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Cognitive and emotional empathy in individuals at clinical high risk of psychosis

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Background: Impairments of social cognition are considered core features of schizophrenia and are established predictors of social functioning. However, affective aspects of social cognition including empathy have far less been studied than its cognitive dimensions. The role of empathy in the development of schizophrenia remains largely elusive.
Methods: Emotional and cognitive empathy were investigated in large sample of 120 individuals at Clinical High Risk of Psychosis (CHR-P) and compared with 50 patients with schizophrenia and 50 healthy controls. A behavioral empathy assessment, the Multifaceted Empathy Test, was implemented, and associations of empathy with cognition, social functioning, and symptoms were determined.
Results: Our findings demonstrated significant reductions of emotional empathy in individuals at CHR-P, while cognitive empathy appeared intact. Only individuals with schizophrenia showed significantly reduced scores of cognitive empathy compared to healthy controls and individuals at CHR-P. Individuals at CHR-P were characterized by significantly lower scores of emotional empathy and unspecific arousal for both positive and negative affective valences compared to matched healthy controls and patients with schizophrenia. Results also indicated a correlation of lower scores of emotional empathy and arousal with higher scores of prodromal symptoms.
Conclusion: Findings suggest that the tendency to 'feel with' an interaction partner is reduced in individuals at CHR-P. Altered emotional reactivity may represent an additional, early vulnerability marker, even if cognitive mentalizing is grossly unimpaired in the prodromal stage. Different mechanisms might contribute to reductions of cognitive and emotional empathy in different stages of non-affective psychotic disorders and should be further explored.

C. Montag[1], L. Brandt[1], A. Lehmann[1], W. De Millas[2], P. Falkai[3], W. Gaebel[4], A. Hasan[3], M. Hellmich[5,6], B. Janssen[4,7], G. Juckel[8], A. Karow[9], J. Klosterkötter[5], M. Lambert[9], W. Maier[10,11,12], H. Müller[5], V. Pützfeld[5], F. Schneider[4,13], H. Stützer[6], T. Wobrock[14,15], I. B. Vernaleken[13], M. Wagner[10,11,12], A. Heinz[1], A. Bechdolf[16,17,18], J. Gallinat[9]

[1]Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Charité Campus Mitte, Berlin, Germany, [2]Department of Psychiatry, Psychotherapy, and Psychosomatics, Vivantes Wenckebach-Klinikum, Berlin, Germany, [3]Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany, [4]Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany, [5]Department of Psychiatry and Psychotherapy, Faculty of Medicine, University Hospital Cologne, Cologne, Germany, [6]Institute of Medical Statistics and Computational Biology, Faculty of Medicine, University Hospital Cologne, Cologne, Germany, [7]LVR-Klinik Langenfeld, Langenfeld, Germany, [8]Department of Psychiatry, Psychotherapy, and Preventive Medicine, Ruhr University Bochum, Bochum, Germany, [9]Department of Psychiatry and Psychotherapy, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, [10]Department of Psychiatry and Psychotherapy, University of Bonn, Bonn, Germany, [11]Department of Neurodegenerative Diseases and Geriatric Psychiatry, University of Bonn, Bonn, Germany, [12]DZNE, German Center for Neurodegenerative Diseases, Bonn, Germany, [13]Department of Psychiatry, Psychotherapy, and Psychosomatics, RWTH Aachen, Aachen, Germany, [14]Department of Psychiatry and Psychotherapy, Georg-August-University Goettingen, Goettingen, Germany, [15]Department of Psychiatry and Psychotherapy, County Hospitals Darmstadt-Dieburg, Groß-Umstadt, Germany, [16]Department of Psychiatry, Psychotherapy, and Psychosomatics, Vivantes Klinikum am Urban and Vivantes Klinikum im Friedrichshain, Berlin, Germany, [17]Faculty of Medicine, University Hospital Cologne, Cologne, Germany and [18]ORYGEN, The National Centre of Excellence in Youth Mental Health, University of Melbourne, Melbourne, Australia

Key words: schizophrenia; Clinical High Risk of Psychosis; prodrome; ultra-high risk; social cognition; empathy

Christiane Montag, Charité Universitätsmedizin Berlin, Campus Mitte (PUK Charité im SHK), Charitéplatz 1, 10117 Berlin. E-mail: christiane.montag@charite.de

*These authors contributed equally to this work.

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Significant outcomes

- Our findings suggest that individuals at Clinical High Risk of Psychosis (CHR-P) show less emotional empathy than controls or individuals with schizophrenia, while individuals with schizophrenia show impaired cognitive empathy.

Limitations

- This study is limited by the use of a single measure of empathy, and results should be confirmed by studies with additional behavioral tasks.
- Longitudinal studies are required to assess the association between reduced emotional empathy and transition rates to psychosis in CHR-P since an assessment was not within the scope of this cross-sectional study.

