

Empathy in individuals clinically at risk for psychosis: brain and behaviour

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Background

Empathy is a basic human ability, and patients with schizophrenia show dysfunctional empathic abilities on the behavioural and neural level.

Aims

These dysfunctions may precede the onset of illness; thus, it seems mandatory to examine the empathic abilities in individuals at clinical high risk for psychosis.

Method

Using functional magnetic resonance imaging, we measured 15 individuals at clinical high risk of psychosis (CHR group) and compared their empathy performance with 15 healthy volunteers and 15 patients with schizophrenia.

Results

Behavioural data analysis indicated no significant deficit in the CHR group. Functional data analysis revealed hyperactivation in a frontotemporoparietal network including

the amygdala in the CHR group compared with the other two groups.

Conclusions

Despite normal behavioural performance, the CHR group activated the neural empathy network differently and specifically showed hyperactivation in regions critical for emotion processing. This could suggest a compensatory mechanism reflecting emotional hypersensitivity or dysfunctional emotion regulation. Further investigations should clarify the role of these neural alterations for development and exacerbation of psychosis.

Declaration of interest

None.

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In schizophrenia, impairments in social cognition as well as metacognition result in poor social functioning¹ and act as a mediator between neurocognition and real-world functioning.^{2,3} Empathy, the ability to infer and share another's internal emotional states, plays a pivotal role in social interaction^{4,5} and is a multidimensional phenomenon; Decety & Jackson⁶ postulated that at least three core components can be identified: (a) recognition of emotions in oneself and others; (b) an affective component, i.e. the ability to experience and share similar emotions as others (affective responsiveness, AR); and (c) a cognitive component, i.e. the ability to take the perspective of another person and infer their feelings (emotional perspective-taking, EPT). Persons with schizophrenia show substantial deficits in nearly every domain also in empathy, with impairments in emotion recognition (ER) being investigated most frequently (for meta-analysis⁷). However, a thorough investigation of all three components demonstrated that individuals with schizophrenia suffer from a significant deficit in every single domain,⁸ thus indicating a much broader emotional deficit. Neuroimaging research extended the behavioural findings by highlighting functional abnormalities during empathy-related tasks in individuals with schizophrenia,^{9,10} which importantly were further associated with social community functioning.¹¹ Compared with the plethora of studies addressing socio-emotional processes in schizophrenia, relatively little is known about empathy in people at risk for psychosis. Few studies investigated emotional abilities in persons genetically at risk for schizophrenia and observed significant behavioural deficits,¹² however, mixed results were reported regarding neural activation compared with controls (amygdala hypofunction;¹³ neural hyperactivation;¹⁴ no difference¹⁵). Even less is known in patients at clinical high risk for psychosis. Behavioural studies in such patients addressing facial or vocal

affect processing reported mixed findings: ranging from a rather general impairment¹⁶ to emotion-specific deficits^{17,18} or no difference.¹⁹ Seiferth *et al*²⁰ investigated neural activation during ER in individuals at clinical high risk of psychosis and observed frontolimbic hyperactivation particularly during neutral face-processing. Notably, there is a lack of studies investigating cognitive and affective empathy in this group of patients. This seems particularly surprising, given the evidence of a significant association between empathy and social functioning in individuals with schizophrenia^{11,21} and consistent findings on social interaction difficulties acting as a precursor of schizophrenia.²²

The aim of the present study therefore was to investigate the behavioural and neural substrates of empathy in individuals at clinical high risk of psychosis and matched controls, enabling more detailed analyses of emotional competencies, their interactions and possible neural dysfunctions in this preclinical group. In addition to group differences, we also analysed potential associations between behavioural performance, neural activation and clinical parameters. Based on inconsistent results regarding ER and previous neuroimaging data in individuals at clinical high risk of psychosis,²⁰ we expected unimpaired recognition accuracy but dysfunctional neural activation. Additionally, to further examine differences and similarities in empathy between individuals at clinical high risk of psychosis and patients with borderline personality disorder, behavioural and neural data of individuals at clinical high risk of psychosis in affective and cognitive empathy was compared with previously published data on individuals with schizophrenia.⁹

Method

Sample

A total of 15 patients at clinical high risk of psychosis (CHR group) and 15 healthy controls (CON group) were included.

