Can cortical thickness analysis in at risk mental state contribute to early detection of psychosis?

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Abstract

Background: We investigated whether systematic analysis of brain MRI might contribute to early detection of psychosis in a multidisciplinary approach. Assuming that early disease-related morphometric changes are most pronounced in the cerebral cortex, we analyzed cortical thickness (CTh) in at risk mental state (ARMS), first episode (FE) psychosis and healthy controls (HC). Normal variations in CTh *between-subjects* are larger than expected disease-related changes. To overcome this limitation, we analyzed established reversed cortical asymmetry in schizophrenia, i.e. difference in CTh between right and left hemisphere *within-subjects*. We tested the hypothesis that FE differ in cortical asymmetry from controls in certain areas of the brain and that these areas also discriminate between ARMS and HC.

Methods: Twenty age and gender matched subjects of each group were recruited within a prospective early detection study. High-resolution magnetization prepared rapid gradient echo (MPRAGE) brain scans were acquired on a 1.5T MR scanner. We analyzed cortical asymmetry, i.e. differences between right and left hemisphere, in 41 corresponding anatomic regions of the Talairach standard brain.

Results: FE mainly differed from controls in seven anatomic regions: Collateral Sulcus, Insula, IntraParietal Sulcus, Lateral OccipitoTemporal Gyrus, Medial OccipitoTemporal Gyrus, Precuneus and Superior Parietal Lobe ($p < 0.0001$). The combination of these seven regions discriminated ARMS from HC (sensitivity 75% and specificity 65%).

Conclusions: CTh analysis discriminated ARMS and HC subjects and might contribute to early detection. At present, the clinical use of CTh analysis is still limited because the post-processing is time-consuming and difficult to standardize.

Abbreviations

ARMS	at risk mental state
CTh	cortical thickness
FE	first episode psychosis
FEPSY	**F**rüh**e**rkennung von **Psy**chosen = early detection of psychosis
HC	healthy control
MRI	magnetic resonance imaging
VBM	voxel based morphometry

Keywords

schizophrenia; MRI; cortical thickness; first-episode; at risk mental state; early diagnosis

Classifications

Early Psychosis, Imaging

Introduction

Schizophrenia has a lifetime prevalence rate of 0,5-1,6% and poses a significant burden to the affected patients and the society (Eaton 1999; Riecher-Rossler et al. 2006). The average time between symptom onset and diagnosis is substantial, in the order of 2-5 years and early treatment significantly improves disease prognosis and outcome (Killackey and Yung 2007). Early diagnosis or identification of individuals at risk for developing psychosis would be beneficial but is challenging based on clinical assessments alone (Broome et al. 2005). We investigated whether a systematic analysis of brain magnetic resonance imaging (MRI) scans might contribute to early detection in addition to clinical and other assessments in a multidisciplinary approach that includes neuroradiology, neuropsychology, psychopathology, previous history and neurophysiology.

The majority of previous brain morphometry studies in schizophrenia aimed to identify disease-related changes of the brain. Consequently, most studies included first episode (FE) or chronic schizophrenia patients and healthy controls (HC) (Shenton et al. 2001; Vita et al. 2006). In contrast to these studies, our objective was early detection very early in the disease process. This requires a high sensitivity. We hypothesized that early disease-related morphometric changes would be most pronounced in the cerebral cortex and investigated cortical thickness (CTh) (Jones et al. 2000). CTh is determined by size, density and arrangement of neurons, neuroglia and nerve fibers. Alteration in CTh may indicate a loss of dendrites, dendritic spines and / or changes in myelination within specific brain systems (Benes and Francine 2003; Harrison 1999). Although cellular characteristics cannot be quantified directly in imaging data, CTh may more closely

reflect cytoarchitectural abnormalities than cortical volume (Thompson et al. 2003; Yoon et al. 2006). Previous CTh studies in schizophrenia investigated only FE and HC subjects (Narr et al. 2005a; Narr et al. 2005b; Yoon et al. 2006). We additionally investigated at risk mental status (ARMS) subjects who are of particular interest in the context of early detection. In further contrast to the above-mentioned studies, we studied gender (Im et al. 2006) and age-matched (Salat et al. 2004) subjects to exclude systematic confounding related to interactions from associations of these variables with, laterality and schizophrenia (Narr et al. 2005a).

