CINGULATE VOLUME ABNORMALITIES IN EMERGING PSYCHOSIS

(RUNNING TITLE: CINGULATE ABNORMALITIES IN PSYCHOSIS)

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ABSTRACT (250 WORDS)

Background

Neuroanatomical abnormalities, including cingulate cortex volume abnormalities, are a common feature in psychosis. However, the extent to which these are related to a vulnerability to psychosis, as opposed to the disorder per se, is less certain.

Aim und Hypotheses

The aim of the present study is to compare cingulate gray matter volumes in different stages of psychosis. We reviewed previous studies of subjects in a prodromal stage of psychosis and tested of cingulate volume changes during the transition to psychosis.

Methods

A cross-sectional MRI study of manually traced cingulate gray-matter volumes in 37 individuals with an At Risk Mental State (ARMS) for psychosis, 23 individuals with First-Episode Psychosis (FEP), and 22 Healthy Controls (HC) was performed using a 1.5T MRI-Scanner. 16 of 37 ARMS individuals (43 %) developed psychosis during follow up (ARMS-T), whereas 21 did not (ARMS-NT). The mean duration of follow up in ARMS was 25.1 months. 8 cingulate subregions were analysed in a region-of-interest analysis.

Results

Compared to HC, subjects with an ARMS had significantly reduced left caudal anterior cingulate cortex volume ($p<0.027$). This finding was also evident at a trend level (p: 0.069) in FEP patients. Within the ARMS, ARMS-T group showed significantly reduced whole right cingulate cortex (p: 0.036), right subgenual cingulate cortex (p: 0.036) and right posterior cingulate cortex (p: 0.012) compared to ARMS-NT.

Discussion

These results suggest that the at-risk mental state is associated with cingulate volume reductions in particular in the left caudal anterior cingulate cortex (CACC). These abnormalities do not only seem to occur with transition to psychosis, but may be a correlate of an increased vulnerability to psychosis.

1. INTRODUCTION

Talairach (1993) describes the cingulate gyrus as follows: Bounded superiorly and in the front of the corpus callosum by the callosomarginal sulcus, the cingulate gyrus extends under the rostrum of the corpus callosum into the subcallosal gyrus, and behind the splenium into the parahippocampal gyrus through a narrow passage, the isthmus (Figure 1). It forms the upper part of the great limbic lobe of Broca [1].

Figure 1: Cingulate Cortex.bmp with legend [53]

The cingulate gyrus is composed of different cytoarchitectural areas, which connect the limbic system with the neocortex. The several subdivisions have many functions such as emotional, cognitive, attentional, nociceptive and motoric processing. The anterior cingulate cortex (ACC) is an integral component of those subdivisions, which controls affective and cognitive functions. The central task of this area is the modulation of internal emotional responses. The ACC has anatomical connections to the dorsolateral prefrontal cortex (DLPFC), motoric areas and the thalamus, depending on the specific subdivision. Those cytoarchitectural subdivisions are the caudal anterior cingulate cortex (CACC, cognitive subdivision) with strong reciprocal connections to prefrontal, parietal, premotor and supplementary areas on one side, and the rostral anterior cingulate cortex (RACC, affective subdivision) with connections to nucleus accumbens, amygdala, insular cortex, hippocampus and orbitofrontal cortex on the other hand [2, 3].

The ACC is therefore an integral component for social recognition, mentalizing and visualizing. This area is mainly activated by emotional stimuli [3, 4]. The “cognitive subdivision” is represented by the CACC, which is involved in the initiation of action, selective perception [5], selection and monitoring of conflicting responses and error detection [6]. The latter has been proven by studies using the stroop task test [7]. The RACC (affective subdivision) seems to be increasingly involved in the modulation of emotional reactions, which evaluates the salience of motivational and emotional information [3, 8]. The subgenual cingulate cortex (SCC), also called Brodmann’s area 25, has strong connections to structures that control emotional behaviour, mood and autonomic reactions to stressors [9]. The posterior cingulate cortex (PCC) is activated by emotional and non-emotional stimuli and plays an important role in memory access, visual and spatial orientation [2, 10, 11].

