Psychological Medicine

cambridge.org/psm

Basic symptoms and gray matter volumes of patients at clinical high risk for psychosis

Daniela Hubl[1,*], Chantal Michel[2,*], Frauke Schultze-Lutter[3], Martinus Hauf[4], Benno G. Schimmelmann[2,5], Michael Kaess[2,6] and Jochen Kindler[2]

[1]Translational Research Center, University Hospital of Psychiatry and Psychotherapy, University of Bern, Bern, Switzerland; [2]University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Switzerland; [3]Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany; [4]Support Center for Advanced Neuroimaging (SCAN), Institute for Diagnostic and Interventional Neuroradiology, University of Bern, Switzerland; [5]University Hospital of Child and Adolescent Psychiatry, University Hospital Hamburg Eppendorf, Hamburg, Germany and [6]Section for Translational Psychobiology in Child and Adolescent Psychiatry, Department of Child and Adolescent Psychiatry, Center for Psychosocial Medicine, University Hospital Heidelberg, Heidelberg, Germany

Original Article

*These authors contributed equally to this work

Cite this article: Hubl D, Michel C, Schultze-Lutter F, Hauf M, Schimmelmann BG, Kaess M, Kindler J (2021). Basic symptoms and gray matter volumes of patients at clinical high risk for psychosis. *Psychological Medicine* **51**, 2666–2674. https://doi.org/10.1017/S0033291720001282

Received: 1 July 2019
Revised: 14 February 2020
Accepted: 16 April 2020
First published online: 14 May 2020

Key words:
Basic symptoms; first-episode psychosis; gray matter volume; psychosis risk; ultra-high risk

Author for correspondence:
Jochen Kindler,
E-mail: jochen.kindler@upd.unibe.ch

Abstract

Background. Clinical high-risk (CHR) for psychosis is indicated by ultra-high risk (UHR) and basic symptom (BS) criteria; however, conversion rates are highest when both UHR and BS criteria are fulfilled (UHR&BS). While BSs are considered the most immediate expression of neurobiological aberrations underlying the development of psychosis, research on neurobiological correlates of BS is scarce.

Methods. We investigated gray matter volumes (GMV) of 20 regions of interest (ROI) previously associated with UHR criteria in 90 patients from the Bern early detection service: clinical controls (CC), first-episode psychosis (FEP), UHR, BS and UHR&BS. We expected lowest GMV in FEP and UHR&BS, and highest volume in CC with UHR and BS in-between.

Results. Significantly, lower GMV was detected in FEP and UHR&BS patients relative to CC with no other significant between-group differences. When ROIs were analyzed separately, seven showed a significant group effect (FDR corrected), with five (inferior parietal, medial orbitofrontal, lateral occipital, middle temporal, precuneus) showing significantly lower GM volume in the FEP and/or UHR&BS groups than in the CC group (Bonferroni corrected). In the CHR group, only COGDIS scores correlated negatively with cortical volumes.

Conclusions. This is the first study to demonstrate that patients who fulfill both UHR and BS criteria – a population that has been associated with higher conversion rates – exhibit more severe GMV reductions relative to those who satisfy BS or UHR criteria alone. This result was mediated by the BS in the UHR&BS group, as only the severity of BS was linked to GMV reductions.

Introduction

In 2010, approximately 38% of the European population, almost 165 million people, suffered from neuropsychiatric disorders: the largest contributor to the overall burden of morbidity in Europe (Wittchen et al., 2011). Psychoses in general, and particularly schizophrenia, are among the disorders that incur high costs and result in many years living with disability (Vigo, Thornicroft, & Atun, 2016). Psychotic disorders have a complex etiology that culminates in a first episode during late adolescence or early adulthood (Kirkbride et al., 2006; Kohler et al., 2009). In the vast majority of cases, the first episode is preceded by a prodrome of 5–6 years on average in which a multitude of mental problems and symptoms, as well as the first psychosocial deficits, occur (Salokangas et al., 2014; Schultze-Lutter et al., 2015*b*). Furthermore, a longer duration of untreated psychosis and its preceding prodrome has been associated with negative outcomes (Penttila, Jaaskelainen, Hirvonen, Isohanni, & Miettunen, 2014). Thus, early detection of and intervention for psychotic disorders during its prodrome – i.e. an indicated prevention of psychosis – has been widely adopted for its potential to alter the course of psychotic disorders (Fusar-Poli et al., 2013; Schmidt et al., 2015; Schultze-Lutter et al., 2015*a*).

Over the past two decades, research has increasingly focused on the identification of sensitive and specific clinical high-risk (CHR) criteria that can inform assessments of psychosis through clinical interviews conducted by trained mental health professionals (Fusar-Poli et al., 2015; Schmidt et al., 2015; Schultze-Lutter et al., 2015*a*). Two major approaches to CHR criteria are currently used to identify an increased psychosis risk (Fusar-Poli et al., 2013; Fusar-Poli et al., 2015; Schultze-Lutter et al., 2015*a*): (1) Symptomatic ultra-high risk (UHR) criteria rely on attenuated or brief intermittent psychotic symptoms (APS and BIPS, respectively) to detect an imminent risk of psychosis within 12 months and additionally

CAMBRIDGE UNIVERSITY PRESS

include the non-symptomatic genetic risk-functional decline criterion (Fusar-Poli et al., 2013). Meta-analyses indicate that UHR criteria achieve conversion rates of 9.6% at 6 months and 37% at >4 years (Schultze-Lutter et al., 2015*a*). (2) Basic symptom (BS) criteria rely on subjective disturbances in thought and perception processes and aim to detect risk of psychosis as early as possible. Fourteen BSs (online Supplemental Table S1) were identified to be specific to the development of first-episode psychosis (FEP) and were employed in two CHR criteria: cognitive disturbances (COGDIS) and cognitive-perceptive basic symptoms (COPER) (Schultze-Lutter, 2009; Schultze-Lutter et al., 2012; Schultze-Lutter, Klosterkotter, Picker, Steinmeyer, & Ruhrmann, 2007*b*). Conversion rates in samples using BS criteria range from 25.3% at 1 year to 61.3% at >4 years (Schultze-Lutter et al., 2015*a*). Importantly, in clinical studies that assessed both UHR and BS, conversion rates were highest when criteria of both approaches were fulfilled (UHR&BS) (Michel, Ruhrmann, Schimmelmann, Klosterkotter, & Schultze-Lutter, 2014; Schultze-Lutter et al., 2012; Schultze-Lutter, Klosterkotter, & Ruhrmann, 2014); moreover, in a community sample of individuals aged 16–40 years, the odds of identifying a mental disorder or functional impairment were by far the highest when the criteria of both approaches were met (Ruhrmann et al., 2010; Schultze-Lutter et al., 2014). Yet, on account of the considerable rate of CHR patients not converting to full-blown psychosis, the use of additional predictors, in particular structural and functional brain aberrations, have been proposed to improve the prognostic value of CHR criteria (Cannon, 2016; Khoury & Nasrallah, 2018; Kindler et al., 2016, 2018; Koutsouleris et al., 2015, 2018; Mikanmaa et al., 2019).

