NEUROBIOLOGY OF SCHIZOTYPAL PHENOTYPES

Schizotypy as a framework for dimensional psychiatry

INAUGURAL-DISSERTATION

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To acknowledging diversity and dimensions.

In science, and in general.

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LIST OF ACRONYMS

DMN	default mode network
ERS	environmental risk score
GMV	grey matter volume
GWAS	genome-wide associations study
GxE	gene by environment
ITG	inferior temporal gyrus
IQ	intelligence quotient
PC	precuneus
PCC	posterior cingulate cortex
PLEs	psychotic-like experiences
PRS	polygenic risk score
SBM	surface-based morphometry
SCL90-R	symptom checklist 90 – revised
SNP	single nucleotide polymorphism
SNS	schizophrenia nuclear signs
SPQ	schizotypal personality questionnaire
SPQ-B	schizotypal personality questionnaire - brief
STS	schizotypal signs
VBM	voxel-based morphometry

1. INTRODUCTION

The development of pathological functions in a system is quite consistent with its usual performance of normal function.

W.B. Cannon, 1953

1.1. Schizotypy as a dimensional risk phenotype: a rationale

Schizotypy describes a complex multimodal phenotype in humans, comprising of trait characteristics resembling key features of psychotic disorders across emotional, behavioural and cognitive dimensions. Those are generally grouped into the three facets *positive* (magical thinking, unusual experiences, beliefs and perceptions), *negative* (introversion, anhedonia, diminished positive affect and reward) and *disorganised/cognitive* (eccentricity, cognitive disorganisation).

The term schizotypy was originally coined by Rado (1953), abbreviating "*schizo*phrenic pheno*type*", to describe subclinical levels of schizophrenic symptoms preceding the disorder, but also stable conditions, not leading into clinical states. Schizotypy is distributed in the general population and thought to represent both an underlying liability to the schizophrenia spectrum (particularly *negative* and *disorganised* facets) or "psychosis proneness" (*positive* facet), and variation of healthy function (Claridge 1997; Kwapil & Barrantes-Vidal 2015). This view is explicated by the continuum model of the psychosis spectrum, assuming a normal distribution of schizotypy, with spectrum disorders at the extreme end (Claridge 1997). Thus, it can also account for schizotypy being associated with beneficial characteristics like enhanced creativity, visual imagery, and personality correlates (Mohr & Claridge 2015; Baas *et al.* 2016). Determining the position on an underlying dimension of adaptive to maladaptive manifestations, protective conditions/resilience mechanisms are thought to play an important role, as shown for e.g. intelligence (Brod 1997; Grant *et al.* 2014a).

There are different approaches to characterising risk phenotypes in the subclinical psychosis spectrum. Schizotypy as a stable personality construct can be distinguished from the (usually) transient expression of psychotic experiences in the absence of the clinical disorder ("psychotic-like experiences", PLEs, van Os *et al.* 2009) and the set of clinical features and risk factors

constituting clinical high risk (CHR) status (Schultze-Lutter *et al.* 2015). PLEs, e.g. hallucinations or delusions, are conceptually closest to the positive facet, and also discussed as expression of positive schizotypy (Barrantes-Vidal *et al.* 2015). CHR status includes attenuated and psychotic symptoms and indications of cognitive deficits, associated with positive and negative facets of schizotypy (Gooding *et al.* 2005; Flückiger *et al.* 2019). The concepts show phenotypic overlap and are not orthogonal, as has been shown for schizotypy and PLEs (Debbané *et al.* 2015), and schizotypy and high risk (Flückiger *et al.* 2019). Partially shared genetic and neurobiological correlates among the constructs (Linscott & van Os 2013; Ettinger *et al.* 2014) further support the idea of a dimensional psychosis continuum.

Continuous, complex phenotypes generally constitute a valuable framework for the study of fundamental neurobiological mechanisms of both psychiatric disorders and interindividual differences. Allowing the analysis of aetiological mechanisms in the absence of confounding factors (e.g. illness progression, medication effects), they surpass animal models in illustrating complex, psychological constructs. Facilitating the deconstruction of psychiatric entities (Gottesman & Gould 2003), they also enable the consideration of resilience factors, preventing conversion into clinical spectra. Within the subclinical psychosis spectrum, schizotypy is best suited as model-phenotype due to its relative temporal stability (opposed to PLEs), and its differentiation into continuous domains (opposed to risk/no risk state).

Similarly, current constructs of psychopathology describe psychiatric phenomena as dimensional continua, from healthy variation to clinical relevance (Cuthbert 2014; Kotov *et al.* 2017). Schizotypy thus not only plays a significant role in the study of genetic and neurobiological mechanisms of the schizophrenia spectrum (Barrantes-Vidal *et al.* 2015), but also provides a general framework for a dimensional and translational approach to psychiatric research, and the study of pathways from health to dysfunction.

1.2. Genetic and neuronal networks of schizotypy

The genetic and neuronal architectures of schizotypy have also increasingly been viewed in the context of continuum models. A shared genetic basis of

schizotypy and the schizophrenia spectrum has long been speculated. Meehl first proposed the existence of a single dominant *schizogene* leading to *schizotaxia*, a dysfunctional neuronal integration. This gene would, dependent on environmental factors and social learning history, be the prerequisite for schizotypy and, in its extreme form, schizophrenia-spectrum disorders (Meehl 1962). Opposing Meehl's single gene proposal, recent molecular genetic studies have identified a large number of relevant genetic loci in genome-wide association studies (GWAS), suggesting a polygenic architecture of schizophrenia. Those include both commonly occurring single nucleotid polymorphisms (SNPs) identified with small effects (Pardiñas *et al.* 2018) and rare genetic variations (e.g. copy number variants, CNVs) with larger impact (Mowry & Gratten 2013; Marshall *et al.* 2017).

A polygenic architecture suggests a dimensional rather than a taxonic view of the psychosis spectrum, yet the inherent idea of a (partially) shared genetic architecture is still supported by current literature. Several SNPs (i.e. variations in a single base-pair at a specific genomic position) that are established risk variants for schizophrenia (e.g. in genes *CACNA1C*, *COMT*, *DRD2*, *ZNF804A*), are also associated with schizotypy (Walter *et al.* 2016), and SNP-based heritability for schizotypal trait dimensions has been reported between 16-30% (Ortega-Alonso *et al.* 2017). Evidence for relatively independent, underlying latent genetic factors highlights the importance of dimension-specific modelling (Linney *et al.* 2003; Tarbox *et al.* 2012).

In addition, familial risk for schizophrenia spectrum disorders, i.e. affected close relatives, is associated with elevated levels of schizotypy (Miller *et al.* 2002; Soler *et al.* 2017). However, *familial* risk does not equal *genetic* risk per se, but includes shared environmental factors and interactional processes. Evidence indicates that about 20% of familial risk for schizophrenia is mediated through (i.e. explained by) polygenic risk (Agerbo *et al.* 2015). Polygenic risk scores (PRS) quantify genetic risk based on a set of multiple genetic markers by calculating (on individual level) a sum of allele dosages associated with the trait in question, weighted by GWAS-based effect sizes (Dudbridge 2013). Evidence for associations of schizotypy dimensions with schizophrenia PRS is, however, inconsistent, with null findings as well as effects in opposing directions

(Sieradzka *et al.* 2014; Zammit *et al.* 2014; Hatzimanolis *et al.* 2018; van Os *et al.* 2019).

Heterogeneous findings indicate that a certain genetic risk is not linearly translated into phenotypic variation, highlighting the urge to consider modulating factors (Ronald & Pain 2018). This has been sporadically (but successfully) done for both single SNP- (de Castro-Catala *et al.* 2017) and (cumulative) PRS-based (Hatzimanolis *et al.* 2018) genetic risk, but pathways of how genotypes and genetic patterns impact schizotypal variance are largely unclear.

In Meehl's tradition – and reiterated, albeit refined, in later models (Siever & Davis 2004; Howes & Murray 2014) –, it might be speculated that genetic effects are mediated through aberrant neuronal development and should thus be detectable in brain morphometry (Jones & Murray 1991). Indeed, many genetic variants carrying schizophrenia risk are involved in brain development (Toulopoulou *et al.* 2015), and a neurodevelopmental approach is supported by data from animal models (Kanyuch & Anderson 2017). In line with this, there is increasing evidence for brain structural correlates of schizotypy, in regions overlapping with those impaired across the schizophrenia spectrum (Nelson *et al.* 2013; Ettinger *et al.* 2014; Modenato & Draganski 2015).

While studies indicate some heterogeneity concerning the direction of associations, they allow to assume the implication of prefrontal (Ettinger *et al.* 2012; Kühn *et al.* 2012; DeRosse *et al.* 2015; Nenadić *et al.* 2015; Wang *et al.* 2015; Wiebels *et al.* 2016; Modinos *et al.* 2018), precuneus and anterior and posterior cingulate cortex (Modinos *et al.* 2010, 2018; Nenadić *et al.* 2015; Tijms *et al.* 2015; Wiebels *et al.* 2016), superior and medial temporal (DeRosse *et al.* 2015; Evans *et al.* 2016; Wiebels *et al.* 2016; Modinos *et al.* 2018) grey matter volume (GMV) changes in schizotypy.

Only few studies have not only looked at volumetric changes of grey matter in terms of voxel-based morphometry (VBM), but also considered variation in surface-based morphometry (SBM), e.g. patterns of cortical surface folding (Stanfield *et al.* 2008). Those are, however, discussed as important indicators of early developmental disruptions (Spalthoff *et al.* 2018), as cortical folding happens very early during brain development (Chi *et al.* 1977). Alterations of those markers in schizophrenia spectrum disorders and high risk individuals

further indicate relevance for the psychosis spectrum (Nenadic *et al.* 2014; Zuliani *et al.* 2018).

This dissertation will focus on grey matter structure, but it should be mentioned that there is also evidence for white matter changes associated with schizotypy, particularly in fronto-temporal connectivity (Volpe *et al.* 2008; Nelson *et al.* 2011; DeRosse *et al.* 2015; Schmidt *et al.* 2015; Grazioplene *et al.* 2016; Lemaitre *et al.* 2018), mirroring findings in clinical domains (Lener *et al.* 2015).

Taken together, the above presented studies indicate that pathological changes in neurobiological networks of schizophrenia lie on a continuum with functional, healthy variation. However, as not all studies have distinguished schizotypal facets, it is unclear whether those findings represent a general vulnerability for schizophrenia spectrum disorders, or define specific functions. It is further unclear at which point exactly on the pathway from genotype to phenotype morphometric variations (and other endophenotypes, e.g. cognition) are situated.

A current model of schizophrenia aetiology integrates neurodevelopmental disruptions facilitated by genetic variants, environmental challenges and adversities with resulting sensitised and subsequently dysfunctional neurotransmission and cognitive biases, leading to the formation and progression of psychotic symptoms (Howes & Murray 2014). This approach can also be applied to other entities of the psychosis spectrum, including schizotypy. Statistical models, incorporating the proposed interacting and mediating pathways are, however, scarce. Hence, a key challenge is to develop and test multimodal models linking genetic factors, neuronal networks and a complex human phenotype.

1.3. Aims and hypotheses

The work in this dissertation aimed to identify neurobiological determinants of schizotypal traits in healthy individuals, for their subsequent use as dimensional phenotypes in biological psychiatry research.

The subsequent objective was to develop a statistically testable model linking genetic and environmental risk markers with brain structural variation to explain phenotypic variation in schizotypy, suited to extrapolate to other continua.

More specifically, the following hypotheses were tested:

H_1: Psychometrically-assessed schizotypy is associated with genetic risk markers of schizophrenia (single nucleotide polymorphisms, polygenic risk) with cognition as a putative intermediate phenotype in this association.

H_2: Schizotypy dimensions show associations with variation in volume- and surface-based brain structural parameters, specifically in the precuneus and the fronto-striatal network (lateral and medial prefrontal cortices, striatum, and thalamus).

H_3: A multivariate moderation/mediation model accounts for the interaction of polygenic risk, environmental risk, and brain structure with dimensions of schizotypy.

2. AGGREGATION OF STUDY RESULTS

2.1. STUDY I: Schizotypy shows sex-dependent associations with risk genes *ZNF804A* and *CACNA1C* and altered attention

Reference: **Meller T.**, Schmitt S., Stein F., Brosch K., Mosebach J., Yüksel D., Zaremba D., Grotegerd D., Dohm K., Meinert S., Förster K., Redlich R., Opel N., Repple J., Hahn T., Jansen A., Andlauer T.F.M., Forstner A.J., Heilmann-Heimbach S., Streit F., Witt S.H., Rietschel M., Müller-Myhsok B., Nöthen M.M., Dannlowski U., Krug A., Kircher T., & Nenadić I. (2019). Associations of schizophrenia risk genes *ZNF804A* and *CACNA1C* with schizotypy and modulation of attention in healthy subjects. *Schizophrenia Research 208,* 67–75. (IF: 4.6)

While schizotypy shares several risk alleles with schizophrenia, pathways and interactions with additional factors are poorly understood. Recent genetic modelling studies in clinical psychosis conclude cognitive deficits and schizophrenia symptoms to share a substantial part of genetic variance (Toulopoulou *et al.* 2007, 2015). This might also be the case for schizotypy, which is associated with relatively decreased cognitive functions (Siddi *et al.* 2017), especially (sustained and selective) attention (Gooding *et al.* 2006; Fuggetta *et al.* 2015; Moreno-Samaniego *et al.* 2017), and linked to attention deficit hyperactivity disorder (Ettinger *et al.* 2006; Legge *et al.* 2019). Cognitive functions, e.g. attention, may represent an intermediate endophenotype of schizophrenia (risk) genotype and (risk) phenotype (Toulopoulou *et al.* 2015, 2018). Yet, it is unclear how genetic influences, schizotypy, and cognition in healthy subjects can be integrated into a joint model. (A dimension of) schizotypy may constitute a mediator on the path between genes and cognition or, vice versa, altered cognitive function may facilitate schizotypal development. Candidate genes for such associations are *ZNF804A* and *CACNA1C*, whose SNPs rs1344706 and rs1006737 have been associated with both schizotypy and attention (Yasuda *et al.* 2011; Roussos *et al.* 2013; Stefanis *et al.* 2013).

In STUDY I, we aimed to (1) clarify the associations of the two SNPs with dimensional schizotypy and attention, and (2) integrate the reported bivariate associations into a joint framework by testing the two opposing mediation models of (a) schizotypy mediating the association between genetic variation and attention (Stotesbury *et al.* 2018) vs. (b) attention explaining the relationship of genetic influence and schizotypy, as suggested for schizophrenia

(Toulopoulou *et al.* 2018). Sex differences have been reported for effects of *ZNF804A* and *CACNA1C* (Strohmaier *et al.* 2013; de Castro-Catala *et al.* 2017), schizophrenia (Abel *et al.* 2010), and schizotypy profiles (Kremen *et al.* 1998), so sex was included as a potential moderator in the regression models.

The results of STUDY I indicate sex-specific effects of both SNPs on different schizotypy dimensions, with a higher number of *ZNF804A* rs1344706 C (non-risk) alleles linked to increased positive schizotypy in women, and the effect of *CACNA1C* rs1006737 A (risk) alleles on decreased negative schizotypy restricted to male participants (Figure I/1, p. 40). Sex-differences in schizophrenia are discussed as result of oestrogenic versus androgenic influences on dopaminergic pathways (Godar & Bortolato 2014). Such processes may also be relevant in the subclinical spectrum, explaining the sex-specific effects of both SNPs on schizotypy. Extending the model by including attention suggests preferential support for a sex-moderated mediation model, with positive schizotypy partially explaining the association between *ZNF804A* rs1344706 and attentional performance in women (Figure I/2, p. 40) – as opposed to the reverse pathway proposed for schizophrenia (Figure I/3, p. 41, Toulopoulou *et al.* 2018). This indicates partially overlapping, but differential pathways along the schizophrenia spectrum and should spark future studies further dissecting this association.

In short, STUDY I further supports the idea of a shared genetic basis of both schizophrenia and schizotypy, and offers a model for the association of genetic risk, schizotypy, and cognitive alterations in dimensions also impaired in schizophrenia. Notably, the study highlights the relevance of accounting for secondary factors, like sex, in modulating those associations.

2.2. STUDY II: Intelligence moderates the association between positive schizotypy and striatal structure in healthy individuals

Reference: **Meller, T.**, Ettinger, U., Grant, P., & Nenadić, I. (2019). The association of striatal volume and positive schizotypy in healthy subjects: Intelligence as a moderating factor. *Psychological Medicine* 2019 Sep 18:1-9, doi: 10.1017/S0033291719002459P (IF: 5.6)

According to aetiological models, beneficial factors may buffer the impact of brain structural variations on phenotypic variance. Besides variation in parietal and temporal structures, increasing evidence suggests fronto-striatal networks

to be critically involved in the generation of psychotic(-like) experiences. This is supported by findings of associations of (primarily positive) schizotypy with brain-structural and -functional alterations in those networks (Mittal *et al.* 2013; Rössler *et al.* 2018; Wang *et al.* 2018; Waltmann *et al.* 2019), but also with expression levels of dopaminergic genes and alterations of dopaminergic neurotransmission (Ettinger *et al.* 2013; Grant *et al.* 2014b; Mohr & Ettinger 2014). Current studies, however, report heterogeneous direction of effects. Striatal size has been discussed as endophenotype for psychosis (Chemerinski 2013), and fronto-striatal mechanisms might lie on a possible pathway from genetic risk through altered neurotransmission and neuronal structure, to phenotypic psychosis-proneness.

Similar propositions are made by a model by Siever and Davis (Siever & Davis 2004): Authors further suggested that enhanced vulnerability to environmental insults caused by genetic risk variants, leading to altered brain structure (and function), might be buffered by resilience factors like cognitive capacity (e.g. intelligence), thus leading to attenuated symptom levels and preventing conversion into the disorder. Such a pattern has in fact been reported for processes of perception in positive schizotypy (Grant *et al.* 2014a).

STUDY II, in line with this model, analysed the association of schizotypy with brain structural parameters, and tested a statistical model with intelligence as a putative moderator of this association. The results of STUDY II indeed confirm this model: The detected association of positive schizotypy with greater GMV in a cluster containing the right putamen and pallidum (see Figure II/1(a), page 50) was moderated by intelligence. With increasing levels of IQ, the strength of the association decreased, indicating a protective influence of general intelligence on the association of striatal structure and positive schizotypy (see Figure II/2, page 51). The negative dimension was further positively associated with GMV in a cluster in the left precentral gyrus, but intelligence did not influence this association (see Figure II/1(b), page 50). There is limited evidence for the role of paracentral cortices in schizotypy, although STUDY III detected a similar association. Gyrification analyses only yielded significant associations of total schizotypy and gyrification in the precuneus and postcentral gyrus in an uncorrected, exploratory approach.

In conclusion, STUDY II supports the role of the fronto-striatal network also in the healthy domain of the psychosis spectrum, extending the dopamine hypothesis of schizophrenia (Howes *et al.* 2017), and presents a pathway for protective influence of resilience factors like general cognitive capacity.

2.3. STUDY III: Psychotic-like, distress-based symptoms are associated with structural variation in brain areas impaired in schizophrenia

Reference: **Meller, T.**, Schmitt S., Ettinger, U., Grant, P., Stein, F., Brosch, K., Grotegerd, D., Dohm, K., Meinert, S., Förster, K., Hahn, T., Jansen, A., Dannlowski, U., Krug, A., Kircher, T., & Nenadić, I. Brain structural correlates of schizotypal signs and subclinical schizophrenia nuclear symptoms in healthy individuals. (submitted manuscript)

It is unclear how distress due to psychotic experiences, as opposed to the frequency of symptoms, is associated with brain structural variation. In healthy individuals, higher levels of trait schizotypy confer greater liability to psychotic-like experiences (Gooding *et al.* 2005; Debbané *et al.* 2015). However, distress associated with PLEs, rather than their frequency, has greater prognostic value for conversion into psychosis (Hanssen *et al.* 2005). The intensity and associated distress of such experiences varies vastly, both inter- and intra-individually (Rössler *et al.* 2007; Linscott & van Os 2013). This variability is thought to be attributable to latent, stable traits (Rössler *et al.* 2013), representing the "trait in action" in response to current environmental challenges (Barrantes-Vidal *et al.* 2015). The *schizophrenia nuclear symptoms* (SNS) and *schizotypal signs* (STS) scales, constructed using items of the Symptom-Checklist-90-R (SCL90-R Derogatis 1977; Rössler *et al.* 2007), assess the level of distress caused by PLEs over the course of four weeks – thus closing a gap between highly variable mood and stable personality traits. While psychometrically well-validated, their neurobiological correlates are yet unclear.
STUDY III tested the association of SNS and STS with voxel- and surface-based brain structural parameters in healthy individuals, to explore whether they show similar morphometric correlates as reported for instruments assessing trait-like personality characteristics. We assessed both rather quickly adaptable (VBM) and more stable, early-determined (SBM) patterns of brain structure.

Results of STUDY III show differential patterns for the scales: SNS, assessing positive, psychotic symptoms, was associated with decreased grey matter volume (GMV) in the right inferior temporal gyrus (ITG), and increased GMV in the left superior parietal lobe including the precuneus (see Figure III/2, p. 66). STS, capturing a milder, personality-like blend of positive and negative symptoms, was negatively associated with GMV in the right and left precentral gyrus (see Figure III/2, p. 66). Gyrification analyses did not detect significant clusters after correction for multiple testing, however, exploratory uncorrected analyses showed positive correlations of gyrification in the left insula and rostral middle frontal gyrus with SNS, as well as gyrification in the right insula and precuneus with STS, and a negative correlation of STS with gyrification in the right inferior/middle temporal gyrus (see Figure III/3, page 67).

Both precuneus and ITG are involved in higher-order, integrative cognitive processes and have previously been linked to symptoms of the psychosis spectrum. The precuneus has repeatedly been associated with psychometrically-assessed schizotypy (Modinos *et al.* 2010, 2018; Nenadic *et al.* 2015), and our results support its association with a more acute higher-risk state of increased distress. Similarly, structural reductions within the ITG have also been associated with PLEs (van Lutterveld *et al.* 2014), and are part of an anatomical pattern predicting later conversion in at-risk individuals (Koutsouleris *et al.* 2010).

The blending (rather than distinguishing) of negative and positive schizotypy facets in STS might explain its restricted associations. Precentral variation, as associated with STS, has been linked to motor dysfunction in schizophrenia (Tanskanen *et al.* 2010), however, its role in schizotypy remains unclear.

In conclusion, the findings of STUDY III demonstrate that, similar to measures of schizotypy and PLEs, distress-related markers are associated with variation in precuneus and ITG, underlining the importance of these structures for the positive symptom dimension. Pointing to distress as a putative mediating factor, they illustrate the relevance of emotional appraisal of psychotic experiences, a process which in turn can be influenced by personality characteristics like schizotypy (Kline *et al.* 2012).

2.4. STUDY IV: Polygenic risk for schizophrenia, depression and bipolar disorder is not associated with schizotypy in non-clinical adults

Reference: Nenadić, I.*, **Meller, T***., Streit, F., Schmitt S., Stein, F., Brosch, K., Mosebach, J., Ettinger, U., Grant, P., Meinert S., Opel, N., Lemke, H., Fingas, S., Förster, K., Hahn, T., Jansen, A., Andlauer, T.F.M., Forstner, A.J., Heilmann-Heimbach, S., Hall, A., Awasthi, S., Ripke, S., Witt, S.H., Rietschel, M., Müller-Myhsok, B., Nöthen, M.M., Dannlowski, U., Krug, A., Kircher, T. Polygenic risk for schizophrenia and schizotypal traits in non-clinical subjects. **contributed equally* (unpublished manuscript)

Schizotypal traits are assumed to be heritable (Ronald & Pain 2018), yet single common genetic variants (like SNPs) only explain smaller parts of its variance. Cumulative genetic risk scores, calculated on the basis of known SNPs, may have greater explanatory power (Mistry *et al.* 2018). Several studies have successfully linked schizotypy dimensions to genetic variants associated with schizophrenia risk (Walter *et al.* 2016), indicating additive effects (Grant *et al.* 2015). The impact of polygenic risk for schizophrenia on schizotypy, however, is still poorly understood, with current evidence restricted to studies with inconsistent results (Hatzimanolis *et al.* 2018; van Os *et al.* 2019).

The aim of STUDY IV was to test the hypothesis that schizotypy is associated with a SNP-based polygenic risk score (PRS) for schizophrenia. To test for specificity, those analyses were extended to PRS for major depressive disorder and bipolar disorder, conducted in two independent samples of psychiatrically healthy adults.

Results of STUDY IV show no significant associations of schizotypy (either total score or dimensions) with PRS for schizophrenia or bipolar disorder, consistent across the discovery and replication sample, confirmed by meta-analytical combination of bootstrapped results. Only in one sample, major depression PRS was associated with increases schizotypy levels.

These findings add important insights to our understanding of the psychosis spectrum by indicating that schizotypy is not linearly and independently linked to polygenic risk for schizophrenia; in spite of partial overlap in single risk genes. However, it has to be considered that PRS only subsumes SNP-based risk of common genetic variants, with limited explanatory value (Marshall *et al.* 2017).

In conclusion, the results of STUDY IV suggest only a minor overlap of schizotypy and (clinical) genetic risk profiles as accounted for in PRS. As the lack of a direct association may also indicate moderating influences, they emphasise the need to consider additional modulating factors in statistical models analysing associations of the neurobiological fundaments of schizotypy.

2.5. STUDY V: An explanatory model: Genes and environment have an interactive impact on schizotypy through changes in brain structure

Reference: **Meller, T**., Schmitt S., Stein, F., Brosch, K., Andlauer, T.F.M., Grotegerd, D., Dohm, K., Meinert, S., Förster, K., Forstner, A.J., Heilmann-Heimbach, S., Streit, F., Witt, S.H., Rietschel, M., Müller-Myhsok, B., Nöthen, M.M., Hahn, T., Jansen, A., Dannlowski, U., Krug, A., Kircher, T., & Nenadić, I. The impact of polygenic and poly-environmental risk factors on a psychosis risk phenotype is mediated through brain structure. (unpublished manuscript)

One of the main challenges in biological psychiatry is to clarify the pathway between genetic risk variants and phenotypic variation. Current aetiology models of psychotic disorders suggest interactive effects of genetic and environmental risk markers impacting on neurodevelopmental processes, and leading to phenotypic variation, with buffering influences of protective factors (Howes & Murray 2014; Carpenter & Strauss 2017). Progressing from simple bivariate association studies, emerging evidence of gene by environment (GxE) studies in phenotypes (Bernardo *et al.* 2017; Leighton *et al.* 2017; Misiak *et al.* 2018) and brain structure (Geoffroy *et al.* 2013) has added valuable insight to our understanding of processes and networks. However, those interactions, too, have mostly been limited to single genes and risk factors. There is a lack of multivariate models, integrating cumulative GxE effects, neuronal biomarkers, cognition, and phenotypes into explanatory pathways.

STUDY V used statistical moderation and mediation analysis to test a model in which GxE effects on the dimensional risk phenotype schizotypy are explained through brain structural changes, allowing for buffering influences of executive function (see Figure V/1, p. 107). To maximise the input of known risk factors for the psychosis spectrum, we approximated genetic risk as PRS for schizophrenia, while aggregating multiple environmental risks in a cumulative, weighted environmental risk score for psychosis (ERS, Vassos *et al.* 2019).

Results of STUDY V support the multivariate model with complex interactive associations of GxE on positive schizotypy (see Figure V/3, p. 115). This association is mediated by GMV in a cluster in the precuneus and posterior cingulate gyrus (Pc/pcG, see Figure V/2, p. 113) and moderated by executive function, strengthening the role of the precuneus for positive schizotypy.