Introduction

Impairments of social cognition are considered core features of schizophrenia (1,2) and are an established predictor of social functioning (3-6). Pioneering studies on social cognition in individuals with schizophrenia suggested state deficits of theory of mind associated with disorganized symptoms (1), paranoid symptoms, and 'behavioral signs' like incoherence or flattening of affect (2-4). Deficits in facial emotion identification in individuals with early stages and first manifestation of psychotic disorders argue for a trait deficit in mentalizing abilities (5,6). Individuals at Clinical High Risk of Psychosis (CHR-P) showed only moderate deficits in their mentalizing ability, which were not more pronounced than general cognitive deficits (7,8). It has hence been hypothesized that the combination of subtle developmental deficits in social cognition, an insecure attachment style, and a reduced stress tolerance could lead to a 'breakdown' in mentalizing abilities and self-coherence when interpersonal challenges increase (9). Threshold situations such as adolescence and separation from important caregivers are considered particularly vulnerable period of time for individuals with these risk factors (9). From a developmental perspective, the formation of the so-called social brain is inextricably linked to the experience of emotional resonance and the emergence of affect regulation capacity (10).

Even though alterations of emotional responsivity have been reported as a core feature of the 'group of schizophrenia' (11), affective aspects of social cognition including empathy have been far less studied than its cognitive dimensions, that is, theory of mind (ToM) (12,13). A recent meta-analysis (14) reported deficits with intermediate effect sizes (Hedges' $g = 0.36$) in emotional empathy in individuals with schizophrenia. The strongest effect sizes were detected in studies with 'performance-based' (Hedges' $g = 1.31$) and not self-report (Hedges' $g = 0.22$) measures of emotional empathy. In particular, the role of empathy

in the development of schizophrenia remains largely elusive (15). Deficits in emotional reactivity of individuals at CHR-P compared to healthy controls have been reported in studies with limited sample sizes between 13 and 29 individuals at CHR-P each (16-20).

Thus, in the here presented large-scale study two core dimensions of empathy were defined: 'Emotional empathy', which describes sharing the emotion of another person and experiencing an other-induced affective reaction, and 'cognitive empathy,' which means identifying and understanding another person's emotion (21).

Aims of the study

In this study, emotional and cognitive empathy were investigated in a sample of individuals at CHR-P compared with individuals with schizophrenia and healthy controls. For this purpose, a behavioral empathy assessment—the Multifaceted Empathy Test (MET) (22)—was implemented. It was our primary hypothesis that individuals at CHR-P would show milder impairments of cognitive and affective dimensions of empathy reflected by MET scores in between those of individuals with schizophrenia (13) and healthy controls. For the exploratory analyses, we determined whether measures of empathy would correlate negatively with measures of cognition, social functioning, and symptoms.

Methods

Ethics and registration

CHR-P individuals in this study were part of the PREVENT trial (ISRCTN identifier: 02658871) and recruited at 9 early detection and intervention centers, which were specialized in early detection and intervention outpatient services designed to provide a low-threshold, non-stigmatizing environment located at the departments of psychiatry and psychotherapy at the Universities of Cologne, Aachen, Berlin, Bochum, Bonn, Düsseldorf, Göttingen, Hamburg, and Munich. The protocol of the trial was approved by the respective institutional review boards at the trial sites together with the primarily responsible ethics committee in Cologne and is available in Appendix S1. The additional study of patients with schizophrenia and healthy controls was approved by the ethics committee of the Charité Berlin. All participants provided written informed consent. Capacity to consent in schizophrenia patients was assessed according to the principles defined by Kröber (23).

Participants

The age of participants ranged between 18 and 40 years. Individuals at CHR-P belonged to one or more of the following four groups of the baseline sample of the PREVENT study, as previously reported (24): (1) attenuated positive symptoms (APS), (2) brief limited intermittent psychotic symptoms (BLIPS), (3) predictive basic symptoms (BS), and/or (4) family risk plus reduced functioning (FRRF).

Individuals at CHR-P were excluded in the following cases: current or past antipsychotic treatment for longer than 1 week, previous psychotic episode for longer than 1 week, current suicidality or dangerous behavior, alcohol or substance dependence, organic brain disease, IQ < 70, living out of area, other medical reasons including current or intended pregnancy, lactation or missing reliable method of contraception, or taking drugs with anticipated interactions (24). $N = 57$ individuals at CHR-P fulfilled diagnostic criteria for one or more personality disorder according to DSM-IV-R, assessed with the structured clinical interview (SKID-II) (25): avoidant: $n = 26$, dependent: $n = 2$, obsessive-compulsive: $n = 6$, negativistic: $n = 5$, depressive: $n = 26$, paranoid: $n = 12$, schizotypal: $n = 5$, schizoid: $n = 3$, histrionic: $n = 2$, Borderline: $n = 5$, narcissistic: $n = 2$, and antisocial: $n = 4$.

In addition, a clinical control group of individuals diagnosed with schizophrenia according to DSM-IV and the subscales of the SKID-II excluding antisocial personality traits (25) were recruited, as well as a healthy control sample, assessed with M.I.N.I. (26) and SKID-II structured diagnostic interviews to exclude any axis-I and axis-II mental disorders. Trained physicians or psychologists performed all assessments. Healthy controls reporting axis-I mental disorders in their first-degree relatives were excluded.

At the time of examination, individuals at CHR-P ($N = 120$) received the following psychopharmacological agents: methylphenidate (1), mirtazapine (1), mirtazapine and citalopram (1), lorazepam, zopiclone, or zolpidem as needed (4), or promethazine as needed (1). The remaining $N = 112$ individuals at CHR-P were not treated with psychotropic agents.

