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The interaction of working memory and emotion in persons clinically at risk for psychosis: An fMRI pilot study

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ABSTRACT

Subtle emotional and cognitive dysfunctions may already be apparent in individuals at risk for psychosis. However, there is a paucity of research on the neural correlates of the interaction of both domains. It remains unclear whether those correlates are already dysfunctional before a transition to psychosis.

We used functional magnetic resonance imaging to examine the interaction of working memory and emotion in 12 persons clinically at high risk for psychosis (CHR) and 12 healthy subjects individually matched for age, gender and parental education. Participants performed an *n*-back task while negative or neutral emotion was induced by olfactory stimulation.

Although healthy and psychosis-prone subjects did not differ in their working memory performance or the evaluation of the induced emotion, decreased activations were found in CHR subjects in the superior parietal lobe and the precuneus during working memory and in the insula during emotion induction. Looking at the interaction, CHR subjects, showed decreased activation in the right superior temporal gyrus, which correlated negatively with psychopathological scores. Decreased activation was also found in the thalamus. However, an increase of activation emerged in several cerebellar regions.

Dysfunctions in areas associated with controlling whether incoming information is linked to emotional content and in the integration of multimodal information might lead to compensatory activations of cerebellar regions known to be involved in olfactory and working memory processes. Our study underlines that cerebral dysfunctions related to cognitive and emotional processes, as well as their interaction, can emerge in persons with CHR, even in absence of behavioral differences.

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1. Introduction

The search for endophenotypes of psychosis is essential for early detection and prevention. Neuropsychological data suggest a performance continuum between healthy subjects, subjects clinically at high risk for psychosis (CHR), and schizophrenia patients (Pukrop et al., 2006). Accordingly, performance decrements in working memory (WM), which have been consistently found in schizophrenia patients, have already been detected in psychosis-prone individuals (Brewer et al., 2006). Functional imaging data on putatively prodromal stages are rare and mainly focus on individuals *genetically* at risk. Correspondingly, in a review on the neurofunctional correlates of vulnerability to psychosis, Fusar-Poli et al. (2007) could only include one functional magnetic resonance imaging (fMRI) study on subjects' *At Risk Mental State* (ARMS). However, only about 10% of the individuals with first-episode psychosis have a positive family history (Brewer et al., 2006). Accordingly, one of the most influential ultra-high risk approaches (Pantelis et al., 2003; Phillips et al., 2000) relies on attenuated and/or brief limited intermittent psychotic symptoms and/or a combination of a significant recent deterioration in global functioning and genetic risk factors. Only during the last few years has the number of imaging studies on persons with clinical high-risk (CHR) or ARMS increased. When performing an *n*-back task, individuals with ARMS revealed activation patterns that could be situated on a continuum between patients with schizophreniform psychosis and controls. Decreased activation was mainly found in the precuneus, inferior and superior parietal and bilateral prefrontal regions (Broome et al., 2009) — key areas of the WM network also found to be dysfunctional in schizophrenia patients (Callicott et al., 2003; Pauly et al., 2008; Schneider et al., 2007a). Crossley et al. (2009), on the other hand, described dysfunctional activation and connectivity of the superior temporal gyrus (STG).

In addition to cognitive dysfunctions, putatively prodromal stages are characterized by subtle emotional changes. Anxiety and depressive symptoms are common (Simon et al., 2006) and emotion-related neurofunctional impairments have been found (Seiferth et al., 2008). Using the same intensive olfactory stimulation applied here in a sample of adult schizophrenia patients, we found increased activation in the middle frontal gyrus and reduced activations in the middle temporal gyrus and the insula (Schneider et al., 2007b), with the latter being known to be especially involved in the processing of disgusting stimuli (e.g. Stark et al., 2007).

Moreover, an increasing number of studies investigate the influence of emotions on cognition and vice versa. We aimed to identify potential accordant dysfunctions in psychosis-prone subjects, which could be of high clinical importance since affective and cognitive symptoms might potentiate or rather obscure each other. Furthermore, due to common cognitive as well as emotional deficits in schizophrenia, especially the interaction of both domains might be a sensitive marker of the disorder. Associated dysfunctions in early-onset schizophrenia patients revealed reduced brain activation in a thalamo-cortical network including the higher polymodal association cortex (Pauly et al., 2008). However, for CHR individuals, corresponding data are missing and it remains unclear whether such brain activation dysfunctions are already present before a transition to psychosis. However, the detection of characteristic dysfunction patterns in persons at risk for psychosis could become an important tool for the early detection, and therefore hopefully also for the early prevention, of psychosis.

