# DIMENSIONS OF PSYCHOSIS

ELUCIDATING THE SUBCLINICAL SPECTRUM USING NEUROIMAGING MARKERS

## INAUGURAL-DISSERTATION

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**TABLE OF CONTENTS**

## 1. LIST OF ACRONYMS

| | |
|---|---|
| ARMS | at-risk mental health state |
| BLIPS | brief limited intermittent psychotic symptoms |
| CAPE | Community Assessment of Psychic Experiences |
| CEN | central executive network |
| CHR | clinical high-risk |
| DLPFC | dorosolateral prefrontal cortex |
| DMN | default mode network |
| GABA | γ-aminobutyric acid |
| GMV | grey matter volume |
| IQ | intelligence quotient |
| MDD | major depressive disorder |
| MTL | medial temporal lobe |
| NMDAR | N-methyl-D-aspartate receptor |
| PLE | psychotic-like experiences |
| PQ-16 | Prodromal Questionnaire (16-item version) |
| PRS | polygenic risk score |
| ROI | region of interest |
| SBM | surface-based morphometry |
| SN | salience network |
| STG | superior temporal gyrus |
| UHR | ultra-high risk |
| VBM | voxel-based morphometry |
| WM | working memory |

# 1. INTRODUCTION

## 1.1. Concept of a continuous spectrum of psychosis phenotypes

The formulation of psychotic illness developed during the 19th and 20th centuries (Berrios & Beer, 1994; Franzek & Musalek, 2009). Kraepelin's nosology of the major psychotic disorders has shaped clinical practice, seeing a continuation of his model's relevance to contemporary practice (Angst & Gamma, 2008). Later Eysenck's theory of personality recognised *psychoticism* as a trait dimension of its own (Eysenck, 1952), reflecting the notion of a continuous distribution of natural phenotypic variations with psychotic illness representing the extreme end (Grant, Green, & Mason, 2018). Although categorical models included increasingly diverse observations of psychotic phenotypes over time (Angst, 2002; Beer, 1996), efforts to deconstruct psychotic (Gaebel & Zielasek, 2008), and psychiatric diagnoses in general (Insel et al., 2010), still prevail today. Psychosis phenotypes show variable stability (fluctuating states and enduring traits) and severity over time. Early psychosis detection by clinician assessment (e.g., McGlashan et al., 2010; Yung et al., 2005) aims to capture variations in state and trait phenotypes, which still require characterisation based on biological and ultimately aetiological underpinnings. For instance, some transient psychosis risk syndromes, e.g., brief limited intermittent psychotic symptoms (BLIPS) describe peak psychotic states of short duration (relative to frank psychosis) (Schultze-Lutter et al., 2015), while *schizotypy* is an arrangement of personality traits that may decompensate into psychosis under given circumstances (Kwapil & Barrantes-vidal, 2015; Nelson, Seal, Pantelis, & Phillips, 2013).

The psychopathological phenomena defining psychotic states include positive (hallucinations and delusions), negative, and disorganised features (American Psychiatric Association, 2013). In the clinical spectrum, phenotype heterogeneity has ushered increased attention to expressions of symptom dimensions (Barch et al., 2013). Evidence for differential relations between symptom dimensions and clinical outcomes (Fulford et al., 2013; Woodward et al., 2014) support the assumption that they may constitute independent risk factors producing additive illness effects (Allardyce, Suppes, & van Os, 2007). In a comparison between psychosis diagnostic groups, symptom dimensions significantly explained clinical characteristics beyond diagnosis alone (Dikeos et al., 2006), and genetic overlap between diagnoses of psychotic disorders among family lineages suggests common underlying disease mechanisms (Tamminga et al., 2013).

There is ample evidence suggesting that positive, negative, disorganised, and affective symptoms prevail in the general population (e.g., Stefanis et al., 2002). Experiences from the positive symptom dimension, such as auditory verbal hallucinations (Baumeister,

Sedgwick, Howes, & Peters, 2017), and paranoid ideation (Bebbington et al., 2013) are found in healthy individuals. These findings suggest that different dimensions of psychosis phenotypes do not pertain to clinical thresholds, as they are not associated with a need for care. Thus, dimensional psychotic phenomena are not restricted to distinctive illness categories, allowing these phenotypes to exists on a spectrum from health to illness (Guloksuz & van Os, 2018) and across psychopathological diagnoses (Reininghaus et al., 2019). This assumption permits investigations of psychosis phenotypes and their aetiology outside of clinical entities.

The *continuum hypothesis* of psychosis proposes a continuous distribution of latent psychotic phenotypes in the general population (Johns & van Os, 2001; Verdoux & van Os, 2002). A meta-analysis by Linscott and van Os (2013) suggested a 7.2% prevalence of psychotic experiences among nonclinical individuals, and in 20% of cases these experiences continue to persist. In 7.4% with baseline psychotic experiences, these were associated with a development of need for care i.e., psychotic disorder. The authors concluded that the prevalence of psychotic experiences exceeds that of psychotic disorders in the general population estimated at ca. 3% (Perälä et al., 2007). Related to the elevated expression of subclinical psychotic symptoms, or psychotic-like experiences (PLE), is the variability of individual stable traits in the population.

Schizotypy is a framework that unifies enduring traits and characteristics that convey a latent liability for schizophrenia (Barrantes-Vidal, Grant, & Kwapil, 2015; Cohen, Mohr, Ettinger, Chan, & Park, 2015; Grant et al., 2018). Models of schizotypy disagree on whether schizotypy is mental illness-based (taxonic and quasi-dimensional; Meehl, 1962) or extends into fully normal (healthy) continuity at the personality level (Claridge & Beech, 1995; for an overview see Grant et al., 2018). Regardless, schizotypy is now generally considered a suitable *endophenotype* of schizophrenia liability (Gottesman & Gould, 2003; Grant et al., 2013; Lenzenweger, 2006). Hence, schizotypy contributes to the contemporary quest for aetiological models of schizophrenia and psychosis (Barrantes-Vidal et al., 2015). This aim also ties in with the overall U.S. National Institute of Mental Health Research Domain Criteria framework (Barrantes-Vidal et al., 2015; Cohen et al., 2015), promoting dimensional approaches in biological psychiatry.

Other intraindividual attributes that may alter the course of nonclinical psychotic phenotypes include (but are not restricted to) cognitive disturbance (Brett, Peters, & McGuire, 2015), the persistence of subclinical PLE (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009) distress (Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005), and personality factors (Alminhana, Farias, Claridge, Cloninger, & Moreira-Almeida, 2017; Barrantes-Vidal, Ros-Morente, & Kwapil, 2009). These observations align with the notion that distinctions between healthy and clinical psychosis phenotypes

are related to quantitative rather than qualitative differences in experiences and behaviours (Johns & van Os, 2001). Thus, a continuous psychosis spectrum also encourages the investigation of mediating and moderating determinants of phenotype trajectories without the constraints of qualitative boundaries. Such relationships may help to determine predictors of later at-risk mental health states (ARMS).

### 1.2. Neurobiological correlates of psychosis phenotypes

As psychotic phenotypes and symptoms unfold over time, they may do so on a biological level, too. Accumulating epidemiological evidence for the psychosis continuum together with genetic and neuroimaging investigations of psychosis prone phenotypes emerged within the last decades (Taylor, Calkins, & Gur, 2020). The conceptualisation of elevated prodromal syndromes has made valuable contributions to the field of early detection and intervention in psychosis. State of the art clinical and biological psychiatry has focused on formulating prodromal stages for the examination of transition to psychosis (McGorry, Hartmann, Spooner, & Nelson, 2018; Schultze-Lutter et al., 2015). This has led to a notable rise of structural and functional imaging studies with individuals meeting clinical (CHR) and ultra-high risk (UHR) for psychosis criteria (Borgwardt, McGuire, & Fusar-Poli, 2011; Fusar-Poli, Radua, McGuire, & Borgwardt, 2012). Structural brain changes associated with psychosis risk typically include grey matter volume (GMV) reductions in temporolimbic and prefrontal regions (Fusar-Poli et al., 2012). More specifically, volumetric decrease of the hippocampus is consistently found in schizophrenia patients (Adriano, Caltagirone, & Spalletta, 2012; van Erp et al., 2016) and demonstrated in schizophrenia genotypes (Harrisberger et al., 2016). The search for psychosis biomarkers is becoming increasingly important in the advent of machine-learning methods in psychiatry (de Wit et al., 2017; Fusar-Poli et al., 2019; Koutsouleris et al., 2012).

Using analysis of cortical volumes based on voxel-based morphometry (VBM) (Ashburner & Friston, 2000), transient changes may be captured, making VBM sensitive enough to detect brain structural deviations in clinical and nonclinincal phenotypes using cross-sectional and longitudinal designs. In healthy individuals, VBM correlates of schizotypal traits were reported in prefrontal regions (Nenadić, Lorenz, et al., 2015) and regions relevant to the frontostriatal system (Ettinger et al., 2012; Meller, Ettinger, Grant, & Nenadić, 2019; Pfarr & Nenadić, 2020). Additionally, regional volume enlargements of the precuneus in the parietal lobe were replicated in several previous investigations in nonclinical psychosis phenotypes (Meller, Schmitt, et al., 2020; Modinos, Egerton, McLaughlin, et al., 2018; Modinos et al., 2010). Twin studies uncover a liability for significant progressive volume changes among unaffected co-twins of schizophrenia patients (Brans et al., 2008). Brain volume also showed susceptibility towards

environmental risk factors for psychopathology, such as lower socioeconomic status and traumatic stress events (Gur et al., 2019). Volume reductions differ across prodromal and first episode stages (Bartholomeusz et al., 2017), and transition status in high-risk individuals (Smieskova et al., 2010). Neurodevelopmental aberrances may explain these converging findings from neuroimaging studies. Two time periods with a pivotal impact on psychotic trajectories through prefrontal neurodevelopment have been proposed: the early and gestational prenatal stages followed by adolescence (Selemon & Zecevic, 2015). Pantelis et al. (2005) suggested that psychotic vulnerability may render the brain particularly vulnerable to anomalous postpubertal neurodevelopment, indicated by accelerated prefrontal GMV loss. Transition to psychotic illness may entail neurodegenerative processes involving medial temporal and orbital prefrontal regions (Pantelis et al., 2005). Critical developmental periods may also exist for stress responsiveness (Grace & Gomes, 2019).

A limitation to VBM is the unknown extent of to which results are confounded by antipsychotics (Fusar-Poli et al., 2011) or illness factors (Owens et al., 2012) typically found in patients. Cortical surface parameters are therefore useful complementary approaches for neurobiological characterisation. This includes morphometry of cortical thickness and gyrification i.e., the folding pattern of gyri and sulci across the cortex (Zilles, Palomero-Gallagher, & Amunts, 2013). Cortical thickness differences in psychosis are linked to environmental risk factors such as urban upbringing (Besteher, Gaser, Spalthoff, & Nenadić, 2017) and developmental trauma and cannabis exposure (Habets, Marcelis, Gronenschild, Drukker, & van Os, 2011). Effects of environmental and genetic influences on cortical thickness also emerge for healthy psychosis phenotypes (Córdova-Palomera et al., 2014). These relationships seem to indicate aetiological gene×environment interactions that may be uncovered using different morphometric parameters. The largest share of cortical folding occurs during early human neurodevelopment. Starting around the 16$^{th}$ ontogenetic week, folding then surges dramatically in the period between the late second trimester and postnatal week 78, when the maximal gyrification index exceeds adult levels (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995). Surface-based morphometry (SBM) of cortical gyrification (Luders et al., 2006; Schaer et al., 2012) can give insight to anomalies during the early phase of brain morphological organisation and relationships with psychopathology (Nenadić, Maitra, Dietzek, et al., 2015; Spalthoff, Gaser, & Nenadić, 2018). A study of lifetime gyrification trajectories showed that overall cortical gyrification indices in normal development and aging were low in adulthood, accompanied by a low decrease rate (Cao et al., 2017). That study also showed deviation in gyrification trajectories in different diagnostic groups compared to healthy controls in adulthood, indicative of altered brain

aging in psychopathology.

In summary, cross-sectional, longitudinal, genetic, and neuroimaging studies reflect a research stream that aims to characterise psychosis phenotypes on a wider spectrum outside of clinical nosology. By aiming to derive biomarkers in combination with extensive psychiatric genotypes these efforts facilitate the achievement of overarching mental health goals in the era of precision psychiatry (Fernandes et al., 2017; Gifford et al., 2017). A prerequisite to these developments includes expanding the amount of investigations in subclinical psychosis phenotypes, thereby filling in the gaps along the psychosis continuum. Thus, the overall purpose of this dissertation is to combine different brain morphological and phenotypic parameters to address the lack of imaging studies in this field.

## 1.3. Research aims and hypotheses

Collectively the presented studies focus on the healthy section of the psychosis continuum. Using neurobiological, psychological and endophenotypic parameters, three studies presented in this dissertation aim to investigate psychosis phenotype diversity. Neurobiological correlates are examined using a set of different models. For this purpose of these objectives, the following hypotheses were examined:

**Hypothesis 1:** Dimensional psychosis phenotypes are differentially associated with cortical gyrification in prefrontal, parietal, and precuneus regions. Associations between psychosis phenotype dimensions and regional cortical gyrification are mediated by cognition, which acts as an intermediate phenotype of psychosis liability.

**Hypothesis 2:** Elevated subclinical psychosis phenotypes are negatively correlated with regional brain volumes, especially in regions implicated in schizophrenia. These associations are modulated by the severity of distress related to positive psychotic-like experiences.

**Hypothesis 3:** The effect of subclinical psychosis phenotypes on medial temporal lobe (MTL) structures, an area implicated in the pathophysiology in schizophrenia, differs between dimensions of stable psychosis phenotypes (traits), psychotic-like experiences, and their interaction.

## 2. SUMMARY OF STUDY RESULTS

### 2.1. **STUDY 1.** Cortical gyrification, psychotic-like experiences, and cognitive performance in nonclinical subjects.

Evermann, U. Gaser, C., Besteher, B., Langbein, K., & Nenadić, I. (2020). Cortical gyrification, psychotic-like experiences, and cognitive performance in nonclinical subjects. *Schizophrenia Bulletin*, *46*(6), 1524–1534. DOI: https://doi.org/10.1093/schbul/sbaa068

Clinical phenomenology shows limited success in the identification of psychosis biomarkers (Hager & Keshavan, 2015). Endophenotypes, or intermediate phenotypes, provide a powerful alternative tools for biological psychiatry (Gottesman & Gould, 2003; Insel & Cuthbert, 2009). These neurophysiological and neurocognitive parameters (Myles, Rossell, Phillipou, Thomas, & Gurvich, 2017; Siever & Davis, 2004; Thaker, 2008) tap into psychosis genotypes, eliminating the limitations associated with the boundaries of clinical syndromes. Cognitive deficits constitute one of the core symptom categories of schizophrenic disorders (Kahn & Keefe, 2013). Cognitive (dys)function in patients is related to illness duration and negative symptoms (Ito et al., 2015). Comparisons have shown that several domains including executive function, working memory (WM), and verbal fluency are consistently affected across the psychosis phenotype spectrum (Hou et al., 2016; Ivleva et al., 2012; Siddi, Petretto, & Preti, 2017), including individuals with a familial liability for schizophrenia (Gur et al., 2007). Furthermore, a neurodevelopmental model of schizophrenia is supported by findings suggesting that cognitive impairment also predates the clinical presentation of psychosis (Bora & Murray, 2014; Sheffield, Karcher, & Barch, 2018). Hence it may be expected that cognitive deficits indicative of prefrontal changes (Baker et al., 2019) are also linked to cortical gyrification (Docherty et al., 2015). Prefrontal gyrification deficits were present in bipolar and schizophrenia patients, which were also associated with measures of WM and intellectual function in the former group (McIntosh et al., 2009). A positive association between general cognitive ability and gyrification in prefrontal and parietal regions was shown in healthy subjects (Gregory et al., 2016). Another study using the gyrification index method (Schaer et al., 2012) has found a positive association between cortical gyrification and both cortical volume and WM performance (Gautam, Anstey, Wen, Sachdev, & Cherbuin, 2015).

A part of the research questions addressed in Study 1 was especially influenced by findings from previous genetic studies (Toulopoulou et al., 2015, 2019) which modelled the causal role of cognition on the pathway to schizophrenia liability. Their results from both twin study (Toulopoulou et al., 2015) and polygenic risk score (PRS) (Toulopoulou et al., 2019) approaches suggested that the effect of genetics on schizophrenia risk passes partially through cognition. Instead of PRS or other genetic risk estimates, cortical

gyrification was implemented as a promising potential endophenotype (White & Gottesman, 2012). Firstly, it indexes early neurodevelopment and aberrances thereof, for example, prematurity impacting adult intelligence quotient (IQ) (Hedderich et al., 2019), and secondly, it is associated with psychosis genotypes (Liu et al., 2016). The general objective of Study 1 was to examine associations between different dimensions of psychotic-like experiences (PLE) assessed by the Community Assessment of Psychic Experiences (CAPE, Stefanis et al., 2002) and cortical gyrification, and whether some variance in PLE dimension explained by regional cortical gyrification passes through estimated cognitive performance. For this purpose, we analysed cortical gyrification using whole-brain vertex-wise mean curvature-based method (Luders et al., 2006).

The findings of Study 1 partially confirmed the predictions. In summary, the pattern underlying the results suggested overall negative phenotype-gyrification relationships, regional differences between PLE dimensions, and specificity for CAPE scales measuring PLE distress rather than PLE frequency (for which there were no relationships). In mediation models predicting PLE by regional gyrification, the pathway through cognition was nonsignificant. The statistically significant clusters were located in the left precuneus and right supramarginal to superior temporal gyrus (and a trend towards significance in the left inferior gyrus). A study in schizophrenia patients showed peak hypogyrification differences in the right precuneus and left supramarginal gyrus (Nesvåg et al., 2014). Hypergyrification of the right temporal lobe in patients with first-episode schizophrenia (Harris et al., 2004), and the prefrontal and left parietal cortices in schizotypal disorder (Sasabayashi et al., 2020) have also been reported. Hence, the parietal and temporal clusters partially converge with neuroanatomical regions showing abnormalities in the schizophrenia spectrum (Matsuda & Ohi, 2018). Assuming increasingly distressed states accompany vulnerability (Hanssen, Bak, et al., 2005), isolated effects of the distress scale in these areas suggest varying degrees of vulnerability among psychosis prone phenotypes.

A cluster within the right supramarginal, postcentral, insular, transverse temporal, and superior temporal regions was associated with depressive PLE. In light of previous findings supporting alterations in superior temporal gyrus (STG) gyrification using comparable morphometric methods (Besteher, Gaser, Langbein, et al., 2017; Schmitgen et al., 2019) there may be transdiagnostic indications attached to this finding. Temporal lobe pathology in psychosis is implicated in the course of illness (Takahashi et al., 2009) and may also result from genetic influences on neurodevelopment in psychopathology (Schork et al., 2019). This supports the impetus of studying neurodevelopmental markers across heterogeneous symptom domains, as findings from cortical gyrification in major depressive disorder (MDD) and psychosis are partially convergent regarding

neuroanatomical location. Study 1 provides partially consistent evidence in nonclinical subjects.

A lack of (false discovery rate corrected) significant correlations between CAPE dimensions and neuropsychological measures suggests that cognitive deficits were too small to exert an effect on this pathway. Some common aetiological factor(s) might underlie all three parameters, and/or their influence on each other. The collective magnitude of effects, including cognitive deterioration, may reach a threshold in the clinical spectrum. A possibility proposed by Toulopoulou et al. (2019) states that genetic risk may first put cognition at increased risk for deficiency through several ways involved in neurodevelopment and may again contribute to symptom deterioration at a later point in time.

In summary, Study 1 showed that positive and depressive subclinical PLE are negatively associated with gyrification of precuneus and supramarginal/temporal regions, respectively. Predicting positive or depressive PLE from regional gyrification was not significantly mediated through cognition. We propose that cognitive deficits may explain brain-behavioural relationship in increasingly vulnerable individuals with PLE and cortical aberrances of temporal regions are not psychotic per se but could signify general psychosis proneness or psychopathological vulnerability in the psychosis continuum.

### 2.2. **STUDY 2.** Distress severity in perceptual anomalies moderates the relationship between prefrontal brain structure and psychosis proneness in nonclinical individuals.

Evermann, U., Schmitt, S., Meller, T., Pfarr, J.-K., Grezellschak, S., & Nenadić, I. Distress severity in perceptual anomalies moderates the relationship between prefrontal brain structure and psychosis proneness in nonclinical individuals. (Manuscript submitted).

In clinical practice, two-stage assessments (screening followed by standardised interviews) enhance discrimination between transient PLE and at-risk psychosis phenotypes (Addington, Stowkowy, & Weiser, 2015; Kline & Schiffman, 2014; Savill, D'Ambrosio, Cannon, & Loewy, 2018). In specialised care settings, some information may be especially useful to clinicians in this process, including affective symptoms (Falkenberg et al., 2015) and distress associated with PLE (Hanssen, Bak, et al., 2005). As previously seen in Study 1, distress is significantly associated with cortical surface morphology. In Study 2, we attempted to combine information from a low-level screening instrument (16-item Prodromal Questionnaire, PQ-16) (Ising et al., 2012) with brain structure to investigate this incongruence further. In addition to the overall PLE-level, we also aimed to investigate whether distress level associated with specific types of PLE would influence such relationships. With this objective, distress serving as an indicator

of PLE appraisal was considered a moderator to brain-phenotype relationships. In Study 2, it was shown that PLE level, but not PLE distress severity, was associated with regional brain structure. PLE total scores from the PQ-16 were associated with larger GMV in prefrontal, occipital fusiform, and lingual regions, while distress severity was not a significant estimator for GMV. Based on the positive PLE-brain structure relationship revealed through regression analysis, regional volumes extracted from the right superior and middle frontal gyri were targeted. These regions of interest (ROIs) were consistent with previous findings, which suggest that the dorsolateral prefrontal cortex (DLPFC) is repeatedly taxed in psychosis (Nenadić, Maitra, Langbein, et al., 2015; Wojtalik, Smith, Keshavan, & Eack, 2017). The PQ-16 assesses positive PLE but also contains two negative items (Ising et al., 2012). To specify distinctive dimensional regressors, the positive items were categorised into 'delusional' and 'perceptual abnormalities' components, which yielded two novel continuous subscales to be used for ROI volume estimation. Testing these two moderators showed that the PLE×perceptual abnormalities distress scale interaction was statistically significant in the regional brain volume of the right superior frontal gyrus, and marginally significant in the right middle frontal gyrus model ($p$=0.06). Distress severity for items conveying unusual thought content/delusional ideas did not moderate PLE associations with either ROI.