Measures

The Multifaceted Empathy Test (MET (22)) allows for the separate assessment of cognitive and emotional empathy as well as unspecific subjective arousal facing empathy-inducing stimuli. Dziobek et al.

reported validity and reliability analyses with a good to highly satisfactory range (22). Initially developed for individuals with Asperger syndrome (22), its usefulness was demonstrated in a sample of individuals with schizophrenia (13). The MET aims for higher ecological validity by not being restricted to interpretation of facial expressions but including subjects in more naturalistic and emotionally charged situations (22). It allows to infer not only basic emotions, but also more complex affective states (22). While the original MET also differentiates between emotional reactions to the depicted person and context, we used a modified version restricted to the scales for cognitive and emotional empathy as well as emotional arousal (13). Forty photographs showing people in positively and negatively emotionally charged situations were presented. Participants were instructed to identify with the protagonist and to 'feel into' the pictured emotions. To assess (1) 'cognitive empathy' (MET-CE), a construct very close to ToM, individuals were required to infer the emotional mental states of the protagonist and to select one out of four written verbal mental state descriptors. To assess (2) 'emotional empathy' (MET-EE), individuals were asked to rate their own tendency to share the specific emotion on a visual analogue scale (VAS) ranging from 0 to 9 (0 = not at all, 9 = very much). A similar VAS was used to evaluate (3) unspecific 'emotional arousal' (MET-EA), explained as participant's level of excitement or distress (vs. calmness and relaxation) when watching the stimuli. All participants received a short training before testing to ensure comprehension of the instruction. *The Positive and Negative Syndrome Scale* (PANSS (27)) is a widely used semi-structured interview to assess the severity of psychopathology associated with schizophrenia (28). It measures a multidimensional array of symptoms on three subscales—'positive symptoms' (P), 'negative symptoms' (N), and 'general psychopathology' (G) (29). PANSS depression factor (G1-4 and G6) was derived by factor analysis as reported by Citrome et al. (28). The *Montgomery–Åsberg Depression Rating Scale* (MADRS (30)) is an observer-rated depression scale that is often used in clinical trials to assess treatment outcome. *The Structured Interview for Prodromal Syndromes* (SIPS (31)) is a structured interview that is intended to identify prodromal syndromes of psychosis. The *Schizophrenia Proneness Instrument, Adult Version* (SPI-A (32)) is a semi-structured interview to assess symptoms associated with proneness for schizophrenia. The items were derived by cluster and confirmatory factor analyses from the Bonn Scale for the Assessment of Basic Symptoms (BSABS (33)). The SPI-A comprises 56 items of 'Basic Symptoms' (BS). BS in SPI-A includes two overlapping clusters, 'Cognitive Disturbances basic symptoms' (COGDIS, 9 items) and 'Cognitive-Perceptive basic symptoms' (COPER, 14 items), as well as 'other BS' (38 items). In addition to the SPI-A sum score of all 56 items, COGDIS was analyzed separately, since it was reported to be associated with a transition rate of 23.9% at 12 months and 46.3% at 24 months (34). The *Digit Symbol Substitution Test* (DSST (35)) was developed for the assessment of associative learning and incorporated into the original Wechsler Bellevue Intelligence Quotient (IQ) test battery (35). The *Social and Occupational Functioning Assessment Scale* (SOFAS (36)) is a rating scale for the overall level of functioning in the DSM-IV axis-V. The SOFAS addresses current social and occupational functioning.

Statistical analyses

Individuals at CHR-P were analyzed (1) as full sample ($N = 120$), and (2) as a subsample of $N = 100$ CHR-P participants who were matched (13) according to age and verbal IQ on a 2:1:1 basis with healthy controls ($N = 50$) and individuals with schizophrenia ($N = 50$).

Statistical calculations were carried out as indicated in the results section using SPSS for Windows 24.0®. All tests were performed with a two-sided $P < 0.05$. Data were tested for normality using the Shapiro–Wilk test.

One-way ANOVA, T- and chi-square tests were used to determine group differences of demographic and illness parameters. One-way ANOVA served to examine group differences of MET scores between the matched CHR-P sample, individuals with schizophrenia, and healthy controls. Given heteroscedasticity, Welch and post hoc Tamhane's T2 tests were used. To explore group differences of MET cognitive and emotional empathy for positive and negative emotional valences ($\text{MET-CE}_{\text{neg}}$, $\text{MET-CE}_{\text{pos}}$, $\text{MET-EE}_{\text{pos}}$, and $\text{MET-EE}_{\text{neg}}$) between groups, MANCOVA, post hoc ANOVA, and post hoc multiple comparisons (Bonferroni-corrected) were used with the factor diagnosis and gender, and the covariates age and verbal IQ. MET emotional arousal (MET-EA) scores were not included in the model due to high correlations with MET emotional empathy (MET-EE). Homoscedasticity was examined by Levene's and Box-M tests; partial η^2 values were given as a measure of effect size.

Within the full CHR-P sample, MET scores in the presence or absence of APS, BLIPS, genetic risk plus reduced functioning, or of COGDIS criteria were compared using independent

samples t-tests. Spearman rank correlation analyses were used to examine associations of MET scores with symptoms and cognitive and social functioning.

Results

Sample characteristics

Demographic and clinical characteristics are summarized in Table 1. Individuals at CHR-P did not differ significantly from healthy controls regarding age and verbal IQ, but showed significantly less years of education. Individuals with schizophrenia had lower verbal IQ and education than controls.

