# TOWARD DISENTANGLING THE HETEROGENEITIY OF PHENOTYPES: MULTIVARIATE STATISTICAL APPROACHES IN NEUROIMAGING FOR PSYCHIATRIC PHENOTYPING

**INAUGURAL-DISSERTATION**

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INAUGURAL-DISSERTATION
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## ABBREVIATIONS

| | |
|---|---|
| AD | Axial diffusivity |
| BD | Bipolar disorder |
| CFA | Confirmatory Factor Analysis |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DTI | Diffusion Tensor Imaging |
| FA | Fractional anisotropy |
| IFOF | Inferior fronto-occipital fasciculus |
| ICD | International Classification of Diseases |
| MDD | Major Depressive Disorder |
| MSS | Multidimensional Schizotypy Scale |
| O-LIFE | Oxford-Liverpool Inventory of Feelings and Experiences |
| PCA | Principal Component Analysis |
| PQ | Prodromal Questionnaire |
| RDoC | Research Domain Criteria |
| ROI | Region of Interest |
| SEM | Structural Equation Model |
| SSDs | Schizophrenia-spectrum disorders |
| SPQ | Schizotypal Personality Questionnaire |
| SZ | Schizophrenia |
| SZA | Schizoaffective disorder |
| UF | Fasciculus uncinatus |

# 1. INTRODUCTION

## 1.1. Defining phenotypes in psychiatric epidemiology

*"Phenotype - The observable structural and functional characteristics of an organism determined by its genotype and modulated by its environment."*[1]

Over the past decades, the phenotype discussion became exceedingly relevant, especially for psychiatric epidemiology (Schulze & McMahon, 2004). In recent years, common approaches to define phenotypes in psychiatry are revisited. Rating the presence or absence of symptoms as defined by clinical diagnostic manuals like the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 1987) or the International Classification of Diseases (ICD) (Organization, 1993) is not sufficient to define a valid and reliable phenotype in psychiatry. The lifetime trajectory of the patients biological and environmental conditions has to be considered (Goldberg, 2015): Psychiatric disorders are not one-factorial, static entities but rather multi-factorial, dynamic constructs continuously influenced by space and time.

This is not new knowledge, but has been taught for decades in psychology, by a conceptual framework named the biopsychosocial model (Engel, 1977, 1981). The biopsychosocial model states that determination of health and illness is always an inextricably interplay of biological, psychological and social factors. All three factors by themselves are anchored on their very own continuum. But to explain the suprasystem of health and illness the continua must be merged. One attempt to transfer this conceptual framework into practical implications for psychiatric research represent the Research Domain Criteria (RDoC) (Cuthbert, 2015; Insel et al., 2010; Kozak & Cuthbert, 2016). The RDoC comprehend mental disorders as spectral dimension encompassing a biological, psychological and phenomenological facet rather than distinct entities.

Elucidating complemental and interpretable biological markers of psychiatric disorders can contribute to this by following the RDoC's proposed deep phenotyping in psychiatry (Gratton et al., 2022). For this, various neuroimaging methods offer a huge promise. However, the underlying

[1] http://www.genomicglossaries.com/content/genomics_glossary.asp

neurobiological mechanisms in psychopathology are still barely tapped (Jollans & Whelan, 2018; Schmaal et al., 2020; Sui et al., 2020). Reproducibility and generalizability of neuroimaging studies or Brain Wide Association Studies (BWAS) of psychiatric disorders is still lacking. Hence, BWAS alone cannot sufficiently contribute to optimize mental health phenotype definitions.

Fortunately, latest research in the field is more and more dedicated to explore reasons for this problem. Multiple studies have already provided potential key starting points for the advancement of evidence of psychiatric neuroimaging studies. Those include, amongst others: Very large sample sizes (Marek et al., 2022; Schmaal et al., 2020); using multivariate rather than univariate statistical approaches (Jollans & Whelan, 2018; Sui et al., 2020); combining data from multiple imaging modalities (Linden, 2012; Zhang et al., 2020); establishing new innovative behavioral measures and scan paradigms (Anderson et al., 2019; Rosenberg & Finn, 2022); validate models (Rosenberg & Finn, 2022); go for samples that actually show substantial variation in brain and behavior (Gratton et al., 2022); longitudinal studies (Jollans & Whelan, 2018).

The shared aim of these proposed and elaborated advances in psychiatric research is to overcome previous common approaches in the field and to provide reliable biomarkers for biologically based predictive models. This is needed as the high rates of comorbidity between mental disorders and the high heterogeneity of symptoms within single disorders limit the predictive power of symptom ratings only (Jollans & Whelan, 2018; Linden, 2012).

### 1.2. Common approaches in psychiatric neuroimaging research

*Univariate statistical analyses:* Mapping brain-behavior relationships with univariate statistical models is still one of the most common approaches in psychiatric neuroimaging research (Sui et al., 2020). The main characteristic of univariate approaches is the statistical manipulation of the brain in multiple separate entities (Mechelli et al., 2005). For the case of single-voxel-based analyses this means that an independent statistical test is run for each voxel (i.e., mass-univariate). This results in two major limitations of univariate statistical analyses:

First, depending on the image resolution, about 1,000,000 voxels are identified which equals 1,000,000 statistical tests, leading to 50,000 false positives at a significance level of $p<.05$ (Mechelli et al., 2005). Correction for multiple comparisons is therefore a necessity. However, it implies further considerations about the choice of a correction method as there are multiple options but no single standard convention (Whitwell, 2009; Zhuang et al., 2020).

Secondly, statistically separating the brain in form of univariate voxel-based analyses limits the results to only focally interpretable outputs. Inter-regional dependencies are not captured but a crucial hallmark of the brain network organization (Alexander-Bloch et al., 2013). Additionally, the issue of correlated noise is overlooked as well (Zhuang et al., 2020).

*Categorical (group comparison) analyses:* For a long time, group comparison analyses were considered the gold standard of mapping altered brain structure as well as function. These analyses assume that one categorical state of behavior is reflected by an altered state of brain structure or function. For example, the state of brain structure and function in a group of patients compared to the state of brain structure and function in healthy controls. Those case-control studies are important to broadly identify brain regions associated with an illness state and use them as potential key nods (or regions of interest, ROI) for more narrow-framed hypotheses or find the most *common* effects independent of their meaning (Bandettini et al., 2022; Jollans & Whelan, 2018). However, conclusions drawn from these approaches can only be used to infer further hypotheses about *group states* but for neither the *state* of an individual nor for individual *prediction* (Arbabshirani et al., 2017; Zhuo et al., 2019).

*Continuous (correlational) analyses:* Correlational analyses, as in form of multiple regression, aim to find a relationship between behavioral measurements and brain structure or functions. Typical correlational investigations in psychiatric neuroimaging research hypothesize a linear relationship between the amount of brain alterations and the amount of variation in the behavioral measurement score (Gratton et al., 2022). One advantage of this dimensional approach compared to the categorical approach is its applicability *within* one set of subjects. It therefore shows more sensitivity toward the spectrum of the investigated phenomenon. However, the complexity of the human brain as well as human behavior limits the explanatory power and

reliability of individual brain-behavior relationships (Gratton et al., 2022; Marek et al., 2022).

### 1.3. Sources of heterogeneity in psychiatric neuroimaging research

The above-mentioned limitations of common approaches in psychiatric neuroimaging research can be directly transferred into the sources of heterogeneity of evidence in psychiatric phenotype research (Satterthwaite et al., 2020). Due to the limited extend of this thesis, only three sources of heterogeneity will be outlined.

First, psychiatric disorders are highly heterogeneous disorders per se. In the case of Major Depressive Disorder (MDD), the DSM lists 9 possible symptoms of which 5 have to be present to fulfill the categorical diagnosis of MDD. Some of the symptoms, however, can be present in opposite directions in different patients (Goldberg, 2011). Hence, two patients showing a different composition of symptom representations both fall into the same DSM-diagnostic category. Subsequently, they will be treated as one group in neuroscientific group-comparison analyses. The same is true for the present state of manifestation: Patients with a concurrent diagnosis of a mental disorder are often placed within the same group as patients in full remission. Forming a heterogeneous phenotype group but assuming an underlying homogeneity when doing group-comparison analyses therefore produces a source of heterogeneity in biological results (Feczko & Fair, 2020; Voineskos et al., 2020).

Thereupon, focusing on comparisons of a single diagnostic group with healthy controls rather than looking at a dimensional system of psychopathology tends to neglect the apparent shared elements in psychopathology between different diagnostic categories (Bornovalova et al., 2020; Feczko & Fair, 2020). As previously mentioned, mental disorders are multidimensional constructs. Approaching psychiatric neuroimaging research only in a top-down manner by using beforehand descriptive categories possibly leads to unreproducible associations if the underlying biological grouping does not represent the diagnostic grouping in the first place (Ivleva et al., 2020).

Furthermore, different studies investigating neural correlates of the same psychological construct often use different measurements to assess this very construct. For example, for assessing the personality trait schizotypy, which is

an important construct for the comprehension of schizophrenia-spectrum disorders (Kwapil & Barrantes-Vidal, 2015), there are at least three commonly used scales for assessment today (Fonseca-Pedrero et al., 2021). Those measurements were developed in different manners and serve different purposes. However, neuroimaging studies tend to compare or generalize results emerging from correlations of the brain with one schizotypy measurement with studies using another schizotypy measurement. This leads to heterogeneity in the neural correlates found as, again, an assumption of homogeneity is made but the measurements used are heterogeneous.

### 1.4. Objectives and hypotheses

The studies in this thesis take a new look at commonly used approaches in psychiatric neuroimaging research in order to contribute to not only improving validity and reliability of psychometric acquisition but also to informing both hypothesis and data-driven imaging and phenotyping in psychiatry. In particular, focuses were on overcoming case-control approaches, application of multivariate statistical analyses on both a neuroimaging level as well as on a psychometric level to resolve inconsistency.

The first study's objective was a hypothesis driven approach applying Structural Equation Modeling (SEM) to integrate clinical variables and a brain structural measurement into one comprehensive multivariate statistical model. Based on a previous published SEM integrating key clinical variables of MDD (anhedonia, neuroticism, anxiety, and cognitive control (Liao et al., 2019)), the first aim of the first study was to successfully replicate this SEM in a new population of patients with MDD ($\mathbf{H_1}$). Secondly, based on previous white matter/diffusion tensor imaging (DTI) studies, we hypothesized anhedonia and neuroticism to be associated with white matter integrity in MDD ($\mathbf{H_2}$). Lastly, integrating the white matter associations into the SEM will show a good overall fit ($\mathbf{H_3}$).

The second study's objective used a data-driven approach applying cluster analysis to gyrification data across a large transdiagnostic patient cohort, in order to find homogeneous groups based on their gyrification pattern without prior imposed clinical grouping. We hypothesized that it is possible to identify patient subgroups among different psychiatric disorders by their pattern of

gyrification using cluster analysis (**$H_4$**). Furthermore, identified groups can be subsequently characterized clinically (**$H_5$**). Based on the multitude of previous studies using a group comparison design to successfully identify differences in gyrification between diagnostic groups, we expected to also find an apparent distinction of cluster groups in diagnoses (**$H_6$**).

The third study's aim was to address phenotypic heterogeneity by reassessing a commonly used transdiagnostically relevant phenotype, i.e., schizotypy. It aims to demonstrate how refining phenotypic assessment might improve neuroimaging studies in psychiatry. Based on previous studies we assumed, that schizotypy is a three-factorial construct but that the different schizotypy (sub)scales tap into different facets of schizotypy (**$H_7$**). Hereupon, we proposed a newly composition of factors (**$H_8$**).

## 2. AGGREGATION OF STUDY RESULTS

### 2.1. STUDY I: Brain structural connectivity, anhedonia, and phenotypes of major depressive disorder: A structural equation model approach

Reference: **Pfarr, J. K.**, Brosch, K., Meller, T., Ringwald, K. G., Schmitt, S., Stein, F., Meinert, S., Grotegerd, D., Thiel, K., Lemke, H., Winter, A., Waltemate, L., Hahn, T., Opel, N., Repple, J., Bauer, J., Jansen, A., Dannlowski, U., Krug, A., Kircher, T. & Nenadić, I. (2021). Brain structural connectivity, anhedonia, and phenotypes of major depressive disorder: A structural equation model approach. *Human Brain Mapping*, *42*(15), 5063-5074. https://doi.org/10.1002/hbm.25600

DTI studies have already gained important insights in the white matter integrity and brain structural connectivity in MDD. Case-control studies comparing the white matter microstructure of large cohorts of patients with MDD and healthy controls identified wide spread white matter alterations in MDD patients (Schmaal et al., 2017; van Velzen et al., 2020). Studies using correlational designs within patient cohorts found more specific associations of white matter alterations with single symptoms of MDD: Yang et al. (2017) and Coloigner et al. (2019) identified significant associations of fractional anisotropy (FA) with anhedonia, a core symptom of MDD, in fronto-limbic circuits as well as the cingulum and corpus callosum. Furthermore, neuroticism, an established risk factor for MDD, was found to be associated with white matter alterations in fronto-limbic circuits and the cingulum bundle as well (Madsen et al., 2009; Mincic, 2015). Thus, brain structural associations of both, anhedonia as well as neuroticism could potentially overlap in patients with MDD.

We investigated this potential brain structural overlap of anhedonia and neuroticism in MDD and further inter-relationships to other main symptom features of MDD. For this, a previous published SEM of clinical variables related to MDD was used as a basis for the final statistical design. The SEM by Liao et al. (2019) included inter-relationships of anhedonia, neuroticism as well as the important comorbid symptom of anxiety, and the cognitive parameter of cognitive control. Our study expanded the already existing model by including white matter associations of anhedonia and neuroticism into the SEM.

First, the original SEM by Liao et al. (2019) was replicated using a large cohort of MDD patients (N=595). In a second step, DTI analyses were performed to find significant associations of brain structural connectivity with anhedonia as well as neuroticism. In a last step, those brain structural associations were successfully implemented in the model. With this study, for the first time, a multivariate statistical design was used to acknowledge the interaction of multiple variables *and* multiple measures in MDD.

STUDY I was able to show, that different clinical variables (i.e., anhedonia, neuroticism) are associated with different DTI parameters as well as different white matter tracts in MDD. Anhedonia was correlated with FA in the right anterior thalamic radiation whereas neuroticism was correlated with axial diffusivity (AD) in the left inferior fronto-occipital fasciculus (IFOF) and fasciculus uncinatus (UF). This reflects and highlights the importance of respecting the heterogeneity of MDD on a biological level. Furthermore, the multivariate SEM clarified the interplay of neuroticism and cognitive control in MDD by elucidating the shared brain structural network as proposed in previous studies (Servaas et al., 2015). Results also have the potential to build a basis for future more differentiated “risk models” or models investigating transdiagnostic hypotheses.

*Manuscript contribution: 70%. JKP and IN conceptualized the study design. JKP conducted a literature review, developed the statistical design and performed the statistical analyses. JKP wrote the original draft of the manuscript and visualized study results. The other authors contributed to subject and data acquisition, data management, and review of the manuscript (KB, TM, KGR, SS, FS, SM, DG, KT, HL, AW, LW, TH, NO, JR, JB) as well as study supervision (AJ, UD, AK, TK).*

## 2.2. STUDY II: Data-driven multivariate identification of transdiagnostic gyrification patterns: A cluster analysis approach

Reference: **Pfarr, J. K.**, Meller, T., Brosch, K., Stein, F., Thomas-Odenthal, F., Evermann, U., Wroblewski, A., Ringwald, K. G., Hahn, T., Meinert, S., Winter, A., Thiel, K., Flinkenflügel, K., Jansen, A., Krug, A., Dannlowski, U., Kircher, T., Gaser, C.*, & Nenadić, I.* Data-driven multivariate identification of gyrification patterns in a transdiagnostic patient cohort: A cluster analysis approach. *NeuroImage*, *281*, 120349. https://doi.org/10.1016/j.neuroimage.2023.120349

Grey matter based parameters have the potential to serve as cortical phenotypes by exploring healthy as well as altered cortical development (Whitwell, 2009). Gyrification, in particular, indicates processes in early brain development which are connected to the evolution of higher cognitive functions (Lui et al., 2011). Multiple studies already investigated associations of regional gyrification among psychiatric disorders (Nenadic et al., 2015; Palaniyappan et al., 2011; Sasabayashi et al., 2021; Spalthoff et al., 2018) as well as related to specific psychopathological symptoms (Kubera et al., 2018; McIntosh et al., 2009; Sasabayashi et al., 2017; Schmitgen et al., 2019). Based on previous findings, gyrification has shown to be associated with vulnerability factors for psychopathology rather than manifested, current psychiatric symptomatology (Al-Haddad et al., 2019; Evermann et al., 2020; Pham et al., 2021; Sanfelici et al., 2022). However, previous studies lack a multivariate approach to investigate gyrification in psychopathology, which is important to elucidate potential heterogeneity of cortical folding within one disorder as well as transdiagnostic profiles (Sasabayashi et al., 2021).

Goal of STUDY II was to address this open question, namely whether gyrification patterns are associated with transdiagnostic vulnerability factors or risk, rather than separate diagnostic categories based on clinical interviews. Here, cluster analysis as a data-driven multivariate approach, was used to investigate this question: Cluster analysis is a useful tool to explore brain measurements without a given a priori hypothesis connected to clinical data. and can (sub)group high-dimensional biological data to identify neurobiological patterns (Lynch et al., 2020; Meng et al., 2021; Sanfelici et al., 2022).

In a large and clinically heterogeneous transdiagnostic cohort of patients (N=1028; MDD: n=783, bipolar disorder (BD): n=129, schizoaffective disorder (SZA): n=44, schizophrenia (SZ): n=72) cluster analysis was applied to gyrification data to identify biological patterns of this cortical phenotype. Subsequently, identified patient subgroups were associated with transdiagnostic factors of risk for psychopathology (i.e., early environmental risk factors and cognitive performance). To further explore the clustering solution in comparison to the classic clinical diagnostic grouping of patients, gyrification patterns of diagnostic groups were drawn as well.

Clustering results showed global gyrification patterns to be discriminative for three subgroups but not discriminative for clinical diagnostic groups. Newly formed subgroups showed significant differences in both gyrification as well as in cognitive performance and early environmental risk. Taken together with a lack of significance of diagnostic group analyses, our results underline transdiagnostic similarities rather than factors of gyrification being directly related to diagnostic categories. Furthermore, additional post-clustering analyses revealed that brain regions in association cortices had the highest impact on the formation of clusters. Also, the main differences in gyrification between the groups were mostly located in association cortices as well, hinting towards a higher variability and discriminative power of association cortices than other cortices.

Results of STUDY II identified important neurobiological underpinnings of gyrification and its relationship to global factors of psychopathology. The approach can serve as basis for further cluster analyses in (sub-)clinical as well as healthy or risk cohorts to investigate the potential of gyrification as a neurobiological marker for psychopathology proneness.

*Manuscript contribution: 65%. JKP, IN and CG conceptualized the study design. JKP conducted a literature review and performed the statistical analyses. JKP wrote the original draft of the manuscript and was responsible for visualization of the results. The other authors contributed to subject and data acquisition, data management, imaging preprocessing, and review of the manuscript (TM, KB, FS, FTO, UE, AW, KGR, TH, SM, AW, KT, KF) as well as study supervision (AJ, AK, UD, TK).*

## 2.3. STUDY III: Trait schizotypy and the psychosis prodrome: Current standard assessment of extended psychosis spectrum phenotypes

Reference: **Pfarr, J. K.**, Meller, T., Evermann, U., Sahakyan, L., Kwapil, T. R., & Nenadić, I. (2023). Trait schizotypy and the psychosis prodrome: Current standard assessment of extended psychosis spectrum phenotypes. *Schizophrenia research*, *254*, 208–217. https://doi.org/10.1016/j.schres.2023.03.004

Schizotypy is a multidimensional construct capturing schizophrenia-like behavioral traits and cognition. This phenotype reflects the vulnerability for multiple psychiatric disorders but especially for schizophrenia-spectrum disorders (SSDs) and thus represents an important concept for schizophrenia research (Barrantes-Vidal et al., 2015; Mason, 2015; Nelson et al., 2013). Alike schizophrenia, most research in schizotypy uses a three-factorial composition of schizotypy covering a positive, negative, and disorganized facet (Fonseca-Pedrero et al., 2021; Kwapil & Barrantes-Vidal, 2015). Beyond association with clinical features, schizotypy has already been successfully associated with genetic risk for SSDs (Kemp et al., 2021; Meller et al., 2019; Nenadić et al., 2022) as well as neurobiological correlates (Meller, Ettinger, et al., 2020; Meller, Schmitt, et al., 2020; Pfarr & Nenadić, 2020; Sahakyan et al., 2020). However, different conceptualizations of different schizotypy measurements make it difficult to directly compare results of biological correlates of schizotypy. This is, because it is not clear to what extend different schizotypy measurements actually capture one and the same construct. Also, it still remains unclear if measurements for prodromal and psychotic syndromes (i.e., the Prodromal Questionnaire (PQ) (Ising et al., 2012; Loewy et al., 2005)) are distinguishable in their scale-conceptualization from schizotypy measurements.

Hence, STUDY III aimed to scale the overlap and divergence of three commonly used schizotypy measurements (Multidimensional Schizotypy Scale (MSS) (Kwapil et al., 2018), Schizotypal Personality Questionnaire (SPQ) (Raine, 1991), Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) (Mason et al., 1995) and the short-form of the low-level screener for psychotic-like experiences of the PQ (PQ-16) (Ising et al., 2012). For this, schizotypy measurements as well as the PQ-16 were conducted from a young sample of

383 psychiatrically healthy participants. Subscale based descriptive analyses as well as correlations between all subscales were conducted. Multiple Principal Component analyses (PCAs) including all subscales of the schizotypy measurements as well as the PQ-16 were performed to extract both the best fitting factor structure as well as refined facets of schizotypy. Subsequently, the fit of these refined facets was tested using Confirmatory Factor Analysis (CFA).

Results of STUDY III show, that 1) included measurements do not discriminate well between a range of schizotypal experiences in a sample of highly educated, healthy subjects, 2) a three-factor model of schizotypy comprising a positive, negative, and disorganized factor is supported, and 3) when modelling new facets based on the subscale level of all measurements, a four-factor model including a separate neuroticism factor shows the best fit.

Conclusions for STUDY III therefore point toward a heterogeneity in operationalization of schizotypy which do not only affect comparability of studies but also affect the conceptualization of the construct of schizotypy per se. It is proposed, that a refined assessment of schizotypy, namely integrating the items of different schizotypy measurements and including a separate factor measuring will lead to better comparability between studies and moreover to a more distinguished operationalization of schizotypy.