Contrary to predictions, the positive relationship adds to previous studies in nonclinical cohorts that evidence larger volumes at higher PLE expressions (Nenadić, Lorenz, et al., 2015), rather than volume reductions (Ettinger et al., 2012; Pfarr & Nenadić, 2020; Satterthwaite et al., 2016; Wang et al., 2015). One possible explanation for these inconsistencies in nonclinical phenotypes may relate to transitory PLE and stable (trait) phenotype estimator effects, or more specifically, the multidimensional structure of psychometric schizotypy and PLE. The positive dimension of the Multidimensional Schizotypy Scale (Kwapil, Gross, Silvia, Raulin, & Barrantes-Vidal, 2018) showed negative associations in the same regions of the dorsolateral prefrontal cortex (DLPFC) (Pfarr & Nenadić, 2020) as the PQ-16 of Study 2. However, only schizotypy was also associated with volume reductions in the anterior cingulate gyrus. On the other hand, PLE were uniquely correlated with volume of occipitotemporal gyrus, unparalleled in multidimensional schizotypy.

As in Study 1, Study 2 utilised an instrument that gauges distress severity in addition to overall PLE load. Building on the findings from Study 1 and volumetric studies (Modinos et al., 2010; Nenadić, Lorenz, et al., 2015; Suzuki et al., 2005), Study 2 investigated whether distress severity modulates brain structural associations with PLE. Thus, Study 2 contributes to the literature by elucidating prefrontal volume variation as a function of other additional attributes associated with psychopathology.

In short, the aim of Study 2 was an investigation of brain structural change in response to low-level PLE, which may be associated with elevated psychosis risk (CHR states) once a clinically meaningful threshold is surpassed. Defining a continuous subclinical phenotype across a preselection criterion threshold showed differential structural associations for the subclinical symptom level (overall screening score) not replicated for the distress level. Increased distress severity associated with perceptual PLE reduced the strength of the positive relationship between GMV and PLE in one of the DLPFC regions. These findings provide neurobiological evidence in keeping with cognitive interpretative models of psychosis (Brett, Heriot-Maitland, McGuire, & Peters, 2014; Brett, Johns, Peters, & McGuire, 2009; Underwood, Kumari, & Peters, 2016), suggesting that subjective interpretations of PLE mark shifts in vulnerability profiles. Furthermore, prefrontal correlates may be associated with compensatory mechanisms protecting individuals with psychosis proneness.

### 2.3. **STUDY 3.** Nonclinical psychotic-like experiences and schizotypy: interactions and differential associations with hippocampal subfield and amygdala volumes.

Evermann, U., Gaser, C., Meller, T., Pfarr, J.-K., Grezellschak, S., & Nenadić, I. Nonclinical psychotic-like experiences and schizotypy: interactions and differential associations with hippocampal subfield and amygdala volumes. (Manuscript submitted).

Phenotype heterogeneity (Cowan & Mittal, 2020; Fusar-Poli et al., 2016; Seiler, Nguyen, Yung, & O'Donoghue, 2020) complicates research within the psychosis continuum. Several classifiers may aid in understanding potentially clinical trajectories in nonclinical phenotypes. Endurance of PLE underlies clinical outcomes (Dominguez, Wichers, Lieb, Wittchen, & van Os, 2011; van Os et al., 2009), and this persistence itself is influenced by further factors including stress reactivity (Collip et al., 2013) and insomnia (Reeve, Nickless, Sheaves, & Freeman, 2018). However, monitoring occasional PLE for their persistence would require thorough longitudinal assessments. On the other hand, the schizotypy framework provides stable personality traits beyond but also closely related to the emergence of PLE (Fonseca-Pedrero & Debbané, 2017; Kwapil et al., 2020). More lodged within the medical tradition of thought (Claridge, 2015), the first conceptualisation of the *schizo*phrenic pheno*type* i.e., *schizotypy* by Rado (1953), describes schizophrenia-like characteristics below the threshold that would distinguish clinical diagnoses. According to the fully dimensional model of schizotypy stemming from the individual differences and personality perspective (Claridge, 2015), schizotypy is a normal and adaptive personality variation that results in dysfunction at the extreme end representing illness.

Study 3 adopted the fully dimensional view of schizotypy and definitions by other authors who propose that schizotypy constitutes stable traits, while PLE are unstable states adhering to a symptoms-based approach (Debbané & Barrantes-Vidal, 2015; Fonseca-Pedrero & Debbané, 2017). Furthermore, it has been suggested that PLE "…like overt psychotic symptoms, can be thought of as manifestations of positive schizotypy" (Barrantes-Vidal et al., 2015, p. S409). The contribution of state and trait phenotypes to subclinical psychosis symptoms also differs across the lifespan (Rössler, Hengartner, Ajdacic-Gross, Haker, & Angst, 2013), suggesting that their peak influences do not necessarily overlap. However, PLE are especially connected to the positive dimension of schizotypy and reflect temporal states in response to exogenous or endogenous events (Barrantes-Vidal et al., 2015).

The aim of Study 3 was to combine trait phenotypes and PLE as estimators for brain structural variation. Since the schizotypy and PLE levels within nonclinical cohorts are expectedly small, a reliable structural outcome measure would be required to increase sensitivity to estimator effects. In schizophrenia, volume abnormalities are replicated in the hippocampus (van Erp et al., 2016), and such reductions already ensue during the prodromal stages of psychosis (McHugo et al., 2018; Walter et al., 2012). In a previous study, we showed that an interaction between schizotypy (negative×disorganised) dimensions explains left anterior and whole hippocampal volume variability, implying that volume is significantly reduced in individuals with high trait expressions on both schizotypy dimensions (Sahakyan et al., 2020). This finding in the so-called extended psychosis phenotype (van Os & Linscott, 2012), together with evidence from high-risk and clinical individuals (McHugo et al., 2018), supports an anterior to posterior gradient of hippocampal volume reduction in psychosis. Thus the anterior to posterior spread of hippocampal deterioration originating in the CA1 subregion is thought to indicate a pathophysiological process (Schobel et al., 2013).

Building on this and a prior study investigating schizotypy only (Sahakyan et al., 2020), MTL structures were chosen. More specifically, this included volumetric estimations of amygdala and hippocampus subfield volumes. Along its longitudinal axis, the hippocampus may be partitioned into the dentate gyrus (DG), cornu ammonis (CA) subdivisons (1-4), subiculum, as well as the stratum radiatum, lacunosum and moleculare (Winterburn et al., 2013). Clinical studies mostly show negative associations between positive (Kühn et al., 2012; Mathew et al., 2014) and negative symptom dimensions (Haukvik et al., 2015; Kawano et al., 2015) and volumes of hippocampal subfields. In Study 3, outcomes were predicted based on these dimensional findings and translated to the four trait dimensions found in schizotypy (Mason & Claridge, 2006; Mason, Claridge, & Jackson, 1995).

The outcomes of Study 3 partially supported the predictions. Trait facets, rather than presumably transient signs of psychosis proneness, significantly explained hippocampal volume variance. It was shown that once all four schizotypy dimensions are entered together with the PLE scale as estimators for five left (uncorrected) and right (corrected for multiple comparisons) hippocampal subfield and amygdala volumes, left subicular and amygdala reductions were significantly explained by trait dimensions only. The approach utilised in Study 3 revealed that trait (positive and impulsive) psychosis phenotypes differentially relate to left subiculum – and partially amygdala - volumes following the longitudinal axis.

# 3. DISCUSSION

The overarching aim of these studies was to contribute neurobiological markers of nonclinical psychosis phenotypes. Building on evidence from the *continuum hypothesis* (Verdoux & van Os, 2002) at the phenotype level, and clinical neuroimaging studies, it was expected that symptom dimensions would result in correlates indicative of a neurobiological continuum. Study 1 examined the relationship between cognitive endophenotypes and a cortical marker of neurodevelopment in dimensional psychosis phenotypes. The findings showed that subclinical phenotypes are associated with regional gyrification reductions. However, prediction of PLE distress by regional gyrification was not mediated through IQ or global cognitive performance, therefore results only partially confirmed hypothesis 1. Study 2 revealed an association between larger regional volumes and PLE, which was contrary to predictions. The modulating effect of positive PLE distress levels on this relationship in two DLPFC regions was present for perceptual but not delusional components in one of these regions. Hence, hypothesis 2 was partially confirmed. Study 3 showed that variation in MTL structures is explained by some specific dimensions of schizotypy rather than PLE, confirming hypothesis 3 to some extent. The overall conclusion is that different subclinical psychosis phenotypes of variable endurance and quality are associated with regional cortical and variation. Furthermore, there was some evidence for modulatory relationships between state and trait psychosis phenotypes. In the following section, these findings will be integrated with each other and the wider literature starting with a brain systems perspective. Finally, an outlook on potential clinical applications and psychosis continuum models will be provided.

## 3.1. Brain networks across the psychosis continuum

### 3.1.1. Frontoparietal network regions

SBM and VBM correlates of subclinical psychosis phenotypes were found in frontal, temporal, parietal, and medial temporal regions. In non-psychiatric individuals reporting

positive PLE, we found cortical gyrification (family-wise error-corrected $p$=0.08) and structural prefrontal correlates. Brain structural deficits in these regions are supported by findings in functional connectivity. Altered frontoparietal connectivity in psychosis (Lewandowski et al., 2019; Peeters et al., 2015) and ARMS (Schmidt et al., 2014) is thought to underlie typical cognitive deficits. A study differentiating psychosis patients by cognitive impairment showed intrinsic frontoparietal connectivity decreases in both groups compared to controls, and augmented reductions associated with cognitive impairment in the patient comparison (Lewandowski et al., 2019). Additionally, frontoparietal network alterations were shown in nonclinical subjects with PLE but without accompanying cognitive deficits (Fukuda et al., 2019). This implies that network disruptions may be a vulnerability antecedent in psychosis phenotypes before cognitive deficits are detectible. The associations between PLE and inferior prefrontal and precuneus gyrification (Study 1), and DLPFC volume (Study 2) are consistent with frontoparietal network nodes. Another clinical study found differences in frontoparietal and executive control resting-state networks, which entailed reduced connectivity in the left precuneus and increased connectivity in right middle and superior frontal gyri (Wolf et al., 2011). Precuneus correlates also underpin traits in agreement with Claridge's model accounting for the adaptive characteristics in schizotypy (Nelson et al., 2013), including for instance, creativity (Burch, Pavelis, Hemsley, & Corr, 2006; Fink et al., 2014; Takeuchi et al., 2011).

#### 3.1.2. Default mode network and salience network regions

An overlap between structural with functional networks, specifically the so-called triple network model (Menon, 2011), encourages multi-modal neuroimaging approaches to understand psychopathology. Structural (white matter) connections correspond to the functional connectivity occurring in resting-state networks (van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009). In schizophrenia, cortical gyrification connectomes showed regional aberrances in anterior insula and DLPFC (Palaniyappan, Park, Balain, Dangi, & Liddle, 2015), and regional folding reductions in left precuneus and right temporal regions (Study 1) support overlaps with default mode (DMN) and salience network (SN) regions. The DMN encompasses the medial prefrontal cortex, posterior cingulate/precuneus, and temporal cortices, and characterises the intrinsic activity of the brain at rest (Raichle, 2015). Connections between anterior cingulate cortex and the insular cortex, with linkage to the limbic regions, encompass the salience network (Menon & Uddin, 2010). The SN is primarily involved with internal and external stimulus integration while also receiving prefrontal inputs that guide behavioural responses (Palaniyappan & Liddle, 2012). Thus, Study 1 implicates the role of the precuneus as part of the DMN (Utevsky, Smith, &

Huettel, 2014) in individuals with positive PLE. Study 1 also demonstrated reduced gyrification of a cluster consisting of right supramarginal to superior temporal and insular regions associated with depressive PLE. This finding is supported by abnormalities in STG structure (Besteher, Gaser, Langbein, et al., 2017) and gyrification (Schmitgen et al., 2019) in the affective spectrum, and volumetric and functional STG abnormalities in psychosis (Crossley et al., 2009; Pettersson-Yeo et al., 2015; Takahashi et al., 2009). STG dysfunction in early psychosis is paralleled by GMV alterations (Pettersson-Yeo et al., 2015) and the association with cortical gyrification in nonclinical subjects partially supports neuroanatomical consistencies between imaging modalities. Crossley et al. (2009) demonstrated STG deactivation failure during WM tasks, suggesting disrupted frontotemporal connectivity in early (and to an intermediary degree in prodromal) psychosis.

Changes to the SN and DMN systems in psychosis and MDD (Shao et al., 2018) are compatible with the notion that psychopathology operates at the level of larger brain circuitry systems (Menon, 2011). DMN hyperconnectivity and hyperactivity occur in both psychotic and affective psychopathology (Whitfield-Gabrieli & Ford, 2012). Mallikarjun et al. (2018) showed activation of superior temporal and DMN regions during auditory hallucinations, and increased functional connectivity between salience and DMN nodes in first-episode psychosis. SN nodes modulate switching between DMN (deactivation) and central executive network (CEN) (activation) (Sridharan, Levitin, & Menon, 2008). In schizophrenia, SN is dysregulated ( White, Gilleen, & Shergill, 2013), and reduction of SN control on DMN/CEN functional connectivity is also related to hallucinatory severity (Manoliu et al., 2014). Insular dysfunction, which is thought to underlie SN alterations is compatible with the dopamine hypothesis of psychosis (Palaniyappan & Liddle, 2012). SN alterations are present at a transdiagnostic level (Peters, Dunlop, & Downar, 2016), where they are responsible for aberrant salience and emotional appraisal in schizophrenia (Lee et al., 2014) and MDD (Jankowski et al., 2018).

In agreement with this, temporal lobe GMV (Kandilarova, Stoyanov, Sirakov, Maes, & Specht, 2019) and functional alterations (Fitzgerald, Laird, Maller, & Daskalakis, 2008) are found in MDD. STG volume decrease is already present in nonclinical individuals with familial schizophrenia liability (Rajarethinam, Sahni, Rosenberg, & Keshavan, 2004). Thus, one interpretation may constitute that temporal and insular regions are neurodevelopmental points of convergence, or fluidity, between depression and psychosis prone phenotypes. Clinical comorbidity between psychosis and depression further supports this (Hartley, Barrowclough, & Haddock, 2013), paralleled by a frequent accompaniment of depressive symptoms in psychosis prodromal stages (Fusar-Poli, Nelson, Valmaggia, Yung, & McGuire, 2014). Study 1 suggested that temporal lobe

folding correlates overlapping in clinical psychopathologies are partially found in the subclinical dimensions. Together with previous studies (Alloza et al., 2020; Orr, Turner, & Mittal, 2014; Schmidt et al., 2015), this lends strength to the argument that brain network alterations in major psychiatric disorders may also be extendible to nonclinical spectra such as the psychosis continuum.

Accumulating evidence for neuroanatomical correlates dependent on general risk factors (Hibar et al., 2015; Popovic et al., 2020) may explain why mental health outcomes are heterogeneous and insufficiently characterised by diagnoses alone. Developing either psychotic or depressive syndromes is steered by multiple factors that could be both additive and interactive. From an aetiological perspective symptom dimensional overlaps might be explained by some common genetic (Lee et al., 2019; Liu et al., 2020) and/or neurodevelopmental pathways with divergent pathogenesis (Lefebvre et al., 2016) and symptomatic unfolding over time. For example, shared vulnerability such as childhood trauma possibly contributes equally to development and persistence of psychotic and depressive symptoms (van Dam et al., 2015). This is supported by polygenic risk for bipolar disorder, and schizophrenia also associating with depression (Musliner et al., 2019). Expanding this idea, neuroanatomical convergence also supports fluidity between psychoses, from schizophrenia to bipolar disorders and psychotic mood disorders. Findings from within the clinical psychosis continuum show presence of frontoparietal network disruptions in schizophrenia and affective psychosis (Baker et al., 2014), and SN abnormalities in schizophrenia, MDD, and bipolar disorder (Yang et al., 2019). Finally, this would even lend support to continuity within psychoses. After all, overlapping clinical presentations had already brought the late Kraepelin to reconsider his strict dichotomisation of manic-depressive insanity and dementia praecox (Angst & Gamma, 2008). Besides spectra of psychotic and affective disorders, further studies aggregating general psychopathology (Caspi et al., 2014) are required to investigate the extent of parietal and temporal lobe alterations in a broad range of psychiatric diagnoses (Baker et al., 2019; Picó-Pérez, Radua, Steward, Menchón, & Soriano-Mas, 2017; Wise et al., 2017). It must also be noted that frontotemporal or salience and default mode network systems require appropriate analyses of functional activity and network connectivity (e.g., Barber, Lindquist, DeRosse, & Karlsgodt, 2018).

### 3.2. Medial temporal lobe structures and striatal dopamine regulation

The major dopaminergic pathways implicated in the pathogenesis of psychosis include the mesocortical (Dandash, Pantelis, & Fornito, 2017) and mesolimbic (Stahl, 2018) pathways. Howes and Kapur (2009) described presynaptic striatal dopamine dysregulation as the final common pathway to psychosis in schizophrenia, and

importantly, psychosis proneness in general. This is further supported by antisaccade movement changes in schizotypy that indicate striatal dopaminergic alterations in endophenotypes (Ettinger et al., 2005; Thomas et al., 2020). The positive schizotypy dimensions may be an intersection between dopaminergic regulation (Grant et al., 2013; Mohr & Ettinger, 2014) and a general proneness of the striatal and MTL systems also related to the emergence of PLE. Howes et al. (2020) showed that striatal dopamine synthesis capacity increased positive symptoms in CHR individuals and proposed that dopamine fluctuations occurring in at-risk states could drive short-term PLE, but their course (persistence and severity) possibly depends on further dopamine dysregulation.

Next to the mainstay mesolimbic dopamine hypothesis (Stahl, 2018), the glutamate hypothesis has important implications for the prefrontal and MTL structures. A relationship between hippocampal glutamate and striatal dopamine is shown in ARMS (Stone et al., 2010) and first-episode psychosis (Jauhar et al., 2018). Hippocampus structure integrity is sensitive to the general effects of trauma (Logue et al., 2018), and MTL neurotransmitter circuitry is implicated in psychotic deterioration (Fusar-Poli et al., 2020; Lieberman et al., 2018). N-methyl-D-aspartate receptor (NMDAR) hypofunction gives rise to γ-aminobutyric acid (GABA)-ergic interneuron disinhibition, which increases the glutamatergic tone of pyramidal cells leading to allostatic adaption and hippocampal volume reductions over time (Davies et al., 2019; Lisman et al., 2008). The resulting increase in hippocampus pyramidal excitatory activity in turn enhances striatal hyperdopaminergia leading to an attenuated psychotic state (Lisman et al., 2008). This pathophysiological model implicates hippocampal structures as markers of disease progress and encourages new treatment approaches in the CHR states (Davies et al., 2019).

Subclinical psychosis phenotypes also present with changes in corticostriatal connectivity (Dandash et al., 2015; Waltmann et al., 2018) and hippocampal activity (Modinos, Egerton, Mcmullen, et al., 2018; Wolthusen et al., 2018). Modinos et al. (2018) reported increased resting perfusion of the right hippocampus in high schizotypy, but not the midbrain and striatum, suggesting that heightened hippocampal activity is represented on the continuum, but resilience may play a role in nonclinical individuals. Stress is an important contributor to hippocampal overactivity leading to increased midbrain dopaminergic responsivity and striatal dopamine (Grace & Gomes, 2019; Lodge & Grace, 2011; Mizrahi et al., 2012). This also fits in with the model of Howes and Kapur (2009), suggesting that positive psychotic symptoms develop against a backdrop of ‘multiple hits’ (effects of e.g. drugs, stress, genes), which underlines the role of general liability and acute alterations in psychosis proneness. Study 3 provided a detailed investigation of the hippocampal structures in association with trait psychosis

phenotypes and PLE. The findings suggested that hippocampal subiculum variation is distributed on the psychosis continuum, as this occurred as a function of the schizotypy×PLE interaction. In study 2, the interaction of PLE and perceptual PLE distress severity was associated with structural differences in the prefrontal regions, which implicates frontostriatal circuitry (Dandash et al., 2017). The effects of distress severity perhaps indicate a proxy for additional psychopathological processes.

Siever and Davis (2004) outline some compensatory factors that could mitigate the impact of psychosis proneness. For example, temporal deficits are countered by increased prefrontal functional capacity, or reduced subcortical dopaminergic responsiveness buffers against frontal hypodopaminergia. This may also explain the absence of an inverse relationship between general cognitive performance or IQ and psychosis proneness reported in Study 1. A neurodevelopmental vulnerability may be mitigated through spared cognition, which would support the buffering model (Siever & Davis, 2004). Additionally, the results of Study 2 are also in line with a previous study in healthy psychosis prone individuals, showing that general intelligence may confer prefrontal compensation in the frontostriatal system (Meller, Ettinger, et al., 2020).

### 3.3. Using neurobiological markers to unravel phenotypic continuity

At the centre of this dissertation is the question of whether neurobiological markers can depict dimensional subclinical psychosis phenotypes, thereby possibly adding towards a better understanding of the latter. Quantitative changes can explain PLE variation in the population ranging from nonclinical signs to a need for care (Johns & van Os, 2001). Several factors pave the way from unspecific PLE to a need for care in prodromal and clinical syndromes, however this relationship may also be discontinuous (Johns & van Os, 2001). Kaymaz and van Os (2010) commented that the continuum model may be, at least partially, confounded by underlying categorical structures consisting of different groups that vary in e.g., cognitive impairments. In a subsequent meta-analysis they then showed that clinical course is modified by severity and persistence of PLE (Kaymaz et al., 2012). In some PLE linked to a need for care (e.g., nonverbal hallucinations) this association is mediated by distress (Bak et al., 2005). Another study showed quasi-continuous relationships between symptom dimensions, genetic and environmental risk factors, and the severity of psychotic symptoms (Binbay et al., 2012). Binbay et al. (2012) suggested that proxy variables for genetic risk impacted psychosis severity in a non-linear positive way. Environmental factors, such as urbanicity and childhood adversity, showed linear effects, while the non-linear effect of cannabis increased risk in the clinical spectrum.