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For comparison, we relied on data of 15 individuals with schizophrenia (SZP group) that have been published previously.⁹ Due to excessive head movement, functional data of two CHR group participants were excluded from functional magnetic resonance imaging (fMRI) data analysis. All patients were White, native German-speaking and were matched for age, parental education and neurocognitive function.

The CHR group were recruited through clinical services at the Department of Psychiatry, Psychotherapy and Psychosomatics (DPPP), RWTH Aachen University. Experienced psychiatrists identified clinical risk for psychosis and diagnostic inclusion criteria were assessed by the Structured Interview for Prodromal Syndromes and the Scale of Prodromal Symptoms (SIPS/SOPS);²³ positive and negative symptoms were also assessed with the Positive and Negative Syndrome Scale (PANSS).²⁴ Based on a two-phase approach,²⁵ participants had to fulfil the criteria for a late initial prodromal state. Attenuated psychotic symptoms (APS) and the Brief Limited Intermittent Psychotic Symptoms (BLIPS) were applied as criteria; thus symptoms of clinical high risk of psychosis were below criteria for a full-blown manifest psychotic episode. Social and occupational functioning (Social and Occupational Functioning Assessment Scale, SOFAS²⁶) and depressive symptoms (Montgomery-Åsberg Depression Rating Scale, MADRS²⁷) were assessed in the CHR group. Four CHR participants had a familial risk for psychosis besides clinical symptoms. Three CHR patients were taking atypical agents (1 aripiprazole, 1 quetiapine and 1 risperidone) and two were on antidepressive medication (selective serotonin reuptake inhibitors).

The SZP group was recruited from in- and out-patient units of the DPPP, received atypical antipsychotics and no other medication. Symptom severity was assessed with standardised scales (PANSS²⁴). Exclusion criteria for all participants included substance abuse within the last 6 months, left-handedness and any other psychiatric or neurological illness based on the Structured Clinical Interview for DSM-IV Disorders.²⁸

Moreover, to assess self-reported empathic abilities the German version of the Interpersonal Reactivity Index²⁹ was

administered and participants were asked to answer 16 items on a 5-point Likert scale ranging from 'Does not describe me well' to 'Describes me very well'. Additionally, all participants completed neuropsychological tests, tapping premorbid crystallised verbal intelligence (Mehrfachwahl-Wortschatz-Intelligenztest, MWT-B),³⁰ information processing speed and executive functions (Trail Making Tests, versions A and B)³¹ as well as working memory (digit spans from WAIS-IV).³² Demographic, clinical and neuropsychological characteristics are shown in Table 1.

After complete description of the study to the participants, written informed consent was obtained. All participants were paid for their participation. The ethics committee of RWTH Aachen University approved the study.

Functional tasks

We used three tasks tapping each empathy component separately, which have been used before in neuroimaging studies.⁹ Every response was recorded and the sum of correct responses added up to an accuracy score for each task that was used for statistical analyses. Analysis of internal consistency across the whole sample revealed Cronbach's alpha of 0.649 (ER), 0.839 (EPT) and 0.882 (AR), indicating acceptable to good reliability.

Emotion recognition

Thirty photographs of White faces depicting five basic emotions (happiness, sadness, anger, fear and disgust) and neutral expressions were presented. Stimuli were selected from a standardised stimulus set.³³ Participants were instructed to choose the correct emotion from two possibilities via button press. Stimuli were presented maximally for 5 s with a randomised, variable interstimulus interval ranging from 8 s to 12 s.