*Manuscript contribution: 65%. JKP, IN and TRK conceptualized the study design. TRK performed statistical analyses. JKP conducted a literature review, wrote the original draft of the manuscript and was responsible for visualization of results. The other authors contributed to subject and data acquisition as well as data management and basic preprocessing (TM, UE, LS).*

## 3. GENERAL DISCUSSION

A key challenge in psychiatric neuroimaging is the search for optimized phenotypes and relating those to imaging marker. Research in the field has tended to focus on case-control studies on a univariate statistical level. This thesis provides a new look at approaches in psychiatric neuroimaging research on a biological as well as a phenotypic level: studies addressed the overarching issue of low reproducibility in the field by 1) calling into question the assessment of an important transdiagnostic phenotype (STUDY III), 2) applying multivariate statistical (as opposed to univariate) approaches as well as multivariate integration for phenotypic as well as neuroimaging analyses (STUDY I, II, & III), and 3) using hypothesis- (STUDY I & II) as well as data-driven approaches (STUDY III).

A current discussion is the lack of reproducibility and generalizability of neuroimaging studies paired with low effect sizes, which ultimately limits the studies' impact for extending psychiatric phenotyping (Gratton et al., 2022; Marek et al., 2022; Satterthwaite et al., 2020). Within the scope of reproducibility and generalizability, the studies in this thesis are dedicated to addressing the short-comings of BWAS. While BWAS are good at observing the most common effects over a large study cohort, the approach lacks determinants for elucidating the meaningfulness of these common effects (Bandettini et al., 2022; Gratton et al., 2022).

One of the challenges for finding optimized phenotypes is the heterogeneity within single disorders. Bandettini et al. (2022) describes this challenge in his paper by referring to the Anna Karenina effect (Finn et al., 2020) which stems from the first sentence of the correspondent novel by Tolstoy: "Happy families are all alike; every unhappy family is unhappy in its own way." (Tolstoj, 1877, book opening). It makes sense that there is no single neural correlate of depression when there is no single biological depression entity. Deriving potentially interesting brain areas from healthy populations and then comparing those in case-control studies to depression populations undermines the variability within this disorder (Bandettini et al., 2022; Ivleva et al., 2020; Lynch et al., 2020). Modelling this variability is an important step towards application of individualized psychiatric neuroimaging diagnostics and therapeutics (Finn et al., 2020). The multivariate SEM in STUDY I evolved from

hypotheses on intercorrelations of trait and states in MDD as well as associations with a popular brain measurement (DTI). It shows that by including different features of MDD in one comprehensive model enhances our understanding of the covariances between these features.

STUDY II focused on the challenge of population sorting and stratification and is directly related to the precedent mentioned challenge of heterogeneity within a single disorder. By sorting mental disorders in BWAS based on clinical diagnosis categorization the multidimensional nature of phenotypes is overlooked as the diagnostic categorization does not equally map on a biological level (Bandettini et al., 2022). The often a priori diagnosis-related grouping of brain morphometric measurements therefore restricts the power of these methods: assuming that there has to be a clear relationship of brain structure or function with a particular disease group overlooks the possibility that there are biological correlates which do not correlate with the disease manifestation itself (which is necessary for the clinical diagnosis) but appear meaningful for the disease trajectory for multiple mental disorders, i.e. shared risk factors. As neuroimaging studies of risk factors in healthy populations have their own challenges, multivariate data-driven approaches in clinical populations can find the neural underpinnings related to a particular brain measurement in a more distinctive way.

Basis of both of the above-mentioned challenges is the reliable assessment of the behavioral phenotypes. Without an agreement on operationalization of a behavioral measurement neuroimaging studies will always have at least one source that limits their reproducibility and generalizability (Gratton et al., 2022). Different measurements for one construct all have their right to exist as of course development of measurements follow the development of conceptualizations. This, however, needs to be addressed at a certain point to ensure reliability of studies exploring neuroimaging or genetic correlates of the constructs. In STUDY III, the personality trait schizotypy was investigated regarding its factor-structure and heterogeneous operationalization across measurements using the multivariate method of PCA. Results show indeed that schizotypy is conceptualized differently across the different measurement, which shows the need for a refinement of the multidimensional phenotype. This is not only necessary to assure

generalizability across studies but also leads to higher reliability as with a refinement of the measurement the multidimensional nature of the construct is captured more veridical.

### 3.1. Impact of multivariate statistical approaches in psychiatric neuroimaging research for phenotyping

The three studies in this dissertation all used multivariate statistical approaches (McIntosh & Mišić, 2013) to address three different sources of heterogeneity in psychiatric neuroimaging phenotyping: clinical heterogeneity within one disorder (STUDY I), imposed heterogeneity of brain measurements across clinical diagnoses (STUDY II), and heterogeneous assessment of a phenotype (STUDY III).

Hypothesis- driven, multivariate models like our SEM are important to explore practical implications of the RDoC for neuroimaging research (Sanislow et al., 2020): Following the RDoC framework, our SEM comprehends two different units of analyses (behavioral and neurobiological) to describe the relationship of MDD features while considering two major functional domains (cognitive systems-cognitive control; negative valence systems-anhedonia) (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/about-rdoc; last visited on 04/11/23). Integrating multiple aspects of the RDoC in one comprehensive model follows RDoC's goal to advance basic science of brain and behavior (Pacheco et al., 2022). Through the illustration of specific directions of relationships in one comprehensive model, it is possible to disentangle neural underpinnings of symptom clusters. This is an important step to define more sophisticated phenotypes of psychiatric disorders. Our model thus can be used to transfer it to risk-phenotype as well as transdiagnostic phenotype models, which is a crucial starting point for understanding the mechanisms and trajectories of psychiatric disorders (Feczko & Fair, 2020; Hawco et al., 2021; Lynch et al., 2020; Meehan et al., 2022; Voineskos et al., 2020). Ultimately, this is hoped to lead to improvement of preventive and therapeutic interventions.

Data driven models like cluster analysis are part of the multivariate, exploratory techniques. Their utility in brain imaging research lies in the extraction of patterns of covariation across all possible brain regions (McIntosh

& Mišić, 2013). Following the interpretation of heterogeneity in psychiatric neuroimaging results by Ivleva et al. (2020), neuroimaging studies in psychiatry show such highly heterogeneous brain alterations within syndromes which yet leads to high biological similarity across syndromes. Hence, the phenomenological division in diagnostic categories does not hold up with biological division derived by brain imaging methods. The authors propose to establish approaches to define "(…) biologically homogenous and specific 'disease units' (and corresponding subgroups of patients) based on brain alterations detectible with imaging, despite phenomenological similarities across the subgroups (…)." (Ivleva et al., 2020, p.1). STUDY II in this thesis was able to show exactly that, namely transdiagnostic similarities in brain patterns as well as environmental and neuropsychological conditions while not finding evidence of homogeneous biological grouping of diagnostic categories. Using data driven models also in transdiagnostic populations are hence of great importance to find biologically homogenous phenotypes beyond diagnostic categories (Clementz et al., 2016; Lynch et al., 2020; Tamminga et al., 2017).

In any case, looking at early environmental conditions such as prenatal stress in various ways has proven its potential as a reliable predictor for mental illnesses (Alabaf et al., 2022; Kappelmann et al., 2022; Newman et al., 2016; Zajkowska et al., 2021). Connecting prenatal stress impacts to brain measurements and finding those impacts still present in adult life independent of diagnostic categories, as shown in this thesis, offers great potential for advancement in diagnostics (Goodkind et al., 2015; Hermens et al., 2019; Stefanik et al., 2018).

A PCA approach serves to derive a set of components from the original variables while maintaining the variance-covariance structure of the original variable set (McIntosh & Mišić, 2013). With this, heterogeneously operationalized constructs can be explored regarding their underlying statistical and phenomenological homogeneity. Considering the rather low effect sizes of (especially morphometric) neuroimaging studies in psychiatry (compared to other fields like e.g., neurodegenerative diseases (Bandettini et al., 2022)) it is exceedingly crucial to have a unifying ontology and further assessment framework of psychological constructs (Gratton et al., 2022). Results of STUDY III show, that to this day the construct of schizotypy is conceptualized differently

in different assessments. However, neuroimaging studies of schizotypy using different assessments are interpreted and compared as if the underlying construct was unified which leads to a tremendous source of heterogeneity in neuroimaging results. This limits not only the comparability of studies but more importantly, it limits the explanatory power of the construct: schizotypy no longer serves as a phenotype for one mental disorder, namely schizophrenia, but indeed shows transdiagnostic impact (Premkumar et al., 2020; Sun et al., 2022; Webster et al., 2022). However, if the construct itself is assessed heterogeneously already, interpreting its impact against the background of heterogeneous disease courses is even harder (Krueger & DeYoung, 2020). Future studies therefore must focus on fitting the phenotype of schizotypy into one strong theoretical framework to make it applicable for transdiagnostic interpretations.

### 3.2. Looking forward: Implications for future phenotype research in psychiatry

Multivariate statistical approaches in psychiatric neuroimaging research are a first step to define more elaborated phenotypes in psychiatry. As mentioned in the introduction, movements for reliable and replicable results in psychiatric neuroimaging need to go toward a more comprehensive approach in neuroimaging (Ressler & Williams, 2021). Beyond multivariate approaches, developments in computational psychiatry might incumbent a big responsibility for future phenotype research in psychiatry: With computational modeling it is possible to provide computational phenotypes that link translational neuroscience and clinical practice (Huys et al., 2016; Patzelt et al., 2018). For single-patient predictions, pathological behavior associated with brain alterations can be modeled by certain parameters which represent individual units in the process of illness (Becht & Mills, 2020). However, these parameters heavily rely on the theory behind mental health and illness (Hitchcock et al., 2022). This means, as long as existing theories about phenotypes are not backed up by valid and reliable evidence, computational modeling methods are restricted in their practical power. Hitchcock et al. (2022) recaps that computational psychiatry still lacks appropriate theoretical frameworks for

mental health as the heterogeneity in mental disorders are not well acknowledged in the models yet.

Already Kendler et al. (2011) emphasized that mental disorders are too complex systems to be traced back to a “single, well-defined etiological agent” (Kendler et al., 2011, p. 1144). This is where multivariate statistical approaches can offer up by overcoming this hypothesis of singularity. With these, variance resulting from heterogeneity, dimensionality, and transdiagnostic features of mental illnesses can be better stratified than with univariate approaches. Results of the studies in this dissertation show the feasibility of multivariate approaches:

The extensive model in STUDY I gives a more comprehensive insight in the interrelationship of brain connectivity networks in MDD with dimensional clinical variables. The data driven approach in STUDY II elucidated the underlying biological grouping of a large transdiagnostic patient cohort. SUTDY III disentangled heterogeneity in the assessment of a personality trait to take a step closer toward a unifying framework for this construct.

Taken together, research in psychiatric phenotyping has to overcome univariate correlation or regression approaches to produce valid and reliable results of relationships between brain and behavior in order to serve computational psychiatry approaches. (Patzelt et al., 2018)

### 3.3. Limitations

Studies in this dissertation show some limitations which should be outlined. While this dissertation applied multivariate statistical approaches for advanced psychiatric phenotyping, all analyses are restricted to cross-sectional data. Based on methodological implications of SEM, equivalent models with even better fits to the model in STUDY I are likely to exist (Kline, 2015). Furthermore, path coefficients of our brain-behavior relationships are relatively small when embedded in recommendations for psychometric research (MacCallum & Austin, 2000). Furthermore, directions of effect in an SEM follow linear relations, which is why the model in STUDY I cannot represent non-linear relationships between the variables. The investigated sample of MDD patients was not stratified regarding clinical aspects like remission state, hospitalizations or medication, which leaves out the possibility of explaining potential interaction effects.

The transdiagnostic sample in STUDY II was composed of significantly more patients with an MDD diagnosis than other psychiatric diagnosis. Furthermore, as cluster analysis is an explorative approach, results are highly dependent on components like sample sizes and clustering algorithm. Results of STUDY II therefore cannot be easily compared to other studies using this approach. Because subgroups were clustered by brain data only and association of the subgroups with clinical data is of correlational nature, clusters cannot be interpreted as holistic defined subgroups.

Study sample in STUDY III consisted of only young, highly educated and overly healthy subjects. Hence, variance in the data used for analyses was low which limits the generalizability of results. Furthermore, composition of components included in the CFA differed from the composition used for PCA, which limits the comparability between the two analyses.

### 3.4. Conclusion

Mental illnesses are complex multi-factorial, dynamic constructs which cannot be explained by distinct univariate analyses. This dissertation showed the feasibility of multivariate statistical approaches when investigating both neuroimaging as well as psychometric data. To transfer results of neuroimaging research in psychiatry to phenotyping which has actual practical implications for the clinic, reproducibility and generalizability of results is a necessity. Multivariate approaches help to disentangle interrelationships on multiple levels and improve psychiatric phenotyping. Besides advanced statistical approaches, Open Science practices like sharing data and code to work collaboratively should be fostered heavily in psychiatric research. Joined data and expertise enables validation of results on a large-scale. This is needed to eventually be able to offer improved, individual therapeutic interventions and care for mental health.

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## SUMMARY

The biopsychosocial model offers a conceptual theoretical framework to explain mental health and illness. It states, that the continua of biological, psychological, and social factors must be seen in interaction in order to determine an individual's risk for mental illness. By defining psychiatric phenotypes this model is transferred into practical application.

Advances in neuroimaging techniques hold big promises to contribute to psychiatric phenotyping. Being able to unravel associations between behavior and the brain, enables the detection of further biomarkers for psychiatric disorders besides genetics. However, considering the complexity of both the brain as well as mental disorders, mapping reliable brain-behavior relationships is challenging. So far, mostly univariate statistical approaches are applied in psychiatric neuroimaging research which do not fully live up to this complexity.

This dissertation applied multivariate statistical approaches to both brain as well as behavioral data to investigate the feasibility of those approaches in neuroimaging research for psychiatric phenotyping. The aim was to go one step further toward disentangling the heterogeneity of phenotypes in psychiatric neuroimaging.

In STUDY I we used the multivariate approach of Structural Equation Modeling (SEM) to build a comprehensive model of brain as well as clinical data in a large sample of patients with major depressive disorder (MDD). A previous published clinical SEM, which included risk, symptom, and cognitive variables was first replicated and then extended by a brain structural connectivity measurement. Findings of this study reflect on our understanding of white matter integrity in MDD and bring new insights into the relationship between an established risk factor as well as a core symptom of MDD with brain structural connectivity.

The data driven approach in STUDY II in form of cluster analysis aimed to explore the underlying biological grouping in a large transdiagnostic cohort. Results show that data driven subgroups based on a brain morphometric parameter do not align with the clinical diagnostic grouping. Results of subsequent correlational analyses with early environmental risk factors as well as neuropsychological variables hint toward a transdiagnostic involvement of

this brain morphometric parameter in psychopathology rather than being bound to clinical diagnostic categories.

In STUDY III, results of Principal Component Analyses showed that conceptualizations as well as assessment of the personality trait schizotypy differ across studies which leads to a source of heterogeneity when this phenotype is used in neuroimaging studies. Confirmatory Factor Analyses provided a newly approach for the assessment of schizotypy.

In conclusion, this dissertation provided novel insights into the feasibility of multivariate statistical approaches in both psychiatric neuroimaging as well as psychometric research. Results of the studies highlight the importance of going beyond simple diagnostic borders to define reliable phenotypes in psychiatry. Future research in this field needs to shift toward more comprehensive approaches to capture the complexity of mental disorders. By this, a reliable foundation for computational models is built to enable the practical application of individual predictions about mental health and illness.

## ZUSAMMENFASSUNG

Das Biopsychosoziale Modell bietet einen konzeptuell theoretischen Rahmen, um mentale Gesundheit und Krankheit zu erklären. Das Modell beschreibt, dass die Kontinua von biologischen, psychologischen und sozialen Faktoren in Interaktion miteinander betrachtet werden müssen, damit man das individuelle Risiko für psychische Erkrankungen bestimmen kann. Dieses theoretische Modell findet praktische Anwendung durch die Bestimmung psychiatrischer Phänotypen.

Weiterentwicklungen in neurowissenschaftlichen Methoden gelten als vielversprechend, um wichtige Beiträge zur Phänotypisierung psychiatrischer Erkrankungen zu liefern. Diese Methoden können den Zusammenhang zwischen Verhalten und Gehirn erforschen und somit neben Genetik weitere biologische Marker für psychiatrische Erkrankungen liefern. Jedoch erschweren sowohl die Komplexität von psychiatrischen Erkrankungen als auch die Komplexität des Gehirns klare und zuverlässige Zusammenhänge zu finden. Bisherige Forschung in diesem Bereich hat sich überwiegend auf univariate statistische Tests gestützt, welche aber diese Komplexität nicht vollends erfassen können.

In dieser Dissertation wurden daher multivariate statistische Ansätze herangezogen, um deren Anwendbarkeit im Rahmen neurowissenschaftlicher Forschung zu psychiatrischen Phänotypen zu untersuchen. Hierfür wurden die multivariaten Ansätze sowohl auf Hirn- als auch auf psychometrische Daten angewendet. Das übergeordnete Ziel dieser Dissertation war die Heterogenität bisheriger Phänotypen in diesem Feld zu entzerren.

In STUDIE I verwendeten wir den multivariaten Ansatz des Strukturgleichungsmodells, um ein umfassendes Modell mit sowohl Hirn- als auch klinischen Daten zu entwickeln. Die verwendeten Daten stammen von einer großen Stichprobe an Patienten mit depressiver Störung. Hierfür wurde ein zuvor publiziertes klinisches Strukturgleichungsmodell herangezogen und zunächst in unserer Stichprobe repliziert. Dieses Modell enthielt sowohl einen etablierten Risikofaktor für Depression als auch Symptome und einen kognitiven Parameter der Depression. Anschließend integrierten wir in dieses Strukturgleichungsmodell einen Parameter für hirnstrukturelle Konnektivität. Die Ergebnisse der Studie erweitern bisheriges Wissen zur Integrität der weißen

Substanz in Depression und bringen neue Erkenntnisse zum Zusammenhang zwischen einem Risikofaktor, einem Hauptsymptom der Depression und hirnstruktureller Konnektivität in Depression.

Die Anwendung eines datengetriebenen Ansatzes auf einen hirnmorphometrischen Parameter in Form der Clusteranalyse in STUDIE II zielte darauf ab, unabhängig von klinischen Diagnosen die reine biologische Gruppierung einer transdiagnostischen Patientenkohorte zu explorieren. Die Ergebnisse der STUDIE II zeigen, dass die durch die Clusteranalyse gebildeten Subgruppen nicht mit den diagnostischen Gruppen einhergehen. Weitere Korrelationsanalysen der Subgruppen mit frühen Umweltrisikofaktoren und neuropsychologischen Variablen geben einen Hinweis darauf, dass der untersuchte hirnmorphometrische Parameter eher eine transdiagnostische Rolle in Psychopathologie spielt als dass dieser differentiell für klinisch diagnostische Gruppen dient.

Durch die Anwendung einer Hauptkomponentenanalyse in STUDIE III konnten wir zeigen, dass sich sowohl die Konzeptualisierungen als auch die psychometrische Erfassung des Persönlichkeitskonstrukts Schizotypie über Studien hinweg unterscheidet. Der Einsatz dieser unterschiedlichen Skalen führt wiederum zu heterogenen Ergebnissen in neurowissenschaftlichen Studien. Einen Vorschlag zur homogeneren Erfassung des Konstruktes haben wir durch die Anwendung von Konfirmatorischer Faktorenanalyse erörtert.

Abschließend lässt sich sagen, dass die vorliegende Dissertation neue Einblicke in die Anwendbarkeit und Nützlichkeit multivariater statistischer Ansätze eröffnet hat. Die Ergebnisse der Studien heben hervor, dass es wichtig ist über die klinisch diagnostischen Grenzen hinaus zu gehen, um verlässliche Phänotypen bestimmen zu können. Es ist von Notwendigkeit, dass zukünftige Forschung in diesem Bereich mehr in Richtung umfassender statistischer Anwendung rückt, um die Komplexität psychischer Erkrankungen ausreichend erfassen zu können. Dadurch kann die Grundlage für rechenbetonte Modellierung psychischer Erkrankungen gelegt werden, um diese dann für individuelle Vorhersagen über mentale Gesundheit und Krankheit anwenden zu können.

# APPENDIX

## I. STUDY I: PUBLICATION PFARR ET AL. (2021)

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RESEARCH ARTICLE

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# Brain structural connectivity, anhedonia, and phenotypes of major depressive disorder: A structural equation model approach

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## Abstract

Aberrant brain structural connectivity in major depressive disorder (MDD) has been repeatedly reported, yet many previous studies lack integration of different features of MDD with structural connectivity in multivariate modeling approaches. In n = 595 MDD patients, we used structural equation modeling (SEM) to test the intercorrelations between anhedonia, anxiety, neuroticism, and cognitive control in one comprehensive model. We then separately analyzed diffusion tensor imaging (DTI) connectivity measures in association with those clinical variables, and finally integrated brain connectivity associations, clinical/cognitive variables into a multivariate SEM. We first confirmed our clinical/cognitive SEM. DTI analyses (FWE-corrected) showed a positive correlation of anhedonia with fractional anisotropy (FA) in the right anterior thalamic radiation (ATR) and forceps minor/corpus callosum, while neuroticism was negatively correlated with axial diffusivity (AD) in the left uncinate fasciculus (UF) and inferior fronto-occipital fasciculus (IFOF). An extended SEM confirmed the associations of ATR FA with anhedonia and UF/IFOF AD with neuroticism impacting on cognitive control. Our findings provide evidence for a differential impact of state and trait variables of MDD on brain connectivity and cognition. The multivariate approach shows feasibility of explaining heterogeneity within MDD and tracks this to specific brain circuits, thus adding to better understanding of heterogeneity on the biological level.

KEYWORDS
anhedonia, connectivity, diffusion tensor imaging, major depressive disorder (MDD), neuroticism, structural equation modeling

## 1 | INTRODUCTION

Major depressive disorder (MDD) has one of the highest lifetime prevalence among psychiatric disorders (Kessler & Bromet, 2013) resulting in significant individual and social burden (Lépine & Briley, 2011). Symptom representations, course of illness, and treatment response are, however, highly heterogeneous, prompting the need for markers for group stratification or links to single facets to brain mechanisms (Goldstein & Klein, 2014).