Abnormalities in gray matter volume (GMV) occurring before the onset of psychosis have been intensively studied in UHR patients over the last decade (Borgwardt et al., 2007). A meta-analysis of neuroimaging studies that collectively investigated the GMV of 896 UHR patients and 701 controls observed widely distributed GMV reductions, especially in the prefrontal, limbic, and temporoparietal cortices, in UHR patients compared to controls (Fusar-Poli et al., 2011*a*). Although BSs have been regarded as the most immediate psychopathological expression of neurobiological aberrations underlying the development of psychosis (Schultze-Lutter, 2009; Schultze-Lutter et al., 2012, 2016, 2020), comparatively less research has considered the neurobiological correlates of BS (Schultze-Lutter et al., 2016): only five studies have hitherto investigated GMV characteristics related to BS in CHR samples (Hurlemann et al., 2008; Koutsouleris et al., 2014, 2009*a*,*b*; Tepest et al., 2013). These studies distinguished indications of early risk of psychosis from late risk: the former is characterized by either COPER or the UHR genetic risk and functional decline criterion (GRFD) in the absence of symptomatic UHR states; the latter, by the fulfillment of APS or BIPS criteria. In comparison to controls, the COPER/GRFD group presented more GMV reductions in the fusiform, superior, middle, and inferior temporal gyri, the amygdala, and the hippocampus. A dearth of studies on the COGDIS criterion and the combined presence of UHR and BS criteria (UHR&BS) remains in the literature. As UHR&BS has been associated with increased clinical conversion rates, it can be assumed that this combination also associates more strongly with neurobiological markers such as GMV abnormalities.

The present study therefore aimed to differentially investigate the GMV of brain regions previously associated with UHR criteria (Fusar-Poli et al., 2011*a*) by separating our CHR sample into three different groups: those who fulfilled only UHR criteria, those who fulfilled only BS criteria, and those who fulfilled both (UHR&BS). We expected the UHR&BS group to feature the most pronounced GMV reductions – similar in severity to the GMV reductions of the FEP group – followed respectively by the BS or UHR groups in comparison to a clinical control group (CC). Furthermore, we assessed whether GMV reductions are differentially related to BS or UHR severity; as BS is considered to more strongly correspond with neural maturation, we predicted that GMV reductions would be more closely linked to BS (Schultze-Lutter et al., 2020).

Method

Participants

The study sample ($N = 90$) was recruited at the Bern Early Recognition and Intervention Center (FETZ Bern, www.upd.ch/fetz). The FETZ Bern is the only psychosis-risk detection center in the Canton of Bern with a catchment area of approximately 1.5 million inhabitants; the center screens ~80 patients/year (age 8–40 years) for psychosis risk symptoms according to state-of-the-art guidelines (Schmidt et al., 2015; Schultze-Lutter et al., 2015*a*). Apart from accepting patients who enroll on their own initiative, patients with various psychiatric symptoms are admitted to the FETZ Bern by physicians and psychosocial institutions whenever there is clinical suspicion of early psychotic development. The clinical basic assessment includes a psychopathological evaluation, a cognitive test battery, cerebral magnetic resonance imaging (cMRI), and a routine blood screening. The present study sample consisted of consecutive attendees assessed from 2010 to 2018. Patients were diagnosed as CHR ($n = 48$), CC ($n = 28$), or FEP ($n = 14$) with full-blown psychotic symptoms. Patients considered to be CC did not fulfil any CHR criterion and had no history of past or present psychosis. Those with CHR were further distinguished as fulfilling BS ($n = 14$), UHR ($n = 16$), or UHR&BS ($n = 18$) criteria. For the current study, we included all patients from the FETZ Bern that (1) were admitted to our center, (2) were diagnosed with CHR or FEP or qualified as CC, (3) were subjected to standardized cMRI, and (4) agreed to the anonymized scientific use of their data.

We received approval for all procedures from the ethics committee of the Canton of Bern. All participants gave informed consent and, in the case of minors, parental informed consent with the child's assent was provided.

Diagnostic assessment

Two sets of CHR criteria were employed (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2015*a*): (1) The UHR criteria (Yung et al., 1998) were evaluated with the Structured Interview for Psychosis-Risk Syndromes (SIPS) (McGlashan, Walsh, & Woods, 2010), which assesses the presence of APS, BIPS, and GRFD criteria. (2) The BS criteria (Klosterkotter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001; Schultze-Lutter et al., 2012, 2016), including COPER and COGDIS, were assessed with the Schizophrenia Proneness Instrument, Adult version (SPI-A) (Schultze-Lutter, Addington, Ruhrmann, & Klosterkotter, 2007*a*), and Child & Youth Version (SPI-CY) (Schultze-Lutter & Koch, 2010), respectively. All interviewers underwent intensive training for 3 months prior to diagnosing patients and supervising ratings during the diagnostic process by Frauke Schultze-Lutter (F.S.-L).

The adult and pediatric versions of the Mini-International Neuropsychiatric (Sheehan et al., 1998, 2010) were used to assess

https://doi.org/10.1017/S0033291720001282 Published online by Cambridge University Press

diagnoses informed by the Diagnostic and Statistical Manual of Mental Disorders IV. Information on concurrent diagnoses made according to the Diagnostic and Statistical Manual of Mental Disorders IV is provided in online Supplemental Table S2. Psychosocial functioning was evaluated with the Social and Occupational Functioning Assessment Scale (SOFAS) (APA, 1994). Antipsychotic medication was converted to chlorpromazine equivalents according to standard guidelines (Leucht, Wahlbeck, Hamann, & Kissling, 2003).

MRI data analysis

Imaging was performed using a 3.0 T Magnetom Verio (Siemens Medical Systems, Erlangen, Germany) with a standard 12-channel radio frequency head coil. High-resolution structural images were obtained using 3D T1-weighted modified driven equilibrium Fourier transform (MDEFT) scans [sagittal slices, 176; 256 × 256 matrix; slice thickness, 1 mm; voxel size, $1 \times 1 \times 1$ mm^3; repetition time (TR), 7.92 ms; echo time (TE), 2.48 ms; flip angle (FA), 16°].

Analysis of gray matter in MR images was performed on a Mac OSX 10.8 workstation using FreeSurfer version software (version 6.0). All data sets were screened for anatomical abnormalities, excessive motion, successful normalization, and artifacts. First-level autoreconstruction was then performed with the images in FreeSurfer. The skull-stripped brains were checked for remaining dura, sinuses, or other artifacts that could interfere with successful segmentation. When artifacts were found, images were edited manually. When deemed sufficiently clean, images were run through second- and third-level autoreconstruction, which allowed for the extractions of GM surface area, thickness, and volume. Finally, automated cortical parcellation was performed using a separate processing pipeline included in the FreeSurfer software package.

A priori, 20 regions of interest (ROI) previously associated with risk of psychosis (Fusar-Poli et al., 2011*a*; Fusar-Poli, Radua, McGuire, & Borgwardt, 2012; Roalf et al., 2017) were defined, and their respective GMVs were calculated: the anterior cingulate (rostral & caudal), caudal middle frontal, entorhinal, hippocampus, inferior parietal, inferior temporal, insula, lateral occipital, lateral orbitofrontal, medial orbitofrontal, middle temporal, pars opercularis, pars triangularis, precentral, precuneus, rostral middle frontal, superior frontal, superior temporal, superior temporal sulcus, and supramarginal (bilaterally).

Statistics

Demographics

SPSS 21.0 was used to compare frequencies and percentages with χ^2-square tests, means of normally distributed interval data with two-sample *t* tests, analysis of variance (ANOVA), and non-normally distributed interval or ordinal data with Kruskal–Wallis and Mann–Whitney *U* tests. Statistical significance of two-sided tests was set at $p \leqslant 0.05$.

Neuroimaging

First, an overall analysis of covariance (ANCOVA) with the ROI as the within-subject factor and the diagnostic group (CC, FEP, BS, UHR, and UHR&BS) as the between-subject factor with a covariate of total intracranial volume (TIV) was calculated. Post-hoc group comparisons were conducted using Bonferroni correction.

Second, 20 separate ANCOVAs with diagnostic group as the fixed factor and GM volume for each ROI with total intracranial volume as the covariate were calculated. False discovery rate (FDR) corrected results are reported. Post-hoc group comparisons were conducted, and Bonferroni corrected results are reported. Effect sizes for ANCOVAs were calculated with Partial Eta Squared (η^2) for pairwise comparisons with Cohen's d (d).