Findings from post mortem neuropathology [12, 13] and structural magnetic resonance imaging of subjects at genetic [14] or clinical high risk of psychosis [15-19] show that ACC is involved in the pathogenesis and the etiology of schizophrenia (for review[20-25]: PET studies [26] have brought increased glutamatergic metabolites [13] and deficits in membrane phospholipids [27] in this region into focus. PET- and SPECT studies with non-treated schizophrenia patients also showed a negative correlation between symptoms such as suspiciousness, hallucinations and delusions with regional blood flow (RBF) in the ACC [28]. Furthermore, Choi *et al.* (2005) showed, that a smaller volume of the caudal anterior cingulate gyrus significantly correlated with more severe positive symptoms of schizophrenia [29]. A number of other studies reported functional deficits of the ACC in FEP individuals such as reduced activation during verbal fluency [30, 31], executive control task [32], manipulation phase of working memory [33]. Qualitatively similar abnormal deficits were found in ARMS subjects [15, 16, 26, 34]. Also a significant activation of the ACC during acoustic verbal hallucination has been shown [35].

Individuals with ARMS have an increased vulnerability for psychosis. Around 35 % of such subjects develop psychosis within 12 months, although the proportion has varied between studies [36-38]. It is well accepted that a dysfunction of cingulate brain region may be a core mechanism in early stage psychosis involving a failure to monitor internally generated actions [33, 39]. The anterior cingulate cortex (ACC) volume was investigated in three studies Melbourne group [40-42]. Yücel [40] found no differences in any of the ACC surface morphological measures between HR-T and HR-NT. Another study showed a trend towards left hemispheric reduced paracingulate sulcus folding and frequent cingulate sulcus interruptions in HR subjects, with no differences between HR-T and HR-NT subjects, in line with the above findings [41].

Fornito [42] used a surface-based anterior cingulate parcellation technique and reported that regional thinning of the ACC is a significant predictor of the time to psychosis onset. They found a bilateral thinning of the rostral paralimbic ACC in HR-T compared to HC. In a voxel-based morphometry study, Borgwardt *et al.* (2007) confirmed the hypothesis of reduced gray matter volumes in a cluster in a midline region that includes the posterior cingulate cortex and the precuneus in ARMS individuals compared to healthy controls [43].

The aim of this study is to use MRI data of individuals with an ARMS to clarify structural abnormalities of the Cingulum, which is presumed to be involved in early stages of this disease. Baseline gray matter volumes of the Cingulum in different states of schizophrenia are compared, particularly ARMS individuals with transition to psychosis (HR-T), ARMS individuals without transition to psychosis (HR-NT), First-episode Psychosis (FEP) and

healthy controls (HC). In particular we tested the hypothesis that cingulate abnormalities are associated with an ARMS. Secondly, we tested whether these volumetric abnormalities were predictive for a future transition to psychosis. By segmenting the cingulate cortex into subdivisions, particularly subgenual cingulate cortex (SCC), rostral and caudal anterior cingulate cortex (RACC and CACC) and posterior cingulate cortex (PCC) we expected to provide evidence for a stage-related distribution of the volume-changes to substantiate a theory of change progression from rostral to caudal.

Table **1**: Cingulate MRI findings in the At Risk Mental State (ARMS).[15, 29, 42-45]

			Baseline MRI Findings	
	N	MRI-Method	Schizophrenic vs. HC	ARMS-T vs. ARMS-NT
Choi *et al.* 2004	22 Schizophrenic Patients vs. 22 Healthy Controls	ROI analysis with baseline magnetic resonance imaging for rostral anterior cingulate gyrus, the caudal anterior cingulate gyrus, the orbitofrontal cortex, the caudate and the thalamus	Volumetric reduction of the right caudal anterior cingulate gyrus was observed in patients with schizo-phrenia as compared with the normal controls	[no control group]
Fujiwara *et al.* 2007	20 Schizophrenic Patients vs. 20 Healthy Controls	ROI analysis with baseline magnetic resonance imaging for anterior cingulate cortex (ACC) volumes	reduced ACC volume, decreased fractional anisotropy in the anterior cingulum bilaterally and a poorly developed paracingulate/cingulate sulcus in the left hemisphere	[no control group]
	N	MRI-Method	ARMS vs. HC	ARMS-T vs. ARMS-NT
Pantelis *et al.* 2003	75 ARMS (23 ARMS-T vs. 52 ARMS-NT)	Voxel-based morphometry (VBM) MRI-analysis	[no control group]	Converters had smaller gray matter volume in the right medial temporal, lateral temporal, inferior frontal cortex, and in the cingulate bilaterally
Borgwardt *et al.* 2007	35 ARMS, 25 FEP, and 22 HC	Voxel-based morphometric (VBM) study using 1.5-T-MRI	Converters had smaller smaller left insula, superior temporal gyrus, cingulate gyrus and precuneus	less gray matter volume in the right insula, inferior frontal and superior temporal gyrus
Fornito *et al.*2008	35 ARMS-T vs. 35 ARMS-NT; 33 HC	ROI analysis with baseline magnetic resonance imaging for ACC morphometry	ARMS-T bilateral thinning of a rostral paralimbic ACC region, ARMS-NT individuals had a relative thickening of dorsal and rostral limbic areas	RACC, rostral paralimbic, limbic and paralimbic subcallosal regions show significant thinning in ARMS-T vs. ARMS-NT
		MRI-Method	FEP vs. HC	ARMS-T vs. ARMS-NT
Koo *et al.*2008	39 FEP vs. 40 HC		FEP showed significantly smaller left subgenual, left and right affective, right cognitive, and right posterior cingulate gyrus gray matter subregions. Less asymmetric paracingulate pattern.	[no control group]