This idea of a seemingly non-linear trajectory or continuum may also translate to the

neural level. Modifiers were supported by Study 2, where distress severity showed a modulatory effect in the right superior frontal gyrus, and Study 3 demonstrated a state-trait interaction effect on subiculum volume. In the clinical spectrum, neurobiological alterations may not map linearly onto early psychosis staging models (Bartholomeusz et al., 2017). Brain structural findings suggest that temporal lobe pathology in psychosis evolves over time, but early neurodevelopmental vulnerability, such as indicated by cortical gyrification alterations, may already be present beforehand (Pantelis et al., 2005; Selemon & Zecevic, 2015). Other aetiologically relevant factors, such as increased environmental risk (e.g. traumatic life events) may increase psychosis proneness through cognitive and emotional pathways (Gibson, Alloy, & Ellman, 2016). Intact cognitive capacities and emotional well-being may protect nonclinical individuals with persistent PLE, despite trauma history comparable to clinical psychosis in some cases (Peters et al., 2016). Incorporating individualised environmental risk scores (Vassos et al., 2020) may further elucidate multifactorial models. For example, obstetric complications linked to reduced prefrontal gyrification in both schizophrenia and healthy controls indicates shared early influences (Haukvik et al., 2012) but through gene×environment interactions (van Os, Rutten, & Poulton, 2008) or the additive effects of both factors (Mittal, Ellman, & Cannon, 2008), negative neurodevelopmental offsets (Gregory et al., 2016; Hedderich et al., 2019) may increase likelihood of later psychotic illness through cognitive deficits (Toulopoulou et al., 2015). Just as psychotic disorders have substantial polygenic variation (International Schizophrenia Consortium, 2009), environmental factors alone are not sufficient to account for psychotic illness (Gibson et al., 2016; Stilo & Murray, 2019). Based on the reviewed studies in frontoparietal, temporal, and hippocampal regions, there is evidence to assume at least partial continuity at a neurobiological level, but protective factors may explain a share of variability.

### 3.4. Implications for clinical applications and future research

The works of this dissertation suggest that SBM and VBM findings can reflect psychosis proneness. The results support a consistent representation of frontoparietal alterations across the psychosis continuum (Schmidt et al., 2015), which could also serve a clinical utility. For example, frontoparietal activity during cognitive control predicted symptom improvement among patients with recent psychosis onset, which could help to stratify early intervention (Smucny, Lesh, & Carter, 2019). Further studies in the subclinical spectrum could combine persistence (Fonville et al., 2019), distress, and neuroimaging makers to investigate their utility in predicting a need for care.

In Study 2, it was shown that structural DLPFC correlates were modulated by distress

levels for perceptual anomalies but not delusional characteristics. The relationship between positive PLE dimensions may explain this. Hanssen et al. (2005) suggested that increased distress levels associated with perceptual PLE form the antecedent for delusion formation. Follow-up assessments in a large cohort showed that psychosis onset forecasted by hallucinatory experiences was significantly augmented when delusion formation took place over the course of observations (Krabbendam et al., 2004). Compared to the occurrence level, impairing, i.e., distressing PLE, are more densely connected to one another, and paranoia is an important contributor to these relationships (Murphy, McBride, Fried, & Shevlin, 2018).

Thus, there may be several routes through which distress and harm emerges in PLE. A need for care is accompanied by an increased engagement of specifically psychotic appraisals (Lovatt, Mason, Brett, & Peters, 2010). Cognitive appraisals of PLE such as 'caused by others' significantly predict distress increase, while 'spiritual' appraisals predict lower distress (Brett et al., 2014). Perhaps severe cognitive deficits would also associate with maladaptive cognitive appraisals of psychotic symptoms in an additive manner. Brett et al. (2009) reported a relationship between cognitive/attentional deficits and maladaptive metacognitive beliefs about PLE. Furthermore, if depression and psychosis prone individuals share abnormal brain circuitry that relates to the emotional appraisal of internal and external events (Peters et al., 2016), both phenotypes could respond to low-level emotion regulation interventions (Liu, Chan, Chong, Subramaniam, & Mahendran, 2020; Osborne, Willroth, DeVylder, Mittal, & Hilimire, 2017; Picó-Pérez et al., 2017).

Together, these investigations showed that PLE and schizotypy provide elegant analogues to clinical studies as they reduce confounds and inadequate assignments to control groups for failure to recognise liability (Barrantes-Vidal et al., 2015; Grant, 2015). Given the low validity of PLE for the prediction of prodromal syndromes (Schultze-Lutter et al., 2014), neuroanatomical correlates of protective features and resilience are worth exploring in future studies. These may concentrate on potentially modulating factors that may influence the course of clinical significance attached to dimensional trait- or state-based subclinical psychotic experiences.

### 3.5. Limitations and conclusions

A general shortcoming is the use of cross-sectional study designs. The presented studies build on the assumption of a continuum where, for example, PLE transience or longevity would influence long-term clinical outcomes (Dominguez et al., 2011). However, temporal changes can only be addressed using longitudinal designs. With the exception of schizotypy (Study 3), the presented models therefore capture neuroanatomical

correlates of PLE, which possibly represent states of unknown duration. Differences between psychometric assessments of PLE could further lead to some inconsistencies. There is an abundance of psychometric assessments of subclinical psychotic experiences without a unifying terminology for these phenomena (Seiler et al., 2020). Since Study 3 was an enlarged sample of Study 2, a common limitation was a skewed age distribution, which may affect the generalisability of VBM findings (Bora & Baysan Arabaci, 2009). In Study 1, cognition was a nonsignificant mediator of the relationship between regional gyrification and PLE, which may have been explained by neurocognitive invariance between high and low PLE scorers. However, without a subgroup comparison of neurocognitive outcomes, this remains speculative. In schizophrenia, the largest effects for cognitive deficits are observed for verbal memory and WM (Fatouros-Bergman, Cervenka, Flyckt, Edman, & Farde, 2014). Using a global measure of cognitive performance, rather than specific tasks known to produce large effects in case-control comparisons, may also contribute to a potential disguise of mediation effects.

Determining the degree of *psychotic* specificity attributed to dimensional correlates also extending into general psychopathology is methodologically challenging. Modinos et al. (2014) demonstrated neuroanatomical subtypes for GMV reductions in UHR with comorbid depression and anxiety disorders relative to UHR without comorbidity. Subclinical neuroimaging studies may need to consider heterogeneity, e.g., developmental stage or genetic risk (Barkhuizen, Pain, Dudbridge, & Ronald, 2020; Fonville et al., 2019). The inclusion of genotype data, such as PRS, would have arguably strengthened the scope of all three studies. Furthermore, while it could be possible that gyrification correlates for the depressive CAPE dimension in Study 1 were mediated by a general latent vulnerability, the positive CAPE dimension was not associated with gyrification of the temporal and supramarginal regions. Mixed regional hypo- and hypergyrification correlates in MDD and schizophrenia implying some neuroanatomical commonalities in clinical spectra require more elucidation in the subclinical phenotypes. Given the unknown extent of (physiological) commonalities and potentially specific neurodevelopmental trajectories, such tentative speculations require further investigations.

To conclude, three cross-sectional studies provide evidence that subclinical psychotic traits and states possess cortical neuroanatomical correlates. A continuum –although probably not linear in nature– implicates the frontal, parietal, and temporal lobe regions as possible targets for future investigations.

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## 5. SUMMARY

Psychosis unifies a collective of disorders characterised by symptom dimensions (Gaebel & Zielasek, 2015). Purposefully delimited clinical descriptors of schizophrenia spectrum and psychotic disorders (American Psychiatric Association, 2013) impose challenges on the identification of aetiological and clinically meaningful predictors. The disassembly of psychiatric diagnoses into their elementary symptom dimensions has helped formulate psychosis phenotypes fitted on a psychosis *continuum* (Verdoux & van Os, 2002). Aetiological models of psychosis may be studied through schizotypy and transient psychotic experiences (Barrantes-Vidal et al., 2015; Nelson, Fusar-Poli, & Yung, 2012), collectively termed subclinical psychosis phenotypes. The dimensional psychometric structures of these phenotypes varying in temporal stability (Linscott & van Os, 2013; Mason et al., 1995; Stefanis et al., 2002), and their implications might be further consolidated when paired with neuroimaging parameters (Siever & Davis, 2004).

Three neuroimaging studies aimed to examine the relationship between subclinical psychotic phenotypes and neurobiology. Surface and volume-based morphometric (VBM) methods were implemented to examine the variety of cortical and subcortical signatures of different phenotype dimensions. Study 1 investigated whether cortical surface gyrification –a maker of genetic and developmental influences on cortical morphology (Docherty et al., 2015; Haukvik et al., 2012)– is associated with dimensional psychosis prone phenomena (Konings, Bak, Hanssen, van Os, & Krabbendam, 2006; Stefanis et al., 2002). Early cortical organisation contributes to cognitive capacities in later life (Gautam et al., 2015; Gregory et al., 2016; Papini et al., 2020). Given that cognitive deficits are present in psychosis prone and clinical samples to varying extents (Hou et al., 2016; Siddi et al., 2017), Study 1 also explored the mediating role of cognition (both as a general measure and intelligence quotient) as a psychosis endophenotype in the relationship between regional gyrification and PLE distress. Study 2 and Study 3 used VBM to investigate structural brain correlates for psychotic-like experiences (PLE) and trait psychosis phenotypes (schizotypy). Different PLE facets (quantity and distress severity) (Hanssen, Bak, et al., 2005; Ising et al., 2012) were used to estimate whole-brain grey matter volume, followed by interaction models in subsequent prefrontal regions of interest (Study 2). The medial temporal lobe includes the hippocampal subfields, which are regions of interest in psychosis pathophysiology (Lieberman et al., 2018; Mathew et al., 2014; Schobel et al., 2013). Based on a previous study in schizoytypy (Sahakyan et al., 2020), Study 3 examined the relationship between schizotypal trait dimensions (Mason et al., 1995) and PLE, and their interactions, and hippocampal subfields and the amygdala.

The results of Study 1 showed that psychometrically assessed PLE were associated with reduced gyrification in parietal and temporal regions, indicating that psychosis proneness correlates with neurodevelopmental factors (Fonville et al., 2019; Liu et al., 2016). A lack of mediating pathways between regional gyrification and PLE suggested that cognition effects may emerge in larger samples (Mollon et al., 2016) and/or increasingly psychosis pone phenotypes. Elaborating on the distinction between PLE quantity versus distress, Study 2 showed that PLE load, but not distress severity, were associated with volume increases in prefrontal and occipitotemporal regions. At increased distress severity for perceptual abnormalities, PLE were associated with regional volume reductions of the superior frontal gyrus. Study 3 showed differential relationships between schizotypy dimensions and volumes of the MTL that are involved in the pathophysiology of schizophrenia. PLE *per se* did not associate with amygdala or hippocampal subfield volumes, but a positive association between the hippocampal subiculum and PLE was moderated by positive schizotypy. Study 3 underscored the enhanced usefulness of schizotypy as an endophenotype in psychosis research when its multidimensional organisation (Grant, 2015; Vollema & van den Bosch, 1995) is respected.

The results support the use of psychosis symptom dimensions, showing different (positive and negative) neuroanatomical associations. While case-control studies in schizophrenia show consistent volume reductions of the prefrontal and temporal cortices (Haijma et al., 2013; Honea, Crow, Passingham, & Mackay, 2005), these findings contribute to more heterogeneous volumetric relationships in nonclinical individuals. Reduced regional cortical gyrification proposes a continuous distribution of neurodevelopmental impacts. Distress severity and schizotypy occasioned modulatory effects in prefrontal and hippocampal subfield volumes, respectively. Collectively, these three cross-sectional studies extend previous research suggesting that dimensional phenotypes show neuroanatomical variation supportive of a psychosis continuum possibly characterised by an underlying non-linearity (Bartholomeusz et al., 2017; Binbay et al., 2012; Johns & van Os, 2001).

# 6. ZUSAMMENFASSUNG

Unter dem Sammelbegriff der Psychosen versteht sich eine Gruppe von Störungen mit vielfältigen Symptomen (Gaebel & Zielasek, 2015). Fall-Kontroll-Studien untersuchen anhand kategorialer Diagnosen (American Psychiatric Association, 2013) neurobiologische Veränderungen einhergehend mit psychotischen Erkrankungen. Im dimensionalen Krankheitsverständnis beruht die Bezeichnung klinischer Phänotypen auf der Annahme eines Kontinuums unterschiedlicher Symptome (Stefanis et al., 2002; Verdoux & van Os, 2002). Dieser dimensionale Ansatz kann das Auftreten psychotischer Merkmale bei Gesunden erklären und gleichzeitig zur erweiterten Erforschung ätiologischer Modelle genutzt werden (Barrantes-Vidal et al., 2015; Nelson et al., 2012). Zu den subklinischen Phänotypen gehören einerseits stabile Merkmale wie schizotype Traits (Mason et al., 1995), so wie vermeintlich transiente psychose-nahe Erlebnisse (Linscott & van Os, 2013; Stefanis et al., 2002). Mittels hirnmorphometrischer Methoden können neuroanatomische Parallelen und Abgrenzungen zu den klinischen Krankheitsbildern untersucht werden (Nenadić, Lorenz, et al., 2015; Siever & Davis, 2004; Taylor et al., 2020).

Drei Querschnittstudien untersuchten mögliche Zusammenhänge zwischen psychometrisch erfassten subklinischen Psychose-Phänotypen und der kortikalen Struktur. Studie 1 widmete sich der Analyse der kortikalen Oberflächengyrierung, welche einen Indikator für die frühe kortikale Entwicklung in Abhängigkeit von genetischen und Entwicklungsfaktoren (Docherty et al., 2015; Haukvik et al., 2012) darstellt. Diese wurde im Zusammenhang mit dimensionalen psychose-nahen Erlebnissen untersucht. Die kortikale Faltung erklärt auch spätere kognitive Leistungen (Gautam et al., 2015; Hedderich et al., 2019; Papini et al., 2020), welche bei PatientInnen, Hoch-Risiko Phänotypen und Gesunden mit einem familiären Psychoserisiko Verschlechterungen aufweisen (Hou et al., 2016; Siddi et al., 2017). Anhand von Mediationsmodellen wurde der Einfluss neurokognitiver Funktionen auf den Zusammenhang zwischen regionaler Gyrifizierung und psychose-nahen Erlebnissen untersucht. Studien 2 und 3 untersuchten hirnstrukturelle Korrelate anhand von Voxel-basierter Morphometrie. Studie 3 verfolgte das Ziel, sowohl die Ausprägung als auch die Facette des entstandenen Belastungsgrades durch subklinische Erlebnisse (Hanssen, Bak, et al., 2005; Ising et al., 2012) auf der hirnstrukturellen Ebene abzubilden. Die Auswirkung des Zusammenspiels dieser beiden Facetten (Ausprägung und dimensionsspezifische Belastung) auf die Struktur präfrontaler Areale wurde mit Moderationsanalysen untersucht. Basierend auf bestehenden Ergebnissen zur Reduktion hippocampaler Volumina in den frühen und späten Stadien psychotischer Erkrankungen (Lieberman et al., 2018; Mathew et al., 2014; Schobel et al., 2013), sowie bei der Schizotypie Gesunder (Sahakyan et al., 2020),

untersuchte Studie 3 die medial temporalen Strukturen. Es wurden die Zusammenhänge zwischen unterschiedlichen Schizotypie-Dimensionen und subklinischen psychose-nahen Erlebnissen, sowie deren Interaktion, mit den Volumina einzelner hippocampaler Teilvolumina und der Amygdala untersucht.

Die Ergebnisse zeigten unterschiedliche regionale oberflächenbasierte Korrelate der kortikalen Faltung in Abhängigkeit von der Merkmalsdimension. Reduktionen der kortikalen Gyrierung in parietalen und temporalen Bereichen stimmten mit den Regionen neuroanatomischer Veränderungen aus klinischen Studien bei Schizophrenie-PatientInnen überein. Der Effekt der Gyrierung auf die Ausprägung subklinischer Phänotypen in diesen und präfrontalen Bereichen wurde jedoch nicht durch die kognitive Leistung vermittelt. Studie 2 zeigte, dass die Ausprägung des subklinischen Phänotyps, jedoch nicht die mit solchen Erlebnissen verbundene Belastung, mit einer Zunahme der grauen Substanz in präfrontalen und okzipitotemporalen Arealen assoziiert waren. Eine Volumenreduktion im Gyrus frontalis superior wurde durch die Interaktion der subklinischen Phänotyp Ausprägung mit der Belastung durch perzeptuelle Merkmale bedingt. Hinsichtlich der Assoziationen in den medial temporalen Strukturen konnte gezeigt werden, dass strukturelle Variation der Amgygdala und einzelner hippocampaler Teilvolumina eher durch stabile schizotype Traits, als durch psychose-nahe Erlebnisse, erklärt wird. Im hippocampalen Subiculum moderierte positive Schizotypie jedoch den Zusammenhang zwischen transienten Erlebnissen und Volumenzunahme. Somit hebt Studie 3 die besondere Rolle stabiler Endophänotypen (Barrantes-Vidal et al., 2015) sowie die Berücksichtigung der Dimensionalität subklinischer Phänotypen (Grant, 2015; Vollema & van den Bosch, 1995) im Psychosespektrum hervor.

Die Ergebnisse der drei Studien unterstützen den dimensionalen Ansatz, bei dem unterschiedliche psychotische Merkmale im Einzelnen untersucht werden. Diese psychose-nahen Erlebnisse wiesen bei Gesunden kortikale Assoziationen in psychose-relevanten präfrontalen und temporalen Arealen auf (Haijma et al., 2013; Honea et al., 2005), welche jedoch im Gegensatz zu klinischen Befunden heterogenere Beziehungen aufweisen. Im subklinischen Bereich ließen sich zudem Abweichungen der kortikalen Faltung feststellen (Fonville et al., 2019; Liu et al., 2016), welche einen kontinuierlichen Zusammenhang mit entwicklungsbedingten Faktoren erkennen lassen. Die modifizierenden Eigenschaften von schizotypen Traits und der Belastung durch perzeptuelle Auffälligkeiten auf jeweils positive und negative Zusammenhänge in hippocampalen und präfrontalen Strukturen deuten darauf hin, dass innerhalb des Psychose-Kontinuum möglichweise nichtlineare kortikale Veränderungen stattfinden (Bartholomeusz et al., 2017; Binbay et al., 2012; Johns & van Os, 2001).

# 7. APPENDIX

## 7.1. Study 1 published article

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# Cortical Gyrification, Psychotic-Like Experiences, and Cognitive Performance in Nonclinical Subjects

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***Background:*** **Psychotic-like experiences (PLE) are present in nonclinical populations, yet their association with brain structural variation, especially markers of early neurodevelopment, is poorly understood. We tested the hypothesis that cortical surface gyrification, a putative marker of early brain development, is associated with PLE in healthy subjects.** ***Methods:*** **We analyzed gyrification from 3 Tesla MRI scans (using CAT12 software) and PLE (positive, negative, and depressive symptom dimensions derived from the Community Assessment of Psychic Experiences, CAPE) in 103 healthy participants (49 females, mean age 29.13 ± 9.37 years). A subsample of 63 individuals completed tasks from the Wechsler Adult Intelligence Scale and Controlled Oral Word Association Test. Estimated IQ and a composite neuropsychological score were used to explore mediation pathways via cognition.** ***Results:*** **Positive PLE distress was negatively associated with gyrification of the left precuneus. PLE depression dimension showed a negative association with gyrification in the right supramarginal and temporal region. There was no significant mediating effect of cognition on these associations.** ***Conclusion:*** **Our results support a neurobiological psychosis spectrum, for the first time linking an early developmental imaging marker (rather than volume) to dimensional subclinical psychotic symptoms. While schizophrenia risk, neurodevelopment, and cognitive function might share genetic risk factors, additional mediation analyses did not confirm a mediating effect of cognition on the gyrification-psychopathology correlation.**

*Key words:* cognitive function/endophenotype/neurodevelopment/subclinical/magnetic resonance imaging (MRI)

## Introduction

Schizophrenia is associated with core cognitive deficits predictive of risk for illness onset,[1] treatment response, and recovery.[2,3] Hallmark dysfunctions consistently include general intellectual ability[4] and domains of attention, working memory, and verbal fluency.[5] While gradual changes in cognitive, perceptual, and negative symptoms mark the prodromal phase in the ultra-high risk (UHR) state, performances in these domains are also reduced in non-afflicted first-degree relatives[6,7] and healthy adults endorsing psychosis phenotypes including schizotypy and psychotic-like experiences (PLE).[8,9] Previously, we reported positive correlations between psychosis proneness in healthy adults and gray matter (GM) volumes in the precuneus, inferior, and parietal cortical areas.[10] GM, white matter, and functional abnormalities in fronto-parieto-temporal network areas,[11,12] parahippocampal, and cingulate gyri are frequently reported in schizophrenia.[13,14] Cortical and subcortical alterations in prefrontal network GM volume[15,16] and functional connectivity between frontal, temporal, hippocampal, and striatal regions across the psychosis continuum[17–20] are evident, yet somewhat inconclusive regarding directionality. Modinos et al[21] detected GM volume increases in the precuneus and anterior cingulate cortex in high schizotypy as well as the medial posterior cingulate areas in high positive PLE. Another study did not support regional prefrontal GM reductions associated with schizophrenia in twins and relatives of patients, suggesting that deficits in prefrontal executive function, rather than GM variation, are attributable to genetic liability for schizophrenia.[22]

Altogether these findings demonstrate that disease-stage and genetic risk profile account for overlap and discrepancies in functional and cortical variation, especially in prefrontal and precuneus regions. Neurobiological correlates of polygenic risk for psychotic disorders and cognitive disturbance support accumulating evidence for 2 neurodevelopmentally meaningful endophenotypes.[23–26]

The shared variance between polygenetic risk for schizophrenia and cognition-related pathways in a causal mediation model suggests that cognitive disturbance lies upstream to schizophrenia liability and not vice versa.[27] This is further supported by putative pathways involving, eg, calcium signaling associated with executive function in schizophrenia.[28]

A growing body of research recognizes cortical gyrification as a neurobiological marker of early genetic and environmental modulation in cortical surface morphology in schizophrenia. Signifying the degree of cortical folding that peaks during early neurodevelopment, gyrification has been strongly implicated as an early endophenotype in psychopathology.[29] Increased spatial resolution is achieved by quantifying the local gyrification of individual surface vertices.[30] A recent study using vertex-wise local gyrification index (GI),[31] for instance, has shown an association with polygenic risk indicating an early neurodevelopmental disturbance in schizophrenia.[32] Compared with cortical thickness, morphometry of cortical gyrification might be less susceptible to heterogeneous illness-related effects.[33] This can aid to delineate etiological phenomena across groups of varying phenotype expression without confounds of acute neuroanatomical changes in schizophrenia[34] and antipsychotic treatment thereof.[35] Thus, gyrification provides a novel approach to map differential phenotype correlates,[36,37] which are continuously expressed in the general population.[38] Case-control studies of gyrification in schizophrenia have pointed to prefrontal and temporal alterations, but have not always been consistent.[37,39–41] While psychotic phenomena such as auditory hallucinations have been linked to cortical folding abnormalities in schizophrenia patients,[42] studies of cortical folding in nonclinical subjects are rare.[43] Hence, there is a paucity in the studies linking gyrification to subclinical phenomena, such as PLE, that form part of the psychosis spectrum. These mostly transitory PLE[38] feature positive (delusional, hallucinatory, and dissociative experiences) and negative (affective flattening, avolition, and social withdrawal) subclinical phenomena corresponding to the typical dimensions of schizophrenia spectrum disorders.[44,45] Recently, a study using local GI found a significant role of the persistence of psychotic experiences during a 2-year follow-up period on gyrification reduction in the left temporal gyrus and brain volume in left occipital and right prefrontal brain regions,[23] thus replicating morphological findings in regions implicated in schizophrenia. Negative associations of cortical volume and local GI in orbitofrontal, parietal, and temporal regions were driven by the interaction of polygenic risk score and psychotic experiences. However, these symptoms were not differentiated by dimensionality or quality, such as PLE frequency or symptom-related distress accounting for cortical variation in relevant areas, including left precuneus and right inferior temporal pole.[46]

Despite some initial volume-based morphometric studies, it is unclear whether more specific morphometric markers related to core processes such as early development/cortical gyrification are related to different dimensions of PLE (positive, negative, and depressive) and cognitive function. Our aims were, therefore, 2-fold: our primary objective, based on previous GM volumetric studies of PLE, was to test the hypothesis that variation in cortical surface morphology is associated with different dimensions of subclinical PLE in healthy nonclinical individuals. Guided by previous voxel-based morphometry (VBM) findings,[10] we expected associations between psychosis proneness (assessed by CAPE) and gyrification in prefrontal, superior parietal, and precuneus regions. Secondly, we tested the hypothesis that PLE-associated gyrification is mediated by cognitive function in this nonclinical cohort. This hypothesis was based on the findings in the clinical spectrum, showing close relations between cognition and clinical outcomes across high-risk, first-episode, and multi-episode patients[47,48] and cognition pathways mediating some genetic risk on schizophrenia in a recent study.[27]

## Methods

### *Subjects*

We included 103 healthy participants (49 males, 54 females; mean age = 29.13 years, SD = 9.37) recruited from the local community. We obtained written informed consent from each participant for the study protocol approved by the local Ethics Committee of the Jena University Medical School and in line with the Declaration of Helsinki. The sample is based on a previously published community sample, which was enlarged subsequently.[10] Mean laterality index for the overall sample was 73.78 (SD = 36.38) right-handedness.[49] Subjects were recruited from the local community by advertising (press releases and word of mouth) and were compensated for study participation. They first underwent telephone screening and subsequent screening in person to assess the inclusion and exclusion criteria. A semi-structured interview was used to screen subjects for the absence of current or previous psychiatric disorders, including substance abuse or dependence, psychiatric or psychological treatment, intake of psychopharmacotherapy, or first-degree family liability for psychotic disorders. Subjects were also excluded if any neurological disorders, untreated major chronic or acute organic medical conditions, history of traumatic brain injury/loss of consciousness, or intellectual disability/ learning impairment (IQ < 80) were present. Next, all subjects underwent screening about lifetime history of psychiatric and general medical health care, and illicit substance and alcohol use. These screening questions were a requirement for subsequent scanning to ensure the inclusion of healthy volunteers from the general population only.