According to previous results we hypothesized brain dysfunctions in CHR persons in mainly prefrontal and/or parietal regions including the precuneus during WM (Broome et al., 2009; Schneider et al., 2007a) as well as activation changes in the insula and the middle temporal gyrus for emotion induction (Schneider et al., 2007b). Finally, for the interaction of WM and emotion we hypothesized dysfunctions in the polymodal association cortex or thalamus (Pauly et al., 2008).

2. Materials and methods

The local ethics committee approved the study protocol in compliance with The Code of Ethics of the World Association (Declaration of Helsinki).

2.1. Subjects

Twelve CHR persons (2 women) and 12 healthy subjects took part in the study. Due to the rather small sample size we matched the subjects of both groups one to one for gender, age (±2 years) and parental education (±3 years) (Table 1). CHR subjects were recruited at the *Early Detection and Intervention Center* of the University Hospital of Cologne and the Department of Psychiatry and Psychotherapy of the RWTH Aachen University. For inclusion in the CHR group, subjects had to fulfill the criteria of a putatively *late initial prodromal state*, defined by either *brief limited intermittent psychotic symptoms* (BLIPS) or *attenuated psychotic symptoms* (Maurer et al., 2006; Phillips et al., 2002; Ruhrmann et al., 2003). Five CHR persons received no medication, five received atypical antipsychotics, and the remaining two received SSRI.

All participants were right-handed (Edinburgh Inventory; Oldfield, 1971). Subjects with mental retardation or medical conditions that could affect the cerebral metabolism were excluded, as well as persons not fulfilling the MRI-related inclusion criteria (no metal implants, etc). The MWT-B (Lehrl, 1989), a multiple choice vocabulary test, was used for crystalline verbal intelligence estimation. Healthy subjects with first-degree relatives with a history of mental illness were excluded. Urine drug screenings confirmed drug abstinence. None of the participants had to be excluded due to insufficient olfactory functioning (Sniffin' Sticks Test; Hummel et al., 2001).

2.2. Data acquisition and analysis

Task and stimuli were described in detail in a previous study (Pauly et al., 2008). In short, participants had to perform a letter 0-back/2-back paradigm presented as a block design of two runs. In one run, negative emotion was induced via the odor of dissolved fermented yeast (Habel et al., 2007; Koch et al., 2007; Pauly et al., 2008; Schneider et al., 2001). Filtered ambient air served as neutral stimulus in the other run. The order was permuted across subjects. After each run,

Table 1
Group comparisons for socio-demographic, psychopathological and neuropsychological data for persons at clinical high risk (CHR) for psychosis and healthy subjects matched for age, gender and parental education (Two-sample *t*-test: mean (±SD), *t*-scores, *df* and *p*-values).

Demographic variable/Test	CHR group mean (±SD)	Healthy subjects mean (±SD)	*t*	*df*	*p*
Age (in years)	24.22 (±4.61)	24.46 (±4.67)	0.13	22.00	0.899
Education (in years)	13.67 (±3.03)	13.83 (±2.48)	0.15	22.00	0.884
Parental education (in years)	13.33 (±1.05)	14.08 (±3.84)	0.49	22.00	0.628
Positive PANSS score [a]	12.50 (±3.80)	7.08 (±0.29)	−4.92	11.18	<0.001**
Negative PANSS score [a]	14.17 (±4.75)	7.58 (±2.02)	−4.42	14.86	0.001**
General PANSS score [a]	26.33 (±8.46)	16.33 (±1.07)	−4.06	11.35	0.002**
HDRS score [b]	9.50 (±5.89)	67 (±0.88)	−4.70	9.34	0.001**
GAF score [c]	57.50 (±12.88)	87.50 (±4.52)	7.61	13.67	<0.001**
MWT-B [d] (IQ)	108.25 (±11.01).	112.33 (±18.22)	0.66	18.09	0.515
Sniffin' Sticks [e]	9.42 (±1.51)	10.33 (±1.44)	1.53	22.00	0.141
LN span [f]	17.92 (±2.31)	18.00 (±2.95)	0.08	22.00	0.939
CPT-IP verbal [g] (% hits)	65.80 (±25.68)	66.53 (±18.85)	0.08	22.00	0.937
CPT-IP spatial [g] (% hits)	73.06 (±26.57)	75.83 (±18.18)	0.30	22.00	0.768
Verbal fluency	39.00 (±10.30)	40.33 (±13.80)	0.47	22.00	0.643
TMT-A (in s) [h]	25.65 (±6.99)	22.33 (±8.09)	−1.07	22.00	0.294
TMT-B (in s) [h]	55.01 (±14.92)	63.92 (±25.20)	1.05	22.00	0.303
PERT (% hits) [i]	83.33 (±5.97)	81.46 (±8.42)	−0.63	22.00	0.536