ARMS: At-Risk-Mental-State, ARMS-T: At-Risk-Mental-State with Transition to psychosis; ARMS-NT: At-Risk-Mental-State without Transition to psychosis
FEP: First Episode Psychosis; HC: healthy controls; ROI: Region of interest

2. METHODS

2.1 Participants

The MRI data were collected in the context of the Basel Early-detection-of-Psychosis (***F***rüh***e***rkennung von ***Psy***chosen: ***FePsy***) and as part of naturalistic, prospective research program (Prediction and early detection of schizophrenia - a prospective multilevel approach), supported by the Swiss National Science Foundation (No. 3200-057216-99; 3200-057216/3). The Basel ethics committee approved all aspects of the study and written informed consent was obtained from each participant.

Subjects with an ARMS and patients experiencing their FE of psychosis were recruited from a service area covering 200.000 inhabitants in and around Basel, Switzerland, through a specialized clinic at the Psychiatric Outpatient Department, University Hospital in Basel. The screening has been described in detail elsewhere [46, 47]. Briefly, the Basel Screening Instrument for Psychosis (BSIP) was used, a 46-item checklist based on risk factors or early signs of psychosis, i.e. "prodromal" symptoms, social decline, previous psychiatric disorders, drug abuse or genetic risk for psychosis [46] and also assesses severity of prepsychotic symptoms. It allows the identification of ARMS individuals similar to the PACE criteria [48]. The BSIP was constructed as a screening to identify those at risk and is followed by a more extensive early detection interview in a next step [43]. The family history of psychosis was obtained using a semi-structured interview from the subject and, whenever possible, a first-degree relative. The frequency of current and previous alcohol use was estimated using a semi-structured interview. To assess the premorbid IQ we used the MWT, an established measure in German-speaking subjects [49]. All assessments were conducted by experienced psychiatrists who underwent regular training.

2.1.1 Inclusion criteria

2.1.1.1 At Risk Mental State (ARMS) Group

The ARMS group n=37 in this study fulfilled PACE criteria, similar to previous MRI studies on this at Risk sample [19, 43, 50-55]. Inclusion thus required one or more of the following: a) "attenuated" psychotic symptoms, b) brief limited intermittent psychotic symptoms (BLIPS), or c) a first degree relative with a psychotic disorder plus at least two indicators of a clinical change, such as a marked decline in social or occupational functioning.

Inclusion because of "attenuated" psychotic symptoms required scores of 2 or 3 on the hallucination item, 3 or 4 on the unusual thought content or suspiciousness items of the BPRS for at least several times a week and persisting for more than one week. Inclusion because of BLIPS required scores of 4 or above on the hallucination item or 5 or above on the unusual thought content, suspiciousness or conceptual disorganization items of the BPRS, with each symptom lasting less than one week before resolving spontaneously. 16 out of 37 ARMS have so far made the transition to schizophrenia (*HR-T: n=16 / HR-NT: n=19*).

2.1.1.2 First Episode Psychosis (FEP) Group

The FE group (n = 23) was defined as subjects who met the operational criteria for first episode psychosis described by Yung *et al.* (1998) [48].

2.1.1.3 Healthy Volunteers as Control Group

Healthy volunteers (n = 22) were recruited from the same geographical area as the other groups through local advertisements [37, 56, 57]. These individuals had no current psychiatric disorder, no history of psychiatric illness, head trauma, neurological illness, serious medical or surgical illness, substance abuse, and no family history of any psychiatric disorder as assessed by an experienced psychiatrist in a detailed clinical interview. After complete description of the study to the subjects, written informed consent was obtained.

2.1.2 Exclusion criteria

The following exclusion criteria applied to all groups: history of previous psychotic disorder (treated with major tranquilizers for more than 3 weeks); psychotic symptomatology clearly due to 'organic' brain disease or substance abuse according to ICD-10 research criteria; psychotic symptoms clearly associated with an affective psychosis or a borderline personality disorder; age under 18 years; inadequate knowledge of the German language; and IQ less than 70.