*CAPE Assessment*

Clinically meaningful levels of psychosis risk can be detected in healthy individuals using self-report measures, such as the 42-item Community Assessment of Psychic Experiences (CAPE).[50] The CAPE is widely used to assess lifetime prevalence of PLE in the general population whilst available in multiple languages. These strengths were recently demonstrated in a meta-analysis[45] and a cross-cultural study,[51] and it may be cost-effectively employed in non-specialized settings to examine traits associated with psychosis proneness.[52,53] Including positive (CAPE-*pos*, 20 items) and negative (CAPE-*neg*, 14 items) subscales, the CAPE provides a comprehensive and reliable[45] self-report measure of the dichotomous symptom dimensions reflecting both frequency and distress related to psychosis-prone traits. Additionally, we also explored the depressive symptom (CAPE-*dep*) subdimension, which consists of an 8-item scale from the 3-factor model.[44]

*Neuropsychological Assessment*

In a subsample of 63 healthy subjects (28 females; mean age 30.32 years, SD = 10.47), we assessed cognitive performance using multiple subtests of the German Wechsler Intelligenztest für Erwachsene (WIE),[54] the German adaptation of Wechsler Adult Intelligence Scale (WAIS-III)[55] neuropsychological testing battery, and the Controlled Oral Word Association Test (COWAT).[56] A general estimate of intelligence (IQ) was obtained from a German-language multiple-choice vocabulary test (Mehrfachwahl-Wortschatz-Intelligenztest, MWT-B).[57] The MWT-B provides a resourceful approximation of crystallized intelligence.[58] The combination of cognitive tasks typically utilized in clinical schizophrenia[25,59] and UHR samples[60] from the 2 extensive test batteries included Letter-Number Sequencing task (LNS), Digit Symbol Coding task (DSCT) of the WAIS-III, Letters FAS, and Animals of the COWAT (table 1).

*MRI Acquisition and Surface-Based Morphometric Analysis*

We obtained high-resolution T1-weighted scans using a 3 Tesla Siemens Tim Trio scanner (Siemens) with standard quadrature head coil and MPRAGE sequence for all subjects. Images were visually inspected followed by automated data quality check with homogeneity bias correction and tissue segmentation of images, followed by surface-based morphometry (SBM) analysis conducted using the CAT12 toolbox, v12.5 r1363 (Christian Gaser, Structural Brain Mapping Group, Jena University Hospital; http://www.neuro.uni-jena.de/cat12/) within SPM12 v7219 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) for Matlab R2017a (The MathWorks, Inc.). This novel pipeline allows for the computation of surface-based parameters based on, eg, the mean curvature. Images were smoothed using a Gaussian kernel with 20-mm full width at half maximum, as recommended for vertex-wise gyrification in the CAT12 user manual (http://www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf). All subjects passed both the visual quality inspection and the CAT12 data quality checks. Together, all scans from 103 participants reached a weighted average (IQR) of 86.01% (range 82.32%–86.55%) corresponding to a quality grade B.

*Statistical Analysis*

For statistical analysis of CAPE-gyrification associations ($N$ = 103), we applied general linear models (GLM) implemented in SPM12 and the CAT12 toolbox using CAPE subscale scores as predictors for local gyrification, while covarying for age and sex nuisance in the vertex-wise analysis (i.e. multiple linear regression models). We applied familywise error (FWE) cluster-level correction at $P < .05$ (with initial $P < .001$ uncorrected peak-level thresholding) for significance testing.[61] Secondly, in the subsample of $n$ = 63 subjects, we examined the relationship between neuropsychological predictors and CAPE outcome variables. Due to previously reported negative relationships between cognitive measures and psychosis proneness,[8] we carried out 1-tailed partial correlations using Statistical Package for the Social Sciences (SPSS, Version 25, IBM Corp.). Finally, in this subsample, we explored mediating effect IQ and cognition on mean extracted predicted values in anatomical regions-of-interest (ROI) from the primary GLM analysis (ie, CAPE-gyrification association) as predictors and CAPE as outcome variables using the ordinary least squares (OLS) regression analysis implemented in PROCESS Version 3.3[62] for SPSS. Model coefficients $P$-values were adjusted with the false discovery rate (FDR)[63] correction for multiple comparisons using R.[64] For mediation model predictors, we used mean gyrification estimates across Desikan-Killiany atlas regions.[65]

## Results

*PLE Measures*

In our whole sample, subjects scored on CAPE-*pos* dimension with mean frequency 1.24 (SD =0.18, range 1.00–2.15, kurtosis = 5.80, skewness = 1.87) and mean distress 1.64 (SD = 0.50, range 1.00–3.13, kurtosis = −0.10, skewness = 0.45), CAPE-*neg* dimension with mean frequency 1.72 (SD = 0.43, range 1.07–3.14, kurtosis = 1.10, skewness = 0.97) and distress mean 1.88 (SD = 0.65, range 1.00–3.50, kurtosis = −0.61, skewness = 0.49), and CAPE-*dep* scale with mean frequency 1.69 (SD = 0.40, range 1.13–3.88, kurtosis = 7.99, skewness = 2.05) and distress mean 2.02 (SD = 0.67, range 1.00–3.83, kurtosis = 0.10, skewness = 0.52).

### *Cortical Gyrification and PLE*

For the CAPE-*pos* scale, we found cluster-level significant ($P = .015$, FWE-corr.) effects in a cluster comprised of 178 vertices in the precuneus/cuneus region of the left hemisphere. We also found a trend-level effect for this scale in a cluster comprising 112 vertices in the left pars triangularis extending from the inferior prefrontal lobe to the pars opercularis region in the left middle frontal region ($P = .080$, FWE-corr.) (figure 1). CAPE-*neg* was associated with gyrification in the right posterior and isthmus cingulate area; however, these correlations were not significant at the chosen $P < .05$ FWE-correction level. GLM with CAPE-*dep* yielded negative associations with gyrification spanning supramarginal to superior temporal gyrus (STG) regions ($P = .001$, FWE-corr.) (figure 2; supplementary table 2). All results significant at the $P < .05$ FWE-threshold concerned CAPE PLE-associated distress levels.

### *Neuropsychological Findings*

Nonparametric and where appropriate parametric correlational analyses between individual raw scores of each neuropsychological subtest and CAPE frequency and distress scores were conducted to explore the relationship between cognitive and PLE phenotype variables. Correlation coefficients from partial 1-tailed correlation analyses controlled for age and sex are shown in table 2.

### *Mediation of ROI-Associated PLE via IQ and Cognition*

Using the extracted mean predicted gyrification values of the 3 ROI identified in the primary analysis of gyrification (left precuneus, right STG, and the FWE-trend-level sig. left inferior prefrontal cluster), we conducted mediation analyses to predict PLE distress levels. A global neuropsychological performance measure was computed from *z*-transformed raw scores added together to obtain a single composite score per participant. In separate models, global cognitive measure and MWT-B IQ estimate were entered as mediators. Global cognitive performance significantly predicted MWT-B estimated IQ [$F(1,61) = 31.16$, $P < .001$, $R^2 = 0.34$]. There was no significant mediating effect of either estimated IQ or global cognitive performance in the prediction of dimensional PLE distress in the subsample. This is seen in the inclusion of null values in 10 000 bootstrap-sampled confidence intervals of indirect effect coefficients in supplementary table S1.

## Discussion

This study tested 2 hypotheses in healthy individuals with varying levels of PLE. First, we tested the effect of PLE on gyrification. Subsequently, we tested the individual explanatory contribution of cognitive performance in brain regions significantly associated with PLE. Both neural and cognitive variables were considered as endophenotypes with some shared genetic variance. In this study, we provide a first evidence of subtle neurodevelopmental variations in cortical areas linked to subclinical psychotic symptoms in nonclinical healthy subjects.

Unlike previous studies on PLE, which used volume-based imaging markers (VBM or cortical thickness), our gyrification approach relates PLE more specifically to the variation of a neurodevelopmental marker. Previous

**Table 1.** Demographic and Cognitive Sample Characteristics of 103 Healthy Adults

| Variable | *N* | Mean | SD | Skewness | Kurtosis |
|---|---|---|---|---|---|
| Age | 103 | 29.13 | 9.37 | 1.80 | 2.68 |
| Female (%) | 49 (47.60%) | | | | |
| IQ (MWT-B estimate) | 103 | 105.28 | 12.08 | 1.30 | 1.20 |
| Neuropsychological assessment | | | | | |
| Age | 63 | 30.32 | 10.47 | 1.52 | 1.48 |
| Female (%) | 28 (44.40%) | | | | |
| IQ (MWT-B estimate) | 63 | 108.70 | 13.42 | 0.94 | −0.10 |
| MWT-B Score | 63 | 29.22 | 3.48 | −0.03 | −0.53 |
| WAIS-III | | | | | |
| Arithmetic | 63 | 16.41 | 3.78 | −0.48 | −0.78 |
| Digit symbol coding task | 63 | 83.63 | 14.93 | −0.04 | −0.48 |
| Matrix reasoning | 63 | 20.89 | 3.45 | −0.72 | −0.21 |
| Digit span | 63 | 19.03 | 3.69 | 0.05 | −0.73 |
| Information | 63 | 19.92 | 5.53 | −0.77 | −0.43 |
| Letter-number sequencing | 63 | 13.17 | 2.55 | −0.44 | −0.51 |
| COWAT | | | | | |
| Letters FAS | 63 | 39.84 | 12.08 | 0.27 | −0.71 |
| Animals | 63 | 25.83 | 6.32 | 0.20 | −0.15 |

*Note*: Of 103 healthy adults, 63 participants also completed neuropsychological tasks from the Wechsler Adult Intelligence Scale (WAIS-III) and Controlled Oral Word Association Test (COWAT). MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest; SD, standard deviation.

**Table 2.** One-Tailed Partial (Covariates Age and Sex) Spearman's ($r_s$) and Pearson's ($r$; in Italics) Correlation Coefficients for Neuropsychological Subtest Raw Scores and IQ Estimated by MWT-B and Global Neuropsychological Composite Scores Correlated With Dimensional Community Assessment of Psychic Experiences (CAPE) Scales With Uncorrected ($P$) and False Discovery Rate Adjusted ($P_{adj}$) Significance Levels

| | | Positive Dimension | | Negative Dimension | | Depressive Dimension | |
|---|---|---|---|---|---|---|---|
| | | Frequency | Distress | Frequency | Distress | Frequency | Distress |
| DSCT | $r/r_s$ | −.132 | −.113 | .027 | −.013 | −.207 | *−.118* |
| | $P$ | .156 | .194 | .418 | .461 | .055 | .182 |
| | ($P_{adj}$) | (.478) | (.478) | (.478) | (.493) | (.374) | (.478) |
| Arithmetic | $r_s$ | **−.399** | −.055 | −.193 | .060 | −.036 | −.058 |
| | $P$ | **.001** | .337 | .068 | .322 | .391 | .327 |
| | ($P_{adj}$) | (.066) | (.478) | (.374) | (.478) | (.478) | (.478) |
| Matrix reasoning | $r_s$ | −.039 | .052 | .027 | −.007 | .023 | −.159 |
| | $P$ | .383 | .344 | .420 | .480 | .430 | .110 |
| | ($P_{adj}$) | (.478) | (.478) | (.478) | (.493) | (.481) | (.433) |
| Digit span | $r/r_s$ | −.063 | .034 | **−.267** | .084 | −.031 | *.048* |
| | $P$ | .314 | .398 | **.019** | .260 | .407 | .358 |
| | ($P_{adj}$) | (.478) | (.478) | (.314) | (.478) | (.478) | (.478) |
| Information | $r_s$ | **−.217** | .156 | −.211 | **.228** | .042 | .008 |
| | $P$ | **.047** | .114 | .052 | **.039** | .375 | .475 |
| | ($P_{adj}$) | (.374) | (.433) | (.374) | (.374) | (.478) | (.493) |
| LNS | $r_s$ | −.001 | .124 | −.058 | .056 | .057 | −.100 |
| | $P$ | .496 | .171 | .329 | .335 | .332 | .221 |
| | ($P_{adj}$) | (.496) | (.478) | (.478) | (.478) | (.478) | (.478) |
| Animals | $r/r_s$ | −.183 | −.005 | −.154 | .070 | .030 | *−.060* |
| | $P$ | .079 | .486 | .118 | .295 | .409 | .323 |
| | ($P_{adj}$) | (.374) | (.493) | (.433) | (.478) | (.478) | (.478) |
| Letters FAS | $r/r_s$ | −.139 | .037 | −.186 | −.007 | −.074 | *−.090* |
| | $P$ | .143 | .390 | .076 | .478 | .285 | .245 |
| | ($P_{adj}$) | (.478) | (.478) | (.374) | (.493) | (.478) | (.478) |
| MWT-B | $r_s$ | **−.279** | .057 | −.044 | .181 | .083 | −.050 |
| | $P$ | **.015** | .331 | .369 | .082 | .262 | .352 |
| | ($P_{adj}$) | (.314) | (.478) | (.478) | (.374) | (.478) | (.478) |
| Global cognitive performance | $r_s$ | **−.225** | .038 | −.178 | .136 | .010 | −.083 |
| | $P$ | **.041** | .385 | .085 | .148 | .469 | .261 |
| | ($P_{adj}$) | (.374) | (.478) | (.374) | (.478) | (.493) | (.478) |
| IQ | $r_s$ | **−.279** | .057 | −.044 | .181 | .083 | −.050 |
| | $P$ | **.015** | .331 | .369 | .082 | .262 | .352 |
| | ($P_{adj}$) | (.314) | (.478) | (.478) | (.374) | (.478) | (.478) |

*Note*: Significant ($P < 0.05$) correlations are bold. DSCT, Digit Symbol Coding Task; LNS, Letter-Number-Sequencing task; MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest.

animal and human studies have shown cortical gyrification to result primarily from complex neurodevelopmental processes, beginning at week 16 of gestation and extending into early childhood.[66] Between ages 2 and 6, the cortical folding organization reaches a peak[29] terminating into a considerably stable marker after adolescence with little variation across the lifespan.[67] A recent study of gyrification in manifest schizophrenia compared with healthy controls found convergence between regions of structural GM alterations and cortical thickness; however, threshold-significant gyrification results were more distinctive.[37] In line with these findings, we report PLE gyrification effects in the prefrontal and temporal regions. Past studies focused on gyrification patterns in clinical psychotic disorders[39,68] but investigations within the subclinical spectrum of psychotic symptoms found across general population cohorts are lacking. A few studies that focused on dimensional PLE were almost exclusively limited to VBM[10] and cortical thickness,[69] leading to a lack of findings to infer on neurodevelopmental alterations within the wider psychosis continuum. In the present sample, a subclinical positive psychosis phenotype correlated negatively with gyrification, a marker linked to perinatal and early neurodevelopment.

Higher PLE distress in the CAPE-*pos* dimension was associated with reduced gyrification in the inferior frontal gyrus of the prefrontal lobe at the subthreshold FWE-corrected significance level. Similar to psychotic samples, positive subclinical psychotic signs are associated with prefrontal cortical organization, underlining their relevance in a dimensional psychosis spectrum. Discriminating gyrification correlates between bipolar disorder I and schizophrenia showed some specificity of alterations in anterior medial prefrontal and orbitofrontal

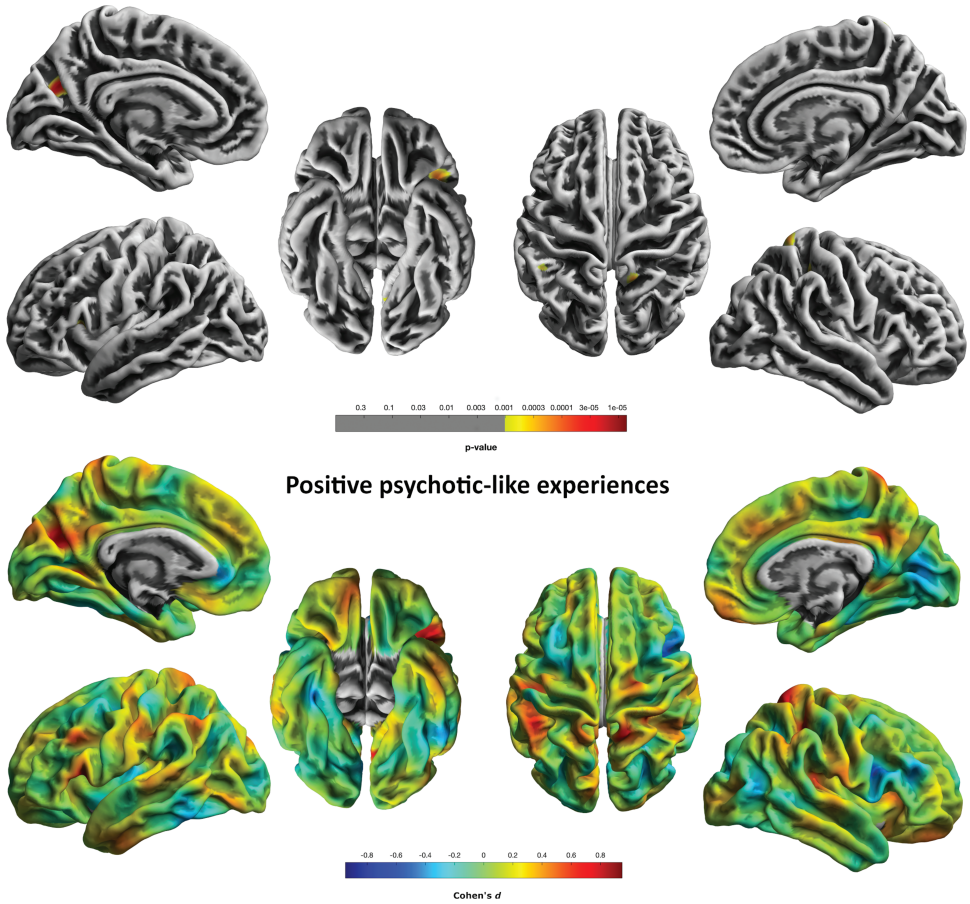


**Fig. 1.** Logarithmic *P*-value maps of significant negative correlations of cortical gyrification and CAPE-*pos* scale in 103 healthy individuals ($P < 0.001$, uncorrected, for display purposes) (top). Cohen's d maps of effect sizes for uncorrected correlations of gyrification with the CAPE-*pos* scale in 103 healthy individuals (bottom).

cortices for schizophrenia compared with controls. While hypergyrification in regions of affective processing was unique in bipolar disorder, regions associated with cognition were pronounced in both diagnostic phenotypes with some anatomical divergence.[40] This raises the question of whether prefrontal correlates of positive psychotic symptoms are a widespread trend at both nonclinical and transdiagnostic levels. Regulatory changes of the dopaminergic and glutamatergic systems linked to typical neurocognitive symptoms of schizophrenia[70,71] and specifically prefrontal variation[72–74] perhaps also translate to prefrontal morphological and functional signatures in individuals with increased positive PLE. In contrast to positive prefrontal effects (gyrification increase) reported in schizophrenia,[37] gyrification patterns in the left inferior frontal gyrus showed a trend for a negative association in our finding. This discrepancy may be reflective of the fluctuations in endophenotype effects across the psychosis spectrum spanning from minor subclinical symptoms in the general population, over increased symptom frequency in high-risk subjects, to those individuals developing schizophrenia spectrum disorders. In order to further support this interpretation, larger nonclinical and clinical samples would have to be combined to test linear vs. nonlinear relationships across such a spectrum.