* $p<0.05$.
** $p<0.003$ (Bonferroni corrected).
[a] PANSS = Positive and Negative Symptoms Scale (Kay et al., 1987).
[b] HDRS = Hamilton Rating Scale for Depression (Hamilton, 1967).
[c] GAF = Global Scale of Functioning (APA, 1994).
[d] MWT-B = Mehrfachwahl-Wortschatz-Intelligenztest-Version B (Lehrl, 1989).
[e] Sniffin' Sticks (Hummel et al., 2001).
[f] LN span = working memory-letter–number span (Gold et al., 1997).
[g] CPT-IP = computerized identical pairs version of the Continuous Performance Test (Numbers (4 digits) and Shapes: Fast (Cornblatt et al., 1998)).
[h] TMT = Trail Making Test (Reitan, 1958).
[i] PERT = Penn Emotion Recognition Test (Kohler et al., 2004).

the experienced intensity of stimulation was assessed, as well as an Emotional Self-Rating (Schneider et al., 1994) and ratings of the valence and arousal (via Self Assessment Manikins; Lang, 1980). Furthermore, an elaborated neuropsychological test battery was conducted (Table 1).

FMRI images were collected on a 1.5 T Siemens Sonata MR scanner at the Research Center Jülich. Functional images were acquired via Echo-Planar Imaging (T2*, TR = 3.2 s, voxel size: $3.125\times3.125\times3\ mm^3$, 64×64 matrix, FoV: $200\times200\ mm^2$, 32 slices, $\alpha=90°$). The TE of the EPI sequence was optimized according to Stöcker et al. (2006). Two runs of 150 functional image volumes were collected.

FMRI data analysis was accomplished via Statistical Parametric Mapping software (SPM2; Wellcome Department of Cognitive Neurology, London). After realignment and stereotaxic normalization ($2\times2\times2\ mm^3$), smoothing was conducted with an 8 mm full-width-at-half-maximum Gaussian blurring kernel. A 0.00781 Hz high-pass filter removed low frequency noise. None of the data sets had to be discarded due to intolerable movement of one voxel size or more. Realignment parameters were included as covariates of no interest. Single-subject contrast images entered second level analysis. A random effects model was implemented for group analyses. Three two-sample *t*-tests investigated group differences for the three contrasts of WM (2-back vs. 0-back), emotion (negative vs. neutral stimulation) and their interaction ([2-back negative vs. 0-back negative] vs. [2-back neutral vs. 0-back neutral]). An error probability of 0.001 uncorrected was adopted (extent threshold: 10 voxels). For the CHR group, scores of the positive and negative symptom subscales of the PANNS were correlated with the local maxima of the brain clusters of all three contrasts in which activation differed significantly between the groups. Furthermore, in spite of the rather small sample size, a more conservative statistical threshold was calculated by Monte Carlo simulations of whole-brain activation. Assuming an alpha-error voxel activation of $p<0.001$, after 10,000 simulations a cluster size of 55 contiguous resampled voxels was indicated to correct for multiple comparisons at $p<0.05$ (Slotnick et al., 2003).

For all metric analyses of the behavioral data, a correction of the degrees of freedom was undertaken if Levene's test for equality of variances revealed significance. Behavioral performance during the *n*-back task was analyzed on the basis of sensitivity (true positives/[true positives + false negatives]) and specificity (true negatives/[true negatives + false positives]) of the responses (Pauly et al., 2008). The log files of four subjects were not recorded due to technical problems. Two three-way repeated measures ANOVAs were performed with the within-subjects factors task (0-back, 2-back) and emotion (neutral, negative) to compare the groups.

3. Results

3.1. Behavioral data

Groups had an identical educational level and also did not differ significantly concerning neuropsychological measures or their olfactory discrimination abilities (Table 1). There was no significant difference in the ratio of smokers ($\chi^2=0.75$, $df=1$, $p=0.667$). The negative odor was judged as significantly more unpleasant, disgusting and intensive than the neutral olfactory stimulation. Additionally, increased level of anger and surprise were found, but these effects did not survive the Bonferroni

correction. No significant differences between the odorants were found for the ratings of happiness, sadness, fear or arousal (Supplementary Table A1). There were no differences in emotion/odor ratings between CHR and healthy participants (Supplementary Table A2).

The repeated measurements ANOVAs for performance sensitivity and specificity only revealed a sensitivity main effect for the task — with a lower performance sensitivity during the 2-back as compared to the 0-back task ($F = 12.44$, $df = 1, 18$; $p = 0.002$).

3.2. fMRI data

3.2.1. Working memory

During WM, CHR subjects showed decreased activation as compared to healthy subjects in the left superior parietal lobe extending to the inferior parietal lobe, the left precuneus (Fig. 1) and the right postcentral gyrus. Increased activation was found in the anterior insula and the precentral gyrus/inferior frontal operculum of the right hemisphere (Table 2).