Finally, in those ROIs with a significant group effect, Spearman rank correlations were conducted in the CHR group between COPER, COGDIS, and APS/BIPS (SISOP total/positive) scores and cortical GM volumes ($p \leqslant 0.05$, 2-sided, FDR corrected).

Results

Demographics

No differences in age, sex (Table 1), or chlorpromazine equivalents ($F_{4,13} = 0.3$, $p = 0.87$) were detected among the groups. Patients with FEP exhibited lower psychosocial function (Table 1).

Among the CHR patients, those with UHR had significantly lower BS total scores than did the patients with BS ($p = 0.018$) or BS&UHR ($p = 0.001$). Additionally, post-hoc group comparisons yielded significantly lower SIPS positive scores among BS patients than BS&UHR patients ($p = 0.037$). No other significant differences were detected.

GMV group differences

Considering total ROIs, the overall ANCOVA yielded a significant group effect ($F_{4,84} = 3.61$, $p = 0.009$, $\eta^2 = 0.147$), indicating significant group differences in GMV. Post-hoc tests indicated significantly lower GMV in FEP when compared to CC (18 244.9 ± 1391.7 μl *v.* 19 649.1 ± 1391.5 μl, $p = 0.028$, d = 1.0), and significantly lower GMV in UHR&BS when compared to CC (18 321.8 ± 1394.7 μl *v.* 19 649.1 ± 1391.5 μl, $p = 0.023$, d = 0.95), but no other significant differences.

When separated for each ROI, seven of the 20 investigated ROIs showed a significant group effect, and remained significant after FDR correction (Fig. 1): entorhinal ($F_{4,84} = 3.2$, $p = 0.017$, $\eta^2 = 0.133$), inferior parietal ($F_{4,84} = 4.4$, $p = 0.003$, $\eta^2 = 0.173$), inferior temporal ($F_{4,84} = 3.3$, $p = 0.015$, $\eta^2 = 0.136$), lateral occipital ($F_{4,84} = 3.6$, $p = 0.009$, $\eta^2 = 0.148$), medial orbitofrontal ($F_{4,84} = 3.8$, $p = 0.007$, $\eta^2 = 0.152$), middle temporal ($F_{4,84} = 3.3$, $p = 0.014$, $\eta^2 = 0.137$), and precuneus ($F_{4,84} = 3.5$, $p = 0.01$, $\eta^2 = 0.145$) (for means and standard error of brain volumes, see online Supplementary Table S3).

Pairwise comparisons of GM volumes between diagnostic groups are depicted in Table 2 and Fig. 2. Six out of seven ROIs remained significant after Bonferroni correction. Three ROIs (inferior parietal, lateral occipital, and medial orbitofrontal) showed significantly lower GMV in UHR&BS and FEP, and another two ROIs (middle temporal, precuneus) showed significantly lower GMV in UHR&BS as compared to CC, whereas entorhinal cortex showed significantly higher GMV in UHR as compared to CC. For the inferior temporal cortex, pairwise comparisons did not yield any significant group difference ($p > 0.05$).

GMV correlations with COGDIS, COPER, and APS/BIPS scores

In CHR patients ($n = 48$), significant negative correlations were detected between COGDIS scores and GMV in two ROIs: inferior parietal ($R = -0.36$, $p \leqslant 0.05$) and middle temporal ($R = -0.34$, $p \leqslant 0.05$).

No significant correlations were detected between COPER or APS/BIPS scores and GMV in any ROI ($R < 0.30$, $p > 0.05$).

https://doi.org/10.1017/S0033291720001282 Published online by Cambridge University Press

Table 1. Sample demographics

	CC $n = 28$		FEP $n = 14$		BS $n = 14$		UHR $n = 16$		UHR&BS $n = 18$		Test value	p
Age (in years); mean (S.D.)	18.8	(5.6)	20.1	(6.1)	20.2	(3.3)	19.5	(6.8)	19.4	(3.7)	0.24	0.92
Sex (m/f)	18 m/10f		7 m/7f		9 m/5f		7 m/9f		6 m/12f		5.5	0.24
SOFAS; mean (S.D.)	65.2	(2.9)	48.1	(3.3)	61.4	(3.1)	63.3	(2.4)	62.1	(2.7)	4.6	0.002
SIPS total; mean (S.D.)	-	-	-	-	28.1	(8.3)	27.9	(11.0)	33.0	(13.1)	1.1	0.34
SIPS pos, mean (S.D.)	-	-	-	-	8.1	(4.4)	8.6	(2.7)	11.0	(4.4)	2.8	0.07
BS total; mean (S.D.)	-	-	-	-	22.4	(18.7)	8.1	(8.2)	28.6	(18.8)	7.2	0.002

CC = clinical controls; FEP = first-episode psychosis; BS = 14 basic symptoms included in COPER and COGDIS; UHR = ultra high risk; Sex m = male, f = female; SOFAS = Social and Occupational Functioning Assessment Scale; SIPS = Structured Interview for Psychosis-Risk Syndromes; SIPS pos = Sum score of the 5 SIPS positive items.
Test value refers to Anova, Kruskal–Wallis or χ^2-square tests. Significance was set at $p < 0.05$, two-sided (uncorrected).

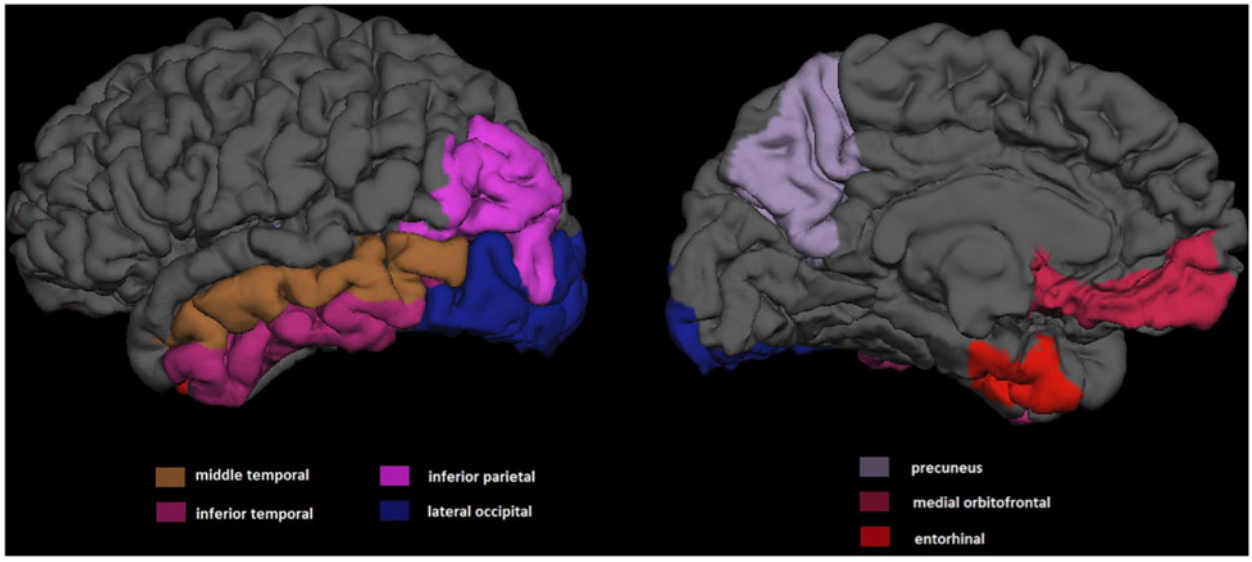

Fig. 1. Freesurfer-based visualization of the seven regions of interest with significant group effects in gray matter volume. The inferior parietal ($p < 0.005$), inferior temporal ($p = 0.05$), lateral occipital ($p < 0.01$), medial orbitofrontal ($p < 0.01$), middle temporal ($p \leqslant 0.05$), precuneus ($p = 0.01$) and entorhinal ($p < 0.05$) cortex, showed a significant group effect (FDR corrected).