Prefrontal structural variation within the psychosis spectrum,[75] extending to psychosis proneness signified by PLE, is robust and associated with neurodevelopmental processes,[76] such as synaptic pruning aberrances.[77] A previous study reported impairments on selective domains such as verbal knowledge and working memory but not processing speed to be associated with PLE.[7] While none of our results survived FDR-corrections, the trends might suggest heterogeneity dependent on scales, dimensions, and cognitive domain. Both estimated IQ and the global cognition scale comprising all individual tasks showed low to medium (uncorrected) negative correlations with the frequency of positive PLE. Together with previous findings of cognition mediating the genetic risk of schizophrenia, ie, cognitive dysfunction preceding schizophrenia-liability,[27,78] this may suggest that increased cognitive performance achieves neuroprotective effects in the presence of PLE. This notion is supported by the positive effects of increased cognitive reserve in first-episode psychosis patients on global function and

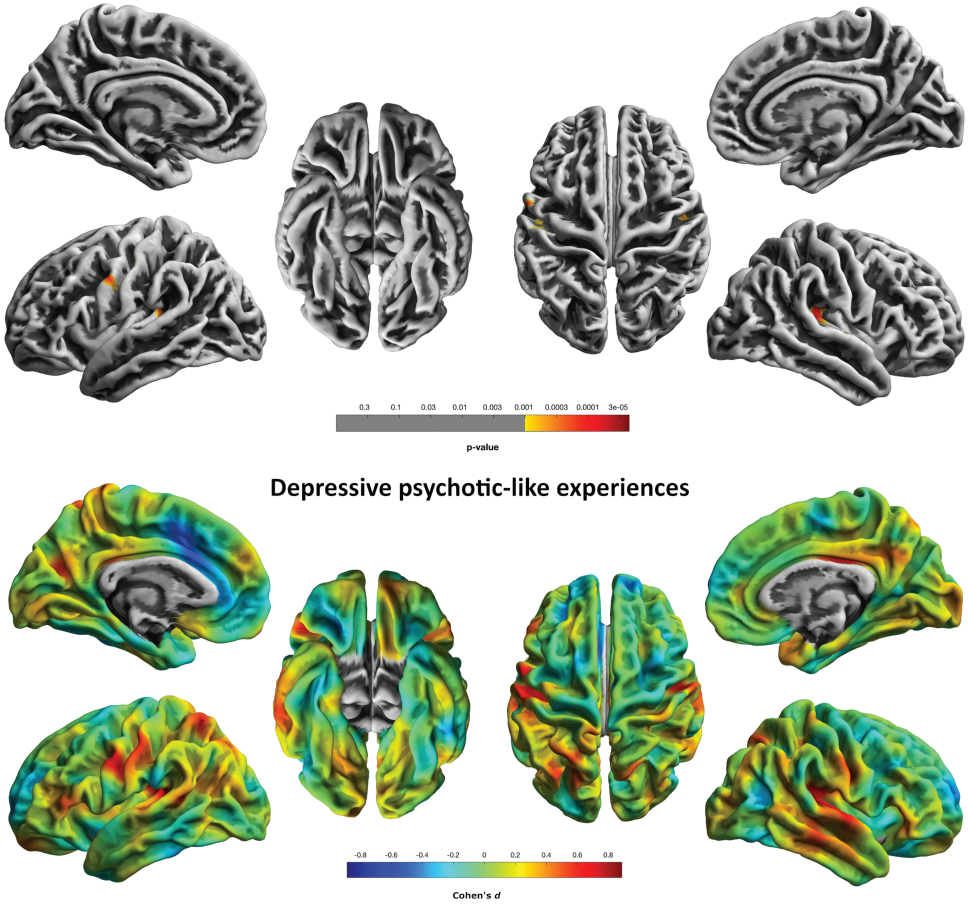


**Fig. 2.** Logarithmic *P*-value maps of significant negative correlations of cortical gyrification and CAPE-*dep* scale in 103 healthy individuals ($P < 0.001$, uncorrected, for display purposes) (top). Cohen's d maps of effect sizes for uncorrected correlations of gyrification with the CAPE-*dep* scale in 103 healthy individuals (bottom).

negative symptoms in a 2-year follow up.[79] The positive association of general intelligence[80] and working memory with regional cortical gyrification[81] further corroborates the functional findings of a parieto-frontal-integration model underlying intelligence variation.[82] Altered prefrontal development might impact on the functional integrity of such networks, thus leading to changes in cognitive function. This neural-behavioral framework established in nonclinical populations may be extended for cognitive reserve and compensatory capabilities in at-risk mental health states. Volumetric integrity of these network nodes, ie, frontal, temporal, and parietal regions, is also featured in UHR subjects resilient against the transition to psychosis over a 6-year period.[83]

We found evidence for the negative effects of depressive symptoms on gyrification in the right STG and supramarginal regions. Left-sided STG also showed GM increase associated with low-level depressive symptoms in another healthy sample.[84] Convergence of decreased functional activity between psychotic disorders and major depressive disorder (MDD) highlights the critical role of the STG within the salience network in major psychiatric diagnoses. Another study also investigated cortical folding in MDD patients based on the whole-cortex mean curvature presented here.[85] Within the patient group, clinical outcomes such as symptom severity were negatively associated with gyrification in parietal, occipitotemporal, and prefrontal cortices. However, the group comparison showed that MDD is associated with right STG hypergyrification pointing toward heightened vulnerability. Here, the endorsement of subclinical depressive states was associated with reduced gyrification of the right STG, which together with hypergyrification in diagnosed MDD proposes plastic alterations associated with the dopaminergic salience system and its role in cognitive interpretative processes ensuing over the course of illness.[86,87] These and our observations in the depressive spectrum, as well as STG-associations in schizotypy and schizophrenia,[88] may also indicate the absence of psychopathological and/or trait specificity, which in turn may be a result of symptom overlap.

There was a notable specificity for the PLE distress scale among the present results. The utility of CAPE as a screening tool for prodromal phenomena in clinical and non-specialized early treatment settings is particularly owed to its distinction of frequency and distress

experienced due to PLE.[89,90] High positive PLE levels, if perceived distressful, may, therefore, tap into higher psychopathological risk burden, supported by the covariance of positive and depressive symptoms.[91] Another study differentiating risk variants demonstrated that the relationship between PLE and subjective distress experienced due to PLE is moderated by the levels of trait schizotypy.[92] Dimensionality and psychosis specificity of the chosen scales may explain discrepancies in the directionality of precuneus GM volume in schizotypy,[10,93] which is further factored into positive and negative psychosis-prone traits with differential cognitive outcomes.[94] Moving along the spectrum, negative clinical outcomes such as imminent transition to psychosis are accompanied by intensified tissue loss and cortical thinning,[95–97] notably in the precuneus, parietal, and temporal regions.[98] In agreement with notions of dynamic neurobiology,[99] our findings map long-term cortical effects associated with subjective negatively perceived PLE, which are not attributed to disease progression but instead to vulnerability. Contrary to significant GM volume findings,[10] the absence of cortical gyrification alterations for the CAPE-*neg* dimension suggests that the surrogate neurodevelopmental surface parameter is not sensitive to the effects of clinical avolition, affective flattening, and social anhedonia reflecting transdiagnostic features of psychosis spectrum disorders.

While we did not find a mediating effect of either estimated IQ or global neuropsychological performance, they showed low to medium (uncorrected) correlations with the frequency of positive PLE. We confined our analysis to ROI correlated with PLE distress levels but propose that PLE frequency may be of greater importance in these models. This conservative approach, together with variation in sample sizes, may cause underestimation of true mediator effects, constituting one of the main limitations of the present study. Siddi et al[8] showed that differences in neuropsychological performance between high and low schizotypy individuals were predominantly small (attention, visuospatial working memory, learning, short-term visual, and long-term memory) to medium (verbal working memory) sized. A post hoc sensitivity analysis with an 85% power criterion showed that the size of the subsample included in the present mediation analysis was only sufficient to detect medium effects ($f^2 = 0.18$) of additional cognitive predictors. This might also explain our lack of significant findings (after multiple comparison correction) for CAPE-cognition associations. Future efforts should, therefore, achieve wider PLE variance and compare metrics of local GI with mean curvature. Additionally, weaknesses regarding the present IQ estimate needs to be pointed out. IQ estimation based on the MWT-B and educational level are not independent,[58] and global estimates from comprehensive neuropsychological batteries could increase robustness. Also, other cognitive tests such as those tapping into visuospatial and motor skills, which were not included in our test battery despite showing heritability in schizophrenia,[100] might be useful for future studies. The cross-sectional design allows for inferences about the natural state of cortical gyrification at an average age of about 30 years when the influence of time-invariant subclinical psychotic traits reaches a peak,[101] but not across the lifespan.[67] Using the gyrification metric as a proxy measure of early genetic influence on cytoarchitecture, its stability may be tested in PLE combined with cumulative risk burden and clinical trait-state markers. Longitudinal designs with increased PLE variability are required to address such time variants and effects of PLE heterogeneity. Despite limited understanding of cytoarchitectural mechanisms involved in gyrification in the psychosis spectrum, this study together with previous neuroimaging research suggests that differences in PLE dimensionality correspond to distinctive genetically determined neurobiological characteristics.

Besides previously mentioned limitations, our explicit investigation of the subclinical spectrum warrants some considerations. To our knowledge, few studies including different patient groups across the psychosis spectrum, eg, schizotypal personality disorder,[41] exist, which calls for further research in the subclinical range. Here, we operationalized CAPE symptom dimensions derived by a 3-factor solution. However, further partitioning of subscales resulting in more PLE phenotypes in exchange for lower indices of construct validity[102] offers an alternative research avenue to these dimensions. Future studies might also consider white matter changes related to PLE, which have been linked to symptom dimensions in schizophrenia.[103,104]

In conclusion, we report evidence for a relationship between variation in cortical gyrification and subclinical psychosis phenotypes in the nonclinical spectrum. If cognition influences psychotic pathogenesis, interactions between cognitive and neurobiological endophenotype levels may be associated with attenuated PLE on the clinical spectrum end.

## Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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## 7.2. Manuscript of Study 2

# Distress severity in perceptual anomalies moderates the relationship between prefrontal brain structure and psychosis proneness in nonclinical individuals

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**Abstract**

In the general population, psychosis risk phenotypes occur independently of attenuated prodromal syndromes. Neurobiological correlates of vulnerability could help to understand their meaningfulness. Interactions between the occurrence of psychotic-like experiences (PLE) and other psychological factors e.g., distress related to PLE, may distinguish psychosis prone individuals from those without risk of future psychotic disorder. We aimed to investigate whether a) correlates of total PLE and distress b) symptom dimension-specific moderation effects exist at the brain structural level in non-help-seeking adults reporting PLE below and above the screening criterion for clinical high-risk (CHR). **Methods:** We obtained T1-weighted whole-brain MRI scans from 104 healthy adults from the community without psychosis CHR states for voxel-based morphometry (VBM). Brain structural associations with PLE and PLE distress were analysed with multiple linear regression models. Moderation of PLE by distress severity of two types of positive symptoms from the Prodromal Questionnaire (PQ-16) screening inventory was explored in regions-of-interest after VBM. **Results:** Total PQ-16 score was positively associated with grey matter volume (GMV) in prefrontal regions, occipital fusiform and lingual gyri ($p$<0.05, FDR peak-level corrected). Overall distress severity and GMV were not associated. Examination of distress severity on the positive symptom dimensions as moderators showed reduced strength of the association between PLE and rSFG volume with increased distress severity for perceptual PLE. **Conclusions:** In this study, brain structural variation was related to PLE level, but not distress severity, suggesting specificity. In healthy individuals, positive relationships between PLE and prefrontal volumes may indicate protective features, which supports the insufficiency of PLE for the prediction of CHR. Additional indicators of vulnerability, such as distress associated with perceptual PLE, weaken the positive brain structure relationship. Brain structural findings may strengthen clinical objectives through disentanglement of innocuous and risk-related PLE.

Word count: 288

**Keywords:** psychological distress, psychotic-like experiences, prodromal questionnaire; psychosis risk

## 1. Introduction

Prevention of psychosis spectrum disorders relies on early risk detection [1]. Prediction of transition to psychosis is particularly enhanced when clinically validated assessments are employed in targeted samples found in specialised mental health services [2]. On the other hand, the use of instruments to assess clinical high risk (CHR) states in general non-help-seeking populations produces weak predictive estimates of the true risk for imminent psychosis [3]. This shortcoming has been encountered by psychometric developments building on two-staged assessments of psychosis CHR states by screening and semi-structured clinical interviews, which enables improved clinical efficiency and accuracy [4]. Originally validated in a general mental health help-seeking population, the abbreviated 16-item version of the Prodromal Questionnaire [5] (PQ-16) sufficiently screens for psychosis ultra-high risk (UHR) states [6]. Together the Prodromal Questionnaires (92, 21, and 16-item versions)[5–7] are among the most widely used CHR screening tools [8]. Previous studies have employed the PQ-16 among help-seeking adults [9] and adolescents [10], as well as nonclinical populations [11, 12] [for a review see ref 13].

The prevalence of subclinical psychotic experiences exceeds that of psychosis in the general population [14], but self-reported psychotic-like experiences (PLE) themselves constitute an inadequate criterion for attenuated psychotic syndromes [15]. Besides clinical prodromal symptoms, screening inventories such as PQ-16, therefore, capture PLE in a broader perspective. Among CHR individuals, motivation to seek help for distressful prodromal symptoms is increased by the burden of affective symptoms leading to greater functional decline [16]; these factors are also captured by semi-structured interviews for attenuated psychotic syndromes [17]. In the general population,

evidence exists that persistence of PLE [18], distress [19, 20], and emotional context [21], depression, and reduced functioning [22] associated with positive PLE indicate elevated clinical relevance. The importance of distress for the differentiation between PLE with reduced clinical significance as, for instance, in developmental cohorts [23] and attenuated psychosis risk was also reflected in the uptake of an additional distress severity subscale to the prodromal screening inventory [7].

Multiple neuroimaging studies compared brain morphology in ultra-high risk (UHR) for psychosis to healthy controls or first-episode psychosis patients [24–27]. In contrast to case-control brain imaging studies, which have focused on UHR and first-episode psychosis [28], the nonclinical spectrum (i.e., the occurrence of sparse PLE in healthy subjects) has received less attention despite recent findings of dimensional relations on the phenotype level [29, 30]. A continuous relationship between infrequent psychotic-like or subclinical symptoms towards a clinical spectrum [31–33] permits a hypothesised relation to neural markers that have been associated with CHR or disease status. This may add to the current understanding of the brain-behaviour relationships in the psychosis spectrum and the development of biomarkers in the early intervention field. Previous studies report associations between subclinical psychotic experiences and brain volume, as well as functional and cortical surface variation [34, 35], some of which converge with alterations typically found in the manifest psychosis spectrum and affective disorders[36]. Across the literature, PLE are associated with structural change in diverse cortical regions, e.g., orbitofrontal and medial temporal lobes [37] and the parietal regions [38]. However, a strong effect for PLE associated with any particular cortical regions derived by meta-analysis is presently lacking. A recent study from our group showed consistent relationships with volume reductions in prefrontal and anterior cingulate regions across multidimensional schizotypy [39], representing a trait-level schizophrenia endophenotype [40, 41]. Furthermore, the relationship between positive schizotypy and PLE [42–44] is considered to reflect biological psychosis prone components within schizophrenia endophenotypes [45, 46]. Thus, extending the search

for neurobiological correlates relating to PLE may shed further light on the dopaminergic fronto-striatal pathway [47, 48] in nonclinical psychosis phenotypes [39, 49].

Building on previous studies [34, 36, 39], we replicate dimensional approaches using whole-brain voxel-wise analysis. Complementary regional analyses are based on primary outcomes to achieve robust targets relevant to the study cohort. The first aim of this investigation was to examine associations between PLE, PLE distress severity, and brain structure. We predict brain structural reductions in association with subclinical PLE and distress severity. Further, we explored the influence of the interaction of PLE and PLE related distress severity on regional brain volume.

## 2. Methods

### *2.1.Sample*

A total of 104 participants (71 females, 33 males; mean age=24.96, SD=4.76, min=18, max=40), all fluent speakers of the German language, were recruited from the local community using advertisements and the university email circulation service. The study procotol adhered to the Declaration of Helsinki[50] and was approved by the local ethics committee of the School of Medicine, Philipps-University of Marburg. Based on an initial telephone screening protocol, we obtained information on exclusion criteria: medical history (neurological or untreated chronic medical condition), past and current substance use, and any history of psychiatric or neurological disorders and treatments including psychotropic medication. Participants aged 18-40 years were then screened using the German version of the *Structured Interview for DSM-IV* [51]. Participants provided written informed consent once invited to complete brain scans and online questionnaires [52], and received financial compensation after participation. Mean laterality quotient of handedness [53] within this cohort was 71.91 (SD=62.07). An estimated intelligence quotient (IQ) [54] below 80 was exclusionary. The mean IQ estimate was 117.46 (SD=14.66).

*2.2. Prodromal Questionnaire (PQ-16)*

We assessed PLE using the 16-item Prodromal Questionnaire (PQ-16)[6], a self-report measure to assess presence of PLE developed from prior versions [5, 7]. The validation of the 16-item version showed that a cutoff of ≥6 endorsed PLE identifies UHR states with 87% sensitivity and 87% specificity [6]. Complementary to the total sum of item endorsements on the 2-point scale ('true'/'false'), a measure of distress severity for each endorsed item is obtained on a 4-point scale from 0 ('none') to 3 ('severe'). In addition to the total symptom score, the distress severity scale cutoff score ≥9 was recommended in a study of non-help seeking subjects [55]. Based on previous psychometric studies [5, 6, 23, 56] and guided by item comparison to the German version of the Structured Interview for Prodromal Syndromes Version 5.0 (SIPS) [17], we assigned items to two positive symptom subscales reflecting '*Perceptual abnormalities/Hallucinations'* (*Perceptual:* items 3, 4, 5, 6, 8, 9, 12, 13, 15), '*Unusual thought content/Delusional ideas'* (*Delusional:* items 2, 10, 11, 14, 16 ), and *Negative symptoms* (items 1 and 7) (Table 1). Table 2 displays Cronbach's alpha as measures of internal consistency for these scales, and frequency of single item endorsements within this community sample is shown in Figure 1.

*2.3.MRI acquisition and voxel-based morphometry (VBM)*

We obtained high-resolution T1-weighted MRI using a 3.0-T Siemens Tim Trio scanner (Siemens, Erlangen, Germany) with standard 12-channel quadrature head coil and a 3D magnetisation-prepared rapid-acquisition gradient echo (MP-RAGE) sequence (4:26 minutes; TE=2.26ms, TI=900ms, TR=1900ms, 1 $mm^3$ isotropic voxel resolution). We then used the Computational Anatomy Toolbox for SPM (CAT12 v12.6, r1450, Christian Gaser, Structural Brain Mapping Group, Jena University Hospital, Germany in SPM12 (v7219, Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK) for correction of homogeneity bias and segmentation of T1-weighted images into grey (GM) and white matter and cerebrospinal fluid. All images passed both visual inspection and CAT12 quality assessment protocols. Internal GM threshold was

set to 0.1 and scans were smoothed with a full width at half maximum Gaussian kernel of 8mm.

### *2.4. Statistical Analyses: General Linear Models*

Multiple linear regression models were conducted in SPM12 running in Matlab (R2017a, The Mathworks Inc., USA) to test associations between grey matter volume (GMV) and total PLE score and distress severity score, respectively. Age, sex, and total intracranial volume (TIV) were entered as control variables to these models. In these voxelwise volumetric analyses, the statistical threshold was set to $p<0.05$ applying false-discovery-rate (FDR) peak-level correction. Anatomical labelling of maximum voxel coordinates was based on the DARTEL neuromorphometrics altas.

### *2.5. Moderation Analyses*

Using the regions-of-interest tool within CAT12.5 (r1363), we extracted estimated mean GMV for each participant based on the neuromorphometrics atlas. These volumes of interest (VOI) were dependent variables in moderation analyses conducted in PROCESS 3.3 [57] for SPSS (Version 25.0, IBM Corp., Armonk, NY). Interactions of Total PLE×distress for *Perceptual* and *Delusional* distress severity were examined as estimators of VOI. Due to the low item and score range, we refrained from including *Negative symptoms* in moderation analyses. We corrected coefficient *p*-values for multiple comparisons for the number of dependent variables (VOI) for each PLE subscale using FDR adjusted *p*-values. FDR-corrections for multiple comparisons [58] were carried out in R [59].

## 3.Results

### *3.1. PLE screening outcomes*

On average, at least one PLE (M=1.30, SD=1.78, scale score range=0-9) and a mean distress dimension score of 1.44 (SD=2.15, scale score range range=0-10) was reported in the present sample. Table 1 provides descriptive statistics for each PQ-16 item, the

three PLE subscales and correlations with the overall distress score with two-sided significance levels. Four participants met the clinical screening threshold (PQ-16 total score ≥6 and/or PQ-16 distress score ≥9) and were invited to a follow-up assessment for CHR status using Schizophrenia Proneness Instrument (SPI-A)[60]. Three participants completed the clinical interview; none met basic symptom criteria.

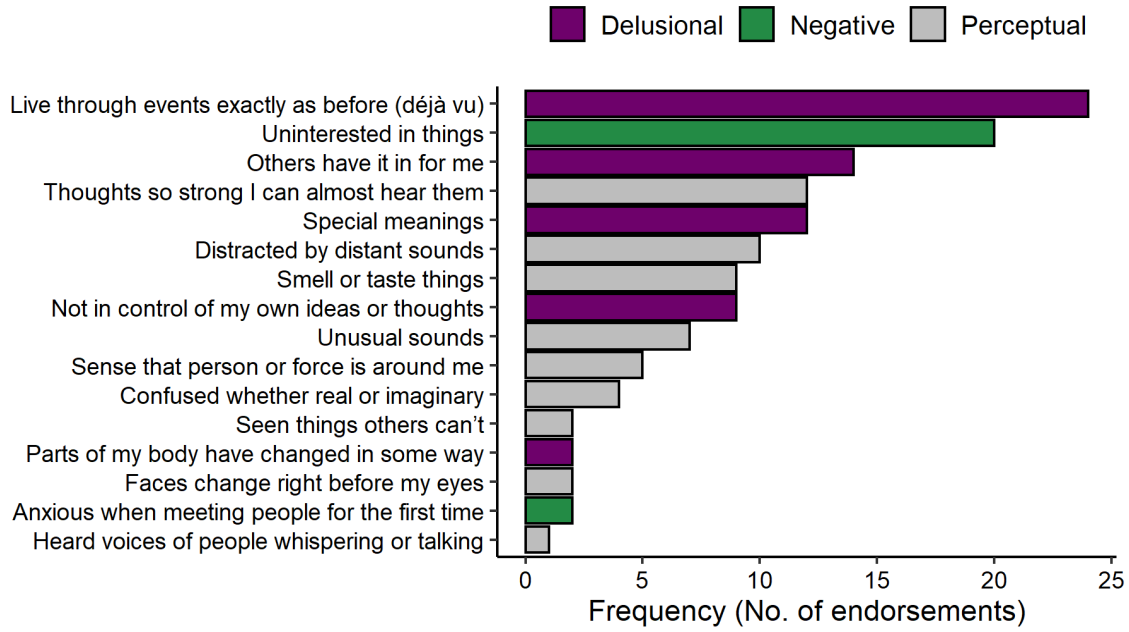


**Fig 1** Distribution of psychotic-like experiences (PLE) captured by the German version of the Prodromal Questionnaire 16 (PQ-16) in 104 nonclinical subjects. Most PLE were assigned to three categories reflecting positive (*Delusional, Perceptual*) and *Negative* PLE based on a comparison to the Structured Interview for Prodromal Syndromes (SIPS). Note: Item descriptions are abbreviated for display purposes. This figure was created using ggplot2[94]

### *3.2. VBM outcomes for PLE*

Total PLE score showed a significant positive association with volume in the right prefrontal region (cluster size k=246) with two significant peaks at the right superior (rSFG, maximum voxel coordinates X/Y/Z=18/−3/56, $t$=5.42, $p$=0.009) and middle frontal gyrus (rMFG) (maximum voxel coordinates X/Y/Z=30/2/52, $t$=5.97, $p$=0.005). PQ-16 associations were significant at the FDR-corrected statistical threshold in the occipital fusiform and lingual gyri (k=45, X/Y/Z=22/−76/−14, $t$=4.73, $p$=0.019), in another small cluster in the rMFG (k=6, X/Y/Z=−34/22/45, $t$=4.40, $p$=0.031) and left precentral gyrus (k=1, X/Y/Z =−39/0/46, $t$=4.18, $p$=0.048) (all FDR-corrected $p$-values). Distress severity

showed no positive or negative relationship with GMV after FDR-correction for statistical significance.