3.2.2. Negative emotion

While a reduced activation was found in the CHR group as compared to healthy subjects in the right insula, the left medial STG and the right middle occipital lobe during olfactory induced negative (vs. neutral) emotion. Increased activation emerged in the midcingulate gyrus and the middle temporal gyrus — both in the right hemisphere (Fig. 2; Table 3).

Table 2
Working memory contrast (SPM2, two-sample *t*-test, $p < 0.001$ uncorr., extent threshold: 10 voxels): a) decreased and b) increased activation in persons at clinical high risk (CHR) for psychosis (MNI coordinates).

Region	Side	*x*	*y*	*z*	k_E	*t*
a) Healthy subjects > CHR						
Superior parietal lobe*	L	−26	−44	54	63	4.90
Precuneus	L	−8	−48	60	28	4.63
Postcentral lobe	R	42	−26	40	16	4.13
b) CHR > healthy subjects						
Precentral gyrus/inferior frontal operculum*	R	48	4	30	62	4.38
Anterior insula	R	40	14	−4	24	4.31

k_E = cluster size.
*Monte Carlo corrected.

3.2.3. Interaction of working memory and negative emotion

During the interaction of verbal WM and negative emotion, increased activations in the CHR group encompassed several clusters of the cerebellum in both hemispheres, whereas healthy subjects revealed an activation decrease. Furthermore, increases of activation were found within the right thalamus and the right inferior temporal lobe. Decreased activations as compared to healthy subjects included the right superior and inferior temporal lobes, the

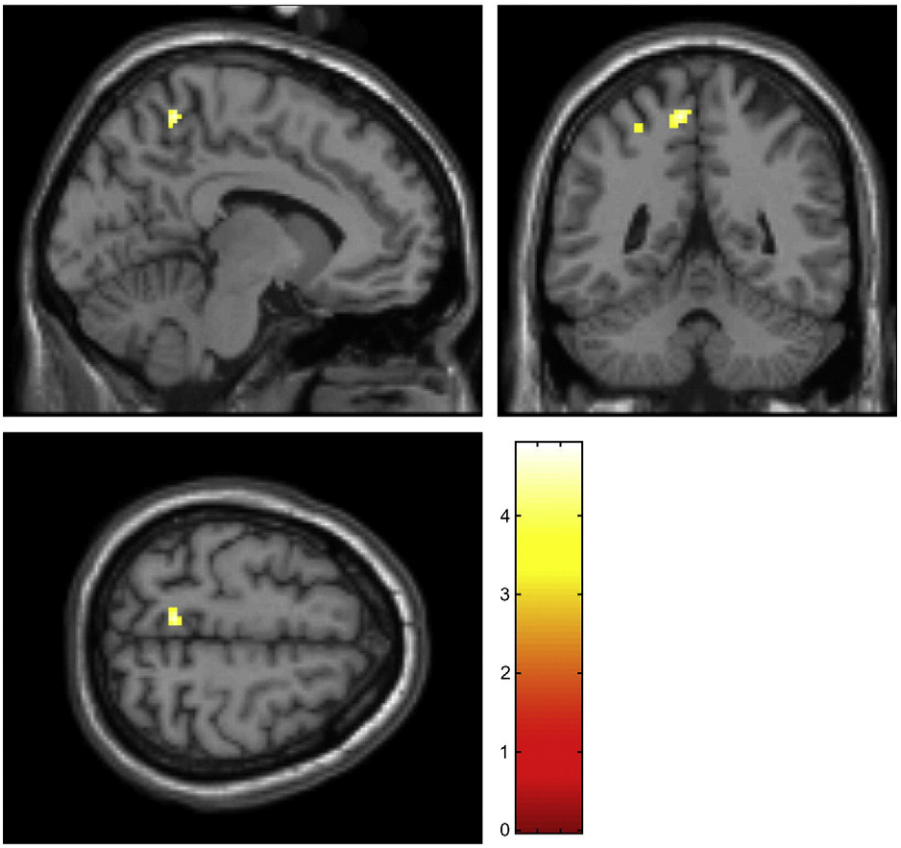

Fig. 1. Decreased activation in the precuneus in subjects clinically at high risk for psychosis during verbal working memory performance.