While neither PRS nor ERS show a main effect on Pc/pcG GMV, their interaction is significant, with the intensity and direction of the PRS effect depending on ERS levels (positive slope for low ERS, negative slope for high ERS). Similarly, the association of Pc/pcG GMV and positive schizotypy is moderated by executive function (positive slope for low, negative slope for high executive function). This supports the notion that in healthy individuals, genetic risk affects brain structure and, subsequently, phenotype dependent on additional factors (Van der Auwera *et al.* 2017). Our findings may explain previous heterogeneous and null findings, highlighting the relevance of complex variance structures and multivariate models.

The reported bidirectional interaction effects advocate moving on from traditional diathesis-stress models to models of differential susceptibility. The latter propose a *general* modulation of susceptibility to environmental influence (both adverse and protective) through genetic disposition (Leighton *et al.* 2017; Assary *et al.* 2018), replacing “vulnerability factors” with “plasticity factors” (Belsky & Pluess 2009).

In conclusion, STUDY V provides a biological framework, integrating the genetic and environmental associations of schizotypy as a psychosis risk phenotype into a testable model. This approach can also be extended to other genotype-phenotype associations of psychiatric disorder spectra.

3. General Discussion

This dissertation presents a neurobiological characterisation of genetic and brain structural markers of schizotypy and psychosis-related symptoms.

Studies I and IV established an association of schizotypy with selected single risk genes (*CACNA1C* and *ZNF804A*, Study I), while failing to show a direct association with polygenic risk for schizophrenia (Study IV) – thus only partly confirming **hypothesis H_1**. Study I additionally indicates that schizotypy mediates effects of genetic variants on cognition, rather than vice versa.

In MR-morphometric Studies II and III, brain structural correlates of schizotypy dimensions were analysed, providing further support for the precuneus and the fronto-striatal network, as well as the inferior temporal gyrus to underlie symptoms of the positive dimension, in line with **hypothesis H_2**. Study II shows a protective effect of increased cognitive functioning, while Study III extends these associations to distress-based schizotypy-like phenotypes, highlighting the relevance of emotional appraisal of symptoms.

Study V integrates the above findings to consider genetic and environmental influences, brain structure, cognition, and schizotypy in a multivariate model, showing that the interaction effect of genes and environment on the phenotype is explained through brain structural variation. The significant model fit confirms **hypothesis H_3** and statistically supports current aetiological models of the schizophrenia spectrum.

Taken together, the five studies add new insights for two neurobiological domains of the dimensional psychosis phenotype schizotypy, i.e. its genetic basis and its neural networks, as well as their integration into a joint framework.

3.1. Genetic basis of schizotypy

Schizotypy dimensions show heritability estimates between 30-50% (Linney *et al.* 2003; Macare *et al.* 2012), and current evidence suggests an underlying polygenic architecture (Grant *et al.* 2013; Brambilla *et al.* 2014). Several SNPs have been associated with schizotypy (Walter *et al.* 2016), and Study I finds further evidence for links to risk variants in *ZNF804A* and *CACNA1C*. Similar to other genes associated with schizotypy (e.g. *BDNF*, *DTBNP1*, *NRG1*), both are

relevant for neuronal development: In the human brain, *ZNF804A* is expressed in the dorsolateral prefrontal cortex and hippocampus, involved in neurite growth and synapse formation, and SNP rs1344706 affects its expression, particularly during prenatal brain development (Hill & Bray 2011, 2012). *CACNA1C* is expressed in the hippocampus and the entire central nervous system. It codes for calcium channel subunit $Ca_v1.2$, mediating synaptic plasticity and also showing altered expression in SNP rs1006737 (Bigos *et al.* 2010). Functionally, both SNPs have been linked to more basal cognitive dysfunctions, as well as altered processing of emotional and social information and associated brain activity and structure (Voineskos *et al.* 2011; Soeiro-de-Souza *et al.* 2012; Mohnke *et al.* 2014; Paulus *et al.* 2014). Implicated in fundamental interpersonal processes, it is not surprising that although *ZNF804A* and *CACNA1C* are established risk genes for schizophrenia, this association is not unique, but extends to other psychiatric and neurodevelopmental disorders (Chang *et al.* 2017; Moon *et al.* 2018). Similarly, while schizotypy is primarily discussed as schizophrenia endophenotype, it also predicts later occurrence of other psychiatric disorders, social functioning, and general mental health outcomes (Rössler *et al.* 2011; Kwapil *et al.* 2013).

This suggests that although several risk genes are shared between schizotypy and schizophrenia, their genetic architectures only partially overlap, as supported by the lack of a direct association in STUDY IV. However, regarding this finding, some aspects need to be considered. Firstly, PRS scores (based on GWAS-identified, common SNPs) can only account for a moderate portion of underlying genetic variance and underestimate phenomenological and biological heterogeneity *within* cases and controls (Marín 2016). Secondly, additional factors may modulate the expression of the phenotype, e.g. biological sex (STUDY I), cognitive function (STUDY II), or environmental influences (STUDY V). In fact, recent evidence suggests interactive effects of schizophrenia PRS with stressful contexts and shared environment in siblings on schizotypy (Hatzimanolis *et al.* 2018; van Os *et al.* 2019).

A prominent approach to explain GxE interactions is the diathesis-stress-model, hypothesising that the impact of environmental events on the development of the actual disorder is potentiated by genetically-determined vulnerabilities (Howes *et al.* 2017). However, STUDY V suggests that, depending on

environmental conditions, high PRS can also have inverse effects, leading to increased function. This is in line with a concept of *differential susceptibility* or *environmental sensitivity*, proposing that genetic "risk" variants may render sensitivity to environmental influences in general – including favourable ones (Leighton *et al.* 2017; Assary *et al.* 2018).

3.2. Neural networks of schizotypy

Schizotypy describes manifestations across multiple domains of cognition, emotion, and behaviour. This dissertation shows that these are associated with variation in highly connected, integrative regions throughout the brain.

STUDIES III and V find associations of positive schizotypal phenotypes with precuneus structure. In fact, structural variation in the precuneus is one of the most robust findings in (positive) schizotypy (Modinos *et al.* 2010, 2018; Nenadic *et al.* 2015; Wiebels *et al.* 2016). The precuneus is extensively connected throughout the brain and can be divided into three anatomical and functional subsections (Cavanna & Trimble 2006). The detected clusters are localised in the central part, functionally connected to parietal, temporal, and prefrontal cortices and attributed to cognitive processes producing a conscious self-percept in relationship to the world (Margulies *et al.* 2009). Those include cause and effect judgements, attributional evaluation and (mis)attribution of personal reference (see Jones & Bhattacharya 2014 for an overview). While the precuneus, also an important node of the default-mode network, has shown to be of transdiagnostic relevance in schizophrenia, anxiety, depression, and obsessive-compulsive disorder (Jones & Bhattacharya 2014), these functions show a striking overlap with characteristics of the positive schizotypy dimension. Findings of STUDY V indicate that this association arises from interactions of genes and environment, as the precuneus cluster is detected in a GxE model *independently* of the phenotype, yet associated with it.

A second central associative network in the human brain constitutes circuits of the fronto-striatal system, connecting striatum, thalamus, orbifrontal, and cingulate regions, and linked to a variety of cognitive, emotional, and behavioural functions (Tekin & Cummings 2002). STUDY II finds an association of striatal structures putamen and pallidum with positive schizotypy. Striatal

function (greatly modulated by dopaminergic neurotransmission) is essential for behavioural regulation through reward processing and associative learning (linking it to anhedonic, negative characteristics), but also for salience attribution and (un)certainty judgements. Inappropriate attributions of salience and certainty are implicated in the formation of delusional thoughts and positive symptoms (Broyd *et al.* 2017), yet the buffering effect of intelligence shown in STUDY II indicates protective influence of preserved or compensatory frontal functioning (Colom *et al.* 2013). Central for striatal functioning, dopaminergic neurotransmission and its genetic fundaments are altered in schizotypy (Mohr & Ettinger 2014), suggesting an extension of the dopamine hypothesis of schizophrenia to the healthy spectrum (Howes *et al.* 2017).

While dopamine receptors show high density in the striatum, they are also found in other brain regions, including the inferior temporal gyrus (ITG). The ITG (connected to both precuneus and prestriate regions) is involved in visual imagery, perceptive integration and attributions of intention in others (Brunet *et al.* 2000; Hamamé *et al.* 2012). In this area, STUDY III also finds altered GMV associated with more state-like, distress-based symptoms within the positive dimension, in line with it being discussed as underlying neuronal correlate of hallucinations in schizophrenia (Goldsmith *et al.* 1997).

Consistent across STUDIES II and III, surface parameters of cortical folding did not exhibit strong enough effects to survive correction, even though they were detected in regions relevant for schizotypy. Given that schizotypy is linked to several genetic factors implicated in neuronal development, this is surprising. Folding parameters are determined early in brain development and, in contrast to grey matter volumes, thought to be relatively stable over time (Chi *et al.* 1977). Comparatively weak associations with schizotypal dimensions indicate certain predispositions, yet suggest that those can be functionally “overwritten” by later developmental processes, and masked by compensatory mechanisms.

3.3. Limitations and implications for future research

Across the studies reported in this dissertation, some limitations have to be considered that bear implications for future research. Firstly, all studies were based on healthy individuals, who on average showed (expectedly) low to

moderate schizotypy. This may restrict variance, but does not invalidate findings, rather speaking for the strength of the effect of even subtle variations. Clinical studies might include individuals with subthreshold or manifest symptom levels to extend these findings across a clinical spectrum (at the cost of higher risk of confounding factors).

Additionally, although PRS and ERS represent cumulative risk estimates, they can each only account for additive effects. PRS scores rely on GWAS-identified, common SNPs with small individual effects, and can only account for a portion (~20%) of underlying genetic variance. In a differential susceptibility approach, a similar genetic predisposition might in one case lead to a clinical disorder while in another prevent exactly that, depending on environmental conditions and translated through different neurodevelopmental correlates. Investigation of associations with rare variants, *de novo* mutations, epigenetic effects, or gene x gene interactions promises extended insights. Lastly, the consideration of GxE *correlations* could help identify additional processes, as genetic predisposition resulting in personality traits would also influence the individual's active creation of environmental conditions (Dick 2011), as has been indicated for schizotypal traits preceding cannabis consume (Schiffman *et al.* 2005).

3.4. Integration

This dissertation shows that schizotypy is linked to genetic variants that impact neuronal development and function and carry risk for schizophrenia. Beyond the single gene approach, the lack of a direct association with schizophrenia PRS suggests limited overlap of the polygenetic architectures of the phenotypes. However, there is evidence for an indirect effect through altered brain structure, depending on environmental conditions and cognitive functions. This suggests that in healthy individuals, the impact of genetic predisposition on schizotypy is modulated by intra- and extrapersonal factors and associated with neurodevelopment. In line with this, schizotypy is associated with variation in brain structures implicated in (higher-level) interpretation and evaluation of sensory information, imaginary processes, and behavioural regulation.

Developmental disturbances of neuronal organisation seem bound to sensitive time windows during which activity-dependent modulations cause long-term

alterations in brain circuits (Marín 2016). Genetic variants may alter the onset and duration of these windows, and render plasticity at glutamatergic and dopaminergic synapses (Hall *et al.* 2015; Genovese *et al.* 2016). However, not only can plastic changes occur beyond those periods (Hübener & Bonhoeffer 2014), but associations are further modulated by buffering factors like cognitive function (which in turn might be indicative of latent genetic and environmental effects). Conceptualised as stable personality trait, schizotypy can be seen as underlying source of more acute responses to environmental challenges expressed in state-like experiences (Barrantes-Vidal *et al.* 2015), while associated distress and its neuronal correlates have predictive value for progression into clinically relevant states. However, favourable environmental conditions and/or compensatory processes can equally lead to the expression of schizotypal predispositions in functionally adaptive behaviours, possibly leading to evolutionary advantages (Nettle & Clegg 2006) and explaining the perseverance of genetic profiles carrying liability to harmful outcomes.

In conclusion, schizotypy is a valuable endophenotype of the psychosis spectrum, demonstrating that even severe pathophysiological disruptions lie on a continuum with subtle variations of healthy function (Venables 1975). However, beyond that, it is an expression of multifaceted behavioural, cognitive, and emotional interindividual variation, with its underlying mechanisms representing an exemplary framework for dimensional phenotypic spectra.

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SUMMARY

Complex, dimensional phenotypes represent a valuable framework for the analysis of fundamental neurobiological mechanisms of psychiatric disorders. They facilitate the deconstruction of diagnostic entities and the study of protective processes that prevent progression into clinical domains. Within the psychosis spectrum, schizotypy describes a multidimensional personality construct with behavioural, cognitive, and emotional characteristics similar to key symptoms of schizophrenia, that can equally be grouped into the dimensions positive (magical thinking, unusual perceptions and beliefs), negative (introversion, anhedonia), and disorganised (cognitive disorganisation, eccentricity). Within a continuum model of psychosis, schizotypy is discussed as variation of healthy function, and as risk phenotype of schizophrenia and psychosis proneness, assuming a (partially) overlapping genetic architecture along the spectrum. Current aetiological models propose an impact of genetic liability, in interaction with environmental risk and modulated by protective factors like cognitive function, through disruptions in neuronal development. In fact, recent studies show that schizotypy is associated with brain structural variation, partially overlapping with regions that are also impaired in patients with schizophrenia spectrum disorders.

This dissertation characterised neurobiological determinants of schizotypy regarding its genetic basis and neural networks, aiming to develop a multimodal model to integrate those into a joint framework.

STUDIES I and IV investigated the genetic structure of schizotypy, demonstrating its association with common variants (single nucleotide polymorphisms, SNPs) in genes (*CACNA1C* and *ZNF804A*) involved in processes of neuronal development and identified as risk genes for schizophrenia and other psychiatric disorders (STUDY I). In this association, biological sex has a moderating role. However, a direct association of a polygenic schizophrenia risk score, based on cumulative SNP-risk, was not established (STUDY IV).

STUDIES II and III analysed brain structural correlates of schizotypy dimensions, finding an association of the positive dimension (and symptom-associated distress) with grey matter volume in associative brain areas precuneus, striatum

and inferior temporal gyrus. STUDY II further indicates that this relationship can be buffered by above average general cognitive function.
Study V ultimately integrates the previous results into a joint multivariate model that proves to explain a substantial amount of phenotypic variance. The model shows that the interaction effect of polygenic and poly-environmental risk on positive schizotypy is mediated through brain structural variation in the precuneus, and modulated by the level of executive function.

In conclusion, this dissertation shows that schizotypy is associated with genetic polymorphisms involved in neuronal development and function. While those are identified as schizophrenia risk variants, the lack of an association with polygenic schizophrenia risk suggests a limited overlap of the genetic architectures of the phenotypes. The confirmation of the multivariate model, however, indicates an indirect effect through variations in brain structure and modulated by intra- and extrapersonal factors. Accordingly, particularly positive schizotypy is associated with structural alterations in brain regions central for the integration, evaluation, and attribution of perceptual information within associative neuronal networks.
Thus, schizotypy is a valuable endophenotype of the schizophrenia spectrum, showing that pathophysiological aberrations lie on a continuum with variation of healthy functioning. Schizotypy, however, also describes the manifestation of interindividual variation in behaviour, cognition, and emotion, with its underlying mechanisms representing an exemplary framework for the study of dimensional, phenotypic spectra.

ZUSAMMENFASSUNG

Komplexe, dimensionale Phänotypen stellen ein wertvolles Paradigma für die Untersuchung fundamentaler neurobiologischer Mechanismen psychiatrischer Erkrankungen dar. Sie vereinfachen die Dekonstruktion von diagnostischen Einheiten und die Untersuchung von protektiven Prozessen, die vor dem Übergang in klinische Störungen schützen. Innerhalb des Psychosespektrums beschreibt Schizotypie ein multidimensionales Persönlichkeitskonstrukt, dessen Merkmale in Verhalten, Kognition und Emotion den Kernsymptomen der Schizophrenie ähneln und ebenfalls auf den Dimensionen positiv (magisches Denken, ungewöhnliche Wahrnehmungen und Überzeugungen), negativ (Introversion, Anhedonie) und desorganisiert (kognitive Desorganisation, Exzentrizität) beschrieben werden können. Im Rahmen des Kontinuum-Modells der Psychose wird Schizotypie sowohl als Variation gesunder Funktion, als auch als Risiko-Phänotyp für Schizophrenie und Psychose-Nähe diskutiert, und von einer (zumindest teilweisen) Überlappung genetischer Grundlagen über das Spektrum hinweg ausgegangen. Aktuelle ätiologische Modelle gehen davon aus, dass genetische Effekte, in Interaktion mit umweltbedingten Risikofaktoren und moduliert durch protektive Faktoren wie kognitive Leistungsfähigkeit, über Veränderungen der neuronalen Entwicklung wirken. Tatsächlich zeigen aktuelle Studien, dass die Ausprägung von Schizotypie bei Gesunden mit hirnstruktureller Variation assoziiert ist. Diese findet sich in Arealen, welche teilweise mit Regionen, die auch bei Patienten mit Erkrankungen des Schizophreniespektrums betroffen sind, überlappen.

Die vorliegende Dissertation hat in fünf Studien neurobiologische Grundlagen der Schizotypie auf genetischer und hirnstruktureller Ebene untersucht, mit dem Ziel der Entwicklung eines multimodalen Modells, welches diese Ebenen in einen gemeinsamen Rahmen integriert.

STUDIEN I und IV haben die genetischen Grundlagen der Schizotypie untersucht und können demonstrieren, dass Schizotypie mit häufigen genetischen Varianten (Single Nucleotide Polymorphismen, kurz SNPs) in Genen (*CACNA1C*, *ZF804A*) assoziiert ist, welche wichtige Funktionen für neuronale Entwicklungsprozesse innehaben, und als Risikogene für Schizophrenie, aber

auch andere psychiatrische Erkrankungen identifiziert wurden (STUDIE I). Geschlecht wirkt hier als moderierender Faktor. Ein direkter Zusammenhang mit einem polygenen Risikoscore für Schizophrenie, basierend auf kumulativem SNP-Risiko, ist jedoch nicht nachweisbar (STUDIE IV).
STUDIEN II und III haben hirnstrukturelle Korrelate der Schizotypiedimensionen analysiert und finden einen Zusammenhang insbesondere der positiven Dimension (und damit assoziierter Belastung) mit dem Volumen der grauen Substanz in den assoziativen Hirnarealen Precuneus, Striatum und inferiorer Temporalgyrus. STUDIE II zeigt zudem, dass dieser Zusammenhang durch überdurchschnittliche kognitive Leistungsfähigkeit abgemildert werden kann.
STUDIE V schließlich integriert die vorangegangenen Befunde in ein gemeinsames, multivariates Modell, welches substantiell phänotypische Varianz aufklärt. Es zeigt sich, dass der Interaktionseffekt von polygenem und kumulativem Umweltrisiko auf (positive) Schizotypie durch Veränderungen der Hirnstruktur im Precuneus vermittelt und durch das Level an exekutiver Funktion moduliert wird.

Zusammenfassend zeigt diese Dissertation, dass Schizotypie mit genetischen Polymorhphismen assoziiert ist, welche Einfluss auf neuronale Entwicklung und Funktion haben. Zwar stellen diese auch Risikogene für Schizophrenie dar, die fehlende Assoziation mit polygenem Risiko spricht jedoch für eine eingeschränkte Überlappung in der genetischen Architektur der Phänotypen. Die Bestätigung des multimodalen Modells indiziert allerdings einen indirekten Effekt auf Schizotypie, vermittelt über veränderte Hirnstruktur, und beeinflusst durch das Wirken intra- und extrapersoneller Faktoren. Übereinstimmend ist insbesondere die positive Schizotypiedimension mit Veränderungen in Hirnregionen assoziiert, die zentral in die Integration, Evaluation und Attribution perzeptueller Information in assoziativen Netzwerken involviert sind.
Schizotypie ist ein wertvoller Endophänotyp des Schizophreniespektrums und zeigt, dass auch pathophysiologische Veränderungen auf einem Kontinuum mit Variation gesunder Funktionen liegen. Darüber hinaus repräsentiert sie die Manifestation von interindividueller Variation in Verhalten, Kognition und Emotion, deren zugrundeliegende Mechanismen ein exemplarisches Paradigma für die Untersuchung dimensionaler, phänotypischer Spektren darstellen.

A. APPENDIX

i. **STUDY I**: Publication Meller et al. (2019a)

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Associations of schizophrenia risk genes *ZNF804A* and *CACNA1C* with schizotypy and modulation of attention in healthy subjects

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ABSTRACT

Schizotypy is a multidimensional risk phenotype distributed in the general population, constituting of subclinical, psychotic-like symptoms. It is associated with psychosis proneness, and several risk genes for psychosis are associated with schizotypy in non-clinical populations. Schizotypy might also modulate cognitive abilities as it is associated with attentional deficits in healthy subjects. In this study, we tested the hypothesis that established genetic risk variants *ZNF804A* rs1344706 and *CACNA1C* rs1006737 are associated with psychometric schizotypy and that schizotypy mediates their effect on attention or vice versa. In 615 healthy subjects from the FOR2107 cohort study, we analysed the genetic risk variants *ZNF804A* rs1344706 and *CACNA1C* rs1006737, psychometric schizotypy (schizotypal personality questionnaire-brief SPQ—B), and a neuropsychological measure of sustained and selective attention (d2 test). *ZNF804A* rs1344706 C (non-risk) alleles were significantly associated with higher SPQ-B Cognitive-Perceptual subscores in women and with attention deficits in both sexes. This schizotypy dimension also mediated the effect of *ZNF804A* on attention in women, but not in men. *CACNA1C* rs1006737-A showed a significant sex-modulated negative association with Interpersonal schizotypy only in men, and no effect on attention. Our multivariate model demonstrates differential genetic contributions of two psychosis risk genes to dimensions of schizotypy and, partly, to attention. This supports a model of shared genetic influence between schizotypy and cognitive functions impaired in schizophrenia.

1. Introduction

Schizotypy is a multidimensional construct of personality traits phenomenologically resembling subclinical schizophrenia symptoms. It is considered a phenotypic marker of psychosis proneness and schizophrenia risk (Barrantes-Vidal et al., 2015) and elevated in patients

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with psychotic disorders (Brosey and Woodward, 2015). Schizotypy, having predictive value for conversion probability into schizophrenia-spectrum disorders (Chapman et al., 1994; Gooding et al., 2005; Kwapil et al., 2013), is also considered a high-risk marker in early intervention research.

The phenotype comprises aspects of deviations in cognition, emotion, speech, and perception (Ettinger et al., 2015), but is also associated with higher creativity (Fink et al., 2014; Mohr and Claridge, 2015), possibly even constituting an evolutionary advantage (Nettle and Clegg, 2006). Schizotypy is often delineated into three dimensions (Dodell-Feder et al., 2019), namely *positive/cognitive-perceptual* (magical thinking, referential ideas, unusual perceptual experiences, and paranoid ideation), *negative/interpersonal* (difficulties in social interaction and blunted affect) and *disorganised* ("odd" speech and behaviour).

While different cognitive dimensions have been linked to schizotypy (Siddi et al., 2017), relative deficits in sustained and selective attention have been robustly reported (Breeze et al., 2011; Fuggetta et al., 2015; Gooding et al., 2006; Moreno-Samaniego et al., 2017). Findings even point to a possible genetic link between attention-deficit hyperactivity disorder and schizotypy (Ettinger et al., 2006). While impaired attention has often been associated with the negative schizotypy dimension (Alvarez-Moya et al., 2007; Chen and Faraone, 2000; Smyrnis et al., 2007), recent evidence also suggests the cognitive-perceptual dimension as a risk factor for attentional difficulties (Gooding et al., 2006; Stotesbury et al., 2018). Attention deficits are also found in schizophrenia patients compared to healthy controls (Elvevåg and Goldberg, 2000; Hill et al., 2008; Lee et al., 2017; Nuechterlein et al., 2004), and in first-degree relatives of schizophrenia patients (Snitz et al., 2005), indicating genetic effects. Attention therefore represents a putative cognitive link between these risk genotypes and phenotypes.

Growing evidence also suggests a partially shared genetic basis between schizotypy and psychotic disorders. Genome-wide association studies (GWAS) have currently identified >120 common genetic variations contributing to the risk for schizophrenia (Pardiñas et al., 2018), and while at least some risk genes are shared among clinical psychosis phenotypes (Craddock et al., 2009; Sheldrick et al., 2008), it seems that polygenic risk scores for psychosis are only marginally associated with schizotypy (Hatzimanolis et al., 2018; Jones et al., 2016). However, recent studies reporting significant associations of schizophrenia risk variants with schizotypy measures support a partially mutual genetic background (Barrantes-Vidal et al., 2015).

Among the most prominent susceptibility genes for schizophrenia is *ZNF804A*, involved in neurodevelopmental processes (Lencz et al., 2010) and coding for the zinc-finger binding protein 804A (Voineskos et al., 2011). The major A allele of the single-nucleotide polymorphism (SNP) rs1344706 was initially reported to be associated with schizophrenia in a GWAS by O'Donovan et al., with an even stronger association to a broader psychosis phenotype that includes bipolar disorder (O'Donovan et al., 2008). This association has since been replicated and shown to be one of the strongest susceptibility variants for schizophrenia (Pardiñas et al., 2018; Riley et al., 2010; Williams et al., 2011). Rs1344706-A has been associated with decreased expression of *ZNF804A* in fetal brain tissue (Hill and Bray, 2012) and with neurocognitive and brain structural variations in schizophrenia patients and in healthy controls (Chang et al., 2017; Donohoe et al., 2011; Nenadic et al., 2015). Two recent studies linked *ZNF804A* rs1344706 with schizotypy (Stefanis et al., 2013; Yasuda et al., 2011), but with heterogeneous dimensional associations: While Yasuda and colleagues found carriers of the rs1344706 major A-allele to have higher disorganised schizotypal levels, Stefanis et al. reported the opposite effect, i.e., a positive association of the minor C-allele with positive schizotypy, calling for further research.

A second gene strongly associated with the psychosis spectrum is *CACNA1C*, encoding a subunit of the calcium channel $Ca_v1.2$, which is involved in the modulation of gene transcription, synaptic plasticity and cell survival in the brain (Bhat et al., 2012). *CACNA1C*'s intronic SNP rs1006737 with risk allele A has been established as a susceptibility variant for schizophrenia (Jiang et al., 2015; Ripke et al., 2013; Ruderfer et al., 2014) and bipolar disorder (Ferreira et al., 2008; Moon et al., 2018; Ruderfer et al., 2014). It has been associated with cognitive variation like decreased attentional performance and reduced corresponding neural activity in risk-allele carriers (Thimm et al., 2011), impaired working memory (Zhang et al., 2012), but also impaired facial emotion recognition (Soeiro-de-Souza et al., 2012) and increased interpersonal distress (Erk et al., 2010). In two previous studies, rs1006737-A has also been linked to elevated positive schizotypy and schizotypal personality disorder (Roussos et al., 2013, 2011). While the influence of *CACNA1C* variants on cognition and its neural correlates has been shown repeatedly (Dietsche et al., 2014; Krug et al., 2014), it is unclear whether the gene is also linked to variation in cognitive function in schizotypy.

Taken together, current research suggests an association of psychosis risk genes *ZNF804A* and *CACNA1C* with impaired cognition and schizotypy in the general population, and an association of both schizophrenia and schizotypy with cognitive deficits. It is, however, lacking models integrating those univariate associations into a joint framework. As there are sex differences in schizophrenia prevalence and symptom profiles (Abel et al., 2010) as well as schizotypy (Kremen et al., 1998; Raine, 1992), and sex-specific effects have recently been reported for both genes (de Castro-Catala et al., 2017; Strohmaier et al., 2013), a differential impact for males and females should be considered.

