of these risks. Hence, there is a pressing need for large-scale, deeply phenotyped, human, longitudinal studies that reach the size of

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epidemiological cohorts [9, 10]. Functional and structural neuroimaging provides a particularly useful tool for bridging the gap between risk factors and clinical presentations by providing a layer beyond symptoms and behaviour [11].

Animal models must parallel human correlational cohorts for establishing causal mechanisms [8]. Ideally, human and animal studies will mutually inform each other regarding novel mechanisms and targets, which can then be validated further in a human sample or mechanistically explored in animal models.

A number of molecular mechanisms have been discussed in the etiology of the MP [12–14]. Altered immune mechanisms [15–17], dysfunctions in neuroplasticity [18, 19] such as abnormal dendritic arborisation, dendritic spine morphology, and reduced altered neurogenesis [20, 21] among others have been implicated in the MP. In rodents, miRNAs were found to regulate cellular phenotypes associated with MP, including the plasticity of dendrites and spines [22–26], expression of neurotransmitter receptors [27–29], and synaptic plasticity [30–33].

Genome-wide association studies (GWAS) are a powerful approach to identify the genetic underpinnings of disorders. In several independent GWAS the *CACNA1C* gene has been implicated as a major shared risk gene across the MP. *CACNA1C* codes for the α1C subunit of the voltage-gated L-type calcium channel (LTCC) Cav1.2. It plays a pivotal role in regulating neuronal excitability, synaptic plasticity, and gene expression. Cav1.2 thus represents a primary target for both drugs and second messengers acting on LTCCs [13, 14]. However, the associated variants in *CACNA1C* are found in its intronic region, and the neurobiological mechanisms whereby such variants modify brain structure and function are not well understood [34–38].

In our research consortium briefly outlined here, we have integrated a large, multi-omics, longitudinal cohort study with deeply phenotyped humans and a parallelised animal model to constitute a neurobiologically informed, pathophysiological model for the etiology and the course of major psychoses.

Research programme

The research consortium FOR2107 comprises a human cohort and animal models. All human subjects ($n = 2500$) have been deeply phenotyped (see Table 2) and are followed up after 2 years. In complementary animal and cell models, gene by environment (GxE) risk and protective factors on brain structure and function are being mechanistically explored. The clinical (human) and experimental (animal) cluster are tailored to reflect each other regarding selected environmental and genetic risk/protective factors and phenotyping procedures (Fig. 1). They include, among others, the characterization of brain structure and function, miRNA biogenesis and profiles, immune signatures, (epi-)genetic analyses and gene expression.

The main aims of the FOR2107 are

1. Establishing consequences (humans, animals), respectively, neurobiological mechanisms (animals) of genetic and environmental risk factors for the major psychoses, particularly on the level of brain structure and function in humans and animal models.
2. Uncovering neurobiological determinants for the course of illness (onset, relapse, diagnostic shifts e.g., from MDD to BD, alterations in brain structure and function over time).
3. De novo subgrouping of homogeneous patient groups based on biological, cognitive, and psychopathological longitudinal data ("biotypes").

Objectives

(a) Baseline deep phenotyping of $N = 2500$, subjects with genetic and/or environmental risk factors, and controls (see Table 1).
(b) Second deep phenotyping after follow-up of 2 years of all participants (see Table 1). Data are stored in professional database and biobank.
(c) Provide reliable neurobiological markers for diagnostic switches (e.g., MDD to BD or SZ). Ultimately, a standardized diagnostic toolkit using clinical, neuroimaging and molecular markers could be provided for early detection and specific treatment of potential individual "switchers".
(d) Implementation and development of MR imaging standards for large-scale clinical MRI studies in a longitudinal design [39].
(e) Development and refinement of statistical analysis tools for clustering multi-dimensional and longitudinal data (including machine learning techniques), facilitating the identification of characteristic genotype–phenotype signatures of MP and their courses.
(f) Acquire information regarding the role of three epigenetic processes (DNA methylation, histone modification, miRNA) in the etiology and clinical course of MP.
(g) Deep phenotyping of GxE rat models for MP, including risk and protection factors, with correspondence to those in the human cohort.
(h) Establishment of miRNAs for the longitudinal course of MP, cross-correlation with functional studies in GxE rodent models.
(i) Analysis of novel immunological markers as biomarkers for the longitudinal course of MP, cross-correlation with functional studies in GxE rodent models.