The *between-subject* variation in CTh in healthy controls of up to 15% (Haug 1987) is more pronounced than the expected disease-related variation in CTh. We avoided this limitation by assuming less *within-subject* variation and analyzed cortical asymmetry between corresponding anatomic regions between both hemispheres. Reversed asymmetry is an established finding in schizophrenia in morphometry (Shenton et al. 2001), functional MRI (Kircher et al. 2002) and electrophysiology (Holinger et al. 1992) and corresponds to functional specializations in healthy controls, e.g. thicker cortex in left-hemispheric language areas (Luders et al. 2006). To further increase the sensitivity, we consider the combination of several regions.

We tested the hypothesis that FE differ in cortical asymmetry from controls in certain areas of the brain and that these areas also discriminate between ARMS and HC in the sense of early detection.

Materials and methods

Subjects

The local ethics committee of the University of Basel approved the study. After complete description of the study to the subjects, written informed consent was obtained from each participant. Subjects were recruited within an ongoing, prospective study for the early detection of psychosis (FEPSY), which has been described in detail elsewhere (Riecher-Rossler et al. 2007). Subjects were classified into FE and ARMS (Yung et al. 1998) as follows:

Subjects in the FE group scored 4 or above on the hallucination scale or 5 or above on the unusual though content or suspiciousness or conceptual disorganisation scale of the Brief Psychiatric Rating Scale, BPRS (Lukoff et al. 1986; Ventura et al. 1993), symptoms at least several times a week, change in mental state lasting more than one week.

Subjects in the ARMS group were defined based on the Basel Screening Instrument for Psychosis, BSIP, a newly developed 46-item checklist (Riecher-Rossler et al. 2007), and BPRS with transition criteria not yet fulfilled. To be considered as ARMS, subjects had to fulfil criteria similar to those described by (Yung et al. 1998), i.e. individuals had to exhibit one of a) attenuated (subthreshold) psychotic symptoms or b) transient psychotic symptoms (lasting less than one week) or c) a first or second degree relative with a history of psychosis and at least two further risk factors or indicators of a beginning disease such as prodromal symptoms or marked social decline.

Healthy control (HC) volunteers were recruited within the same geographical area as the clinical subjects through local advertisements. These subjects had – as assessed by a clinical interview - no current psychiatric disorder, no history of psychiatric illness, head

trauma, neurological illness, serious medical or surgical illness, substance abuse, or family history of psychiatric disorders.

Exclusion criteria were: schizophrenia previously diagnosed and treated with neuroleptics, substance-induced psychosis, psychotic symptomatology secondary to an 'organic' disorder, synthymic psychotic symptoms within a clearly diagnosed severe depression , age under 18 years, inadequate knowledge of the German language, and IQ less than 70.

Subjects were recruited between March 1st, 2000 and February 28th2004. 25 FE (8 females), 36 ARMS (13 females) and 22 HC (9 females) subjects had MRI scans of acceptable quality. We included 20 (8 females and 12 males) age-matched subjects of each group. The mean age ± standard deviation at MRI scan for the females was FE 28.3 ± 9.9, ARMS 25.8 ± 8.3 and HC 23.6 ± 3.9 years. There was no significant difference in age between groups (ANOVA group comparison not significant, pair-wise Bonferroni corrected comparison not significant). Correspondingly, mean age ± standard deviation for the males was FE 24.4 ± 4.2, ARMS 24.0 ± 5.5 and HC 23.4 ± 4.6 years without significant differences between groups. Details of the included subjects are provided in **Table 1**.