Therefore, the first aim of the present study was to analyse the differential effects of *ZNF804A* rs1344706 and *CACNA1C* rs1006737 on dimensional schizotypy as a phenotypic psychosis proneness marker, considering sex-dependent modulations. Secondly, we tested the opposing models of (a) the relatively stable personality trait schizotypy mediating genetic influence on attention, expecting the *Cognitive-Perceptual* dimension to particularly affect cognition as recently suggested (Stotesbury et al., 2018) and (b) attentional variation mediating genetic influence on schizotypal traits, as derived from recent studies of cognition in schizophrenia (Toulopoulou et al., 2018, 2015).

2. Material and methods

2.1. Sample

We analysed data of 615 healthy Central European subjects (age 18–65 years, mean = 32.77, standard deviation (SD) = 12.50) drawn from the FOR2107 cohort, a multi-centre study, recruiting through newspaper advertisements and mailing lists from the areas of Marburg and Muenster in Germany (Kircher et al., 2018). Ethics approval was obtained from the ethics committees of the Medical Schools of the Universities of Marburg and Muenster, respectively, in accordance with the Declaration of Helsinki. All subjects volunteered to participate in the study and provided written informed consent. Subjects of non-European origin were excluded from the analyses because of known population differences in the studied genetic polymorphisms. Exclusion criteria were current or former psychiatric disorders (assessed with SCID-I interviews (Wittchen et al., 1997) by trained raters), history of neurological or other severe medical disorders, verbal IQ <80 (Multiple Choice Word Test-B (Lehrl, 1995)), or current psychotropic medication. The resulting sample comprised 232 (37.7%) male and 383 (62.3%) female participants.

2.2. Assessment of psychometric schizotypy

Self-reported schizotypy was assessed with the German version (Klein et al., 1997) of the Schizotypal Personality Questionnaire-Brief (SPQ-B (Raine and Benishay, 1995)). Based on Raine's original SPQ (Raine, 1991), it has recently been validated across multi-national studies, including the German version (Fonseca-Pedrero et al., 2018). Beside a total schizotypy score, the SPQ-B provides measures on the *Cognitive-*

Perceptual, *Interpersonal*, and *Disorganised* dimensions delineated by previous factor analyses (Axelrod et al., 2001; Compton et al., 2009). For the questionnaire as a whole and its subscores, adequate internal consistency and criterion validity have been demonstrated (Fonseca-Pedrero et al., 2018; Klein et al., 2001). In our sample, the SPQ-B showed acceptable reliability (Cronbach's $\alpha = 0.737$, for subscore values see supplementary table S5).

2.3. Neurocognitive testing

Participants underwent standardised neurocognitive testing for sustained and selective attention with the d2 test of attention (Brickenkamp, 2002). It is a cancellation test assessing the continuous ability to focus on task-relevant characteristics while ignoring similar characters, requiring constant visual perceptual speed and accuracy. Despite its simple structure and implementation, the d2 test has been shown to be a reliable and valid measure of attention capacity, both in healthy subjects and in schizophrenia patients (Brickenkamp, 2002; Lee et al., 2017). The *concentration performance* parameter (the error-adjusted number of hits) was used in this analysis as it is resistant to deception attempts and has shown high reliability in the reference sample (Brickenkamp, 2002) and a randomly drawn subset of our own sample ($n = 100$, Cronbach's alpha $\alpha = 0.981$).

2.4. Genotyping and quality control

Genomic DNA was extracted from blood samples acquired onsite. Genotyping and further preparation of genomic data was performed blinded to phenotype data at the Institute of Human Genetics of the University Hospital Bonn, Germany and at the Max Planck Institute of Psychiatry, Munich, Germany. Genotyping was conducted using the Infinium PsychArray BeadChip (Illumina, San Diego, CA, USA), according to standard protocols. Clustering and initial QC was conducted in GenomeStudio v.2011.1 (Illumina, San Diego, USA) with the Genotyping Module v.1.9.4. Full QC was performed in PLINK v1.90b5 (x) and *R* v3.3.3, based on a larger dataset of which the present subjects constituted a subset. Individuals were removed if they met any of the following criteria: genotyping call rate <98%, gender mismatches or other X-chromosome-related issues, genetic duplicates, cryptic relatives with pi-hat ≥12.5%, genetic outlier with a distance from the mean of >4 SD in the first eight ancestry components, or a deviation of the autosomal or X-chromosomal heterozygosity from the mean > 4 SD.

2.5. Statistical analyses

Sex differences in schizotypy, age, and neurocognitive performance were analysed using Student's *t*-tests for independent samples or Mann-Whitney *U* tests where the assumption of normal distribution was violated. Distributions of allelic frequencies between sexes were compared with chi-squared (χ^2) tests. Associations of genotypes and schizotypy were analysed via linear regression models, using the IBM Statistical Package for Social Sciences (SPSS, version 22, IBM, Armonk, NY) and the PROCESS macro v3.1 for SPSS (Hayes, 2013). Multidimensional scaling (MDS) analyses to estimate population stratification in the sample were conducted in PLINK (Purcell & Chang; Chang et al., 2015), the first three MDS components were included as covariates in SNP association analyses. Leave-one-out cross-validation was used to calculate the root mean PRESS (predicted residual error sum of squares) as a model fit parameter in stepwise regressions (√mPRESS). As SPQ-B scales are correlated, *p*-values were adjusted (p_{adj}) to correct for multiple comparison according to Bonferroni-Holm (Holm, 1979), using *R* (R Core Team, 2018).

3. Results

3.1. Distribution of schizotypy, attention, and allele frequencies

Descriptive statistics for SPQ-B subscores as well as genotype frequencies for *ZNF804A* rs1344706 and *CACNA1C* rs1006737 are shown in Table 1. Neither rs1344706 (χ^2(degrees of freedom (*df*) = 2) = 0.79, $p = 0.675$) nor rs1006737 ($\chi^2(2) = 3.80$, $p = 0.150$) showed significant differences in minor allele counts between sexes. We also found no significant sex differences for age ($t(613) = -0.379$, $p = 0.704$; male mean = 32.52, SD = 11.49, female mean = 32.92, SD = 13.09) or d2 performance ($t(613) = -1.45$, $p = 0.148$). Mean d2 scores for the whole sample (mean = 191.40, SD = 42.25), as well as for males (mean = 188.24, SD = 41.75) and females (mean = 193.32, SD = 42.49), were within the average range for healthy subjects, according to standard tables (Brickenkamp, 2002). As observed in previous studies (Kremen et al., 1998; Raine, 1992), we found significant sex differences for the SPQ-B *Sum* score ($U = -2.45$, $p = 0.014$, $p_{adj} = 0.028$), the *Interpersonal* ($U = -2.43$, $p = 0.015$, $p_{adj} = 0.028$) and *Disorganised* ($U = -3.84$, $p = 1.3 \times 10^{-4}$, $p_{adj} = 3.9 \times 10^{-4}$) subscores, with higher scores in males than in females; but not for the *Cognitive-Perceptual* ($U = -0.96$, $p = 0.336$) subscore.

3.2. Associations of ZNF804A, CACNA1C and schizotypy dimensions

To explore the prediction of the three schizotypy dimensions, we performed separate stepwise multiple regression analyses, entering the two SNPs, SNP × sex interaction terms, sex, age, and MDS components as possible regressors (Table 2, Suppl. Table S1a-1c).

For the *Cognitive-Perceptual* dimension (*model 1a*, √mPRESS = 1.12, Fig. 1), we found a significant effect of age ($\beta = 0.018$, $p = 5.05 \times 10^{-7}$, $p_{adj} = 2.53 \times 10^{-6}$) and rs1344706 × sex ($\beta = 0.089$, $p = 0.015$, $p_{adj} = 0.033$), with a higher number of C alleles associated with higher *Cognitive-Perceptual* schizotypy in females ($\beta = 0.212$, $p = 0.007$), but not in males ($\beta = -0.071$, $p = 0.458$).

For the *Interpersonal* dimension (*model 1b*, √mPRESS = 1.71, Fig. 1), we also found a significant effect of age ($\beta = 0.011$, $p = 0.044$, $p_{adj} = 0.044$) and rs1006737 × sex ($\beta = -0.150$, $p = 0.011$, $p_{adj} = 0.033$), with a higher number of A alleles associated with lower *Interpersonal* schizotypy in males ($\beta = -0.399$, $p = 0.035$), but not in females ($\beta = -0.162$, $p = 0.209$).

For the *Disorganised* dimension (*model 1c*), only sex was identified as a significant regressor ($\beta = -0.390$, $p = 2.16 \times 10^{-4}$, $p_{adj} = 8.64 \times 10^{-4}$).

Table 1
Distribution of schizotypy and allele frequencies for both sexes.

	total mean (SD[a])	male mean (SD[a])	female mean (SD[a])
SPQ-B			
Sum	3.42 (2.99)	3.78 (3.07)	3.20 (2.93)
Cognitive perceptual	0.90 (1.15)	0.81 (1.03)	0.95 (1.21)
Interpersonal	1.72 (1.72)	1.92 (1.76)	1.60 (1.68)
Disorganized	0.80 (1.27)	1.04 (1.43)	0.65 (1.15)
	total no. (%)	male no. (%)	female no. (%)
ZNF804A rs1344706			
AA	217 (35.3)	85 (36.6)	132 (34.5)
AC	295 (48.9)	106 (45.7)	189 (49.3)
CC	103 (16.7)	41 (17.7)	62 (16.2)
CACNA1C rs1006737			
GG	292 (47.5)	118 (50.9)	174 (45.4)
AG	267 (43.4)	99 (42.7)	168 (43.9)
AA	56 (9.1)	15 (6.5)	41 (10.7)

[a] SD = standard deviation.

Table 2
Summary of model specifications for *models 1a, 1b and 2*. Full documentation in suppl. Tables S1–S2.

model 1a	($F(2,614) = 16.00$, $p = 1.7 \times 10^{-7}$, $R^2 = 0.050$)			
prediction of Cognitive-Perceptual *schizotypy*			√mPRESS[b] = 1.12	
	coefficient (se[a])	*t*	*p*	p_{adj}
age	0.018 (0.004)	4.34	5.05×10^{-7}	**2.53×10^{-6}**
rs1344706 × sex	0.283 (0.124)	2.28	0.015	**0.033**
rs1344706 (sex = m)	−0.073 (0.094)	−0.74	0.458	
rs1344706 (sex = f)	0.212 (0.079)	2.79	0.007	
model 1b	($F(2,614) = 16.58$, $p = 0.003$, $R^2 = 0.015$)			
prediction of Interpersonal *schizotypy*			√mPRESS[b] = 1.71	
	coefficient (se[a])	*t*	*p*	p_{adj}
age	0.011 (0.006)	2.02	0.044	**0.044**
rs1006737 × sex	0.283 (0.124)	−2.57	0.011	**0.033**
rs1006737 (sex = m)	−0.399 (0.188)	−2.13	0.035	
rs1006737 (sex = f)	−0.162 (0.129)	−1.26	0.209	
model 2	($F(4,610) = 38.89$, $p = 5.13 \times 10^{-29}$, $R^2 = 0.203$)			
prediction of d2 performance			√mPRESS[b] = 37.99	
	coefficient (se[a])	*t*	*p*	p_{adj}
age	−1.342 (0.125)	−10.76	7.85×10^{-25}	**3.14×10^{-24}**
rs1344706	−15.551 (5.208)	−2.99	0.003	**0.006**
rs1344706 × sex	6.553 (2.944)	2.23	0.026	**0.026**
rs1344706 (sex = m)	−8.145 (3.399)	−2.40	0.017	
rs1344706 (sex = f)	−3.041 (2.881)	−1.06	0.292	
Cognitive-Perceptual schizotypy	−4.509 (1.367)	−3.30	0.001	**0.003**

In bold Bonferroni-Holm-adjusted p-values after correction.
[a] SE = standard error.
[b] √mPRESS = root mean predicted residual sum of squares.

Total schizotypy was neither associated with *ZNF804A* rs1344706 (β = −0.317, $p = 0.591$) nor *CACNA1C* rs1006737 (β = −0.227, $p = 0.120$).

3.3. Associations of ZNF804A, CACNA1C, schizotypy dimensions and attention

To explore significant predictors of d2 performance, we calculated a separate stepwise multiple regression *model 2* with the two SNPs, SNP × sex interaction terms, sex, age, the three schizotypy subscores, and MDS components as possible regressors (√mPRESS = 37.99, Table 2, Suppl. Table S2). Here, age (β = −1.342, $p = 7.82 \times 10^{-25}$, $p_{adj} = 3.14 \times 10^{-24}$), *Cognitive-Perceptual* schizotypy (β = −4.509, $p = 0.001$, $p_{adj} = 0.003$), *ZNF804A* rs1344706 (β = −15.551, $p = 0.003$, $p_{adj} = 0.006$) and rs1344706 × sex (β = 6.553, $p = 0.026$, $p_{adj} = 0.026$), with a higher number of rs1344706-C associated with lower d2 performance in males (β = −8.145, $p = 0.017$) but not in females (β = −3.041, $p = 0.292$), were detected as significant regressors.

3.4. Mediation models of ZNF804A, schizotypy and attention

To analyse the proposed mediating relationship of schizotypy and attention, we hypothesised two models, derived from the associations detected in the regression models *1a-c* and *2*. *Model 3a* (Fig. 2, Suppl. Table S3) proposes *Cognitive-Perceptual* schizotypy as a risk factor for impaired cognition, thus mediating the effect of rs1344706 on d2 performance ($F(3,611) = 48.78$, $p < 1 \times 10^{-100}$, $R^2 = 0.197$). We found a significant direct effect of the dosage of *ZNF804A* rs1344706-C ($c' = -5.038$, $t(611) = -2.31$, $p = 0.021$, $p_{adj} = 0.032$) as well as a significant indirect effect of the SNP via *Cognitive-Perceptual* schizotypy (β = −4.210, $t(611) = -2.94$, $p = 0.003$, $p_{adj} = 0.013$) on d2 performance. However, the latter was again moderated by sex: Only for females (β = −0.890) but not for males (β = 0.300), a bootstrap-based

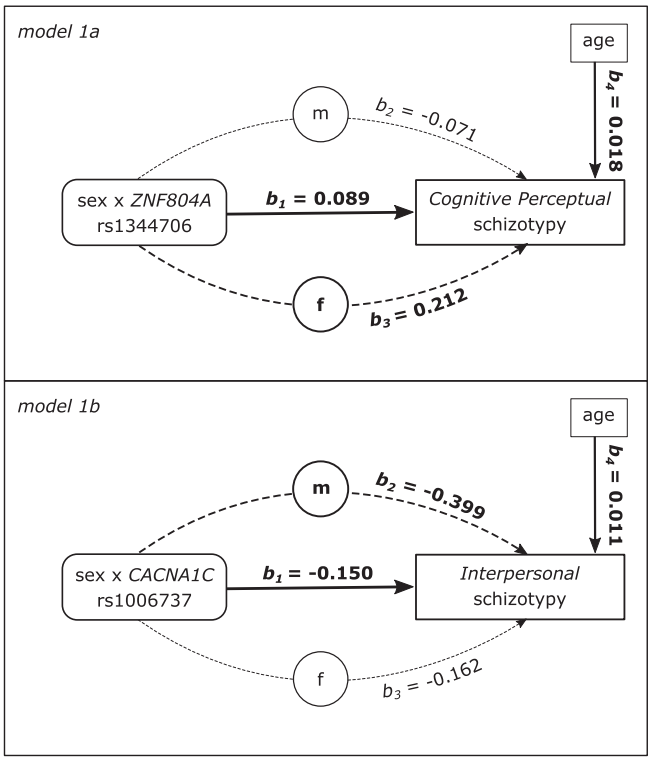

Fig. 1. Sex-moderated *models 1a* and *1b* of the effect of *ZNF804A* rs1344706-C and *CACNA1C* rs1006737-A on differential schizotypy dimensions. $b_{1\text{-}3}$ indicate unstandardised regression coefficients for each path; statistically significant paths are shown in bold.

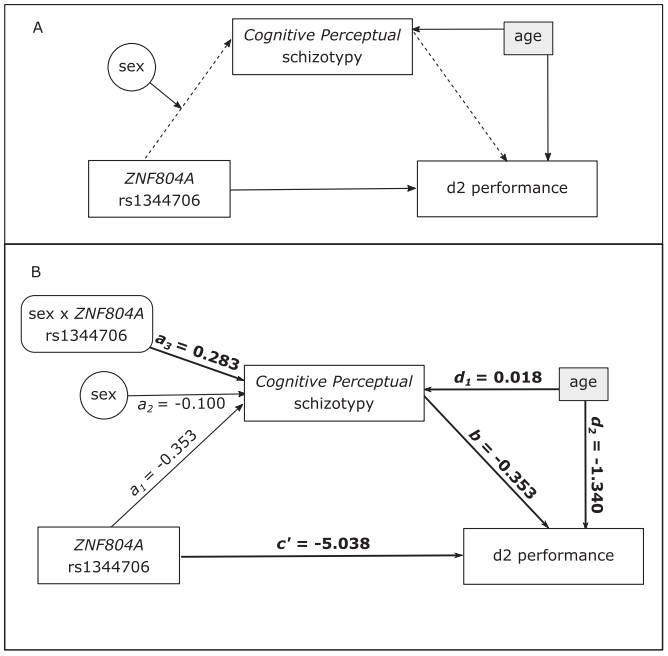

Fig. 2. Sex-moderated mediation *model 3a* of the effect of *ZNF804A* rs1344706-C on d2 performance, mediated by *Cognitive-Perceptual* schizotypy. Conceptual (A) and statistical (B) diagram. a_1–d_2 indicate unstandardised regression coefficients for each path; statistically significant paths are shown in bold.

confidence interval calculated using 10,000 bootstrap samples was consistently below zero, confirming a conditional indirect effect.

We additionally considered the opposing model, assuming cognition at an intermediate position between genes and phenotype. We tested this assumption in our data, with d2 performance mediating the sex-moderated effect of rs1344706-C on *Cognitive-Perceptual* schizotypy. This *model 3b* (Fig. 3, suppl. Table S3), although significant, explained a smaller proportion of the variance ($F(5,609) = 6.90$, $p = 2.4 \times 10^{-6}$, $R^2 = 0.071$) than *model 3a*. Post hoc *t*-tests comparing absolute z-transformed bootstrapped coefficient estimates from *models 3a* and *3b* revealed a stronger effect of rs1344706 on *Cognitive-Perceptual* schizotypy than on d2 performance (mean absolute difference (mad, *3a*) = 0.130, SD = 0.117; mad(*3b*) = 0.134, SD = 0.117) in both models ($t(9999) = -111.49$, $p < 1 \times 10^{-100}$; $t(9999) = -114.47$, $p < 1 \times 10^{-100}$, respectively).

There was no indication of a mediating effect of *Interpersonal* schizotypy on the association of CACNA1C rs1006737-A on attention or vice versa (suppl. Table S4a-b).

4. Discussion

This is the first large-scale study addressing the interplay between candidate susceptibility genes for psychotic disorders with different dimensions of schizotypy and neurocognitive performance as a putative endophenotype for psychosis in healthy subjects. Our analysis provides first support for a multivariate model of the interaction of genotype, phenotype, and cognition, linking schizotypy in the general population to a dimensional schizophrenia model. This includes two major findings: We observe, for the first time, a sex-moderated association of *ZNF804A* rs1344706 with the SPQ-B *Cognitive-Perceptual* dimension and of *CACNA1C* rs1006737 with the SPQ-B *Interpersonal* dimension. We suggest a moderated mediation model showing that in women, the effect of rs1344706 on attention is mediated by *Cognitive-Perceptual* schizotypy. Our results have implications for the role of *ZNF804A* rs1344706 and CACNA1c rs1006737 in schizotypy and cognitive function, and suggest a sex-modulated interaction between them.

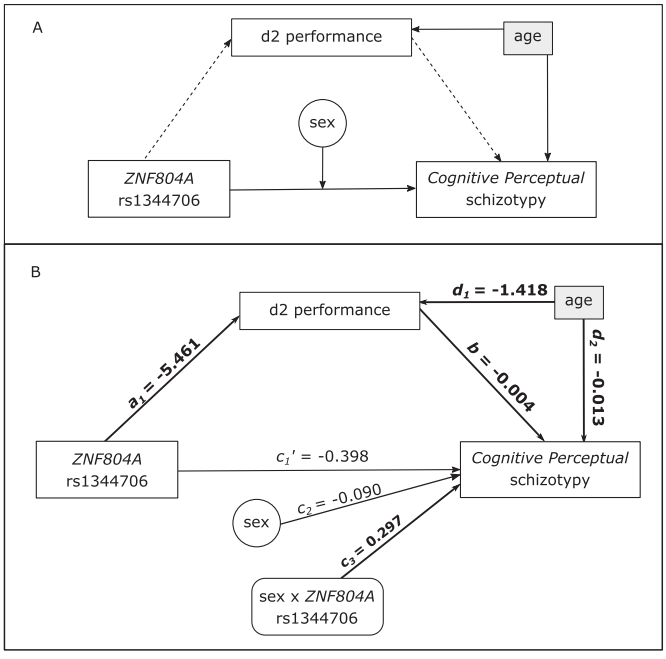

Fig. 3. Sex-moderated mediation *model 3b* of the effect of *ZNF804A* rs1344706-C on *Cognitive-Perceptual* schizotypy, mediated by d2 performance. Conceptual (A) and statistical (B) diagram. a_1–d_2 indicate unstandardised regression coefficients for each path; statistically significant paths are shown in bold.

Concurrent with previous findings (Stefanis et al., 2013; Yasuda et al., 2011), we further confirmed *ZNF804A* rs1344706 as susceptibility SNP for schizotypy. While this association has previously been reported, we provide a more detailed link to particular schizotypy dimensions, modulated by sex. Initially, Yasuda et al., reported a positive relationship between *ZNF804A* rs1344706-A and *Disorganised* schizotypal traits in healthy subjects (Yasuda et al., 2011). Concurrent with our own findings, however, Stefanis et al. reported an inverse relationship, with a higher number of rs1344706-A associated with decreased schizotypy. This effect was found for a primarily "positive" schizotypy endophenotype, including referential ideas and perceptual aberrations (Stefanis et al., 2013), in line with our results linking rs1344706 to the *Cognitive-Perceptual* dimension. Differences to Yasuda's findings might be attributed to divergent study populations and genetic backgrounds (Japanese vs. Central-European) and different A allele frequencies in those populations (38% and 61%, respectively (Clarke and Cardon, 2010; Yasuda et al., 2011)).

We now extend the simple model of a direct dependence of schizotypal features on rs1344706 allelic load by introducing sex as moderator. While previous studies on rs1344706 were either confined to all male samples (Stefanis et al., 2013) or did not test for such an interaction (Yasuda et al., 2011), a similar finding for another schizophrenia susceptibility SNP of *ZNF804A* (rs7597593, in medium linkage disequilibrium with rs1344706; $r^2 = 0.395$ calculated with LDlink for the CEU population (Machiela and Chanock, 2015)) has recently been reported, as only female C allele carriers showed elevated schizotypy levels compared to A-homozygotes (de Castro-Catala et al., 2017). Sex-dependent effects of rs7597593 are also evident in clinical measures and post-mortem brain mRNA expression levels in schizophrenia (Zhang et al., 2011). Thus, our findings can be explained with clinical and molecular mechanisms causing sex × SNP interactions for *ZNF804A* in the development of schizotypal traits.

In addition, we confirmed recent findings relating *ZNF804A* rs1344706 to neurocognitive function in general, and attention in particular (Chang et al., 2017). In healthy participants, the A allele and A/A genotype was associated with deficits in the executive control dimension of attention (Balog et al., 2011). Proposing a neural correlate of functional alterations, rs1344706-A homozygotes showed reduced thickness within the anterior cingulate cortex (Voineskos et al., 2011) and changes in functional coupling of the dorsolateral prefrontal cortex with the hippocampus (Esslinger et al., 2009; Paulus et al., 2013). Interestingly, in patients with schizophrenia, A allele load has been associated with fewer cognitive deficits (Van Den Bossche et al., 2012; Walters et al., 2010) and decreased cortical alteration (Schultz et al., 2014). It has been suggested that *ZNF804A* rs1344706 may enhance susceptibility to a certain schizophrenia subtype with less cognitive impairment (Walters et al., 2010), but also that the effects of rs1344706 might differ between healthy participants and patients (Hargreaves et al., 2012).

While Stefanis et al. linked *ZNF804A* SNPs to schizotypy, they did not detect an effect of rs1344706 on neurocognition (Stefanis et al., 2013). Differences in test batteries aside, the discrepancy between their findings and our own may be caused by marked differences in sample characteristics. Their sample comprised of young male army recruits while ours combined female and male participants within a wide range of age. Given the well-known age effects on neurocognitive measures (Lufi et al., 2015), a very selective sample with reduced variance might thus underestimate correlation or regression measures.

Despite evidence linking *ZNF804A* rs1344706 to illness susceptibility and psychosis proneness, neurocognitive functions, and variations in brain structure and function, its exact biological pathway is still unclear. *ZNF804A* is expressed widely in the human brain (Sun et al., 2015), especially within the dorsolateral prefrontal cortex and the hippocampus (Hill and Bray, 2012). Rs1344706 is non-coding but thought to have effects on *ZNF804A* expression (Hill and Bray, 2011), particularly during early prenatal brain development (Hill and Bray, 2012). *ZNF804A* has

also been associated with regulation of dopamine receptors (Girgenti et al., 2012), and alterations of dopamine concentration, and expression of dopaminergic genes have been linked to psychosis etiology (Howes and Kapur, 2009) and schizotypy (Grant et al., 2014; Mohr and Ettinger, 2014). In addition, sex-specific effects of genes involved in dopamine transmission have been discussed in schizophrenia, with oestrogens and androgens differentially modifying the development of schizophrenia symptoms through dopaminergic pathways (Godar and Bortolato, 2014). Similar mechanisms might influence the development of subclinical symptoms in schizotypy and thus explain sex-dependent effects of *ZNF804A* on schizotypal traits.

Taken together, compelling evidence suggests that effects of *ZNF804A* rs1344706 polymorphisms have a relevant impact long before potential illness manifestation. Affected brain areas and neurocognitive functions have shown to be relevant for schizophrenia as well as schizotypy. Using genetic modelling in twin samples, Toulopoulou et al. showed that a substantial part of the phenotypic overlap between schizophrenia and cognition is explained by shared genetic variability (Toulopoulou et al., 2007). The authors concluded that the next step would be to identify specific genes that influence schizophrenia together with cognitive quantities. Our results support *ZNF804A* rs1344706 as such a genetic variant relevant for schizotypy, an intermediate schizophrenia phenotype. As has been reported recently (Stotesbury et al., 2018), we particularly regard the *Cognitive-Perceptual* dimension as a risk factor for attentional difficulties.

However, Toulopoulou et al. subsequently argued that schizophrenia liability is partially expressed through cognitive deficits (Toulopoulou et al., 2015) and that cognitive functions lie upstream of schizophrenia (Toulopoulou et al., 2018). Relevant loci should then have a bigger effect on cognitive function than on schizophrenia (Toulopoulou et al., 2015). Our results, however, fail to confirm this prediction for the schizotypy phenotype. In both models tested, *ZNF804A* rs1344706 showed a larger effect on schizotypy than on cognitive function. While aware that this cannot definitively be resolved in our cross-sectional study, we believe that our results should inspire further dissection of the proposed models. Considerably, Toulopoulou's model is based on net genetic influences rather than single risk variants. It also relies on patient data and thus on the schizophrenia phenotype rather than schizotypy (Hargreaves et al., 2012) and *ZNF804A* expression seems to differ between schizophrenia patients and healthy controls (Guella and Vawter, 2014). The underlying mechanisms of schizophrenia and schizotypy are overlapping, but most likely not identical. Besides a balanced proportion of male and female participants, the application of multiple measures of both schizotypy and cognitive performance should be considered to overcome limitations of our own study.