After these exclusion criteria had been applied, subjects were assessed using the 'Basel Screening Instrument for Psychosis' (BSIP) [46], the Brief Psychiatric Rating Scale (BPRS) [58, 59], and the Scale for the Assessment of Negative Symptoms (SANS) [60]. The BSIP was used to evaluate 'prodromal' symptoms (defined according to DSM-III-R) occurring in the last 5 years; nonspecific 'prodromal' signs [61] in the last 2 years; previous or current

(pre-)psychotic symptoms, psychosocial functioning over the last 5 years, substance dependency; and psychotic disorders among first and second degree relatives [46] and to apply the operational criteria of an ARMS resp. FE according to Yung et al. ‘98.

2.1.3 Clinical Follow-up

The ARMS subjects were followed up at monthly intervals during the first year, at 3-month intervals during the second and third year and annually thereafter. At each assessment, subjects were examined using the BPRS. The criteria for transition to psychosis were those defined by Yung *et al.* (1998) [48].

2.2 Structural MRI

2.2.1 MRI Image Acquisition

Subjects were scanned using a Siemens (Erlangen, Germany) Magnetom Vision 1.5 T scanner at the University Hospital Basel. Head movement was minimized by foam padding and velcro straps across the forehead and chin. A three-dimensional volumetric spoiled gradient recalled echo sequence generated 176 contiguous, 1 mm thick sagittal slices. Imaging parameters were: time-to-echo, 4 msec; time-to-repetition, 9.7 msec; flip angle, 12; matrix size, 200 x 256; field of view, 25.6 x 25.6 cm matrix; voxel dimensions, 1.28 x 1 x 1 mm.

2.2.2 Cingulate volume measurement

We focused upon anterior (ACC) and posterior cingulate cortex (PCC) both right and left as our Region-of-interest (ROI). ACC underwent a further segmentation in functional subdivisions, particularly rostral anterior (RACC), caudal anterior (CACC) and subgenual cingulate cortex (SCC), both right and left. Cingulate volume was calculated by summing up all the marked voxels, using the software for medical imaging amira™, which displays all three planes simultaneously. To reach an equal tracing of those ROI's, for each and every patient the same approach was used including clearly defined landmarks and lines. Tracing was made individually with a mouse-driven cursor for each sagittal and coronal plane, only one person was involved to avoid differences between individual samples (MR).

Preceding anatomical definition of the ACC and PCC was made by using Talairach Co-Planar Stereotaxic Atlas [1]. Before tracing began, several reference lines needed to be drawn on the most medial sagittal slice of each hemisphere. Two landmarks where used to reach a standard segmentation Figure 2):

- CA-CP-Line: this line passes through the superior edge of the anterior commissure and the inferior edge of the posterior commissure. It follows a path essentially parallel to the hypothalamic sulcus, dividing the thalamic from the sub-thalamic region. This line defines the horizontal plane [1].

- VCA-Line: this line is a vertical transversing the posterior margin of the anterior commissure. This line is the basis for the vertical plane [1].

Figure 2: Reference Lines.bmp with legend [53]

By setting the VCA-line with the grid-function offered by the medical imaging software amira™ at the most superior-posterior edge of the Commissura anterior, we were able to reach a reference-associated segmentation of the cingulate gyrus in an anterior and a posterior part (Figure 3).

Figure 3: Cingulate Subdivisions (legend).bmp

For a standard definition of the subdivision of the ACC, a line, defined by the coronal plane passing through the most anterior tip of the inner surface of the genu of the corpus callosum, was used as the border between the RACC and the CACC on one hand. A different line, which was set by using the coronal plane passing through the most anterior tip of the outer surface of the genu of the corpus callosum, served as border between the RACC and the SCC (Figure 4 and 5). This was described before by Crespo-Facorro *et al.* (1999) [62].

Figure 4: Dividing right Cingulum (legend).bmp

Figure 5: Dividing left Cingulum (legend).bmp

The PCC was bounded by the VCA-line on the one side (as mentioned to be the border between ACC and PCC), and by a line, which was found by the coronal plane touching the most posterior tip of the outer surface of the splenium of the corpus callosum. This line was used to have an equal reference for the dorsal border of the PCC.
Using the most sagittal plane of each hemisphere and considering the reference lines described before, the four RIO's (both left and right) were marked by with a mouse-driven cursor in eight different colours (Figure 4). The paracingulate gyrus was considered to be a part of the anterior cingulate gyrus, as assumed commonly and practiced by several studies before [45, 62]. For an accurate assessment and tracing of the gray matter associated to the overall eight different ROI's, tracing was made in a serial of coronal planes starting on the first plane showing marked RACC tissue (defined in the sagittal plane before) and was continued caudally. With this strategy, the area defined in the sagittal plane was consequently extended in each coronal plane to gain a three-dimensional information of the cingulate gray matter volume. The deepest point of the callosal sulcus and the most medial point of the dorsal bank of the cingulate sulcus were used as the inner and the outer boundaries of the ACC and the PCC in each coronal slice. If there was a paracingulate gyrus, the next superior sulcus associated to its gray matter was used as upper border (Figure 6).