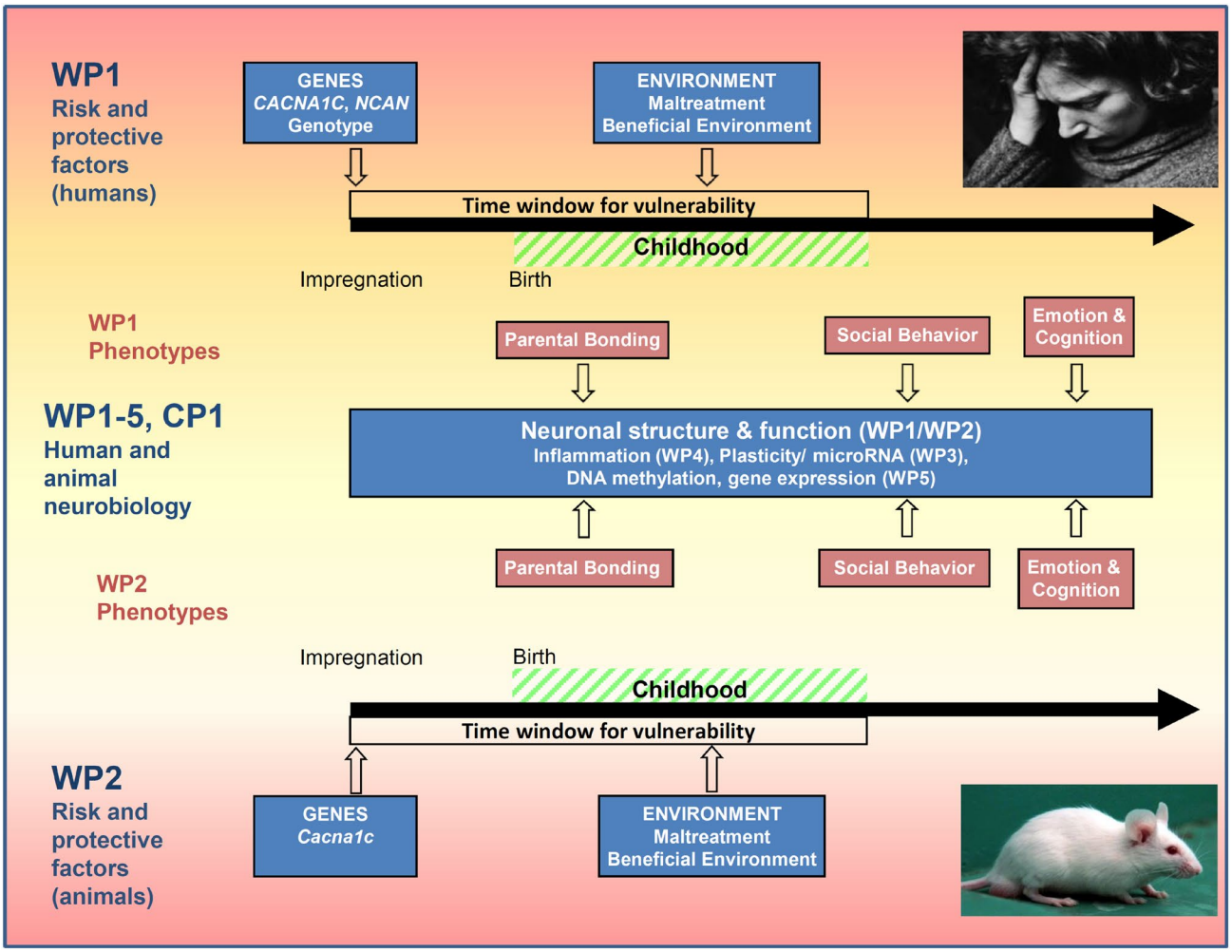

Fig. 1 Parallel structure of the human and animal clusters. A common genetic risk factors in the human and animal part is (blue boxes) CACNA1C. Common environmental risk factor is maltreatment, protective factor is a beneficial environment [such as social support (humans)/enrichment (animals)]. Common phenotypes are (red boxes): bonding; social behavior; emotion and cognition. *WP* work project, *CP* central project

(j) Analysis of selected causal effects of GxE risk on brain structure and function in animals.
(k) Cooperation and biobanking with the national DGPPN cohort, DFG KFO 241; further collaboration with other large-scale imaging studies for validation (BMBF BiDirect, BMBF BIPOLIFE, BMBF PROTECT-AD, DGBS) resting state initiative, SHIP/ SHIP-TREND, and others. Regarding data sharing policy, collaborators submit their suggestions to one of the authors, i.e. a short outline of their project or data analysis strategy. This will be evaluated by the data sharing committee (elected PIs), and if positive, data are transferred to the collaborators.

Work programme

Below we will describe the human (Work Package 1; WP1) and the animal backbone studies (WP2), the microRNA (WP3), the immunological (WP4), (Epi-)genetic (WP5), machine learning, statistics and quality control (WP6) and biobank (CP1) projects. The study and all procedures have been approved by the respective local Ethics committees and by the data protection committees, and are in accordance with the Declaration of Helsinki.