Emotional perspective-taking

Participants viewed 35 scenes showing two White people involved in social interaction thereby portraying the emotions described

Table 1 Mean and standard deviation (in parentheses) of sociodemographic and neuropsychological characteristics of participants with clinical high risk for psychosis (CHR), healthy controls (CON), and patients with schizophrenia (SZP)

	CHR (n = 15)	CON (n = 15)	SZP (n = 15)	P
Gender, females:males	3:12	3:12	5:10	–
Age, years	27.1 (7.3)	29.0 (9.8)	34.2 (9.1)	0.086
Education, years	13.3 (2.3)	15.8 (2.4)	12.4 (3.5)	0.237
Education (father), years	13.1 (2.2)	12.7 (3.7)	11.2 (3.7)	0.202
Education (mother), years	12.0 (2.4)	12.3 (3.9)	10.5 (3.8)	0.480
SIPS/SOPS score				
Positive	8.1 (2.8)			
Negative	14.1 (4.6)			
Disorganised	3.8 (1.7)			
General	7.0 (3.0)			
PANSS total score	52.6 (13.4)		52.0 (7.8)	
Positive	12.5 (3.7)		12.3 (3.8)	
Negative	13.6 (5.5)		14.6 (3.7)	
Global	26.5 (7.1)		24.5 (4.4)	
SOFAS score	62.8 (11.4)			
MADRS score	19.9 (4.4)			
MWT-B score	27.2 (4.1)	29.7 (4.2)	30.2 (3.3)	0.112
TMT-A, sec	23.9 (8.8)	22.9 (6.3)	28.9 (9.0)	0.292
TMT-B, sec	41.8 (12.8)	46.3 (15.9)	54.6 (24.8)	0.237
Digit span score	14.0 (4.2)	15.3 (2.8)	14.5 (2.8)	0.565
SIPS/SOPS, Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms; PANSS, Positive and Negative Syndrome Scale; SOFAS, Social and occupational functioning scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest-B measuring premorbid verbal crystallised intelligence; TMT, Trail Making Test measuring executive functions; digit span, assessing working memory. Groups did not differ significantly in age, education, parental education and neuropsychological performance.				

above. The face of one person was masked, and participants were asked to infer the emotional expression of the masked face. Stimuli were shown for 4 s and participants responded immediately afterwards by selecting between two different facial expressions that were taken from the stimulus pool described above.

Affective responsiveness

We presented 35 short written sentences describing real-life situations inducing one of the emotions described above. Participants were asked to imagine how they would feel if they were experiencing those situations. Sentences were presented for 4 s and response format was the same as for EPT.

All stimuli were presented by goggles (VisuaStimDigital, Resonance Technology Inc, Los Angeles, California, USA). Presentation of images, recording of responses and synchronisation with the scanner was achieved using Presentation (Neurobehavioral Systems, Inc, Albany, California, USA).

Behavioural data analysis

Statistical analyses were performed by SPSS 20.0 and level of significance was set at $P=0.05$. Correct responses of each empathy task acquired during scanning were analysed by mixed effects analysis of variance (ANOVAs) with task as within-participant factor and group as between-participant factor. Bonferroni corrected P -values are reported for all *post hoc* comparisons.

Group differences in self-report data were assessed by univariate ANOVAs. For the self-report empathy scale we used sums of the four subscales (each made up of four different items) for further analyses. Regarding the statistical analysis of neuro-psychological tests, we relied on the sum of correctly marked words in the MWT-B. For the TMT-A and TMT-B we used reaction time to finish the tasks and regarding digit span we relied on the sum of the correct forward and backward trials.

Correlations between accuracy measures and self-report scores were computed using Pearson correlations, except for AR where performance scores were not normally distributed (here Spearman's rank correlations were applied). For the CHR group, additional analyses investigating potential associations between clinical parameters and behavioural measures as well as self-report scores were performed by Pearson correlations, again with the exception of analyses involving AR scores. All correlation significance tests were two-tailed and corrected for multiple testing.

fMRI acquisition parameters and data processing

All participants were examined with a 3T whole-body scanner (Philips, Best, The Netherlands) at the Medical Faculty of RWTH Aachen University. Functional imaging was performed by gradient-recalled EPI; 35 oblique axial slices were acquired by asymmetric k -space sampling (repetition time = 2200 ms, echo time = 31 ms).