Figure 6: Coronal tracing (without legend).bmp

2.2.3 Intra-Rater Reliability

To assess the intra-rater reliability, a manual segmentation in ten consecutive cases within two weeks was accomplished by the same person (MR). The intra-rater reliability ranged from $\kappa_{left} = 0.93$ to $\kappa_{right} = 0.95$, mean value of $\kappa_{total} = 0.94$. An inter-rater reliability could not be calculated as there was only one tracer (MR). The researcher who traced the cingulate volumes was blind to the group status at any time of the study. Once the gray matter of the cingulate cortex had been traced, volumes (in mm^3) were calculated by computing the number of voxels from each traced image.

2.3 Statistical analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences, version 16 (SPSS© 16.0 for Windows, Rel, 16.0, SPSS© Inc., Chicago, Illinois). Clinical and ROI data were compared using the one-way analysis of variance (ANCOVA) adjusted for age, sex, and gray matter volume, Student's t-tests for psychopathology scores (interval-scaled or continuous variables), chi-square test and Fisher's exact test for categorical variables. The following ROS's were analysed: tCC: total Cingulate Cortex; tCCr : total Cingulate Cortex right; tCCl: total Cingulate Cortex left; tACCr: total Anterior Cingulate Cortex right; tACCl: total Anterior Cingulate Cortex left; CACCr: Caudaler Anterior Cingulate Cortex right; CACCl: Caudal Anterior Cingulate Cortex left; RACCr: Rostral Anterior Cingulate Cortex right; RACCl: Rostral Anterior Cingulate Cortex left; SCCr: Subgenual Cingulate Cortex right; SCCl: Subgenualer Cingulate Cortex left; PCCr: Posterior Cingulate Cortex right; PCCl: Posterior Cingulate Cortex left. All pairwise comparisons used Bonferroni adjustment for multiple testing was applied. To test our hypothesis, two sets of analysis were performed: Analysis 1: comparison of ARMS, FEP and HC; Analysis 2: ARMS-T, ARMS-NT, FEP and HC. Within each analysis, patient groups were compared with the healthy control group.

Results of statistical tests are given as mean ± standard deviation (SD). The level of statistical significance was set to $p < 0.05$ a trend was considered $p < 0.1$.

3. RESULTS

3.1 Characteristics of the samples

ARMS, FEP and HC did not differ significantly with respect to age (χ^2 = 7.7, df = 4, p = 1.00), sex (χ^2 = 1.5, df = 2, p = .468) and handedness (χ^2 = 3.1, df = 2, p = .208). Educational level was significantly higher in HC (χ^2 = 14.0, df = 4, p = 0.007) (Tables 2 and 3). The groups were matched for premorbid IQ: ARMS: 109 (14), FEP: 103 (15), HC: 108. The ARMS and FEP groups had a similar proportion of patients with a family history of psychosis. The FE group was older than the ARMS and HC groups and the ARMS and FE groups had achieved a lower educational level at school than the HC group. The FE group had higher total BPRS scores than the ARMS group (Table 2).

Table **2**: Demographic and clinical characteristics (ARMS, FE, HC).

Characteristics	ARMS (n=37)	FE (n=23)	HC (n=22)	p
Age at Baseline [years] (mean years, SD)	24.7 (5.6)	26.78 (6.5)	23.0 (4.3)	nv[a,c]
Sex (male) [n, %]	22 (59 %)	17 (74 %)	13 (59 %)	nv[d]
Handedness (mixed or left)*	4 (11 %)	5 (22 %)	6 (29 %)	nv[d]
Individuals with a first degree relative with schizophrenia	4 (11 %)	4 (17 %)		ns[e]
Educational level				p < 0.5[d]
< 9 years	11 (30 %)	12 (52 %)	2 (9 %)	
9-11 years	14 (38 %)	8 (34 %)	7 (32 %)	
12-13 years	8 (22 %)	1 (4 %)	10 (46 %)	
> 13 years	4 (11 %)	2 (9 %)	3 (14 %)	
BPRS global score at intake (mean, SD)	39.2 (9.0)	52.7	nv[b]	p <