**Table 1** Descriptive statistics of PLE in 104 healthy adults assessed by Prodromal Questionnaire (PQ-16)

| **Prodromal Questionnaire (PQ-16)** | **Total Scale** | | **Distress Scale** | | | |
|---|---|---|---|---|---|---|
| | **Mean** | **SD**[a] | **Mean** | **SD**[a] | ***r***[b] | $p_{FDR}$[c] |
| PLE score | 1.30 | 1.78 | 1.44 | 2.15 | 0.92 | <0.001 |
| *Perceptual abnormalities/Hallucinations* | 0.50 | 1.01 | 0.56 | 1.21 | 0.68 | <0.001 |
| I sometimes smell or taste things that other people can't smell or taste. | 0.09 | 0.28 | 0.09 | 0.34 | 0.37 | <0.001 |
| I often hear unusual sounds like banging, clicking, hissing, clapping or ringing in my ears. | 0.07 | 0.25 | 0.08 | 0.39 | 0.33 | 0.001 |
| I have been confused at times whether something I experienced was real or imaginary. | 0.04 | 0.19 | 0.06 | 0.31 | 0.31 | 0.001 |
| When I look at a person, or look at myself in a mirror, I have seen the face change right before my eyes. | 0.02 | 0.14 | 0.02 | 0.14 | 0.22 | 0.026 |
| I have seen things that other people apparently can't see. | 0.02 | 0.14 | 0.02 | 0.14 | 0.24 | 0.019 |
| My thoughts are sometimes so strong that I can almost hear them. | 0.12 | 0.32 | 0.14 | 0.51 | 0.37 | <0.001 |
| Sometimes I feel suddenly distracted by distant sounds that I am not normally aware of. | 0.10 | 0.30 | 0.10 | 0.33 | 0.39 | <0.001 |
| I have heard things other people can't hear like voices of people whispering or talking. | 0.01 | 0.10 | 0.02 | 0.20 | 0.15 | 0.126 |
| I have had the sense that some person or force is around me, even though I could not see anyone. | 0.05 | 0.21 | 0.04 | 0.19 | 0.36 | <0.001 |
| *Unusual thought content/Delusional ideas* | 0.59 | 0.89 | 0.65 | 1.10 | 0.75 | <0.001 |
| I often seem to live through events exactly as they happened before (déjà vu). | 0.23 | 0.42 | 0.26 | 0.61 | 0.47 | <0.001 |
| I sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around me. | 0.12 | 0.32 | 0.12 | 0.43 | 0.48 | <0.001 |
| Sometimes I have felt that I'm not in control of my own ideas or thoughts. | 0.09 | 0.28 | 0.10 | 0.38 | 0.37 | <0.001 |
| I often feel that others have it in for me. | 0.13 | 0.34 | 0.18 | 0.50 | 0.45 | <0.001 |
| I feel that parts of my body have changed in some way, or that parts of my body are working differently than before. | 0.02 | 0.14 | 0.00 | 0.00 | 0.21 | 0.033 |
| *Negative symptoms* | 0.21 | 0.43 | 0.23 | 0.58 | 0.47 | <0.001 |
| I feel uninterested in the things I used to enjoy. | 0.19 | 0.40 | 0.21 | 0.53 | 0.43 | <0.001 |
| I get extremely anxious when meeting people for the first time. | 0.02 | 0.14 | 0.02 | 0.14 | 0.25 | 0.015 |

[a]SD = standard deviation

[b]*r*=Spearman correlation coefficient

[c]$p_{FDR}$= *p*-value after false discovery rate (FDR) adjustment

**Table 2** Reliability measures for subscales derived from the Prodromal-Questionnaire (PQ-16)

| PQ-16 Scale | Min | Max | Skew | Kurtosis | α[a] |
|---|---|---|---|---|---|
| Total PLE | 0 | 9 | 1.84 | 3.65 | 0.69 |
| Total PLE Distress | 0 | 10 | 1.77 | 2.79 | 0.58 |
| Perceptual Scale | | | | | |
| Total | 0 | 5 | 2.79 | 8.48 | 0.62 |
| Distress | 0 | 6 | 2.61 | 6.81 | 0.47 |
| Delusional Scale | | | | | |
| Total | 0 | 4 | 1.51 | 1.84 | 0.46 |
| Distress | 0 | 5 | 1.79 | 2.88 | 0.28 |
| Negative Scale | | | | | |
| Total | 0 | 2 | 1.79 | 2.20 | 0.13 |
| Distress | 0 | 3 | 3.01 | 10.00 | 0.18 |

[a]α=Cronbach's alpha

*3.3. Moderating effects of PLE distress severity*

The prefrontal VBM cluster showed two local maxima in the DLPFC, indicating the middle (rMFG) and superior frontal gyri (rSFG). For *Delusional,* no effect was observed in either rMFG or rSFG model. A moderating effect of *Perceptual* in the rMFG was only significant at trend-level [unstandardized coefficient=−0.15, SE=0.08, $t(97)=-1.90$, $p_{FDR}=0.060$], while the overall significant model for the rSFG [$F(6,97)=22.06$, $p<0.001$, $R^2=0.52$] showed a significant moderation of *Perceptual* distress scores ≥2.75 [unstandardised coefficient=−0.09, SE=0.04, $t(97)=-2.32$, $p_{FDR}=0.044$], with increased *Perceptual* distress resulting in decreased GM value (Table 3). Due to an overrepresentation of females, the additional nonsignificant moderating effect of sex on this pathway (i.e. PLE×Perceptual PLE distress×Sex interaction) was inspected with the PROCESS macro.

**Table 3** Regression models

| | | **Perceptual PLE** | | | | | | **Delusional PLE** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $F(6,97)=22.06$, $p<0.001$, $R^2=0.52$ | | | | | | $F(6,97)=19.17$, $p<0.001$, $R^2=0.51$ | | | | | |
| Dependent variable | Predictor | Coefficient (SE)[a] | *t* | *p* | $p_{FDR}$[b] | LLCI[c] | ULCI[c] | Coefficient (SE)[a] | *t* | *p* | $p_{FDR}$[b] | LLCI[c] | ULCI[c] |
| **Superior frontal gyrus** | Intercept | 2.85 (1.90) | 1.50 | 0.137 | 0.274 | −0.92 | 6.62 | 2.80 (1.98) | 1.41 | 0.161 | 0.245 | −1.14 | 6.73 |
| | Sex | 0.38 (0.33) | 1.12 | 0.263 | 0.526 | −0.29 | 1.04 | 0.38 (0.34) | 1.09 | 0.277 | 0.554 | −0.31 | 1.06 |
| | Age | −0.07 (0.02) | −3.47 | 0.001 | 0.001 | −0.11 | −0.03 | −0.07 (0.02) | −3.24 | 0.002 | 0.002 | −0.12 | −0.03 |
| | TIV | 0.01 (0.00) | 8.34 | $5\times10^{-13}$ | $5\times10^{-13}$ | 0.01 | 0.01 | 0.01 (0.00) | 8.09 | $2\times10^{-12}$ | $2\times10^{-12}$ | 0.01 | 0.01 |
| | Total PLE | 0.07 (0.10) | 0.69 | 0.493 | 0.493 | −0.13 | 0.26 | 0.01 (0.13) | 0.05 | 0.959 | 0.959 | −0.25 | 0.26 |
| | Distress | 0.40 (0.18) | 2.23 | 0.028 | 0.056 | 0.04 | 0.76 | 0.14 (0.24) | 0.61 | 0.544 | 0.544 | −0.33 | 0.62 |
| | *PLE×distress* | −0.09 (0.04) | −2.32 | 0.022 | 0.044 | −0.17 | −0.01 | −0.02 (0.05) | −0.47 | 0.640 | 0.640 | −0.13 | 0.08 |
| **Middle frontal gyrus** | | **Perceptual PLE** | | | | | | **Delusional PLE** | | | | | |
| | | $F(6,97)=43.67$, $p<0.001$, $R^2=0.64$ | | | | | | $F(6,97)=37.17$, $p<0.001$, $R^2=0.66$ | | | | | |
| | Predictor | Coefficient (SE)[a] | *t* | *p* | $p_{FDR}$[b] | LLCI[c] | ULCI[c] | Coefficient (SE)[a] | *t* | *p* | $p_{FDR}$[b] | LLCI[c] | ULCI[c] |
| | Intercept | 2.57 (2.78) | 0.92 | 0.358 | 0.358 | −2.95 | 8.09 | 3.39 (2.90) | 1.17 | 0.245 | 0.245 | −2.36 | 9.13 |
| | Sex | −0.18 (0.45) | −0.39 | 0.700 | 0.700 | −1.08 | 0.72 | −0.26 (0.45) | −0.57 | 0.572 | 0.572 | −1.15 | 0.64 |
| | Age | −0.11 (0.04) | −3.28 | 0.001 | 0.001 | −0.18 | −0.05 | −0.13 (0.04) | −3.59 | 0.001 | 0.002 | −0.20 | −0.06 |
| | TIV | 0.01 (0.00) | 9.56 | $1\times10^{-15}$ | $2\times10^{-15}$ | 0.01 | 0.02 | 0.01 (0.00) | 9.01 | $2\times10^{-14}$ | $4\times10^{-14}$ | 0.01 | 0.02 |
| | Total PLE | 0.19 (0.16) | 1.21 | 0.231 | 0.462 | −0.12 | 0.51 | 0.40 (0.39) | 1.04 | 0.303 | 0.606 | −0.37 | 1.17 |
| | Distress | 0.52 (0.31) | 1.70 | 0.093 | 0.093 | −0.09 | 1.13 | 0.43 (0.51) | 0.85 | 0.396 | 0.544 | −0.57 | 1.44 |
| | *PLE×distress* | −0.15 (0.08) | −1.90 | 0.060 | 0.060 | −0.30 | 0.01 | −0.24 (0.31) | −0.77 | 0.444 | 0.640 | −0.86 | 0.38 |

[a]SE=Cribari-Neto heteroskedasticity-consistent standard error

[b]$p_{FDR}$= *p*-value after false discovery rate (FDR) adjustment

[c]LLCI= 95% lower (LLCI) and upper (ULCI) limit confidence interval

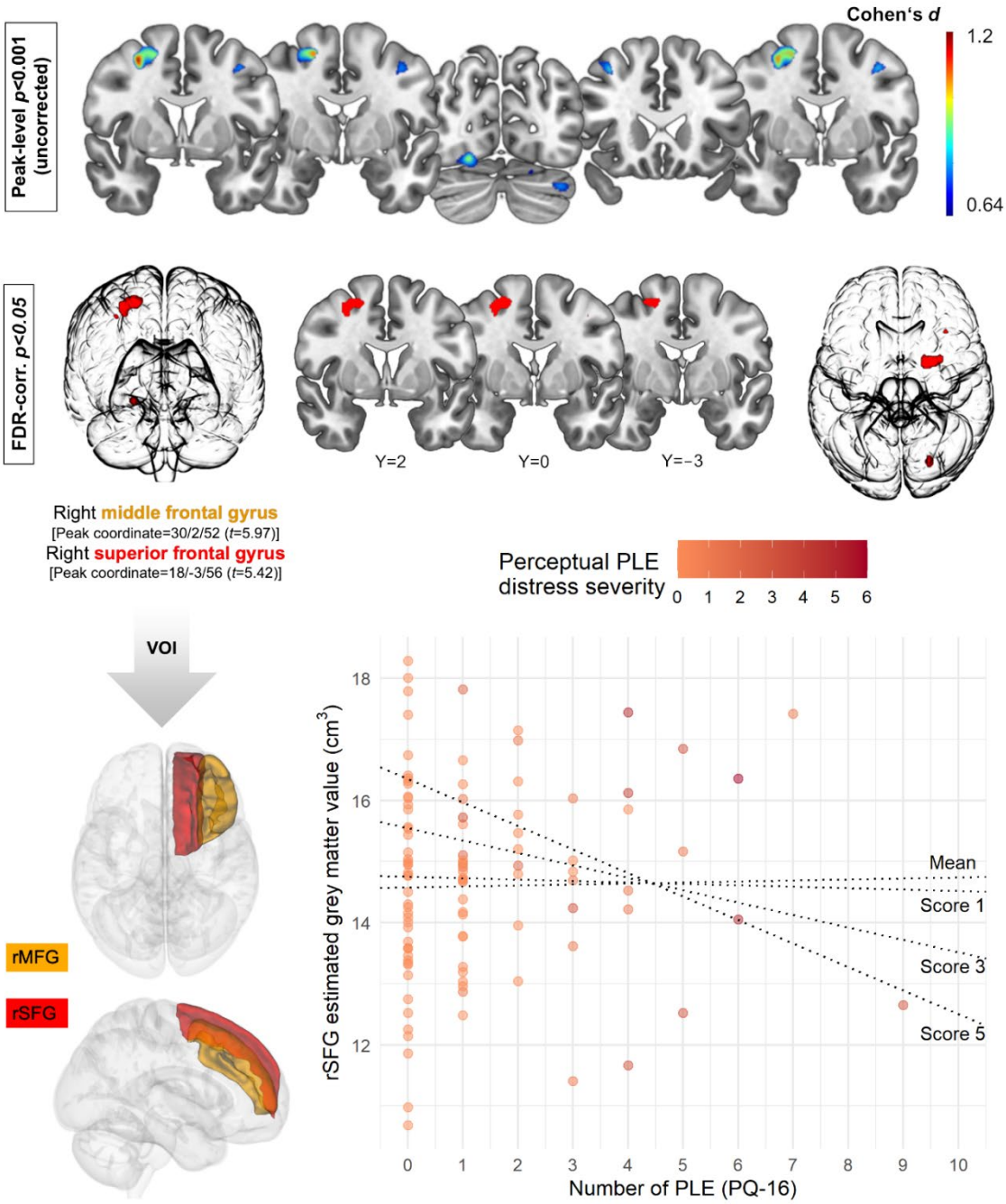


**Fig 2** Upper panel shows statistical significance (thresholded at FDR-corrected $p$<0.05) and effect size (thresholded at uncorrected peak-level $p$<0.001) maps for structural correlates of total psychotic-like experiences (PLE), assessed by the Prodromal Questionnaire (PQ-16). Mean volumes of interest (VOI) were extracted from two prefrontal regions: right superior (rSFG) and middle frontal gyri (rMFG), which enclose the largest cluster of size k=246. Lower panel shows the effect of distress and PLE interaction on predicted rSFG volume. At higher *Perceptual* PLE distress severity (scale score ≥2.75), overall PLE are associated with predicted rSFG volume reductions. This figure was created using MRIcroGL (https://www.mccauslandcenter.sc.edu/mricrogl/), ggplot2[94], 3D Slicer (https://www.slicer.org)[95] and GIMP (https://www.gimp.org/).

## 4. Discussion

The present study aimed to elucidate the relationship between brain structure and PLE in nonclinical subjects devoid of attenuated risk for psychosis. The results revealed a positive association between PLE and volume in right dorsolateral prefrontal, fusiform and occipital brain regions, which was not present for the distress severity scale. However, exploratory analysis of the whole right superior and middle frontal gyral volumes showed a modulating effect of distress severity.

The main finding of this study is that PLE applicable for psychosis risk screening are associated with neurobiological changes independent of UHR case-control status, conversion [61], and UHR phenotype heterogeneity (e.g., genetic risk deterioration syndrome, attenuated psychotic syndrome, brief limited intermittent psychotic symptoms) [62]. Correlates for subclinical PLE were detected in the right hemisphere. This differs from clinical findings in schizophrenia, showing either left lateral or bilateral GM reductions in the medial and superior temporal lobes [63, 64] and a linkage with severity of auditory hallucinations [65]. However, GM alterations in the right dorsolateral prefrontal cortex are also represented in studies of schizophrenia and diverse prodromal stages [63, 66–69]. Regional GM differences between healthy, genetic-high risk, and first-episode schizophrenia individuals also highlight genetic components [70]. Our significant regional findings align with some of those found in the genetic-high risk group in Chang et al.[70], such as larger volumes in rMFG and fusiform gyrus compared to healthy controls. Interestingly, a large genome-wide association study recently demonstrated shared genetic liability between PLE and multiple psychiatric conditions [71].

Magnitude of GMV loss shows some variability over disease progression [72], and progressive structural differences were also seen in reduced white matter growth in UHR adolescents [73]. Accelerated prefrontal GMV loss may indicate differential pathological processes at different neurodevelopmental stages in schizophrenia [74]. This would be in line with potentially non-linear patterns of brain structural changes dependent on transition and illness phase [75]. However, another comparison of CHR youths to controls could not confirm structural and cortical thickness differences regardless of later transition to psychosis [76]. In that study, the

critical role of sample uniqueness, especially the absence of illicit drug use, including cannabis, are discussed. An extension of our design would be an exploration of the effect of illicit drug use on the observed PLE-brain structural relationship.

Contrary to predictions, we found a positive direction for the association between PLE and GMV. In the earlier analysis [39], positive schizotypal traits were associated with GMV reductions in superior and middle frontal gyri. Tact-based white matter and GMV analyses implicated alterations in fronto-striatal network regions in schizotypy. However, it remains speculative whether all schizotypy dimensions equally reflect neural deficits or vulnerability. The proximity between PLE and positive schizotypy is further supported by their anatomical overlap, however, PLE correlated with larger volumes in a prefrontal cluster. Together the findings from these two studies do not support a linear continuum ranging from the subclinical phenotypes to CHR and schizophrenia spectrum disorders [31, 77].

The right superior and middle frontal gyri, which are cortical correlates in CHR and transition status [26, 78], could imply modulation by intraindividual psychological factors that may convey vulnerability or resilience in nonclinical individuals, too. Larger DLPFC volumes may be explained by compensatory mechanisms, e.g., in response to upstream striatal alterations [77]. Compensatory processes were also proposed for larger precuneus and posterior cingulate cortex volumes in association with nonclinical psychosis proneness [34, 79, 80], despite volume reductions in the clinical spectrum being common [68, 81, 82]. In that case, larger regional prefrontal volumes at higher PLE levels, but reductions related to the interaction of overall PLE and distress severity of perceptual anomalies, may indicate attenuated protective features. This buffering explanation was earlier proposed by Meller et al. [49], showing that the association between positive schizotypy and larger striatal volume is decreased by general intelligence (a functional substrate of the frontal regions). Preservation of prefrontal functions and GMV [83] may be pivotal determinants of clinical deterioration and prevention. A comparison of brain developmental trajectories in resilient and non-resilient UHR youths found larger frontal volumes over time in the higher functioning group [27]. Resilience [84] may

contribute to prefrontal cortical variation in nonclinical subjects as well. This would be in keeping with the notion that PLE are manifestations of the positive schizotypy dimension [43], which correlates with psychosis-relevant genotypes involved in dopamine regulation [45]. A specific effect for the perceptual PLE component also fits in with the striatal dopamine hypothesis underlying psychosis in schizophrenia and general psychosis proneness [47].

Additionally, the right occipital fusiform and lingual regions were positively associated with PLE. This finding in the occipitotemporal region indicates unique PLE correlates that were not present in multidimensional schizotypy. Involvement of the fusiform gyrus in perception and face recognition [85, 86], together with occipitotemporal GMV reductions in schizophrenia and psychosis [87–89], underpins deficits related to facial processing in the clinical spectrum [90]. One PQ-16 item ('When I look at a person, or look at myself in a mirror, I have seen the face change right before my eyes') may have been especially relevant to the diametrically opposed outcome in nonclinical individuals. Another study reported associations between positive PLE distress and precuneus volume, which were not present in trait psychosis proneness [38]. Our findings for a positive association for PLE load located in the dorsolateral cortical regions as opposed to parietal brain regions may be explained by differences between purely quantitative PLE levels, and measures relating to the qualitative burden of PLE. Failure to replicate precuneus correlates for PLE distress in the present study may be attributed to differing psychometric PLE measures related to different aspects of psychosis proneness. Nonetheless, they complement each other in that they underline the impact of perceiving positive symptoms as worrisome in brain regions implicated across the psychosis spectrum.

Some limitations of this study require evaluation. Although the present cohort consists of young adults, we must acknowledge that cross-sectional designs do not permit prediction of subsequent psychopathological development. Another inherent problem of studies with nonclinical designs is a non-normal PLE distribution [e.g. 91]. Also, the size of the study cohort was limited, which might have hampered the detection of smaller effects. Adoption of instrument (long vs. short PQ versions), setting, and UHR enrichment are sources of detection

threshold variability [13]. Self-reported PLE are poor measures of clinician-rated psychosis risk [15], and current recommendations state clinical CHR assessment should only be extended to those distressed by symptoms [1]. Note also that symptom dimensions were based on the assessment of item contents but require validation using factor analysis. This is especially recommended for positive items where the latent delusional or perceptual character is ambiguous. Brandizzi and colleagues' [23] analysis of PQ-92 positive items yielded factors reflecting 'perceptual abnormalities', 'bizarre experiences', as well as 'conceptual disorganisation and suspiciousness' and 'magical ideation' also found in schizotypy. Additionally, Kotzalidis et al. [56] identified a four-factor solution, including a heterogenous 'functional' dimension. While this provides options for replication using the extended versions of the Prodromal Questionnaire, the translation of these factors to the 16-item screening inventory seems unlikely.

While further replication in larger samples is warranted, our findings go beyond symptom-structure associations by showing the moderating impact of the distress dimension on the anatomical underpinnings of PLE. This posits a crucial distinction for future dimensional model studies as the marked distinction between (positive) subclinical symptoms with varying degrees of subjective impact is stressed. It is currently expected that neuroimaging studies will provide complementary tools for predicting transition to psychosis [92] and long-term clinical outcomes [93]. Our study supports these attempts by isolating the neurobiological uniqueness of PLE in the nonclinical part of the psychosis spectrum. We suggest that future investigations might also address the neurobiological characterisation of resilience in genotypes and phenotypes related to psychosis proneness.