We further showed a sex-modulated association of the psychosis susceptibility variant rs1006737 in *CACNA1C* with the *Interpersonal* schizotypy dimension. While sex-dependent effects of rs1006737 or its proxy rs10774035 have been reported for schizophrenia-spectrum disorders (Heilbronner et al., 2015) and emotional lability and resilience (Strohmaier et al., 2013), this is, to our knowledge, the first study detecting a sex-dependent effect of rs1006737 on schizotypy. In contrast to previous studies (Roussos et al., 2013, 2011), associating rs1006737-A with higher *Paranoid Ideation*, we find an inverse relationship, i.e. with lower *Interpersonal* schizotypy scores in men only. Beside the possibility of chance findings, this might be due to differences in sample characteristics, as both studies by Roussos et al. analysed young male army recruits, while our sample comprised males and females of a wide age range. Other discrepancies include the schizotypy measures and possible population differences (Greek vs. Central European) across studies (Clarke and Cardon, 2010).

As *CACNA1C* is suggested to be a susceptibility gene for a more general risk for mental illness (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), divergent effects in different studies might represent a less specific impact of the SNP. This would implicate the need for more studies with diverse samples. However, *CACNA1C* rs1006737 has repeatedly been associated with socially relevant tasks like emotion recognition and processing (Nieratschker et al., 2015; Soeiro-de-Souza et al., 2012; Tesli et al., 2013), as well as alterations in social interaction in animal models (Dedic et al., 2018; Moon et al., 2018). Thus, variations in rs1006737 seem to affect social functioning on a behavioural level, as well as brain structural and functional correlates. It might be concluded that rs1006737 primarily affects the *Interpersonal* and, as such, social dimension of schizotypy.

The results from our study provide evidence for the involvement of schizophrenia genetic susceptibility variants in psychometric schizotypy, a risk phenotype for psychosis. Our findings further provide an account of how those risk variants might modulate different dimensions of individual schizotypal traits even in healthy subjects, affecting neurocognitive performance in domains frequently impaired in schizophrenia.

Conflict of interest

None.

Contributors

TM performed the statistical analyses, TM and IN wrote the first draft of the manuscript. TFMA helped with chosing the statistical design and wrote the genetic methods part. SS, FS, KB, JM, DY, DZ, DG, KD, SM, KF, RR, NO, JR, TH and AJ participated in data acquisition, quality checking and preparation, and assisted in literature search and analyses. TFMA, AJF, SH-H, FS, SHW, MR, BM-M and MMM performed genotyping as well as further preparation and quality control of the genetic data. IN, UD, AK and TK designed the study protocol. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

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ii. **STUDY II**: Publication Meller et al. (2019b)

The association of striatal volume and positive schizotypy in healthy subjects: intelligence as a moderating factor.

Tina Meller, Ulrich Ettinger, Phillip Grant and Igor Nenadić

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The association of striatal volume and positive schizotypy in healthy subjects: intelligence as a moderating factor

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Abstract

Background. Schizotypy, a putative schizophrenia endophenotype, has been associated with brain-structural variations partly overlapping with those in psychotic disorders. Variations in precuneus structure have been repeatedly reported, whereas the involvement of fronto-striatal networks – as in schizophrenia – is less clear. While shared genetic architecture is thought to increase vulnerability to environmental insults, beneficial factors like general intelligence might buffer their effect.

Methods. To further investigate the role of fronto-striatal networks in schizotypy, we examined the relationship of voxel- and surface-based brain morphometry and a measure of schizotypal traits (Schizotypal Personality Questionnaire, with subscores *Cognitive-Perceptual*, *Interpersonal*, *Disorganised*) in 115 healthy participants [54 female, mean age (S.D.) = 27.57(8.02)]. We tested intelligence (MWT-B) as a potential moderator.

Results. We found a positive association of SPQ *Cognitive-Perceptual* with putamen volume ($p = 0.040$, FWE peak level-corrected), moderated by intelligence: with increasing IQ, the correlation of SPQ *Cognitive-Perceptual* and striatal volume decreased ($p = 0.022$). SPQ *Disorganised* was positively correlated with precentral volume ($p = 0.013$, FWE peak level-corrected). In an exploratory analysis ($p < 0.001$, uncorrected), SPQ total score was positively associated with gyrification in the precuneus and postcentral gyrus, and SPQ *Disorganised* was negatively associated with gyrification in the inferior frontal gyrus.

Conclusions. Our findings support the role of fronto-striatal networks for schizotypal features in healthy individuals, and suggest that these are influenced by buffering factors like intelligence. We conclude that protective factors, like general cognitive capacity, might attenuate the psychosis risk associated with schizotypy. These results endorse the idea of a continuous nature of schizotypy, mirroring similar findings in schizophrenia.

Introduction

Current dimensional models of psychopathology (e.g. Kotov *et al.*, 2017) suggest that phenomena associated with clinical syndromes and disorders are continuous in nature and extend also into the realm of health as dimensions of personality. This suggestion, however, is not new (e.g. Eysenck, 1952), and regarding psychotic disorders, relevant traits are most commonly subsumed under the (wide) rubric of schizotypy or psychosis-proneness (Rado, 1953; Meehl, 1962; Claridge, 1997; Grant *et al.*, 2018). Evidence of associations between variations in different brain circuits shared between clinical entities like schizophrenia (Bakhshi and Chance, 2015) and states of ultra-high risk as well as schizotypal traits in healthy individuals (Ettinger *et al.*, 2015; Nenadic *et al.*, 2015a) support this notion.

Like all traits, schizotypy is seen as a relatively stable personality framework that, like schizophrenia, consists of three major sub-facets, namely positive, negative and disorganised facets (Vollema and van den Bosch, 1995; Oezgen and Grant, 2018). The positive facet resembles positive symptoms of psychosis (e.g. as magical ideation and unusual experiences), is linked to psychotic-like experiences (PLEs) (Kline *et al.*, 2012) and has been suggested as an endophenotype of psychosis-in-schizophrenia (Howes and Kapur, 2009; Barrantes-Vidal *et al.*, 2015; Grant, 2015).

Negative and disorganised schizotypy, however, have been suggested as more related to schizophrenia-liability than mere proneness to psychotic and PLEs, as these facets – unlike positive schizotypy (Tarbox and Pogue-Geile, 2011; Tarbox *et al.*, 2012) – are also elevated in patients with psychotic disorders and their healthy relatives (Brosey and Woodward, 2015). Schizotypy,

albeit sharing variance with schizophrenia-liability, is a relatively stable trait (Venables and Raine, 2015; Janssens *et al.*, 2016), with low conversion rates into the clinical domain (Kwapil *et al.*, 2013). This is, however, expected (Meehl, 1990; Grant *et al.*, 2018) and, thus, does not disqualify schizotypy as an important construct for understanding schizophrenia-spectrum pathology (Debbané and Mohr, 2015; Kwapil and Barrantes-Vidal, 2015). Additionally, familial association studies underline the necessity of distinguishing between positive and negative/disorganised facets of schizotypy (Tarbox and Pogue-Geile, 2011; Tarbox *et al.*, 2012). This is in line with findings by Schultze-Lutter and co-workers, showing that conversion form clinical high risk (CHR) to frank psychosis is best predicted by negative/disorganised schizotypy (Flückiger *et al.*, 2016, 2019).

Nonetheless, psychometrically-assessed estimates of schizotypy (like schizotypal traits, measured through scales based on DSM-criteria for Schizotypal Personality Disorder) have, repeatedly, been associated with variations in brain structures also implicated in schizophrenia. One finding replicated in several studies is that of structural and functional variation within the precuneus: Evidence for an association of schizotypy and schizotypal traits with increased grey matter volume (GMV) in the precuneus has been reported in several structural imaging studies (Modinos *et al.*, 2010, 2018; Nenadic *et al.*, 2015b), although not in all (Ettinger *et al.*, 2012; Kühn *et al.*, 2012). Furthermore, PLEs have been shown to be associated with increased precuneus activation (van Lutterveld *et al.*, 2014).

Additionally, there is growing evidence for fronto-striatal circuits to be involved in the generation of PLEs. Recent studies have suggested positive schizotypal traits to be associated with variations in frontal volume, but the direction is unclear, with increases (Kühn *et al.*, 2012; Nenadic *et al.*, 2015b; Modinos *et al.*, 2018) as well as decreases (Ettinger *et al.*, 2012; DeRosse *et al.*, 2015) being reported. As most studies have focused on variations in volumetric parameters, apart from one study finding increased right prefrontal lobe gyrification in participants scoring above *v.* below a clinical cut-off (Stanfield *et al.*, 2008), there is no study using a dimensional approach to schizotypy and folding analysis. Those, however, are of particular interest as cortical folding, happening early during brain development (Chi *et al.*, 1977), might indicate disruption in neurodevelopmental processes (Nenadic *et al.*, 2014), and has also been reported to be altered in psychosis and high risk (Spalthoff *et al.*, 2018; Zuliani *et al.*, 2018).

Striatal regions have also been reported to correlate with the level of subclinical psychotic-like traits or symptoms: Psychotic experiences in healthy subjects are associated with smaller putamen volumes (Mittal *et al.*, 2013), and psychoticism has been shown to be correlated with greater activation in putamen and pallidum (Ettinger *et al.*, 2013), while positive schizotypy has been linked to reduced BOLD signal during antisaccades (Aichert *et al.*, 2012). *Interpersonal* schizotypal traits have been associated with decreased task-related activation in the striatum and amygdala (Yan *et al.*, 2016).

In addition, highlighting the role of the fronto-striatal network, positive and negative schizotypy have recently been associated with variations in cortico-striatal resting state functional connectivity (Rössler *et al.*, 2018; Wang *et al.*, 2018; Waltmann *et al.*, 2019). SPQ *Disorganised* has, furthermore, been associated with a higher availability of striatal dopamine (Chen *et al.*, 2012).

Together, these findings – to some extent – mirror those in psychotic disorder. Specifically, schizophrenia patients, and (to a lesser degree) their unaffected siblings, show increased volume of striatal regions putamen and pallidum (Mamah *et al.*, 2008; Okada *et al.*, 2016; van Erp et al., 2016) and greater putamen volume variability compared to healthy controls (Brugger and Howes, 2017). Pallidum volume has been positively associated with symptom severity in schizophrenia patients (Spinks *et al.*, 2005) and there is evidence for altered extra-striatal functional connectivity in schizophrenia patients during a psychotic episode (Peters *et al.*, 2017).

It has been suggested that these overlaps in phenotype and concurring neuroanatomy might be, at least partially, explained by overlapping genetic architecture (Walter *et al.*, 2016). The current literature, however, also implies that genetic risk is not linearly represented through overall schizotypal traits, as studies show only marginal associations with polygenic risk scores in healthy individuals, and an influence of environmental factors like stress contexts (Hatzimanolis *et al.*, 2018).

Those findings fit well into a model by Siever and Davis, proposing that common genetic variants increase schizophrenia risk through elevated vulnerability for environmental insults, leading to brain structural changes within temporal or striatal regions (Siever and Davis, 2004). In contrast to schizophrenia patients, however, in schizotypal individuals, independent genetic variants and/or beneficial environmental contexts, leading to preserved or increased frontal volume or cognitive protectors like general intelligence, buffer the effect of susceptibility variants and thus lead to a subclinical level of PLEs (Siever and Davis, 2004). The issue of a moderating effect of intelligence has also been suggested by Brod (1997) – regarding highly creative individuals – and substantiated by findings that intelligence moderates the tendency of highly positive schizotypal individuals to see meaning in random noise (Grant *et al.*, 2014*a*).

Indeed, dysfunctions in prefrontal networks are often reported in psychotic disorders (Dandash *et al.*, 2017). Dysregulation of the striatum, a centre for the integration of high-level cognitive, motor and limbic processes (Simpson *et al.*, 2010), seems to be contributing to the manifestation of psychotic symptoms in schizophrenia (Howes and Kapur, 2009) and possibly also (positive) schizotypy (Ettinger *et al.*, 2013; Mohr and Ettinger, 2014).

To further examine the relationship of morphometric variations in fronto-striatal networks with dimensional schizotypal traits, we analysed voxel- and surface-based brain structural parameters in association with psychometrically-assessed schizotypy in healthy individuals. We hypothesised associations of frontal and striatal volume variations with both positive and negative schizotypal traits. Based on a fronto-thalamo-striatal model of the psychosis continuum, brain structural effects in both medial and lateral prefrontal cortex are observed in both positive and negative dimensions of schizophrenia, and in the thalamus for the negative dimension (Koutsouleris *et al.*, 2008; Nenadic *et al.*, 2010, 2015*c*). Assuming the possibility of general cognitive capacity buffering psychosis risk (Brod, 1997; Siever and Davis, 2004), we also tested for a moderating effect of intelligence on the relationship of brain morphometry and schizotypal traits. This is, to our knowledge, the first study investigating intelligence as a moderator in the association of brain structural variation and estimates of schizotypy.

Material and methods

Sample

We analysed data of $N = 115$ healthy participants [54 female, aged 18–50 years, mean age = 27.57 years (S.D. = 8.02)], recruited

through advertisements in and around Munich, Germany. All experimental procedures were approved by the research ethics committee of the Faculty of Medicine at the University of Munich, in accordance with the current division of the Declaration of Helsinki. Participants were included after thorough clinical screening and only if they did not meet any of the exclusion criteria: any DSM-IV Axis I disorders, first-grade relatives with psychotic disorders, former or current neurological disorders, current physical conditions, current medication except for contraceptives, uncorrected visual impairments. Further inclusion criteria were age between 18 and 55 and German as a first language. All subjects volunteered to take part in the study, gave written informed consent and received a financial compensation for their participation.

Psychometric assessment of schizotypal traits and IQ

All participants completed the German version (Klein *et al.*, 1997) of the Schizotypal Personality Questionnaire (SPQ, Raine, 1991), assessing schizotypal traits on the three dimensions *Cognitive-Perceptual* (measuring positive schizotypy), *Disorganised* (related to eccentricity and – somewhat – disorganised schizotypy) and *Interpersonal* (tapping into negative schizotypy) as delineated by previous factor analyses (Axelrod *et al.*, 2001; Compton *et al.*, 2009). For the questionnaire as a whole and its subscores, adequate internal consistency and criterion validity have been demonstrated (Klein *et al.*, 2001; Fonseca-Pedrero *et al.*, 2018). In our sample, the SPQ subscales showed acceptable to good reliability (Cronbach's α for the total score $\alpha = 0.882$, for the subscales *Disorganised* $\alpha = 0.832$, *Negative* $\alpha = 0.848$, *Positive* $\alpha = 0.757$).

For an estimation of intelligence, we applied the Multiple Choice Word Test-B (MWT-B, Lehrl, 1995). The MWT-B consists of 37 items in ascending difficulty, each requiring identification of one truly existing word opposed to three distractors. It has been shown to be an economic, easy to administer and robust estimate of global crystallised intelligence, highly correlated with both verbal and general intelligence measured with extensive tests like the HAWIE, the German version of the Wechsler Adult Intelligence Scale (Satzger *et al.*, 2002). In our sample, the MWT-B showed an internal consistency of Cronbach's $\alpha = 0.664$.

Image acquisition and preprocessing

We acquired high-resolution, T1-weighted structural images on a 3T MAGNETOM Verio scanner (Siemens, Erlangen, Germany) using a 12-channel head matrix Rx-coil. We used a three-dimensional MPRAGE sequence with a repetition time of TR = 2400 ms, echo time TE = 3.06 ms, flip angle = 9 degrees with 160 slices, slice thickness = 1.0 mm, voxel size = 1.0 × 1.0 × 1.0 mm, field of view FOV = 256 mm.

Images were preprocessed with the CAT12 toolbox (Computation Anatomy Toolbox for SPM, v12.3, build r1318, http://www.neuro.uni-jena.de/cat), based on SPM12 v7219 (Statistical Parametric Mapping, version 12) running under MATLAB R2017a (The MathWorks, Natick, MA, USA). Images were spatially registered using tissue probability maps implemented in SPM12, segmented and spatially normalised using the optimised shooting algorithm (Ashburner and Friston, 2011), with an inhomogeneity correction of 0.5. All images passed visual quality inspection for movement artefacts and image quality, as well as the quality assurance protocols implemented in CAT12 (grade B or higher). During preprocessing, total intracranial volume (TIV) was calculated.

Additionally, we extracted gyrification parameters to analyse surfaced-based morphometry with the CAT12 toolbox, using a recently developed algorithm to calculate cortical surface parameters (Dahnke *et al.*, 2013), based on absolute mean curvature (Luders *et al.*, 2006). Gyrification images were smoothed with a Gaussian kernel of 20 mm (FWHM).

Statistical analyses

Statistical analyses were conducted using general linear regression models (GLM) in SPM and CAT12. Given the discussed specificity of the different schizotypy dimensions (Tarbox and Pogue-Geile, 2011; Grant, 2015), we conducted separate GLMs for each of the subscores. We further tested a GLM using SPQ total score as a regressor. In a supplementary analysis, we entered all three subscores into the GLM (and set + 1/−1 in the contrast) to assess the overall effect of schizotypal traits (see online Supplementary SF1).

For both VBM and gyrification analyses, we used age and sex as covariates (setting them to zero to remove related variance), and for VBM we additionally defined TIV as a covariate to remove global brain size differences. For all analyses, we considered significance at $p < 0.05$ FWE peak level-corrected threshold. For gyrification analyses, that did not survive FWE peak level correction, we conducted additional exploratory analyses at $p < 0.001$ uncorrected.

To test for a modulating effect of IQ on the association of SPQ-levels and structural variation, we set up a moderation model using the PROCESS macro v3.3 (Hayes, 2013) running on IBM Statistical Package for Social Sciences (SPSS, version 24, IBM, Armonk, NY, USA). It is unclear, whether particular aspects of intelligence or cognitive functions might serve as better factors or predictors in such models. Given the limited availability of cognitive data from this data set, we therefore focused on IQ to be included as a moderator in the model. For schizotypal traits, the respective dimension scores were entered, while for structural data we considered a wider cluster comprising peak and surrounding voxels at an uncorrected $p < 0.001$ threshold, taking into consideration voxels might not reach corrected significance in direct association statistics (due to the assumed moderation effects), but might add to moderation. Here, we used extracted eigenvariate values as an approximation of mean volume inside the clusters, a weighted mean more robust to heterogeneous voxel values. Correcting for the two models tested, significance was assumed at $p < 0.025$.

Results

Descriptive statistics and intercorrelations

Demographic details and descriptive statistics for SPQ sum score and subscores are shown in Table 1. IQ was significantly negatively correlated with SPQ *Cognitive-Perceptual* ($r = -0.196$, $p = 0.036$), indicating that higher IQ is associated with lower schizotypy scores. There were no significant correlations of IQ with the *Disorganised* ($r = -0.030$, $p = 0.746$) or *Interpersonal* ($r = -0.104$, $p = 0.268$) dimensions.

Voxel-based morphometry

Regression analyses showed significant correlations of the positive and disorganised dimensions of the SPQ with GMV (Fig. 1*a*, *b*).

Table 1. Demographic characteristics of the sample

	Mean (s.d.)	Range	Kurtosis	Skewness
Sex	54 female/61 male	–	–	–
Age	27.57 (8.02)	18–50	0.34	1.17
IQ	112.54 (12.26)	88–143	−0.47	0.57
SPQ total score	8.14 (7.11)	0–35	2.03	1.37
SPQ *Cognitive-Perceptual*	3.15 (3.08)	0–15	1.36	2.1
SPQ *Disorganised*	2.28 (2.99)	0–14	3.81	1.92
SPQ *Interpersonal*	3.67 (3.82)	0–18	2.59	1.61

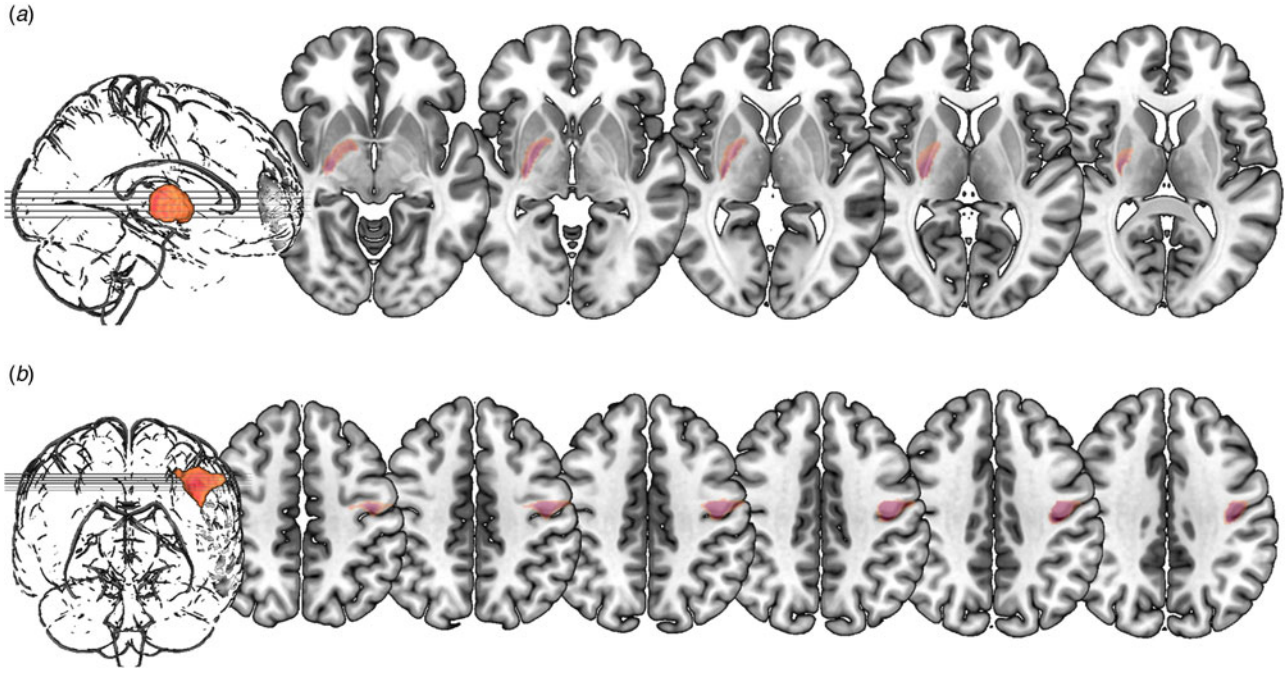

Fig. 1. Clusters of positive correlation between grey matter volume and the SPQ *Cognitive-Perceptual* dimension in the striatum (*a*, upper panel) and the *Disorganised* dimension in the pre- and postcentral gyri (*b*, lower panel); for illustration purposes and highlighting the putamen/pallidum cluster selected for moderation analysis, these images are thresholded at $p < 0.001$ (uncorrected). Note that parts of both clusters also survive $p < 0.05$ FWE peak level-correction (illustration prepared with MRIcroGL; www.nitrc.org/projects/mricrogl and depicted in radiological orientation).

Cognitive-Perceptual was positively correlated with GMV in a cluster containing the right pallidum and putamen ($k = 6$ voxels, $x/y/z = 22/-12/-2$, $T = 4.75$, $p = 0.040$ FWE peak level-corrected). *Disorganised* was positively correlated with GMV in a cluster including the left precentral gyrus ($k = 67$ voxels, $x/y/z = -40/-12/42$, $T = 4.90$, $p = 0.013$ FWE peak level-corrected). There were no significant negative correlations of the two subscales with GMV and not any significant associations of GMV and the SPQ total score, the *Interpersonal* SPQ dimension, or the GLM including all three subscores after FWE-peak-level-correction (see online Supplementary Fig. SF1).

Surface-based analysis of gyrification

We did not find any significant associations at $p < 0.05$ FWE peak level-correction for gyrification with either total SPQ score or subscores. In a subsequent, exploratory analysis ($p < 0.001$, uncorrected, see online Supplementary Fig. SF2), however, we found a positive correlation of the SPQ total score with gyrification in the left precuneus ($k = 10$ voxels, $x/y/z = -19/-65/25$, $T = 3.31$, $p < 0.001$ uncorrected), as well as a negative correlation with the gyrification in the right postcentral gyrus ($k = 57$ voxels, $x/y/z = 28/-34/69$, $T = 3.70$, $p < 0.001$ uncorrected). Additionally, we found a negative association of the *Disorganised* score with gyrification in the right inferior frontal gyrus ($k = 22$ voxels, $x/y/z = -43/29/-1$, $T = 3.47$, $p < 0.001$ uncorrected).

Moderation analysis

We tested whether intelligence, as a measure for general cognitive capacity, has a moderating effect on the association of striatal structure and schizotypy. Based on the results of the voxel-based-morphometry analyses, we tested this assumption for the association of the cluster around the detected peak voxel in a cluster containing the putamen and pallidum and *Cognitive-Perceptual*, with age, sex and TIV as covariates (model 1). This

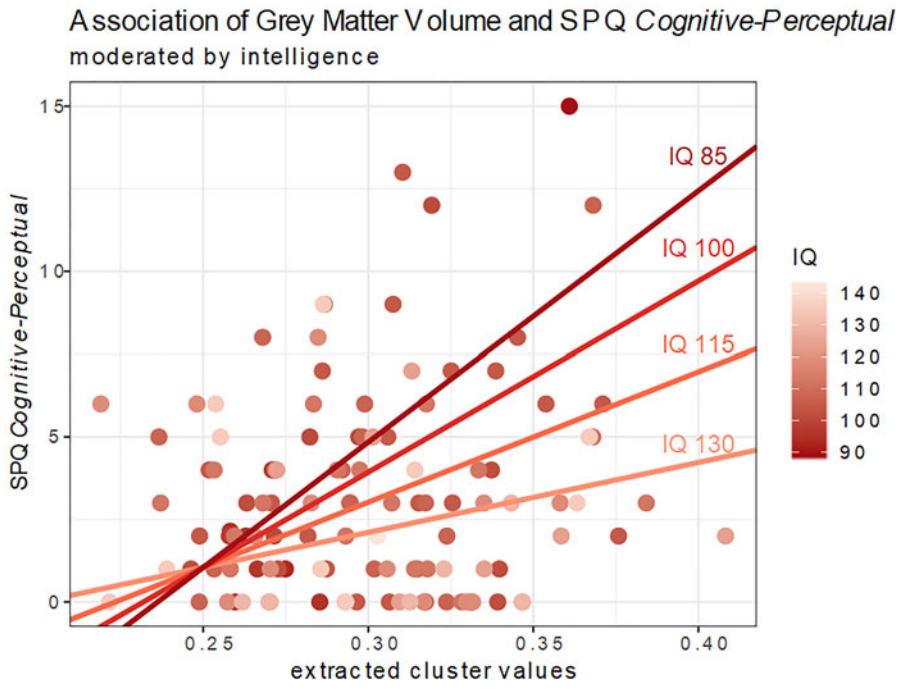

Fig. 2. Scatterplot, depicting the association of extracted grey matter values within the significant striatal cluster and the level on the SPQ Cognitive-Perceptual dimension, dependent on IQ. The colour of the dots represents IQ value. To illustrate the moderating effect of IQ, regression lines have been fitted for IQ values of 85, 100, 115 and 130, represented by the colour of the lines in accordance with the figure legend. Illustration prepared with the ggplot2 package (Wickham, 2016) in RStudio v1.1.456 (RStudio Team, 2016).

model was significant overall [$F_{(6,108)} = 6.93$, $p < 0.001$, $R^2 = 0.28$] and furthermore revealed a significant moderation effect of MWT-B IQ estimation on the association of striatal volume and *Cognitive-Perceptual* [regression coefficient $b = -5.41$, $F_{(1,108)} = 5.38$, $p = 0.022$]: With increasing MWT-B values, the association between striatal structure and schizotypy decreased (Fig. 2). In a separate model, we tested the equivalent assumption of the association of the *Disorganised* dimension and the significant paracentral cluster being moderated by IQ. This model, however, was not significant [$F_{(6,108)} = 1.13$, $p = 0.350$, $R^2 = 0.06$].