		(13.6)		0.001[c]
SANS at intake (mean, SD)	8.0 (5.0)	10.0 (5.3)	nv[b]	ns[e]
Patients with antipsychotics at MRI-Scan	4 (11 %)	9 (39 %)	nv[b]	p <0.05[e]
Duration of illness [months] (mean, SD)	44.1 (46.0)	54.9 (74.1)	nv[b]	ns[e]

[a] : not significant [c] : ANOVA [e] : Fisher's exact test

[b] : not applicable [d] : χ^2-test

All the participants were Caucasian. 89% of the ARMS subjects had no antipsychotics or mood stabilizers at MRI scanning, and were receiving nonspecific psychological support or anti-depressive/sedative medication on an outpatient basis (Table 1). A large proportion of FEP patients were scanned within 1-3 days of first contact, therefore most of the FEP patients (15 / 25; 60 %) were also antipsychotic-naive. Six had been taking antipsychotics for less than 1 month and 4 had been taking them for 1-3 months. None of the healthy controls (HC) had previously received antipsychotic medication.

The mean duration of follow up of the ARMS individuals was 25.1 months (ARMS-T 12.3 months, ARMS-NT 33.1 months). Sixteen of 37 ARMS individuals (43%) made the transition to psychosis. Ten of the transitions occurred during the first year of follow up, five in the second year and one in the following years. At intake into the FePsy study, subjects who consequently made the transition to psychosis (ARMS-T) did not differ from ARMS-NT in age ($t = 1.46$, $df = 35$, $p = 0.155$), sex (Fisher's exact test $p = 0.500$), handedness (Fisher's exact test $p = 0.287$), education ($\chi^2 = 2.0$, $df = 3$, $p = 0.580$), mean BPRS global score ($t = 1.63$, $df = 35$, $p = 0.113$; Mean SANS: $t = 1.66$, $df = 35$, $p = 0.106$) and exposure to antipsychotic medications (Fisher's exact test $p = 1.00$) (Table 3).

Table **3**: Demographic and clinical characteristics (ARMS-T, ARMS-NT).

Characteristics	ARMS-T (n=16)	ARMS-NT (n=21)	p
Age at Baseline (mean years, SD)	24.44 (6.5)	23.4 (6.0)	ns[a]
Sex (male)	11 (69 %)	11 (52 %)	ns[b]
Handedness (mixed or left)*	3 (19 %)	1 (5 %)	ns[b]
Individuals with a first degree relative with schizophrenia	1 (6 %)	3 (13 %)	ns[b]
Educational level			ns[c]
< 9 years	4 (25 %)	7 (35 %)	
9-11 years	6 (38%)	8 (39 %)	
12-13 years	5 (31 %)	3 (13 %)	
> 13 years	1	3 (13 %)	
Mean BPRS global score at intake (SD)	41.9 (10.6)	37.2 (7.1)	ns[a]
Mean SANS at intake (SD)	9.5 (5.4)	6.8 (4.4)	ns[a]
Patients with antipsychotics at MRI-Scan	2 (13 %)	2 (9 %)	ns[b]
Duration of illness (mean months, SD)	42.6 (39.5)	43.2 (53.7)	ns[a]

[a] : Student's t-Test [c] : χ^2-test

[b] : Fisher's exact Test

3.2 Cingulate Volumes

Raw volumes and statistical analysis of the cingulate volumes co-varied for age, sex and total gray matter are shown in the tables 4 and 5.

Table **4**: Cingulate gray matter volume differences in ARMS vs. HC[1] and FEP vs. HC[2] (co-variance: age, gender, gray matter):

GROUP	ARMS (n = 37)		FEP (n = 23)		HC (n = 22)		univariate-test		pairwise comparison	
	mm^3	SD	mm^3	SD	mm^3	SD	F-Value	p-Value	p-Value 1	p-Value 2
tCC	1.84 e^4	2949.085	1.84 e^4	3211.121	1.94 e^4	3965.858	0.392	0.667	0.419	0.453
tCCr	9303.46	2239.918	9093.09	1397.087	9620.86	9620.86	0.136	0.873	0.819	0.608
tCCl	9137.65	1664.356	9351.40	2297.515	9787.68	2681.057	0.509	0.603	0.320	0.496
SCCr	497.57	187.357	507.17	172.755	557.41	175.381	0.581	0.562	0.293	0.657
CACCr	1368.51	508.902	1364.30	412.942	1530.18	351.474	0.536	0.587	0.311	0.467
RACCr	3110.19	1161.827	2796.17	749.268	2950.64	891.063	0.720	0.490	0.389	0.855
SCCl	533.14	177.795	542.13	215.841	524.32	244.381	0.009	0.991	0.916	0.899
CACCl	1247.70	344.216	1278.00	463.551	1513.32	494.448	2.770	0.69	**0.027**	**0.069**
RACCl	3041.49	1040.272	3275.22	1241.641	3217.68	1555.146	0.191	0.827	0.628	0.975
PCCr	4327.19	939.278	4425.44	744.903	4582.64	962.102	0.309	0.735	0.436	0.690
PCCl	4315.32	641.885	4256.05	894.435	4532.36	905.750	0.519	0.597	0.442	0.326