Anhedonia is a core symptom of depression and predominantly manifests emotionally as a lack of feeling pleasure, as well as reduced motivation and drive on the behavioral level (Watson, Harvey, McCabe, & Reynolds, 2020). Indeed, the diagnostic criteria of depression in the Diagnostic and Statistical Manual of Mental Disorders (fifth ed.; American Psychiatric Association, 2013) consider anhedonia as one of the two main symptoms (besides depressed mood) necessary for a clinical MDD diagnosis. Previous studies have already shown the importance of anhedonia impacting on severity of illness course, shaping the disease course, as well as effectiveness of drug treatment and psychotherapy for MDD (Auerbach, Pagliaccio, & Pizzagalli, 2019; Craske, Treanor, Dour, Meuret, & Ritz, 2019; McMakin et al., 2012; Snaith, 1993; Trøstheim et al., 2020; Watson et al., 2020). Also, there is a strong relationship between expression of anhedonia and suicidal behavior, even independently of an MDD diagnosis (Auerbach et al., 2019; Auerbach, Millner, Stewart, & Esposito, 2015; Ducasse et al., 2018; Winer et al., 2014). Anhedonia is also associated with endophenotypes of depression, including psychosocial functioning and neuroticism (Gong et al., 2018; Langvik, Hjemdal, & Nordahl, 2016; Liao et al., 2019; Vinckier, Gourion, & Mouchabac, 2017). Genetic risk scores of depression phenotypes were found to be correlated with anhedonia-related phenotypes (Guffanti et al., 2019). In addition, cognitive impairments, such as attention, were related to anhedonia more strongly than depression per se (Grillo, 2016).

Recent brain imaging studies suggest associations of anhedonia with white matter microstructure of particular fiber tracts. In contrast to large case–control imaging showing wide-spread gray and white matter alterations in MDD (Schmaal et al., 2017; van Velzen et al., 2020), structural connectivity analyses focusing specifically on anhedonia found significant associations of fractional anisotropy (FA) in the left cingulum and forceps minor/anterior corpus callosum as well as radial diffusivity (RD) in the anterior thalamic radiation (ATR), corticospinal tract, superior longitudinal fasciculus (SLF), and uncinate fasciculus (UF; Yang et al., 2017). Similarly, a more recent study identified white matter abnormalities in patients with MDD related to anhedonia in the fronto-limbic circuits (Coloigner et al., 2019), which differed from associations with anxiety, which was associated with lower FA in the corpus callosum as well as anterior corona radiata and posterior thalamic radiation. Both, the cingulum bundle and the UF have also been found to be associated with neuroticism (Madsen et al., 2009; Mincic, 2015), a less specific risk factor for MDD, suggesting a structural overlap of brain structural correlates of anhedonia and neuroticism, although findings are not entirely consistent (Avinun, Israel, Knodt, & Hariri, 2020; Servaas et al., 2013). In addition, functional imaging studies focusing on anhedonia show a network of subcortical structures including the nucleus accumbens, ventral pallidum, and amygdala to underlie processing of pleasure (Berridge, Kringelbach, Arbor, & Hospital, 2016). In patients with MDD, these reward circuits are functionally impaired and functional hypoconnectivity of the fronto-striatal network contributes to the behavioral manifestations of anhedonia (Höflich, Michenthaler, Kasper, & Lanzenberger, 2018; Li et al., 2018).

Although there is now a better understanding of specific neural networks related to anhedonia in MDD, previous studies have often been limited to singular associations between a clinical symptom and brain markers, often in smaller samples. Larger multicenter studies, however, mostly lack analyses for specific symptom clusters or potential subgroups in depression (Schmaal et al., 2017; van Velzen et al., 2020).

MDD, however, manifests as a combination of different symptom phenotypes, for example, anxiety, somatic symptoms, cognitive restraints. Respecting the dimensionality of those markers (e.g., neurophysiological, biochemical, neuroanatomical, cognitive data) rather than their categories, contributes to disentangle the full range of psychiatric disorders (Gottesman & McGue, 2014; Kozak & Cuthbert, 2016).

Despite some advances, there is a paucity of multivariate approaches integrating brain, cognitive, and clinical data, which so far have been mostly analyzed in separate studies. Multivariate modeling might improve our understanding of how these biological parameters interact with risk factors and clinical symptom dimensions like anhedonia—and might thus relate to the multidimensional nature of MDD. Multivariate models additionally offer the advantage to test both multiple direct and indirect effects within an overall model (Stein, Morris, Hall, & Nock, 2017).

Structural equation modeling (SEM) is a multivariate approach, which has already been used to integrate clinical and risk factors of MDD (Rezaei, Ghazanfari, & Rezaee, 2016; Tse, Rochelle, & Cheung, 2011). A recent clinical study described—on the phenotype/clinical level—a model of how anhedonia as well as anxiety interact with the depression-related phenotypes of neuroticism and cognitive control (Liao et al., 2019). With the proposed SEM, the authors acknowledge the impact of anhedonia and anxiety on MDD state and course, as well as their high intercorrelation. Besides symptom representations, risk factors like personality traits and cognitive aspects should be considered for a more integrated view on MDD or psychiatric disorders per se, respectively. Liao et al. (2019) considered a relationship between the mentioned symptoms and neuroticism as well as cognitive control, as they are established risk endophenotypes for MDD (Goldstein & Klein, 2014).

These models provide a basis for integrating structural connectivity mapping with differentiated SEM models to address and dissect multiple facets of MDD phenotypes. However, to this date, there is no such application drawing on large MDD samples in the field. This approach builds on the recent clinical/cognitive model by Liao et al. (2019) described above; we expand on this by integrating structural connectivity parameters, expected to differentially correlate to these clinical variables in a large sample of MDD patients.

We test the hypothesis that white matter tract integrity is associated with anhedonia, as well as anxiety, neuroticism, and cognitive control in different regional tracts. For this purpose, we first test a SEM integrating anhedonia, neuroticism, anxiety, and cognitive control, based on an extension of a previous study by Liao et al. (2019). We then analyzed white matter connectivity associations with clinical variables and finally integrated those into a testable multivariate model using SEM. More precisely, based on several studies on brain imaging and anhedonia described above, we expected anhedonia to be associated with brain structural aberrations mainly in tracts involved in emotion regulation, for example, ATR, UF (Coloigner et al., 2019; Yang et al., 2017). As previous studies on DTI and negative related emotions showed an involvement of the UF, we expected to find an association in this tract with neuroticism as well as with anxiety (Mincic, 2015).

We modeled cognitive control as executive function or inhibition ability, respectively, based on former studies finding those to not just be impaired in MDD but also to be related to particular risk factors for MDD (Crow, 2019; Pan et al., 2019).

## 2 | METHODS

### 2.1 | Study cohort

We analyzed $n = 595$ subjects with a lifetime diagnosis of MDD (365 female, 230 male; mean age 36.14 years, $SD = 13.09$) from the FOR 2107 consortium (Kircher et al., 2019), applying criteria of the DSM-IV based on face-to-face interviews using the German version of the SCID-I interview (Strukturiertes Klinisches Interview für DSM-IV Achse I Störungen; First & Gibbon, 2004; Wittchen, Wunderlich, Grushwitz, & Zaudig, 1997). We included patients within an age range of 18–65 years with at least one current or past MDD episode. We excluded patients with a history of traumatic brain injury or central nervous system neurological disorders, physical disorders that could have an impact on brain morphology (e.g., autoimmune diseases, cancer, and infections), substance dependence, as well as general contraindications to MRI scanning. Further exclusion criteria were intellectual impairment/learning disability, defined as verbal intelligence quotient lower than 80 (estimated with the German MWT-B test; Mehrfach-Wortschatz-Intelligenztest B; Lehrl, Triebig, & Fischer, 1995).

Participants were recruited within the Departments of Psychiatry at the University of Marburg and University of Münster, local psychiatric hospitals, outpatient departments and healthcare centers, as well as through local advertisements and flyers.

Clinical diagnostic assessment by trained interviewers as well as MRI scanning took place at the Departments of Psychiatry and Psychotherapy Marburg or Münster Universities, Germany, respectively. All subjects gave written informed consent before participation to a study protocol approved by the local Ethics Committee of the school of medicine, University of Marburg and University of Münster, according to the current version of the Declaration of Helsinki (World Medical Association, 2013). Subjects were financially compensated for participation. Following previous multivariate modeling studies, we focused on a clinical sample only, given that healthy control samples typically show little or no expressions of anhedonia, and a lack of significant associations between their low to moderate levels of neuroticism and brain structure (Avinun et al., 2020). The study cohort consisted of patients with one or more MDD episode(s) in an acute or (partially) remitted state (derived from SCID-I interviews and based on DSM-IV criteria), with or without psychiatric comorbidity as well as with a medicated/unmedicated state and/or receiving psychotherapy/no psychotherapy.

Clinical sample characteristics are presented in Table 1.

**TABLE 1** Clinical characteristics of our $N = 595$ major depressive disorder (MDD) patients

| | M (*SD*) or *n* (%) | | |
|---|---|---|---|
| | **Marburg $n = 283$** | **Münster $n = 312$** | **Total $N = 595$** |
| Age of onset first depressive episode (in years) | 26.25 (13.3) | 25.02 (11.82) | 25.60 (12.55) |
| Lifetime characterization depressive episodes | | | |
| Single episode | 86 (30.4%) | 129 (41.3%) | 215 (36.1%) |
| Recurrent | 197 (69.6%) | 183 (57.7%) | 380 (63.9%) |
| Remission status | | | |
| Current MDD episode | 144 (50.9%) | 111 (35.6%) | 255 (42.9%) |
| Partially remitted | 78 (27.6%) | 75 (24%) | 153 (25.7%) |
| Fully remitted | 61 (21.6%) | 126 (40.4%) | 187 (31.4%) |
| Number of depressive episodes | 5.09 (7.45) | 2.89 (2.86) | 3.88 (5.55) |
| Duration in depressive status (in months) | 53.75 (81.17) | 39.55 (63.54) | 45.29 (71.46) |
| Number of psychiatric hospitalizations | 1.59 (2.08) | 1.33 (1.76) | 1.46 (1.92) |
| Duration of lifetime psychiatric hospitalization (in weeks) | 10.18 (13.83) | 11.69 (19.43) | 10.98 (17.03) |

## 2.2 | Phenotyping

### 2.2.1 | Anhedonia

We assessed concurrent anhedonia using the German version of the Snaith–Hamilton Pleasure Scale (SHAPS-D; Franz et al., 1998; Snaith et al., 1995), a 14-item self-rating scale used in several previous studies (e.g., Franken, Rassin, & Muris, 2007; Trøstheim et al., 2020). SHAPS measures hedonic attributes or the amount of ability to experience pleasure, respectively, by subjects giving their accordance to statements like "I would enjoy being with family or close friends" in the last 14 days on a 4-point Likert scale ("Strongly Agree," "Agree," "Disagree," "Strongly Disagree"). Higher SHAPS total scores within a range of 0–14 indicate higher levels of anhedonia.

### 2.2.2 | Anxiety

We used the STAI-S of the State–Trait Anxiety Inventory (STAI; Laux, Glanzmann, Schaffner, & Spielberger, 1981; Spielberger, 1983) to assess state anxiety given the high correlation between depression and the construct of anxiety (Watson, 2009), but state anxiety is more likely to represent an emotional state or present feelings of tension (hence symptom representation), respectively (Spielberger & Reheiser, 2009), rather than anxiety as a trait. Statements are presented with a 4-point Likert scale in a manner of agreement ("not at all," "somewhat," "moderately," "very much so"). Total score range is 20–80 and higher scores indicate greater anxiety.

### 2.2.3 | Neuroticism

Trait neuroticism was measured using the German version of the Revised NEO Personality Inventory (NEO-FFI; Costa & McCrae, 1989). The neuroticism subscale contains 12 items on a 5-point Likert response format. Subjects indicate the degree to which they agree or disagree with each of the statements (0 = strongly disagree, 4 = strongly agree). Individual Neuroticism subscale scores were calculated as cumulative values of the 12 items, and can thus vary between 0 and 48 points.

## 2.3 | Neurocognitive assessment

Using a neuropsychological variable to reflect executive function/inhibition performance, we chose the Trail Making Test Version B (TMT-B; Allen & Haderlie, 2010; Army, 1944) which is part of the FOR2107 neuropsychological test battery (Kircher et al., 2019). It shares aspects of monitoring executive function and inhibition ability with the Flanker Task used in Liao et al. (2019). Besides, the TMT-B is well suited to model cognitive control as this concept is seen not just as the ability to show top-down processing by goal-directed but also flexible behavior (Badre & Nee, 2018; Miller & Cohen, 2001).

**TABLE 2** Descriptive statistics and correlations for all measurements used in this study

| Measurement | 1 | 2 | 3 | 4 | Mean | *SD* |
|---|---|---|---|---|---|---|
| 1. SHAPS | – | .57* | .39* | .02 | 3.5 | 3.5 |
| 2. STAI-S | – | – | .66* | .09 | 50.5 | 12.99 |
| 3. NEOFFI-neuroticism | – | – | – | .11* | 28.33 | 8.92 |
| 4. TMT-B | – | – | – | – | 55.9 | 22.54 |

Abbreviations: NEOFFI-neuroticism, NEO-FFI-Neuroticism Scale; SHAPS, Snaith–Hamilton Pleasure Scale; STAI-S: State–Trait Anxiety Inventory-State Anxiety; TMT-B, Trail-Making Test-Version B (measured in RT).
*$p < .01$.

Descriptive statistics and correlations for all measurements used in this study are shown in Table 2.

## 2.4 | Diffusion tensor imaging acquisition and preprocessing

We obtained diffusion-weighted images on 3T MRI scanners (Münster: Prisma, Siemens, Erlangen, Germany; Marburg: Tim Trio, Siemens, Erlangen, Germany) using a 20 channel head matrix Rx-coil in Münster and a 12 channel head matrix Rx-coil in Marburg. At both sites, PAT mode was GRAPPA with an acceleration factor of 2 (TR 7300 ms, TE 90 ms, 56 slices with a 3 mm slice thickness, isotropic voxel resolution of $2.5 \times 2.5 \times 2.5$ mm$^3$). We acquired a total of 2x30 diffusion-weighted images with a *b*-value of 1000 s/mm$^2$ and four nondiffusion-weighted images ($b = 0$ s/mm$^2$).

Quality assurance methods included several aspects: First, we used an ongoing quality assurance protocol covering all MRI scans obtained in the FOR2107 study (Vogelbacher et al., 2018); Second, we visually inspected all scans for major artifacts and anatomical abnormalities ahead of preprocessing; Third, the TBSS approach in the FSL software (version 6.0; the Oxford Centre Functional Magnetic Imaging Software Library; Oxford, UK; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith et al., 2006) was used for DTI preprocessing and analysis. DTI data were corrected for Eddy-Current-artifacts as well as motion artifacts (Andersson & Sotiropoulos, 2016). We displayed each subject image and selected an optimal fractional intensity threshold (FIT) for brain masking to remove nonbrain structures.

Maps of the four DTI parameters (FA, RD, axial diffusivity AD, and mean diffusivity MD) were generated for whole brain analyses and nine major association tracts (derived from previous DTI studies of major depression): inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), cingulum bundle, cingulum hippocampus, SLF, SLF temporal part, forceps minor and major (i.e., anterior and posterior parts of the corpus callosum), and UF, as well as for two projection tracts: the corticospinal tract (CST) and the ATR (Warrington et al., 2020). Following to the automated nonlinear registration tool FNIRT implemented in FSL (Andersson, Jenkinson, & Smith, 2007;

Andersson, Jenkinson, & Smith, 2010) all subjects data were aligned to a standard space. A mean FA skeleton was created and used for projection of FA, RD, AD, and MD data with a threshold <0.2 to counteract for alignment errors.

## 2.5 | Statistical analyses

First, SEM analysis was run in R using the R package *lavaan* (Rosseel, 2012) to replicate and extend the clinical-cognitive model by Liao et al. (2019). Error-adjusted latent variables were created by the standard measurement sum scores of the variables of interest and applying the factor loading to 1.0 for each observed variable. We adopted the reported relationships of the final model by Liao et al. (2019) to our sample: SHAPS and STAI-S as endogenous variables, NEOFFI-neuroticism and TMT-B as exogenous variables, leading to the proposed relationships as shown in Figure 1a.

SEM was estimated by maximum likelihood estimation and goodness of fit was assessed by the model fit indices $\chi^2$, $\chi^2/df$, Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Root mean square error of approximation (RMSEA; Ullman & Bentler, 2003), based on recommendations of a study evaluating SEM fit indices regarding their robustness when analyzing large sample sizes and multivariate normality (Cangur & Ercan, 2015). Both direction and power of effects are specified by path coefficients.

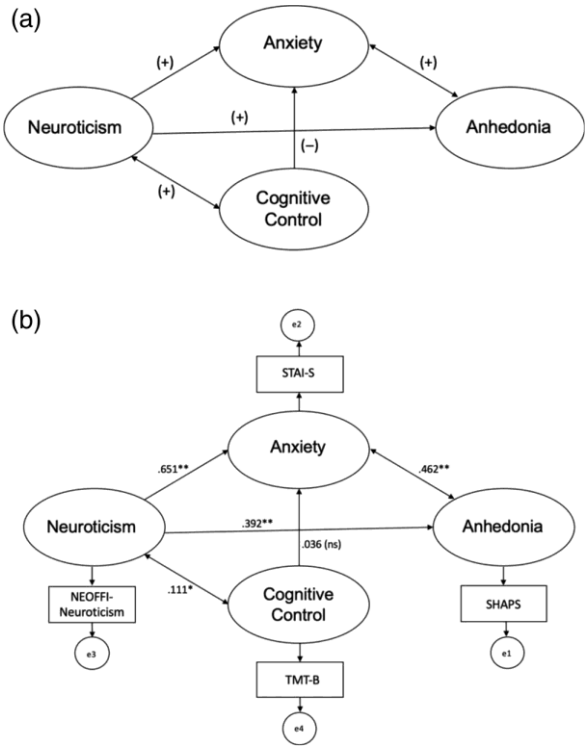


**FIGURE 1** (a) Proposed relationships of the clinical-cognitive model. Rectangles represent the observed variables, ovals represent the error-adjusted latent variables. (+) and (−) indicate the hypothesized direction of the relationships to reach significance at $p < .05$. One-headed arrows stand for regressions, double-headed arrows stand for correlations. (b) Estimated clinical-cognitive model. Numbers show the standardized path coefficients with ** = $p < .001$ and *$p < .05$. (ns) indicates a nonsignificant relationship

Correlation analyses shown in Table 2 indicate the absence of multicollinearity.

Second, we computed multiple regression analyses applying the GLM approach implemented in FSL. We set up separate models for each variable of interest described above (SHAPS, STAI-S, NEOFFI-neuroticism, and TMT-B), including age, sex, site and TIV as nuisance variables. Exchange of the body-coil in Marburg during scanning period was accounted for by including it as an additional nuisance variable (pre body-coil change: yes/no; post body-coil change: yes/no). We used threshold-free-cluster-enhancement (TFCE) running voxel-wise analyses using the FSL program *randomise*. Contrasts were generated with 5,000 permutations (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) and tested with FA, RD, AD, and MD. We applied the JHU DTI 81 white-matter labels atlas (Mori, Van Zijl, & Tamminga, 2007) for anatomical labeling. Clusters were considered significant at a statistical threshold $p < .05$ after correcting for family-wise error (FWE).

Third, we established a multivariate model based on those two proceeding analyses to include the clinical and brain structural data.

# 3 | RESULTS

## 3.1 | Clinical-cognitive model/ SEM

Our first SEM analysis of clinical-cognitive data based on Liao et al. (2019) showed good fit ($\chi^2 = 0.36$, $p = .55$, $\chi^2/df = 0.36$, CFI = 1.000, TLI = 1.007, RMSEA < 0.001) and we, therefore, replicated all proposed significant relationships except for the negative association of cognitive control and anxiety (unstandardized coefficient = 0.021, standardized coefficient = 0.036, $p = .13$; see Figure 1b). Path coefficients show that greater neuroticism is associated with increased anhedonia (unstandardized coefficient = 0.154, standardized coefficient = 0.392, $p < .001$), as well as increased anxiety (unstandardized coefficient = 0.948, standardized coefficient = 0.651, $p < .001$). There was a positive correlation between neuroticism and cognitive control ($r = .11$, $p < .001$), as well as a positive correlation of anhedonia and anxiety ($r = .46$, $p < .001$).

## 3.2 | DTI-phenotype association analyses

We identified the following main correlations between white matter structure and phenotype variables (all *p*-values FWE corrected; *k* denotes number of voxels):

SHAPS correlated positively with FA and RD in the right ATR and the forceps minor ($p = .03$, $k = 49$; $p = .04$, $k = 18$; see Figure 2a). Furthermore, analyses showed a positive correlation with MD in the

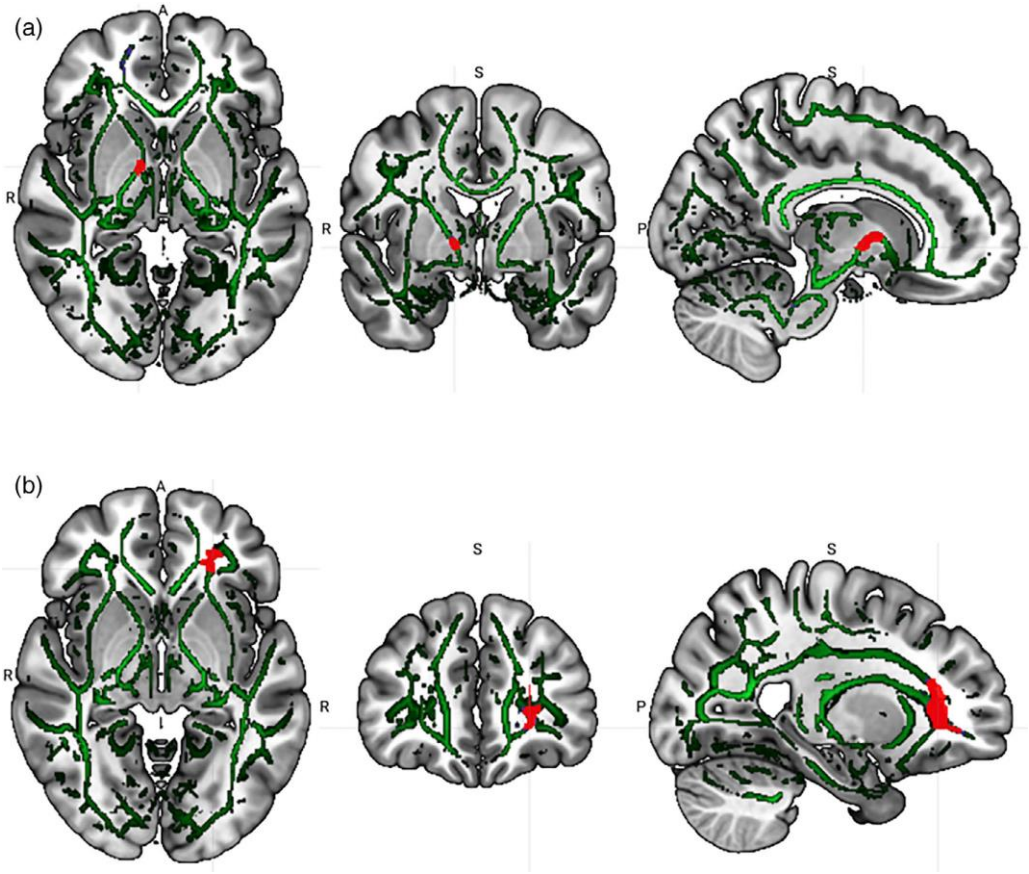


**FIGURE 2** (a) Significant ($p < .05$ after FWE-correction) association of SHAPS with FA in the right ATR and forceps minor (coordinates maximum intensity voxel = 69/172/87). (b) Significant ($p < .05$ after FWE-correction) association of NEOFFI-neuroticism with AD in the left IFOF/UF (coordinates maximum intensity voxel = 114/162/74). Maximum intensity voxels coordinates were used for cutting plane placement. Illustrations were prepared using MRIcroGL (version v2.1.52-0; https://www.nitrc.org; © Copyright 2007, NITRC). ATR, anterior thalamic radiation; AD, axial diffusivity; FA, fractional anisotropy; FWE, family-wise error; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus

left UF ($p = .04$, $k = 18$), as well as a negative correlation in the left cingulum hippocampus ($p = .02$, $k = 11$) and the CST ($p = .04$, $k = 22$).