Discussion

We found an association of the positive dimension of the SPQ with greater right striatal volume in healthy controls, which was moderated by IQ as a measure of general cognitive capacity. Additionally, we found an association of the *Disorganised* factor with increased volume of the left precentral gyrus.

In several previous studies, primarily variations in precuneus structure and function have, repeatedly, been associated with schizotypal traits and subclinical PLEs (Modinos *et al.*, 2010, 2018; van Lutterveld *et al.*, 2014; Falkenberg *et al.*, 2015; Nenadic *et al.*, 2015b). It is, therefore, unexpected that we did not find any association with any of the SPQ dimensions in this region in our data.

We did, however, find further evidence of fronto-striatal circuits to be involved in the aetiology of PLEs in healthy individuals. Our finding echoes previous studies suggesting that variations in striatal structure and function are associated with psychotic experiences in healthy subjects (Chen *et al.*, 2012; Ettinger *et al.*, 2013; Mittal *et al.*, 2013), partially paralleling findings in frank psychosis: In a mega-analysis by the ENIGMA schizophrenia consortium, patients with schizophrenia showed greater pallidum volumes than healthy controls, and putamen and pallidum volumes were correlated with illness duration (van Erp *et al.*, 2016). Further support comes from several studies showing that similar to schizophrenia patients, their healthy relatives also show increased GMV within the putamen (Knöchel *et al.*, 2016). In healthy controls, the genetic risk for schizophrenia and bipolar disorder has been associated with volumetric abnormalities within those regions (Caseras *et al.*, 2015). It has, thus, been suggested that striatal size might be an important endophenotype for psychosis (Chemerinski *et al.*, 2013). Putamen size and function might even play a role in risk stratification, predicting clinical course: Subjects at CHR for psychosis showed increased striatal cerebral blood flow (Hubl *et al.*, 2018) and in CHR subjects, smaller putamen volume was associated with the reduction of positive symptoms over a course of six months (Hong *et al.*, 2015).

Dopaminergic neurotransmission is central to striatal functioning, and findings from several (although not all; Ettinger *et al.*, 2012) experimental and pharmacological studies implicate an association of altered dopamine neurotransmission with schizotypy and psychosis-proneness (Ettinger *et al.*, 2013, 2014; Mohr and Ettinger, 2014). Schizotypy has, additionally, been associated with expression levels of dopaminergic genes (Grant *et al.*, 2014b) and dopamine receptor gene polymorphisms (Ettinger *et al.*, 2006; Grant *et al.*, 2013; Gurvich *et al.*, 2016), including additive effects thereof (Grant *et al.*, 2015). Taken together, those findings suggest that the dopamine hypothesis of schizophrenia (Howes *et al.*, 2017) also extends into the healthy domain (Grant *et al.*, 2015).

Additionally, we detected an association of greater GMV with higher levels of disorganised schizotypy in the left precentral gyrus. Previous findings linking this region to schizotypy are limited. There is some evidence for reduced paracentral volume in individuals with schizotypal personality disorder (Koo *et al.*, 2006). Another study in subjects with high risk for psychosis and first episode patients also found reduced precentral volume compared to healthy controls (Chang *et al.*, 2016).

Those regions have primarily been associated with motor functions, and while there is clear evidence for motor

dysfunctions in schizophrenia and other psychotic disorders (Peralta and Cuesta, 2001; Cuesta *et al.*, 2018; Hirjak *et al.*, 2018), there is limited evidence in schizotypy (Roché *et al.*, 2015). As motor functions were not assessed in this study, we can neither assume nor exclude such an association in our data. It should be noted, however, that the reported cluster lies within the lateral frontal eye field and that schizotypy has repeatedly been associated with impairments in oculomotor function (Aichert *et al.*, 2012; Meyhöfer *et al.*, 2015).

An additional perspective comes from functional imaging studies, suggesting connections of striatal regions with areas in the pre- and postcentral gyri. Several functional connectivity studies – in healthy subjects as well as schizophrenia patients – have indeed shown important projections from striatal regions to motor areas in the pre- and postcentral cortex, and caudate and putamen seeds were reported to predict resting state activity in pre- and postcentral regions (Postuma and Dagher, 2006; Di Martino *et al.*, 2008; White *et al.*, 2016). Given the focus of grey matter structure in our study, however, we can only speculate on similar associations in our sample.

Further evidence for the notion that brain networks, rather than single structures are involved in the generation of psychotic experiences comes from recent studies analysing resting state connectivity in schizotypy. Several studies report reduced functional connectivity of striatal and cortical regions in association with (primarily positive) schizotypy, indicating an association of this dimension with striatal hypoconnectivity or cortico-striatal decoupling (Wang *et al.*, 2018; Waltmann *et al.*, 2019). Such dysconnectivity might be facilitated by altered striatal dopamine levels, as has been suggested based on results in animal studies (Grace *et al.*, 2007; Waltmann *et al.*, 2019). There is, in fact, evidence for striato-cortical decoupling associated with positive schizotypy being induced by altered dopaminergic neurotransmission (Rössler *et al.*, 2018).

Our results also indicate, however, that protective factors may act as a buffer to decrease the risk for psychotic experiences induced by striatal alterations, in line with arguments by Brod (1997) or Siever and Davis (2004). The model assumes that genetic risk variants render the vulnerability for the impact of environmental factors, but can be attenuated by other genetic variants leading to preserved frontal volume or capacity, possibly expressed in an elevated cognitive capacity like general intelligence (Siever and Davis, 2004). Indeed, even though we did not find any association of schizotypy dimensions with GMV in frontal regions, our moderation model showed that IQ (as a measure for cognitive capacity known to be associated with frontal lobe structure, Colom *et al.*, 2013) influences the association of pallidal volume and positive schizotypy: With higher IQ, that association decreased to the point of non-significance. This fits well in line with evidence of cognitive performance or IQ having substantial predictive value for the outcome of individuals at risk for psychosis and with schizophrenia (Leeson *et al.*, 2009; Woodberry *et al.*, 2010; Ziermans *et al.*, 2014; Metzler *et al.*, 2016). However, we would like to stress that, both in our results and in previous work; it might be that general intelligence rather acts as a proxy for other, possibly psycho-social, resilience factors.

We did not find an association of SPQ scores with gyrification patterns at corrected threshold levels, but the exploratory, uncorrected analysis revealed associations in regions thought to be relevant for psychosis as well as schizotypy (Honea *et al.*, 2005; Ettinger *et al.*, 2015; Nenadic *et al.*, 2015a). It might be speculated that while those effects indeed are of interest, our analysis did not provide the necessary power for them to reach statistical significance. This should spark further studies in larger samples. So far, our findings do not provide robust evidence for gyrification to show a dimensional relationship with schizotypy.

Limitations to the generalisation of our findings arise from the relatively restricted sample size and the fact that our participants showed rather low to moderate SPQ levels, compared to a recent validation sample (Barron *et al.*, 2018). This, however, only leads to a reduction in statistical power, but does not invalidate our findings (Eysenck, 1952).

Additionally, since the SPQ is derived from clinical criteria of schizotypal personality disorder (Raine, 1991), it differs in both conceptualisation and phenotypal characterisation from other self-rating measures, which needs to be taken into account (for further details, see Gross *et al.*, 2014; Grant *et al.*, 2018). While the *Cognitive-Perceptual* dimension of the SPQ seems to map well on positive schizotypy, the *Interpersonal* factor taps into negative schizotypy less specifically and includes aspects of Neuroticism, which could account for the lack of associations with this dimension in our analysis in contrast to previous work.

Furthermore, we have to consider that the MWT-B is only an approximating measure of particularly crystallised intelligence, necessitating further studies to replicate the moderation model with the use of an extensive intelligence battery. As due to the study design, several risk factors for psychotic diseases, but also for schizotypy were excluded to rule out confounding influences, our results might only represent part of the subclinical spectrum.

Taken together, our findings suggest that the involvement of fronto-striatal circuits in psychosis aetiology extends into the healthy domain of schizotypy and PLEs, thus, supporting a continuous model of the psychosis spectrum.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719002459

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Conflict of interest. None.

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.

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iii. STUDY III: Manuscript

Brain structural correlates of schizotypal signs and subclinical schizophrenia nuclear symptoms in healthy individuals

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Key words: SCL-90R; psychotic-like experiences; schizotypy; brain structure; morphometry; VBM; SBM

Abstract

Subclinical psychotic-like experiences, resembling key symptoms of psychotic disorders, are common throughout the general population and possibly associated with psychosis risk. There is evidence that such symptoms are also associated with structural brain changes.

In 672 healthy individuals, we assessed psychotic-like experiences and associated distress with the symptom-checklist-90R (SCL-90R) scales “schizotypal signs” (STS) and “schizophrenia nuclear symptoms” (SNS) and analysed associations with voxel- and surfaced-based brain structural parameters derived from structural MRI at 3T with CAT12.

For SNS, we found a positive correlation with the volume in the left superior parietal lobule and the precuneus, and a negative correlation with the volume in the right inferior temporal gyrus (p<0.05, FWE cluster level-corr.). For STS, we found a negative correlation with the volume of the left and right precentral gyrus (p<0.05, FWE cluster level-corr.). Surface-based analyses did not detect any significant clusters with the chosen statistical threshold of p<0.05. However, in explorative analyses (p<0.001, uncorrected) we found a positive correlation of SNS with gyrification in the left insula and rostral middle frontral gyrus and of STS with the left precuneus and insula, as well as a negative correlation of STS with gyrification in the left temporal pole. Our results show that brain structures in areas implicated in schizophrenia are also related to psychotic-like experiences and its associated distress in healthy individuals. This pattern supports a dimensional model of the neural correlates of symptoms of the psychotic spectrum.

1. Introduction

Suspiciousness, paranoid thinking, as well as feelings of alienation and isolation are key symptoms of psychotic disorders like schizophrenia. However, it is well-established that reports of psychotic-like experiences are also frequently found in the general population, sparking a continuum model of psychosis-proneness (Claridge, 1997; van Os, Hanssen, Bijl, & Ravelli, 2000). In contrast to the schizophrenia prevalence of ~1% (Simeone, Ward, Rotella, Collins, & Windisch, 2015), psychotic symptoms (e.g. hallucinations) in the absence of the disorder have a lifetime prevalence of ~6-7% in the general population (Linscott & van Os, 2013; McGrath et al., 2015), and are considered a risk phenotype for psychosis (Kelleher & Cannon, 2011). A considerable ~34% of healthy individuals between the age of 20 and 41 report at least mild psychotic signs (Rössler et al., 2015), in child cohorts even up to >60% (Downs, Cullen, Barragan, & Laurens, 2013).

The subclinical psychosis spectrum comprises different domains: The construct of a stable, multidimensional set of schizophrenia-like personality traits is often conceptualised as “schizotypy” and seen as continuous phenotypic marker of psychosis proneness (Barrantes-Vidal, Grant, & Kwapil, 2015; Martin Debbané & Barrantes-Vidal, 2015; Grant, 2015). The expression of psychotic experiences in non-clinical populations is conceptually closer to (but not necessarily associated with) the clinical disorder and is often referred to as “psychotic-like experiences” (PLEs) (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). In contrast to the rather stable nature of schizotypy, in the majority of individuals, PLEs remit over time and only persist in about 20%, while ~7% of affected individuals convert into a psychotic disorder (Linscott & van Os, 2013). Lastly, the concept of “clinical” or “ultra-high risk” captures risk factors and clinical features relevant for early detection and prevention of transition into psychosis (Schultze-Lutter et al., 2015). These concepts have also been linked with variations in cognitive functions (Fusar-Poli et al., 2012; Siddi, Petretto, & Preti, 2017; Simons, Jacobs, Jolles, van Os, & Krabbendam, 2007) that are impaired in

schizophrenia (Nuechterlein et al., 2004). These concepts overlap substantially and may coincide, such as in clinical high risk and high schizotypy (Debbané et al., 2015; Michel et al., 2019), where combined assessment improves psychosis prediction (Flückiger et al., 2016).

A recent line of research (Rössler et al., 2007) delineates two dimensions of state-like, subclinical psychotic experiences: *schizotypal signs* versus *schizophrenia nuclear symptoms* (Bakhshaie, Sharifi, & Amini, 2011; Breetvelt et al., 2010; Rössler et al., 2015; Rössler, Hengartner, Ajdacic-Gross, Haker, & Angst, 2013, 2014; Rössler, Hengartner, et al., 2011; Rössler, Vetter, et al., 2011; Zhornitsky, Tikàsz, Rizkallah, Chiasson, & Potvin, 2015). Assessed with the widely used SCL-90R symptom checklist (Derogatis, 1977), a questionnaire capturing subjective distress symptoms across several psychological and physical dimensions, they show good internal consistency and validity (Rössler et al., 2015; Rössler et al., 2007).

The s*chizotypal signs* (STS) scale addresses distress evoked by interpersonal deficiencies, reduced capacity for close relationships, suspiciousness and paranoid ideation, resembling the criteria for schizotypal personality disorder and positive and negative dimensions of schizotypy. *Schizophrenia nuclear symptoms* (SNS) assess distress caused by delusions of control, auditory hallucinations, thought-broadcasting and thought-intrusion, representing nuclear symptoms of schizophrenia (see Figure 1).

Although the two scales partially overlap with measures of schizotypy, rather than assessing a general personality disposition, they measure the level of *distress* caused by such experiences in a recent temporal interval. This level may vary across time, as suggested by studies investigating courses of PLE, STS and SNS (Linscott & van Os, 2013; Rössler et al., 2007). By focussing on symptom distress during the last four weeks, STS and SNS close a gap between extremely variable mood and stable personality structure (Franke, 1995).

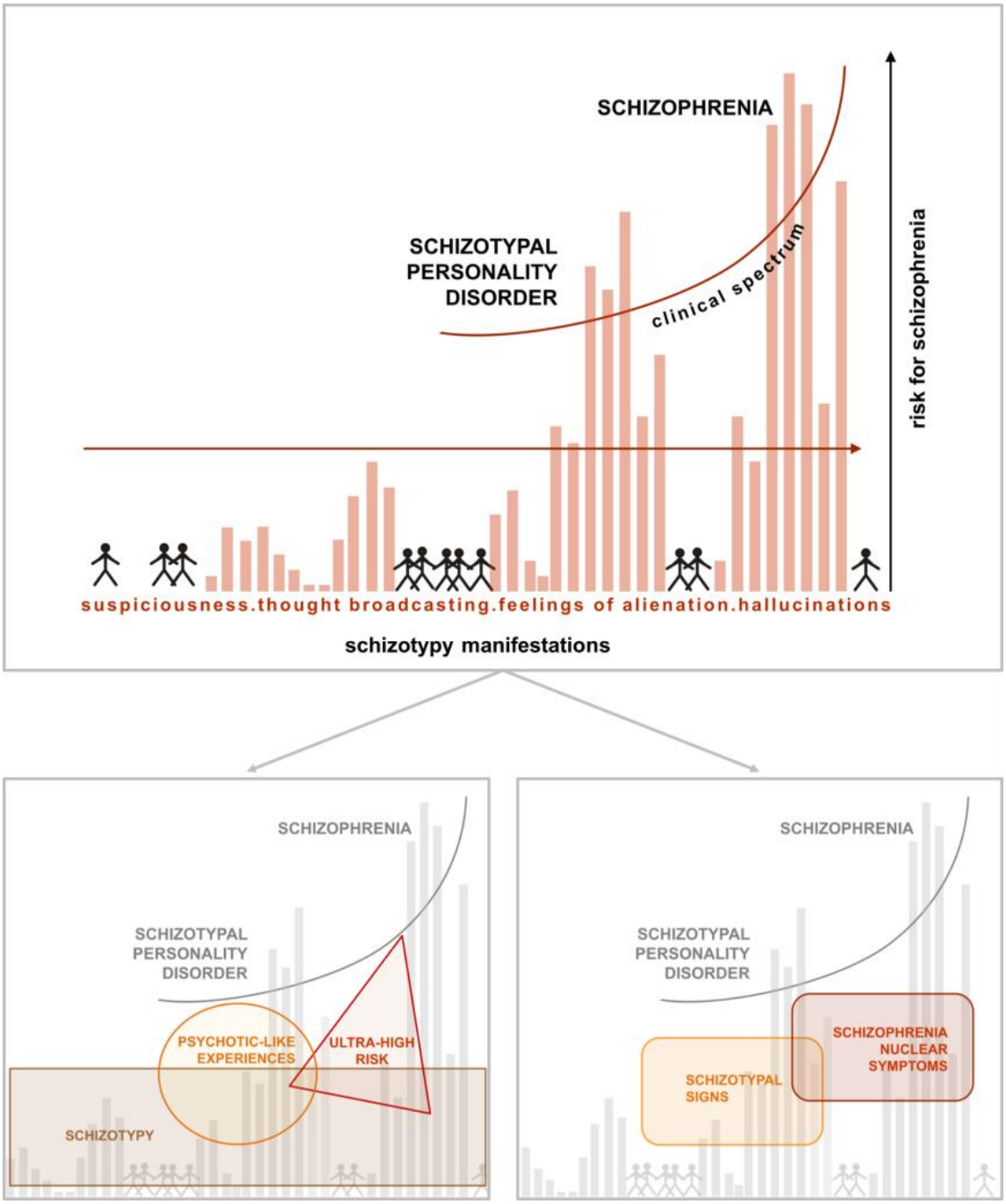

Figure 1. Psychosis continuum model incorporating the STS vs SNS dimensions.

Upper half (modified from Claridge & Beech (Claridge & Beech, 1995) shows a model of the psychosis continuum where, from the non-clinical towards the clinical parts of the spectrum symptoms like suspiciousness, thought broadcasting, alienations and hallucinations increase in intensity in the general population. The model emphasises a dimensional transition across this spectrum, where distress may play an important role in conversion probability.

Lower half: Within the non-clinical part of the spectrum, different concepts like schizotypy, PLEs and ultra-high risk have been used to capture either trait-like person features or state-related clinical aspects (left). The model on the right, depicting STS and SNS, specifically focuses on the distress caused by more trait-related, distress-associated schizotypal personality features (STS) vs. schizophrenia nuclear symptoms

(SNS) closer to the clinical part of the spectrum (right). The overlap of STS and SNS acknowledges the dimensional nature of this alternative approach.

While the temporally restricted assessment implies state-like rather than trait-like character of the scales, longitudinal studies show high expression of STS or SNS in adolescence is associated with a higher risk for common mental disorders in later life (Rössler, Hengartner, et al., 2011).

This suggests that the variability of state expression can be (partially) attributed to latent, stable traits and shows “the trait in action”, possibly representing responses to environmental challenges (Barrantes-Vidal et al., 2015; Rössler et al., 2013).

Growing evidence suggests that both state- (PLEs) and trait-like (schizotypy) expression of such attributes is associated with morphometric variation in certain brain regions, particularly in inferior and superior frontal and superior and medial temporal cortical areas and the precuneus. Variations in these regions have been consistently shown to be associated with schizotypy (Ettinger et al., 2012; Modinos et al., 2010; Nenadic, Lorenz, et al., 2015; Wang et al., 2015; Wiebels, Waldie, Roberts, & Park, 2016), and PLE in healthy individuals (Schmidt et al., 2015; van Lutterveld, Diederen, Otte, & Sommer, 2014; van Lutterveld, van den Heuvel, et al., 2014), as well as individuals at ultra-high risk for psychosis (Dietsche, Kircher, & Falkenberg, 2017; Fusar-Poli et al., 2011; Nenadic, Dietzek, et al., 2015). This suggests that PLEs might have common neuroanatomical correlates along the psychosis spectrum (Modinos et al., 2010), as those regions also overlap with alterations in schizophrenia (Siever & Davis, 2004). While previous literature strongly supports volumetric correlates of PLEs, the association with brain surface morphometry, such as cortical folding or gyrification, still remains largely unknown. Opposed to the high plasticity of volumetric structure, cortical folding, determined during early brain development (Chi, Dooling, & Gilles, 1977), is thought to be a sensitive and stable marker of neurodevelopmental variation (Nenadic, Yotter, Sauer, & Gaser, 2014; Yotter, Nenadic, Ziegler, Thompson, & Gaser, 2011). It might thus indicate neuronal processes long before symptom onset and serve as a surrogate of early neurodevelopmental insult. As altered gyrification patterns

within superior temporal, prefrontal, and cingulate cortex have been identified both in psychosis and high risk, the parameter has been suggested as a neurodevelopmental marker for psychosis (Damme et al., 2019; Zuliani et al., 2018).

STS and SNS are psychometrically well-validated, whereas their neuroanatomical correlates still remain unclear. Therefore, the aim of the present study was to test in a large, healthy cohort drawn from the general population the hypothesis that the phenomenologically delineated dimensions *schizotypal signs* and *schizophrenia nuclear symptoms* are associated with volume- and surface-based brain structural correlates similar to those found for schizophrenia and PLEs. Based on current evidence from brain imaging studies, we hypothesised reduced volume in frontal and medial temporal cortical areas and increased volume in the precuneus with increasing symptom load. In addition, we tested the hypothesis that altered gyrification in part of these regions, as seen in schizophrenia (Spalthoff, Gaser, & Nenadić, 2018), would be related to schizophrenia nuclear symptoms.

2. Methods

2.1 Sample

We analysed data from 672 healthy participants (424 female (63.1%), 248 male (36.9%); mean age=32.51 years, SD=12.23), a subset of the FOR2107 cohort (Kircher et al., 2018), a multi-centre study recruiting from the areas of Marburg and Münster in Germany. All experimental procedures were approved by the local ethics committees of the Medical Schools of the Universities of Marburg and Münster, respectively, in accordance with the current version of the Declaration of Helsinki. We included healthy adults between the age of 18 and 65 years. Exclusion criteria were current or former psychiatric disorders (assessed with SCID-I interviews (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) by trained raters), neurological, or other severe medical disorders, current drug use, verbal IQ<80 (estimated with Multiple Choice Word Test-B (Lehrl, 1995)) as well as common MRI contraindications. All participants volunteered to

take part in the study, gave written informed consent and received a financial compensation afterwards.

2.2 Assessment of schizotypal signs and schizophrenia nuclear symptoms

All participants completed the German version (Franke, 1995) of the SCL-90R-checklist (Derogatis, 1977) as part of a larger test battery (Kircher et al., 2018) within 14 days of MRI scanning. The SCL-90R is a well-established self-report questionnaire assessing the distress of 90 psychological symptoms across nine dimensions on a five-point Likert scale, including the dimensions psychoticism and paranoid thinking. Participants were asked to rate symptoms over the past four weeks. Based on previous studies (Rössler et al., 2015; Rössler et al., 2013, 2007), we computed the sum of the scales "schizotypal signs" (STS; 8 items) and "schizophrenia nuclear symptoms" (SNS; 4 items) that were derived from factor analysis in a large longitudinal cohort study, based on the items of the original SCL-90R scales "paranoid ideation" and "psychoticism" (Rössler et al., 2007). Table 1 shows a list of items for both scales and respective descriptive statistics. SCL-90R has been shown to possess good internal consistency and test-retest-reliability (Derogatis & Cleary, 1977; Schmitz, Hartkamp, & Franke, 2000). The STS and SNS subscales have been derived and validated in epidemiological studies (Rössler et al., 2015; Rössler et al., 2007).

2.3 MRI acquisition

High resolution, T1-weighted structural images were acquired on a 3T MRI system in Marburg (12-channel head matrix Rx-coil; Tim Trio, Siemens, Erlangen, Germany) or Münster (20-channel head matrix Rx-coil; Prisma, Siemens, Erlangen, Germany). At each site, a three-dimensional MPRAGE sequence with a repetition time of TR=1.9ms, echo time TE=2.26ms, inversion time TI=900ms, flip angle=9° with 176 slices, slice thickness=1.0mm, voxel size=1.0 x 1.0 x 1.0mm, field of view FOV=256mm was used. Imaging data from both centres were pooled based on extensive quality assurance protocols (Vogelbacher et al., 2018).

2.4 MRI data pre-processing

Pre-processing and voxel-based morphometry (VBM) analyses (Ashburner & Friston, 2000) were executed using the pipeline of the CAT12 toolbox (version 1184, Structural Brain Mapping group, Jena University Hospital, Jena, Germany) building on SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK), running under MatLab (v2017a, The MathWorks, USA) with default parameter settings.

For VBM analyses, images were segmented into grey matter, white matter and cerebrospinal fluid and spatially normalised with the DARTEL algorithm (Ashburner, 2007). All images passed visually quality control (inspection for artefacts and image quality) and the homogeneity control implemented in the CAT12 toolbox. Images were smoothed with a Gaussian kernel of 10mm (FWHM).

We extracted surfaced-based morphometry (SBM) parameters with the CAT12 toolbox, that uses a novel algorithm to extract the cortical surface (Dahnke, Yotter, & Gaser, 2013), allowing to calculate additional information on cortical parameters. We analysed cortical gyrification, based on absolute mean curvature (Luders et al., 2006). Gyrification images were smoothed with a Gaussian kernel of 20mm (FWHM).

2.5 Statistical analyses

Statistical analyses were conducted using general linear models (GLM) in CAT12 with a multiple regression design. For both SCL-90R subscales (STS, SNS), separate models were set up to test for associations with grey matter volume (GMV) and gyrification, respectively. To control for the influence of confounding variables, age, sex and site were included in the model as nuisance variables. We also accounted for an Rx coil change after 386 of 445 scans at the Marburg site by including head coil as an additional nuisance variable (Vogelbacher et al., 2018). In VBM analyses, total intracranial volume was included as an additional covariate. We analysed positive and negative correlations of SCL-90R subscale sum values (STS, SNS) with morphometric parameters in whole-brain analyses. Results were considered significant at $p<0.05$,

FWE cluster level-corrected for multiple comparisons after an initial cluster-forming threshold of $p<0.001$.

3. Results

3.1 Demographic characteristics

Neither SNS nor STS were correlated with sex ($r=0.041$, $p=0.289$; $r=-0.030$, $p=0.433$, respectively). STS was correlated with age ($r=0.077$, $p=0.046$), but SNS was not ($r=0.001$, $p=0.971$). SNS and STS showed a significant intercorrelation ($r=0.355$, $p=1.9\times10^{-21}$). There were significant differences in age ($p=7.3\times10^{-11}$) and SNS ($p=0.023$) between the Marburg and Münster sub-cohorts.

Table 1. *Items of the SCL-90R scales* schizotypal signs *and* schizophrenia nuclear symptoms *with group means and standard deviations (SD).*

	SCL-90R item no.	**schizophrenia nuclear symptoms scale**	mean (SD)	
How much were you distressed by…	7	Someone else can control your thoughts.	0.03 (0.21)	0.11 (0.47)
	16	Hearing voices other people do not hear	0.00 (0.06)	
	35	Other people being aware of your private thoughts	0.05 (0.25)	
	62	Having thoughts that are not your own	0.03 (0.22)	
	SCL-90R item no.	**schizotypal signs scale**	mean (SD)	
	8	Others are to blame for your troubles	0.15 (0.44)	1.68 (2.48)
	18	Feeling most people cannot be trusted	0.16 (0.51)	
	43	Feeling you are watched by others	0.16 (0.45)	
	68	Having ideas others do not share	0.18 (0.45)	
	76	Others not giving you proper credit	0.32 (0.62)	
	77	Feeling lonely even when with people	0.24 (0.58)	
	83	Feeling people take advantage of you	0.22 (0.52)	
	88	Never feeling close to another person	0.25 (0.62)	

Items are rated („How much were you distressed by…“) over the last 4 weeks on a 5 point Likert scale between 0 (“not at all”), 1 (“a little bit”), 2 (“moderately”), 3 (“quite a bit”), and 4 (“extremely”) for each item, resulting in scale ranges of 0-16 (*SNS*) and 0-32 (*STS*).