Discussion

To the best of our knowledge, this is the first neuroimaging study to differentially evaluate GMV reductions in patients fulfilling different CHR criteria – namely, the UHR and BS criteria, and the combination of both – in comparison to FEP and CC.

GMV group differences in total

As expected, when all 20 investigated ROIs were considered together, the GMV reductions of patients presenting with UHR&BS criteria and, hence, the highest risk of psychosis were found to be the most similar to those of FEP: both groups showed significantly lesser GMV than did the CC group. When the ROIs were separated, five regions – inferior temporal, inferior parietal, lateral occipital, medial orbitofrontal, precuneus – were both: (1) following our primary hypothesis of significantly lower gray matter in FEP and UHR&BS as compared to CC and (2) remaining significant after FDR correction. Importantly, the findings were of medium-to-large effect sizes. In line with what has been reported for conversion prediction (Schultze-Lutter et al., 2014) and for clinical relevance of CHR symptoms and criteria (Schultze-Lutter, Michel, Ruhrmann, & Schimmelmann, *2018a*), our results indicate an additive effect of the two major evaluative approaches to CHR criteria also in detecting early neurobiological aberrations potentially related to the future development of psychosis, such as GMV reductions.

In line with the conceptualization of BS as the most immediate symptomatic expression of the neurobiological processes leading to psychosis (Schultze-Lutter et al., 2016) and of cognitive deficits as a core dimension of psychoses (Fluckiger et al., 2019; Heckers et al., 2013; Insel, 2010; Mollon, David, Zammit, Lewis, & Reichenberg, 2018), the severity of the cognitive BS, included in COGDIS, correlated with GMV reductions; foremost in parietal and temporal regions. Thus, as the UHR&BS patients exhibited the most severe BS, their GMV reductions might be moderated by BS: especially the cognitive symptoms included in COGDIS, which have been recommended for inclusion in the definition of CHR status by the European Psychiatric Association (EPA) (Schultze-Lutter et al., 2015*a*) in addition to the APS and BIPS UHR criteria.

BSs are a heterogeneous set of subtle self-experienced disturbances in cognition, body perception, motor action, affect, drive,

https://doi.org/10.1017/S0033291720001282 Published online by Cambridge University Press

Table 2. Pairwise comparisons of gray matter volumes of the seven ROIs, significant in overall ANCOVA

Region	Group 1		Group 2	*p*-value		effect size
Middle temporal	CC	>	UHR&BS	0.008	**	1.07
Inferior parietal	CC	>	FEP	0.032	*	0.88
	CC	>	UHR&BS	0.003	**	1.11
Lateral occipital	CC	>	FEP	0.021	*	1.00
	CC	>	UHR&BS	0.047	*	0.89
Medial orbitofrontal	CC	>	FEP	0.039	*	0.95
	CC	>	UHR&BS	0.01	**	0.95
Precuneus	CC	>	UHR&BS	0.019	**	0.93
Entorhinal	UHR	>	CC	0.022	*	0.87
Inferior temporal	-	-	-	N.S.		N.S.

CC = clinical controls, FEP = first-episode psychosis, BS = basic symptoms, UHR = ultra-high risk, *p*-values refer to ANCOVA with gray matter volume as a dependent variable, group (UHR, BS, UHR&BS, FEP, CC) as a fixed factor and intracranial volume as a covariate, Cohen's d was calculated to measure effect size, N.S. not significant, * significant at $p < 0.05$, **significant at $p < 0.01$, Bonferroni corrected.

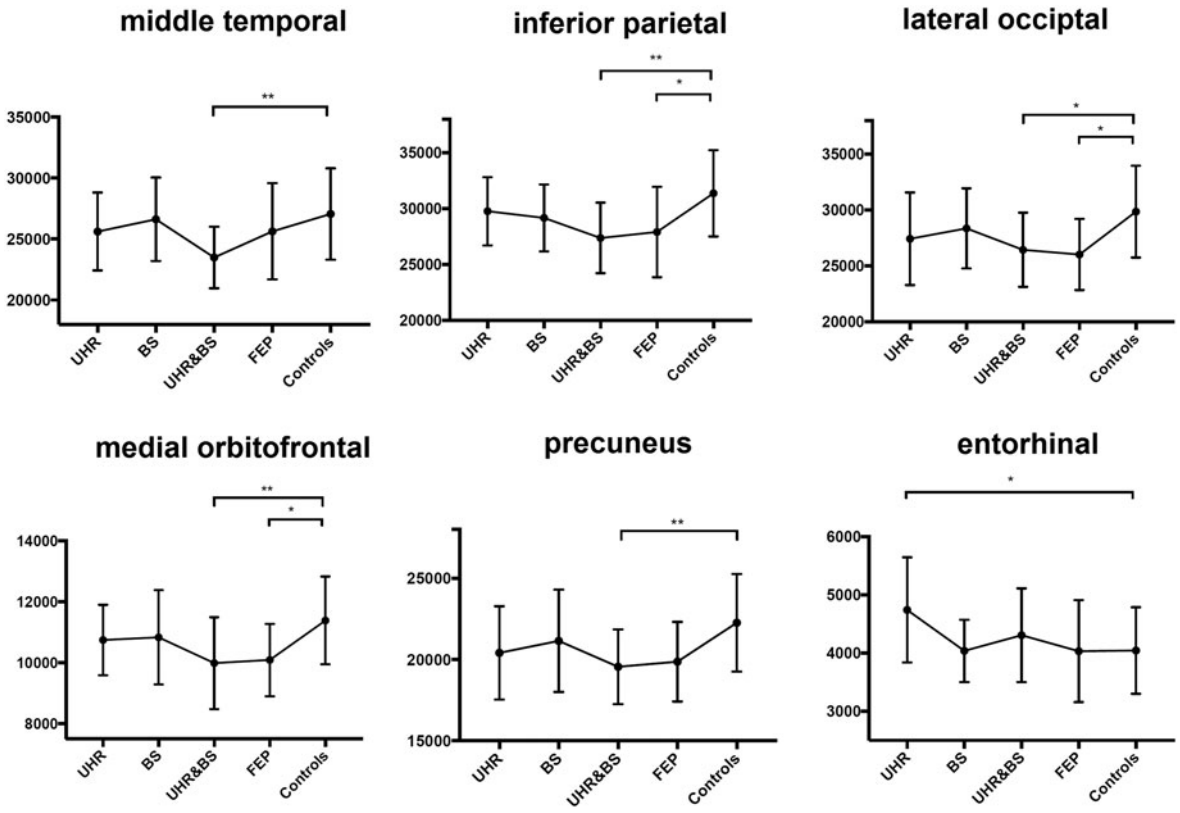

Fig. 2. Gray matter volumes in diagnostic subgroups, pairwise comparisons. Controls = clinical controls, FEP = first-episode psychosis, BS = basic symptoms, UHR = ultra-high risk. Gray matter cortical volume in μl. Five areas (inferior temporal, inferior parietal, lateral occipital, medial orbitofrontal, precuneus) showed the lowest GMV in FEP and/or UHR&BS, whereas the entorhinal cortex showed highest GMV in UHR..*significant 2-group differences at $p < 0.05$, ** significant at $p < 0.01$ (Bonferroni corrected).

and stress tolerance that are distinct from the attenuated psychotic symptoms included in the symptomatic UHR criteria (Fluckiger et al., 2016; Schultze-Lutter et al., 2012, 2016). Among the BSs, 14 psychosis-specific cognitive and perceptual symptoms (Table S1) were included in COPER and COGDIS (Schultze-Lutter, 2009, 2012); under physiological conditions, the ROIs in which significant differences in GMVs were found are responsible for mental functions that, when disturbed, correspond to the disturbances in mental processes captured by these more specific BS (Schultze-Lutter, 2009; Süllwold & Huber, 1986). In the following discussion, we will focus

https://doi.org/10.1017/S0033291720001282 Published online by Cambridge University Press

on potential associations among ROIs, functions, and BSs, with special emphasis on regions that showed a significant group effect (FDR < 0.05) and followed our assumptions of lowest GMV in FEP and UHR&BS groups compared to CC.