MET dimensions in individuals at CHR-P, individuals with schizophrenia, and healthy controls

To compare MET dimensions between the three matched groups, one-way ANOVA was performed (Table 2). Post hoc analyses revealed significantly lower MET cognitive empathy (MET-CE) scores in individuals with schizophrenia compared to healthy controls (e.g., 14% reduction in CE_{sum}). Individuals at CHR-P showed no significant difference compared to healthy controls. Individuals with schizophrenia did not differ from healthy controls regarding MET-EE and MET-EA. Of note, individuals at CHR-P showed significantly lower MET-EE and MET-EA scores compared to healthy controls (e.g., 20% reduction in MET-EE_{sum} and 19% reduction in MET-EA_{sum} for the matched subsample) and also significantly reduced emotional empathy for only positive valences, MET-EE_{pos}, compared to individuals with schizophrenia (e.g., 24% reduction in MET-EE_{pos} for the matched subsample).

To control for the effects of gender, age, and non-social cognition, MANCOVA (factors: diagnosis, gender; covariates: age, verbal IQ) was carried out, which revealed significant multivariate effects of diagnostic group and gender as well as verbal IQ. Post hoc ANOVA indicated significant main effects of diagnosis and a positive impact of verbal IQ on MET cognitive empathy for positive emotions. Diagnosis and gender had significant impact on MET emotional empathy for both positive and negative valences, with females showing higher values irrespective of valence or diagnostic group. However, no significant interaction between

Table 1. Demographic, neuropsychological data, and illness characteristics in individuals at Clinical High Risk of Psychosis (CHR-P; full sample and matched subsample), individuals with schizophrenia (SZ) and healthy controls (HC); group comparisons between CHR-P matched subsample, SZ, and HC

	CHR-P full sample	CHR-P matched subsample	Individuals with schizophrenia	Healthy controls	Statistics*
N	120	100	50	50	100/50/50
Gender m/f	78/42	62/38	36/14	28/22	$\chi^2 = 2.861$, n.s.[a]
Age (years)	24.0 ± 4.8	25.0 ± 4.5	26.7 ± 3.6	26.3 ± 4.2	$F[2,197] = 3.104$*, post hoc: n.s.
Verbal IQ	104.1 ± 13.7	105.3 ± 13.8	100.8 ± 12.3	108.9 ± 10.7	$F[2,197] = 5.162$**, post hoc: SZ vs. HC: $P = 0.005$
Education (years)	12.6 ± 2.1	12.9 ± 2.0	12.4 ± 3.3	15.7 ± 2.1	$F[2,197] = 29.059$***, post hoc: SZ vs. HC: $P < 0.001$ CHR-P vs. HC: $P < 0.001$
DSST	55.8 ± 12.1	56.2 ± 12.5	–	–	–
PANSS pos.	10.5 ± 2.9	10.4 ± 2.9	16.6 ± 6.3	–	$T[59,398] = -6.560$***,[b]
PANSS neg.	10.7 ± 4.2	10.6 ± 4.3	18.4 ± 8.6	–	$T[61,632] = -6.003$***,[b]
PANSS general	25.0 ± 6.4	25.2 ± 6.6	33.3 ± 12.7	–	$T[62,743] = -4.287$***,[b]
PANSS depression[†]	10.1 ± 3.0	10.3 ± 3.1	18.4 ± 8.6	–	$T = [70,224] = -1,1507$[b]
MADRS sum.	19.4 ± 8.0	19.4 ± 8.3	–	–	–
SIPS pos.	6.9 ± 3.9	6.7 ± 4.0	–	–	–
SIPS neg.	10.2 ± 5.2	9.9 ± 5.3	–	–	–
SIPS desorg.	3.8 ± 2.5	9.9 ± 5.3	–	–	–
SIPS general	7.7 ± 3.4	7.6 ± 3.7	–	–	–
APS [*n* (%)]	87 (72.5)	72 (72)	–	–	–
BLIPS [*n* (%)]	4 (3.3)	3 (3)	–	–	–
FRRF [*n* (%)]	21 (17.5)	17 (17)	–	–	–
COGDIS [*n* (%)]	63 (52.5)	55 (55)	–	–	–

APS, Attenuated Positive Symptoms; BLIPS, Brief Limited Intermittent Psychotic Symptoms; COGDIS, Cognitive Disturbances; DSST, Digit Symbol Substitution Test; FRRF, family risk plus reduced functioning; MADRS, Montgomery–Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SIPS, Structured Interview for Prodromal Syndromes.

Means ± standard deviations, unless otherwise indicated; *: group comparisons between matched CHR-P subsample ($n = 100$), schizophrenia patients and healthy controls; one-way ANOVA: *F*[df], p; post hoc multiple comparisons (Bonferroni). [a]: χ^2-Test; [b]: independent samples *t*-test (two-sided).

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

[†]PANSS depression factor by Citrome (28).