3.2 VBM results

Regression analyses revealed significant correlations between the two scales and clusters in the following brain regions (see Figure 2):

Schizophrenia Nuclear Symptoms (SNS)

SNS were positively correlated with GMV in the left superior parietal lobe, including parts of the precuneus (k=406 voxels, x/y/z=-18/-62/45, T=4.56, p<0.05 FWE cluster level-corrected); and negatively correlated with the GMV within the right inferior temporal gyrus, extending into fusiform gyrus (k=915 voxels, x/y/z=36/-8/-50, T=3.92, p<0.05 FWE cluster level-corrected).

Schizotypal Signs (STS)

STS were negatively correlated with the GMV in the right (k=1035, voxels, x/y/z=38/-10/70, T=4.16) and left (k=298 voxels, x/y/z=-34/-10/75, T=3.86) precentral gyrus (all p<0.05 FWE cluster level-corrected).

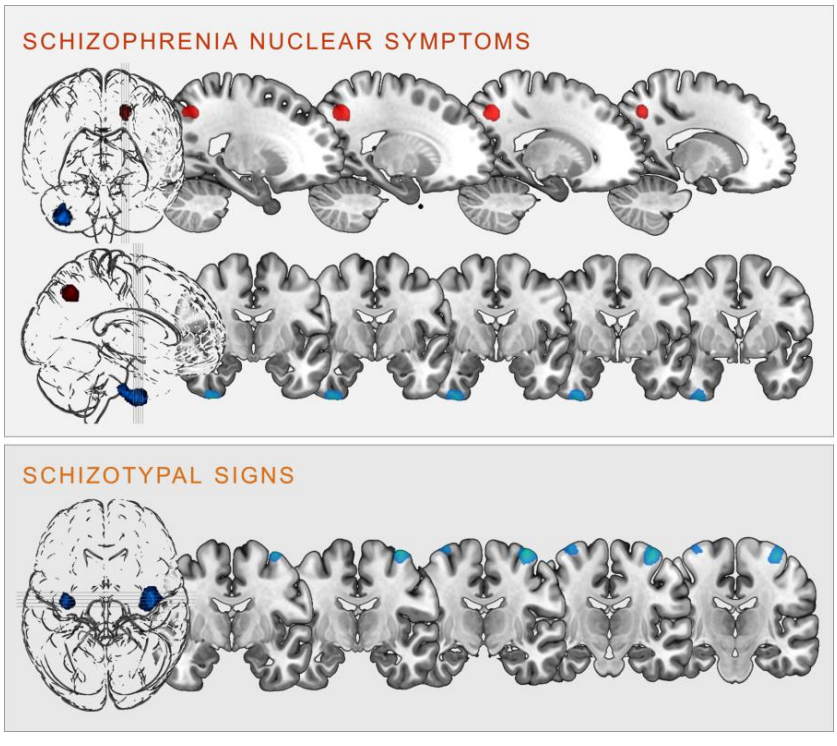

Figure 2. Clusters of significant positive (red) and negative (blue) correlation between grey matter volume and SCL-90R-scales schizophrenia nuclear symptoms (upper panel) and schizotypal signs (lower panel) at p<0.05, FWE cluster level-corrected (illustration prepared with MRIcroGL www.nitrc.org/projects /mricrogl).

3.3 SBM results

Schizophrenia Nuclear Symptoms (SNS)

There were no significant FWE cluster level-corrected associations of the SNS score with gyrification. However, performing an exploratory analysis (p<0.001 uncorrected), we identified a positive correlation of SNS with gyrification in the left insula (k=27 voxels, x/y/z=-34/-24/5, T=3.32) and the left rostral middle frontal gyrus (k=13 voxels, x/y/z=-23/38/34, T=3.30, see Figure 3).

Schizotypal Signs (STS)

There were no significant FWE cluster level-corrected associations of STS with gyrification. An exploratory analysis (p<0.001 uncorrected), however, revealed that STS was positively correlated with gyrification in the insula (k=29 voxels, x/y/z=40/-2/0, T=3.31) and the precuneus (k=13 voxels, x/y/z=23/-62/21, T=3.27), as well as negatively correlated with gyrification in the inferior/middle temporal gyrus (k=42 voxels, x/y/z=-41/3/-37, T=3.78 see Figure 3).

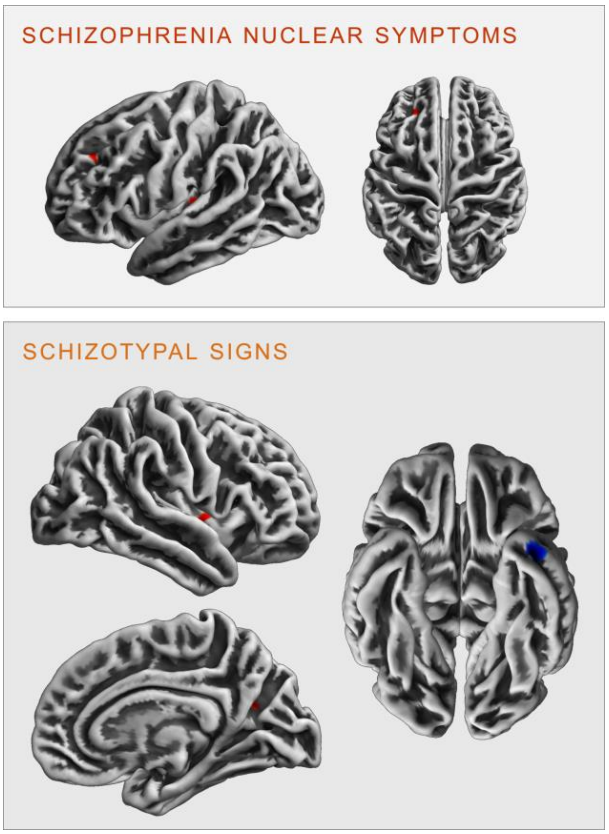

Figure 3. Clusters of significant positive (red) and negative (blue) correlation between gyrification and SCL-90R-scales schizophrenia nuclear symptoms (upper panel) and schizotypal signs (lower panel) revealed in the exploratory analysis at p<0.001 (uncorrected).

4. Discussion

In the present study, we demonstrated that the level of distress related to psychotic-like experiences in healthy adults is correlated with brain structural variation, similar to previously reported findings for measures of schizotypy and PLEs. *Schizophrenia nuclear symptoms* (SNS), capturing primarily positive, subpsychotic aspects closer to the clinical spectrum, were positively correlated with precuneus volume and negatively correlated with the volume in the inferior temporal gyrus. *Schizotypal signs* (STS), reflecting a milder, personality trait-associated dimension of negative and positive symptoms, were negatively correlated with precentral volume.

A main finding of our study is the disentangling of precuneus volume being linked to distress associated with positive, psychotic-like symptoms (SNS), but not to personality related STS. This reinforces a spectrum model (shown in Figure 1) in which sub-psychotic features closer to the clinical spectrum (as captured in SNS) are associated with precuneus variation. Therefore, our results provide strong evidence for differential brain structural associations of schizotypy and PLEs.

To date, this is the largest study analysing the association of brain structure and experiences from the schizotypal spectrum in a cohort of healthy individuals, including a broader demographic spectrum than most preceding studies. Our results further endorse a dimensional model of neural correlates of schizotypy and psychosis-proneness, and highlight the role of emotional appraisal of psychotic-like experiences in the healthy spectrum. This closes an existing gap between psychometrically-assessed schizotypy (Claridge, 1997; Grant, 2015) and clinically-derived concepts (PLEs, ultra high risk).

Importantly, the level of distress associated with psychotic experiences, rather than the symptom level, has a higher predictive value for conversion into clinical stages and psychotic disorders (Hanssen, Bak, Bijl, Vollebergh, & Van Os, 2005; Hanssen, Krabbendam, De Graaf, Vollebergh, & Van Os, 2005). Schizotypy appears to play a

crucial role in differentiating between those two subgroups, as it moderates the association between PLEs and distress: Individuals showing high levels of schizotypy reported more PLEs, but at the same time less distress associated with them, compared to individuals with low trait schizotypy (Kline et al., 2012).

Our finding of the association with precuneus structure thus suggests its crucial role in mediating a higher risk stage. Precuneus structure has previously been linked to psychometrically-assessed schizotypy, indeed this is one of the few findings that has been replicated across several studies (Modinos et al., 2010; Gemma Modinos et al., 2018; Nenadic, Lorenz, et al., 2015). There is also evidence of links to functional changes: Non-clinical individuals with verbal hallucinations show increased precuneus activation (van Lutterveld, van den Heuvel, et al., 2014), and individuals at clinical high risk for psychosis show a failure to deactivate the precuneus in a working memory task (Falkenberg et al., 2015). These structural and functional findings corroborate the role of the precuneus for symptoms within the psychosis spectrum.

The precuneus, part of the medial parietal cortex, has vast structural and functional connections with multiple brain regions and is thought to be involved in various higher-order cognitive processes (Cavanna & Trimble, 2006; Leech & Sharp, 2014; Zhang & Li, 2012). Its involvement in self-reflection, discrimination of self-versus-others, and cognitive biases like thought-action fusion, reality distortion and self-referential ideas has been shown in studies in obsessive-compulsive disorder and the psychosis spectrum (Cavanna & Trimble, 2006; Jones & Bhattacharya, 2014; Rikandi et al., 2017). Those findings are in line with our own results, linking precuneus volume to thought intrusion and broadcasting, verbal hallucinations and control delusions, as assessed by the SCL-90R *schizophrenia nuclear symptoms* scale.

In line with our finding of a negative correlation between SNS and inferior temporal grey matter volume, cortical thinning in the inferior temporal gyrus (ITG) has been linked to PLEs, i.e. verbal hallucinations in nonclinical individuals (van Lutterveld, van den Heuvel, et al., 2014). In one smaller study, volume reductions were also

associated with attenuated psychotic symptoms in UHR individuals (Nenadic, Dietzek, et al., 2015). ITG reductions were also part of a pattern distinguishing at-risk individuals with later conversion from non-converters (Koutsouleris et al., 2010), and have been shown as longitudinal changes following transition from risk status to psychosis onset (Borgwardt et al., 2008).

While these findings suggest PLEs and clinically-derived markers to be associated with ITG structural variations, there is no evidence for such an association with schizotypy. This is consistent with the notion that SNS and STS might tap different parts of the psychosis spectrum. Given the overall low SNS scores in our sample, these findings appear all the more impressive, suggesting similar neuroanatomical correlates of even subtle subclinical variations as shown across the psychosis spectrum.

In our data, associations with the *schizotypal signs* scale were less prominent and restricted to a negative correlation in a cluster within the right and left precentral gyrus. While precentral gyrus volume decreases are generally associated with motor dysfunctions in schizophrenia (Tanskanen et al., 2010), and one study found a similar pattern in high risk and first episode individuals compared to healthy controls (Chang et al., 2016), it does not generally feature in studies of PLEs in nonclinical individuals. There is, however, evidence for variations in adjacent regions, as reduced grey matter density in the dorsolateral prefrontal cortex has been reported in high vs. low schizotypy (Wang et al., 2015) and postcentral grey matter reduction was reported in women with vs. without schizotypal personality disorder (Koo et al., 2006).

We did not detect associations of the STS scale with areas recently linked to psychometrically-assessed schizotypy, such as the precuneus, prefrontal or temporal structures. STS in parts certainly overlaps with commonly used schizotypy measures, still there are distinct differences: While other measures also often imply distress-proneness, the STS primarily and directly rates the *distress* level rather than that of the symptoms causing it. Also, blending of positive (e.g. suspiciousness) and negative (e.g. social anhedonia) dimensions rather than distinguishing them may dilute effects. While

there is compelling evidence for the role of distress in conversion to clinical dimensions, as well as elevated distress and impaired quality of life in both long-term and first episode schizophrenia patients (Addington, Penn, Woods, Addington, & Perkins, 2008; Gaite et al., 2002) and clinical high risk states (Paolo Fusar-Poli et al., 2015; Hui et al., 2013), in schizotypy, the association to quality of life seems to be less distinct and more dimension-specific (Cohen, Auster, MacAulay, & McGovern, 2014; Fumero, Marrero, & Fonseca-Pedrero, 2018).

Taken together, we show distinct associations with neuroanatomical correlates between SNS and STS, and to recent findings in schizotypy. The spectrum of psychotic-like experiences towards psychotic symptoms is often seen as a continuum (Claridge, 1997). This phenomenological continuum, however, is likely not monotonic and unidimensional, but falls into several (potentially overlapping) dimensions or facets (Grant, Green, & Mason, 2018), represented by different brain structural (and functional) correlates and networks. It has been suggested that there are partially distinct susceptibilities to the schizophrenia spectrum (Barrantes-Vidal et al., 2015): While shared genetic variations render certain vulnerabilities to environmental events, other factors might buffer this influence and decrease the impact of schizophrenia risk factors by preserved or increased regional brain volume or stabilised neurotransmitter activity (Siever & Davis, 2004). These models have been mostly explored in schizophrenia versus schizotypal personality disorder patients, but should be extended to the full spectrum including schizotypy in healthy individuals. Our study further highlights the role of emotional appraisal that might modulate the impact of psychotic-like experiences on brain structure and subclinical vs. clinical course.

While we did not find an association of the SNS and STS scales with gyrification patterns at corrected threshold levels, the exploratory, uncorrected analysis is of interest due to the associations with the precuneus as well as frontal and temporal regions. So far, there are no cortical folding or gyrification studies analysing associations of those dimensions with developmentally early and rather stable brain

structural patterns, so additional studies are warranted. Although the SNS and STS are state-dependent, longitudinal analyses in a large, general population study showed that their variability is largely (75-89%) associated by stable traits (Rössler et al., 2013). This, in line with our results, hints to a possible association of the scales with early, developmental markers, possibly indicating a vulnerability to the psychosis spectrum. In a developmental approach, it has also been argued that an underlying high level of psychometrically-assessed schizotypy may constitute an increased liability to state-like subclinical PLE, suggesting an overlap of the partially distinct concepts (Debbané & Barrantes-Vidal, 2015).

Our study addresses the nonclinical spectrum of schizotypal and sub-psychotic symptoms; therefore, as expected, the population shows low symptom loadings and restricted variance. This, however, only reduces statistical power, but should not invalidate the findings (Eysenck, 1952) as it speaks to a robustness of the effects.

Taken together, our results support the notion that structural brain abnormalities in psychosis occur prior to or even independent of the development of full-blown symptoms, may progressively worsen over the course of the illness (Jung, Borgwardt, Fusar-Poli, & Kwon, 2012) and are modulated by emotional appraisal. As such, the phenomenological continuum seems to be reflected in a (at least partial) continuum of neurobiological correlates. It has to be pointed out, however, that the idea of a monotonic linear continuum appears to be overly simplified. Further, the existence of different concepts and phenomenological definitions as well as the use of instruments based thereon might contribute to mixed findings in current research, highlighting the importance of concise conceptualisation (Grant et al., 2018; Lee et al., 2016; Oezgen & Grant, 2018).

Conflicts of interest

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.

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All PIs take responsibility for the integrity of the respective study data and their components. All authors and co-authors had full access to all study data.
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iv. STUDY IV: Manuscript

Polygenic risk for schizophrenia and schizotypal traits in non-clinical subjects

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Abstract

Schizotypy is a putative risk phenotype for psychosis liability. While sharing some risk genes with schizophrenia, the overlap of genetic architectures is poorly understood. We tested the hypothesis that dimensions of schizotypy (assessed with the SPQ-B) are associated with a polygenic risk score (PRS) for schizophrenia in a sample of 623 psychiatrically healthy, non-clinical subjects from the FOR2107 multi-centre study and a second sample of 1133 blood donors. We did not find a correlation of schizophrenia PRS with either overall SPQ or specific dimension scores, nor with adjusted schizotypy scores derived from the SPQ (addressing inter-scale variance). Also, PRS for affective disorders (bipolar disorder and major depression) were not significantly associated with schizotypy. This important negative finding demonstrates that despite some overlap in single risk alleles, schizotypy might share less mutual genetic risk factors with schizophrenia than previously assumed (and possibly less compared to psychotic-like experiences), but might rather reflect a risk phenotype with some overlap in particular genetic variants across the psychosis spectrum.

Key words: bipolar disorder; depression; major depressive disorder; schizophrenia; schizotypy; psychosis; psychosis proneness

Introduction

Genetic studies of schizophrenia (SZ) have typically focused on case-control study designs, comparing samples with a diagnosis of schizophrenia to those without. The recent surge of large genome-wide association studies (GWAS) using this case-control design has led to a dramatic improvement of our understanding of the genetic architecture of common versus rare genetic variants (Henriksen *et al.*, 2017, Hyman, 2018, Sullivan and Geschwind, 2019). The identification of schizophrenia-associated single nucleotide polymorphisms (SNP) has also allowed the construction of polygenic risk scores (PRS) allowing the quantification of SNP-based genetic risk for schizophrenia. So far, however, linking these PRS to putative biomarkers of SZ has proven difficult (Mistry *et al.*, 2017). In contrast to case-control designs, dimensional models of psychopathology are based state or trait markers present not only in patients but across the general population. Hence, they can serve as risk phenotypes to study neurobiological continuum models across both non-clinical and clinical populations.

Schizotypy is a trait that can be assessed psychometrically (through self-report) and is considered to reflect psychosis proneness and schizophrenia liability (Grant *et al.*, 2018). Given the ease of applying reliable and valid schizotypy questionnaires in large population studies, schizotypy lends itself as a candidate risk phenotype for the psychosis/schizophrenia spectrum (Barrantes-Vidal *et al.*, 2015). Schizotypy does not imply a psychiatric diagnosis; in fact, schizotypy is neither identical nor conceptually congruent with schizotypal personality disorder, which is a clinical condition that has often been used to study the schizophrenia spectrum (Siever and Davis, 2004). Rather, schizotypy is conceptualized as a trait distributed throughout the general population and associated with proneness for psychosis (Flückiger *et al.*, 2019, Nelson *et al.*, 2013). As such, schizotypy is a complex phenotype that encompasses multiple domains relevant to the schizophrenia spectrum, including positive, negative, and disorganized domains of variation in cognition, emotion, and behavior (Ettinger *et al.*, 2015, Fonseca-Pedrero *et al.*, 2018, Oezgen and Grant, 2018) as well as subclinical

features such as delayed motor development (Filatova *et al.*, 2018). It is more frequent in first-degree relatives of schizophrenia patients (Soler *et al.*, 2019) and prodromal states (Racioppi *et al.*, 2018).

Importantly, there are are several lines of evidence that schizotypy is associated with variation in biological markers of the schizophrenia spectrum, including cognitive, brain imaging, and genetic parameters (Ettinger *et al.*, 2015, Walter *et al.*, 2016). Non-clinical subjects who are high in schizotypy (*i.e.*, without a psychiatric diagnosis) show lower performance in attention, working memory, and executive functions in general (Lui *et al.*, 2018, Matheson and Langdon, 2008, Siddi *et al.*, 2017, Steffens *et al.*, 2018). Also, higher schizotypy in psychiatrically healthy cohorts has been associated with brain structural variation in brain areas identified to show grey matter loss prefrontal cortices (similar to schizophrenia, Ettinger *et al.*, 2012), as well as precuneus and other areas (Modinos *et al.*, 2010, Nenadic *et al.*, 2015). Functional imaging has demonstrated similar effects with high-schizotypy subjects showing changes in fronto-striatal systems intermediate between low-schizotypy and clinical schizophrenia subjects (Taurisano *et al.*, 2014), paralleled by recent resting state fMRI studies(Waltmann *et al.*, 2019, Wang *et al.*, 2018), anti-saccade fMRI (Aichert *et al.*, 2012), as well as studies on the dopamine system (Rössler *et al.*, 2018, Woodward *et al.*, 2011).

The molecular genetics of schizotypy are, however, poorly understood (Grant, 2015, Walter *et al.*, 2016). There are several studies linking single schizophrenia risk genes to psychometric schizotypy. Such effects have been shown for risk markers like *ZNF804A* (Meller *et al.*, 2019, Soler *et al.*, 2019, Stefanis *et al.*, 2013a, Yasuda *et al.*, 2011), *DTNBP1 (Kircher et al., 2009, Stefanis et al., 2007)*, *ERBb4* (Stefanis *et al.*, 2013b), *GLRA1* (Vora *et al.*, 2018), *MMP16* (Morton *et al.*, 2017), and other schizophrenia-linked risk loci like *CACNA1C* (Roussos *et al.*, 2013). Altogether, however, these studies provide some evidence that schizotypy shares part of its genetic architecture with schizophrenia. At the same time, several of these risk markers have also been linked to other psychiatric disorders, which parallels the overlap of

genetic risk for schizophrenia with risk for other psychiatric conditions, especially bipolar disorder (Smeland *et al.*, 2019). Only few studies have used genome-wide approaches to study the genetic overlap of schizotypy and schizophrenia, which might quantify the intersection (Fanous *et al.*, 2007). A genome-wide association study of 4269 nonpsychotic subjects from the Northern Finland Birth Cohort of 1966 found an association of a schizotypy-related measure (Chapman scale) with schizophrenia risk genes (incl. *CACNA1C*, Ortega-Alonso *et al.*, 2017). In one study of male army recruits, PRS for schizophrenia was shown to be negatively associated with positive and disorganized schizotypy, but only under stressful conditions (Hatzimanolis *et al.*, 2018). This is paralleled by studies of related risk phenotypes, such as psychotic-like experiences (PLEs), showing an inverse relationship with GWAS-derived genetic schizophrenia-risk in healthy adults, and in part also with studies in adolescents (Pain *et al.*, 2018, Sieradzka *et al.*, 2014). Taken together, despite some initial evidence, it is still unclear whether and to what extent schizotypal traits overlap genetically with the risk for schizophrenia (at whole-genome level), and in particular with polygenic risk scores that have been used to relate endophenotypes or subclinical phenotypes to schizophrenia risk (Mistry *et al.*, 2017).

In the present study, we tested the hypothesis of an association of SNP-related polygenic risk for schizophrenia with schizotypal traits in non-clinical subjects of the multi-centre FOR2107 cohort and a replication sample of blood donors. We tested for associations for overall schizotypal traits, which we followed up with post-hoc analyses for the three dimensions thereof. Also, we controlled for relative specificity by testing associations with polygenic risk for affective disorders (bipolar disorder and major depressive disorder).

Methods

Subjects

For the test sample, we analysed data from 623 healthy subjects recruited into the multi-center cohort study FOR2107, as part of the Marburg and Münster affective

cohort study (MACS, Kircher *et al.*, 2018). All subjects gave written informed consent to a study protocol approved by the local ethics committees of the Philipps-University Marburg and Westfälische-Wilhelms-Universität Münster.

Both samples included nonclinical psychiatric healthy subjects (without life-time psychiatric disorder), all of whom had undergone the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I, Wittchen *et al.*, 1997) to confirm absence of a psychiatric axis I diagnosis. Additional exclusion criteria were history of traumatic brain injury, current or previous neurological disease of the central nervous system, uncontrolled general medical diseases, current or previous substance abuse or dependence, as well as current psychotropic medication. Subjects were recruited from the local communities in Marburg and Münster, respectively.

This sample of N=623 included 392 (62.9%) female and 231 (37.1%) male participants; mean age was 32.62 years (SD=12.47), ranging from 18 to 65 years. There was no indication of differences in sex-distribution across sites (Marburg 151 male, 253 female; Münster 80 male, 139 female; chi-square-test one tailed, p=.835). As participants recruited in Münster were significantly ($F(1,622)=44.535$, $p=5.54\times10^{-11}$) younger (M=28.24, SD=10.35) than Marburg participants (M=34.99, SD=12.89), we included age as a covariate in all analyses. We administered clinical interviews and schizotypy assessments and obtained blood samples for genetic analysis within a week.

The Mannheim replication sample consisted of a control cohort of n=1133 subjects (mean age=44.63, SD=12.85, range 18–70 years; 516 male (45.5%), 617 female (54.5%)) recruited at blood donation events in the state of Baden-Württemberg, Germany. Written informed consent was obtained from all subjects, and the study was approved by the local ethics committee of the Medical Faculty Mannheim, University of Heidelberg. Subjects were handed a questionnaire assessing demographic information and information about their mental and somatic health at the blood donation event which they then mailed back to the study centre.

Phenotyping / Assessment of schizotypal traits

We administered the SPQ-B (Schizotypal Personality Questionnaire, brief version) to assess schizotypy through self-report. The SPQ-B is the short form of the well-validated SPQ questionnaire first introduced by Raine (Raine, 1991). It has been validated in its German translation in previous studies (Barron *et al.*, 2018, Fonseca-Pedrero *et al.*, 2017, Klein *et al.*, 1997). In addition to providing an overall assessment of schizotypal traits, the SPQ-B also allows analysis of the three major dimensions thereof: a *Cognitive-Perceptual* factor (measuring positive schizotypy), a *Disorganized* factor (measuring mainly eccentricity), and an *Interpersonal* factor (tapping into negative schizotypy and neuroticism). These dimensions reflect the three-factor structure seen in many other schizotypy questionnaires (Asai *et al.*, 2011, Gross *et al.*, 2014, Oezgen and Grant, 2018).

Given that psychometric assessments of schizotypy often tend to show substantial overlap with facets of neuroticism (e.g., Gross *et al.*, 2014, Macare *et al.*, 2012), we also calculated an adjusted schizotypy score, along with scores for its three dimensions (Oezgen and Grant, 2018), and adapted for the brief version of the SPQ. These adjusted factors aim to reduce variance between schizotypy measures (due to slight conceptual differences) by re-assigning items to higher-order factors thought to mirror the common ground between the inventories. The resulting scales are: Adjusted Positive, Adjusted Negative, Adjusted Cognitive and Adjusted Eccentricity. These adjusted schizotypy scores were used for additional testing to confirm that the association was not driven by conceptual contaminants and to enable generalisation across instruments (Oezgen and Grant, 2018).

Genotyping and polygenic risk score (PRS) calculation

Genotyping from blood samples in all subjects of the MACS test sample was performed according to previously published methods using the Infinium PsychArray-24 v1.3 BeadChip (Opel *et al.*, 2018). Quality control was conducted in PLINK v1.90b5 (Chang *et al.*, 2015) and R v3.3.3. Individuals were removed if they met any of the following

criteria: genotyping call rate <98%, gender mismatches or other X-chromosome-related issues, genetic duplicates, cryptic relatives with pi-hat ≥0.125, genetic outlier with a distance from the mean of >4 *SD* in the first eight ancestry components, or a deviation of the autosomal or X-chromosomal heterozygosity from the mean >4 *SD*. Genotype data were imputed to the 1000 Genomes Phase 3 reference panel using SHAPEIT and IMPUTE2 (Delaneau *et al.*, 2011, Howie *et al.*, 2012, Howie *et al.*, 2009).

PRS for schizophrenia (SZ), bipolar disorder (BPD), and major depression (MDD) were calculated in R v3.33 by summing the minor allele dosages of the linkage disequilibrium (LD)-independent SNPs in our test sample, weighted by GWAS effect sizes (SZ: Ripke *et al.*, 2014, BD: Stahl *et al.*, 2019, MDD: Wray, 2018). The weighted PRS thus represent an estimation of cumulative, additive risk. PRS were calculated at *p*-value thresholds that showed the best discrimination of case-control status in the original GWAS (SZ: *p*=.05, BD: *p*=.01, MDD: *p*=.05).