Regional specifics of GMV

The parietal cortex shows the earliest and most extensive GMV changes in childhood-onset and chronic schizophrenia (Thompson et al., 2001; Weinberg et al., 2016), respectively. In the inferior parietal cortex, volume (Borgwardt et al., 2008) and thickness (Cannon et al., 2015) reductions have previously been reported in UHR samples, and a steeper rate of GMV loss in the parietal cortex has been associated with conversion to psychosis (Chung et al., 2017). The inferior parietal cortex is a heteromodal association area that is essential to the assimilation and communication of visual and auditive information to higher sensory and motor areas; hence, this area is integral to sensory integration, perception, self-awareness, executive functioning, semantic processing, social cognition and emotion regulation: functions that are impaired in psychosis (Keefe & Harvey, 2012; Penn, Sanna, & Roberts, 2008). On a symptom level, BSs included in COGDIS (Table S1), such as the inability to divide attention, captivation of attention, thought blockages, interference or pressure, disturbance of receptive and expressive speech, and disruption of abstract thinking or unstable ideas of reference, might be closely related to parietal cortical functioning: this region not only yielded the highest effect size but also showed a negative correlation with COGDIS scores.

Further findings include GMV reduction in the medial orbitofrontal cortex, wherein volume reductions and reduced neuronal activity have previously been associated with UHR, FEP, and chronic schizophrenia (Borgwardt et al., 2008; Chakirova et al., 2010; Jung, Borgwardt, Fusar-Poli, & Kwon, 2012; Kindler et al., 2018). This region is reportedly responsible for building associations among context, locations, events, and emotional responses; hence, it is implicated in decision-making and memory (Euston, Gruber, & McNaughton, 2012). Moreover, the orbitofrontal cortex is important for reward processing (Rolls, 2000). Specific attenuated psychotic symptoms such as ideas of reference, magical thinking, and suspiciousness, have been linked to orbitofrontal volume reductions in patients with psychosis (Borgwardt et al., 2008). Of these symptoms, only ideas of references is closely related to the BS of 'unstable ideas of reference': the patient immediately recognizes that inadequate salience is attached to random stimuli without – as in ideas of reference – considering a relation to him or herself for even a moment. More research on non-specific BS, such as memory disturbances, disturbance of the comprehension of visual or acoustic stimuli, reduced emotional responsiveness, increased indecisiveness, and reduced spontaneity, and their potential association with GMV in the orbitofrontal cortex is needed to better understand the relationship between neurobiology and human experiences (Schultze-Lutter, Schmidt, & Theodoridou, 2018*b*).

In the lateral occipital cortex (Reavis et al., 2017), cortical thickness is reduced in schizophrenia patients who exhibit abnormalities in visual perception. Disturbances of visual perception, as included in COPER (e.g. porropsia, micropsia, distorted shape-perception or colour vision), might be specifically associated with this area but were likely too infrequent to contribute to a significant correlation between the overall severity of all 10 COPER-BS and the GMV of the lateral occipital cortex. Thus, the GMV reduction may be principally moderated by, in terms of UHR, the more frequent attenuated hallucinations.

The precuneus cortex is involved in visuo-spatial imagery, memory, and experience of agency (Cavanna & Trimble, 2006), and plays an important role in the regulation of the default mode network (Kindler et al., 2015). Reductions in its GMV were associated with UHR and reported in youths at risk of developing psychosis (Borgwardt et al., 2007; Satterthwaite et al., 2016); the present study found that these reductions were mainly observed in the UHR groups. BS associated with the integration of information (*Gestalt*) relating to perception of the environment and with recollection and memory, as well as with self-perception, such as derealization and the inability to discriminate ideas and perceptions, as well as non-specific auto- and somatopsychic depersonalization might be specifically related to precuneus cortical activity: a possible relation not evinced by the results of the total severity of COPER and COGDIS-BS.

Further, a significant group effect was detected in the middle temporal cortex, showing significantly lower GMV in the BS&UHR group than in the CC; this agrees with previous studies (Brent et al., 2016; Cullen et al., 2013; Onitsuka et al., 2004; Ziermans et al., 2012). The middle temporal cortex is involved in functions such as semantic and memory processing as well as visual processing, e.g. recognition of familiar faces. Nevertheless, no difference was detected between FEP and CC; hence, our assumptions were not fully confirmed.

With regard to the entorhinal cortex, the highest GMV was detected in UHR, and the GMV of CC did not differ from those of FEP or BS&UHR. Thus, this result was not following the primary hypothesis of the current study.

Strengths and limitations

The performance of in-depth psychopathological assessments and the inclusion of FEP patients as a reference for neurobiological analyses constitute the principal strengths of our study. While the present study is subject to the limitation of a modest sample size, the sensitivity of the 3-T MRI was reported to be high enough to detect GMV differences of medium-to-large effect sizes in samples of $n \sim 15$–20 per group (Weinberg et al., 2016); and several previous reports have used similar sample sizes (Borgwardt et al., 2008; Fusar-Poli et al., 2011b; Smieskova et al., 2012*a*,*b*). The potential adequacy of our study population notwithstanding, investigations with larger sample sizes are warranted to reveal additional findings of smaller effect size that might have been missed in the current study. Another shortcoming of the present study is its cross-sectional nature, which prevents the drawing of causal conclusions.

In contrast with earlier studies, no healthy control group was included in this study. However, the CC included in the present study, who had initially been referred to our service on account of the clinical suspicion of psychosis, likely served as a much more effective comparison group: they were matched to the CHR patients for sex, age, and chlorpromazine equivalents, and did not differ from them in terms of SOFAS scores. Thus, the identified GMV differences can be considered to reflect both general findings related to ill mental health and disorder-specific aberrations.

Implications

Overall, our results support the hypothesis that combining UHR and BS criteria – in particular COGDIS – not only improves clinical predictive value but also achieves a better correlation with GMV reductions in many ROIs relative to the use of UHR or BS alone.

https://doi.org/10.1017/S0033291720001282 Published online by Cambridge University Press

Furthermore, as recently suggested (Schultze-Lutter et al., 2018*b*), our results demonstrate that the detailed differential examination of the link between neurobiology and psychopathology can improve insight into the processes indicative of a risk of developing psychosis, as well as those involved in the early stages of the disorder. Studies on UHR samples usually do not evaluate BS. However, in line with previous studies (Schultze-Lutter et al., 2015*a*), we found that more than half (53%) of the patients who fulfilled UHR criteria also satisfied BS criteria. It is therefore possible that the extent of GMV reductions reported in previous studies that exclusively evaluated UHR criteria are strongly influenced by patients who also fulfilled BS criteria that have gone undetected.

Conclusions

In summary, our study indicates that the combined UHR&BS was more similar to FEP with respect to GMV reductions than was either UHR or BS alone; thus, the GMV reductions observed in the UHR&BS patients were the most different from those of CC patients. To the best of our knowledge, this study is the first to demonstrate that patients who fulfill the criteria of both UHR and BS – a population already associated with higher conversion rates – exhibit more severe GMV reductions than do patients that satisfy BS or UHR criteria alone. This result appears to have been mediated by patients with more severe BS in the UHR&BS group, as only the severity of BS was linked to GMV reductions, and thus may provide evidence for the suggested link between BS and neurobiological aberrations (Schultze-Lutter et al., 2016).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720001282.