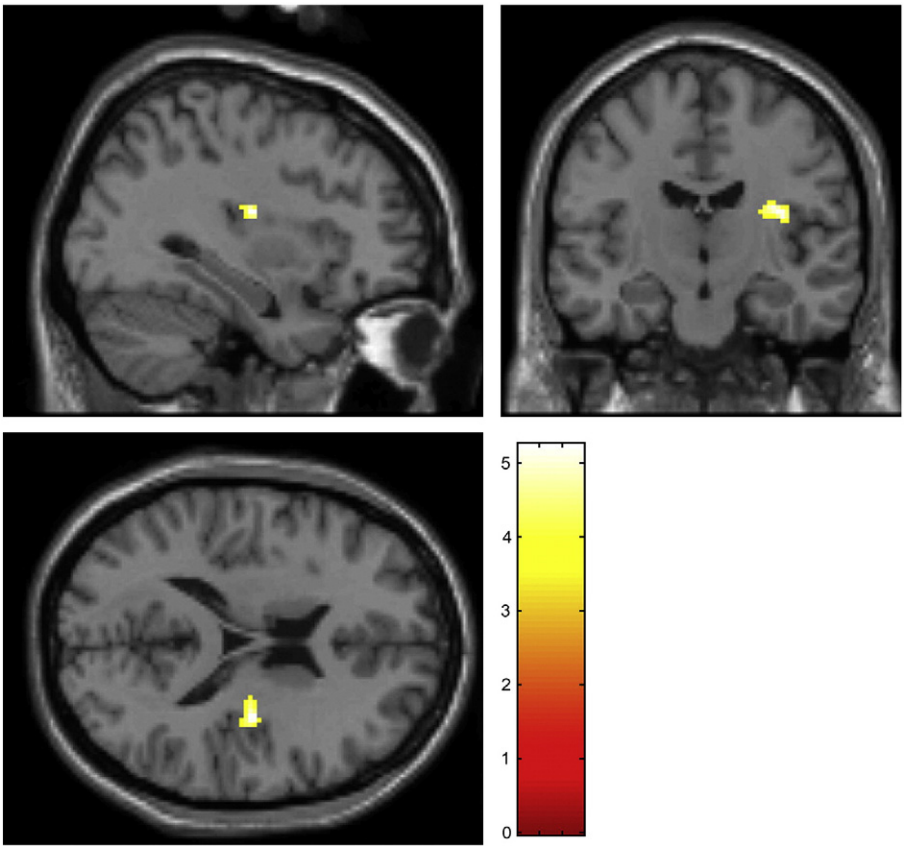

Fig. 2. Decreased activation in subjects clinically at high risk for psychosis as compared to healthy control subjects in the right insula for the contrast of negative vs. neutral olfactory stimulation (see also Table 3).

left rolandic operculum and right supramarginal gyrus, the right insula, right caudate nucleus, the left precentral lobe and the right postcentral gyrus (Fig. 3; Table 4).

3.2.4. Correlations between brain activation and psychopathology

Brain activation found for the two main effects for task and emotion was not correlated with PANSS scores of the CHR group. Negative correlations, however, were found for the interaction contrast between the positive symptom scores and brain activation in the left rolandic operculum ($r = -0.65$; $p = 0.022$) and between negative symptom scores and activation in the right STG ($r = -0.61$; $p = 0.037$) and the left rolandic operculum ($r = -0.73$; $p = 0.007$; Fig. 3).

Overall, comparisons of the brain activation of medicated and unmedicated CHR subjects revealed no activation differences in regions reported in the context of the group comparisons.

Table 3
Negative emotion contrast (SPM2, two-sample *t*-test, $p < 0.001$ uncorr., extent threshold: 10 voxels): a) decreased and b) increased activation in persons at clinical high risk (CHR) for psychosis (MNI coordinates).

Region	Side	*x*	*y*	*z*	k_E	*t*
a) Healthy subjects > CHR						
Posterior insula*	R	34	−14	18	61	5.23
Middle occipital lobe	R	28	−74	26	13	4.34
Medial superior temporal lobe	L	−44	−18	0	12	4.30
b) CHR > healthy subjects						
Middle/posterior cingulate gyrus	R	4	−26	42	15	4.53
Middle temporal gyrus	R	58	−4	−22	10	4.50

k_E = cluster size.
*Monte Carlo corrected.

4. Discussion

Given the unimpaired cognitive performance and olfactory discrimination abilities of our CHR sample, brain activation differences are not attributable to behavioral differences. The latter is in line with the study of Brewer et al. (2003) who found no accordant olfactory impairments in a CHR group. However, in following the group for 18 months, reduced olfactory identification abilities were found in those participants who later developed a schizophrenia spectrum disorder. The 2-back condition was probably not difficult enough to disclose potential subtle executive dysfunctions. Also Broome et al. (2009) and Crossley et al. (2009) did not find group differences during their letter 0-, 1- and 2-back tasks. Vulnerability to psychosis might only be unmasked by more demanding conditions (Brewer et al., 2006).