NEOFFI-neuroticism was negatively correlated with AD in the left UF, left ATR and left IFOF ($p = .03$, $k = 74$; see Figure 2b). Negative correlation with AD also showed one significant cluster mainly located in the left ATR ($p = .02$, $k = 192$) and two clusters in right ATR and right IFOF ($p = .04$, $k = 49$ and $p = .04$, $k = 28$). There were no significant clusters associated with NEOFFI-neuroticism with either FA, MD, or RD.

For the STAI-S, only one positive association with AD in the left UF reached significance ($p = .03$, $k = 149$), with no further associations to FA, MD, or RD. Analyses of the TMT-B also yielded significant correlations with AD only. There was one positive cluster in the left CST ($p = .02$, $k = 351$) and two negative clusters in the right cingulum hippocampus ($p = .009$, $k = 71$) and in the right IFOF ($p = .04$, $k = 88$), respectively.

### 3.3 | Multivariate SEM models

Based on the above findings, we tested an integrated multivariate SEM including the variables from the replicated basic clinical-cognitive SEM and ATR-FA (which was correlated with anhedonia) and IFOF/UF-AD correlated with neuroticism. In defining this model, we considered to only include the most robust brain associations to avoid inflated fit estimates while providing a parsimonious model (Kline, 2015).

Based on previous brain structural findings (Cologner et al., 2019; Madsen et al., 2009; Mincic, 2015; Yang et al., 2017), we focused on the positive correlation of SHAPS with FA in the right ATR/forceps minor, and the negative correlation of NEOFFI-neuroticism with AD in the left IFOF/UF and the left ATR.

Hypothesized relationships between brain structural correlates and clinical-cognitive variables are shown in Figure 3. We considered a putative relationship between the ATR-FA cluster associated with

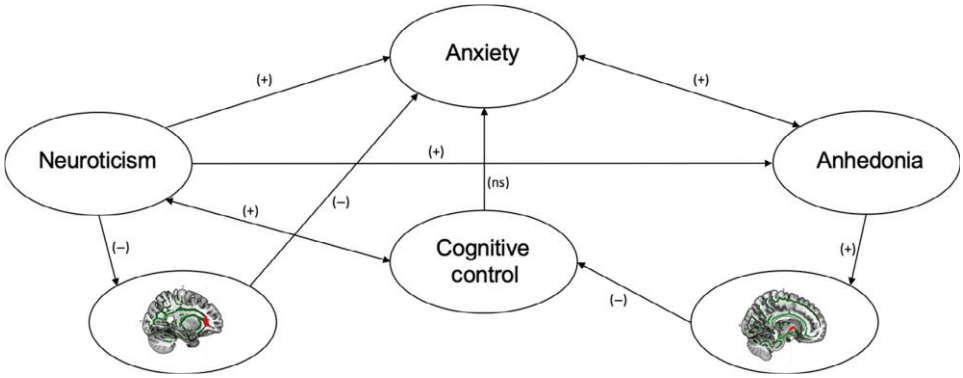


**FIGURE 3** Proposed relationships of the multivariate model. Rectangles represent the observed variables, ovals represent the error-adjusted latent variables. (+) and (−) indicate the hypothesized direction of the relationships to reach significance at $p < .05$. One-headed arrows stand for regressions, double-headed arrows stand for correlations. Proposed relationships to brain imaging data: Neuroticism—IFOF/UF-AD cluster—anxiety; Anhedonia—ATR-FA cluster—cognitive control. ATR, anterior thalamic radiation; AD, axial diffusivity; FA, fractional anisotropy; FWE, family-wise error; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus

anhedonia and cognitive control, as well as a relationship between the IFOF/UF-AD cluster associated with neuroticism and anxiety, based on previous literature showing those associations on a behavioral level (Grahek, Shenhav, Musslick, Krebs, & Koster, 2019; McIntyre et al., 2016; Servaas et al., 2015). Although the path between cognitive control and anxiety did not reach significance, we modeled this path in our multivariate SEM again, as nonsignificant paths also can explain meaningful variance in the overall model (Steinmetz, 2015).

We extracted eigenvalues of the significant brain structural clusters of interest and further z-transformed them. Clusters were integrated in the clinical-cognitive SEM as described above with a factor loading of 1.0. Analyses were re-run in in R using the R package *lavaan* (Rosseel, 2012).

Results showed a moderate fit of the model ($\chi^2 = 13.39$, $p = .02$, $\chi^2/df = 2.68$, CFI = 0.985, TLI = 0.955, RMSEA = 0.055).

Path coefficients indicated a decrease of cognitive control with the ATR-FA cluster associated with anhedonia (unstandardized coefficient = −2.064, standardized coefficient = −0.092, $p = .029$). The proposed relationship between anxiety and the IFOF/UF-AD cluster associated with neuroticism did not reach significance (unstandardized coefficient = 0.242, standardized coefficient = 0.019, $p = .53$) and in line with the clinical-cognitive SEM, there was no significant relationship between anxiety and cognitive control (unstandardized coefficient = 0.020, standardized coefficient = 0.035, $p = .15$). We, therefore, excluded those two paths from re-estimation of our model. Modification indices indicated a significant improvement of model fit by considering a path between the cluster associated with neuroticism and cognitive control (mi = 10.34), wherefore we included this path in the re-estimation of the model.

The modified model showed a good fit ($\chi^2 = 4.05$, $p = .40$, $\chi^2/df = 1.01$, CFI = 1.000, TLI = 1.000, RMSEA = 0.005). The path between cognitive control and the IFOF/UF-AD cluster associated with neuroticism reached significance (unstandardized coefficient = −2.929, standardized coefficient = −0.130, $p = .004$). The estimated final model is shown in Figure 4.

## 4 | DISCUSSION

This study integrates, in a multivariate model, brain structural connectivity variability with clinical, risk phenotype variables, and cognition in MDD. Focusing on anhedonia as a core symptom, we demonstrate new insights into brain structural connectivity networks in a large sample of MDD patients. This study reveals two important aspects: (a) Bivariate association analyses demonstrates correlation between anhedonia and FA in the right ATR as well as a correlation between AD and neuroticism in the left IFOF/UF in MDD. (b) Our multivariate model collaborates and expands a previous model conceptualizing the relation between clinical/cognitive and brain connectivity measures by acknowledging the fact of interactions of multiple variables and measures in MDD.

DTI results showed among others an association of SHAPS and FA in the right ATR and forceps minor and an association of NEOFFI neuroticism and AD in the left IFOF/UF. In our multivariate SEM, findings revealed an impact of differential associations between the ATR-FA cluster as well as the IFOF/UF-AD cluster on cognitive control. Results bring several implications:

DTI results of anhedonia and neuroticism yielded associations with different DTI parameters (i.e., anhedonia-FA, neuroticism-AD). FA measures the overall expanse of the directionality of water diffusion along the fibers, AD displays the amount of water diffusion parallel to white matter tracts (Winklewski et al., 2018). Although interpretation of DTI parameters is still inconclusive, FA is interpreted as a combined measure of axon density and myelin content (Friedrich et al., 2020), while AD tends to indicate mostly the axonal conditions and/or orientation of axons (De Erausquin & Alba-Ferrara, 2013). The differential effects on FA versus AD might in part reflect effects on

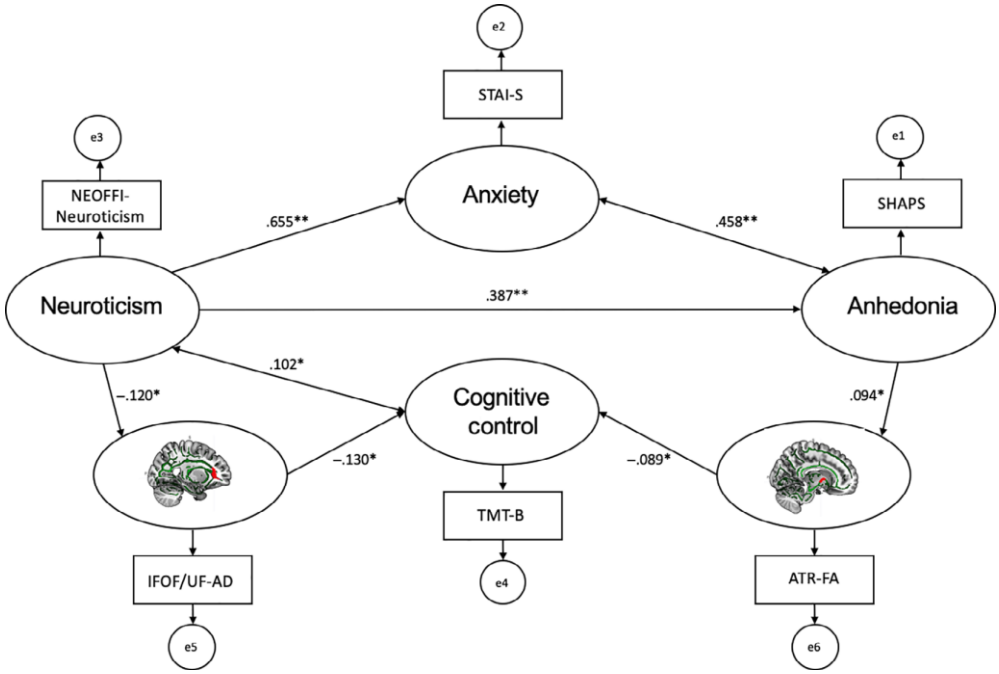


**FIGURE 4** Estimated final model after modification. Numbers show the standardized path coefficients with ** = $p < .001$ and *$p < .05$

fiber orientation versus myelination as influenced by both anatomical variation and dynamic expressions of myelination across the lifespan. In particular, given the rather low scores of anhedonia in our sample, the positive correlation of FA and anhedonia in the ATR might reflect early stages (e.g., compensation mechanisms) of alterations impacting the brains pleasure system. The negative correlation of AD and neuroticism in the left IFOF/UF, however, can be interpreted as a result of stress reactivity to constant experience of negative emotions.

Anhedonia and neuroticism indeed can be linked to distinct white matter tracts and different DTI parameters while concurrently either showing an impact on cognitive functioning, hence giving new insights on intercorrelations on a biomarker level. DTI results in our large MDD sample clarify frontal-limbic circuit abnormalities found in previous smaller structural/functional neuroimaging studies of anhedonia (Coloigner et al., 2019; Gong et al., 2018; He et al., 2020; Henderson et al., 2013; Mincic, 2015; Rizvi, Lambert, & Kennedy, 2018; Yang et al., 2017). Findings elucidate a brain structural overlap between anhedonia and cognitive control, expanding previous studies stating a relationship between brain structures like the PFC (including ACC) and cognitive control in MDD (Joormann, Yoon, & Zetsche, 2007). With a substantial multivariate approach, our model thus underpins previous hypotheses about a neural overlap between anhedonia and cognitive mechanisms (Barrett, Mesquita, Ochsner, & Gross, 2007; Berridge et al., 2016; Phelps, 2006).

Moreover, our model suggests a more comprehensive involvement of the ATR in cognitive control mechanisms in addition to the already demonstrated role of ATR in memory-guided attention (Leszczyński & Staudigl, 2016). This link between FA in the ATR and cognitive control is also consistent with the finding, that decreased FA in frontal and temporal lobes is linked to poorer executive function (Grieve, Williams, Paul, Clark, & Gordon, 2007).

Although the ATR connects the (dorsolateral) prefrontal cortex with thalamic nuclei, it may also play a crucial role in the salience network. Regarding the Research Domain Criteria, anhedonia is yet associated with the negative valence domain whereas cognitive control represents (among others) the cognitive systems domain (Kozak & Cuthbert, 2016). Our finding of a brain structural overlap of anhedonia and cognitive control taken together with the already proposed major cortical nodes of the salience network (i.e., dorsolateral anterior cingulate cortex, anterior insula, mediodorsal thalamus; Peters, Dunlop, & Downar, 2016) puts a stronger focus on emotional regulation within the salience network and might help brain stimulation improvement.

In this large MDD sample, we replicated and extended a recent clinical-cognitive model of anhedonia (Liao et al., 2019) and demonstrate a relation of anhedonia to neuroticism and anxiety as well as cognitive functioning/cognitive control.

Refining the role of anhedonia in MDD, the indirect effect of anhedonia on cognitive control mediated by connectivity alterations illustrates an important impact of anhedonic features on a biomarker level beyond the overall effect of MDD. Anhedonia is an important treatment target in affective disorders (Höflich et al., 2018) and there is clearly a strong connection between anhedonia and cognitive control in individuals with MDD on a behavioral (Grahek et al., 2019; McIntyre et al., 2016) and brain structural level. Future studies might further examine the underlying common neural correlates of

anhedonia and cognitive control to use it in cognitive-behavioral therapy for affective disorders.

This multivariate approach also includes an established risk phenotype, that is, neuroticism, serving as a trait component to be compared with clinical variables. Findings elucidate the white matter tracts involved in a proposed shared network of neuroticism and cognitive control (Servaas et al., 2015) as well as a specific direction of the effect. Furthermore, our results indicate a stronger relation of neuroticism to cognitive control than supposed so far (Servaas et al., 2015), which points toward the need to consider both emotional and cognitive subnetworks when investigating the impacts of high neuroticism. Our model can thus be used to test these intercorrelations in cohorts of high-risk individuals, leading to findings important for early intervention. Moreover, a multivariate model of these two MDD phenotypes together with genetic and environmental factors of neuroticism could result in a differentiated "risk model."

SEM makes it possible to illustrate specific directions of relationships which allow to better describe the actual impacts of the variables on one another. Our results show, that distinct phenotypes of MDD are represented by overlapping brain structural correlates and also demonstrate the feasibility to use DTI in deconstructing the more complex MDD phenotype into single facets and associations with symptoms or symptom clusters. These points toward the potential of multivariate models when unraveling illness heterogeneity of MDD.

Moreover, for future transdiagnostic research, the approach of multivariate modeling is of particular importance. Multivariate models like ours can help to further unravel the dimensionality of psychiatric disorders and eventually to better predict individual disease course. Therefore, future research on psychiatric disorders should focus more on multivariate stratification.

We are aware that our approach has some limitations. Effects of the brain imaging data are not large considering the fact that path coefficients should ideally show an effect of ≥0.2/−0.2 to indicate a meaningful relationship, as considered by some standards (Chin, 1998); however, these recommendations mostly arose from psychometric research in social science (MacCallum & Austin, 2000) and therefore do not completely serve interpretation of multivariate models integrating brain imaging data. Furthermore, although the final model showed a good fit to our data, the method of SEM implicates the existence of equivalent models (Kline, 2015). In case of an extremely heterogeneous illness like MDD, it is obvious that our model cannot capture every possible effect or relationship, also especially due to the limitations of the SEM method (Kline, 2015). Our SEM approach also has some limitations in fitting nonlinear relations, which might, for example, lead to different directions of correlations depending on the range of phenotype expression (see for example, Besteher, Gaser, & Nenadić, 2020). We also did not examine effects of remission state, duration of hospitalization or medication effects due to our novel model approach. Constructive future studies using this kind of approach can take those variables into account to unravel possible unknown interaction effects. In our study, we focused on DTI data and some clinical-cognitive variables. To further examine the potential of SEM as a method to model intercorrelations of psychometric and brain imaging data, more studies of this kind with varying variables of interest (e.g., environmental factors, functional brain imaging data and so forth) are needed.

## 5 | CONCLUSION

Our findings advance the current understanding of white matter microstructure of MDD by specifying shared connectivity networks of phenotype variables of MDD. Brain structural correlates found in our DTI analyses showed two autonomous connectivity paths, one representing the impact of a personality trait on brain structure and one representing the impact of a main symptom representation on brain structure in an MDD sample. Both, however, had an effect on cognitive control independently of each other. This indicates a more reliant "disconnection syndrome" in MDD than initially proposed by previous studies investigating brain connectivity networks in MDD (Li et al., 2018). Our study thus adds meaningful insights into interrelations of features of MDD on a brain structural level compared to previous brain connectivity studies of MDD (Jiang et al., 2019; Nugent et al., 2019; Repple et al., 2017, 2020). Also, findings provide a connectome approach to disentangling symptom clusters neural underpinnings, which can ultimately serve personalized treatment planning, as demonstrated in recent neurostimulation studies (Siddiqi et al., 2020).

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### CONFLICT OF INTERESTS

Biomedical financial interests or potential conflict of interests: Tilo Kircher received unrestricted educational grants from Servier, Janssen, Recordati, Aristo, Otsuka, neuraxpharm. Julia-Katharina Pfarr, Katharina Brosch, Tina Meller, Kai Gustav Ringwald, Simon Schmitt, Frederike Stein, Susanne Meinert, Dominik Grotegerd, Katharina Thiel, Hannah Lemke, Alexandra Winter, Lena Waltemate, Tim Hahn, Nils Opel, Jonathan Repple, Jochen Bauer, Andreas Jansen, Udo

Dannlowski, Axel Krug, and Igor Nenadić reported no biomedical financial interests or potential conflict of interests.

## DATA AVAILABILITY STATEMENT

Research data are not shared due to privacy and ethical restrictions.

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## II. STUDY II: PUBLICATION PFARR ET AL. (2023)

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# Data-driven multivariate identification of gyrification patterns in a transdiagnostic patient cohort: A cluster analysis approach

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ABSTRACT

*Background:* Multivariate data-driven statistical approaches offer the opportunity to study multi-dimensional interdependences between a large set of biological parameters, such as high-dimensional brain imaging data. For gyrification, a putative marker of early neurodevelopment, direct comparisons of patterns among multiple psychiatric disorders and investigations of potential heterogeneity of gyrification within one disorder and a transdiagnostic characterization of neuroanatomical features are lacking.
*Methods:* In this study we used a data-driven, multivariate statistical approach to analyze cortical gyrification in a large cohort of $N = 1028$ patients with major psychiatric disorders (Major depressive disorder: $n = 783$, bipolar disorder: $n = 129$, schizoaffective disorder: $n = 44$, schizophrenia: $n = 72$) to identify cluster patterns of gyrification beyond diagnostic categories.
*Results:* Cluster analysis applied on gyrification data of 68 brain regions (DK-40 atlas) identified three clusters showing difference in overall (global) gyrification and minor regional variation (regions). Newly, data-driven subgroups are further discriminative in cognition and transdiagnostic disease risk factors.
*Conclusions:* Results indicate that gyrification is associated with transdiagnostic risk factors rather than diagnostic categories and further imply a more global role of gyrification related to mental health than a disorder specific one. Our findings support previous studies highlighting the importance of association cortices involved in psychopathology. Explorative, data-driven approaches like ours can help to elucidate if the brain imaging data on hand and its a priori applied grouping actually has the potential to find meaningful effects or if previous hypotheses about the phenotype as well as its grouping have to be revisited.

## 1. Introduction

Multivariate statistical approaches offer the opportunity to investigate multi-dimensional interdependences between a large set of objects. This is particularly relevant to brain imaging data, where spatially distributed patterns are more powerful approaches to

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characterizing the healthy and diseased brain (Etkin, 2019). Yet, many statistical approaches focus on univariate group-level comparisons in which brain regions are tested independently from another. In addition, data-driven approaches aimed at identifying patterns based on multivariate statistics have gained significant importance, as they allow (sub) grouping based on biological (rather than clinical) parameters (e.g., (Lynch et al., 2020; Meng et al., 2021; Sanfelici et al., 2022). These are particularly important in identifying associations of neural signatures spanning beyond prototypical disease categories, including transdiagnostic phenotypes or risks factors (Yeung et al., 2021), as well as subgroups within diagnostic categories (Lalousis et al., 2021; Wang et al., 2021).

Several structural brain imaging meta-analyses, for example, show large overlaps of gray matter loss across affective and psychotic disorders, including the anterior cingulate cortex or insula (Goodkind et al., 2015). At the same time, the case-control design of many original studies does not allow identification of subgroups (either within each diagnostic category or across these) that might be linked to more specific brain structural signatures due to their a priori defined subgrouping. This illustrates the need for novel approaches to analyzing MRI data (Feczko and Fair, 2020; Stein et al., 2021; Voineskos et al., 2020). Identifying stable patterns beyond clinical categories, however, requires not only deep phenotyping of clinical cohorts at multiple levels (e.g., (Bycroft et al., 2018; Kircher et al., 2019)) but also a stable brain structural parameter. As the awareness of the replication crisis in brain imaging research has risen (Marek et al., 2022), it becomes more and more important to go back to "pure data" and revisit commonly used cortical phenotypes (Bandettini et al., 2022; Ivleva et al., 2020).

### 1.1. Gyrification and its relationship to psychopathology

Cortical gyrification/folding might be particularly suitable as it is expressed early in life, are considered an indicator of early brain development, and yet remains rather stable (compared to other brain morphologic parameters like gray matter volume; (Hogstrom et al., 2013)) throughout most of the life-span (White et al., 2010). This cortical phenotype appears only in mammals, is considered to relate to the development of higher cognitive functions (Lui et al., 2011) and is predominantly formed prenatal: Patterns which emerge up to gestational week 32 seem to be relatively even between individuals (Abe et al., 2003). Folding after gestational week 36 and up to 2 years of age happens predominantly in association cortices (Matsuda and Ohi, 2018) and these patterns are more individualistic and also prone to effects of e.g., gender and early childhood circumstances (Kelly et al., 2013; Luders et al., 2008; Raznahan et al., 2011; White et al., 2010).

Compared to healthy controls, regional gyrification is shown to be altered across psychiatric disorders (Nenadic et al., 2015; Palaniyappan et al., 2011; Sasabayashi et al., 2021; Spalthoff et al., 2018) as well as in relation to disorder specific psychopathology (Kubera et al., 2018; McIntosh et al., 2009; Sasabayashi et al., 2017; Schmitgen et al., 2019). However, considering the high impact of genetic and biological factors on early cortical development and relative stability of global gyrification patterns over lifetime, transdiagnostic evaluation of gyrification and its relationship to early risk-factors could be more meaningful (Sanfelici et al., 2022). This is also supported by studies that show that aberrant gyrification in (sub-)clinical populations is associated with lifetime-manifestations (such as vulnerability factors for psychopathology per se) rather than current/transient disorder specific symptomatology (Al-Haddad et al., 2019; Birnbaum and Weinberger, 2017; Evermann et al., 2020; Mareckova et al., 2020; Papini et al., 2020; Pham et al., 2021; Sanfelici et al., 2022).