Insert Table 1 around here

Image acquisition

We used a routine 1.5T MR scanner (SIEMENS Erlangen, Germany, MAGNETOM VISION) and three-dimensional T1 weighted magnetization prepared rapid gradient

echo (MPRAGE) sequence: matrix size, 256x256; field of view, 25.6x25.6 cm, 170 contiguous, 1 mm thick sagittal slices, time-to-echo, 4 msec; time-to-repetition, 9.7 msec, inversion time 300ms, flip angle 12°, one average, resulting voxel dimensions 1x1x1 mm.

Image analysis

Image analysis was performed according to standard procedure in BrainVoyager QX version 1.7 (Brain Innovation, Maastricht, The Netherlands, www.brainvoyager.com) as described in detail elsewhere (Goebel et al. 2006). After automatic cortex segmentation into white and grey matter, inner and outer boundaries of the grey matter were reconstructed. CTh was estimated in individual hemispheres based on the Laplace method (Jones et al. 2000). Additionally, individual cortex surface representations were automatically generated and corrected manually if necessary after visual control. These surfaces were inflated into spheric representations, while the curvature of gyri and sulci was maintained. We implemented a cortex-based alignment (Fischl et al. 1999) and aligned all individual cortices to a standard brain in Talairach space (Talairach and Tournoux 1988). This cortex-based alignment improved the matching of corresponding brain areas. To visualize this effect, average spheres and average cortex reconstructions were calculated prior and post cortex-based alignment (**Figure 1)**. The improved alignment of corresponding cortical structures results in clearer average spherical representation of cortex curvature (**Figure 1B**) and a more detailed average hemisphere (**Figure 1D**). This high-quality alignment procedure is fundamental for the later exact comparison of CTh between groups. Furthermore, CTh is analyzed *prior* to cortex-based alignment and then referenced to the aligned brain. This procedure

reduces alignment-induced putative systematic mis-estimation as compared to e.g. VBM (Ashburner and Friston 2000) that analyzes grey matter concentration *after* normalization.

Individual average CTh was estimated in 41 anatomic regions-of-interest (ROIs) based on the Talairach standard brain (Talairach and Tournoux 1988).

Insert Figure 1 around here

Absolute *between-subjects* CTh

For each of the two hemispheres, group differences in average absolute CTh across all 41 anatomic ROIs were assessed using an ANCOVA model with cofactor sex and covariate age. Normality of residuals was tested using the Shapiro-Wilk test.

Relative *within-subjects* cortical asymmetry

The analysis focused on *within-subject* cortical asymmetry. We assume differences in the absolute average CTh *between-subjects* and consequently z-transformed asymmetries in CTh across the 41 regions (including all three groups). For each subject, we then computed the average (AV(41)) and the standard deviation (SD(41)) of the 41 z-scores. Trends in AV(41) and SD(41) across groups were assessed using the Jonckheere-Terpstra test and pairwise comparisons were done using the Mann-Whitney-U-test. Note that the SD(41)-values are individual parameters, not standard deviations in the classical sense (i.e., measuring variation between subjects).

A posteriori, we identified those ROIs that predominantly contributed to the significant difference between FE and controls. This subset was derived empirically using a jackknife technique applied to the statistic of interest, i.e. the difference between FE and controls in the group means of individual standard deviations of z-scores. In each of 5000 replications, we randomly omitted about half of the regions. Each region was assigned a score by averaging the values of the test statistic across all replications involving it. Parameters were then ordered by decreasing size of this score. We reasoned that the parameters with the highest scores would be the ones that were mainly responsible for the difference between FE and controls. In analogy to the analysis of all 41 ROIs above, we compared summary measures of these 7 regions (i.e., AV(7) and SD(7)) between groups (i.e., again by means of the Jonckheere-Terpstra test and the Mann-Whitney-U-test).