The decreased brain activations during the WM contrast found in persons with CHR are in accordance with the idea of a continuum of dysfunctions between healthy controls,

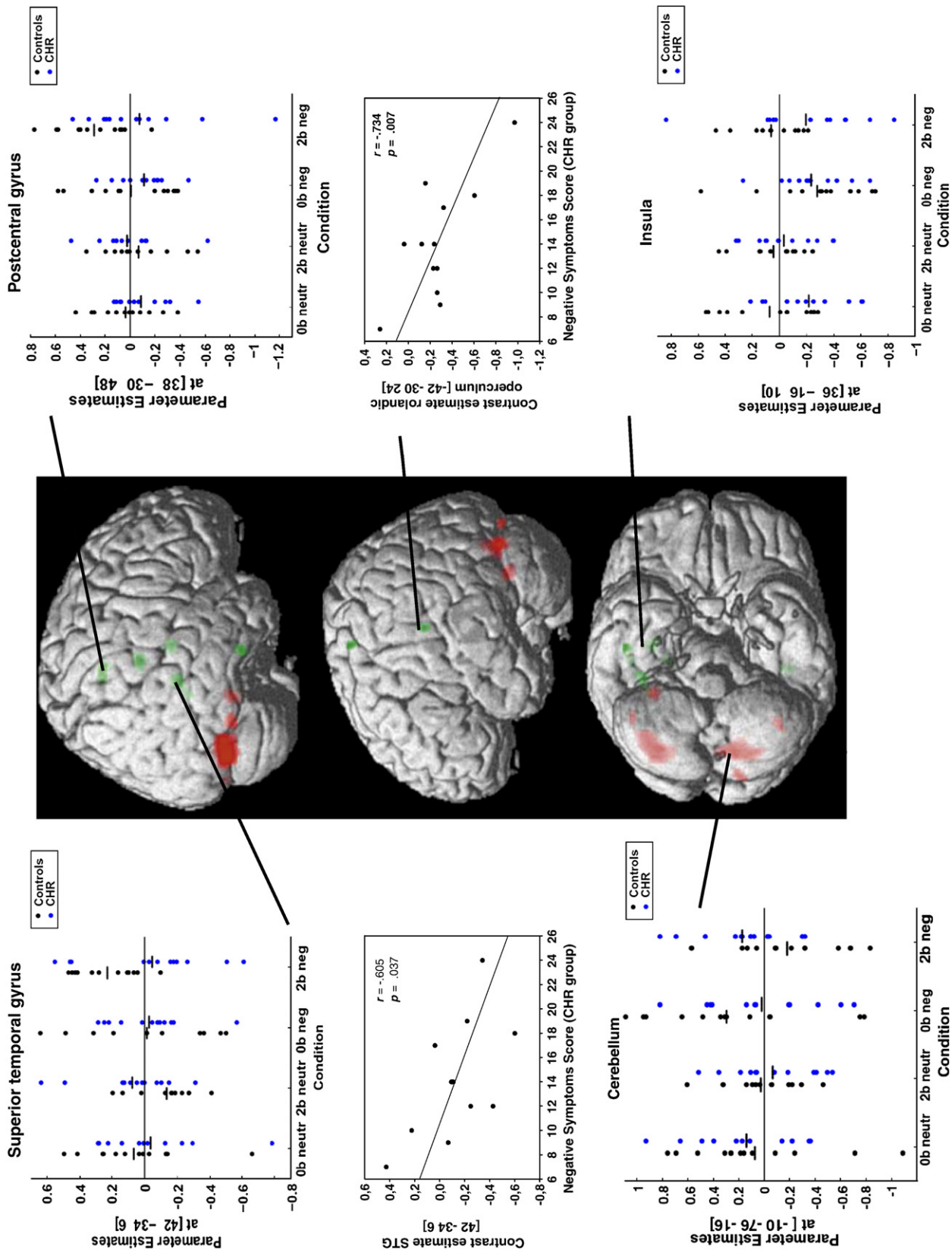
Superior temporal gyrus
Controls
CHR
Parameter Estimates at [42 -34 6]
0b neutr 2b neutr 0b neg 2b neg
Condition
Contrast estimate STG [42 -34 6]
r = -.605
p = .037
Negative Symptoms Score (CHR group)
Cerebellum
Parameter Estimates at [-10 -76 -16]
Postcentral gyrus
Parameter Estimates at [38 -30 48]
Contrast estimate rolandic operculum [-42 -30 24]
r = -.734
p = .007
Insula
Parameter Estimates at [36 -16 10]

Table 4
Interaction of working memory and negative emotion (SPM2, two-sample *t*-test, $p<0.001$ uncorr., extent threshold: 10 voxels): a) decreased and b) increased activation in persons at clinical high risk (CHR) for psychosis (MNI coordinates).