Functional data were pre-processed by SPM8 (www.fil.ion.ucl.ac.uk/spm/spm8.html). Images were slice-timing corrected, realigned and normalised into the standardised stereotactic space. Functional data-sets were spatially smoothed by an isotropic Gaussian kernel with a full-width-at-half-maximum of 8 mm. Prior to pre-processing, a signal artefact correction algorithm was employed to reduce large, slice-wise signal fluctuations in the fMRI time-series as previously reported.⁹

fMRI data analysis

For this event-related design, each stimulus type was modelled with a separate regressor by a delta function convolved with the

hemodynamic response function. For EPT and AR the initial task stimulus (scene/sentence) and the response option were modelled with separate regressors. First-level models included motion parameters as regressors of no interest.

To detect group differences, contrast images from all participants for each task were included in a second-level random effects analysis. We performed a 3 (group) \times 3 (task) mixed effects ANOVA and significant F -contrasts were explored by subsequent *post hoc t*-contrasts. For EPT and AR only activation related to the initial task stimulus was analysed at the second level.

For whole-brain analyses we applied a correction for multiple comparisons at the cluster-level based on Monte-Carlo simulations by AlphaSim.³⁴ According to 1000 simulations based on a cluster-defining threshold of $P<0.001$ (uncorrected) and the spatial properties of the residual image an extent threshold of 55 contiguous voxels sufficed to comply with a family-wise error of $P<0.05$. All results were depicted at this threshold.

Region of interest (ROI) analysis

We performed an ROI analysis for the amygdala region due to its role in emotion processing and previous studies observing functional abnormalities of the amygdala in individuals at clinical high risk for psychosis²⁰ and those with schizophrenia.⁹ Based on previous results,³⁵ values for both amygdala ROIs were extracted drawing two spheres (10 mm) centred at $[x,y,z: \pm 20, 0, -20]$. A three-way ANOVA was applied with group as between-participant factor, and task and laterality as repeated factors.

Corollary analyses

Pearson correlations were performed with accuracy data from ER and EPT and mean amygdala parameter estimates (taken from the ROI analysis). Spearman's rank correlation was used for correlation analyses between amygdala activation and AR scores. For the CHR group, additional Pearson correlations between amygdala activation and clinical parameters (SIPS/SOPS, PANSS, MADRS, SOFAS) were conducted.

Results

Behavioural performance

Analysis of percent correct demonstrated a significant task effect ($F(2,40)=17.141$, $P<0.001$) and a significant group effect ($F(2,40)=4.156$, $P=0.025$), but no task \times group interaction ($F(2,40)=1.568$, $P=0.194$). Bonferroni corrected *post hoc* tests of the task effect revealed significantly worse performance in EPT compared with AR ($P<0.001$) and ER ($P=0.003$), whereas performance in ER did not differ significantly from AR ($P=0.069$). Regarding the group effect, the CON group outperformed the

Table 2 Performance accuracy of the empathy tasks (percent correct) and self-reported empathic abilities for each group (means and standard deviations)

	CHR ($n=15$)	CON ($n=15$)	SZP ($n=15$)
Emotion recognition	89.5 (3.3)	94.0 (4.1)	88.9 (6.7)
Perspective-taking	87.1 (10.1)	89.6 (5.7)	79.0 (13.5)
Affective responsiveness	96.5 (5.0)	97.2 (2.9)	88.4 (16.7)
SPF fantasy	11.5 (3.2)	14.4 (3.2)	12.8 (2.4)
SPF perspective-taking	13.8 (3.2)	15.4 (2.8)	15.3 (2.4)
SPF empathic concern	13.6 (2.0)	14.2 (3.3)	13.7 (3.2)
SPF distress	11.0 (3.7)	8.5 (2.4)	11.4 (2.8)

CHR, individuals at high clinical risk for psychosis; CON, healthy controls; SZP, individuals with schizophrenia; SPF, Saarbrückener Persönlichkeitsfragebogen, German version of the Interpersonal Reactivity Index (IRI).

SZP group ($P=0.025$), whereas no difference emerged between the other groups (CON-CHR: $P=1.000$; CHR-SZP: $P=0.200$).