Table 1 Inclusion and exclusion criteria of the FOR2107 study population ($n = 2500$)

Condition	Affective disorders (MDD $n = 700$; BD $n = 300$)	Psychotic disorders (SZ $n = 200$; SZA $n = 100$)	Group			
			Healthy subjects without risks ($n = 1000$)	Healthy subjects, genetic risk ($n = 200$)[e]	Healthy subjects, environmental risk ($n = 200$)[f]	Healthy subjects, environmental and genetic risk ($n = 100$)[e,f]
Verbal IQ > 80	+	+	+	+	+	+
West-European ancestry	+	+	+	+	+	+
MRI compatibility[a]	+	+	+	+	+	+
Substance-related disorders	–	–[c]	–	–	–	–
History of severe neurological b or medical disorders[d]	–	–	–	–	–	–
At least one 1st degree relative with life time diagnosis MDD or BD	+	+	–[e]	+	–[e]	+
At least one CTQ-subscale reaching the threshold for maltreatment	+	+	–[f]	–[f]	+	+
Family history of any psychiatric disorder	+	+	–	–[g]	–	–[g]
Current psychotropic medication	+	+	–	–	–	–
Current benzodiazepine use	–[i]	–[i]	–	–	–	–
Past or present SCID-diagnosis[h]	+	+	–	–	–	–

[a]Exclusion due to, e.g., metal implants, pacemakers, claustrophobia, pregnancy, etc.

[b]E.g., seizures, stroke, multiple sclerosis, dementia, traumatic brain injury

[c]In case of SZA and SZ cannabis abuse is tolerated, these patients are included, other comorbid substance-related diagnoses are excluded

[d]E.g., cancer, auto-immune disorders, chronic inflammatory diseases, and cardio-vascular diseases

[e]Subjects with at least one relative with the diagnosis of MDD or BD

[f]At least one subscale of the CTQ reaching the threshold for maltreatment

[g]Include in case of family history (fist degree relative) of MDD or BD is inclusion criterion, otherwise exclude

[h]SCID-confirmed diagnosis of MDD and BD (any polarity); according to DSM-IV criteria (296.xx) or SZ (295.1-3/295.9); and SZA (295.7). Dysthymia and cyclothymia are not inclusion criteria, but are allowed as comorbid disorders within any patient group

[i]Wash-out of > 3 half-lives required to be included (within patients only)

Deeply phenotyped human longitudinal cohort (WP1)

Subjects

We have characterized $n = 2500$ individuals across 6 samples with the T1 battery at baseline (first subject in 9/11/2014). We re-evaluate these subjects with the T2 battery after 2 years of follow-up at Marburg and Münster Universities, Germany. See Table 1 for inclusion and exclusion criteria and Table 2 for acquired data:

1. $n = 700$ patients suffering from MDD.
2. $n = 300$ patients suffering from BD.
3. $n = 200$ patients suffering from SZ.
4. $n = 100$ patients suffering from SZA.
5. $n = 500$ healthy subjects at genetic risk ($n = 200$), environmental risk ($n = 200$) or both ($n = 100$).

Table 2 Data acquired at baseline T1 and after 2 years of follow-up T2

Psychopathology		Baseline	Follow-up
Diagnosis (DSM-IV)	SCID-I, II [1]	X	X
Psychiatric symptoms	OPCRIT 4 [2]	X	X
Personality	SPQ-B [3], NEO-FFI [4]	X	
	TAS-20 [5], ADP-IV [6]		X
Attachment style	RSQ [7]	X	
Subclinical affective symptoms	TEMPS-M [8]		X
Subclinical psychotic symptoms	CAPE [9]		X
Anhedonia	SHAPS-D [10]	X	
Depression level	BDI-II [11], HAMD [12]	X	X
Suicidality	SBQ-R [13]		X
Anxiety	STAI-T [14]	X	
	STAI-S [14], HAMA [15]	X	X
	PROMIS I-VI/ CROSS-D [16], ASI-3 [17]		X
Positive symptoms	SAPS [18]	X	X
Negative symptoms	SANS [19]	X	X
Mania symptoms	YMRS [20]	X	X
Clinical course	Life chart [21]	X	X
Global/social functioning	GAF [1]	X	X
	SOFAS [22], FAST [23], WHODAS 2.0 [24]		X
Physical activity	IPAQ [25]		X
General symptoms	SCL-90-R [26]	X	X
Lithium response	Alda-Skala [27]		X
MRI			
fMRI	Emotion processing [28]	X	X
	Memory [29]	X	X
	Subliminal face processing [30]	X	X
	Resting state	X	X
sMRI	T1	X	X
	DTI	X	X
General data			
Family history		X	X
Sociodemographics		X	X
Ethnical background		X	X
Employment/salary		X	X
General health	SF-36 [31]	X	X
Smoking	FTQ [32]	X	X
Alcohol consumption	Audit	X	X
Drugs		X	X
Diet	FFQ2 [33]		X
Past and current medication		X	X
Handedness	HQ [34]	X	
Neuropsychology			
Memory	VLMT [35]	X	X
Verbal intelligence (IQ)	MWT-B [36]	X	X
Executive function	TMT-A and -B [37], digit-coding	X	X
Semantic processing	Verbal fluency [38]	X	X
Attention	d2 [39]	X	X
Verbal working memory	Letter–number span [40]	X	X
Visuospatial WM	Block span	X	X