Region	Side	*x*	*y*	*z*	k_E	*t*
a) Healthy subjects > CHR						
Superior temporal gyrus	R	42	−34	6	33	5.01
Posterior insula	R	36	−16	10	24	4.52
Rolandic operculum	L	−42	−30	24	19	4.38
Postcentral gyrus	R	38	−30	48	27	4.26
Supramarginal gyrus	R	48	−24	26	17	4.07
Inferior temporal gyrus	R	52	−18	−30	12	4.04
Precentral lobe	L	−36	−20	66	12	4.04
Caudate nucleus	R	26	−24	26	14	3.98
b) CHR > healthy subjects						
Cerebellum*	L	−10	−76	−16	186	6.26
Cerebellum*	R	38	−72	−22	262	5.73
Cerebellum (Crus 1)	L	−14	−90	−22	13	5.35
Cerebellum	R	34	−42	−24	31	4.80
Posterior inferior temporal lobe	R	48	−58	−24	19	4.60
Cerebellum	L	−38	−62	−26	24	4.06
Thalamus	R	4	−22	14	12	3.79

k_E = cluster size.
*Monte Carlo corrected.

individuals with CHR and patients with schizophrenia. The decreased activations found in the (left) parietal lobe and in the precuneus were also seen in adolescent-onset schizophrenia patients performing an *n*-back task (Pauly et al., 2008). Furthermore, decreased activations in the precuneus and parietal (postcentral) lobe have been linked to *n*-back performance in a first-episode schizophrenia patient sample (Schneider et al., 2007a). There is increasing evidence for the role of the parietal cortex in schizophrenia (Leube et al., 2006). However, patients with manifest schizophrenia also showed cerebral dysfunctions in mainly prefrontal areas in the context of WM and other executive function tasks (Callicott et al., 1999; Pauly et al., 2008; Schlösser et al., 2003). We only found an increase of activation in the frontal operculum in the CHR group. A lack of prefrontal activation decrease might explain the rather good WM performance of the CHR group. Interestingly parietal group differences were also more pronounced than the prefrontal dysfunctions in the study of Broome et al. (2009) who found decreased activation in several parietal regions (including the precuneus), but not in frontal areas during the 1-back task, as well as more affected parietal areas (with larger clusters) than prefrontal areas during the 2-back task. Differences between studies might be attributed to methodological reasons (such as the subtraction of the 0-back high-level baseline). However, further studies on the role of parietal dysfunctions in CHR should allow for the fact that the parietal cerebral dysfunctions seem to be an especially stable result manifesting before illness onset. Prefrontal dysfunctions on the other hand may become more prominent with increasing task difficulty (or decreasing cognitive resources).

Consistent with our hypothesis, the most robust group difference during negative emotion induction was a decreased activation in individuals with CHR in the (right) insula — a region mainly considered as a key structure for the processing of negative, largely disgusting stimuli (Schneider et al., 2007b; Stark et al., 2007). Accordingly, activation changes in this area might be linked to first emotional symptoms in the course of a developing psychosis. However, changed activation in the right insula was found for all three contrasts (WM, negative emotion and their interaction). While we found increased activation in the right anterior insula in the CHR group during WM (see also Schneider et al., 2007a), activation in the posterior insula was decreased for the negative emotion contrast and the interaction. The latter was due to an on average constant deactivation of the posterior insula in the CHR sample (Fig. 3). The rather "unemotional" WM condition might reveal an impaired down-regulation of perhaps distracting, inherent emotions resulting in an increased activation of the anterior insula. Activation changes in the posterior and anterior insula emerged during different executive tasks in subjects with ARMS or psychosis (Broome et al., 2009). Additionally, structural changes of the insula have been assumed to be related to a changed processing of affect-laden information in psychotic patients (O'Daly et al., 2007).

Other activation changes found for the negative emotion contrast included an increased activation in the junction of the middle and posterior cingulate gyrus. Again, similar activation changes have been described in schizophrenia patients during negative olfactory emotion induction or an emotion labeling task (in addition to other hyperactivations; Crespo-Facorro et al., 2001; Hempel et al., 2003; Pauly et al., 2008). Further decreased activation was found in the left medial STG in CHR subjects. Olfactory stimulation has repeatedly proven to activate the superior temporal gyrus and sulcus bilaterally in healthy subjects (Kettenmann et al., 1996; Schneider et al., 2001). An imbalance of activation in this area in CHR subjects might result in an impaired higher order odor processing, which is related to an impaired corresponding emotion processing. Accordingly, decreased brain activation in the superior and middle temporal areas was also found during odor processing in schizophrenia patients (Crespo-Facorro et al., 2001; Schneider et al., 2007b), however, not in their healthy relatives (Schneider et al., 2007b). The latter underlines the necessity of the investigation of samples clinically at high risk.