Figure DS1 in an online data supplement to this paper illustrates performance on the empathy tasks across groups, and Table 2 gives details on performance accuracy.

Empathy questionnaire

Direct comparison of self-report scores demonstrated significant group effects for the fantasy scale ($F(2,40)=3.340$, $P=0.047$) and the distress scale ($F(2,40)=3.525$, $P=0.040$), whereas no other significant difference emerged ($P_s > 0.269$). *Post hoc* analyses showed that the CHR group had significantly lower fantasy scores than the CON group ($P=0.043$) but did not differ from the SZP group ($P=0.825$) who also did not differ from the CON group ($P=0.569$). Regarding the distress scale, *post hoc* tests revealed no significant difference between the groups ($P_s > 0.071$). Please see Table 2 for means and standard deviations for each group.

Functional data

Separate group analyses for the CHR, SZP and CON groups showed activation of a widespread cortical-subcortical network including frontal regions, orbitofrontal cortex, temporal gyri, fusiform gyri, inferior parietal cortex and cingulate cortex across all tasks. Please note that differences between the SZP and CON groups will not be reported since they were not the focus of the current paper and resemble findings from a previously published study.⁹

The mixed effects ANOVA revealed significant group differences across all empathy tasks in several regions, for example bilateral amygdala, left inferior and middle frontal gyrus, middle cingulate cortex, and left temporoparietal junction (online Fig. DS2(a) and Table 3).

Moreover, a significant task effect and a significant task \times group interaction emerged. *Post hoc t*-tests revealed several significant findings (online Fig. DS2(b) and Table DS1).

For ER, the CHR group showed stronger activation compared with the CON group in a widespread network, including bilateral amygdala, right inferior frontal gyrus (IFG), right middle temporal gyrus (MTG), left parahippocampal gyrus, right middle cingulate gyrus and left thalamus. Comparing the CHR group with the SZP group, stronger recruitment of left amygdala, left thalamus, and inferior frontal gyri bilaterally was apparent in the CHR group. The CON and SZP groups showed no stronger activation than the CHR group.

For EPT, the CHR group showed a stronger neural response in the right IFG, left superior medial frontal gyrus, right middle and left inferior temporal gyrus as well as left parahippocampal gyrus than the CON group. The CHR group also exhibited stronger activation than the SZP group of the amygdala bilaterally, left superior medial frontal gyrus, bilateral parahippocampal gyrus, left putamen, bilateral middle frontal gyrus and right lingual gyrus. Again, the CON and SZP groups demonstrated no stronger activation than the CHR group.

Regarding AR, group comparisons revealed stronger activation of the CHR group than the CON group only in the left MTG, whereas the CON group recruited bilateral superior temporal gyrus and right temporoparietal junction more strongly. In comparison with the SZP group, the CHR group showed stronger neural response of the amygdala bilaterally, right IFG, bilateral superior frontal gyrus and thalamus. Again, the SZP group exhibited no stronger activation than the CHR group.

ROI analysis

The ANOVA demonstrated a significant task effect ($F(2,80)=17.675$, $P < 0.001$), a significant group effect ($F(2,40)=5.104$, $P=0.011$), and a significant task \times laterality interaction ($F(2,80)=6.304$, $P=0.003$). Moreover, a trend towards a task \times group interaction occurred ($F(2,80)=2.482$, $P=0.051$), but no significant laterality effect ($F(2,40)=2.367$, $P=0.133$) and no other interaction reached significance ($P_s > 0.068$). *Post hoc* analysis of the task effect showed that amygdala activation was stronger during ER compared with both other tasks

Table 3 Results from the mixed effects ANOVA with group and task as factors, showing a significant main effect of group (threshold: $F=7.32$, $P < 0.05$ cluster level corrected) and a significant group \times task interaction (threshold: $F=4.95$, $P < 0.05$ cluster level corrected)