So far, results of univariate associations of psychiatric disorders and regional gyrification are still inconclusive as there is evidence for both increased and decreased gyrification in relation to different mental illnesses (Depping et al., 2018; Matsuda and Ohi, 2018; Nanda et al., 2014; Palaniyappan et al., 2011). Although there are studies comparing gyrification between different psychiatric disorders (e.g., (Cao et al., 2017; Madeira et al., 2020)), investigations of potential heterogeneity of gyrification within one disorder and a transdiagnostic characterization of neuroanatomical features are lacking (Sasabayashi et al., 2021).

### 1.2. Cluster analyses of biological and phenotypic data

Cluster analysis is a multivariate approach to find similarities between given objects (or data points) and to cluster those objects based on their amount of similarity into smaller, homogeneous chunks of data. The goal is to identify groups which are homogenous within but as a whole separate to the other groups (Hennig et al., 2015). Compared to other statistical methods, cluster analysis operates without a priori defined characteristics, hence unsupervised and solely exploratively (Landau and Chis Ster, 2010). This also means that an adjustment of the data by covariates for the initial cluster analysis is not in the nature of the method. In contrast to case-control studies, which are typically tied to (current) clinical conceptualisations of disease categories with little or no basis in biological data, clustering therefore has the potential to identify and establish subgroups across large cohorts sharing particular brain structural or functional features (Hawco et al., 2021; Wang et al., 2021; Yeung et al., 2021).

This approach has been applied to genetic (Pelin et al., 2021), inflammation (Lempriere, 2020), cognitive (Van Rheenen et al., 2017), imaging combined with phenotypic/inflammation data (Lizano et al., 2021; Talpalaru et al., 2019; Van Dam et al., 2017), and also to neuroimaging data on its own (Hawco et al., 2021, 2019). Thus, clustering indeed provides a useful data-driven approach to identify patterns of neurobiological parameters independent of clinical data.

### 1.3. Goal of the present study

We argue that by sorting mental disorders based on clinical diagnosis categorization the multidimensional nature of phenotypes is partly overlooked as the diagnostic categorization does not necessarily uniformly map on a biological level (Bandettini et al., 2022). The often a priori diagnosis-related grouping of brain morphometric measurements therefore might miss the possibility that there are biological correlates which do not correlate with the disease manifestation itself but appear more impactful for the disease trajectory for multiple mental disorders, i.e., shared risk factors. As the morphometric measurements of cortical thickness and gray matter volume are heavier impacted by factors such as age (Fjell et al., 2009; Lee et al., 2018; Madan and Kensinger, 2018) compared to gyrification and multiple previous studies confirmed a relationship of gyrification with vulnerability for psychopathology (see Section 1.1), gyrification as one morphometric phenotype has the potential to be investigated with an exploratory method.

Consequently, the goal of this study is to elucidate the question whether gyrification offers the potential to delineate subgroups beyond diagnoses from the Diagnostic and Statistical Manual of Mental Disorders (DSM). This addresses the currently open question whether gyrification patterns might be associated with transdiagnostic markers of psychopathology or risk, rather than distinct clinical diagnostic categories (Sasabayashi et al., 2021). Besides a primary methodological goal of this study, results might also have implications in the process of early detection of psychopathology.

For this purpose, our study used data-driven multivariate cluster analysis of a large and clinically heterogeneous transdiagnostic patient cohort ($N$ = 1028 including patients with Major depressive disorder (MDD), bipolar disorder (BD), schizoaffective disorder (SZA), and schizophrenia (SZ)) to identify biological patterns of cortical gyrification and further to relate these to transdiagnostic and sub-group related factors of risk for psychopathology. With this approach we are able to identify a structure based on gyrification that is already present in the data, thus biologically defined subgroups that are similar in their gyrification pattern, independent of a priori imposed structuring. To

further validate the behavioral relevance of the newly formed subgroups, we considered variables for associations which are not confounded by state effects or clinical parameters associated with patient age (e.g., disease duration, number of hospitalizations etc.) rather than early neurodevelopmental impacts. Hence, cognitive performance as well as early environmental risk factors are used for post-clustering association analyses with clusters. To acknowledge the possibility of important clinical parameters affecting the clustering results of our heterogeneous patient cohort, we calculated the differences in hospitalization, age of onset, and Medication-Index (Benkert and Hippius, 2021; Reynolds, 2008) for both, the DSM groups as well as the cluster groups. Furthermore, we used DSM-IV-diagnoses labelled groups to examine if diagnostic labeling is able to discriminate gyrification patterns unique to diagnostic groups.

We did not include healthy controls in our cluster analysis as our objectives of this study are specifically drawn toward the distribution of gyrification within the psychiatric disease spectra and therefore healthy controls would only bring an increase in variance but not contributing qualitatively to the aim of our analyses.

## 2. Methods

### 2.1. Participants

We analysed data from 1028 patients drawn from the ongoing, multicentric FOR2107 study (http://for2107.de; (Kircher et al., 2019)). Participants were recruited via university wide emails, local advertisements as well as local in- and out-patient departments in Marburg and Münster, Germany. We included individuals with at least one major psychiatric disorder (MDD: $n = 783$, BD: $n = 129$, SZA: $n = 44$, SZ: $n = 72$) as diagnosed by the Structured Clinical Interview (SCID-I; (Wittchen et al., 1997)) based on the DSM-IV-TR administered by trained raters. Our transdiagnostic approach included patients from the affective and psychotic disorder spectrum, incl. MDD, BD, SZA, and SZ; hence, we focus on patients with severe mental disorders. We included individuals with available brain imaging data and excluded participants with an IQ<80, history of head trauma, current benzodiazepine intake, and neurological illness.

The study protocol was approved by the Ethic Committees of the Philipps-University of Marburg, School of Medicine, and the University of Münster according to the latest Declaration of Helsinki. All subjects gave written informed consent to our study protocol and received financial compensation after participation. Descriptive characteristics of our sample are shown in Table 1.

### 2.2. Neuroimaging

#### 2.2.1. MRI acquisition

MR-scanning took place at two sites, Marburg and Münster, using a 3-Tesla MRI (Münster: Prisma, Siemens, Erlangen, Germany, 20-channel head matrix Rx-coil; Marburg: Tim Trio, Siemens, Erlangen, Germany, 12-channel head matrix Rx-coil). Acquisition and pooling of MRI data was performed according to an extensive and already published quality assurance protocol (Vogelbacher et al., 2019, 2018).

A 3D MP-RAGE sequence was used to obtain T1-weighted images (slice thickness=1.0 mm, voxel size=1.0 × 1.0 × 1.0 mm, FOV=256 mm) with the following parameters in Marburg: TR=1.9 s, TE=2.26 ms, TI=900 ms, flip angle=7°; and in Münster: TR=2.13 s, TE=2.28 ms, TI=900 ms, flip angle=8°

#### 2.2.2. Preprocessing and ROI extraction

T1-weighted scans were preprocessed using the pipeline of the CAT12 toolbox (r1184, Structural Brain Mapping Group, Jena University Hospital, Jena, Germany, http://www.neuro.uni-jena.de/cat/) implemented in SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK) running under MATLAB (version R2017a, The MathWorks, USA) with default parameter settings. Cortical surfaces were extracted using a projection-based approach (Dahnke et al., 2013), applying topological correction (Yotter et al., 2011) and surfaces were spherically registered with an adopted diffeomorphic DARTEL algorithm (Ashburner, 2007). We then estimated cortical gyrification by local absolute mean curvature (Luders et al., 2006) and extracted ROI-based measures from the Desikan-Killiany-40 (DK-40; (Desikan et al., 2006)) atlas. DK-40 atlas by Luders et al. (Luders et al., 2006) combines the two existing gyrification index definitions, i.e., perimeter-based method and curvature-based method by defining a local gyrification index and smoothing the magnitude of the mean curvature, which brings useful information about the surface bending.

### 2.3. Neuropsychological and risk-factor assessment

Neuropsychological data was chosen from the extensive neuropsychological test battery in the FOR2107. As we only used neuropsychological data for secondary analyses and some of the assessed tests measure the same cognitive domain, we chose one test that best represented each of the four subdomains of cognition: 1. Digit Symbol Substitution Test (DSST; (Wechsler, 1958)) for executive functioning/associative ability, 2. the d2 Test of Attention (d2; (Brickenkamp, 1962)) for sustained attention, 3. the Corsi block-tapping test (CBTT total score; (Berch et al., 1998)) for visuospatial working memory performance, and 4. the verbal fluency test (VF; (Aschenbrenner et al., 2000)) for semantic processing (for an overview of the complete neuropsychological test battery in FOR2107 see (Kircher et al., 2019)).

Based on self-reported data of the participants we calculated a prenatal risk-score as well as a birth-complication risk score, as prenatal and early postnatal development potentially most impact gyrification (Abe et al., 2003). For the prenatal risk-score participants were asked if at least one of the following prenatal influences were given: maternal infection, maternal alcohol- or drug-abuse, maternal malnutrition, maternal or paternal smoking. For birth-complication risk score participants were asked if at least one of the following birth complications were given: ventouse birth, forceps delivery, casarean delivery or others. For both risk scores, scoring was in a yes-/no-manner (no risk=0, at least one risk=1).

The Medication-Index was calculated based on conversion and cut-off recommendations by Reynolds (2008) and Benkert and Hippius (2021). Patients are assigned a score of 0, 1, or 2 according to their daily psychiatric medication doses. Psychiatric medications include

**Table 1**
Descriptives of our $N = 1028$ sample, total and divided for DSM-labelled groups.

| Sample Group | n | Mean Age | Sex | Mean Age of Onset | Mean Hospitalization Duration in Weeks | Mean Medication-Index |
|---|---|---|---|---|---|---|
| Total | 1028 | 37.41 | 390 m, 638 f | 25.34 | 17.68 | 1.66 |
| MDD | 783 | 36.74 | 270 m, 513 f | 26.01 | 12.05 | 1.38 |
| BD | 129 | 41.24 | 58 m, 71 f | 24.12 | 32.41 | 2.52 |
| SZA | 44 | 38.39 | 20 m, 24 f | 20.95 | 49.25 | 3.18 |
| SZ | 72 | 37.25 | 42 m, 30 f | 22.74 | 37.73 | 2.32 |
| $p$ Welch-ANOVA/$\chi^2$ | | .003* | <0.001** | <0.001** | <0.001** | <0.001** |

* $p<.05$.
** $p<.001$.

antipsychotics, antidepressants, lithium, mood-stabilizer, benzodiazepines, as well as Z-drugs.

### 2.4. Statistical analyses

#### 2.4.1. Pre-clustering analyses

Descriptive analyses and Welch-ANOVA for the above-mentioned clinical parameters were run. Additionally, ahead of the cluster analysis, several statistical analyses were run on the original gyrification data matrix to assure plausibility for the choice of applying a clustering procedure and further regarding clustering method, dissimilarity-matrix computation as well as clustering algorithm (for an overview for recommended steps applying cluster analysis see (Landau and Chis Ster, 2010)):

We ran correlation analyses between all 68 brain areas included as well as between subjects. Furthermore, to better understand how gyrification across regions is distributed in our sample, we applied the PHATE visualization method (Moon et al., 2019) to our data using the R package *phateR*. PHATE brings high dimensional biological data into lower-dimensional embeddings (2 dimensions) while capturing both local and global nonlinear structure. Fig. 1 shows gyrification data of the 68 DK-40 regions embedded in 2 dimensions as well as color labelled for diagnostic groups as classified by DSM-IV-TR. Based on the results of the computed pre-clustering analyses (see Section 3.1), data appeared to be suited for applying hierarchical agglomerative cluster analysis using ward-algorithm on a computed dissimilarity-matrix using Euclidean distance. Briefly, hierarchical clustering was chosen as no previous information on number of clusters was apparent from other studies. On the same incentive, agglomerative clustering was chosen to cluster the data in a bottom-up manner. The ward-algorithm was chosen due to showing the highest computed agglomerative coefficient (AC=0.9) compared to other algorithms. See Supplement S1. for description of argumentation for procedure selection.

#### 2.4.2. Cluster analysis

Cluster analysis was run on the dissimilarity matrix (computed with the function *daisy* implemented in R) with the package *cluster* in R using the *agnes*-function for hierarchical clustering. Dissimilarity matrix was computed using Euclidean distance and non-standardized gyrification data. Clusters were fused by ward-algorithm. We did not apply a standardization on gyrification data, as we only included data with the same metric for the cluster analysis. To validate the choice of number of clusters, Jaccard-bootstrapping with 100 permutations was run (function *clusterboot* implemented in R) for all possible cluster solutions of $k = 2$ to $k = 10$. *Clusterboot* resamples the data and computes Jaccard similarities of the original clusters to the resampled data. It then uses the mean over these similarities for stability of clusters (Hennig, 2007). For further validation of choice of cluster solution, cluster analysis and some of the post-clustering analyses were run again on 80% of the initial data.

#### 2.4.3. Post-clustering analyses

To evaluate which brain regions had the highest impact (importance) on forming the cluster solution, effect sizes were calculated for each brain region. To evaluate the association with basic cognition, we ran an ANOVA for the neuropsychological tests reported above as well as for the clinical parameters hospitalization, age of onset, and Medication-Index. Furthermore, we applied a $\chi^2$-test for association between our prenatal risk-score as well as the birth-complication risk-score and clusters. Likewise, we ran binomial tests for comorbidity vs. no comorbidity to evaluate if our cluster solution also maps on an overall index of comorbidity. We also ran subsequent binomial tests to see if diagnostic groups are equally distributed over clusters and no diagnostic group is over- or underrepresented in a cluster.

Secondary goal of this study was to see if diagnostic groups show significant different gyrification patterns to exclude the possibility of diagnostic groups being the best solution to explain gyrification variability.

Even though scanning protocols between the two sites were harmonized (Vogelbacher et al., 2018) and a quality assurance protocol was followed (Vogelbacher et al., 2019) we ran a *t*-test for the gyrification data to consider possible effects of the different scanning sites. Results did not yield any significant differences in gyrification between the two sites ($p<.0007$ after correction for multiple comparisons; see complete output table here: https://github.com/julia-pfarr/cluster_supplements/tree/main/supp_analyses).

Furthermore, although we did not include a healthy control group in the primary analysis of this paper (=cluster analysis), as the goal was a transdiagnostic one, we plotted the distribution of gyrification in a


**Fig. 1.** Scatterplot of gyrification data as distributed in our $N = 1028$ sample, coloured by DSM-groups. Figure shows a diffuse distribution of DSM-IV-TR diagnostic groups embedded in the two gyrification dimensions.
*Note:* Axes of the figure are the two PHATE dimensions after applying the PHATE (=Potential of Heat diffusion for Affinity-based Transition Embedding) algorithm for dimensionality reduction to our data matrix. Values of the axes represent the normalized affinities after embedding distances and affinities of the data matrix using Multidimensional Scaling method (Carroll and Arabie, 1998).

healthy control group ($n$ = 901; mean age 34,91; $m$ = 332, $w$ = 569) together with the gyrification distribution of our newly formed cluster groups as an additional reference for comparison or interpretation of the clusters.

## 3. Results

### 3.1. Pre-clustering results

Table 1 shows descriptive statistics and results of the Welch-ANOVA for clinical parameters of DSM-labelled groups. Descriptive analyses of the gyrification data showed to be normally distributed over subjects and identified expected variability in range and mean of individual areas (see Supplement S2.-Table 1 for descriptive table). Correlation of gyrification data between brain areas yielded overall low to moderate correlation with highest correlation coefficient being $r = 0.66$ ($p<.001$) between the right and left superiorfrontal cortex (see Supplement S3.-figure 1 for complete correlation matrix). Furthermore, correlation of gyrification data between subjects showed overall high correlation coefficients (see Supplement S4.-figure 2 for correlation matrix), indicating a rather globally underlying relationship between subjects based on their gyrification than a local one.

Fig. 1 shows a diffuse distribution of DSM-labelled groups in the reduced 2-dimensional scatterplot of gyrification data, hence indicating that clinical diagnoses do not cluster patients in homogeneous gyrification groups.

### 3.2. Clustering results

Decision on number of clusters was made using the elbow method on a screeplot, which was based on the total-within-distances of 10 clusters (for screeplot and dendrogram see Supplement S5.-figure 3a and b). Screeplot indicated the optimal number of clusters to be 3. Bootstrapping showed cluster 1 to be highly stable and cluster 2 and cluster 3 to be quite stable (cluster stabilities: cluster 1 = 0.79, cluster 2 = 0.75, cluster 3 = 0.72; (Mount and Zumel, 2019); cluster stabilities for further cluster solutions are listed in Supplement S6). Results of the cluster analysis on 80% of the initial data yielded similar results (with some expected variation) and can be found in Supplement S7.

### 3.3. Post-clustering results

Descriptive statistics and Welch-ANOVA results of the clusters are shown in Table 2. Subsequent binomial tests showed that diagnostic groups are equally distributed over clusters and no diagnostic group is over- or underrepresented in a cluster (see Supplement S8.-Table 2). Additionally, in Fig. 2 mean gyrification (sorted frontal-parietal-temporal-occipital) for clusters was plotted. Results show, that 1) cluster analysis identified a global, rather than local pattern of gyrification and 2) cluster 2 globally shows highest, cluster 1 moderate and cluster 3 lowest gyrification. Further, some local variations in gyrification can be found mainly in cluster 1: different to its global pattern (mid-high gyrification), cluster 1 shows highest gyrification in the left pars opercularis, pars orbitalis, pars triangularis, and the right transverse temporal cortex. In the left caudal anterior cingulate, the left and right parahippocampal gyrus as well as the left and right entorhinal cortex, cluster 1 shows lowest gyrification (see Supplement S9.-Table 3 for ANOVA post-hoc tests for gyrification between data-driven groups). Fig. 3 shows brain regions with $\eta^2>0.14$ (see Supplement S13.-Table 5 for all effect sizes).

Cluster 3 shows overall lowest performance (see Fig. 4) and ANOVA yielded significant differences ($p<.05$, Bonferroni-correction for multiple comparisons) for VF, DSST and CBBT. Prenatal-risk score showed significant association with our cluster solution ($\chi^2(4)=11.035$, $p=.026$). Largest contribution to the $\chi^2$ statistic comes from cluster 2 which shows more subjects without and less subjects with prenatal risk than statistically expected. Cluster 3 shows significantly less subjects without prenatal risk and trends toward more subjects with prenatal risk than statistically expected (see Table 3). Birth-complication score was not significantly associated with our cluster solution. Binomial tests for comorbidity (comorbidity vs. no comorbidity; test proportion 0.42/0.58) did not yield significant results (cluster 1: $p=.208$, cluster 2: $p=.368$, cluster 3: $p=.362$).

Results of the ANOVA between diagnostic groups yielded significant difference of gyrification in only seven of the 68 brain areas included ($p<.05$; see Supplement S10.-Table 4 and Supplement S11.-figure 4 for results).

The plot of gyrification data in a healthy control group together with the distribution of gyrification in our cluster groups shows that the gyrification distribution of the healthy control group is the most similar to the gyrification distribution in cluster group 1 (see Supplement S12.-figure 5).