To adjust for genetic heterogeneity within our sample, we computed multi-dimensional scaling (MDS) components based on the pairwise identity-by-state distance matrix calculated on the genotype data in PLINK v1.90b5. Based on screeplot inspection, the first three components (C1–C3) were included as covariates in the analyses.

The Mannheim replication sample served as part of the control cohort in the framework of a case-control GWAS of Borderline Personality Disorder for which details have been published previously (Witt *et al.*, 2017). Analyses in the present manuscript are based on an updated quality control and imputation carried out using the RICOPILI GWAS pipeline (Lam *et al.*, 2019).

Individuals and SNPs were removed if they met any of the following exclusion criteria in the first round of quality control: genotyping call rate for given SNPs or individuals <98%, difference in SNP genotyping call rate between cases and controls >2%, deviation for the autosomal heterozygosity from the mean (|Fhet|>0.2), or a deviation from Hardy-Weinberg equilibrium ($p<1x10^{-10}$ in cases; $p<1x10^{-6}$ in controls). Genotype data were imputed using a publicly available reference panel consisting of 54,330

phased haplotypes with 36,678,882 variants from the haplotype reference consortium (EGAD00001002729) with the pre-phasing/imputation stepwise approach in EAGLE/MINIMAC3 (default parameters and a variable chunk size of 132 genomic chunks, Das *et al.*, 2016, Loh *et al.*, 2016) . In the second round of quality control, relatedness testing and population structure analysis were performed using a SNP subset that fulfilled strict quality criteria after imputation (INFO >0.8, missingness <1%, minor allele frequency >0.05), and which had been subjected to LD pruning (r^2>0.02). This subset comprised 66,240 SNPs. For cryptic relatives with pi-hat >0.2, one member of each pair was removed at random following the preferential retention of cases over controls. To obtain a highly informative SNP set with minimal statistical noise for PRS calculation, the following were excluded: low frequency SNPs (minor allele frequency <0.1), low-quality variants (INFO <0.9), and indels in each of three GWAS (SZ: Ripke *et al.*, 2014, BD: Stahl *et al.*, 2019, MDD: Wray, 2018). Subsequently, the remaining SNPs were clumped. From the major histocompatibility complex region, only one variant with the strongest significance was retained. These SNPs were then used as weights to calculate PRS for each individual in the cohort. Five MDS components (C1–C4 and C7) were used to adjust for genetic heterogeneity within the Mannheim cohort along with sex and age in subsequent analysis.

Statistical analysis

Statistical analysis was performed using SPSS (SPSS, version 24, IBM, Armonk, NY) and R/Rstudio(R Core Team, 2018, RStudio Team, 2015). Distributions of sex and differences in age and SPQ scores were assessed using chi-square tests and univariate and multivariate analyses of variance (ANOVA), respectively. As is to be expected, schizotypy scores showed substantial skewness that remained after common transformation attempts. Schizotypy scale variables were z-transformed to ensure comparability between test and replication samples.

To test our main hypothesis, we performed a multiple regression analysis between schizophrenia PRS and the SPQ-B total score; with age, sex, and MDS components (C1–C3 in test sample, C1–C4 and C7 in replication sample) as covariates. We then tested separate multiple regression models *post-hoc* with each of the three SPQ-B dimensions and the adjusted schizotypy scores as the outcome variable. To account for the remaining skewness in the variables, robust standard errors were calculated using bootstrapping (*N*=1000) and bootstrapped *p*-values are reported.

To aggregate results across samples, combined *p*-values were calculated with the Stouffer meta-analysis method(Stouffer *et al.*, 1949) using the R package gmeta (https://cran.r-project.org/web/packages/gmeta/index.html) to weight by the different sample sizes (*N*=623 vs. *N*=1133).

Finally, given the genetic overlap between schizophrenia and affective disorders, we examined potential associations with affective disorders using the PRS for bipolar disorder and for major depression as independent variables in further multiple regression models. Since SPQ-B scales (as well as adjusted factors) display significant intercorrelations, *p*-value thresholds were adjusted to account for multiple comparisons according to the Bonferroni-Holm method for the eight schizotypy scores tested for each of the PRS (Eichstaedt *et al.*, 2013).

Power Analysis for Correlations

Based on the literature reported, we expected small local effect sizes of PRS prediction of schizotypy scores (Cohen's $f^2 \geq 0.02$). To determine the effect size we were able to detect with our data, we conducted an *a posteriori* power analysis, using the sensitivity test in GPower (v3.1.9.4,(Faul *et al.*, 2007)) for multiple regression models. Given the sample size of *N*=623 (*N*=1133), an alpha level of 0.05 and a power of 0.80, in a linear multiple regression model with one tested predictor and six (eight) predictors in total, resulting in 616 (1124) degrees of freedom, we would have had enough power to

detect a local effect size of Cohen's $f^2 \geq 0.013$ (test sample), $f^2 \geq 0.007$ (replication sample), respectively.

Results

Distribution of schizotypal traits

Descriptive statistics for the original scales and adjusted schizotypy scores are shown in table 1. Both age ($F(1,622)=4.95$, $p_{adj}=.026$, partial Eta^2 (η^2)=.008) and sex ($F(1,622)=6.61$, $p_{adj}=.020$, $\eta^2=.010$) were significantly associated with total schizotypy. Therefore, both variables were included into subsequent correlation analyses.

Table 1. Distribution of schizotypy scor**es**

Schizotypy scale	MACS sample			Mannheim sample		
	Mean (*SD*)	**Range**	**Skewness**	**Mean (*SD*)**	**Range**	**Skewness**
SPQ-B total score	3.38 (2.97)	0–16	1.07	3.58 (3.34)	0-18	1.22
Cognitive-Perceptual	0.90 (1.16)	0–6	1.48	1.54 (1.64)	0-10	1.24
Interpersonal	1.70 (1.70)	0–8	1.06	2.14 (2.11)	0-10	0.94
Disorganized	0.78 (1.25)	0–6	1.81	0.54 (1.05)	0-6	2.32
Adj. *Positive*	0.14 (0.19)	0–1.05	1.54	0.16 (0.20)	0-1.05	1.33
Adj. *Negative*	0.23 (0.25)	0–0.94	0.63	0.24 (0.25)	0-0.94	0.68
Adj. *Cognitive*	0.18 (0.26)	0–1.25	1.76	0.23 (0.31)	0-1.25	1.49
Adj. *Eccentricity*	0.16 (0.19)	0–0.83	1.38	0.14 (0.18)	0-0.97	1.86

Note. SD=standard deviation

Association of PRS-SZ and schizotypal traits

Neither the SPQ-B total score, nor the subscores *Cognitive-Perceptual*, *Interpersonal*, or *Disorganized* showed significant associations with the schizophrenia PRS in any of the two samples (see Table 2 for details). This observation was also confirmed by meta-analysing the *p*-values of each sample. Likewise, analyses of the adjusted factors showed no significant correlation with the PRS for schizophrenia.

Table 2. Model statistics of regression models with **PRS SZ** as predictor.

dependent variable	MACS sample			Mannheim sample			**comb. *p****
	ß PRS SZ	f^2 PRS SZ	*p*(ß)	**ß PRS SZ**	f^2 PRS SZ	*p*(ß)	
SPQ-B total score	0.003	9.2×10^{-6}	0.955	-0.045	0.002	0.340	0.818
Cognitive-Perceptual	0.006	3.8×10^{-5}	0.873	-0.028	0.001	0.228	0.610
Interpersonal	0.007	5.0×10^{-5}	0.882	-0.035	0.001	0.223	0.618
Disorganized	-0.007	5.0×10^{-5}	0.851	-0.002	4.3×10^{-6}	0.882	0.942
Adj. *Positive*	0.019	3.0×10^{-4}	0.635	-0.003	9.4×10^{-6}	0.339	0.480
Adj. *Negative*	-0.013	1.7×10^{-4}	0.743	0.000	3.3×10^{-8}	0.956	0.952
Adj. *Cognitive*	-0.012	1.4×10^{-4}	0.807	-0.005	2.6×10^{-5}	0.258	0.561
Adj. *Eccentricity*	0.009	8.2×10^{-5}	0.833	-0.001	1.1×10^{-6}	0.588	0.800

Note. Age, sex, and MDS components C1–C3 (MACS)/C1–C4 (Mannheim) were included as covariates in all models. All *p*- and ß- values after z-transformation and bootstrapping with N=1000. **p*-values were combined with the Stouffer meta-analysis method. All *p*-values are above the threshold for statistical significance (p_T=.00625–.05).

Association of PRS-BD and schizotypal traits

In follow-up analyses testing the association of the PRS for bipolar disorder (BD) with schizotypy, we did not find a significant correlation between BD PRS and any of the SPQ dimensions in either of the samples (see Table 3).

Association of MDD PRS and schizotypal traits

Findings for associations of the PRS for major depression (MDD) and schizotypy were inconsistent, as we detected a significant association only in the Mannheim sample. However, all combined *p*-values were above the significance thresholds after correcting for multiple testing (see Table 4).

Table 3. Model statistics of regression models with **PRS BD** as predictor.

dependent variable	MACS sample			Mannheim sample			**comb. *p****
	ß PRS BPD	f^2 PRS BPD	*p*(ß)	**ß PRS BPD**	f^2 PRS BPD	*p*(ß)	
SPQ-B total score	-0.010	1.0×10^{-4}	0.824	0.067	0.005	0.044	0.292
Cognitive-Perceptual	-0.044	0.002	0.247	0.038	0.002	0.203	0.142
Interpersonal	0.007	5.0×10^{-5}	0.871	0.065	0.004	0.117	0.483
Disorganized	0.009	8.4×10^{-5}	0.801	0.033	0.001	0.060	0.308
Adj. *Positive*	-0.034	0.001	0.384	0.006	3.8×10^{-5}	0.147	0.171
Adj. *Negative*	-0.014	2.0×10^{-4}	0.734	0.005	2.6×10^{-5}	0.330	0.552
Adj. *Cognitive*	0.014	2.0×10^{-4}	0.715	0.013	1.7×10^{-4}	0.041	0.204
Adj. *Eccentricity*	0.003	9.2×10^{-6}	0.940	0.004	1.7×10^{-5}	0.194	0.688

Note. Age, sex, and MDS components C1–C3 (MACS)/C1–C4 (Mannheim) were included as covariates in all models. All *p*- and ß- values after z-transformation and bootstrapping with *N*=1000. **p*-values were combined with the Stouffer meta-analysis method. All *p*-values are above the threshold for statistical significance (p_T=.00625–.05).

Table 4. Model statistics of regression models with **PRS MDD** as predictor.

dependent variable	MACS sample			Mannheim sample			**comb. *p****
	ß PRS MDD	f^2 PRS MDD	*p*(ß)	**ß PRS MDD**	f^2 PRS MDD	*p*(ß)	
SPQ-B total score	-0.026	6.9×10^{-4}	0.543	0.328	0.114	**0.001**	0.017
Cognitive-Perceptual	-0.039	0.002	0.348	0.130	0.018	**0.002**	0.010
Interpersonal	-0.012	1.4×10^{-4}	0.762	0.185	0.035	**0.001**	0.046
Disorganized	-0.008	6.6×10^{-5}	0.848	0.089	0.009	**0.002**	0.095
Adj. *Positive*	-0.042	0.002	0.325	0.008	6.7×10^{-5}	0.104	0.113
Adj. *Negative*	-0.020	4.1×10^{-4}	0.632	0.020	4.2×10^{-4}	**0.001**	0.258
Adj. *Cognitive*	0.013	1.7×10^{-4}	0.743	0.022	5.0×10^{-4}	**0.007**	0.101
Adj. *Eccentricity*	-0.021	4.5×10^{-4}	0.607	0.018	3.5×10^{-4}	**0.001**	0.023

Note. Age, sex, and MDS components C1–C3 (MACS)/C1–C4 (Mannheim) were included as covariates in all models. All *p*- and ß- values after z-transformation and bootstrapping with *N*=1000. **p*-values were combined with the Stouffer meta-analysis method. Only *p*-values in bold are below the threshold for statistical significance (p_T=.00625–.05).

Discussion

In this study, we provide a large-scale analysis in two independent samples testing the hypothesis that schizotypy is significantly associated with the SNP-based polygenic risk for schizophrenia. Neither overall SPQ scores nor subscores / dimensions or adjusted schizotypy factors were associated with PRS for SZ, BP, or MDD. This finding contributes important new aspects to our understanding of the psychosis spectrum at both the phenotype and genotype levels, thus extending previous findings (Hatzimanolis *et al.*, 2018, Zammit *et al.*, 2014).

For the interpretation of our findings, we will discuss the use of schizotypy in phenotypic characterization across the psychosis spectrum (contrasting findings in schizotypy vs. those in PLEs), factors related to the timing of impact of genetic risk (*i.e.*, schizotypy and PLEs in adolescence *vs.* adult life), as well as methodological factors.

Schizotypal traits are increasingly used as a phenotypic marker of psychosis liability improving our understanding of the psychosis spectrum (Nelson *et al.*, 2013). They share variance with other measures, such as PLEs and clinical criteria of subjects at ultra-high risk for psychosis (Barrantes-Vidal *et al.*, 2013, Flückiger *et al.*, 2019). In contrast to a growing number of association studies of schizotypy with clinical or cognitive phenotypes or endophenotypes of schizophrenia (Ettinger *et al.*, 2015, Nenadic *et al.*, 2015), there have hardly any genetic studies investigating more than one risk gene in relation to schizotypy (for overview, see Meller *et al.*, 2019)).

First, our findings diverge from association studies using PLEs as subclinical markers. While schizotypy is linked to clinical risk for psychosis (Flückiger *et al.*, 2016, Kwapil *et al.*, 2013), thus emphasising its predictive clinical utility in prodromal screening(Schultze-Lutter *et al.*, 2019), it is not fully congruent with PLEs or at-risk states. Most high- schizotypy individuals are likely not to convert to psychotic disorders (Chapman *et al.*, 1994, Gooding *et al.*, 2007, Kwapil *et al.*, 2013), suggesting schizotypy to encompass more than just schizophrenia liability. In addition, we also need to consider that different schizotypy instruments are based on somewhat

incongruent conceptual backgrounds. For example, the SPQ is based on early DSM criteria of schizotypal personality disorder, while other questionnaires, such as the Multi-Dimensional Schizotypy Scales (MSS) are developed with an explicitly multi-dimensional approach to study the general population (Kwapil *et al.*, 2018).

A recent large study of psychosis proneness using multiple psychometric measures found an association with physical anhedonia and hypomanic features but not with other core aspects of schizotypy (Ortega-Alonso *et al.*, 2017); also, the study only found modest heritability across the phenotypes. Findings from the ALSPAC study have suggested that polygenic risk for schizophrenia links to anxiety and negative symptoms in adolescence but not depressive or psychotic symptoms (Jones *et al.*, 2016). Furthermore, a recent study from the UK biobank using a health questionnaire on frank psychotic experiences in non-clinical subjects found an indication for associations of psychotic experiences with PRS for schizophrenia, but also associations with PRS for bipolar disorder and major depressive disorder, as well as schizophrenia copy number variants (CNV, Legge *et al.*, 2019). Importantly, these phenotypes reflect a more state-related emergence of quasi-psychotic symptoms, which is different from the enduring trait-like quality of core schizotypy features. Our findings could, thus, be reconciled considering the difference between state- versus trait-like features of liability markers. Across the phenotype itself, cognitive disorganization and anhedonia might show higher SNP-heritability than more narrow positive symptom dimensions (Pain *et al.*, 2018), which is consistent with some older twin studies examining “Meehlian”-based measures of schizotypy (Hay *et al.*, 2001). Incidentally, analyses of (fully) dimensional schizotypy conceptualizations show similar heritability estimates of positive and negative schizotypy by individual latent genetic factors, which both equally explain variance in disorganized schizotypy (Linney *et al.*, 2003).

However, studies identifying associations between subclinical psychosis symptoms in population-drawn samples have either failed to show associations with schizophrenia

PRS (Sieradzka *et al.*, 2014, Zammit *et al.*, 2014) or have shown such associations only when pooling patients and controls, but not in non-clinical samples only (Derks *et al.*, 2012). It has to be considered, however, that those studies are based on the first-wave GWAS data that relied on a smaller sample and therefore significantly less power than the following GWAS. So far, a comprehensive study assessing both state and trait features of the psychosis spectrum is still lacking. Overall, our findings suggest that neither total schizotypy nor individual dimensions of the construct are substantially related to genetic psychosis risk. In contrast to other studies using the SPQ as a measure for schizotypy, which differs conceptually from “true” schizotypy, we also used the adjustment method suggested by Oezgen and Grant to reduce inter-scale conceptual variance und, potentially, provide a closer approximation of „true“ schizotypy from the SPQ-items (Oezgen and Grant, 2018). It is unclear whether the above spectrum phenotypes might be related to polygenic risk for other psychiatric disorders like major depression, as suggested from a recent systematic review of studies (Ronald and Pain, 2018), since unlike our study, many other previous studies did not include PRS scores for other disorders in their analyses. The significant positive association of schizotypy scales and MDD-PRS suggests further research is needed to understand a potential link to genetic risk for affective disorders.

The lower heritability of psychosis spectrum features (schizotypal traits vs. PLEs) also points to the problem of the timing of emerging risk phenotypes and the interaction with environmental risk. Association studies have variably used adolescent and adult samples. For example, the ALSPAC study relied on population-drawn cohorts of adolescents (Jones *et al.*, 2016), while other mentioned studies analysed adult data (e.g., Ortega-Alonso *et al.*, 2017). Some schizotypal features show only moderate temporal stability in late adolescence only, which might make them more prone to variation than other phenotypes, while others are more temporally stable (Ericson *et al.*, 2011, Rosa *et al.*, 2000, Venables and Raine, 2015).

The different risk backgrounds of genetic association studies of psychosis proneness also point to environmental risk factors as mediators of genetic risk. Like psychosis, schizotypy as a trait emerges from complex gene-environment interactions (Barrantes-Vidal *et al.*, 2015). Indeed, particularly those subjects scoring high on both types of risk factors might be at particular risk of developing manifest psychosis. Such effects for schizotypy and other risk phenotypes have been demonstrated for interactions with environmental risk factors like stress (Hatzimanolis *et al.*, 2018) or urban environment (Grech *et al.*, 2017).

The current understanding of the genetic architecture of the psychosis continuum has largely benefited from recent studies linking particular risk phenotypes like PLEs to schizophrenia PRS. Our findings indicate that schizotypy as one of the main spectrum phenotypes may not be robustly linked to schizophrenia polygenic risk. In the non-clinical part of the psychosis spectrum, this emphasizes the role of other factors, including environmental risk (Karcher *et al.*, 2019, van Os *et al.*, 2019). This is in accordance with the limited variance of common intermediate phenotypes that PRS explain (Mistry *et al.*, 2018), however, they do not capture the genetic contribution of rare variants like copy number variants (Mowry and Gratten, 2013), but only account for the additive risk deriving from common SNPs. We also need to consider the possibility that polygenic risk factors, while successful in case-control studies, might be inherently limited in quantitative measures or risk phenotypes. While integrating multiple biological pathways, only part of the genes and pathways of a PRS might be relevant to schizotypy. However, part of these relevant gene groups might have transdiagnostic impact, which is not limited to the psychosis spectrum (Ronald and Pain, 2018). This ultimately results in a multi-dimensional continuum or continua (van Os, 2014, van Os and Reininghaus, 2016), especially considering transdiagnostic overlap with affective disorders.

A methodological aspect to consider in view of our negative results is the sample variance. Correlational or regression-based analyses will often lead to null results when

sample-variance is low. As these methods depend on shared variance between variables, low variance in the variables will lead to null results, although the true correlation may, in fact, be higher. The short scales of inventories, such as the SPQ-B, are inherently less capable of capturing the same amount of variance as are full scales (Oezgen and Grant, 2018); therefore, also the adjustment method by Oezgen and Grant cannot perform as well when short scales are used (compared to full scales). Thus, our findings may have been different, had more schizotypal variance been captured within a sample not as ardently screened for psychiatric health. Yet, even within the Mannheim replication sample, in which in which no filtering was performed with regard to psychiatric phenotypes, no association with SZ-PRS was found. Additionally, as the effect-size of the (putative) association between schizotypy and the PRS for schizophrenia is, so far unknown, our sample may have lacked the power necessary to detect it. In comparison, Hatzimanolis and colleagues found a relationship between full SPQ scores and PRS for schizophrenia (albeit an inverse one), but only in a male sample almost twice as large as ours, under stressful conditions for the participants (*i.e.*, army recruits) and avoiding potential gender effects (their sample was entirely male, Hatzimanolis *et al.*, 2018).

In conclusion, the findings of our multi-centre study call for a reappraisal of suitable risk phenotypes and delineation within polygenic risk factors for both schizophrenia as well as affective disorders for an improved understanding of the biological continuum model of psychosis. Instead, understanding schizotypy as a wider phenotype (compared to merely harbouring risk for schizophrenia or psychosis) and gathering data in a fashion more suitable to this wider understanding of the schizotypy construct may be an important step forward. This is not only crucial for understanding those aspects of schizotypy that are, indeed, associated with schizophrenia liability, but also (and maybe even more) those factors that are not, or even protective with regards to decompensation into frank psychosis in highly schizotypal individuals.

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v. STUDY V: Manuscript

Impact of poly-genic and poly-environmental risk factors on a psychosis risk phenotype explained through brain structure

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Key words: psychosis; schizotypy; magnetic resonance imaging (MRI); mediation model; genetic risk; environmental risk; GxE; voxel-based morphometry (VBM)

Abstract

Objective: While single, genetic and environmental, risk factors for psychosis have been studied for their impact on brain structure and function, there is little understanding of how they interact to generate psychosis liability on the neural level. Direct associations between cumulative genetic risk scores and risk phenotypes are often weak, and analyses of G×E interactions are scarce. We developed and tested a multivariate model, in which the effects of cumulative environmental and genetic risk on a dimensional phenotype are mediated by brain structural variation.

Methods: In a data set of 440 non-clinical subjects, we tested a moderated mediation model with an interaction of an environmental (ERS) and a polygenic risk score (PRS) for schizophrenia, impacting on the subclinical psychosis spectrum phenotype schizotypy. We propose this effect to be mediated by grey matter volume variation, derived from voxel-based morphometry. In addition, cognitive function was considered as a potential moderator.

Results: We identified a significant multivariate model (R^2=10.91%, p=4.9×10^{-5}) in which precuneus/posterior cingulate volume mediated the impact of a PRS×ERS interaction on the positive schizotypy dimension. Furthermore, variation in executive function modulated this effect (p=0.027).

Conclusions: Our finding is the first to integrate polygenic and poly-environmental markers with MRI parameters to demonstrate that the interaction of these cumulated risk factors leads to the emergence of subclinical symptoms through changes in brain structure. This also provides a testable model that can be applied to other clinical spectra.

Introduction

Multiple genetic and environmental risk factors for psychosis impact different neuronal circuits to modulate risk for disease or expression of risk phenotypes[1]. Although aetiological models agree on multivariate interactions of risk and protective factors across multiple levels[2], the majority of studies conducted univariate associations of single risk factors. Thus, the complex interplay of different factors, as well as their cumulative effects, has often been neglected. Partially, the interplay of risk factors is addressed in gene by environment (G×E) interaction studies, yet often restricted to single risk factors[1]. Multivariate models are, therefore, needed to integrate different risk factors and their effects on the neurocircuit level into a joint framework.

Genetic liability may modulate environmental vulnerability by affecting brain structure and function, while protective influences and compensatory processes may buffer the impact of genetic risk[3,4]. Surprisingly, previous studies analysing the impact of polygenic risk on brain structure in non-clinical or clinical cohorts show only weak effects[5], and statistically tested models of gene by environment (G×E) interactions, including specific pathways, are scarce. Such models are required to establish a mechanistic account for the emergence and maintenance of psychopathology.

While most studies of G×E interactions in psychiatry have focussed on depression[1], there is also a growing number of research within the psychosis spectrum. For example, polymorphisms in risk genes *COMT* and *FKBP5* affect the outcome in schizophrenia spectrum disorders depending on cannabis consume and early life stress, respectively[6]. Moreover, interactions between genetic variants involved in serotonergic neurotransmission and neurodevelopment and the exposure of early and late life environmental risk factors modulate the risk for first episode psychosis[7]. While studies focussing on single genetic and environmental factors are valuable for analysing specific pathways, none of these exert their effects in isolation, but are part of complex interactions. On the genetic level, genome-wide association studies (GWAS) have provided polygenic risk scores as cumulative expression of common

single nucleotide polymorphism-related risk[8]. Recently, aggregated scores integrating multiple environmental risk pathways have been developed[9]. This creates a multi-dimensional space, in which pathways of risk and protective factors unfolding during a subject's life-time can be explored.

Another limitation of previous studies is the lack of dimensionality in analysed phenotypes, as many studies relied on case-control designs. In view of psychosis-spectrum models[10], the case/control approach can only explain minor parts of the total phenotypic variation[11]. In addition to the heterogeneity *within* clinical dimensions, it is well established that the expression of psychotic or psychotic-like symptoms also extends to the non-clinical population[4]. Well-established dimensional phenotypes are, for example, dimensions of schizotypy, which can be assessed in healthy subjects, yet share a fully dimensional relationship with schizophrenia[10,12]. With schizotypy as a risk phenotype, G×E interactions established in schizophrenia can also be extended to the non-clinical spectrum. Recent examples include interactions of cannabis use and variants of *DRD2*[13], and childhood maltreatment and *FKBP5* variants[14]. Similarly, polygenic risk for schizophrenia impacts schizotypy in interaction with stressful life conditions[15] and the shared environment of siblings[15].

For most of these associations, it is unclear how effects unfold on the neural level. Both disease status and dimensional markers like schizotypy are associated with brain structural and functional variation. Key regions seem to be inferior and superior frontal, superior and medial temporal cortices, as well as the precuneus[16–19]. Those are also shown in non-clinical samples, where confounding effects of disease onset or medication are avoided. This concurs with the (early) idea that even severe psychopathological alterations are preceded by subtle variations of healthy brain structure and function[20]. Such alterations might mediate the association of G×E interactions and phenotypes. Studies are limited[8], but, for example, indicate an interaction of polygenic risk and cannabis on cortical thickness in females[21].

The present study sought to develop and test a multivariate model that would overcome some of the limitations of previous studies. In this model, we incorporated both cumulative genetic and environmental risk scores as well as structural brain imaging data and cognition to explain variance in psychopathology, using schizotypy as a dimensional phenotype. Based on the central assumption of a relationship of genetic risk and psychopathology, we constructed a model that incorporates the mediation of this relationship through brain structural parameters, while allowing moderation by environmental risk and cognitive function (figure 1). The latter has been proposed as a buffer against emerging psychopathology in schizophrenia spectrum models[3] with empirical evidence in schizotypy[22], at-risk individuals[23], and schizophrenia[24].

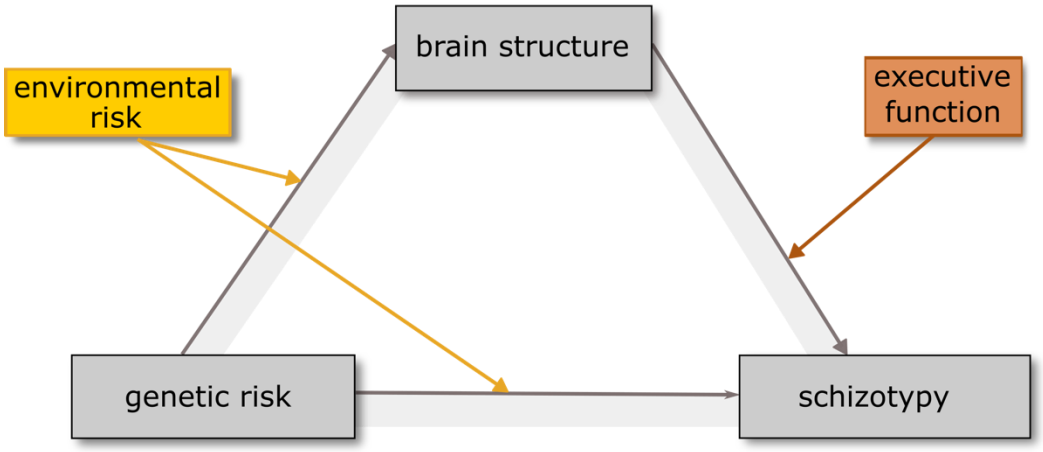

Figure 1. Conceptual moderated mediation model of the effect of genetic x environmental risk on schizotypy, mediated by variation in brain structure, and moderated by level of executive function.