Table 2. Multifaceted Empathy Test (MET) in individuals at Clinical High Risk of Psychosis (CHR-P; full sample and matched subsample), individuals with schizophrenia (SZ) and healthy controls (HC); group comparisons between CHR-P matched subsample, SZ, and HC

MET	CHR-P full sample	CHR-P matched subsample	Individuals with schizophrenia (SZ)	Healthy controls (HC)	Statistics*
N	120	100	50	50	100/50/50
CE_{sum}	24.4 ± 4.5	24.3 ± 4.4	21.0 ± 4.7	24.5 ± 3.5	*F*[2,108.267] = 10.280***, post hoc: CHR-P vs. HC: n.s. CHR-P vs. SZ: $P < 0.001$ SZ vs. HC: $P < 0.001$
CE_{neg}	11.7 ± 2.8	11.7 ± 2.7	10.7 ± 2.2	12.0 ± 2.4	*F*[2,112.230] = 4.407*, post hoc: CHR-P vs. HC: n.s. CHR-P vs. SZ: n.s. SZ vs. HC: $P = 0.019$
CE_{pos}	12.7 ± 2.5	12.7 ± 2.5	10.3 ± 3.0	12.5 ± 2.1	*F*[2,103.961] = 11.826***, post hoc: CHR-P vs. HC: n.s. CHR-P vs. SZ: $P < 0.001$ SZ vs. HC: $P < 0.001$
EE_{sum}	167.1 ± 62.6	169.9 ± 63.2	206.8 ± 73.8	211.9 ± 42.8	*F*[2,108.264] = 12.291***, post hoc: CHR-P vs. HC: $P < 0.001$ CHR-P vs. SZ: $P = 0.01$ SZ vs. HC: n.s.
EE_{neg}	89.9 ± 34.0	92.0 ± 33.5	103.7 ± 34.1	110.9 ± 23.4	*F*[2,111.122] = 7.990***, post hoc: CHR-P vs. HC: $P < 0.001$ CHR-P vs. SZ: n.s. SZ vs. HC: n.s.
EE_{pos}	77.3 ± 34.0	77.9 ± 34.2	102.7 ± 43.1	101.0 ± 27.2	*F*[2,104.543] = 12.393***, post hoc: CHR-P vs. HC: $P < 0.001$ CHR-P vs. SZ: $P = 0.002$ SZ vs. HC: n.s.
EA_{sum}	157.2 ± 60.0	160.6 ± 61.8	190.0 ± 72.5	197.9 ± 48.3	*F*[2,103.281] = 8.753***, post hoc: CHR-P vs. HC: $P < 0.001$ CHR-P vs. SZ: n.s. SZ vs. HC: n.s.
EA_{neg}	86.3 ± 32.9	87.5 ± 33.7	100.2 ± 36.7	107.5 ± 27.1	*F*[2,104.389] = 7.853***, post hoc: CHR-P vs. HC: $P < 0.001$ CHR-P vs. SZ: n.s. SZ vs. HC: n.s.
EA_{pos}	70.9 ± 31.2	73.1 ± 31.1	89.8 ± 42.8	90.4 ± 29.7	*F*[2,96.676] = 6.656**, post hoc: CHR-P vs. HC: $P = 0.004$ CHR-P vs. SZ: $P = 0.055$ SZ vs. HC: n.s.

$CE_{sum/pos/neg}$, MET cognitive empathy (sum score, positive, and negative emotions); $EA_{sum/pos/neg}$, MET emotional empathy (sum score, positive, and negative emotions).
Means ± standard deviations, unless otherwise indicated; *: group comparisons between matched CHR-P subsample ($N = 100$), schizophrenia patients ($N = 50$) and healthy controls ($N = 50$); one-way ANOVA: *F* (Welch test) [df], p; post hoc multiple comparisons (Tamhane's T2).
$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

diagnosis and gender was detected. Post hoc multiple comparisons (Bonferroni-corrected) confirmed a worse performance in MET cognitive empathy of individuals with schizophrenia compared to healthy controls and individuals at CHR-P, which remained restricted to positively valenced emotions. Controlling for verbal IQ and age, significant group differences between individuals at CHR-P, and healthy controls as well as individuals with schizophrenia appeared for both positive and negative valences of emotional empathy. Exploratory exclusion of $n = 8$ CHR-P participants who fulfilled diagnostic criteria for histrionic, borderline, narcissistic, or antisocial personality disorders did not alter results (data not shown). Levene's tests indicated a weak tendency toward heterogeneity of error variances for MET-EE, but a Box-M value = 77.692, $P = 0.021$, was interpreted as non-significant and thus covariance matrices between the groups were assumed to be equal (37) (Table 3).

Associations of empathy with cognition, social functioning, and symptoms in the CHR-P sample

Within the complete CHR-P group ($n = 120$), emotional MET dimensions appeared to be positively related to age (MET-EE_{sum}: $r_s = 0.192$, $P = 0.035$; MET-EA_{sum}: $r_s = 0.261$, $P = 0.004$). Moreover, weak associations were found between cognitive empathy and verbal IQ (MET-CE_{sum}: $r_s = 0.289$, $P = 0.001$). No associations were found between MET-CE_{sum}, EE_{sum}, and EA_{sum} and DSST and SOFAS scores (all $P \geq 0.05$).