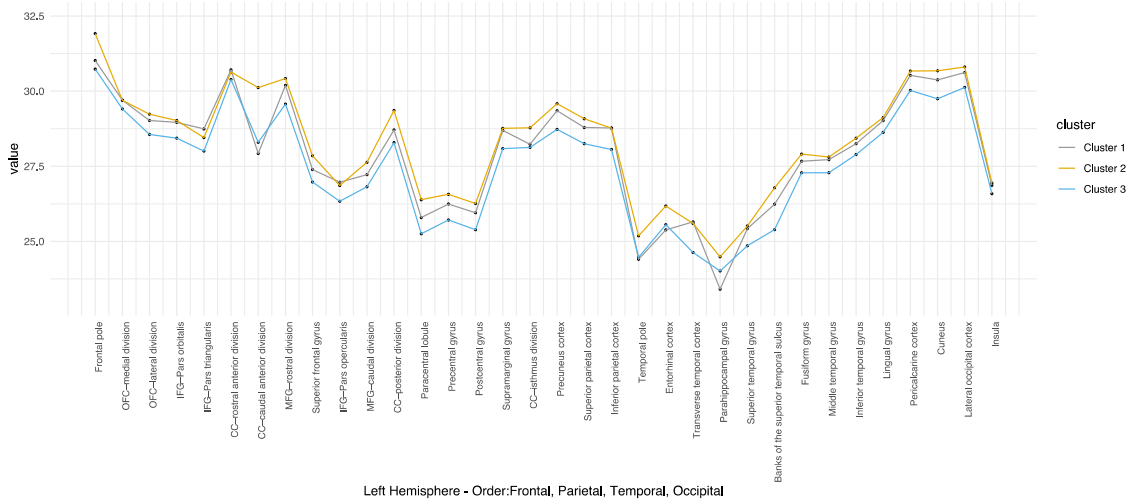
## 4. Discussion

In this study we investigated gyrification as a cortical phenotype and its relationship to basic psychopathology rather than DSM-IV-TR diagnoses using a data-driven multivariate approach. Cluster analysis identified three clusters which did not delineate along diagnostic groups but rather point towards transdiagnostic, global gyrification patterns underlying a considerable portion of variation in the data. These clusters are characterized by both differences in gyrification as well as differences in cognitive performance and early environmental risk. Main differences in gyrification between clusters and regions important for

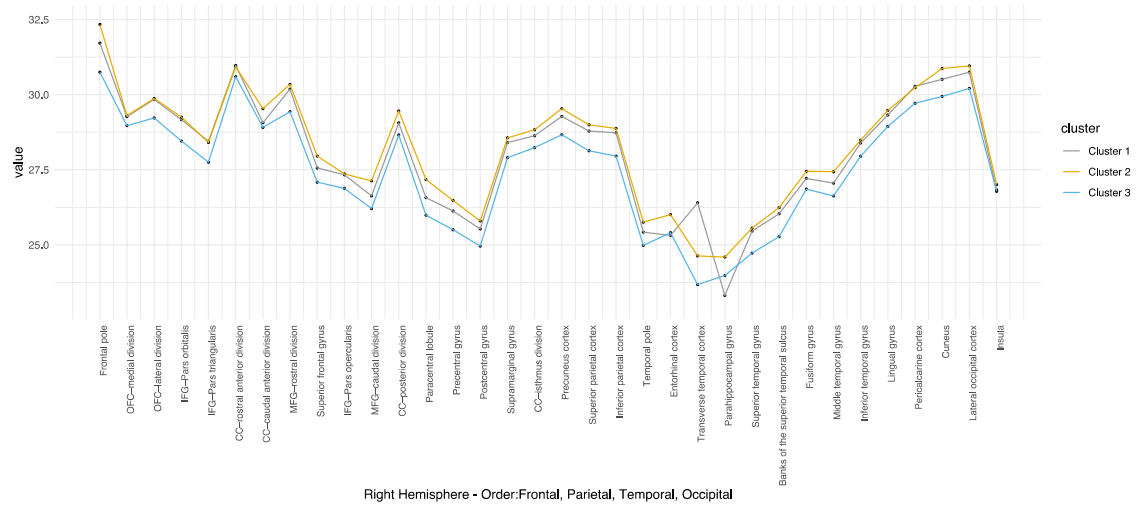
**Table 2**
Descriptives for our $k$ = 3 cluster solution.

| Cluster | n | Frequency DSM-groups within cluster | Mean age | Sex | Mean Age of Onset | Mean Hospitalization Duration in Weeks | Mean Medication-Index |
|---|---|---|---|---|---|---|---|
| 1 | 256 | MDD=193, *75.4%*<br>BD=36, *14.1%*<br>SZA=12, *4.7%*<br>SZ=15, *5.9%* | 40.04 | 91 m, 165 f | 26.92 | 16.71 | 1.53 |
| 2 | 378 | MDD=292, *77.2%*<br>BD=48, *12.7%*<br>SZA=11, *2.9%*<br>SZ=27, *7.1%* | 34.24 | 118 m, 260 f | 23.05 | 16.48 | 1.62 |
| 3 | 394 | MDD=298, *75.6%*<br>BD=45, *11.4%*<br>SZA=21, *5.3%*<br>SZ=30, *7.6%* | 38.74 | 181 m, 213 f | 26.51 | 19.49 | 1.79 |
| $p$ Welch-ANOVA/ $\chi^2$ | | | <0.001** | <0.001** | <0.001** | .238 | .149 |

** $p<.001$.




(a)




(b)

**Fig. 2.** a&b Plot of mean gyrification index per cluster for every region, ordered frontal-parietal-temporal-occipital. a) Left hemisphere, b) right hemisphere.

forming the cluster solution are mostly located in association cortices (superior frontal gyrus, middle frontal gyrus, cingulate cortex, superior temporal cortex, superior and inferior lateral parietal cortex, paracentral, postcentral, and precentral gyrus as well as precuneus; see Fig. 3) which further underlines transdiagnostic similarities in gyrification. The lack of significance of DSM-group analyses points toward super-ordinate factors that are only indirectly related to diagnostic categories. These findings have important implications for our understanding of data-driven classification based on biological parameters in general, as well as the usefulness of gyrification/cortical folding as a marker of risk for psychiatric disorders or life-time psychopathology:

First, our findings of the cluster analysis showed global vs. regional variations of gyrification and transdiagnostic effects in specific regions. The identified clusters are characterized by an overall global pattern, namely a separation by the degree of gyrification over all brain regions, as well as an even distribution of diagnostic groups over clusters. This was also confirmed by an additional cluster analysis including only 80% of the data. Cluster 1 however shows some variation apart from its global gyrification pattern, mainly in fronto-temporal regions. This can be embedded in results of previous studies of gyrification showing involvement of fronto-temporal regions in (early) risk for psychopathology (Evermann et al., 2020; Pham et al., 2021; Rosa et al., 2021), as cluster 1 also showed to be highly stable after bootstrapping. It furthermore speaks for the argument, that a transdiagnostic evaluation of global gyrification patterns is well suited to evaluate the relationship of gyrification and basic risk factors for psychopathology. This is supported by the fact that these local shifts in fronto-temporal regions only appear present in our newly formed, transdiagnostic cluster but not in the DSM-defined group comparison (see Supplement S11.-figure 4).

Yet, our cluster solution is associated with cognitive and prenatal markers of psychopathology, which cross diagnostic boundaries, and rather reflect transdiagnostic risk for life-time psychopathology: cluster

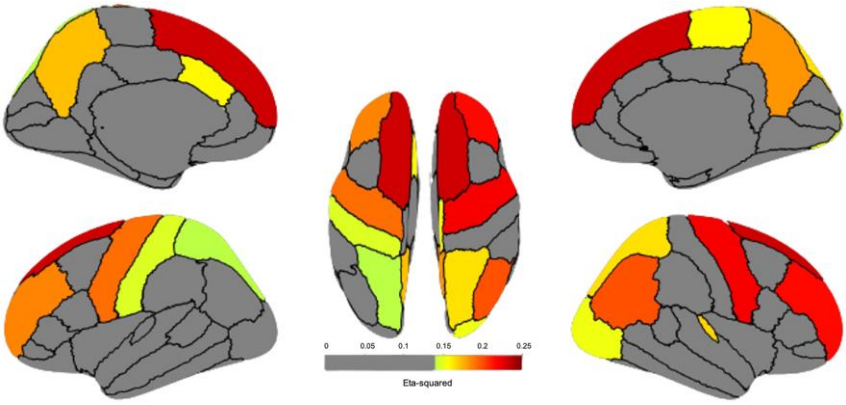



**Fig. 3.** Figure shows brain regions that contributed most to our cluster solution ($\eta^2$>0.14; brain regions with an effect-size $\eta^2$<0.14 are colored in gray).

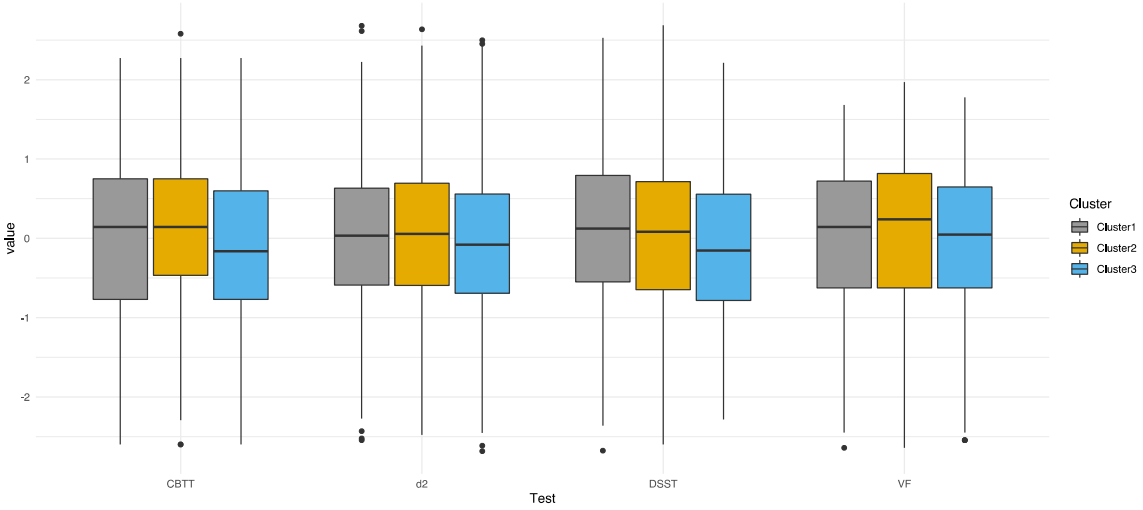



**Fig. 4.** Boxplots for neuropsychological test scores (z-standardized), grouped by clusters. Cluster 3 shows significantly poorest performance across all tests.
*Note: CBTT=Corsi block-tapping test; d2=d2 Test of Attention; DSST=Digit Symbol Substitution Test; VF=Verbal fluency.*

3 shows overall lowest gyrification and overall lowest performance in cognitive tasks. Furthermore, cluster 3 contains more individuals with a prenatal risk and less individuals without prenatal risk than statistically expected. Although not significantly, cluster 3 also has the highest mean in hospitalization duration as well as the Medication-Index. Being able to relate overall low gyrification, low performance in cognitive tasks, and higher prenatal risks further supports the hypothesis of a high impact of early developmental influences to manifest in gyrification (Al-Haddad et al., 2019; Birnbaum and Weinberger, 2017; Pham et al., 2021). Although there are no significant differences between cluster 1 and 2 in prenatal risk, birth complications, cognitive tasks or clinical variables, plotting the gyrification distribution of our newly formed clusters together with the gyrification distribution of a healthy control group (Supplement S12.-figure 5) points toward cluster 1 showing the distribution most similar to gyrification in individuals without psychiatric disorders. Cluster 1 also does not show significant results of prenatal risk (other than cluster 2; Table 3) which also speaks for this cluster being the most "normative". Future studies could therefore apply a cluster analysis on gyrification data of subclinical populations for identification of similar gyrification patterns of individuals without clinical psychopathology but high prenatal risk. This could break down the actual potential of gyrification as a neurobiological marker for mental illness proneness.

Our cluster groups do show different gyrification patterns, but differences are partly restricted to particular brain regions. Cluster 3, in comparison to Cluster 1 and 2, shows significant lower gyrification in almost every brain region. Significant differences in local gyrification between these two clusters can primarily be found in the association cortices. This is in line with the fact, that diverse or transdiagnostic symptom representations are consistently found to be rather associated with alterations in association cortices than regions of lower hierarchy (Sydnor et al., 2021). In addition, brain regions important for discriminating groups of individuals and hence forming our cluster solution (regions with effect-sizes of $\eta^2$>0.14; Fig. 3) can be characterized as brain regions of association cortices (Sydnor et al., 2021). Our cluster solution therefore might reflect that variability in association cortices is higher and that group differences based on gyrification should rather be investigated in those areas, as these tend to have the power to discriminate between groups. Together with evidence showing that late prenatal and postnatal cortical folding primarily happens in association cortices (Matsuda and Ohi, 2018), our cluster solution can serve as a basis for further narrowing brain regions included for association with particular prenatal and postnatal variables.

Given the significant difference in mean age between the cluster

**Table 3**
Results of the $\chi^2$-test of prenatal risk * cluster groups. Adjusted residuals >1.96 or >−1.96 indicate a significantly different number of expected counts (positive value = more counts than expected; negative value = less counts than expected). Largest contribution to the $\chi^2$ statistic ($\chi^2(4)=11.035$, $p=.026$) comes from cluster 2 which shows more subjects without and less subjects with prenatal risk than statistically expected. Cluster 3 shows significantly less subjects without prenatal risk than statistically expected.

| | | Missing values | 0 = no prenatal risk | 1 = at least one prenatal risk | Total |
|---|---|---|---|---|---|
| Cluster 1 | Count | 14 | 108 | 134 | 256 |
| | Expected Count | 12.2 | 117 | 126.8 | |
| | Adjusted Residual | .6 | −1.3 | 1 | |
| Cluster 2 | Count | 14 | 198 | 166 | 378 |
| | Expected Count | 18 | 172.8 | 187.2 | |
| | Adjusted Residual | −1.2 | 3.3 | −2.7 | |
| Cluster 3 | Count | 21 | 164 | 209 | 394 |
| | Expected Count | 18.8 | 180.1 | 195.1 | |
| | Adjusted Residual | .7 | −2.1 | 1.8 | |

*Note:*.
Count = Observed number of subjects within the respective cluster in our data.
Expected Count = Statistically expected number of subjects within the respective cluster in our data.
Adjusted Residual = raw residuals (or the difference between the observed counts and expected counts) divided by an estimate of the standard error.

groups, discussion of this result is needed. Even though gyrification shows relative stability over lifetime in comparison to other morphometric measurements, significant age effects on gyrification have been shown in previous studies (e.g., (Hogstrom et al., 2013)). With the data included without prior control for age, we cannot exclude an effect of age on our cluster solution but there are multiple arguments which let us conclude that age did not play a significant role: 1) Age only showed a small effect size of $\eta^2$=0.036 for our cluster solution. 2) Brain areas identified by Hogstrom et al. (2013) with linear age effects for gyrification are indeed brain areas that contributed strongly to our cluster solution ($\eta^2$ between 0.129 to 0.241) but so did frontal lobe areas (amongst others) as well which Hogstrom et al. (2013) found to be non-linear and not significantly correlated with age. Furthermore, additional regression analyses showed that age is a significant predictor for gyrification in some of the brain areas but not systematic for the brain areas that contributed most to our cluster solution (see Supplement S13.-Table 5). 3) The healthy control group with its mean age of 34,91 showed the most similar pattern with cluster 1. The healthy control group is significantly younger than cluster 1 but still the most similar in gyrification. 4) Cluster 1 and 3 are not significantly different in age ($p$=.610) but in gyrification. Future studies could build upon this result by e.g., comparing cluster solutions between samples with and without age regressed out prior to clustering.

Sex also showed a significant difference between the cluster groups ($\chi^2(2)=18.586$, $p<.001$, Cramer's $V = 0.27$). Sex composition in cluster 1 was not significant, cluster 2 contains significantly more female and less male individuals than expected. Cluster 3 contains significantly more male and less female individuals than expected (see output table here: https://github.com/julia-pfarr/cluster_supplements/tree/main/supp_analyses). Previous studies identified significant sex differences in gyrification which are restricted to certain brain areas (e.g., (Forde et al., 2017; Mutlu et al., 2013; Papini et al., 2020). We therefore need to acknowledge that our cluster solution might partly be due to the effect of sex which should be addressed in future studies.

Using DSM-IV-TR diagnoses for definition of subgroups within the cohort had little, if any, power in discriminating global gyrification patterns (see Supplement S10.-Table 4 and Supplement S11.-figure 4). Mean comparison of gyrification between diagnostic groups yielded significant differences in only seven of the 68 brain regions included in our analysis. As shown in Fig. 1 this is not a surprising result, as distribution of groups within gyrification dimensions is diffuse and do not tend to form separate data-clouds. This does not mean that DSM-labelled grouping is not an appropriate approach for investigating local differences is gyrification specific to diagnoses, as small, locally based effects cannot be captured with a simple mean comparison. However, it could imply that meaningful impacts of altered gyrification on psychopathology in general are missed due to the categorical clinical grouping.

This study contributed to approaching the challenge of population sorting in psychiatric neuroimaging studies. A priori defined groups based on clinical diagnoses limits the power of brain structural and functional analyses by oversimplifiying the neural correlates associated with mental disorders (Bandettini et al., 2022). Classic Brian Wide Association Studies (BWAS) are helpful and necessary for identifying the most common effects over a large study cohort, but the most common effects do not necessarily equal the most meaningful effects for a particular disorder (Gratton et al., 2022). With data-driven approaches like ours, biological underpinnings of a disease can be detected which would have been left unknown with a classic BWAS approach.

There are some limitations to our study that need to be addressed. Individuals with a diagnosis of MDD were overrepresented in our sample (see output of a cluster analysis with MDD patients only of our sample here: https://github.com/julia-pfarr/cluster_supplements/tree/main/supp_analyses/MDDonly). For a more comprehensive transdiagnostic evaluation the sample would need a more even ratio of diagnostic groups. To be able to have more certainty on parameters regarding the cluster analysis (which was the main analysis) we did not go with a smaller, matched sample but went with the higher sample size. Cluster analysis is an explorative approach. It is expected that changes, e.g., in sample size yield a different cluster solution than ours. Results of cluster analyses are also highly dependent on the clustering algorithm used which is based on external characteristics unique to the data included, making comaprisons between studies with different clustering algorithms difficult. Furthermore, as we only included brain data but no other phenotypic data in our initial cluster analysis, the identified clusters can only be certainly characterized by their gyrification data and pattern but not as holistic defined subgroups. As well, we only included rather broad brain regions (DK40 atlas). Using another, more specific brain atlas might capture more complex patterns in the data.

## 5. Conclusion

Our study is the first to identify gyrification patterns based solely on themselves. Explorative, data-driven approaches like ours can help to elucidate if the brain imaging data on hand actually has the potential to find meaningful associations in relation to diagnostic categories (as commonly described by univariate approaches) or if the underlying biological structure implies another embeddedness of psychopathology.

Our findings implicate transdiagnostic risk factors for life-time psychopathology to be associated with global (and some regional) variation in gyrification rather than associations with narrowed diagnostic categories. Results of this study might thus have implications in the process of early detection of psychopathology as identified gyrification patterns are not bound to specific diagnostic categories but offer a broader perspective on psychopathology risk and therefore on risk evaluation. Group-analyses based on DSM categories thus might not be the best way to actually detect meaningful associations. Therefore, finding transdiagnostic similarities regarding gyrification and underlying factors responsible for its variation might be more promising for elucidating the global relationship of gyrification and psychopathology.

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## Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The FOR2107 cohort project was approved by the Ethics Committees of the Medical Faculties, University of Marburg (AZ:07/14) and University of Münster (AZ:2014–422-b-S).

## Data and code availability statement

Original data matrix cannot be shared due to privacy restrictions but can be requested from the corresponding author (upon reasonable request and data user agreement). Use of R codes is described in the methods section and R code as well as output tables of additional analyses can be found in this GitHub repository: https://github.com/julia-pfarr/cluster_supplements.

## CRediT authorship contribution statement

**Julia-Katharina Pfarr:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Tina Meller:** Data curation, Investigation. **Katharina Brosch:** Data curation, Investigation, Writing – review & editing. **Frederike Stein:** Data curation, Investigation, Writing – review & editing. **Florian Thomas-Odenthal:** Data curation, Investigation, Writing – review & editing. **Ulrika Evermann:** Data curation, Investigation, Writing – review & editing. **Adrian Wroblewski:** Data curation, Writing – review & editing. **Kai G. Ringwald:** Data curation, Investigation. **Tim Hahn:** Validation, Writing – review & editing. **Susanne Meinert:** Data curation, Investigation, Writing – review & editing. **Alexandra Winter:** Data curation, Investigation, Writing – review & editing. **Katharina Thiel:** Data curation, Investigation. **Kira Flinkenflügel:** Data curation, Investigation, Writing – review & editing. **Andreas Jansen:** Funding acquisition, Resources, Supervision, Writing – review & editing. **Axel Krug:** Funding acquisition, Project administration, Supervision. **Udo Dannlowski:** Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. **Tilo Kircher:** Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing. **Christian Gaser:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Igor Nenadić:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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Biomedical financial interests or potential conflicts of interest: Tilo Kircher received unrestricted educational grants from Servier, Janssen, Recordati, Aristo, Otsuka, neuraxpharm. All other authors declare no conflict of interest.

## Data availability

Data will be made available on request.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2023.120349.

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# Trait schizotypy and the psychosis prodrome: Current standard assessment of extended psychosis spectrum phenotypes

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ABSTRACT

Schizotypy has become an increasingly important construct for elaborating psychotic disorders that vary along the schizophrenic spectrum. However, different schizotypy inventories vary in conceptual approach and measurement. In addition, commonly used schizotypy scales have been seen as qualitatively different from screening instruments for prodromal schizophrenia like the Prodromal Questionnaire-16 (PQ-16).

Our study investigated the psychometric properties of three schizotypy questionnaires (the Schizotypal Personality Questionnaire–Brief, Oxford-Liverpool Inventory of Feelings and Experiences, and the Multidimensional Schizotypy Scale) as well as the PQ-16 in a cohort of 383 non-clinical subjects. We initially evaluated their factor structure using Principal Component Analysis (PCA) and used Confirmatory Factor Analysis (CFA) to test a newly proposed composition of factors.

PCA results support a three-factor structure of schizotypy that accounts for 71 % of the total variance, but also shows cross-loadings of some schizotypy subscales. CFA of the newly composed schizotypy factors (together with an added neuroticism factor) shows good fit. Analyses including the PQ-16 indicate considerable overlap with measures of trait schizotypy, suggesting that the PQ-16 might not be quantitatively or qualitatively different from schizotypy measurements.

Taken together, results indicate that there is good support for a three-factor structure of schizotypy but also that different schizotypy measurements grasp facets of schizotypy differently. This points towards the need for an integrative approach for assessing the construct of schizotypy.

## 1. Introduction

Schizotypy describes a phenotype capturing a broad set of schizophrenia-like trait representations and thereby illustrating vulnerability for schizophrenia-spectrum disorders, which makes the schizotypy construct increasingly important for schizophrenia research (Barrantes-Vidal et al., 2015; Mason, 2015; Nelson et al., 2013). Similar to schizophrenia, schizotypy is often conceptualized using a three-factor construct (Fonseca-Pedrero et al., 2021; Kwapil and Barrantes-Vidal, 2015; Polner et al., 2021), comprising positive, negative, and disorganized facets: Positive schizotypy includes psychotic-like experiences such as perceptual biases and odd beliefs, negative schizotypy is characterized by deficits in functioning such as flattened affect, diminished motivation, and social disinterest, and disorganized schizotypy is characterized by disruptions in the organization and expression of thought, speech, behavior, and emotions.

The construct of schizotypy is well suited to further elucidate schizophrenia-spectrum disorders (SSD) by associating schizotypy not only with clinical features of SSD but also in studies exploring genetic risk (Ettinger et al., 2014; Kemp et al., 2021; Meller et al., 2019b; Nenadić et al., 2022; Walter et al., 2016), as well as neurobiological (Ettinger et al., 2015; Kirschner et al., 2022; Meller et al., 2019a, 2020; Pfarr and Nenadić, 2020; Sahakyan et al., 2020; Tonini et al., 2021) and cognitive correlates (Carrigan and Barkus, 2017; Ettinger et al., 2015;

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Karamaouna et al., 2020; Sahakyan and Kwapil, 2016; Steffens et al., 2018).

While there is some consensus that schizotypy, like schizophrenia, should be seen as a multidimensional construct varying along a continuum of health and illness, terminology and assessment of schizotypy is still used heterogeneously (Oezgen and Grant, 2018), prompting the need for further evaluation and definition of the construct (Rivera Tapia, 2022; Grant et al., 2018; Kwapil and Barrantes-Vidal, 2015).

### 1.1. Delineating schizotypy

Although schizotypy is not (always) necessarily seen as a psychopathological construct itself, it is an important part of the psychosis continuum (van Os et al., 2009), which spans from non-clinical manifestations of schizotypal traits to those associated with schizophrenia spectrum pathology. This continuity is indeed described elaborately in the literature (e.g., Claridge and Beech, 1995; Grant et al., 2018; Kwapil and Barrantes-Vidal, 2015). However, within the psychosis continuum, conceptual ambiguity about the construct of schizotypy makes it difficult to define what is part of this continuum and what these parts of the continuum actually mean with regards to content (Grant et al., 2018). A unifying conceptualization of the construct of schizotypy therefore remains open.