Methods

Sample

We analysed data of N=440 healthy subjects with complete data in all necessary markers (age 18-65 years, mean=32.77, standard deviation (SD)=12.12; 172 (39.1%) male and 268 (60.9%) female), who were part of the FOR2107 cohort, a bi-centre study recruiting from the areas of Marburg and Muenster, Germany[25]. All procedures were approved by the ethics committees of the Medical Schools of the Universities of Marburg and Muenster, in accordance with the Declaration of Helsinki. Participants were thoroughly screened for exclusion criteria, *i.e.*, current or former psychiatric disorders (tested by trained raters through SCID-I interviews[26]), neurological or other severe medical disorders, current drug use, verbal IQ<80 (estimated with Multiple Choice Word Test-B[27]) and common MRI contraindications. All subjects volunteered to take part in the study, gave written informed consent and received a financial compensation for participation.

Magnetic resonance imaging (MRI) data acquisition and voxel-based morphometry (VBM) pre-processing

We acquired high resolution, T1-weighted structural images on a 3T MRI system in both Marburg (12-channel head matrix Rx-coil; Tim Trio, Siemens, Erlangen, Germany) and Münster (20-channel head matrix Rx-coil; Prisma, Siemens, Erlangen, Germany). We used a 3D MPRAGE sequence with slice thickness=1.0mm, voxel size=1.0x1.0x1.0mm, field of view FOV=256mm and the following parameters in Marburg: repetition time of TR=1.9s, echo time TE=2.26ms, inversion time TI=900ms, flip angle=7°; and Münster: TR=2.13s, TE=2.28ms, TI=900ms, flip angle=8°. Based on extensive quality assurance protocols[27], imaging data from both centres were pooled.

Pre-processing and voxel-based morphometry (VBM) analyses were executed using the pipeline of the CAT12 toolbox (version 1184, Gaser, Structural Brain Mapping group, Jena University Hospital, Jena, Germany) building on SPM12 (Statistical

Parametric Mapping, Institute of Neurology, London, UK), running under MatLab (The MathWorks, USA) with default parameter settings. Images were segmented into grey matter, white matter, and cerebrospinal fluid and spatially normalised with the DARTEL algorithm. All images passed visually quality control (inspection for artefacts and image quality) and the quality and homogeneity controls implemented in CAT12. Images were smoothed with a Gaussian kernel of 8mm (full width at half maximum, FWHM).

Assessment of dimensional schizotypy

Schizotypy was assessed with the German version[28] of the Schizotypal Personality Questionnaire-Brief (SPQ-B). This short version of the original SPQ has been validated in cohorts of multiple nationalities[29]. We calculated adjusted dimensional scores (table 1) for positive (AdjPos), negative (AdjNeg), cognitive (AdjCog) and eccentricity (AdjEcc) facets of schizotypy. Those adjusted scores have been constructed based on a factorial analysis of the major schizotypy instruments to identify their overlapping common ground, and represent a more instrument-independent, general account of those dimensions[30].

Table 1. Sample descriptives.

	mean	**SD**	**range**
ERS score	-0.35	2.71	-4.5 - 7.0
schizotypy dimensions			
positive	0.15	0.19	0.00 - 1.05
negative	0.25	0.26	0.00 - 0.94
cognitive disorganisation	0.17	0.26	0.00 - 1.25
eccentricity	0.15	0.19	0.00 - 0.83

SD = standard deviation

Polygenic risk score (PRS): Genotyping, quality control, and PRS calculation

Genotyping was performed with genomic DNA extracted from blood samples using the Infinium PsychArray-24 v1.3 BeadChip. Quality control was conducted in PLINK v1.90b5[31] and R v3.3.3. Individuals were removed if they met any of the following criteria: genotyping call rate <98%, gender mismatches or other X-chromosome-related issues, genetic duplicates, cryptic relatives with pi-hat ≥12.5%, genetic outlier with a distance from the mean of >4 SD in the first eight ancestry components, or a deviation of the autosomal or X-chromosomal heterozygosity from the mean >4 SD.

Schizophrenia PRS was calculated by summing the minor allele dosage of LD-independent single nucleotide polymorphisms, weighted by GWAS-derived effect size, in R. PRS was calculated based on variants surpassing a GWAS *p*-value threshold of p_T=0.05, which showed the best discrimination between schizophrenia cases and controls in the original GWAS[32]. Multi-dimensional scaling (MDS) components were calculated in PLINK and included as covariates to adjust for population stratification.

Environmental risk score (ERS) calculation

Calculation of the environmental risk score (ERS) was conducted according to the Maudsley Environmental Risk Score for Psychosis[9] (see table 1 for descriptives). For this score, six environmental risks were selected based on the amount of replicated evidence, exposure before illness onset and relatively easy assessment: ethnic minority status, urbanicity, high paternal age, obstetric complications, cannabis use, and childhood adversity. Point scores for categorical levels of each risk factor have been calculated by Vassos and colleagues based on relative risks (RR) compared to an “average” exposure, (as only a marginal proportion of the population are not exposed to *any* risk), rescaled, multiplied and rounded to construct a simpler scale[9] (see table 2). The resulting categories, respective point values, and operationalisations are shown in table 2. The ERS was calculated by summing the points of each category,

resulting in a range from -4.5 (lowest risk) to 16 (maximum risk), where 0 equals an average risk for psychosis.

Table 2. Operationalisation and respective point values for environmental risk factors in the calculation of the ERS in the study sample.

risk factor	operationalisation	ERS points
ethnic minority	native	-0.5
	white	2
	other	2.5
urbanicity	low (Lederbogen‡ score 15)	-1.5
	medium (Lederbogen‡ score 15-30)	0
	high (Lederbogen‡ score 30-45)	1.5
paternal age	<40	0
	40-50	0.5
	>50	2
obstetric complications	birth weight ≥ 2.5kg and no other complications	0
	birth weight < 2.5kg or any other complication	2
cannabis	no exposure	-1
	little to moderate	0
	high exposure	3
childhood adversity	no exposure (no CTQ† scale above cut-off)	-1.5
	any exposure (≥ 1 CTQ† scale above cut-off)	2.5

‡Lederbogen urbanicity score[46]; †CTQ: childhood trauma questionnaire[47]

Neurocognitive testing

As an indicator of working memory and executive function, we chose a subtest of the Wechsler Adult Intelligence Scale (WAIS, German version), the letter-number-sequencing task (LNS). Participants are asked to recall a given sequence of letters and numbers in increasing (numbers) and alphabetical (letters) order, respectively. The LNS indexes working memory and executive function, assessing sequential processing, cognitive flexibility, and fluid intelligence, and compared to traditional measures of digit span, surpasses those by including processing speed and visual spatial memory[34].

Statistical analyses

VBM analysis

To identify clusters of grey matter volume significantly affected by the interaction effect of schizophrenia PRS and ERS, we conducted a whole-brain analysis using general linear modelling (GLM) in SPM12/CAT12 with a full factorial design. Age, sex, site, total intracranial volume (TIV), and MDS components were included as covariates to control for potentially confounding effects. We accounted for an Rx coil change after 247 of 296 scans at the Marburg site by including head coil as an additional nuisance variable[35].

As interactions can only be tested between one continuous variable and categorical variables in SPM, we categorised participants into three groups (low, medium, high) according to their ERS score: Scores ≤0.5 were considered as “low” (63.4%), scores between 0.5 and 3.5 as “medium” (29.5%), and scores >3.5 as “high” (6.4%). Categorisation cut-offs were chosen similar to suggestions by Vassos et al.[9], resulting in an expected distribution of the three categories. Results were considered significant at $p<0.05$ FWE (Family Wise Error) cluster level-correction for multiple comparisons, after an initial cluster-forming threshold of $p<0.001$.

Moderated mediation model

Testing of the moderated mediation model was conducted with multiple linear regression models, using the PROCESS macro v3.4 for SPSS[36], running under IBM Statistical Package for Social Sciences (SPSS, version 24, IBM, Armonk, NY). In the model (figure 1), PRS was entered as the predictor, schizotypy dimension score as the outcome, extracted cluster values as a mediator, and ERS and LNS as moderators. Age, sex, MDS components, site, TIV, and head coil were entered as covariates.

Results

Voxel-based morphometry (VBM) analysis of PRS X ERS interaction

The VBM analysis detected a significant interaction effect of PRS x ERS in a cluster (figure 2; k=910, x/y/z=-4/-50/33, p=0.024 FWE cluster-level corrected) including the left precuneus (Pc, 64%), left posterior cingulate gyrus (pcG, 33%) and left superior parietal lobule (2%), for the comparison of individuals in category 1 (low risk) to category 2 (moderate risk). This cluster did not reach significance, when comparing groups 1 (low risk) and 2 (moderate risk) to group 3 (high risk), possibly due to the small sample size of group 3.

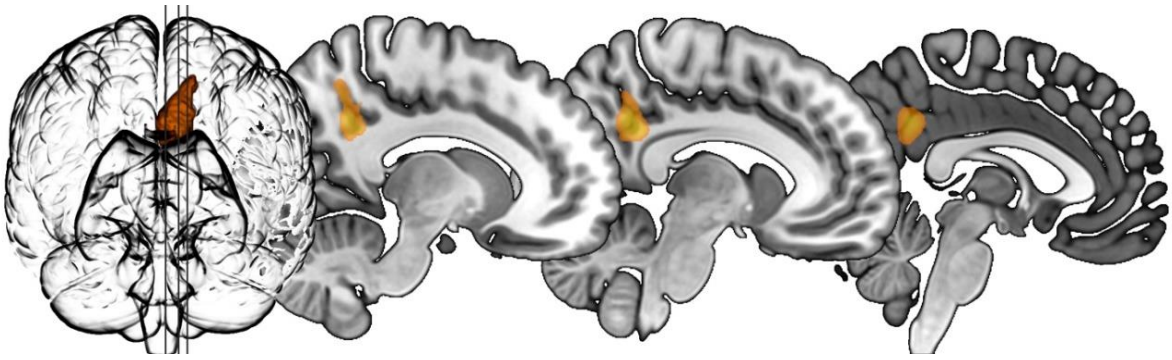

Figure 2. Cluster of significant association of the interaction of ERS x PRS and grey matter volume in the precuneus and posterior cingulate gyrus (p<0.05 FWE cluster level-corrected, illustration prepared with MRIcroGL; www.nitrc.org/projects/mricrogl).

Moderated mediation model

The moderated mediation model was overall significant for the prediction of positive (AdjPos) schizotypy (F(17,422)=3.04, p=4.9×10-5, R^2=10.91%, figure 3/panel A). In

predicting Pc/pcG grey matter value variation (R^2=51.69%, p<0.001), the model shows that while neither PRS (path a_1, b=0.638, p=0.830) nor ERS (a_2, b=0.001, p=0.416) had a main effect on grey matter variation within the extracted cluster, their interaction was significant (a_3, b=-3.13, p=0.002; figure 3/panel B): The intensity and direction of the effect of PRS on cluster variation was moderated by level of ERS, with a positive slope for low ERS (*i.e.,* decreased environmental risk), and a negative slope for high ERS.

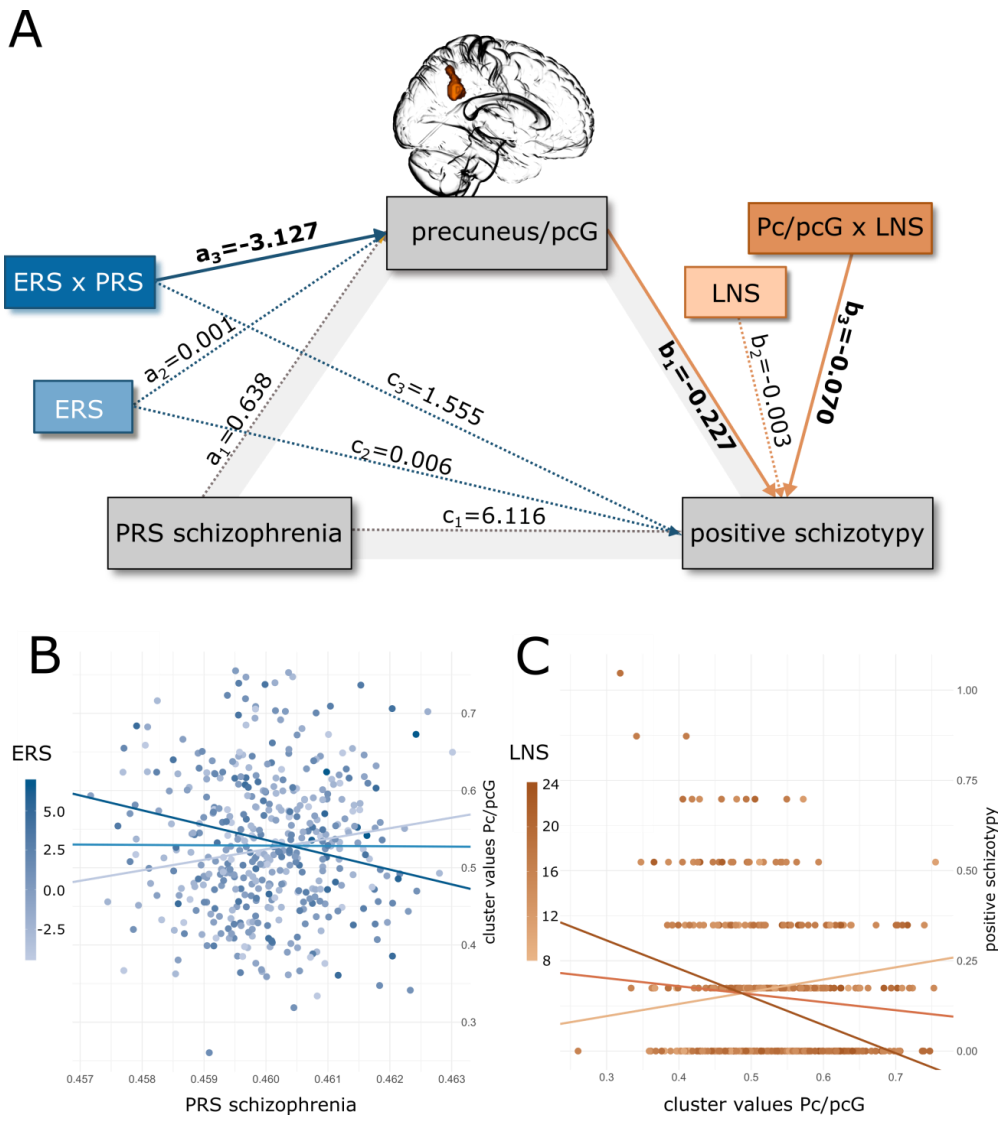

Figure 3. **A.** Statistical moderated mediation model with path coefficients, indicating that the interactive effect of ERS x PRS on positive schizotypy is mediated through brain structural variation within a cluster in the left precuneus/posterior cingulate gyrus, and moderated by executive function (LNS). Bold print indicates significant paths. **B.** Plot of the path a_3, showing a significant interaction of ERS x PRS on cluster volume, with fitted regression lines for low, average, and high ERS scores. Colours indicate the ERS level. **C.** Plot of the path b_3, a significant interaction of Pc/pcG x LNS on positive schizotypy, with fitted regression lines for low, average, and high LNS scores. Colours indicate LNS performance level.

In the prediction of positive schizotypy, the direct effects of PRS (c_1, *b*=6.116, *p*=0.477), ERS (c_2, *b*=0.006, *p*=0.068), and their interaction (c_3, *b*=1.555, *p*=0.604) were not significant (although a trend toward significance was observed for ERS). However, the model revealed an indirect effect through brain structural variation, showing a significant mediation (index=0.223, bootstrapped [n=10.000] confidence interval lower level=0.004, upper level=0.542). Cluster value variation had a significant main effect on positive schizotypy (b_1, *b*=-0.277, *p*=0.049), but was also modulated by the level of executive function, with a positive slope for low LNS scores, and a negative slope for high LNS scores, showing a second significant interaction (b_3, *b*=-0.070, *p*=0.027, figure 3/panel C). At the same time, the main effect of LNS on positive schizotypy was not significant (b_2, *b*=-0.003, *p*=0.319).

Discussion

The present study provides proof for a multivariate model predicting the impact of both polygenic and poly-environmental risk on a psychosis risk phenotype, mediated through brain structure. Extending previous studies focusing on singular risk factors (e.g., cannabis use or single risk genes), the particular strength of this model is the integration of multiple facets of genetic and environmental risk, intermediate phenotypes (brain structure and cognition), as well as a commonly used dimensional phenotype for the psychosis spectrum.

The resulting model provides several novel insights. First, we showed that the interaction of polygenic and poly-environmental risk was significantly associated with grey matter volume within a cluster in the precuneus/posterior cingulate gyrus (pcG). Structural variation in this region has already repeatedly been linked to positive schizotypy in non-clinical cohorts[18,37,38]. As part of the default mode network (DMN), connectivity in this region was also altered in high-risk subjects and first-episode and chronic schizophrenia across multiple-studies and meta-analyses[39,40]. We have now identified grey matter volume in this region to be affected by a cumulative G×E

interaction effect – that is detected *independently* of the phenotype, in a model not including a phenotypic variable.

The precuneus is a highly associative region and has extensive structural and functional connections throughout the brain. It is an important node of the default mode network, involved in sensory information integration, mental imagery, self-other-discrimination, and introspection[41] – functions relevant to manifestations of psychosis, especially the positive symptom domain.

Interestingly, the precuneus association with genetic and environmental risk is bidirectional: While under high environmental risk load, a higher PRS was linked to *reduced* precuneus/pcG volume, this effect was reversed under low environmental risk load (figure 3/panel B). These findings indicate higher sensitivity of individuals with high PRS not only to adverse, but also to beneficial environmental factors, with opposing effects. Conventional diathesis-stress models propose increased vulnerability specifically to *adverse* events; our model extends this to suggest an inverted effect for high PRS and low ERS subjects, where regional volumes showed relative increase. Under favourable environmental conditions, an increased genetic load might paradoxically result in low psychopathology outcomes or gain of function, supporting the notion of genes associated with schizophrenia as “plasticity genes” rather than simple risk factors[1,42].

In the framework of our multivariate model, brain structure is shown to act as an intermediate modulating the emergence of psychopathology. Such moderation effects cannot be detected by simple univariate associations. By extending the interaction model to include a (moderated) mediating pathway, we showed that a significant part of the phenotypic variance in positive schizotypy could be explained through changes in brain structure (precuneus/pcG) arising from G×E interactions.

Finally, our model confirms cognitive performance as a protective factor. With lower executive function, higher precuneus volume was associated with higher positive schizotypy; this association changed with increasing executive function, resulting in a

reversal at higher levels of cognitive functioning (figure 3/panel C). Cognition, therefore, may act as a buffer, although our analyses do not provide a neural-level account for this process. Similar findings, however, have been reported for general cognitive measures in schizophrenia and schizotypy[22,43,44], indicating that above-average levels of cognitive function can compensate for dysfunctional processes that arise from altered neurodevelopment, potentially leading to a manifest disorder. Such compensatory mechanisms are crucial for understanding resilience, as they explain the existence of high (positive) symptom load in unaffected individuals.

Our model explained a substantial amount of variance: while current genetic, PRS-based schizophrenia case versus control differentiation in large-scale GWAS can explain up to ~20%[32] of the variance, our model explained ~11% of the phenotypic variance even within a non-clinical cohort, thus surpassing other endophenotypic markers and measures. To put our findings in perspective, other studies found, for example, schizophrenia PRS to explain 9% of the variance between first episode psychosis versus control status[45], 1% of global functioning in schizophrenia patients and healthy controls[46], and <1% in cognitive performance in psychotic patients and controls[47]. However, it has to be taken into account that, while schizophrenia and dimensional phenotypes are highly polygenic, PRS capture only part of the genetic variance, *i.e.* incorporating only common single nucleotide polymorphisms at a certain *p*-value threshold. PRS do not account for rare genetic variants (e.g., copy number variants), epigenetic effects, non-additive risk effects, or gene×gene interactions. Thus, an increased genetic risk due to those might still show as a low polygenic risk modelled in standard PRS values[11]. Calculations of PRS also depend on dichotomous case-/control comparisons, thus not accounting for heterogeneity *within* each of the categories or for diverging pathways of specific symptom dimensions. This limitation might be overcome by using gene expression profiles in addition to static genotype information. Similarly as is the case for PRS, the ERS score does not fully account for E×E interactions.

In conclusion, one of the main challenges in biological psychiatry has been to establish a link between genetic risk variants and clinical disorders, and current models propose a pathway through neurodevelopmental processes. Using a dimensional risk phenotype, we present a model of how brain structure mediates the interaction effect of environmental and polygenic risk on phenotypic variance. This model can be extended to other genotype-phenotype associations. Our results may explain heterogeneous results in previous studies and highlight the importance of considering multivariate models in the future. These results further advocate the use of schizotypy and other dimensional, continuous phenotype markers as a valuable framework for detecting multifactorial associations in a dimensional perspective on psychopathology.

Conflicts of interest

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.

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All PIs take responsibility for the integrity of the respective study data and their components. All authors and co-authors had full access to all study data. The FOR2107 cohort project (WP1) 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).

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vi. MANUSCRIPT CONTRIBUTIONS

adapted from Contributor Roles Taxonomy (CRediT) www.casrai.org/credit.html

STUDY I

Meller T., Schmitt S., Stein F., Brosch K., Mosebach J., Yüksel D., Zaremba D., Grotegerd D., Dohm K., Meinert S., Förster K., Redlich R., Opel N., Repple J., Hahn T., Jansen A., Andlauer T.F.M., Forstner A.J., Heilmann-Heimbach S., Streit F., Witt S.H., Rietschel M., Müller-Myhsok B., Nöthen M.M., Dannlowski U., Krug A., Kircher T., & Nenadić I. (2019). Associations of schizophrenia risk genes *ZNF804A* and *CACNA1C* with schizotypy and modulation of attention in healthy subjects. *Schizophrenia Research 208,* 67–75. (Impact Factor: 4.6)

Contribution: 50%. TM carried out formal analysis and, together with IN, developed the statistical approach and moderation/mediation models. TM wrote the original draft and was responsible for data visualisation.

STUDY II

Meller, T., Ettinger, U., Grant, P., & Nenadić, I. (2019). The association of striatal volume and positive schizotypy in healthy subjects: Intelligence as a moderating factor*. Psychological Medicine* 2019 Sep 18:1-9, doi: 10.1017/S0033291719002459P (IF: 5.6)

Contribution: 65%. TM conceptualised the moderation model and carried out all formal data analyses. TM wrote the original draft and created visualisations.

STUDY III

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Contribution: 60%. TM and IN conceptualised the methodological approach, TM carried out all formal data analyses, wrote the original draft and created visualisations.

STUDY IV

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Contribution: 30%. TM, together with AH, carried out formal data analyses. TM wrote method and result sections of the original draft.

STUDY V

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Contribution: 75%. TM conceptualised the methodological approach, developed the multivariate model and carried out all formal analyses. TM wrote the original draft and created data visualisations.

Die Seiten 124-125 (Lebenslauf) enthalten persönliche Daten. Sie sind deshalb nicht Bestandteil der Online-Veröffentlichung.

viii. VERZEICHNIS DER LEHRENDEN

Meine akademischen Lehrenden waren in Marburg:

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Ich weiß nicht, wie ich das hier ohne Euch geschafft hätte, aber ich bin sehr dankbar, dass ich es gar nicht erst versuchen musste.

X. EHRENWÖRTLICHE ERKLÄRUNG

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin Marburg zur Promotionsprüfung eingereichte Arbeit mit dem Titel „Neurobiologie schizotyper Phänotypen“ in der Klinik für Psychiatrie und Psychotherapie unter Leitung von Prof. Dr. Igor Nenadić ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation aufgeführten Hilfsmittel benutzt habe. Ich habe bisher an keinem in- oder ausländischen Medizinischen Fachbereich ein Gesuch um Zulassung zur Promotion eingereicht, noch die vorliegende oder eine andere Arbeit als Dissertation vorgelegt.

Ich versichere, dass ich sämtliche wörtlichen oder sinngemäßen Übernahmen und Zitate kenntlich gemacht habe. Mit dem Einsatz von Software zur Erkennung von Plagiaten bin ich einverstanden.

Vorliegende Arbeit wurde/wird in folgenden Publikationsorganen veröffentlicht:

Meller T., Schmitt S., Stein F., Brosch K., Mosebach J., Yüksel D., Zaremba D., Grotegerd D., Dohm K., Meinert S., Förster K., Redlich R., Opel N., Repple J., Hahn T., Jansen A., Andlauer T.F.M., Forstner A.J., Heilmann-Heimbach S., Streit F., Witt S.H., Rietschel M., Müller-Myhsok B., Nöthen M.M., Dannlowski U., Krug A., Kircher T., & Nenadić I. (2019). Associations of schizophrenia risk genes *ZNF804A* and *CACNA1C* with schizotypy and modulation of attention in healthy subjects. *Schizophrenia Research 208,* 67–75. (Impact Factor: 4.6)

Meller, T., Ettinger, U., Grant, P., & Nenadić, I. (2019). The association of striatal volume and positive schizotypy in healthy subjects: Intelligence as a moderating factor. *Psychological Medicine* 2019 Sep 18:1-9, doi: 10.1017/S0033291719002459P (Impact Factor: 5.6)

Meller, T., Schmitt S., Ettinger, U., Grant, P., Stein, F., Brosch, K., Grotegerd, D., Dohm, K., Meinert, S., Förster, K., Hahn, T., Jansen, A., Dannlowski, U., Krug, A., Kircher, T., & Nenadić, I. Brain structural correlates of schizotypal signs and subclinical schizophrenia nuclear symptoms in healthy individuals. (under review)

Nenadić, I.*, **Meller, T***., Schmitt S., Brosch, K., Mosebach, J., Ettinger, U., Grant, P., Meinert S., Opel, N., Lemke, H., Fingas, S., Förster, K., Hahn, T., Jansen, A., Andlauer, T.F.M., Forstner, A.J., Heilmann-Heimbach, S., Hall, A., Awasthi, S., Ripke, S., Witt, S.H., Rietschel, M., Müller-Myhsok, B., Nöthen, M.M., Dannlowski, U., Krug, A., Stein, F.[#], Kircher, T.[#] Polygenic risk for schizophrenia and schizotypal traits in non-clinical subjects. *[#]*contributed equally* (submitted for publication)

Meller, T., Schmitt S., Stein, F., Brosch, K., Andlauer, T.F.M., Grotegerd, D., Dohm, K., Meinert, S., Förster, K., Forstner, A.J., Heilmann-Heimbach, S., Streit, F., Witt, S.H., Rietschel, M., Müller-Myhsok, B., Nöthen, M.M., Hahn, T., Jansen, A., Dannlowski, U., Krug, A., Kircher, T., & Nenadić, I. The impact of polygenic and poly-environmental risk factors on a psychosis risk phenotype is mediated through brain structure. (unpublished manuscript)

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Ort, Datum, Unterschrift Doktorandin

Die Hinweise zur Erkennung von Plagiaten habe ich zur Kenntnis genommen.

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Ort, Datum, Unterschrift Referent