Table 2 (continued)

Psychopathology		Baseline	Follow-up
Risk factors			
Maltreatment	CTQ [41]	X	X
Maltreatment in childhood and youth	ACE [42]	X	
Life events	LEQ [43]	X	X
	THQ [44]	X	
Perceived stress	PSS [45]	X	X
Obstetric complications		X	
Protective factors			
Social support	F-SozU [46]	X	X
Positive life events	Life event-Q [47]	X	
Parental bonding	PBI [48], FEB	X	
Resilience	RS-25 [49]	X	X
Biomaterial			
EDTA blood	Sarstedt tubes EDTA	X	X
PAX gene	PAX-gene tube	X	X
Cell separation	BD Vacutainer CPT 1&2	X	X
Urine	Sterile and DNA-free PE tubes white	X	X
Feces	Sterile and DNA-free stool sample tubes (PE)	X	X
Hair	Sterile and DNA-free Eppendorf tubes	X	X
Heparin blood	Sarstedt tube heparinzed	X	X
Serum blood	Sarstedt tube serum	X	X

For references, please see supplementary material

6. $n = 1000$ healthy subjects without any of these risk factors.

MRI scanning

The MRI scanning consists of T1-weighted high-resolution anatomical images, a DTI sequence and four fMRI paradigms: (1) face matching. This paradigm is widely published and robustly elicits amygdala responses to fearful and angry faces (e.g., [40–42]). (2) Episodic memory encoding and retrieval. This face-encoding task induces robust activation of the hippocampal formation and cortical areas during episodic memory processes [43–45]. A retrieval task is presented outside the scanner. (3) Subliminal affective priming. This task uses an event-related subliminal priming design presenting affectively neutral faces from a standardized battery [46–49]. (4) Resting state sequence. All MRI sequences were kept as similar as possible in Marburg and Münster, which was possible due to the same scanner platform (Siemens 3T) [39]. The MRI battery takes less than 60 min scanning time in one session.

Measures for data quality assurance

We have introduced several measures for quality assurance regarding MRI data, human phenotype data, as well as biomaterial processing, storage, and distribution.

MRI data We have implemented a comprehensive quality assurance (QA) protocol for assessing the general quality of the MRI data, to detect potential malfunctions in the scanning equipment, and to evaluate inter-site differences that need to be accounted for in subsequent analyses. The QA protocol is based on the regular measurement of an MRI phantom and an extensive variety of published QA statistics [39]. Human MRI data were assessed including the following procedures: All structural images are visually inspected by trained staff and processed with the SPM CAT12-Toolbox providing ratings for image noise and bias. All gray matter segments undergo the "check data quality using covariance" procedure, which additionally identifies segmentation outliers due to anatomical abnormalities and/or artifacts. All image abnormalities are categorized as (A) exclusion of all participant data (e.g., due to pathologies meeting exclusion criteria a posteriori), (B) exclusion of all MRI data only due to anatomical abnormalities without pathological significance (e.g., abnormally large ventricles; these participants will be followed up but without MRI), (C) exclusion of structural MRI data only due to image artifacts (but will be invited for follow-up MRI). Finally, the "check data quality using covariance" is able to robustly detect dual participation of subjects.

For all fMRI data, movement parameters are extracted, allowing for exclusion of participants due to excessive head

movement for each paradigm. Furthermore, individual activation maps (1st level data) are generated for each subject and paradigm in an automated pipeline showing the "effects of interest" contrast at an exploratory threshold. These images are inspected for "abnormal" activation, e.g., non-activation of the visual cortex, artifacts at tissue borders, etc. All individual MRI quality measures are entered into the Coordination Centre for Clinical Trials (KKS) Marburg database.

Phenotype data Interview ratings are conducted by trained PhD students at both sites according to detailed SOPs. All raters undergo standardized training, and interviews are regularly supervised and videotaped. Videotaped interviews are regularly rated by all other raters, reliability measures are generated and potential mismatches of ratings are discussed and fine-tuned. Problematic cases are discussed at a weekly conference. Currently, the overall intra-class correlations (ICC) across all videotaped interviews are HAMD (ICC = 0.918), HAMA (ICC = 0.959), YMRS (ICC = 0.829), SANS (ICC = 0.845), and SAPS (ICC = 0.923).