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## Declarations


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### Conflict of interest/Competing interests

The authors declare that they have no conflict of interest.

### Availability of data and material

All original data are on record and accessible to inspection, but are not available publicly based on local and national data protection regulations.

### Code availability

All software used in the analyses is based on publicly available code.

### Author's Contributors

S.G. and I.N. designed the study and obtained funding. U.E., S.S., J.-K.P. and T.M. recruited, assessed and scanned subjects. T.M. preprocessed MRI data. U.E. performed statistical analysis. I.N. supervised analyses. U.E. wrote the first draft of the manuscript, and all authors contributed to critical revisions of the draft and approved the manuscript.

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## 7.3. Manuscript of Study 3

# Nonclinical psychotic-like experiences and schizotypy: interactions and differential associations with hippocampal subfield and amygdala volumes

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**Abstract**

**Background:** Schizotypy and psychotic-like experiences (PLE) form part of the wider psychosis continuum and may have brain structural correlates in nonclinical cohorts. This study aimed to compare the effects of differential schizotypy dimensions, PLE, and their interaction on hippocampal subfields and amygdala volumes in the absence of clinical psychopathology. **Methods:** In a cohort of 367 psychiatrically healthy individuals, we assessed schizotypal traits using the Oxford-Liverpool Inventory of Life Experiences (O-LIFE), and PLE using the short form of the Prodromal Questionnaire (PQ-16). Based on high-resolution structural MRI scans, we used automated segmentation to estimate volumes of limbic structures. Sex and total intracranial volume (step 1), PLE and schizotypy dimensions (step 2), and their interaction terms (step 3), were entered as regressors for five bilateral hippocampal subfield and amygdala volumes in hierarchical multiple linear regression models. **Results:** Positive schizotypy, but not PLE, was negatively associated with left amygdala and subiculum volumes. O-LIFE Impulsive Nonconformity, as well as the two-way interaction between positive schizotypy and PLE were associated with larger left subiculum. None of the estimators for right hemispheric hippocampal subfield volumes survived correction for multiple comparisons. **Conclusions:** Our findings support differential associations of hippocampus subfield volumes with trait dimensions rather than PLE, and support overlap and interactions between psychometric positive schizotypy and PLE. In a healthy cohort without current psychosis risk syndromes, the positive association between PLE and hippocampal subfield volume occurred at a high expression of positive schizotypy. Further studies combining stable, transient, and genetic parameters are required.

**Keywords:** schizotypy, psychosis proneness, hippocampus, amygdala, neuroimaging

## Introduction

Psychotic-like experiences (PLE) signify psychosis risk, yet only a considerably small portion of persons reporting such transient expressions of psychosis proneness will go on to develop a psychotic disorder (Linscott & van Os, 2013). PLE are elevated in individuals displaying schizotypal traits, which are behavioural, emotional and cognitive characteristics resembling the core symptoms of psychotic disorders along a health-illness spectrum (Claridge & Beech, 1995; Grant, Green, & Mason, 2018; Kwapil & Barrantes-vidal, 2015). Schizotypy encompasses the positive, negative, and disorganised dimensions (Debbané & Barrantes-Vidal, 2015) found in psychotic disorders, with each trait dimension showing differential associations with psychopathology (Kwapil, Gross, Silvia, & Barrantes-Vidal, 2013), affective states (Kemp, Gross, Barrantes-Vidal, & Kwapil, 2018), and perceptual and cognitive outcomes (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014; Ettinger et al., 2015).

This highlights the multifaceted nature of schizotypy and its value in the detection of clinical high risk (CHR) states (Barrantes-Vidal, Gross, et al., 2013; Flückiger et al., 2016). For example, increased PLE levels are especially observed in positive schizotypy (Barrantes-Vidal, Chun, Myin-Germeys, & Kwapil, 2013; Kwapil et al., 2020), as well as depression and anxiety (Varghese et al., 2011), demonstrating that the emergence of psychopathology, PLE and schizotypal traits are intertwined in a dynamic fashion (Barrantes-Vidal, Grant, & Kwapil, 2015). The *fully dimensional* conceptualisation of schizotypy also accounts for the non-pathological phenotypes (Nelson, Seal, Pantelis, & Phillips, 2013), such as 'benign schizotypes' characterised by high positive schizotypy, but low negative and disorganised traits (Mohr & Claridge, 2015). Hence, the positive schizotypy facet (together with low negative and disorganised facets) is related to higher PLE levels independently of induced stress states (Grant & Hennig, 2020), while the emergence of distressing PLE outside of familiar positive traits may convey increased psychosis vulnerability (Debbané & Barrantes-Vidal, 2015). The positive relationship between trait schizotypy and PLE is matched by PLE distress reduction as a function of schizotypy in nonclinical subjects (Kline et al., 2012), supporting a schizotypal context for PLE rooted in health or resilience.

Previous studies demonstrated that trait schizotypy and PLE correlate with cortical changes in areas consistently observed in clinical psychosis. They found brain structural (Ettinger et al., 2012; Meller et al., 2020; Modinos et al., 2010; Pfarr & Nenadić, 2020) and cortical surface variability (Evermann, Gaser, Besteher, Langbein, & Nenadić, 2020) associations with these phenotypes. These findings suggest that subclinical psychosis prone phenotypes show brain correlates in regions affected clinical psychosis, which are not necessarily a sign of vulnerability but could also indicate compensatory processes (Kühn, Schubert, & Gallinat, 2012; Mohr & Claridge, 2015). Investigating replicated brain regions involved in psychosis pathophysiology may facilitate the demarcation of vulnerable or disease progressive states.

Abnormalities of medial temporal lobe hippocampal (HC) and amygdala structures observed in schizophrenia (van Erp et al., 2016), propose neuroanatomical targets for psychosis spectrum research (Lieberman et al., 2018). Hippocampal subfield analyses point to volume reductions in the cornu ammonis (CA) and dentate gyrus (DG) sections (Haukvik, Tamnes, Söderman, & Agartz, 2018; Nakahara, Matsumoto, & van Erp, 2018), which are paralleled by functional studies indicating CA1 and possibly also subiculum hyperactivity (operationalised as increased cerebral blood volume) in patients (Schobel et al., 2013, 2009; Talati et al., 2014). Volume reductions in total hippocampal volume and subfields might already be present at disease onset (Briend et al., 2020) and, more importantly, already at CHR stages preceding disease onset (Ganzola, Maziade, & Duchesne, 2014; Wood et al., 2010), although findings are not entirely consistent across cohorts (for a review see Walter et al., 2016).

Post mortem studies in schizophrenia show differential involvement of CA1, CA3, and DG subfields (Bobilev, Perez, & Tamminga, 2020; Perez et al., 2020), which is supported by differential associations between HC segments and positive and negative clinical symptoms in *in vivo* studies. Left CA2/3 and CA4/DG (Kawano et al., 2015) and subiculum (Haukvik et al., 2015) volumes show inverse associations with negative symptom severity in schizophrenia. Further studies report CA1 and CA2/3 (Kühn et al., 2012) and subiculum (Mathew et al., 2014) volume deficits in association with positive symptoms of psychosis. Mathew et al. (2014) found negative correlations between positive symptoms and hallucinations scale scores based on

the Positive and Negative Syndrome Scale (PANSS, Kay, Fiszbein, & Opler, 1987) for schizophrenia and CA4/DG, presubiculum, subiculum, and whole HC volumes. These pathological medial temporal changes appear to be exaggerated in the left hemisphere (Velakoulis et al., 2006; Wood et al., 2010).

In addition to abnormalities reported in frank psychosis, examinations of HC volumes as potential biological markers have emerged in the nonclinical part of the psychosis spectrum, too. A developmental study demonstrated flattened bilateral hippocampal volume trajectories in adolescents with elevated psychometric disorganised schizotypy (Derome et al., 2020). Recently we reported that HC subfields are indeed altered by the interaction of negative and disorganised schizotypy dimensions, which predicted volumetric reductions in anterior and whole left HC (Sahakyan et al., 2020). Structural effects in schizotypy and ultra-high risk (UHR) states are also paralleled by functional alterations, such as augmented right hippocampal perfusion in high positive schizotypy (Modinos et al., 2018) and increased hippocampal perfusion in UHR (Allen et al., 2018, 2015; Bossong et al., 2019). Hypermetabolism spreading from the CA1 subregion could explain gradual hippocampal atrophy (Schobel et al., 2013, 2009).

Besides detailed volumetry of HC subfields, contemporary automated segmentation methods also provide high-resolution structural delineation of the amygdala. In the wider limbic system, similar investigations show bilateral whole amygdala volume reductions in first-episode psychosis (FEP) (Watson et al., 2012), as well as smaller amygdala subnuclei in CHR and FEP (Armio et al., 2020). Superimposed organisational patterns suggest demarcated ventral HC (CA1 and subiculum) connectivity with the amygdala (Strange, Witter, Lein, & Moser, 2014). Emotion recognition is a functional amygdala substrate showing alterations in schizophrenia (Mier et al., 2014), adolescents at UHR (Bartholomeusz et al., 2014), and schizotypy (Statucka & Walder, 2017; Wang et al., 2018). Another study reported a significant negative relationship between blunted affect and left amygdala activation in schizophrenia patients during positive affect processing (Rahm et al., 2015). Additionally, asymmetric amygdalar surface volumes in CHR with violent ideation (Feng et al., 2019) implicates a

relationship with aggression and impulsivity. Thus, investigating amygdala volumes as an extension of the longitudinal HC axis may be a valuable addition to existing studies.

The present study aims to explore interactions between continuous schizotypal traits and PLE in a general population cohort in association with HC subfields and amygdala volumes. We hypothesise that medial temporal lobe structures show differential associations with schizotypy dimensions and PLE, as well as their interaction. Based on previously described patterns of volume reductions in incipient and early psychosis patients, we predict that positive schizotypy and PLE are associated with left CA1 volume reduction. Further, we expect positive and negative schizotypy to associate with subiculum, CA2/3 and CA4/DG volume reductions, and amygdala volume to vary as a function of impulsive and negative schizotypy. Based on a previous report (Sahakyan et al., 2020), we predict that interactions between PLE and schizotypy dimensions are associated with left medial temporal lobe structural decreases.

## Methods

### *Study cohort*

This study included 367 German language proficient individuals (aged 18 to 40) from the general community, volunteering in response to university-based email circulation, local and online advertisements. Participants were screened by phone using Structured Clinical Interview for DSM-IV (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997), and selected for study inclusion if no history of mental health, neurological or chronic medical conditions were present. This study protocol was in agreement with the Declaration of Helsinki (World Medical Association, 2013) and approved by the local ethics committee of the Medical School of the Philipps-University of Marburg. Participants provided written informed consent, completed phenotype self-report measures online, and received financial compensation upon study completion. Overall, 383 participants were initially scanned. Following exclusion of 16 individuals due to insufficient T1-image quality or incompleteness of survey data, full phenotyping and HC volume estimates were available from 367 [238 (64.85%) females, 129

males (35.15%)] healthy adults (Mean age= 23.85, SD=3.75 years, min=18, max=39) included in the analysis. In this study, we extended the sample previously described in Sahakyan *et al.* (2020). Seven (1.91%) participants scored PLE equal to or above the CHR screening criteria applied in previous studies (Chen et al., 2016; Ising et al., 2012). CHR was ruled out in all four out of seven (51.14%) participants who also agreed to follow-up assessments with Schizophrenia Proneness Instrument (Adult version) (Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007). The mean laterality quotient according to the Edinburgh Handedness Inventory (Oldfield, 1971) was 78.65 (SD=53.22), and mean IQ estimated by the Mehrfachwahl-Wortschatz-Test B (Lehrl, 2005) was 116.38 (SD=14.02, min=92, max=145).

*Imaging data acquisition and preprocessing*

T1-weighed brain images were obtained with a 3-T Siemens Tim Trio magnetic resonance scanner (Siemens, Erlangen, Germany) using a 12-channel quadrature head coil and MPRAGE sequence with a duration of 4:26 minutes (TE=2.26ms, TI=900ms, TR=1900ms). Homogeneity bias correction and tissue segmentation were conducted using Computational Anatomy Toolbox for SPM, (CAT12.7, r1598, Gaser, Dahnke, Kurth, & Luders, 2020) in SPM12 (version 12, v7771, Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, London, UK) running in Matlab (R2017a, The Mathworks Inc). Hippocampal regions of interest volumes were estimated in unsmoothed native grey matter images.

*Assessment of trait schizotypy*

Schizotypal traits were measured using the German version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE, Mason, Claridge, & Jackson, 1995). Based on 104 items the O-LIFE measures scores on four individual dimensions, which reflect the heterogeneous positive (*UnEx*), negative (*IntAn*), disorganised (*CogDis*) as well as behaviourally odd (*ImpNon*) facets of schizotypy. *UnEx* corresponds to perceptual anomalies and magical thinking, while *CogDis* taps into attention and thought aberrances reflecting disorganised symptoms of psychosis. The *IntAn* dimension measures anhedonic phenomena related to social and physical activities, and *ImpNon* refers to impulsive and socially non-conforming

behaviour (Mason & Claridge, 2006; Mason et al., 1995). Descriptive statistics of sample characteristics and dimensional internal consistencies are shown in Table 1.

*Assessment of Psychotic-like experiences (PLE)*

PLE were assessed using the 16-item version of the Prodromal Questionnaire (PQ-16) (Ising et al., 2012), which provides a total PLE score on a two-point scale (answers' true' =1,' false'=0), and a measure of distress severity induced by PLE ('none' =0 to 'severe' =3). Cut-off scores of 6 on the total PLE scale and 9 on the distress scale have been identified as sufficient detection criteria for psychosis proneness (Chen et al., 2016; Ising et al., 2012). All questionnaires were completed online (www.soscisurvey.de, Leiner, 2019) and inspected for PLE above the recommended screening cut-off after study completion.

*Hippocampal subfield volume estimation and extraction*

We selected six bilateral limbic regions that were of a priori interest. These included the HC subfields labelled subiculum, cornus ammonis (CA)1, CA2/3, CA4/dentate gyrus (DG), SR/SL/SM [stratum radiatum (SR), stratum lacunosum (SL), stratum moleculare (SM)] as well as the whole amygdala. We used the novel segmentation tool implemented in CAT12.7, which uses the CoBra (Computational Brain Anatomy Laboratory at the Douglas Institute, Verdun, Canada) atlas (Winterburn et al., 2013) based on high-resolution (1 mm isotropic voxel size) images of HC subfields and amygdala (manual segmentation described in Entis, Doerga, Feldman, & Dickerson, 2012; atlas described in Treadway et al., 2015). Figure 1 displays subfield segmentations and Table 4 shows summarised average volumes across all subjects. Merging HC subfields, such as CA2/3, into a single label circumvents reliability issues related to particularly small subfields sizes. This offers a robustness advantage when anatomical segmentation is based on T1 images only.

## Statistical analysis

*Phenotype associations with amygdala and hippocampal subfield volumes*

HC and amygdala volumes were analysed with hierarchical linear regression models in R (Version 3.6.3, R Core Team, 2020). We conducted 12 separate models, using the six bilateral volumes as dependent variables. Two-tailed Spearman correlations between subfield volumes and variables sex and total intracranial volume (TIV) (all *p*' s<0.05) were significant but insignificant for age (all *p*' s>0.05). Sex and TIV were entered at the first step for the covariate models. In the second step, trait schizotypy dimensions (*UnEx, CogDis, IntAn, ImpNon*) and PLE (PQ-16) scores were entered simultaneously (main effects models), followed by the phenotype interaction terms of PLE×schizotypy dimension in the third step. We standardised dependent and independent variables, compared models using analysis of variance (ANOVA), and examined two-way interactions using the Johnson-Neyman method through the PROCESS macro (Hayes, 2018). Since phenotype scales correlated (Table 1), multicollinearity at each step was controlled for by observation of variance inflation factor (>5 criterion) and tolerance (<0.1 criterion) using the olsrr package (Hebbali, 2020) in R. Since we did not have an a priori hypothesis for right hemispheric subfields, we applied false detection rate (FDR) correction for multiple comparisons for right-sided models.

**Results**

In our analysis of the differential effects of trait schizotypy and PLE on HC subfield volumes, we observed significant effects for single schizotypy dimensions as well as a two-way interaction among trait and PLE scales. To facilitate comparisons between scales, we report standardised regression coefficients (β) with their individual *p*-values (Table 2).

The main effect of positive schizotypy (*UnEx*) showed a significant association with left amygdala and subiculum volume reductions (Table 3). *ImpNon* was also positively associated with left subicular volume. The main effect of negative schizotypy (*IntAn*) emerged at trend-level significance ($p$=0.073) in the left amygdala (Table 2). We did not find any effect of the *CogDis* dimension on HC subfield volumes, and model regressors of right hemispheric HC subfield models did not survive FDR-correction.

Left subiculum subfield volume increase was associated with the two-way interaction of positive schizotypy and PLE, which significantly explained volume variability beyond main effects (Table 3b). Examination of regression slopes showed that PLE levels were significantly associated with a predicted subiculum volume increase at higher positive schizotypy levels. This moderation effect occurred in high positive schizotypy (observed UnEx score≥6.95 equalling $UnEx_{mean}$ +2.07×SD) (Figure 1). Based on the two-way interaction's significance interval, we used *UnEx*≥6.95 as a cut-off to conduct an exploratory subgroup comparison of state and trait profiles (Figure 1). The high positive schizotypy subgroup (n=20) showed significantly higher trait levels in all other schizotypy facets, PLE, and PLE associated distress (supplementary table 1). An interaction between PLE and positive schizotypy showed a trend ($p$=0.077) for an association with CA1 volume increase. *UnEx* and PLE showed the largest correlation in our sample ($r$=0.54, $p$<0.001). Hence the possibility of a covert non-linear association was explored with a polynomial regression model, exchanging the interaction term for a quadratic *UnEx* term, which produced a comparable model (supplementary figure 1).

**Table 1.** Descriptive statistics of psychotic-like experiences (PLE) and schizotypy dimensions with Spearman correlation coefficients.

| | Mean | SD | Min | Max | Skew | Kurtosis | UnEx | CogDis | IntAn | ImpNon | Total | Crobach's α |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **O-LIFE Scale** | | | | | | | | | | | | |
| UnEx | 1.86 | 2.46 | 0 | 16 | 2.31 | 7.16 | | 0.45** | 0.08 | 0.33** | 0.60** | 0.75 |
| CogDis | 5.21 | 4.31 | 0 | 21 | 0.96 | 0.56 | | | 0.35** | 0.19** | 0.81** | 0.84 |
| IntAn | 4.06 | 3.51 | 0 | 19 | 1.59 | 3.02 | | | | 0.02 | 0.58** | 0.77 |
| ImpNon | 6.10 | 2.88 | 0 | 15 | 0.44 | 0.09 | | | | | 0.53** | 0.58 |
| Total | 17.23 | 8.69 | 3 | 54 | 0.88 | 0.82 | | | | | | 0.85 |
| **PQ-16** | | | | | | | | | | | | |
| PLE | 1.08 | 1.51 | 0 | 9 | 1.97 | 4.88 | 0.54** | 0.46** | 0.11* | 0.30** | 0.52** | 0.62 |
| PLE Distress | 1.17 | 1.89 | 0 | 15 | 2.66 | 10.59 | 0.52** | 0.45** | 0.10* | 0.29** | 0.51** | 0.60 |

O-LIFE=Oxford-Liverpool Inventory of Life Experiences, PQ-16= Prodromal Questionnaire, UnEx =Unusual Experiences, CogDis= Cognitive Disorganisation, IntAn=Introvertive Anhedonia, ImpNon= Impulsive Nonconformity, ** $p$<0.001, * $p$<0.05 (two-tailed)

**Table 2.** Standardised regression coefficients and significance values of hierarchical regression models.

| | **Step 1** | | | | **Step 2** | | | | | | | | | | **Step 3** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Covariates** | | | | **O-LIFE Dimension** | | | | | | | | **PQ-16** | | **2-way interactions** | | | | | | | |
| | Sex | | TIV | | UnEx | | CogDis | | IntAn | | ImpNon | | PLE Score | | PLE × UE | | PLE × CD | | PLE × IA | | PLE × IN | |
| | β | *p* | β | *p* | β | *p* | β | *p* | β | *p* | β | *p* | β | *p* | β | *p* | β | *p* | β | *p* | β | *p* |
| Left Hemisphere | | | | | | | | | | | | | | | | | | | | | | |
| Amygdala | -0.197 | **0.000** | 0.599 | **0.000** | -0.109 | **0.029** | 0.063 | 0.172 | -0.071 | 0.073 | 0.061 | 0.135 | 0.077 | 0.130 | 0.012 | 0.582 | 0.000 | 0.991 | -0.002 | 0.945 | -0.008 | 0.824 |
| CA1 | -0.007 | 0.880 | 0.662 | **0.000** | -0.036 | 0.510 | 0.009 | 0.862 | -0.038 | 0.377 | 0.079 | 0.073 | 0.032 | 0.566 | 0.040 | 0.077 | -0.020 | 0.534 | 0.019 | 0.599 | 0.045 | 0.259 |
| CA2/3 | -0.042 | 0.449 | 0.392 | **0.000** | 0.030 | 0.648 | -0.054 | 0.378 | 0.023 | 0.659 | 0.030 | 0.577 | 0.045 | 0.501 | -0.024 | 0.383 | -0.039 | 0.324 | 0.002 | 0.964 | -0.027 | 0.586 |
| CA4/DG | -0.027 | 0.586 | 0.593 | **0.000** | -0.020 | 0.725 | 0.009 | 0.864 | -0.033 | 0.472 | 0.076 | 0.106 | 0.027 | 0.641 | 0.020 | 0.400 | -0.029 | 0.391 | -0.003 | 0.930 | 0.009 | 0.826 |
| Subiculum | 0.001 | 0.979 | 0.728 | **0.000** | -0.112 | **0.024** | 0.058 | 0.201 | -0.052 | 0.186 | 0.088 | **0.030** | 0.051 | 0.307 | 0.053 | **0.011** | 0.015 | 0.617 | 0.014 | 0.669 | 0.022 | 0.547 |
| SR/SL/SM | -0.052 | 0.260 | 0.638 | **0.000** | -0.063 | 0.247 | 0.013 | 0.797 | -0.042 | 0.330 | 0.064 | 0.146 | 0.075 | 0.172 | 0.017 | 0.454 | -0.028 | 0.385 | 0.005 | 0.884 | 0.021 | 0.604 |
| Right Hemisphere | | | | | | | | | | | | | | | | | | | | | | |
| Amygdala | -0.168 | **0.000*** | 0.644 | **0.000*** | -0.089 | 0.299* | 0.067 | 0.763* | -0.069 | 0.174* | 0.087 | 0.156* | 0.013 | 0.952* | 0.001 | 0.970* | -0.008 | 0.780* | -0.002 | 0.940* | -0.021 | 0.943* |
| CA1 | -0.044 | 0.661* | 0.588 | **0.000*** | -0.012 | 0.903* | 0.019 | 0.862* | -0.061 | 0.216* | -0.006 | 0.981* | 0.004 | 0.952* | 0.001 | 0.970* | -0.021 | 0.780* | -0.037 | 0.669* | -0.003 | 0.943* |
| CA2/3 | -0.021 | 0.688* | 0.502 | **0.000*** | 0.019 | 0.903* | -0.010 | 0.862* | -0.071 | 0.216* | -0.016 | 0.981* | -0.016 | 0.952* | -0.032 | 0.664* | -0.027 | 0.780* | -0.073 | 0.468* | -0.021 | 0.943* |
| CA4/DG | -0.044 | 0.661* | 0.608 | **0.000*** | -0.007 | 0.903* | 0.026 | 0.862* | -0.080 | 0.174* | 0.011 | 0.981* | -0.012 | 0.952* | -0.009 | 0.970* | -0.028 | 0.780* | -0.047 | 0.631* | -0.018 | 0.943* |
| Subiculum | -0.025 | 0.661* | 0.725 | **0.000*** | -0.081 | 0.299* | 0.049 | 0.834* | -0.042 | 0.275* | 0.068 | 0.265* | 0.042 | 0.952* | 0.033 | 0.664* | -0.008 | 0.780* | 0.008 | 0.940* | 0.003 | 0.943* |
| SR/SL/SM | -0.028 | 0.661* | 0.649 | **0.000*** | -0.040 | 0.903* | 0.034 | 0.862* | -0.074 | 0.174* | -0.001 | 0.981* | 0.024 | 0.952* | -0.003 | 0.970* | -0.025 | 0.780* | -0.023 | 0.784* | -0.015 | 0.943* |