Previous work has studied associations of schizotypy with other psychopathological dimensions separately, which is important to gain more conceptual clarity. Lewandowski et al. (2006) elaborated on associations of schizotypy with symptoms of mood and anxiety disorders, finding anxious and depressive symptoms to be highly correlated with positive psychometric schizotypy in a non-clinical sample. More recently, Kemp et al. (2018) included disorganized schizotypy and found that clinical and non-clinical manifestations of negative emotions were better accounted for by disorganized schizotypy. In another study, affective and anhedonic features were found to be correlated with negative schizotypy (Kwapil et al., 2020). Diminished affect and anxiety often result in decreased social behavior (de Lijster et al., 2018; Kupferberg et al., 2016), raising the question to which extent affective or anhedonic features as well as anxiety are part of schizotypy conceptually (or only result in similar behavioural markers) and how they should be considered when measuring psychometric schizotypy. As another example, non-mood psychotic disorders vs. SSDs show qualitatively different symptoms and can be clearly separated from each other on a categorical level but overlap on a dimensional level. As a part of the psychosis continuum, it is obvious that schizotypy should also represent these diverse facets. However, it is still unclear whether and to which amount related mood and anxiety symptoms and/or varying symptom representations within the spectrum of schizophrenic disorders should also be considered when measuring the construct of schizotypy. Recent findings (e.g., Kemp et al., 2018; Kwapil et al., 2020) suggested that mood and anxiety symptoms are most strongly associated with the disorganized schizotypy dimension, which appears to involve dysregulation of the experience of emotion, as well as disorganized thought, communication, and behavior.

Schizotypy has also been linked to other non-clinical personality concepts, e.g., the Big-Five personality traits or the PID-5 factors (Personality Inventory for DSM-5) (Cicero et al., 2019; Kemp et al., 2022). However, these associations need to be interpreted with caution: for example, distress-based wording for assessing neuroticism can indeed tap into schizotypy dimensions when those items are phrased distress-based, too (Asai et al., 2011; Oezgen and Grant, 2018). If this overlap should be considered by using items that reflect neuroticism or not, is still in debate. Note, however, that Kemp et al. (2022) found that associations of the schizotypy facets (using the Multidimensional Schizotypy Scale) with the PID-5 domains did not appear to be due to redundant items in the two measurements.

Moreover, there is some inconsistency about whether capturing psychosis proneness with certain measurements should be qualitatively considered the same as measuring schizotypy (Bang et al., 2019). Arguments have been offered that measurements aiming to screen for prodromal and psychotic syndromes are distinguishable from schizotypy measurements (e.g., Prodromal Questionnaire, PQ) (Ising et al., 2012; Loewy et al., 2005). More precisely, the PQ-16 represents a low-level screener of mostly positive psychotic-like experiences (PLE) (McDonald et al., 2019) to capture prodromal symptom representations. However, the PQ-16 does not consider the important aspect of time for determining a prodromal stage. Previous work on the relationship of schizotypy measurement and the PQ-16 found substantial correlation as well as a moderating effect of schizotypy for number of experienced PLEs (Kline et al., 2012), raising the question if the PQ-16 actually qualitatively differs from common schizotypy measurements.

In a study by Fonseca-Pedrero et al. (2016) the approach of latent profile analysis (LPA) was applied to schizotypy as well as prodromal measurements to identify different psychometric profiles of individuals with regard to schizotypy and clinical high-risk symptoms. Although the authors indeed found moderately high correlations between the PQ-16 and the positive and disorganized subscales of the included schizotypy measurements, the PQ-16 appeared to be useful to distinguish between the two classes of “high positive schizotypy” and “psychosis high risk”.

### 1.2. Conceptualisations of schizotypy measurements

In a comparative study Oezgen and Grant (2018) investigated and compared the outcome of three commonly used schizotypy questionnaires in one sample and showed that results indeed depend on the particular schizotypy measurement used. The variability across schizotypy measurements lies not only in range and length but also in content and factor-structure (Cohen et al., 2015; Mason, 2015). This can be mostly attributed to the fact that current schizotypy measurements were derived from different conceptualizations of the schizotypy construct and different scale development methods, which are shortly outlined in the following:

Early schizotypy measurements like the Wisconsin Schizotypy Scales (WSS) can be described as *distress-based*, aimed at capturing different schizophrenia-like symptom features (i.e., physical anhedonia, perceptual aberration, magical ideation, social anhedonia) on separate scales (Chapman et al., 1995). For scale development, the authors of the WSS closely followed the checklist of schizotypic experiences proposed by Meehl (1964), hence items in the WSS were chosen based on detailed trait specification using rationale scale development methods. Subsequent analysis showed that the underlying dimensional structure of the WSS is a two-factor (positive and negative) one, lacking a disorganized dimension (Gross et al., 2014; Kwapil et al., 2008). In order to not obfuscate, it should be noted that the WSS sometimes are referred to as the Chapman Psychosis Proneness Scales (Smith et al., 2016).

The Schizotypal Personality Questionnaire (SPQ) by Raine (1991) is another distress-based questionnaire that shows considerable overlap in latent factors with the WSS (Wuthrich and Bates, 2006). However, the SPQ is technically not a measure of schizotypy: The SPQ was developed to assess schizotypal personality disorder traits based on the nine diagnostic criteria of schizotypal personality disorder defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) (American Psychiatric Association, 1987). While Raine et al. (1994) argue for a three-factor solution of the SPQ, confirmatory factor analyses in other studies are still inconclusive regarding the actual underlying factor structure (Gross et al., 2014; Moussa-Tooks et al., 2021; Zhang and Brenner, 2017).

The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) (Mason et al., 1995) initially identified a four-factor structure for schizotypy based on exploratory factor analysis of a large set of schizotypy and personality items. Mason and Claridge (2006) subsequently suggested that schizotypy is limited to the first three factors, whereas Oezgen and Grant (2018) suggested a four-factorial solution when comparing the O-LIFE to the SPQ and the WSS. The authors of the O-LIFE

developed the scale in an atheoretical manner based on a wide range of scales, i.e., the Chapman's anhedonia scales (Chapman et al., 1976), Eysenck's Personality Questionnaire (EPQ) which includes neuroticism (Eysenck and Eysenck, 1975), or Claridge's Schizotypal Trait Questionnaire (STQ) which also taps on Borderline personality (Claridge and Broks, 1984). As a result, the O-LIFE also comprises several "atypical" schizotypy features.

The most recently developed schizotypy questionnaire for assessing schizotypy within the general population, the Multidimensional Schizotypy Scale (MSS) (Kwapil et al., 2018b), follows the three-factorial model of schizotypy and its subscales are designated as positive, negative and disorganized dimensions of schizotypy. The authors' assumptions were trait-based and items were then phrased to map on those, considering the multidimensional structure of schizotypy and non-distress based as well as culturally unbiased wording (Kemp et al., 2020; Kwapil et al., 2018b). Using confirmatory factor analyses, Kwapil et al. (2018a) reported that, as hypothesized, a three-factor structure provided the best fit for the items. However, Christensen et al. (2019) suggested that the negative schizotypy factor comprised two facets (affective and social anhedonia).

For a brief overview of the development of the different schizotypy scales regarding conceptualization, content, as well as their relationship to each other see Fig. 1.

### 1.3. Goals of the present study

Taken together, it is unlikely that the current commonly used schizotypy questionnaires actually share an identical latent structure and that the subscales of the different questionnaires can be used interchangeably. Understanding the scales' overlap and divergence as well as finding a unifying approach to assess schizotypy and its multidimensional structure are important for dealing with heterogeneity within the construct itself and further to use it as a useful framework for exploring schizophrenia-spectrum psychopathology. Detailed psychometric evaluation of the schizotypy measurements as well as the use of techniques to investigate and confirm overall dimensionality and factor structure of the construct are needed to gain further insights.

In the present study, we analyzed different schizotypy scales obtained in a young population sample of psychiatrically healthy subjects to address the questions of overlap (vs. differences) between conceptualization and psychometric features across the instruments introduced above, as well as their relation to the PQ-16 inventory, a commonly used questionnaire developed for assessing of prodromal signs within the schizotypy continuum. We hypothesize, that schizotypy measurements show psychometric results congruent to their method of development but differences among each other in psychometric properties as well as with regards to content. Given that the psychosis prodrome is conceptualized to be an expression of the schizotypy continuum and the fact that the PQ-16 is largely comprised of items assessing experiences found in positive schizotypy, we expect that the scale will exhibit substantial associations with the schizotypy questionnaires, especially measures of positive schizotypy.

## 2. Methods

### 2.1. Study cohort

We included 383 psychiatrically healthy participants (mean age = 23.97 years, SD = 4.18; 250 females, 133 males) recruited from the local community by circular emails, local and online advertisements. The study cohort overlaps with a recently analyzed cohort published in Nenadić et al. (2021). Prior to participation, individuals were screened using the screening instrument of the Structured Clinical Interview for DSM-IV (Wittchen et al., 1997) to ensure the absence of any current or former clinical psychiatric condition(s). Further exclusion criteria were: non-native German speaker and/or not of central European descent, psychotropic medication, general intellectual impairment/learning disability, defined as intelligence quotient (IQ) lower than 80 (estimated with the German Mehrfach-Wortschatz-Intelligenztest-B) (Lehrl et al., 1995) and exceedance of the PQ-16 cut-off as defined by Chen et al. (2016) (see Section 2.2.4 for further description). We did not specifically exclude participants with a first-degree relative suffering from a psychotic disorder.

Individuals gave written informed consent prior to participation and received financial compensation afterwards. Our study protocol was approved by the local Ethics Committee of the School of Medicine,

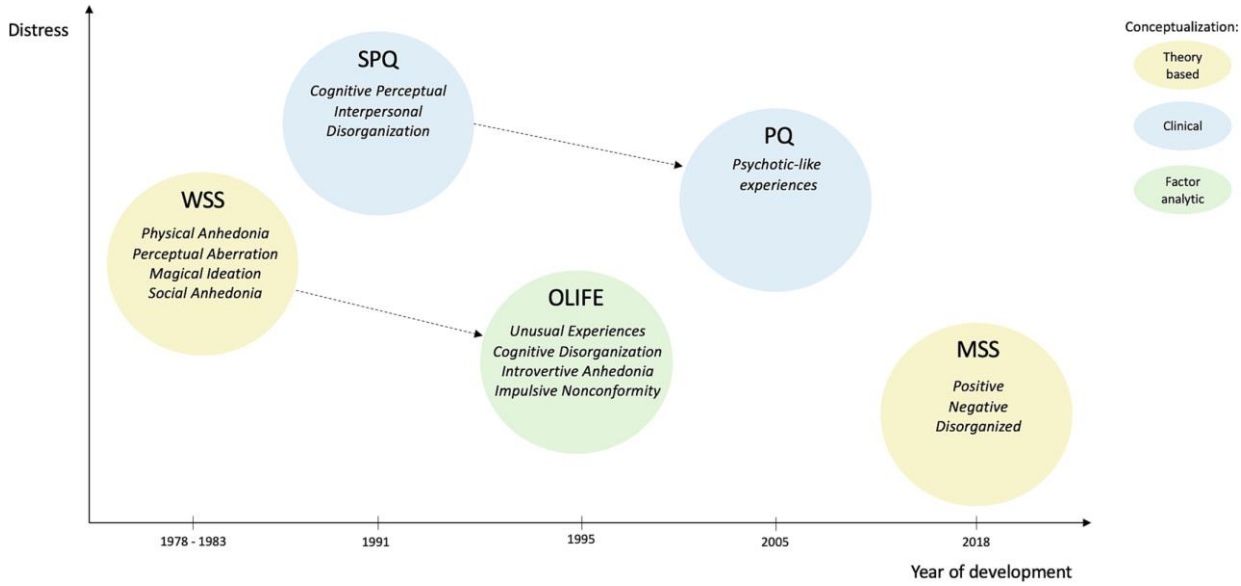


**Fig. 1.** Overview of different schizotypy scales.
*Abbreviations:* WSS=Wisconsin Schizotypy Scales, SPQ = Schizotypal Personality Questionnaire, OLIFE = Oxford-Liverpool Inventory of Feelings and Experiences, PQ = Prodromal Questionnaire, MSS = Multidimensional Schizotypy Scale.

Philipps-University Marburg (protocols no. 61/18 and 79/18), according to the latest version of the Declaration of Helsinki (World Medical Association, 2013).

### 2.2. Psychometric schizotypy self-report measurements

Participants received a personalized link to an online-survey platform (https://www.soscisurvey.de/; Leiner, 2019) to complete the schizotypy questionnaires within a larger test battery. All participants included in analyses had fully completed questionnaires.

Following the original validation studies (Compton et al., 2007; Kwapil et al., 2018b; Mason et al., 1995; Mason and Claridge, 2006), we calculated the subscores and sumscores of all questionnaires used, leading to a total of 13 (sub)scales for analyses. Given that our emphasis was on the dimensional structure of schizotypy, we focused our analyses on the dimensional subscales rather than total schizotypy scores. All questionnaires were administered in their German versions which were already used in previous studies (SPQ—B: (Klein et al., 1997), O-LIFE: (Grant et al., 2013), MSS: (Pfarr and Nenadić, 2020; Nenadić et al., 2021), PQ-16: (Evermann et al., 2021), BDI: (Kammer, 1983)).

#### 2.2.1. Schizotypal Personality Questionnaire-Brief (SPQ—B)

Based on 22 yes/no-items the SPQ-B measures schizotypy on three subscales, namely the 8-item *Cognitive-Perceptual (SPQB-CP)* subscale, which taps positive schizotypy, 8-item *Interpersonal (SPQB-IP)* subscale that taps aspects of negative schizotypy, along with social anxiety and disocomfort, and the 6-item *Disorganized (SPQB-DO)* subscale that taps eccentricity (Raine, 2001). Items responded to with "yes" score 1, whereas items responded to with "no" score 0 (possible total range 0–22). Higher scores indicate higher levels of psychometric schizotypy.

#### 2.2.2. Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)

The O-LIFE comprises four subscales with 104 yes/no-items in total: *Unusual Experiences (UnEx), Cognitive Disorganization (CogDis), Introvertive Anhedonia (IntAn), Impulsive Nonconformity (ImpNon)* (Grant et al., 2013; Mason and Claridge, 2006). UnEx aims to tap the positive schizotypy dimension with 30 items, CogDis refers to the disorganized dimension of schizotypy although the subscale contains 24 items that assess a mix of experiences including difficulty in thinking, anxiety, and moodiness. IntAn represents the negative schizotypy dimension distributed over 27 items largely assessing physical and social anhedonia, and ImpNon captures an anti-social and eccentric form of behavior with 23 items. Items affirmatively endorsed score 1 and scoring of inversed phrased items was reversed for calculations (possible total range 0–104). Higher scores indicate higher levels of psychometric schizotypy.

#### 2.2.3. Multidimensional Schizotypy Scale (MSS)

The MSS uses 77 true/false-items to measure schizotypy on three subscales, named according to which schizotypy dimension they capture: *MSS-Negative* with 26 items, *MSS-Positive* with 26 items as well as *MSS-Disorganized* with 25 items (Kwapil et al., 2018b). Positively endorsed items scoring 1 and negatively endorsed items scoring 0. Scoring of inversed phrased items was reversed for calculations (possible total range 0–77). Higher scores indicate higher levels of psychometric schizotypy.

#### 2.2.4. Prodromal Questionnaire (PQ-16)

The short version of the Prodromal Questionnaire (Loewy et al., 2005) measures psychotic-like experiences (PLEs) with 16 true/false-items on a single scale (Ising et al., 2012), with positively endorsed items scoring 1 and negatively endorsed items scoring 0 (possible total range 0–16). Answers are then summed up to a PLE total score as well as a PLE distress score which indicates current distress severity by PLEs ("none" = 0 to "severe" = 3).

Chen et al. (2016) used this short version of the PQ-16 in a comparable sample to ours and concluded that individuals exceeding cut-off scores indicate the necessity of further psychopathological evaluation. We used these cut-offs in our sample and did not include individuals exceeding these thresholds in our analyses. Thus, no individuals in our sample were help-seeking and/or at elevated risk.

#### 2.2.5. Beck Depression-Inventory (BDI)

Negative symptoms of schizotypy share some phenomenological similarities with depressive symptomatology, but can be different in both quantity as well as quality (Lewandowski et al., 2006). Hence, the two constructs should be administered separately but compared. To ensure an elaborated evaluation of the actual schizotypal characteristics of our sample, subjects completed the BDI (Beck et al., 1987) additional to the schizotypy measurements. With 21 items the depressive state of the past week is assessed. Scoring is based on declaration of current presence of symptoms (0 = symptom was not experienced during the past week; 3 = symptom was experienced predominantly during the past week). Higher scores indicate a higher level of current depressive state.

### 2.3. Analyses

We first computed descriptive statistics on the subscales as well as the correlation matrix. As the OLIFE_ImpNon subscale conceptually captures anti-social and impulsive/eccentric behavior rather than schizotypy (Cochrane et al., 2010) and showed very little correlation with all other scales in our analyses, this subscale was excluded from further analyses.

Second, we performed multiple Principal Component Analyses (PCAs) including the subscales of the schizotypy measurements as well as the PQ-16 in two of the PCAs, to extract the most important independent factors. PCA reduces dimensionality of a dataset by deriving a smaller number of variables (principal components) from a higher number of original variables while maintaining most of their variability (Jolliffe, 2005).We conducted three PCAs in total with the following specifications: 1. PCA: all subscales included, free factor solution; 2. PCA: all subscales included, forced three-factor solution; 3. PCA: PQ-16 excluded, forced three-factor solution.

Lastly, Confirmatory Factor Analyses (CFAs) were run to test our hypotheses regarding factor-structure of newly composed schizotypy factors. Specifically, we compared 1, 2, and 3-factor models of the schizotypy dimensions, as well as a 4-factor model with a separate neuroticism factor. The CFA analyses were differentiated from the PCA analyses by testing specific hypotheses and the use of item parcels. In order to produce robust estimates and following Kwapil et al. (2008), we computed item parcels out of the subscales which resulted in multiple parcels for positive, negative, and disorganized schizotypy, as well as neuroticism (see Little et al., 2002). Each parcel was constructed to have a comparable proportion of items from the beginning, middle, and end of the relevant subscale. Items that did not fit for content or had no variance were dropped. Discussion of our CFA approach can be found in the supplements S1 and the exact composition of the parcels as well as the dropped-out items are shown in supplementary Table S2. We hypothesized that the 3-factor model would have the best fit for the CFA analyses that only included the schizotypy parcels, and that the 4-factor model would have the best fit for the CFA analyses that included the neuroticism parcels.

## 3. Results

Table 1 shows the descriptive statistics and Cronbach's α of all (sub) scales used in this study, Table 2 shows their correlation coefficients. Besides SPQ subscales (Cronbach's α = 0.36/0.68) and the PQ16 (Cronbach's α = 0.62) all other measurements show good reliability (Cronbach's α = ≥0.74).

The first PCA with a free-factor solution across the MSS (with its three subscales), the SPQB (with its three subscales), the OLIFE (with

**Table 1**
Descriptive statistics and Cronbach's a of all scales used in this study in $N = 383$ subjects.

| Scale | Mean | SD | Range | Possible Range | Coefficient Alpha | Kurtosis | Std. Err. | Skew | Std. Err. |
|---|---|---|---|---|---|---|---|---|---|
| Beck Depression Inventory | 3.67 | 3.98 | 0–26 | 0–63 | 0.79 | 1.65 | 0.12 | 3.82 | 0.25 |
| Multidimensional Schizotypy Scale | 4.20 | 4.25 | 0–28 | 0–77 | 0.82 | 1.94 | 0.12 | 4.93 | 0.25 |
| Positive Schizotypy | 0.58 | 1.38 | 0–10 | 0–26 | 0.74 | 3.83 | 0.12 | 17.35 | 0.25 |
| Negative Schizotypy | 2.58 | 2.70 | 0–18 | 0–26 | 0.77 | 2.04 | 0.12 | 5.58 | 0.25 |
| Disorganized Schizotypy | 1.04 | 2.12 | 0–14 | 0–25 | 0.82 | 3.23 | 0.12 | 12.49 | 0.25 |
| Schizotypal Personality Questionnaire | 2.57 | 2.67 | 0–13 | 0–22 | 0.74 | 1.37 | 0.12 | 1.83 | 0.25 |
| Cognitive-Perceptual | 0.48 | 0.80 | 0–5 | 0–8 | 0.36 | 1.99 | 0.12 | 4.67 | 0.25 |
| Interpersonal | 1.49 | 1.65 | 0–7 | 0–8 | 0.68 | 1.09 | 0.12 | 0.39 | 0.25 |
| Disorganized | 0.60 | 1.11 | 0–6 | 0–6 | 0.68 | 2.33 | 0.12 | 5.77 | 0.25 |
| Oxford-Liverpool Inventory of Feelings & Experiences | 17.39 | 8.83 | 3–54 | 0–104 | 0.85 | 0.91 | 0.12 | 0.89 | 0.25 |
| Unusual Experiences | 1.91 | 2.51 | 0–16 | 0–30 | 0.75 | 2.27 | 0.12 | 6.70 | 0.25 |
| Introvertive Anhedonia | 4.09 | 3.50 | 0–19 | 0–27 | 0.77 | 1.54 | 0.12 | 2.83 | 0.25 |
| Cognitive Disorganization | 5.30 | 4.40 | 0–21 | 0–24 | 0.84 | 0.95 | 0.12 | 0.52 | 0.25 |
| Impulsive Nonconformity | 6.09 | 2.88 | 0–15 | 0–23 | 0.58 | 0.44 | 0.12 | 0.13 | 0.25 |
| Prodromal Questionnaire Total | 1.09 | 1.51 | 0–9 | 0–16 | 0.62 | 1.95 | 0.12 | 4.71 | 0.25 |
| Prodromal Questionnaire Distress | 1.18 | 1.90 | 0–15 | 0–48 | 0.60 | 2.64 | 0.12 | 10.21 | 0.25 |

three of its four subscales) and the PQ-16 total score yielded a two-factor solution (cumulative total variance explained: 60.89 %; see Table 3) with an unclear factor structure: MSS_Pos, SPQB_CP, OLIFE_UnEx and PQ16_Total load highly on factor 1 and are unrelated to factor 2. MSS_Neg, SPQB_IP, and OLIFE_IntAn load highly on factor 2 and are unrelated to factor 1. MSS_Dis, SPQB_DO, and OLIFE_CogDis cross-load on both factors with higher loadings on factor 1. Components correlate with $r = 0.32$. The second PCA with the subscales described above and a forced three-factor solution (cumulative total variance explained: 69.89 %; see Table 4) showed a more coherent factor structure: MSS_Pos, SPQB_CP, OLIFE_UnEx, and PQ16_Total load highly on factor 1 and are unrelated to factor 2 and 3, except PQ16_Total with cross-loadings on factor 2. MSS_Dis and OLIFE_CogDis load highly on factor two. MSS_Neg and OLIFE_IntAn load highly on factor 3. SPQ_DO splits across the three factors, SPQB_IP cross-loads on factor 2 and 3. Correlations of the factors: $r = 0.54$ for factor 1 and 2, $r = 0.16$ for factor 1 and 3, and $r = 0.39$ for factor 2 and 3. The third PCA (excluding PQ16_Total) with a forced three-factor solution showed the most coherent factor structure (cumulative total variance explained: 70.97 %; see Table 5): MSS_Pos, SPQB_CP, and OLIFE_UnEx load highly on factor 1 and are unrelated to factor 2 and 3. MSS_Neg and OLIFE_IntAn load highly on factor 2. MSS_Dis and OLIFE_CogDis load highly on factor 3 whereas SPQB_IP cross-loads on factor 2 and 3 and SPQB_DO cross-loads on factor 3 and 1. Thus, forced three-factor solutions accounted for more variance than the two-factor solution. However, unlike the MSS and OLIFE subscales, the SPQB_IP and SPQ_DO subscales do not show good fidelity with the negative and disorganized dimensions, respectively, as they have moderate cross-loadings across multiple factors.