Contrast	MNI coordinates			Cluster size	F	L/R	Region
	X	Y	Z				
Group effect	-20	-4	-20	26271	41.93	L	Amygdala
	24	0	18	1135	33.12	R	Amygdala
	-52	-56	-20	321	23.63	L	Inferior temporal gyrus
	20	-94	-2	133	22.06	R	Cuneus
	38	-62	20	466	21.05	R	Middle temporal gyrus
	-30	18	38	438	14.83	L	Middle frontal gyrus
	-26	-90	-14	66	13.91	L	Lingual gyrus
	-52	32	22	113	13.70	L	Inferior frontal gyrus
	-16	-56	48	507	11.93	L	Precuneus
	-42	-66	-10	202	11.69	L	Middle occipital gyrus
	-46	-62	48	80	9.93	L	Temporoparietal junction
	4	-24	58	96	9.44	R	Middle cingulate cortex
	Group \times task interaction	48	-64	-10	1721	36.45	R
-8		-102	2	1362	25.45	L	Cuneus
-44		-76	-4	917	23.22	L	Middle occipital gyrus
6		-66	42	488	9.23	R	Precuneus
40		-48	52	261	8.73	R	Temporoparietal junction
46		26	24	247	8.15	R	Inferior frontal gyrus
-48		26	-14	59	6.72	L	Inferior frontal gyrus
24		-42	-20	82	7.84	R	Cerebellum
62		-28	26	118	6.19	R	Supramarginal gyrus

MNI, Montreal Neurological Institute; L, left; R, right.

($P_s < 0.001$), whereas activation did not differ between EPT and AR ($P = 1.000$). Regarding the group effect, *post hoc* tests demonstrated significantly less amygdala activation in the SZP group compared with the CON group ($P = 0.024$) and the CHR group ($P = 0.030$), whereas the CHR group did not differ from the CON group ($P = 1.000$). The significant task \times laterality interaction revealed a laterality effect only for AR, where the left amygdala showed a significantly stronger response than the right ($P = 0.008$). Both other tasks showed no laterality difference ($P_s > 0.069$).

Correlation analyses

Behavioural data

Positive symptoms as assessed via SIPS/SOPS showed a significant correlation with accuracy in EPT ($r = -0.704$, $P = 0.007$). No other correlation regarding symptom severity (SIPS/SOPS, PANSS) or depression scores (MADRS) reached significance ($P_s > 0.197$). SOFAS scores correlated with performance in ER ($r = 0.793$, $P = 0.001$) and EPT ($r = 0.625$, $P = 0.022$), but not with AR ($P = 0.234$).

Functional data

Correlation analyses between performance accuracy and task-specific amygdala activation failed to show significant associations in any group ($P_s > 0.184$).

Regarding clinical parameters in the CHR group, positive symptoms as well as depression scores correlated significantly with amygdala activation during EPT (SIPS_P: $r = 0.580$, $P = 0.038$; MADRS: $r = -0.563$, $P = 0.045$). A trend for a similar correlation emerged for depression scores and amygdala activation during AR ($\rho = -0.572$, $P = 0.052$), whereas all other associations did not reach significance ($P_s > 0.062$).

Discussion

The aim of the current study was to explore behavioural and neural correlates of the core components of empathy, namely ER, EPT and AR in persons at clinical high risk of psychosis compared with healthy controls and individuals with schizophrenia. To the best of our knowledge, no neuroimaging study has addressed a broader range of emotional competencies in the CHR group.

The CHR group showed similar behavioural performance compared with the CON group, thereby supporting findings on unimpaired ER/differentiation in individuals at clinical high risk of psychosis¹⁹ and extending such evidence to further empathy components. In line with previous work,²⁰ the CHR group differed markedly in their neural activation from the CON group. Comparing neural activation of the CHR and SZP groups demonstrated significant differences across all tasks, with the CHR group showing hyperactivation mainly in emotion-related areas. Additionally, significant correlations between performance, neural activation, clinical parameters and social functioning emerged.