[1]: ARMS vs. HC [2]: FEP vs. HC

Table **5**: Cingulate gray matter volume differences in ARMS-T vs. ARMS-NT (co-variance: age, gender, gray matter):

GRUPPE	ARMS-T (n = 16)		ARMS-NT (n = 21)		Levene's Test		ANOVA		Test between Subjects	
	mm^3	SD	mm^3	SD	F-Wert	p-Wert	F-Wert	p-Wert	F-Wert	p-Wert
tCC	1.78 e^4	2879.792	1.90 e^4	2963.192	0.49	0.827	1.527	0.225	1.266	0.304
tCCr	8647.75	1827.231	9803.05	2433.291	0.877	0.355	2.518	0.122	2.923	**0.036**
tCCl	9112.00	1876.774	9157.19	1530.852	0.840	0.366	0.007	0.936	0.328	0.857
SCCr	454.25	166.565	530.57	199.329	0.000	0.997	1.529	0.224	2.929	**0.036**
CACCr	1243.37	441.439	1463.86	545.841	0.378	0.542	1.740	0.196	1.330	0.280
RACCr	2768.31	986.621	3370.67	1238.912	0.470	0.498	2.546	0.120	1.165	0.345
SCCl	518.81	169.218	544.05	187.443	0.715	0.403	0.179	0.675	0.245	0.911
CACCl	1255.19	374.547	1242.00	328.602	0.286	0.596	0.13	0.910	0.613	0.656
RACCl	2984.25	1217.189	3085.10	912.206	1.878	0.179	0.083	0.775	0.144	0.964
PCCr	4181.81	811.557	4437.95	1031.639	0.25	0.874	0.669	0.419	3.822	**0.012**
PCCl	4353.75	691.776	4286.05	616.955	0.485	0.485	0.098	0.775	1.616	0.194

Analysis 1 (comparison of ARMS vs. HC[1] and FEP vs. HC[2]) revealed a significant group effect (p: 0.027 in the ARMS vs. HC) and a trend (p: 0.069 in the FEP vs. HC) for the adjusted left CACC with smaller volumes in the ARMS and FEP compared to controls. The adjusted right CACC did not differ (p: 0.311 in the ARMS vs. HC group and 0.467 in the FEP vs. HC group) (table 4).

Analysis 2 (comparison of ARMS-T vs.ARMS-NT) revealed a significant group effect for the adjusted right total CC (F: 2.923, p: 0.036), for the adjusted right SCC (F: 2.929, P: 0.036) and the adjusted right PCC (F: 3.822, p: 0.012) with smaller volumes in the ARMS-T compared to ARMS-NT, whereas no significant difference was found for the left cingulate cortex (table 5).

4. DISCUSSION

It is of great interest to describe neurobiological and anatomical changes, which are involved in the pathophysiological steps leading to psychosis. The neurobiological basis of the predisposition for psychosis by some authors is described in abnormal interactions or disconnections between prefrontal cortex, cingulate cortex, temporal lobe and subcortical regions [63-66]. The present study provides evidence that changes in cingulate gray matter volume are found before first onset of psychosis (FEP), and that there are differences in cingulate gray matter volumes between ARMS individuals with transition to psychosis (ARMS-T) and those without (ARMS-NT). Based on those findings we want to suggest that a dysfunction of the cingulate cortex is one of the mechanisms in very early stages of psychosis.