No significant associations were found between MET dimensions and PANSS positive, negative,

Table 3. MANCOVA to determine effects of diagnosis, gender, age, and verbal IQ on MET cognitive and emotional empathy in individuals at Clinical High Risk of Psychosis (CHR-P, matched subsample), individuals with schizophrenia (SZ), and healthy controls (HC)

Factors/covariates → Dependent variables↓	Diagnosis	Gender	Diagnosis × Gender	Verbal IQ	Age
MANCOVA	5.124*** [8,378] $_p\eta^2 = 0.098$	2.880* [4,189] $_p\eta^2 = 0.057$	0.733 [8,378]	5.966*** [4,189] $_p\eta^2 = 0.112$	0.626 [4,189]
Post hoc ANOVA					
CE_{neg} (adjusted $R^2 = 0.031$)	2.821 [2,192]	0.786 [1,192]	0.484 [2,192]	2.472 [1,192]	0.454 [1,192]
CE_{pos} (adjusted $R^2 = 0.208$)	7.801*** [2,192] $_p\eta^2 = .075$	0.624 [1,192]	1.013 [2,192]	22.547*** [1,192] $_p\eta^2 = .105$	0.639 [1,192]
EE_{neg} (adjusted $R^2 = 0.096$)	6.105** [2,192] $_p\eta^2 = 0.060$	11.587*** [1,192] $_p\eta^2 = 0.057$	0.544 [2,192]	0.153 [1,192]	0.268 [1,192]
EE_{pos} (adjusted $R^2 = 0.117$)	10.623*** [2,192] $_p\eta^2 = 0.100$	5.142* [1,192] $_p\eta^2 = 0.026$	0.471 [2,192]	0.793 [1,192]	0.722 [1,192]
Multiple comparisons:	CHR-P vs. HC:	CHR-P cs. SZ:	SZ vs. HC:		
CE_{neg}	$P = 1.000$	$P = 0.102$	$P = 0.097$		
CE_{pos}	$P = 0.822$	$P < 0.001$	$P = 0.030$		
EE_{neg}	$P = 0.007$	$P = 0.040$	$P = 1.000$		
EE_{pos}	$P = 0.003$	$P < 0.001$	$P = 1.000$		

$CE_{sum/\ pos/\ neg}$, MET cognitive empathy (sum score, positive, and negative emotions); $EA_{sum/pos/neg}$, MET emotional empathy (sum score, positive, and negative emotions).
Group comparisons in matched CHR-P subsample ($N = 100$), individuals with schizophrenia ($N = 50$) and healthy controls ($N = 50$); MANCOVA, post hoc ANOVAs (F (Wilks' lambda) [df], $_p\eta^2$) and multiple comparisons (adj. Bonferroni): p; Box-M value = 77.692, $P = 0.021$; Levene's tests: $CE_{neg/pos}$: $P > 0.05$; EE_{neg}: $P = 0.040$; EE_{pos}: $P = 0.024$. *$P < 0.05$; $P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

or general scores, the PANSS depression factor (28), PANSS item 20 (depression), or MADRS sum scores (all $P \geq 0.05$). However, SIPS negative scores were significantly related to MET emotional empathy (EE_{sum}: $r_s = -0.233$, $P = 0.010$) and MET arousal (EA_{sum}: $r_s = -0.248$, $P = 0.006$). No other associations were found with SIPS positive, negative, or disorganization scores. Levels of basic symptoms, as measured with SPI-A (sum score), were unrelated to MET scores.

No significant group differences of MET scores were detected regarding the presence or absence of COGDIS predictive basic symptoms, BLIPS, or FRRF (all $P \geq 0.05$). However, the presence of attenuated positive symptoms (APS) was associated with significantly lower scores for MET emotional empathy ($MET\text{-}EE_{pos}$) and emotional arousal ($MET\text{-}EA_{pos}$), when positive emotions were presented (Fig. 1).

Discussion

In this study, we investigated cognitive and emotional empathy in three samples of individuals at CHR-P, individuals with schizophrenia, and healthy controls. To our knowledge, this is one of the largest studies on emotional and cognitive empathy in individuals at CHR-P currently published. Our main findings are (1) a similar performance regarding cognitive empathy of persons at CHR-P and healthy controls, in contrast to significant alterations in the schizophrenia group, (2) a significant reduction of emotional empathy in the CHR-P group, compared to healthy controls and individuals with schizophrenia, and (3) an association of lower scores of emotional empathy and arousal with the pronounced expression of prodromal symptoms.

Cognitive empathy in individuals at ultra-high risk of psychosis

Based on previous meta-analyses and larger studies suggesting moderate but significant deficits of affect recognition in faces and ToM in CHR-P compared to healthy controls (7,38-40) as well as on our previous finding of subtle reductions of cognitive empathy in individuals at genetic risk for schizophrenia (41), we anticipated MET-CE scores in CHR-P in between those of individuals with schizophrenia and healthy controls. Contrary to our expectation, individuals at CHR-P showed no significant difference in MET-CE scores compared to controls. Only individuals with schizophrenia were characterized by significantly reduced scores of MET-CE compared to both healthy controls and individuals at CHR-P. Of note, there were no associations of MET-CE with symptom severity, DSST scores, FRRF, or COGDIS predictive basic symptoms in individuals at CHR-P.