Abnormalities in the neural empathy network in the CHR group

Compared with the CON group, neural activation of the CHR group was mainly characterised by hyperactivation of the IFG, the middle cingulate cortex and the parahippocampal gyrus. Interestingly, the MTG showed hyperactivation during all tasks. Elevated MTG activation was recently reported during application

of an emotion regulation strategy (distancing) in healthy participants.³⁶ Here, the CHR group showed stronger activation of the MTG during all tasks but particularly during AR, the only self-centred task where we asked participants to imagine going through a certain situation and how this would make them feel. The stronger activation of the MTG might indicate that the CHR group was actively using this strategy to prevent them from reacting too emotionally. Since the MTG is only one node in the neural network underlying emotion regulation³⁶ and due to multiple functions of each brain region as well as the limited data available in the CHR group, this interpretation needs additional support from the literature. Alternatively, the MTG was proposed to play a major role in mentalising and understanding other people's intentions and emotions.³⁷ Stronger activation of the CHR group might then reflect compensatory mechanisms, probably the reason for their unimpaired behavioural performance.

Activation of the IFG was repeatedly observed during various emotional processes including empathy.^{9,10} In our data, the CHR group demonstrated hyperactivation of this region particularly during ER and EPT compared with the CON group and during ER and AR compared with the SZP group. Seiferth *et al*²⁰ reported stronger activation of the IFG during processing of neutral faces, probably reflecting aberrant attributions of motivational/emotional salience to neutral stimuli, which were also proposed to characterise individuals with schizophrenia.³⁸ However, direct comparison indicated that, although the SZP group showed a significant reduction in IFG activation across all three tasks,⁹ the CHR group mainly demonstrated hyperactivation of this region. These diverging activation patterns might point to neural changes before illness onset. Given the functionality of sub-regions of the IFG for action observation, imitation, mentalising and emotion processing,³⁹ we speculate that the hyperactivation in the CHR group might reflect compensation mechanisms that enabled the CHR group to perform similar to the CON group, whereas the hypoactivation in the SZP group indicates the consequences of illness onset and denotes one important substrate of an impaired capacity to spontaneously simulate another person's subjective world.

Another region that showed elevated activation in the CHR group compared with the CON group as well as the SZP group was the parahippocampal gyrus. Recently, grey matter volume reductions in individuals at ultra-high risk for psychosis were investigated and persons who later developed a psychotic disorder showed distinct reductions of parahippocampal cortex volume.⁴⁰ Hence, volume alterations of this region may be crucial to the expression of illness.

Notably, we observed greater activation of the amygdala bilaterally in the CHR group compared with the CON group during ER and compared with the SZP group across all tasks. This exaggerated activation might be due to disturbed frontolimbic connectivity in the CHR group, which was recently shown in children and adolescents with familial risk for psychosis.⁴¹ This dysfunctional connectivity could lead to elevated emotional arousal, hypersensitivity for emotional stimuli, particularly facial expressions of emotions, causing heightened negative affect and stress. The assumption of amygdala involvement in the pathophysiology of psychosis stems from studies demonstrating amygdala dysfunction in the SZP group and patients with bipolar disorder with psychotic history⁴² and findings of elevated amygdala activation in psychosis-prone individuals,⁴³ which was also accompanied by less prefrontal-amygdala coupling. Interestingly, in our study positive symptoms were associated with less accuracy and higher amygdala activation during perspective-taking, perhaps also reflecting less prefrontal amygdala coupling during this cognitive empathy task.

Mechanism of empathy abnormalities in individuals at clinical high risk of psychosis

There is very limited evidence on neural correlates of emotional abilities in individuals at clinical high risk of psychosis. Seiferth *et al*²⁰ investigated ER performance and observed stronger activation in visual areas in participants at clinical high risk of psychosis compared with controls for all stimuli, whereas neutral facial expressions prompted marked hyperactivation in frontolimbic regions. They suggested that this hyperactivation might reflect hypersensitivity to affectively irrelevant stimuli in brain areas relevant for attributing affective salience.

Greater activation in people at clinical high risk of psychosis in regions known to be essential for emotion and sociocognitive processing were also reported in studies addressing theory of mind.^{44,45} Brüne *et al*⁴⁵ concluded that their findings indicate that individuals at clinical high risk of psychosis were emotionally more aroused during task performance and may show compensatory hyperactivation, suggesting a 'graded' activation pattern, with people at clinical high risk of psychosis showing the highest activation and individuals with schizophrenia the least activation. Similar to our study, none of these three studies reported behavioural impairments in individuals at clinical high risk of psychosis.