TIV= Total intracranial volume, UnEx (UE)= Unusual Experiences, CogDis (CD)=Cognitive Disorganisation, IntAn (IA)=Introvertive Anhedonia, ImpNon (IN)=Impulsive Nonconformity, PLE=Psychotic-like experiences. Bold face indicates significance at $p$<0.05, *False discovery rate-adjusted $p$-value

**Table 3.** Summary of regression models predicting volume of the left amygdala and subiculum.

| | Table 3a | | | | | | Table 3b | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Left Amygdala** | | | | | | **Left Subiculum** | | | | | |
| | Step 1 (Covariates) | | Step 2 (Main effects) | | Step 3 (2-way interaction) | | Step 1 (Covariates) | | Step 2 (Main effects) | | Step 3 (2-way interaction) | |
| | β | SE | β | SE | β | SE | β | SE | β | SE | β | SE |
| **Intercept** | 0.000 | 0.036 | 0.000 | 0.036 | −0.008 | 0.039 | 0.000 | 0.036 | 0.000 | 0.036 | −0.035 | 0.038 |
| **Sex** | −0.197*** | 0.043 | −0.199*** | 0.045 | −0.197*** | 0.046 | 0.001 | 0.042 | 0.011 | 0.045 | 0.022 | 0.045 |
| **TIV** | 0.599*** | 0.043 | 0.597*** | 0.043 | 0.599*** | 0.043 | 0.728*** | 0.042 | 0.726*** | 0.042 | 0.737*** | 0.042 |
| **UnEx** | | | −0.109* | 0.050 | −0.124* | 0.057 | | | −0.112* | 0.049 | −0.179** | 0.056 |
| **CogDis** | | | 0.063 | 0.046 | 0.068 | 0.047 | | | 0.058 | 0.045 | 0.085 | 0.046 |
| **IntAn** | | | −0.071 | 0.039 | −0.073 | 0.040 | | | −0.052 | 0.039 | −0.060 | 0.039 |
| **ImpNon** | | | 0.061 | 0.041 | 0.064 | 0.041 | | | 0.088* | 0.040 | 0.104* | 0.040 |
| **PLE** | | | 0.077 | 0.051 | 0.065 | 0.055 | | | 0.051 | 0.050 | −0.002 | 0.054 |
| **PLE×UnEx** | | | | | 0.012 | 0.021 | | | | | 0.053* | 0.021 |
| **df** | 2, 364 | | 7, 359 | | 8, 358 | | 2, 364 | | 7, 359 | | 8, 358 | |
| $R^2$ | 0.518 | | 0.526 | | 0.525 | | 0.526 | | 0.535 | | 0.542 | |
| $\Delta R^2$ | | | 0.015 | | 0.000 | | | | 0.015 | | 0.008 | |
| ***F*** | 197.566*** | | 59.022 | | 51.583 | | 204.233*** | | 61.061 | | 55.077 | |
| $\Delta F$ | | | 2.249* | | 0.304 | | | | 2.316* | | 6.566* | |

TIV= Total intracranial volume, UnEx= Unusual Experiences, CogDis=Cognitive Disorganisation, IntAn=Introvertive Anhedonia, ImpNon=Impulsive Nonconformity, PLE=Psychotic-like experiences, $R^2$ = adjusted $R^2$, SE= Standard error, ***$p$<0.001, **$p$<0.01, *$p$<0.05

**Table 4.** Means and standard deviations (SD) for left and right hemispheric subfield volumes.

| | **Mean volume (SD) ($mm^3$)** | |
|---|---|---|
| | **Left hemisphere** | **Right hemsiphere** |
| Amygdala | 1733.22 (186.06) | 1733.30 (180.93) |
| CA1 | 1016.14 (107.16) | 1074.99 (118.91) |
| CA2/3 | 208.21 (29.01) | 236.46 (30.55) |
| CA4/DG | 728.15 (79.10) | 731.99 (82.62) |
| Subiculum | 512.98 (56.91) | 537.91 (59.56) |
| SR/SL/SM | 548.60 (58.76) | 562.14 (64.55) |

CA= cornu ammonis, DG=Dentate gyrus, SR=stratum radiatum, SL=stratum lacunosum (SL), SM=stratum moleculare.

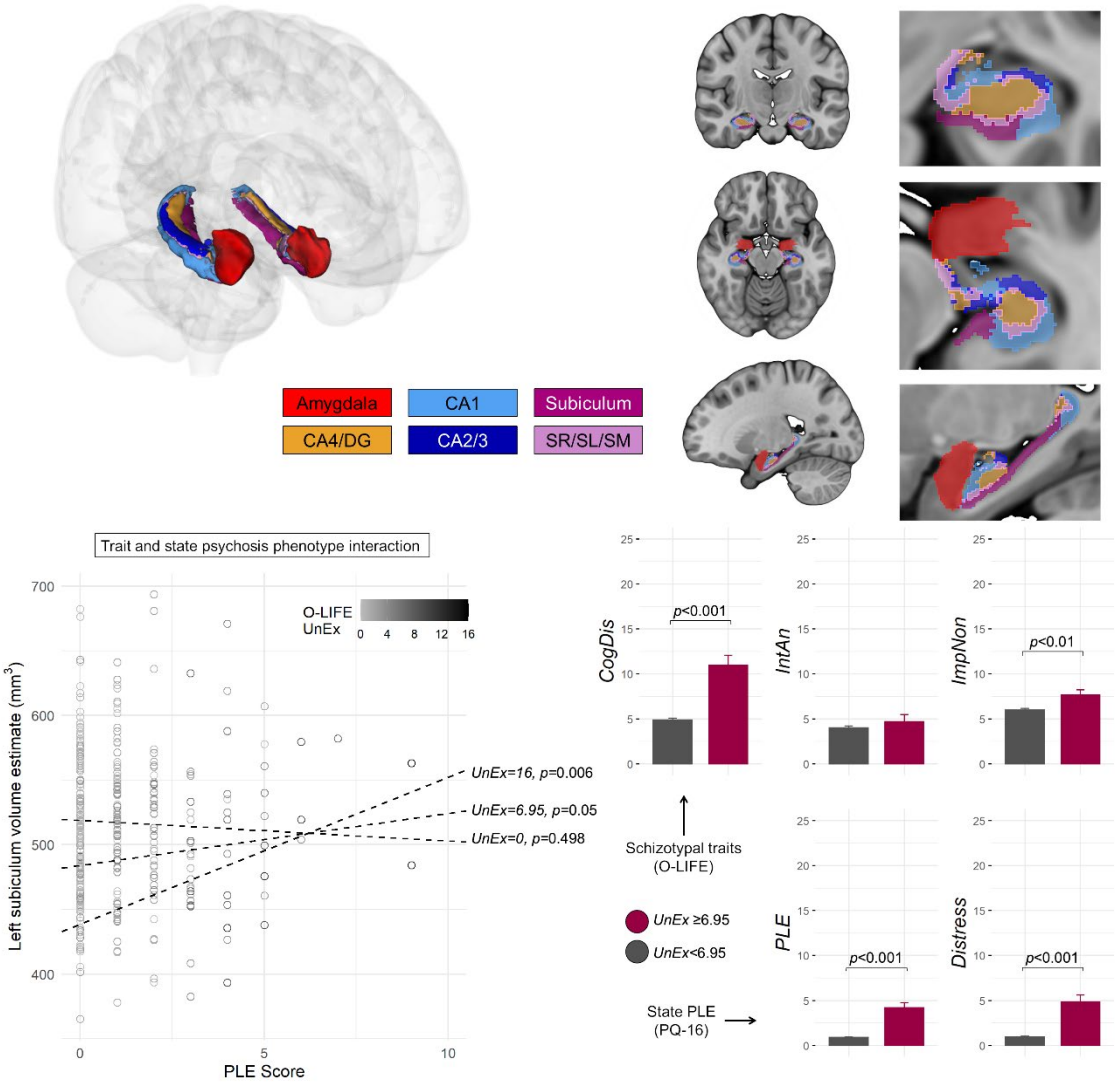


**Figure 1** Visualisation of hippocampal subfield and amygdala segmentation using CoBra atlas (Winterburn et al., 2013) implemented in Computational Anatomy Toolbox (CAT12.7, Gaser et al., 2020) (top panel). Prediction of left subicular volume by psychotic-like experiences [assessed by Prodromal Questionnaire (PQ-16)] is moderated by high levels of positive trait schizotypy (scores ≥6.95) as measured by the Unusual Experiences (*UnEx*) scale of the Oxford-Liverpool Inventory of Life Experiences (O-LIFE) (bottom left). Bottom right side displays mean (±1 standard error) levels of negative (IntAn), disorganised (CogDis), impulsive (ImpNon) traits, PLE and PLE distress severity in a subgroup (n=20) with positive schizotypy levels ≥6.95 compared to the rest of the sample (n=347). Bar graphs show statistically significant group differences based on the Mann-Whitney *U* test. CA= cornu ammonis, DG= dentate gyrus, SR=stratum radiatum, SL=stratum lacunosum (SL), SM=stratum moleculare. Figures were prepared using 3D Slicer (https://www.slicer.org) , MRIcroGL (https://www.mccauslandcenter.sc.edu/mricrogl/) , ggplot2 (Wickham, 2016) and ggpubr (Kassambara, 2020) packages.

## Discussion

The aim of this study was an investigation of state and trait psychosis prone phenotypes within the nonclinical section of a putative psychosis spectrum of neurobiological abnormalities (Nelson et al., 2013; Siever & Davis, 2004; Taylor, Calkins, & Gur, 2020). By examining individuals considered psychiatrically healthy rather than at CHR, we aimed to decouple HC variability from psychopathological states. This objective also underlines the importance of finding psychosis biomarkers applicable to the entire psychosis spectrum. If potential neurobiological markers show graded changes, then subtle correlations with phenotype markers (or interactions thereof) may be expected in the nonclinical part of the spectrum. For this purpose, we chose schizotypy, which represents stable personality dimensions, and PLE that are putatively transitory in nature.

In the main effect analyses, *UnEx*, i.e. positive schizotypy, was a significant estimator of left amygdala and subiculum volume decrease. Additionally, left subicular volume was positively associated with impulsive nonconformity (*ImpNon*). The modest internal consistency of *ImpNon* was comparable to previous reports from an online community sample, which also suggested that *ImpNon* does not dilute the classical three-factor model of schizotypy (Polner et al., 2019). Our findings support the utility of impulsive nonconformity as a separate psychosis phenotypic estimator for brain structural variation. Consistent with previous findings suggesting that failure to distinguish between positive and negative schizotypy dimensions could result in reduced estimator robustness (Barrantes-Vidal, Gross, et al., 2013; Barrantes-Vidal, Lewandowski, & Kwapil, 2010), we found differences in the direction between the regressors that reflect the unique explanatory contribution of each schizotypy dimension. PLE score was not associated with subfield volumes when included alongside schizotypy, indicating that PLE do not explain HC volume variability when accounting for schizotypal traits. The significant main effect of the positive dimension is not confirmed by a previous study (Sahakyan et al., 2020) employing the Multidimensional Schizotypy Scale (MSS; Kwapil, Gross, Silvia, Raulin, & Barrantes-Vidal, 2018). This inconsistency may be attributed to differences between psychometric instruments that provide three (MSS) or four (O-LIFE) phenotype dimensions

entered as model predictors. If the positive O-LIFE dimension reflects the core components of psychosis as supported by associations with dopamine regulating gene variants (Grant, Gabriel, Kuepper, Wielpuetz, & Hennig, 2014), its impact on hippocampal volume would be expectedly higher. Although positive schizotypy did not consistently associate with subfield volume, selective effects in the subiculum partially support a sensitivity to endogenous factors (Alnæs et al., 2019) that may be featured in positive schizotypy to a higher degree.

While the main effect of positive schizotypy on left subiculum volume was negative, the interaction with PLE was associated with volume increases. In the left CA1, this interaction emerged at trend-level significance. Schizotypy *with* PLE relative to schizotypy *without* PLE may signify a dynamic state within the positive trait dimension. A longitudinal behavioural study found that the expression of transient subclinical psychotic features is influenced by time-invariant traits (Rössler, Hengartner, Ajdacic-Gross, Haker, & Angst, 2013). As schizotypal personality organisation bestows an individual with a predisposition for stress response (Grattan & Linscott, 2019; Soliman et al., 2011), PLE could indicate an ongoing susceptibility to latent states and stressors (Barrantes-Vidal, Chun, et al., 2013; Rössler et al., 2013), genetic and environmental influences (Barkhuizen, Pain, Dudbridge, & Ronald, 2020; Brambilla et al., 2014). Extending this to neurobiological measures demonstrated that the positive relationship between PLE and left subicular volume depended on increased positive trait schizotypy. In those individuals at higher positive schizotypy driving this effect, levels of disorganised and impulsive traits, and more importantly, distress severity were augmented. Increased PLE distress severity in high schizotypy is contrary to a previous finding (Kline et al., 2012). Thus, a consistent expression of 'benign' or 'happy schizotypy' (Farias, Underwood, & Claridge, 2013; Grant & Hennig, 2020; Mohr & Claridge, 2015) which could explain the observed positive correlation between PLE and schizotypy does not match the phenotype presented in this study.

We extended the longitudinal HC axis by the inclusion of the amygdala, which, together with the subiculum, showed an unexpected negative association with positive schizotypy. A linkage between these two regions is supported by substantial inputs to the amygdala from the (temporal end of the) CA1, and the subiculum (Pitkänen, Pikkarainen, Nurminen, & Ylinen,

2000), although we did not find the association between positive schizotypy and CA1 region. CA1 volume change may especially demarcate CHR trajectories as it was the only HC subfield associated with progressive global symptomatic deterioration in UHR individuals (Ho et al., 2017). An association between the anterior HC, which includes CA1, and negative schizotypy was dependent on high disorganised schizotypy measured by the MSS (Sahakyan et al., 2020). Still, in alignment with our findings, no main effect of the positive dimension was present. This may reflect results from nonclinical individuals displaying persistent PLE, suggesting that cognitive deficits may be more relevant for poorer outcomes than positive PLE (Brett, Peters, & McGuire, 2015). In UHR individuals, CA1 and subiculum volumes were positively correlated with verbal performance (Vargas et al., 2018), and subicular volume was also associated with negative symptoms in schizophrenia and cognitive deficits in bipolar disorder (Haukvik et al., 2015). Examining how cognitive endophenotypes (Siddi, Petretto, & Preti, 2017) relate to medial temporal lobe structures (Antoniades et al., 2018) in the nonclinical psychosis spectrum may help close a gap in the literature.

Contrary to expectations, we did not find that amygdala volume is related to negative or impulsive trait expressions. Building on previous clinical studies that assessed psychotic symptoms using the PANSS (Kawano et al., 2015; Kühn et al., 2012; Mathew et al., 2014), we could neither confirm associations between negative schizotypy and CA2/3 or CA4/DG. Other studies report functional specialisation in these regions compatible with cognitive impairments (Haukvik et al., 2018; Vargas et al., 2018). Tamminga *et al.* (2012) propose a model in which homeostatic plasticity of CA3 in response to reduced glutamate DG signaling may lead to psychotic memory impairments. A study of first-episode schizophrenia did not confirm HC subfield volume correlations with negative or total PANSS scores, but instead found a positive relationship between right CA1 volume and positive PANSS score (Hýža, Kuhn, Češková, Ustohal, & Kašpárek, 2016). Across the psychosis continuum, relationships between different symptom domains and HC subfields (notably the subiculum) are emerging – especially in the nonclinical part– with variable consistency.

The main effects of disorganised and negative schizotypy dimensions on subfield volumes were insignificant, partially supporting the explanation that high positive schizotypy is the main driver. In the light of previous findings demonstrating that prediction of prodromal outcomes was explained by additive effects of positive and negative schizotypy (Barrantes-Vidal, Gross, et al., 2013), this may suggest that within individuals displaying increased positive schizotypy, these proneness profiles are not wholly enough expressed to effect noticeable differences across all longitudinal volumes utilised in this study. Consistent with this explanation, interactions between positive, negative, and disorganised dimensions reach significance in the anterior, but not the posterior portion of the hippocampus (Sahakyan et al., 2020), supporting an anterior-posterior gradient of pathological hippocampal volume changes in clinical subjects (McHugo et al., 2018). Apart from longitudinal, opposed to anterior/posterior subdivisions, usage of different automated segmentation methods may further explain discrepancies among studies.

In this study, HC subfield volume correlates corresponded to psychosis phenotypes absent of a clinically manifest vulnerability. Notably, this does not necessitate exemption from vulnerability in the form of genotypes associated with PLE and schizotypy (Legge et al., 2019; Meller et al., 2019), or hippocampal subfield volumes (Alnæs et al., 2019; van der Meer et al., 2020). As indicated by moderation, in healthy participants with PLE not indicative of CHR, the effect on HC subfield volume was trait schizotypy driven. Lack of association between PLE and medial temporal structures over and above the schizotypal traits may be explained by comparatively small effect sizes or reduced PLE persistence (Dominguez, Wichers, Lieb, Wittchen, & Van Os, 2011; Hanssen, Bak, Bijl, Vollebergh, & Os, 2005; Nelson, Fusar-Poli, & Yung, 2012). Since the PQ-16 does not provide a measure of PLE persistence, longitudinal investigations are required to address this issue. The present findings imply a sensitivity of the limbic structures to time-invariant traits rather than PLE. Furthermore, while considerable overlap appears between the positive schizotypy dimension and PLE in both healthy and CHR cohorts (Barrantes-Vidal, Gross, et al., 2013), and their relationship with neurobiological targets, unusual experiences in the context of positive schizotypy and PLE might not be

interchangeable phenomenological entities. We advocate a phenotype distinction based on transience (PLE) and stability (traits) (Pedrero & Debbané, 2017; Seiler, Nguyen, Yung, & O'Donoghue, 2020). However, to our best knowledge, no assessment of the discriminant validity between positive psychometric schizotypy and PLE so far exists. There was a considerable overrepresentation of females and an absence of psychopathology in the present cohort, limiting comparability with other studies reporting expectedly higher CHR screening rates in the general population (McDonald et al., 2018).

This study was also the first to use CAT12 automated segmentation for HC subfield delineation. This achieves an alternative route to limbic subfield characterisation compared anterior and posterior HC subdivisions applied elsewhere (McHugo et al., 2018; Sahakyan et al., 2020). Our findings from a novel toolbox call for replication so that results from different HC subfield volumetry methods will expectedly accumulate. We provide evidence for an association between elevated trait schizotypy and left subiculum volume reductions. This result complements the dose-response relationship of left subfield volume reductions in the clinical part of the psychosis spectrum (Vargas et al., 2018). Additionally, an interaction between psychosis prone traits and transitory PLE may reflect schizotypy dynamics, resulting in medial lobe structural variation. Together with previous findings, we propose that future studies involving PLE could explore (and control for) variance explained by positive schizotypy, PLE distress, or persistence. Aetiological studies involving endophenotypes capturing genetic psychosis liability, especially in association with medial lobe structures, could benefit from incorporating individual differences.

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**Conflicts of interest**

All authors declare no conflicts of interest.

**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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## 7.4. Authorship contributions

Contributor roles were adopted from the Contributor Role Taxonomy (CRediT, http://credit.niso.org) outlined in Brand, A., Allen, L., Altman, M., Hlava, M., & Scott, J. (2015). Beyond authorship: Attribution, contribution, collaboration, and credit. Learned Publishing, 28(2), 151–155. https://doi.org/10.1087/20150211

**Study 1:** Evermann, U., Gaser, C., Besteher, B., Langbein, K., & Nenadić, I. (2020). Cortical gyrification, psychotic-like experiences, and cognitive performance in nonclinical subjects. *Schizophrenia Bulletin, 46*(6), 1524–1534. DOI: https://doi.org/10.1093/schbul/sbaa068(IF: 7.958)

Contributions: 65%, UE conceptualised mediation models, conducted formal analyses, wrote the original draft of the manuscript and was responsible for the visualisation of results.

**Study 2:** Evermann, U., Schmitt, S., Meller, T., Pfarr, J.-K., Grezellschak, S., & Nenadić, I. Distress severity in perceptual anomalies moderates the relationship between prefrontal brain structure and psychosis proneness in nonclinical individuals. (submitted to *European Archives of Psychiatry and Clinical Neuroscience*)

Contributions: 75% UE was involved in project coordination, collected data, developed statistical models, conducted the formal analyses, wrote the original draft and was responsible for results visualisation.

**Study 3:** Evermann, U., Gaser, C., Meller, T., Pfarr, J.-K., Grezellschak, S., & Nenadić, I. Nonclinical psychotic-like experiences and schizotypy: interactions and differential associations with hippocampal subfield and amygdala volumes. (submitted to *Psychological Medicine*)

Contributions: 75% UE was involved in project coordination, collected data, developed statistical models, conducted the formal analyses, wrote the original draft and was responsible for results visualisation.

## 7.5. Curriculum Vitae

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Meine akademischen Lehrer/-innen waren in Brighton:

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