However, possibly in agreement with our results, meta-analyses have reported associations of social cognitive performance with the duration of illness in individuals with schizophrenia (42,43). In contrast to other studies that implemented tests of affect recognition in faces or visual ToM tasks to individuals at CHR-P (7,38,39), we administered the MET-CE, which, in addition to facial

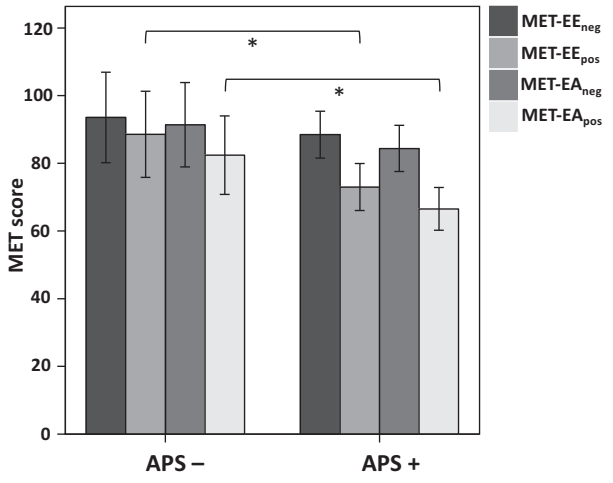

Fig. 1. MET emotional empathy and emotional arousal in CHR-P individuals with and without attenuated positive symptoms (APS). $N = 120$, MET mean scores [CI 95%], *t*-test for independent samples, $*P < 0.05$. APS, attenuated positive symptoms; MET-EE$_{pos/neg}$, MET emotional empathy for negative/positive valences; MET-EA$_{pos/neg}$, MET emotional arousal for negative/positive valences.

expressions of complex emotions, includes situational context in pictures (22), and it could be hypothesized that the provision of context helps CHR-P subjects with cognitively inferring emotional states. MET-CE might therefore rather draw on emotional perspective-taking than on emotion recognition, which was shown to be unimpaired at behavioral testing in a CHR-P sample (44). Van Donkersgoed et al. (2015) reported non-significant effect sizes for ToM reductions in individuals at CHR-P compared to healthy controls from visual ToM tasks like the Reading the Mind in the Eyes Test as opposed to verbal tasks (38). Moreover, MET stimuli, in comparison with other facial affect recognition tasks, depict only emotions of moderate intensity, which may cause less interfering arousal when focusing on affective mentalizing. These methodological differences in assessing cognitive empathy could have contributed to the non-significant differences between individuals at CHR-P and controls in this study compared to other studies.

Emotional empathy in individuals at ultra-high risk of psychosis and schizophrenia

Individuals at ultra-high risk of psychosis showed significantly lower scores of MET-EE and MET-EA compared to healthy controls and individuals with schizophrenia. Differences between groups applied to both positive and negative affective valences. Results also indicated lower MET-EE and MET-EA in individuals with a larger degree of prodromal symptoms: (1) Individuals with attenuated positive symptoms (APS) showed significantly lower MET-EE and MET-EA for positive affective valences than individuals without APS. (2) Low MET-EE and MET-EA were significantly related to high scores of prodromal negative symptoms (i.e., SIPS negative score).

Findings suggest that the tendency to 'feel with' an interaction partner, for example, to vicariously experience an other-induced emotion, is reduced in individuals at CHR-P compared to healthy controls and to individuals with schizophrenia. Our result is in line with other studies reporting an impaired emotional reactivity of individuals at CHR-P compared to healthy controls (16,18-20). Diminished emotional reactivity in individuals at CHR-P might correspond to the use of dysfunctional emotion regulation strategies like suppression (45) or to altered emotional awareness (46). In comparison, Derntl et al. (2015) (44) investigated a small sample of individuals at clinical high risk (CHR) regarding 3 aspects of emotional empathy —emotion recognition, emotional perspective-taking, and affective responsiveness— and did not show evidence of behavioral abnormalities compared to healthy controls. However, CHR individuals showed a task-related hyperactivation of the empathy network assessed with functional magnetic resonance imaging, which was interpreted as a compensatory mechanism reflecting emotional hypersensitivity or dysfunctional emotion regulation by the authors. Strong activation of the medial temporal gyrus in this study during the affective responsiveness task might have corresponded to an active distancing as an emotion regulation strategy (44,47). Brain imaging studies in non-clinical, psychosis-prone individuals also indicate frontotemporoparietal hyperactivation, reduced prefrontal-amygdala coupling, and insufficient down-regulation of the amygdala during the reappraisal of negative emotion (48). This raises the question, whether the results of our behavioral study may reflect either altered emotional awareness or an attempt to suppress emotional experience due to impaired cognitive control of emotion in individuals at CHR-P.

In contrast, individuals with schizophrenia were characterized by unaltered MET-EE and MET-EA in the present study. Individuals with schizophrenia showed intact abilities to 'feel with' and empathize emotionally (i.e., intact emotional empathy) with another person even though they may have difficulties to correctly identify and understand another person's emotional state (i.e., impaired cognitive empathy). This is in agreement

with unimpaired MET-EE reported previously (13) and an intact experiential reaction to emotional stimuli in individuals with schizophrenia (18,49,50). However, results from these experimental emotional evocations of empathy differ from naturalistic studies implementing experience sampling methods, which showed amplified negative emotional states in individuals with schizophrenia (51,52) and findings of an increased limbic activation to negative and blunted responses to affectively positive cues (53). Of note, emotional empathy measured by MET-EE scores was reported to be unimpaired in individuals with schizophrenia while trait self-ratings of emotional experience, 'personal distress', and emotional contagion suggested deficits in the regulation of negative emotions and interpersonal tension (13). A comparison of our findings with the above-mentioned literature (51,52) raise the question whether the seemingly normal MET-EE scores in individuals with schizophrenia in our study reflect a maintained emotional empathy but aspects of emotion processing, in particular, of negative emotions, may be altered (13).