Cingulate volumes associated with vulnerability and transition to psychosis

In this study we show that gray matter volume of the left CACC is significantly reduced in the ARMS-group compared to the HC-group and a statistical trend for a reduced volume in this region comparing the FEP-group with healthy controls. Similar results were found by Choi *et al.* (2005) in a study with FEP-individuals, who showed that a smaller volume of the right CACC was correlated with more severe positive symptoms of schizophrenia [29]. Fornito *et al.* (2008) reported in their study a bilateral thinning of a rostral paralimbic ACC region negatively correlating with negative symptoms in ultra-high-risk patients with transition to psychosis, whereas ultra-high-risk individuals without transition displayed a relative thickening of dorsal and rostral limbic areas, correlating with anxiety ratings [42]. Vidal CN *et al.* (2006) could provide evidence, that the earliest post-onset manifestation in schizophrenic individuals with onset in childhood are found in the paralimbic region and that those changes distribute over the entire ACC within a timeframe of 5 years [67].

Analysing the cingulate volumes of the ARMS-group regarding transition to psychosis (ARMS-T), three regions emerged to be significantly reduced compared to individuals without later transition to psychosis (ARMS-NT): complete CC, right SCC and right PCCr. We assume that these anatomic ACC abnormalities represent specific risk markers [42]. Min-Seong Koo *et al.* (2008) reported significantly reduced cingulate volumes in FEP-individuals, particularly left SCC, left RACC and RACCr “affective ACC“, right CACC “cognitive ACC“and right PCC . During follow-up patients showed a distinct progression of the change of volume in the mentioned subdivisions [45]. Fornito *et al.* (2008) described a longitudinal reduction of the gray matter in dorsal paralimbic regions during transition to psychosis [15, 42]. More precisely, the rostral paralimbic, limbic and paralimbic

subcallosal regions are mentioned besides the RACC, which show a significant thinning in ultra-high-risk patients with later transition to psychosis compared to individuals without transition to psychosis [42]. We also suggest progressive anterior cingulate changes associated with the development of disease, in line with previous works indicating that at risk subjects who later develop psychosis show dynamic longitudinal alterations in this region [22, 68].

Role of cingulate cortex during the development of psychosis

The functional diversity of the anterior cingulate cortex, that includes executive, social cognitive, affective functions, suggests that structural and functional abnormalities in this region may partly explain the difficulties in cognitive and emotional integration that characterize the clinical manifestations of psychosis [42]. The ACC has distinct anatomical connections to the dorsolateral prefrontal cortex, motor areas and the thalamus with specialized subdivisions, which are distinguished by cytoarchitectural criteria. The central task of this region is initiation of action, selective perception, selection and monitoring of conflicting responses [5] as well as error detection [6]. Its dysfunction results in a failure to monitor and modulate internally generated actions, which was shown in different functional [39] and structural neuroimaging studies [42, 43].

Studies of patients after the first onset of psychosis report a progression of changes in the ACC, developing from rostral caudally to the posterior and subcallosal paralimbic regions [42]. In our study, a significant reduction of the cingulate gray matter volume of the left CACC could be shown in the ARMS-group compared to HC. The hypothesis of a progression of cingulate volume changes from rostral caudally to dorsal limbic areas correlating to the onset of a first episode of psychosis (FEP) is supported by our results as well. We report significantly reduced cingulate gray matter volumes of the right cingulate cortex, particularly total volume, SCC and PCC as Fornito *et al.* (2008) [42] found. The described changes seem to progress into surrounding limbic areas, correlating with the duration of the disease [42]. Dysfunction of the ACC supports the thesis of a deficit already in the early stages of psychosis with a failure to monitor internally generated actions. Recent studies supported a core role for ACC dysfunction revealing alterations in the cellular and synaptic architecture of the region [69]. There is also specific functional imaging evidence indicating abnormal anterior cingulate engagement in the early phases of psychosis [30, 33], in subjects at genetic risk for psychosis [70, 71] and in subjects at clinical risk for psychosis [18, 72].

A major limitation of our study is the relatively small sample size with the consequence that we may be unable to detect small group differences because of limited statistical power. Furthermore, the cross-sectional nature of the

data limits interpretation. Cingulate volume abnormalities may be an epiphenomenom of another underlying disease pathology. Additionally, the present sample was not drug-naive, bearing the risk that medication effects might have influenced cingulate volumes. Recent structural imaging studies have clarified that antipsychotic exposure can affect GM volume in the early phases of psychosis influencing the cingulate cortex [73]. However, most of the ARMS subjects were naive to these medications and the few ARMS subjects who received antipsychotic medications were treated only for behavioral control and over a very short time period.

In conclusion, the present study provides further evidence that cingulate volume abnormalities in particular in the left caudal anterior cingulate cortex (CACC) are associated with the at-risk mental state for psychosis. These cingulate abnormalities do not only seem to occur with transition to psychosis, but may be a correlate of an increased vulnerability to psychosis. Future studies investigating cingulate abnormalities should use longitudinal approaches using multiple MR scanning with larger sample sizes.

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