Rating and questionnaire sets from the probands are generated as PDF files with an individualized barcode for each subject and are handed out in paper form. These forms are then scanned (using Remark Office OMR software) under quality-controlled conditions based on an annotated CFR (aCRF) (1st quality control) and converted to a database-compatible file structure. Through the data import pipeline, all datasets are checked for plausibility (e.g., range of values, missing data) according to comprehensive aCRFs. For each data import, quality control protocols are generated which gives the data quality manager an immediate and detailed feedback and enables to correct data directly (2nd quality control). By implementing a mirrored test server, this process is repeated until the error rate is zero percent (i.e. error reduction loop). Once this value is reached, data sets are released for export and can be downloaded. Pseudonymization is used for data storage for all subjects. Data storage and supervision of data management according to GCP Guidelines lie with the KKS Marburg.

Biomaterial All biomaterial acquisition is performed by thoroughly trained technical staff, according to SOPs. The quality is constantly monitored by trained staff; the biobank has been certified (http://www.cbbmr.de).

Animal backbone study (WP2)

In WP2, we experimentally address the question how *Cacna1c* affects brain structure and function by studying the effects of *Cacna1c* haploinsufficiency in rats. To this aim, we use a newly developed genetic *Cacna1c* rat model and compare wild-type ($Cacna1c^{+/+}$) and constitutive heterozygous ($Cacna1c^{+/-}$) males and females. Initially, we perform deep and longitudinal behavioral phenotyping in $Cacna1c^{+/-}$ rats as compared to $Cacna1c^{+/+}$ littermate controls, including both sexes and spanning the period from early postnatal days to adulthood. For behavioral phenotyping of rat models for neuropsychiatric disorders, several readouts with face validity to human core symptoms are available [50]. This includes psychomotor activity (e.g., open field behavior), behavioral despair/passive coping to stress (e.g., immobility in the forced swim test), anxiety (e.g., elevated plus-maze), anhedonia (e.g., sucrose consumption), cognition (e.g., object recognition, attention, risk-taking), and social behavior. Regarding affect and social behavior, rodent ultrasonic vocalizations (USV) have become an important tool, which cannot only be used as readout of positive and negative affect, but also as a means to study a subject's responsiveness to social stimuli, which is of major importance in models of neuropsychiatric disorders, typically characterized by social deficits [51].

Rodents are highly social animals, displaying a rich repertoire of social behaviors and emitting distinct types of USV. Such USV serve as situation-dependent socio-affective signals [51]. In rats, three types of USV are known. Pups emit 40-kHz USV ("distress calls") when socially isolated from mother and littermates, probably reflecting a negative affective state akin to anxiety. Adult rats emit 50-kHz USV ("rat laughter") in appetitive situations such as social investigation and play or when exposed to psychostimulants, such as amphetamine, while 22-kHz USV ("alarm calls") occur in aversive situations such as predator exposure, fear conditioning or social defeat. Measuring USV emission does not only provide a unique tool to gauge affective states in rodents, but they also help to detect changes in affective information processing that are not detectable by conventional behavioral approaches. For instance, we found that maternal immune activation during pregnancy via poly-I:C affects the production of 22-kHz USV emitted during fear conditioning in adult offspring [52]. Poly-I:C administration to pregnant rats during specific gestational periods mimics a viral infection and leads to behavioral impairments in the offspring with relevance to neuropsychiatric disorders in humans. In our fear-conditioning paradigm, poly-I:C exposure during pregnancy caused an increase of 22-kHz USV emission to 300% of saline controls. However, despite this strong effect, a detailed analysis of visible behavior, including freezing, did not reveal any group differences, highlighting the importance of assessing 22-kHz USV as a measure of affective state. Most recently, we have introduced a novel technique to model mania-like elevated mood together with elevated drive. Specifically, we showed that amphetamine treatment leads not only to increased levels of locomotor activity but also to strongly enhanced levels of 50-kHz USV [53] and social responsivity [54], reflecting mania-like elevated mood

and heightened levels of social interest. Notably, amphetamine-induced 50-kHz calling can be blocked by lithium treatment [53]. This allows us to conduct pharmacological studies on the effects of potential anti-manic drugs in *Cacna1c* haploinsufficient rats, as compared to the gold standard lithium. All types of USV serve important communicative functions and induce call-specific behavioral responses in the receiver. While aversive 22-kHz USV induce freezing, indicating an alarming function, appetitive 50-kHz USV induce social approach behavior, suggesting that they serve as social contact calls [55]. These opposite behavioral responses are paralleled by distinct brain activation patterns (22-kHz USV: "fear circuit", e.g., amygdala; 50-kHz USV: "pleasure circuit", e.g., nucleus accumbens, where they evoke phasic release of dopamine [56]). Importantly, social approach evoked by playback of pro-social 50-kHz USV can be used as readout for detecting social deficits and is sensitive for aversive experiences during early development, such as post-weaning social isolation [57].