Overall, individuals at CHR-P in our study showed a different profile of empathic responding compared to individuals after the first manifestation of schizophrenia. It could be hypothesized that different mechanisms may contribute to alterations of social cognition and empathy in the course of the disease (44,54). While reduced MET-EE in individuals at CHR-P might be related to a compensatory mechanism in light of emotional hypersensitivity and dysfunctional emotion regulation, a potential increase of MET-EE has been reported in the course of normal aging (55). Moreover, in individuals with schizophrenia, MET-EE scores were negatively related to the age of first psychotic manifestation and positively to duration of illness as well as antipsychotic treatment years (13). Both observations might be related to increasing affective lability due to cognitive, that is, executive dysfunction and poor inhibitory control over time. More research is needed to assess additional moderators as well as the functionality of the empathic response in individuals with schizophrenia.

In contrast to some previous studies in CHR-P (19,20) and meta-analytic evidence for a reduced self-reported emotional experience in individuals with major depressive disorder compared to healthy controls (56), reductions of MET-EE and -EA were not linked to depressive psychopathology, but to SIPS negative symptoms in our sample. Moreover, lowest MET-EE scores for positive valences were found in individuals who had experienced APS in the past. This is compatible with the notion of a link between dysfunctional emotion processing and the emergence of paranoid symptoms in stressful interpersonal situations (57), and with findings from experience sampling studies in individuals with schizophrenia that indicate a role of expressive suppression when confronted with negative emotions and state paranoia at a following point in time (58). Alternatively, a pronounced impairment of empathy for positive emotional experiences may be related to an altered processing of reward and its neurobiological correlates (59).

Studies in women with borderline personality disorder (BPD) suggest differential effects of psychosocial stress on MET-EE: While healthy controls show an increase in empathy, social cognition, and pro-social behavior during stressful conditions, acute stress leads to a decrease of MET-EE in individuals with BPD (60). Individuals with APS and negative symptoms may also experience a higher degree of distress and threat sensitivity in interpersonal situations, thus leading to 'fight or flight' responses and reductions of emotional empathy. Using a slightly different version of the MET, Ritter et al. (2011) reported that individuals with narcissistic personality disorder were less able to mirror emotions and less emotionally responsive to another person's emotional state compared to healthy controls, while MET-CE was preserved (61). This pattern of empathic responding has also been reported in individuals with antisocial personality traits (62) and resembles the constellation in CHR-P participants detected in our sample. Sensitivity analysis was therefore performed, but excluding individuals with DSM-IV-TR cluster B personality disorders did not change results.

Assuming a substantial overlap of prodromal psychotic, affective, and anxiety symptoms, and personality traits in CHR-P samples (63), as well as a considerable heterogeneity regarding transition rates to psychosis (64), our findings could also be attributed to diagnostic heterogeneity in the CHR-P group. However, reduced self-reported emotional empathy and arousal might rather reflect a common vulnerability factor for anhedonia and reduced interpersonal resonance and might not be specific for prodromal schizophrenia (20).

In our study, gender had a significant impact on MET-EE, with females showing higher values irrespective of valence or diagnostic group in our study. Gender differences in neural network activation when processing empathic stimuli (17,65) and higher performance of females at theory of mind tests and self-rated empathy measures (66-68) have been reported by other authors. More research is

needed to confirm, whether females are less affected by alterations of emotional empathy in schizophrenia (69).

Limitations

A limitation of this study is the use of a single instrument to measure aspects of empathy. Results should be confirmed with a broader array of tasks and should optimally be accompanied by vegetative and/or imaging data. However, we used a multidimensional test with validity in schizophrenia, individuals with genetic risk for psychosis and a number of clinical conditions (13,22,41,60,61). The cross-sectional design of this study limits the interpretation of the findings and does not allow to investigate the relationship between reduced emotional empathy and transition rates to psychosis in CHR-P. Future longitudinal studies should investigate individuals at CHR-P together with those of prodromal syndromes of affective psychoses and other prodromal groups suffering from emotion dysregulation to assess the specificity of findings.

In addition, conceptualizing empathy as having emotional and cognitive aspects does not constitute a full assessment of all aspects of empathy and other concepts of empathy such as motor empathy have also been proposed (22,70). Future studies should also observe related constructs of handling interpersonal emotions such as general emotional responsiveness and emotion regulation.

Medical treatment in individuals with schizophrenia could hypothetically have influenced findings. Even though acute effects of antipsychotic treatment were not shown (71), the increase in emotional empathy in medicated individuals with schizophrenia might reflect a restorative effect compared to the neuroleptic-free prodromal phase (20). However, negative long-term effects of antipsychotics on other measures of empathy or frontal function in general cannot be excluded (13,72-74).

Our findings suggest that individuals at CHR-P show less emotional empathy than controls or individuals with schizophrenia, while individuals with schizophrenia show impaired cognitive empathy. Whether impaired emotional empathy is a crucial marker for the risk of conversion to schizophrenia or an epiphenomenon in individuals at CHR-P remains to be clarified. While cognitive mentalizing is considered a well-established trait-marker for non-affective psychoses (7,8), the role of affective mentalizing should be further explored and linked to stage-dependent mechanisms in the course of psychotic illness.

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Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13178. [Correction added on 14 October 2020, after first online publication: Peer review history statement has been added.]

Data availability statement

The data that support the findings of this study are available from the corresponding author, [C.M.], upon reasonable request.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Trial protocol.