Acknowledgements. The FETZ Bern is a cooperation of the University Hospitals of Psychiatry and Psychotherapy and Child and Adolescent Psychiatry and Psychotherapy, University of Bern and the Soteria Bern. This study was supported by internal funding from the University Hospitals of Psychiatry and Psychotherapy and of Child and Adolescent Psychiatry and Psychotherapy, University of Bern and the Soteria Bern.

Conflict of interest. The authors report no biomedical financial interests or potential conflicts of interest relevant to this project.

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.

References

APA (ed.). (1994). *Diagnostic and statistical manual of mental disorders* (4th ed., pp. 760–761). Washington: American Psychiatric Press.

Borgwardt, S. J., McGuire, P. K., Aston, J., Gschwandtner, U., Pfluger, M. O., Stieglitz, R. D., … Riecher-Rossler, A. (2008). Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. *Schizophrenia Research*, *106*(2–3), 108–114. doi: 10.1016/j.schres.2008.08.007.

Borgwardt, S. J., Riecher-Rossler, A., Dazzan, P., Chitnis, X., Aston, J., Drewe, M., … McGuire, P. K. (2007). Regional gray matter volume abnormalities in the at risk mental state. *Biological Psychiatry*, *61*(10), 1148–1156. doi: 10.1016/j.biopsych.2006.08.009.

Brent, B. K., Rosso, I. M., Thermenos, H. W., Holt, D. J., Faraone, S. V., Makris, N., … Seidman, L. J. (2016). Alterations of lateral temporal cortical gray matter and facial memory as vulnerability indicators for schizophrenia: An MRI study in youth at familial high-risk for schizophrenia. *Schizophrenia Research*, *170*(1), 123–129. doi: 10.1016/j.schres.2015.11.013.

Cannon, T. D. (2016). Brain biomarkers of vulnerability and progression to psychosis. *Schizophrenia Bulletin*, *42*(Suppl 1), S127–S132. doi: 10.1093/schbul/sbv173.

Cannon, T. D., Chung, Y., He, G., Sun, D., Jacobson, A., & van Erp, T. G., … North American Prodrome Longitudinal Study, C. (2015). Progressive reduction in cortical thickness as psychosis develops: A multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biological Psychiatry*, *77*(2), 147–157. doi: 10.1016/j.biopsych.2014.05.023.

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: A review of its functional anatomy and behavioural correlates. *Brain*, *129*(Pt 3), 564–583. doi: 10.1093/brain/awl004.

Chakirova, G., Welch, K. A., Moorhead, T. W., Stanfield, A. C., Hall, J., Skehel, P., … McIntosh, A. M. (2010). Orbitofrontal morphology in people at high risk of developing schizophrenia. *European Psychiatry: the Journal of the Association of European Psychiatrists*, *25*(6), 366–372. doi: 10.1016/j.eurpsy.2010.03.001.

Chung, Y., Haut, K. M., He, G., van Erp, T. G. M., McEwen, S., & Addington, J., … North American Prodrome Longitudinal Study, C. (2017). Ventricular enlargement and progressive reduction of cortical gray matter are linked in prodromal youth who develop psychosis. *Schizophrenia Research*, *189*, 169–174. doi: 10.1016/j.schres.2017.02.014.

Cullen, A. E., De Brito, S. A., Gregory, S. L., Murray, R. M., Williams, S. C., Hodgins, S., & Laurens, K. R. (2013). Temporal lobe volume abnormalities precede the prodrome: A study of children presenting antecedents of schizophrenia. *Schizophrenia Bulletin*, *39*(6), 1318–1327. doi: 10.1093/schbul/sbs128.

Euston, D. R., Gruber, A. J., & McNaughton, B. L. (2012). The role of medial prefrontal cortex in memory and decision making. *Neuron*, *76*(6), 1057–1070. doi: 10.1016/j.neuron.2012.12.002.

Fluckiger, R., Michel, C., Grant, P., Ruhrmann, S., Vogeley, K., Hubl, D., … Schultze-Lutter, F. (2019). The interrelationship between schizotypy, clinical high risk for psychosis and related symptoms: Cognitive disturbances matter. *Schizophrenia Research*, *210*, 188–196. doi: 10.1016/j.schres.2018.12.039.

Fluckiger, R., Ruhrmann, S., Debbane, M., Michel, C., Hubl, D., Schimmelmann, B. G., … Schultze-Lutter, F. (2016). Psychosis-predictive value of self-reported schizotypy in a clinical high-risk sample. *Journal of Abnormal Psychology*, *125*(7), 923–932. doi: 10.1037/abn0000192.

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rossler, A., Schultze-Lutter, F., … Yung, A. (2013). The psychosis high-risk state: A comprehensive state-of-the-art review. *JAMA Psychiatry*, *70*(1), 107–120. doi: 10.1001/jamapsychiatry.2013.269.

Fusar-Poli, P., Borgwardt, S., Crescini, A., Deste, G., Kempton, M. J., Lawrie, S., … Sacchetti, E. (2011a). Neuroanatomy of vulnerability to psychosis: A voxel-based meta-analysis. *Neuroscience & Biobehavioral Reviews*, *35*(5), 1175–1185. doi: 10.1016/j.neubiorev.2010.12.005.

Fusar-Poli, P., Broome, M. R., Woolley, J. B., Johns, L. C., Tabraham, P., Bramon, E., … McGuire, P. (2011b). Altered brain function directly related to structural abnormalities in people at ultra high risk of psychosis: Longitudinal VBM-fMRI study. *Journal of Psychiatric Research*, *45*(2), 190–198. doi: 10.1016/j.jpsychires.2010.05.012.

Fusar-Poli, P., Cappucciati, M., Rutigliano, G., Schultze-Lutter, F., Bonoldi, I., Borgwardt, S., … McGuire, P. (2015). At risk or not at risk? A meta-analysis of the prognostic accuracy of psychometric interviews for psychosis prediction. *World psychiatry: Official Journal of the World Psychiatric Association*, *14*(3), 322–332. doi: 10.1002/wps.20250.

Fusar-Poli, P., Radua, J., McGuire, P., & Borgwardt, S. (2012). Neuroanatomical maps of psychosis onset: Voxel-wise meta-analysis of antipsychotic-naive VBM studies. *Schizophrenia Bulletin*, *38*(6), 1297–1307. doi: 10.1093/schbul/sbr134.

Heckers, S., Barch, D. M., Bustillo, J., Gaebel, W., Gur, R., Malaspina, D., … Carpenter, W. (2013). Structure of the psychotic disorders classification in DSM-5. *Schizophrenia Research*, *150*(1), 11–14. doi: 10.1016/j.schres.2013.04.039.

Hurlemann, R., Jessen, F., Wagner, M., Frommann, I., Ruhrmann, S., Brockhaus, A., … Maier, W. (2008). Interrelated neuropsychological and anatomical evidence of hippocampal pathology in the at-risk mental state. *Psychological Medicine*, *38*(6), 843–851. doi: 10.1017/S0033291708003279.

Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, *468*(7321), 187–193. doi: 10.1038/nature09552.

Jung, W. H., Borgwardt, S., Fusar-Poli, P., & Kwon, J. S. (2012). Gray matter volumetric abnormalities associated with the onset of psychosis. *Frontiers in Psychiatry*, *3*, 101. doi: 10.3389/fpsyt.2012.00101.

Keefe, R. S., & Harvey, P. D. (2012). Cognitive impairment in schizophrenia. *Handbook of Experimental Pharmacology*, *213*, 11–37. doi: 10.1007/978-3-642-25758-2_2.

Khoury, R., & Nasrallah, H. A. (2018). Inflammatory biomarkers in individuals at clinical high risk for psychosis (CHR-P): State or trait? *Schizophrenia Research*, *199*, 31–38. doi: 10.1016/j.schres.2018.04.017.