In a second step, we will apply a GxE interaction approach. Specifically, we will analyze whether an established maltreatment, namely post-weaning social isolation, can induce or exaggerate deficits in *Cacna1c* haploinsufficient rats, and whether beneficial environment, namely social and physical enrichment can prevent a deficit. Control subjects are kept in normal group housing. Besides deep and longitudinal behavioral phenotyping, we analyze brain neurochemistry (biogenic amines), hippocampal morphology and plasticity (neurogenesis), as well as neuronal activation patterns (immediate early genes). Together with the other WPs, we further study the role of the immune system and how microRNAs affect brain structure and function in a genotype-dependent manner, comparing *Cacna1c*$^{+/-}$ rats and *Cacna1c*$^{+/+}$ littermate controls exposed to different environmental conditions. In a first study, we showed that post-weaning social isolation leads to a strong increase in hippocampal miRNA-134 expression levels [58]. This effect was paralleled by an increase of an alternative transcript encoding for the ubiquitin ligases Ube3a and Ube3a1. In line with the behavioral alterations evident following post-weaning SI [57, 58], UBE3A duplications are among the most frequent copy number variations associated with social deficits and intellectual disabilities in humans [59]. It is planned to extend our current experimental approach by including additional rat models, e.g., with genetic modifications targeting *ANK3, NCAN*, or *TCF4*, in future projects.

miRNA (WP3)

microRNAs (miRNAs), a large family of small non-coding RNAs, have been demonstrated to control synaptic plasticity in hippocampal neurons in vitro and in vivo [60]. Studies suggest an important pro-resilient function of miRNA-dependent gene regulation in various stress-related diseases, including affective disorders (AD) [61]. However, it is not known how stressful events (e.g., maltreatment) impair miRNA function to promote depressive behaviur.

We pursue four different aims to test the hypothesis that impaired Ca^{2+}-dependent miRNA biogenesis at the level of the Dicer1 pre-miRNA processing complex is causally involved in the etiology of endophenotypes of MP in humans. First, we will attempt to characterize modifications of the Dicer1 complex in the rat hippocampus in response to maltreatment. Second, we will try to decipher the signaling pathways that are engaged in neurons of maltreated rats to control miRNA processing activity, with a focus on Ca^{2+}-dependent signaling cascades. The biomaterial for these biochemical and molecular biology experiments will be obtained from the rat gene–environment (GxE) cohort run in WP2. Third, in collaboration with WP2, we plan to restore activity of the Dicer1 complex in the hippocampus of maltreated rats by recombinant viral transgene expression and pharmacological treatment. Fourth, in collaboration with WP5, we will perform an integrative analysis of transcriptome and epigenome signatures of miRNA biogenesis factors based on large-scale longitudinal datasets from AD patients with childhood trauma and available data on course of illness. This extensive expression analysis will be complemented by the identification of rare genetic variants in miRNA biogenesis genes using genome-wide genotyping data of AD cohorts that are available through WP5.

In conclusion, our project promises to obtain novel insight regarding the function of altered miRNA activity in AD etiology and course of illness. Hence, miRNA biogenesis genes might emerge as novel candidates for biomarkers and treatment strategies.

Immunology (WP4)

Immune dysregulations represent a longstanding enigma in the pathophysiology of the MP [62]. For example, individuals diagnosed with AD exhibited elevated peripheral blood levels of pro-inflammatory cytokines, e.g., IL-1β, TNF, and IL-6 [63]. Besides that, early life stress such as childhood maltreatment was associated with long-term alterations in immune responses and concomitantly increased vulnerability to AD [63]. Studies in rodents and humans suggested a link between peripheral inflammatory cytokines and perturbed microglial function in the brain that may significantly contribute to depression-associated behaviur [64]. Since the underlying mechanisms of GxE interactions in MP and associated immune alterations are largely unknown, longitudinal studies are needed in humans exposed to GxE interactions and in related animal models to gain novel insights into immune signatures.