Taken together, previous studies exploring emotional or social cognitive abilities and their neural underpinnings mostly reported hyperactivation in individuals at clinical high risk of psychosis compared with controls and individuals with schizophrenia. The possible mechanism underlying these findings is currently unclear, however, some suggestions have been made: Kapur³⁸ proposed that the development of psychosis is characterised by a stage of 'heightened awareness and emotionality', possibly caused by changes in cerebral dopamine metabolism. Phillips & Seidman⁴⁶ speculated that an overactive amygdala – as apparent in the present study – might not only lead to stronger arousal but may also signal a threat where it does not exist causing increased negative affect and stress. Frontolimbic connectivity was shown to be disturbed in persons with first-episode and chronic schizophrenia⁴⁷ but also in children and adolescents at familial risk for schizophrenia,⁴¹ further supporting the notion that neural abnormalities in emotion processing and emotion regulation might be apparent prior to illness onset and before detectable behavioural deficits arise.

Our finding of hyperactivation in emotion-related brain regions corroborates data from neuroimaging studies in unaffected siblings, i.e. persons genetically at risk for psychosis.¹⁴ However, several other studies in these individuals observed hypoactivation of the neural circuitry of emotion¹³ indicating that clinical symptoms, as apparent in individuals at clinical high risk of psychosis, lead to partly divergent neural activation patterns and behavioural performance than just the genetic risk.

Limitations

The CHR group was relatively small even for neuroimaging studies and it remained unknown how many persons were about to develop a manifest illness. Thus, we are unable to firmly draw the conclusion that greater activation of frontolimbic regions in the CHR group is in any way linked to a disease process. This aspect can only be addressed in longitudinal studies, testing non-converters and converters prior and after manifestation of psychosis. Moreover, not only empathic but also metacognitive abilities might be of interest as previous studies in individuals at clinical high risk of psychosis, first-episode psychosis and chronic schizophrenia indicated developmental changes throughout the course of the disorder, although findings are not always consistent.^{48–50} Additionally, besides the one third that may convert to develop psychosis, Addington *et al*⁵¹ pointed out that the other two-thirds will most likely be further characterised by

low functional outcome. Hence, they also might benefit from treatment interventions addressing empathic, social cognitive and metacognitive abilities^{52,53} and thus better characterisation of their resources and deficits are needed.

Our sample was heterogeneous with respect to gender and medication. Gender differences in empathy were reported previously in healthy individuals.⁵⁴ Thus, future studies should explore whether female and male individuals at clinical high risk of psychosis are also characterised by distinct neural responses. Three individuals in the CHR group were taking antipsychotic medication. Re-running all analyses without these individuals revealed similar results, with the main findings remaining significant. Moreover, in our previous neuroimaging study on empathy in schizophrenia we observed similar results when controlling for medication as covariate,⁹ which was in line with non-significant findings from a meta-analysis.⁷ Previous neuroimaging studies were very inconsistent in whether to exclude or include medicated participants. As it is unclear how antipsychotic medication actually affects symptomatology, behaviour and neural activation in individuals at clinical high risk of psychosis, future research should be dedicated to further investigate this aspect.

In comparison to matched healthy controls and individuals with schizophrenia, individuals clinically at risk for psychosis showed frontotemporolimbic hyperactivation during empathy despite unimpaired behavioural performance. Our results are consistent with findings from previous fMRI studies addressing social cognitive aspects in this group, which also reported neural hyperactivation. Possible mechanisms driving this greater activation besides compensatory overactivation might be hypersensitivity to emotional stimuli, elevated negative affect as well as dysfunctional emotion regulation. Further investigations will have to clarify the role of the described neural alterations for the development and exacerbation of psychotic symptoms. Particularly, specificity and prognostic value of these brain activation differences in psychosis-prone patients need to be examined, thereby gaining information on early diagnosis and treatment possibilities.

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