Kindler, J., Jann, K., Homan, P., Hauf, M., Walther, S., Strik, W., … Hubl, D. (2015). Static and dynamic characteristics of cerebral blood flow during the resting state in schizophrenia. *Schizophrenia Bulletin*, *41*(1), 163–170. doi: 10.1093/schbul/sbt180.

Kindler, J., Schultze-Lutter, F., Hauf, M., Dierks, T., Federspiel, A., Walther, S., … Hubl, D. (2018). Increased striatal and reduced prefrontal cerebral blood flow in clinical high risk for psychosis. *Schizophrenia Bulletin*, *44*(1), 182–192. doi: 10.1093/schbul/sbx070.

Kindler, J., Schultze-Lutter, F., Michel, C., Martz-Irngartinger, A., Linder, C., Schmidt, S. J., … Walther, S. (2016). Abnormal involuntary movements are linked to psychosis-risk in children and adolescents: Results of a population-based study. *Schizophrenia Research*, *174*(1–3), 58–64. doi: 10.1016/j.schres.2016.04.032.

Kirkbride, J. B., Fearon, P., Morgan, C., Dazzan, P., Morgan, K., Tarrant, J., … Jones, P. B. (2006). Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: Findings from the 3-center AeSOP study. *Archives of General Psychiatry*, *63*(3), 250–258. doi: 10.1001/archpsyc.63.3.250.

Klosterkotter, J., Hellmich, M., Steinmeyer, E. M., & Schultze-Lutter, F. (2001). Diagnosing schizophrenia in the initial prodromal phase. *Archives of General Psychiatry*, *58*(2), 158–164.

Kohler, S., van der Werf, M., Hart, B., Morrison, G., McCreadie, R., Kirkpatrick, B., … Allardyce, J. (2009). Evidence that better outcome of psychosis in women is reversed with increasing age of onset: A population-based 5-year follow-up study. *Schizophrenia Research*, *113*(2–3), 226–232. doi: 10.1016/j.schres.2009.05.017.

Koutsouleris, N., Davatzikos, C., Borgwardt, S., Gaser, C., Bottlender, R., Frodl, T., … Meisenzahl, E. (2014). Accelerated brain aging in schizophrenia and beyond: A neuroanatomical marker of psychiatric disorders. *Schizophrenia Bulletin*, *40*(5), 1140–1153. doi: 10.1093/schbul/sbt142.

Koutsouleris, N., Kambeitz-Ilankovic, L., Ruhrmann, S., Rosen, M., Ruef, A., Dwyer, D. B., … Consortium, P. (2018). Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or With recent-onset depression: A multimodal, multisite machine learning analysis. *JAMA Psychiatry*, *75*(11), 1156–1172. doi: 10.1001/jamapsychiatry.2018.2165.

Koutsouleris, N., Meisenzahl, E. M., Davatzikos, C., Bottlender, R., Frodl, T., Scheuerecker, J., … Gaser, C. (2009a). Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. *Archives of General Psychiatry*, *66*(7), 700–712. doi: 10.1001/archgenpsychiatry.2009.62.

Koutsouleris, N., Riecher-Rossler, A., Meisenzahl, E. M., Smieskova, R., Studerus, E., Kambeitz-Ilankovic, L., … Borgwardt, S. (2015). Detecting the psychosis prodrome across high-risk populations using neuroanatomical biomarkers. *Schizophrenia Bulletin*, *41*(2), 471–482. doi: 10.1093/schbul/sbu078.

Koutsouleris, N., Schmitt, G. J., Gaser, C., Bottlender, R., Scheuerecker, J., McGuire, P., … Meisenzahl, E. M. (2009b). Neuroanatomical correlates of different vulnerability states for psychosis and their clinical outcomes. *The British Journal of Psychiatry: the Journal of Mental Science*, *195*(3), 218–226. doi: 10.1192/bjp.bp.108.052068.

Leucht, S., Wahlbeck, K., Hamann, J., & Kissling, W. (2003). New generation antipsychotics versus low-potency conventional antipsychotics: A systematic review and meta-analysis. *Lancet (London, England)*, *361*(9369), 1581–1589. doi: 10.1016/S0140-6736(03)13306-5.

McGlashan, T., Walsh, B., & Woods, S. (2010). *The psychosis-risk syndrome. Handbook for diagnosis and follow Up*. New York: Oxford University Press.

Michel, C., Ruhrmann, S., Schimmelmann, B. G., Klosterkotter, J., & Schultze-Lutter, F. (2014). A stratified model for psychosis prediction in clinical practice. *Schizophrenia Bulletin*, *40*(6), 1533–1542. doi: 10.1093/schbul/sbu025.

Mikanmaa, E., Grent-'t-Jong, T., Hua, L., Recasens, M., Thune, H., & Uhlhaas, P. J. (2019). Towards a neurodynamical understanding of the prodrome in schizophrenia. *NeuroImage*, *190*, 144–153. doi: 10.1016/j.neuroimage.2017.11.026.

Mollon, J., David, A. S., Zammit, S., Lewis, G., & Reichenberg, A. (2018). Course of cognitive development from infancy to early adulthood in the psychosis spectrum. *JAMA Psychiatry*, *75*(3), 270–279. doi: 10.1001/jamapsychiatry.2017.4327.

Onitsuka, T., Shenton, M. E., Salisbury, D. F., Dickey, C. C., Kasai, K., Toner, S. K., … McCarley, R. W. (2004). Middle and inferior temporal gyrus gray matter volume abnormalities in chronic schizophrenia: An MRI study. *The American Journal of Psychiatry*, *161*(9), 1603–1611. doi: 10.1176/appi.ajp.161.9.1603.

Penn, D. L., Sanna, L. J., & Roberts, D. L. (2008). Social cognition in schizophrenia: An overview. *Schizophrenia Bulletin*, *34*(3), 408–411. doi: 10.1093/schbul/sbn014.

Penttila, M., Jaaskelainen, E., Hirvonen, N., Isohanni, M., & Miettunen, J. (2014). Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: Systematic review and meta-analysis. *The British Journal of Psychiatry: the Journal of Mental Science*, *205*(2), 88–94. doi: 10.1192/bjp.bp.113.127753.

Reavis, E. A., Lee, J., Wynn, J. K., Engel, S. A., Jimenez, A. M., & Green, M. F. (2017). Cortical thickness of functionally defined visual areas in schizophrenia and bipolar disorder. *Cerebral Cortex (New York, N.Y.: 1991)*, *27*(5), 2984–2993. doi: 10.1093/cercor/bhw151.

Roalf, D. R., Quarmley, M., Calkins, M. E., Satterthwaite, T. D., Ruparel, K., Elliott, M. A., … Turetsky, B. I. (2017). Temporal lobe volume decrements in psychosis spectrum youths. *Schizophrenia Bulletin*, *43*(3), 601–610. doi: 10.1093/schbul/sbw112.

Rolls, E. T. (2000). The orbitofrontal cortex and reward. *Cerebral Cortex (New York, N.Y.: 1991)*, *10*(3), 284–294.

Ruhrmann, S., Schultze-Lutter, F., Salokangas, R. K., Heinimaa, M., Linszen, D., Dingemans, P., … Klosterkotter, J. (2010). Prediction of psychosis in adolescents and young adults at high risk: Results from the prospective European prediction of psychosis study. *Archives of General Psychiatry*, *67*(3), 241–251. doi: 10.1001/archgenpsychiatry.2009.206.

Salokangas, R. K., Heinimaa, M., From, T., Loyttyniemi, E., Ilonen, T., & Luutonen, S., … group, E. (2014). Short-term functional outcome and premorbid adjustment in clinical high-risk patients. Results of the EPOS project. *European psychiatry: the Journal of the Association of European Psychiatrists*, *29*(6), 371–380. doi: 10.1016/j.eurpsy.2013.10.003.