In WP4, we perform a longitudinal study in MP patients and in healthy participants of the FOR 2107 cohort, including those with familial genetic risk and exposure to early life stress (childhood maltreatment). We established a cellular large-scale multi-parameter flow cytometry screen for cell-type-specific characterisations of inflammatory responses in MP and immune signatures of specific cell subsets which shall harbor prognostic potential. Further, we investigate whether the altered immune signatures identified in patients are also associated with GxE risk interaction in the Cacna1c$^{+/-}$ rat model in conditions of social isolation or enriched environment in the presence or absence of an additional immune stimulus. The rat model and derived microglial cultures allow for mechanistic analyses of interactions between the altered peripheral immune capacity and neuro-inflammatory responses in defined GxE risk settings. Together, this translational approach will provide new insights into immune signatures in subsets of peripheral immune cells in animals and humans exposed to GxE risk factors for MP.

Integrative analyses of genetic, epigenetic, transcriptomic, and environmental vulnerability factors of affective disorders (WP5)

The aim of WP5 is to identify how genetic and environmental factors impact the etiology and course of MP, using genetic, epigenetic and transcriptomic methods. To achieve this aim, systematic genome-wide genotyping of FOR2107 probands is performed. Epigenome-wide methylation and expression profiles are assessed in a subsample at baseline and follow-up. Longitudinal analyses of the methylation and expression profiles are performed in relation to the course of illness or the occurrence of life events. This dataset allows us to further analyze the impact of the cumulative effect of genetic variation on subphenotypes. In addition, bisulfite sequencing analysis of CACNA1C is performed longitudinally in part of the sample.

Using data from different platforms, we perform integrative analyses of the genetic, epigenetic and expression data in collaboration with WP1, WP3, WP4 and WP6. This includes multimarker, polygenic and pathway analyses to identify yet undetected genotype–phenotype and GxE effects and the current large GWAS datasets of the PGC. The data are used particularly for in-depth analysis of genes which are interaction partners or in pathways of the risk gene CACNA1C. The results of our analyses will elucidate disease-specific factors, as well as factors which are of relevance across diagnostic boundaries.

Analyses of data generated so far have already led to several important findings. For example, besides CACNA1C, we also investigated further candidate genes for MP, such as *NCAN*, for which we showed an association with limbic gray matter deficits in healthy subjects and MDD patients [65]. Using genome-wide genetic data, it was demonstrated that polygenic risk for schizophrenia affects working memory and its neural correlates in healthy subjects [66]. With respect to common mechanisms in affective disorders, we identified shared risk loci and pathways for bipolar disorder and schizophrenia [67]. Results from a genome-wide analysis of microRNA-coding genes in BD suggest that BD-associated microRNAs might be enriched within known microRNA loci [68]. We expect that the wealth of forthcoming longitudinal data will further lead to a large number of important new insights.

Multimodal cross-disorder biotype identification and multi-method data analytic support (WP6)

Diagnosis and treatment in psychiatry still relies almost exclusively on a phenotype-based approach. Although this renders the validity of psychiatric classification questionable and severely hampers biomarker discovery, establishing a system of biologically meaningful groups—so-called biotypes—has remained elusive for decades. Building on the large-scale dataset acquired in the FOR2107, it is now finally possible to apply state-of-the-art tools from the fields of machine learning and multivariate statistics to a rich, multimodal database, thereby bringing robust biotype identification across disorders within reach.

In WP6, we identify and validate biologically plausible, homogeneous biotypes across disorders within and across modalities, enable a de novo subgrouping of homogeneous patient groups based on biological, cognitive, and psychopathological longitudinal data. Drawing on all other WPs, from molecular genetics to whole-brain neuroimaging, we will (1) employ domain-knowledge-based and deep learning-based automatic feature engineering to address the curse of dimensionality, (2) develop a principled approach to confounder removal in linear and non-linear multivariate models, and (3) ensure reliability and internal validity by optimizing cluster solution stability within and across modalities. Crucially, the longitudinal design of this FOR2107 allows us to assess the validity of our cluster solutions based solely on predictive utility. We will thereby directly use clinical relevance as the core criterion for evaluating clustering results. Specifically, predictive biomarker models, such as those designed to predict disease trajectory and outcome, will be trained using our cluster solutions. We expect them to substantially outperform the same models trained on classic disorder groups.

Within this framework, we are uniquely positioned to uncover biologically plausible patient clusters across disorders, which will strengthen the validity of psychiatric classification and crucially simplify biomarker discovery in the future.

Biobanking (CP1)

Structured biomaterial biobanks contribute to translational biomedical research by facilitating quality-controlled acquisition, processing, documentation and dissemination of human bio-specimens. A tailor-made biobank with specimens collected from FOR2107 probands (WP1) was implemented (http://www.cbbmr.de/da). Core of the repository is a large collection of blood compounds to allow deep phenotyping of probands by assessment of genetic, epigenetic, immunologic and physiologic parameters. In addition, stool and buccal swabs were collected for further microbiome analyses. We employed quality-controlled workflows which includes core processes such as recruitment, transport, processing, storage and dissemination for 12 different matrices collected within the biobank. Storage of sample data was organized in a secured and for the FOR2107 biobank parametrized section of biobank-information-management system CentraXX (Fig. 2).