CFAs including the positive, negative, and disorganized parcels (see supplementary Table S2 for exact composition of all parcels) yielded the best fit for the three-factor model, with good fit indices and the parcels loading on their respective factor (CFI = 0.92, TFI = 0.91, RMSEA = 0.052, SRMR = 0.063; see Table 6 for further fit-indices as well as factor loadings and correlations of the three-factor model). CFAs including the positive, negative, disorganized, and neuroticism parcels showed the best fit for the four-factor solution with factors being a positive, negative, and disorganized schizotypy factor as well as an additional neuroticism factor (CFI = 0.90, TFI = 0.88, RMSEA = 0.059, SRMR = 0.069; see Table 7 for further fit-indices as well as correlations of the three and four-factor model).

## 4. Discussion

The present study aimed to analyze schizotypy phenotypes derived from commonly used inventories. Besides providing a detailed description at the subscale level, we used a PCA approach to provide refined phenotype facets of schizotypy as well as CFAs to test the fit of these refined facets in an overall model.

Results show support for a three-factor model of schizotypy with positive, negative, and disorganized schizotypy factors, as well as for a four-factor model with a separate neuroticism factor in addition to the traditional schizotypy factors. Our results add several implications to a refined assessment of an extended psychosis spectrum phenotype:

First, while intercorrelation indices among items are moderate to high we found single items with low endorsement rates even with some items not being endorsed at all. Even though low endorsement rates are expected for a sample comprising mainly individuals of high educational level and selected for lack of history for mental disorders/ treatment, the measurements should ideally be able to discriminate between a range of schizotypal experiences within the general population. The results therefore indicate that this might not be the case but that those measurements (or certain items within these) actually tap only one specific stage within the psychosis continuum but fail to map a wider range at the lower end of the continuum. Alternatively, it may reflect items that did not work well in translation from their original English. Including qualitatively similar items that range in their quantity of certain symptom representations could lead to better item-discrimination as well as item-difficulty which would make the questionnaires more suitable for detecting subtle differences in schizotypal behavior. Additionally, different response formats beyond the common dichotomous yes/no answers could help elucidate fine discriminations. On the other hand, such formats can invite participants to normalize the items and over-report schizotypal experiences, which are presumed to be relatively rare in the general population.

Second, our comparison of schizotypy scales with the PQ-16 allows us to compare these commonly used schizotypy scales with a commonly used prodrome screening questionnaire for psychosis risk. Measuring the schizophrenia prodrome and identifying individuals at risk for developing schizophrenia has become an important and legitimate step for early intervention research as well as early intervention application (Fusar-Poli et al., 2013). Our analyses of the PQ-16 showed fairly high correlations with the schizotypy scales, especially with items of the positive schizotypy subscales. A review of the PQ-16 items indicates that they are closely comparable in wording and content to items from positive schizotypy; for example the PQ-16 item, *"I have had the sense that some person or force is around me, even though I could not see anyone"*, and the SPQ-B item, "*Have you ever had the sense that some person or force is around you, even though you cannot see anyone?"*, or the PQ-16 item, "*My thoughts are sometimes so strong that I can almost hear them"*, and the O-LIFE item, "*Are your thoughts sometimes so strong that you can almost hear them?*". However, so far, the PQ-16 has been seen as qualitatively different from schizotypy measurements (Hinterbuchinger and

**Table 2**
Correlation matrix for all measurements used in this study, $N = 383$.

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 BDI | | | | | | | | | | | | | | | |
| 2 MSS_Sum | **0.43**$^{***}$ | | | | | | | | | | | | | | |
| 3 MSS_Pos | 0.17$^{**}$ | **0.51**$^{***}$ | | | | | | | | | | | | | |
| 4 MSS_Neg | 0.22$^{***}$ | **0.75**$^{***}$ | 0.06 | | | | | | | | | | | | |
| 5 MSS_Dis | **0.48**$^{***}$ | **0.72**$^{***}$ | 0.29$^{***}$ | 0.20$^{***}$ | | | | | | | | | | | |
| 6 SPQ_Sum | **0.49**$^{***}$ | **0.65**$^{***}$ | **0.43**$^{***}$ | **0.42**$^{***}$ | **0.50**$^{***}$ | | | | | | | | | | |
| 7 SPQ_CP | 0.20$^{***}$ | **0.33**$^{***}$ | **0.47**$^{***}$ | 0.07 | 0.26$^{***}$ | **0.56**$^{***}$ | | | | | | | | | |
| 8 SPQ_IP | **0.47**$^{***}$ | **0.55**$^{***}$ | 0.21$^{***}$ | **0.48**$^{***}$ | **0.36**$^{***}$ | **0.84**$^{***}$ | 0.21$^{***}$ | | | | | | | | |
| 9 SPQ_DO | **0.34**$^{***}$ | **0.52**$^{***}$ | **0.37**$^{***}$ | 0.26$^{***}$ | **0.47**$^{***}$ | **0.75**$^{***}$ | **0.33**$^{***}$ | **0.39**$^{***}$ | | | | | | | |
| 10 OLIFE_Sum | **0.58**$^{***}$ | **0.68**$^{***}$ | **0.41**$^{***}$ | **0.44**$^{***}$ | **0.53**$^{***}$ | **0.68**$^{***}$ | **0.43**$^{***}$ | **0.57**$^{***}$ | **0.48**$^{***}$ | | | | | | |
| 11 OLIFE_UnEx | **0.32**$^{***}$ | **0.46**$^{***}$ | **0.68**$^{***}$ | 0.10$^{*}$ | **0.35**$^{***}$ | **0.46**$^{***}$ | **0.53**$^{***}$ | 0.23$^{***}$ | **0.39**$^{***}$ | **0.64**$^{***}$ | | | | | |
| 12 OLIFE_IntAn | 0.26$^{***}$ | **0.58**$^{***}$ | 0.04 | **0.72**$^{***}$ | 0.22$^{***}$ | **0.48**$^{***}$ | 0.09 | **0.57**$^{***}$ | 0.25$^{***}$ | **0.59**$^{***}$ | 0.07 | **0.32**$^{***}$ | | | |
| 13 OLIFE CogDis | **0.64**$^{***}$ | **0.49**$^{***}$ | 0.28$^{***}$ | 0.19$^{***}$ | **0.56**$^{***}$ | **0.56**$^{***}$ | **0.31**$^{***}$ | **0.52**$^{***}$ | **0.37**$^{***}$ | **0.82**$^{***}$ | **0.45**$^{***}$ | | 0.21$^{***}$ | | |
| 14 OLIFE ImpNon | 0.22$^{***}$ | 0.22$^{***}$ | 0.20$^{***}$ | 0.10 | 0.20$^{***}$ | 0.24$^{***}$ | 0.27$^{***}$ | 0.07 | 0.28$^{***}$ | **0.54**$^{***}$ | **0.32**$^{***}$ | 0.04 | **0.50**$^{***}$ | 0.28$^{***}$ | |
| 15 PQ16_Total | **0.42**$^{***}$ | **0.53**$^{***}$ | **0.55**$^{***}$ | 0.16$^{***}$ | **0.50**$^{***}$ | **0.51**$^{***}$ | **0.41**$^{***}$ | **0.33**$^{***}$ | **0.44**$^{***}$ | **0.58**$^{***}$ | **0.66**$^{***}$ | 0.14$^{**}$ | **0.50**$^{***}$ | 0.28$^{***}$ | **0.90**$^{***}$ |
| 16 PQ16_Distress | **0.44**$^{***}$ | **0.53**$^{***}$ | **0.50**$^{***}$ | 0.20$^{***}$ | **0.48**$^{***}$ | **0.48**$^{***}$ | **0.33**$^{***}$ | **0.32**$^{***}$ | **0.45**$^{***}$ | **0.58**$^{***}$ | **0.62**$^{***}$ | 0.16$^{**}$ | **0.50**$^{***}$ | 0.28$^{***}$ | |

*Abbreviations*: BDI—Becks Depression Inventory. MSS_Sum—total score of the Multidimensional Schizotypy Scale (MSS). MSS_Pos—Positive schizotypy subscale of the MSS. MSS_Neg—Negative schizotypy subscale of the MSS. MSS_Dis—Disorganized schizotypy subscale of the MSS. SPQB_Sum–total score of the Schizotypal Personality Questionnaire-Brief (SPQ—B). SPQB_CP–Cognitive Perceptual subscale of the SPQ—B. SPQB_IP–Interpersonal subscale of the SPQ—B. SPQB_DO–Disorganized subscale of the SPQ-B. OLIFE_Sum—total score of the Oxford and Liverpool Inventory of Feelings and Experiences (OLIFE). OLIFE_UnEx—Unusual experiences subscale of the OLIFE. OLIFE_CogDis—Cognitive disorganization subscale of the OLIFE. OLIFE_IntAn—Introvertive anhedonia subscale of the OLIFE. OLIFE_ImpNon—Impulsive nonconformity subscale of the OLIFE. PQ16_Total—total score of the Prodromal Questionnaire-16 (PQ16). PQ16_Distress—Distress subscore of the PQ16.
Medium effect sizes in bold, large effect sizes in bold & italics.
$^{*}$ $p < .05$.
$^{**}$ $p < .01$.
$^{***}$ $p < .001$.

**Table 3**
First Principal Component Analysis (PCA): free factor solution with Promax rotation of the following scales: MSS_Pos, MSS_Neg, MSS_Dis, SPQB_CP, SPQB_IP, SPQB_DO, OLIFE_UnEx, OLIFE_CogDis, OLIFE_IntAn, and PQ-16_Total, $N = 383$. Table shows correlation coefficients for variables loaded on the three PCs extracted as well as the totals of the Eigenvalues, and the sums of variability and cumulative squared loadings in percent.

| | PC1 | PC2 |
|---|---|---|
| MSS_Pos | 0.829 | −0.190 |
| MSS_Neg | −0.142 | 0.866 |
| MSS_Dis | 0.534 | 0.276 |
| SPQB_CP | 0.707 | −0.109 |
| SPQB_IP | 0.180 | 0.735 |
| SPQB_DO | 0.531 | 0.279 |
| OLIFE_UnEx | 0.890 | −0.144 |
| OLIFE_CogDis | −0.149 | 0.926 |
| OLIFE_IntAn | 0.535 | 0.348 |
| PQ16_Total | 0.814 | 0.023 |
| Eigenvalues | 4.143 | 1.925 |
| Variability (%) | 41.432 | 19.253 |
| Cumulative (%) | 41.432 | 60.685 |

**Table 4**
Second PCA: Forced three-factor solution with Promax rotation of the following scales: MSS_Pos, MSS_Neg, MSS_Dis, SPQB_CP, SPQB_IP, SPQB_DO, OLIFE_UnEx, OLIFE_CogDis, OLIFE_IntAn, and PQ16_Total, $N = 383$.

| | PC1 | PC2 | PC3 |
|---|---|---|---|
| MSS_Pos | 0.912 | −0.107 | −0.013 |
| MSS_Neg | 0.060 | −0.162 | 0.943 |
| MSS_Dis | -,122 | 0.961 | −0.111 |
| SPQB_CP | 0.807 | −0.123 | 0.059 |
| SPQB_IP | −0.027 | 0.395 | 0.583 |
| SPQB_DO | 0.244 | 0.456 | 0.142 |
| OLIFE_UnEx | 0.843 | 0.082 | −0.049 |
| OLIFE_CogDis | −0.031 | 0.849 | 0.018 |
| OLIFE_IntAn | −0.031 | 0.849 | 0.018 |
| PQ16_Total | 0.532 | 0.423 | −0.060 |
| Eigenvalues | 4.143 | 1.925 | 0.920 |
| Variability (%) | 41.432 | 19.253 | 9.202 |
| Cumulative (%) | 41.432 | 60.685 | 69.887 |

**Table 5**
Third PCA: Forced three-factor solution with Promax rotation of the following scales: MSS_Pos, MSS_Neg, MSS_Dis, SPQB_CP, SPQB_IP, SPQB_DO, OLIFE_UnEx, OLIFE_CogDis, and OLIFE_IntAn, N = 383.

| | PC1 | PC2 | PC3 |
|---|---|---|---|
| MSS_Pos | 0.894 | −0.021 | −0.061 |
| MSS_Neg | 0.042 | 0.954 | −0.168 |
| MSS_Dis | −0.084 | −0.129 | 0.949 |
| SPQB_CP | 0.799 | 0.032 | −0.057 |
| SPQB_IP | −0.013 | 0.571 | 0.398 |
| SPQB_DO | 0.261 | 0.120 | 0.478 |
| OLIFE_UnEx | 0.824 | −0.052 | 0.112 |
| OLIFE_CogDis | 0.002 | 0.000 | 0.845 |
| OLIFE_IntAn | −0.063 | 0.924 | −0.002 |
| Eigenvalues | 3.628 | 1.841 | 0.918 |
| Variability (%) | 40.307 | 20.456 | 10.202 |
| Cumulative (%) | 40.307 | 60.763 | 70.965 |

Mossaheb, 2021), even though development of the original 92 item PQ originates in schizotypy as most items were adopted from the SPQ (Loewy et al., 2005). This is mainly due to its purpose to screen for the psychosis prodrome rather than measuring the trait schizotypy (Brandizzi et al., 2014; Savill et al., 2018). However, given the conceptual background of the scale (namely the close adaption from the SPQ) together with our results, the PQ-16 might actually not quantitatively or qualitatively differ from common schizotypy measurements, but the only difference being that it largely only measures one schizotypy

**Table 6**
Fit-indices for all models run in the first CFA as well as correlations for the three-factor model.

Fit-indices.

| Model | CFI | TFI | RMSEA | SRMR | AIC | BIC | AdjBIC |
|---|---|---|---|---|---|---|---|
| 1 Factor | 0.47 | 0.41 | 0.133 | 0.151 | 21,150 | 21,398 | 21,198 |
| 2 Factor | 0.78 | 0.75 | 0.086 | 0.091 | 20,213 | 20,466 | 20,262 |
| 3 Factor | 0.92 | 0.91 | 0.052 | 0.063 | 19,776 | 20,036 | 19,827 |

Note: Indicators of good fit: CFI, TFI > 0.90; RMSEA <0.08; SRMR <0.08; AIC, BIC, AdjBIC – lower values indicate better fit.

Pearson correlations coefficients.

| | Positive Schizotypy factor | Negative Schizotypy factor | Disorganized Schizotypy factor |
|---|---|---|---|
| Positive Schizotypy factor | 1 | 0.14 | 0.53 |
| Negative Schizotypy factor | 0.14 | 1 | 0.33 |
| Disorganized Schizotypy factor | 0.53 | 0.33 | 1 |

**Table 7**
Fit-indices for all models run in the second CFA as well as correlations for the four-factor model.

Fit-indices.

| Model | CFI | TFI | RMSEA | SRMR | AIC | BIC | AdjBIC |
|---|---|---|---|---|---|---|---|
| 3 Factor | 0.87 | 0.85 | 0.066 | 0.072 | 21,686 | 21,970 | 21,742 |
| 4 Factor | 0.90 | 0.88 | 0.059 | 0.069 | 21,573 | 21,869 | 21,631 |

Note: Indicators of good fit: CFI, TFI > 0.90; RMSEA <0.08; SRMR <0.08; AIC, BIC, AdjBIC – lower values indicate better fit.

Pearson correlations coefficients.

| | Positive Schizotypy factor | Negative Schizotypy factor | Disorganized Schizotypy factor | Neuroticism factor |
|---|---|---|---|---|
| Positive Schizotypy factor | 1 | 0.14 | 0.53 | 0.44 |
| Negative Schizotypy factor | 0.14 | 1 | 0.33 | 0.38 |
| Disorganized Schizotypy factor | 0.53 | 0.33 | 1 | 0.66 |
| Neuroticism factor | 0.44 | 0.38 | 0.66 | 1 |

dimension, namely positive schizotypy. Furthermore, the prodrome can simply be understood as an expression of the schizotypy continuum. Looking back at early but still valid definitions of a prodrome in a clinical context, the main common feature refers to the aspect of time: prodrome is the temporal correlation of certain behaviors with illness onset (Beiser et al., 1993; Keith and Matthews, 1991; Loebel et al., 1992). Thus, to evaluate if a person is in a prodromal stage, an instrument measuring psychosis prodrome should also consider the aspect of time, i.e., for how long a person has already been experiencing subclinical psychotic symptoms (Hinterbuchinger and Mossaheb, 2021; Schultze-Lutter et al., 2015). Research on the psychosis prodrome and schizotypy has indeed shown, that schizotypy represents a (weak, but significant) predictor of psychosis (Barrantes-Vidal et al., 2013; Debbané et al., 2015) and could thus be useful as a screening for psychosis-proneness within the general population. Taken together, when using a questionnaire specifically as a screening instrument for the psychosis prodrome rather than measuring the trait schizotypy, it should also consider the time aspect (e.g., by item wording) to sharpen its specificity.

The present results indicate that the three schizotypy scales investigated in this paper tend to measure the factors of schizotypy well. PCA analyses show that the subscales aiming to measure positive schizotypy build a coherent factor. The correlations among the schizotypy factors from the CFAs are generally consistent with findings for individual scales (e.g., Kwapil et al. (2018b)).

Note that the PCA and CFA analyses used different measured indicator variables (in part because it would be redundant to run PCA and CFA on the same indicators from the same sample). The PCA used scores computed from the full scales/subscales, whereas the CFA used parcels computed from most of the items comprising these measures (items were dropped because they did not measure specific schizotypy dimensions or due to lack of variance). The PCA was a largely exploratory approach to examine the latent structure underlying the original format of these measures, whereas the CFA compares competing models of the factor structure of schizotypy not constrained by the specific measures. This approach provided both conceptual information about schizotypy and potential problematic items in these extant measures.

The correlations of the neuroticism factor with positive and disorganized schizotypy likewise is consistent with previous studies (e.g., Kwapil et al. (2018a)). The unexpected correlation of negative schizotypy with neuroticism likely reflects the inclusion of the SPQ-IP subscale items that were not specifically designed to tap negative schizotypy and tend to be saturated with neuroticism and social anxiety. The subscales that aim to measure negative or disorganized schizotypy load indeed on their predominantly factor in the PCAs, but show fairly sufficient loadings with the other factor as well. The SPQ_IP subscale, which is usually taken as the negative schizotypy facet of the SPQ, contains some items that rather tend to measure social anxiety/neuroticism (e.g., *"I feel very uncomfortable in social situations involving unfamiliar people."*), which makes those items relate more to the OLIFE_CD subscale than to the negative schizotypy factor per se. It is important to point out that Raine (1991) constructed the SPQ_IP subscale to tap 'interpersonal discomfort' rather than creating an exclusively negative schizotypy subscale. Hence, items that prompt social anxiety/neuroticism are expected for the SPQ_IP subscale but add something new to the construct of schizotypy as those symptoms are rather unspecific for schizotypy per se. This is also the case for some items of the OLIFE_CD that tap neuroticism (e.g., *"Do you often worry about things you should not have done or said?"*, *"Are you a person whose mood goes up and down easily?"*) more so than the schizotypy factor of disorganized thoughts or behavior. This is confirmed by

our CFA analyses which showed a good fit for a three-factor schizotypy model when items of SPQ_IP and OLIFE_CD that measure neuroticism/social anxiety are excluded but also showed a good fit for a four-factor model when those items were included by a separate neuroticism-factor. Hence, some items do not seem to fit into the typical schizotypy dimensions which is important to consider when using schizotypy as a unifying construct to assess an underlying vulnerability for schizophrenia-spectrum disorders. From a clinical perspective, evaluating neurotic and anxious tendencies when assessing risk-states for SSDs is plausible (Brown et al., 2008; Kemp et al., 2018; Lewandowski et al., 2006), however, when speaking of the construct of schizotypy from a psychometric standpoint, those facets should be examined independently.

Lastly, correlations with the BDI are considerably high. This can be seen as further reassurance that schizotypy is closely related to affective anomalies, especially social anhedonia (Cohen et al., 2015), as some items in the here investigated schizotypy scales are intended to measure exactly this. Consistent with Kemp et al. (2018), BDI scores appear to have their strongest associations with the disorganized dimension of schizotypy. This is also consistent with Kemp et al.'s (2021) finding that disorganized, but not positive or negative schizotypy predicted interview-assessed major depressive disorder. Interestingly, Kemp et al. (2018) further found that modest associations of negative schizotypy with the BDI were driven by items tapping diminished positive affect but not heightened negative affect.

This study has some limitations that need to be addressed. First, our study sample consisted mostly of young, psychiatrically healthy college students. While we expect that meaningful information regarding schizophrenia-spectrum psychopathology can be identified in non-clinically ascertained samples, inclusion of a larger sample that was enriched for participants with elevated levels of schizotypy would likely enhance our power to detect meaningful relationships. We did not assess random responding, which limits the reliability of the scores administered. Furthermore, Cronbach's α for the PQ-16 as well as the SPQB_CP subscale were low. This limitation warrants investigation in further studies.

## 5. Conclusion

Almost every current model of schizophrenia and psychosis recognizes that there is a broad continuum of clinical and subclinical expression of symptoms and impairment. Schizotypy offers a useful and unifying framework for capturing this continuum. Furthermore, schizotypy, like schizophrenia, is best conceptualized as a multidimensional construct. However, the utility of schizotypy, especially in early-detection/−intervention research, requires clear operationalization and measurement (Rivera Tapia, 2022).

With this study we contributed to this discussion by applying two different comprehensive multivariate statistical approaches to a set of well-validated schizotypy measurements (including the MSS as a relatively new scale) as well as a prodromal questionnaire. We conclude that the construct of schizotypy is psychometrically defined differently across measurements and are proposing a newly composition for revised phenotype facets.

## Declaration of competing interest

All authors declare no conflict of interests.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.03.004.

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## IV. CURRICULUM VITAE

Die folgenden Seiten 75-84 (Lebenslauf) enthalten persönliche Daten. Sie sind deshalb nicht Bestandteil der Veröffentlichung.

## V. VERZEICHNIS DER LEHRENDEN

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## VI. DANKSAGUNG

Die Seiten 86-87 (Danksagung und ehrenwörtliche Erklärung) wurden vor Drucklegung entfernt und sind daher nicht Bestandteil der Veröffentlichung.