Satterthwaite, T. D., Wolf, D. H., Calkins, M. E., Vandekar, S. N., Erus, G., Ruparel, K., … Gur, R. E. (2016). Structural brain abnormalities in youth with psychosis spectrum symptoms. *JAMA Psychiatry*, *73*(5), 515–524. doi: 10.1001/jamapsychiatry.2015.3463.

Schmidt, S. J., Schultze-Lutter, F., Schimmelmann, B. G., Maric, N. P., Salokangas, R. K., Riecher-Rossler, A., … Ruhrmann, S. (2015). EPA Guidance on the early intervention in clinical high risk states of psychoses. *European psychiatry : the Journal of the Association of European Psychiatrists*, *30*(3), 388–404. doi: 10.1016/j.eurpsy.2015.01.013.

Schultze-Lutter, F. (2009). Subjective symptoms of schizophrenia in research and the clinic: The basic symptom concept. *Schizophrenia Bulletin*, *35*(1), 5–8. doi: 10.1093/schbul/sbn139.

Schultze-Lutter, F., Addington, J., Ruhrmann, S., & Klosterkotter, J. (2007a). *Schizophrenia Proneness Instrument*, *Adult version* (*SPI-A*). Rom.

Schultze-Lutter, F., Debbane, M., Theodoridou, A., Wood, S. J., Raballo, A., Michel, C., … Uhlhaas, P. J. (2016). Revisiting the basic symptom concept: Toward translating risk symptoms for psychosis into neurobiological targets. *Frontiers in Psychiatry*, *7*, 9. doi: 10.3389/fpsyt.2016.00009.

Schultze-Lutter, F., Klosterkotter, J., Picker, H., Steinmeyer, E. M., & Ruhrmann, S. (2007b). Predicting first-episode psychosis by basic symptom criteria. *Clinical Neuropsychiatry: Journal of Treatment Evaluation*, *4*(1), 11–22.

Schultze-Lutter, F., Klosterkotter, J., & Ruhrmann, S. (2014). Improving the clinical prediction of psychosis by combining ultra-high risk criteria and cognitive basic symptoms. *Schizophrenia Research*, *154*(1–3), 100–106. doi: 10.1016/j.schres.2014.02.010.

Schultze-Lutter, F., & Koch, E. (2010). *Schizophrenia Proneness Instrument, Child & Youth version* (*SPI-CY*) (G. Fioriti Ed.). Rom.

Schultze-Lutter, F., Michel, C., Ruhrmann, S., & Schimmelmann, B. G. (2018a). Prevalence and clinical relevance of interview-assessed psychosis-risk symptoms in the young adult community. *Psychological Medicine*, *48*(7), 1167–1178. doi: 10.1017/S0033291717002586.

Schultze-Lutter, F., Michel, C., Schmidt, S. J., Schimmelmann, B. G., Maric, N. P., Salokangas, R. K., … Klosterkotter, J. (2015a). EPA Guidance on the early detection of clinical high risk states of psychoses. *European Psychiatry: the Journal of the Association of European Psychiatrists*, *30*(3), 405–416. doi: 10.1016/j.eurpsy.2015.01.010.

Schultze-Lutter, F., Rahman, J., Ruhrmann, S., Michel, C., Schimmelmann, B. G., Maier, W., & Klosterkotter, J. (2015b). Duration of unspecific prodromal and clinical high risk states, and early help-seeking in first-admission psychosis patients. *Social Psychiatry and Psychiatric Epidemiology*, *50*(12), 1831–1841. doi: 10.1007/s00127-015-1093-3.

Schultze-Lutter, F., Ruhrmann, S., Fusar-Poli, P., Bechdolf, A., Schimmelmann, B. G., & Klosterkotter, J. (2012). Basic symptoms and the prediction of first-episode psychosis. *Current Pharmaceutical Design*, *18*(4), 351–357.

Schultze-Lutter, F., Ruhrmann, S., Michel, C., Kindler, J., Schimmelmann, B. G., & Schmidt, S. J. (2020). Age effects on basic symptoms in the community: A route to gain new insight into the neurodevelopment of psychosis? *European Archives of Psychiatry and Clinical Neuroscience*, *270*, 311–324. doi:10.1007/s00406-018-0949-4.

Schultze-Lutter, F., Schmidt, S. J., & Theodoridou, A. (2018b). Psychopathology-a precision tool in need of Re-sharpening. *Frontiers in Psychiatry*, *9*, 446. doi: 10.3389/fpsyt.2018.00446.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., … Dunbar, G. C. (1998). The Mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59* (Suppl 20), 22-33;quiz 34-57.

Sheehan, D. V., Sheehan, K. H., Shytle, R. D., Janavs, J., Bannon, Y., Rogers, J. E., … Wilkinson, B. (2010). Reliability and validity of the Mini international neuropsychiatric interview for children and adolescents (MINI-KID). *Journal of Clinical Psychiatry*, *71*(3), 313–326. doi: 10.4088/JCP.09m05305whi.

Smieskova, R., Allen, P., Simon, A., Aston, J., Bendfeldt, K., Drewe, J., … Borgwardt, S. J. (2012a). Different duration of at-risk mental state associated with neurofunctional abnormalities. A multimodal imaging study. *Human Brain Mapping*, *33*(10), 2281–2294. doi: 10.1002/hbm.21360.

Smieskova, R., Fusar-Poli, P., Aston, J., Simon, A., Bendfeldt, K., Lenz, C., … Borgwardt, S. J. (2012b). Insular volume abnormalities associated with different transition probabilities to psychosis. *Psychological Medicine*, *42*(8), 1613–1625. doi: 10.1017/S0033291711002716.

Süllwold, L., & Huber, G. (1986). *Schizophrene basisstoerungen*. Berlin: Springer.

Tepest, R., Schwarzbach, C. J., Krug, B., Klosterkotter, J., Ruhrmann, S., & Vogeley, K. (2013). Morphometry of structural disconnectivity indicators in subjects at risk and in age-matched patients with schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, *263*(1), 15–24. doi: 10.1007/s00406-012-0343-6.

Thompson, P. M., Vidal, C., Giedd, J. N., Gochman, P., Blumenthal, J., Nicolson, R., … Rapoport, J. L. (2001). Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(20), 11650–11655. doi: 10.1073/pnas.201243998.

Vigo, D., Thornicroft, G., & Atun, R. (2016). Estimating the true global burden of mental illness. *The Lancet. Psychiatry*, *3*(2), 171–178. doi: 10.1016/S2215-0366(15)00505-2.

Weinberg, D., Lenroot, R., Jacomb, I., Allen, K., Bruggemann, J., Wells, R., … Weickert, T. W. (2016). Cognitive subtypes of schizophrenia characterized by differential brain volumetric reductions and cognitive decline. *JAMA Psychiatry*, *73*(12), 1251–1259. doi: 10.1001/jamapsychiatry.2016.2925.

Wittchen, H. U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., … Steinhausen, H. C. (2011). The size and burden of mental disorders and other disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, *21*(9), 655–679. doi: 10.1016/j.euroneuro.2011.07.018.

Yung, A. R., Phillips, L. J., McGorry, P. D., McFarlane, C. A., Francey, S., Harrigan, S., … Jackson, H. J. (1998). Prediction of psychosis. A step towards indicated prevention of schizophrenia. *The British Journal of Psychiatry. Supplement*, *172*(33), 14–20.

Ziermans, T. B., Schothorst, P. F., Schnack, H. G., Koolschijn, P. C., Kahn, R. S., van Engeland, H., & Durston, S. (2012). Progressive structural brain changes during development of psychosis. *Schizophrenia Bulletin*, *38*(3), 519–530. doi: 10.1093/schbul/sbq113.