Finally, the interaction of negative emotion and WM revealed a patchy pattern of decreased and increased bilateral activations. In line with the idea of a continuum between healthy subjects and patients with schizophrenia, we found group differences in a small cluster of the thalamus. In our previous study, schizophrenia patients revealed an imbalance of activation in the thalamus depending on the WM demand and emotional stimulation (Pauly et al., 2008). Due to its function in filtering converging incoming information from various sensory systems, the thalamus is involved in emotional as well as cognitive processes. Accordingly, dysfunctions may end up in some of the typical symptoms of psychosis. However, further research is needed before we will be able to predict when psychosis-prone subjects reveal either a decrease or an increase of activation.

Fig. 3. Interaction of verbal working memory and olfactory induced negative emotion: increased (red) and decreased activation (green) in subjects clinically at high risk for psychosis as compared to healthy control subjects (see also Table 4).

As reported above, the STG, as well as the insula (both found less activated in the CHR group during the interaction contrast), have been found to be essentially involved in the processing of (negative) affect-laden stimuli (see also Bach et al., 2008). Of course, the STG is involved in many more functions. Crossley et al. (2009) described brain activation changes in the STG during *n*-back performance in patients with schizophrenia and (to a smaller degree) in patients with ARMS. Other functions of the STG include the integration of cross modal (e.g. visual and auditory) information (Robins et al., 2009), which is in good accordance with the fact that we combined a visual cognitive task with olfactory stimulation. One might assume that the right STG is more generally responsible for controlling whether incoming verbal information is linked to emotional content and for the integration of (emotional) input from different modalities. Additionally, white matter decrease was found in the right STG in subjects with ultra-high risk and may be responsible for a disturbed cerebral connectivity (Witthaus et al., 2008). In accordance with increasing dysfunctions in the course of illness, we found a relationship between activation and psychopathology (also in the rolandic operculum) reflecting decreasing activation with an increase of (foremost negative) symptoms.

Interestingly, against our expectations the most robust finding for the interaction contrast was a bilaterally increased activation in the cerebellum. There is an increasing body of literature suggesting that the cerebellum has far more functions than coordination and motor control. Cerebellar activation has been found in the context of verbal WM processes (Chen and Desmond, 2005; Kirschen et al., 2005), decision making under uncertainty (Blackwood et al., 2004) and other higher cognitive functions (Garrard et al., 2008). In their review of the role of the cerebellum in schizophrenia, Picard et al. (2008) additionally reported hypo- and hyperactivations in the cerebellum during emotional tasks in the majority of the studies. Furthermore, cerebellar activation has been linked to odor discrimination (Savic-Berglund, 2004). Correspondingly, in patients with cerebellar disorders or damage, olfactory dysfunctions have been reported (Applegate and Louis, 2005), as well as selective deficits of the phonological encoding during verbal WM (Ravizza et al., 2006). Increased cerebellar activation in CHR individuals could be seen as a compensatory mechanism reflecting more effort necessary to complete the cognitive task during the distracting emotion induction. Interestingly, in this context Stone et al. (2009) also reported increased cerebellar gray matter volume in subjects with ARMS. Accordingly, the cerebellum seems very well-suited as an area providing "cognitive resources" in CHR persons. Looking at the good behavioral performance of the CHR sample, such coping strategies seem to be effective — at least before illness onset, which might be related to a breakdown of such compensatory networks.

4.1. Limitations and conclusions

Like many other clinical imaging studies, we acknowledge the problem of small sample size. Subtle group differences might have been obscured by the rather small statistical power of our preliminary results. Furthermore, the investigation of CHR samples underlines the necessity of longitudinal studies to identify biomarkers that can predict a later transition to psychosis. We were not able to follow up all of our participants and potential sub-groups would have been too small to allow for further group analyses. Therefore, we could not clarify if deficits would have increased after a possible transition to psychosis.

In summary, we found brain activation alterations in individuals with CHR during verbal WM, negative emotion and their interaction. Most dysfunctions were in line with the idea of a continuum between healthy and psychotic states indicating that some brain areas might already be affected before illness onset, while others show normal activation patterns before a transition to psychosis. However, we also found brain activation differences between CHR and healthy subjects, especially during the interaction of emotion and cognition, that qualitatively did not resemble cerebral dysfunctions in schizophrenia. One reason might be that CHR individuals with or without transition may further differ in their activation of brain networks. On the other hand, brain activation in CHR samples may partly be related to compensatory strategies which only might work successfully before illness onset.

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Contributors

KP, UH and SR interpreted the results; KP wrote the first draft of the manuscript; UH and FS designed the study and wrote the protocol; KP, NYS and BD recruited the participants and collected the neuropsychological/psychopathological data; KP, NYS, TK and VB completed the MRT measurements; TK and VB contributed in programming the paradigm; KP and TK undertook the statistical analysis. SR, JK, FS and TTK made possible the recruitment of the CHR sample. Author NJS provided the technical imaging equipment and methodological advice for the fMRI acquisition. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2009.12.008.

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