Discussion and limitations

The FOR 2107 is an exemplary programme for translational research in mental disorder. Basic neuroscience research findings are applied in a large-scale, deeply phenotyped human longitudinal cohort. Experimental projects allow a multimodal evaluation of pathophysiological and causal etiological processes. The collected data range from behavioral, psychophysiological, neural and (epi)genetic to clinical self-report measures, thus linking various levels of information [see current R-DoC matrix, National Institute of Mental Health (NIMH), 2016] [69].

A particularly important feature is the longitudinal approach of the FOR2107 with a 2-year follow-up of all data domains and an in-depth characterization of clinical course and environmental factors during the follow-up interval. Large, longitudinal cohorts are largely missing in the field, particularly in neuroimaging research [70], although this is the only way to draw conclusions regarding temporal associations and causal mechanisms of clinical presentations and neurobiological underpinnings, and also for the prediction of clinical trajectories from baseline data. From smaller studies, there is evidence that neuroimaging markers can be related to specific aspects of disease course in major depression [71], and that differences in disease course severity are associated with brain volume changes over time [72].

A further advantage of longitudinal designs is the possibility to investigate to which extent baseline data can be employed to predict clinical outcomes regarding treatment response, relapse, and other aspects of longitudinal clinical presentations. It appears that single markers derived from univariate statistics are inferior compared to multivariate approaches, particularly machine learning techniques as implemented in WP6, e.g., using machine learning on still limited sample sizes, prediction of treatment response to psychotherapy [73] or electroconvulsive treatment [74] has been successfully shown. Furthermore, diagnostic features such as comorbidity [75], or the differentiation of unipolar and bipolar depression [5] have been predicted by machine learning on brain imaging data.

The data acquisition programme is time consuming and demanding for the human participants. This might have led to a sampling bias. As yet, dropout rates during baseline and after the 2-year follow-up are in line with comparable studies. The inclusion of comorbid diagnoses such as anxiety, somatoform disorders, or obsessive–compulsive disorder as a secondary diagnosis is useful to generalize findings. Multiple quality control procedures on all level of data acquisition and analyses minimize heterogeneity of primary data. Diagnoses are established via SCID interviews, done by trained psychologists. This is a high, international research standard and gives reliable results,

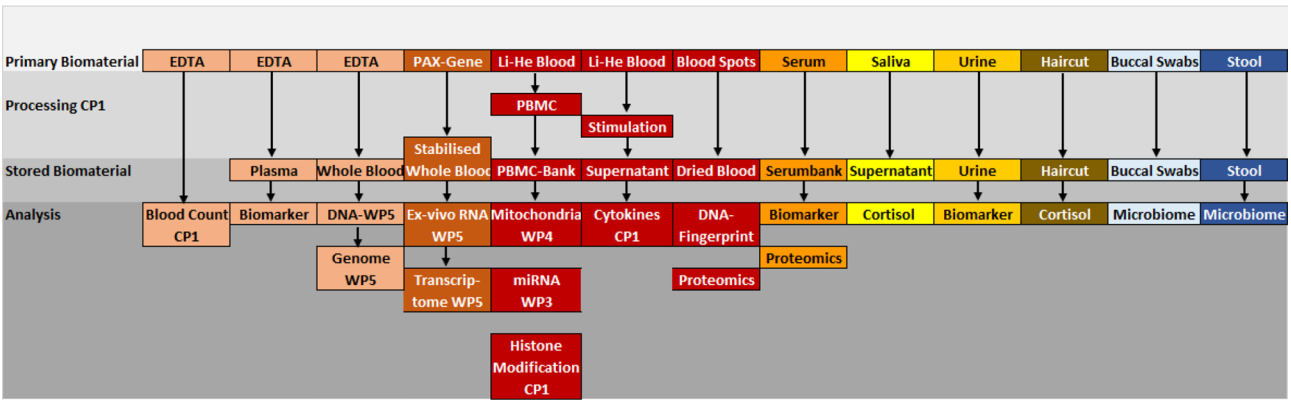

Fig. 2 Samples and processes of the biobank

which, however, might not be as valid as if the interviews were done by certified, experienced psychiatrists or psychotherapists.

In sum, the FOR2107 will make a large contribution to the understanding of molecular pathways and neurobiological mechanisms of genetic and environmental risk markers for affective disorders and their course. These results will serve future experiments in disentangling the mechanisms and pathways leading from individual biological risk factors to the clinical presentation of symptoms.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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