The essential data analysis steps are illustrated in **Figure 2**.

Results

Absolute *between-subjects* CTh

Essential parameters including mean and standard deviation of the absolute CTh across all regions is listed **Table 2.** The direct *between-subjects* analysis showed no significant difference between groups (ANOVA).

Insert Table 2 around here

Relative *within-subjects* cortical asymmetry

Concerning the *within-subject* cortical asymmetry, FE differed from controls with respect to AV(41) (p=0.04) and SD(41) (p=0.007) when considering all 41 ROIs.

ROI analysis

Seven most informative regions were identified without apriori knowledge: Collateral Sulcus, Insula, IntraParietal Sulcus Lateral OccipitoTemporal Gyrus, Medial OccipitoTemporal Gyrus, Precuneus and Superior Parietal Lobe. These seven variables provided a p-value < 0.0001 for the difference between FE and controls in SD(7) across the seven regions. The respective group means of standard deviations were HC: 0.756; ARMS: 0.876; FE: 1.179 (Table 3). Thus, there is increasing variability in cortical asymmetry from HC to ARMS to FE.

Analysis of prediction / early detection tool

The score defined by SD(7) discriminated between FE and controls (sensitivity 70%, specificity 85%) and between ARMS and HC (sensitivity 75%, specificity 65%).

Discussion

We investigated whether the systematic analysis of CTh derived from brain MRI might contribute to early detection of schizophrenia in a multidisciplinary approach. Consequently, the focus of the present investigation are the at risk mental state (ARMS) subjects.

The presented analyses are based on the asymmetry of CTh, i.e. *within-subject* differences of CTh between corresponding anatomic regions of both hemispheres. We chose this novel and complex approach to overcome a methodological problem: the established *between-subject* variation of CTh (Haug 1987; Luders et al. 2006) is more pronounced than the expected disease-related changes in prodromal and early phases of psychosis. We assume less variation *within-subjects* and make use established reversed asymmetries in schizophrenia (Holinger et al. 1992; Kircher et al. 2002; Shenton et al. 2001).

As predicted, our novel *within-subject* analysis of cortical asymmetry showed a higher sensitivity as compared to direct *between-subject* analysis of CTh. Over the whole brain, the *within-subject* analysis discriminated groups, whereas the direct *between-subject* analysis did not.

Assuming that psychosis preferentially affects certain brain regions (Narr et al. 2005a; Narr et al. 2005b; Shenton et al. 2001; Vita et al. 2006; Wiegand et al. 2004; Yoon et al. 2006), we identified in a next step those regions with the strongest asymmetry between FE and controls. This cluster of seven regions discriminated FE versus controls and ARMS versus HC. At present, the CTh analysis was compared to the classification into the different groups according to the clinical multidisciplinary assessment. The reported sensitivity any specificity values correspondingly represent the comparison of CTh versus clinical assessment as ‘gold standard’. The ‘true’ gold standard however should be those subjects who eventually develop psychosis in the future course of the FEPSY study. Obviously, the present results must be validated in future studies and it is of

particular interest whether the reported seven regions will also discriminate between those ARMS subjects who develop psychosis and the other ones who do not.

Only few studies have analysed CTh in patients with schizophrenia, and none of them also analysed ARMS individuals. Cth was analyzed in 53 patients with schizophrenia and 52 control subjects with the intention to discriminate groups using principal component analysis (Yoon et al. 2006). This method allowed a classification of at a best mean accuracy of over 90%. This higher accuracy as compared to the present investigation might be explained by the fact that patients with presumably longer duration of schizophrenia were included (detailed information about duration of the disease was not given). We investigated patients with a first episode of psychosis at a very early stage. Differences in CTh probably become more pronounced in later stages of the disease. As at risk subjects were not included (Yoon et al. 2006), it is not known whether the proposed principal component analysis would also discriminate between at risk subjects and controls. This is obviously an important aspect in the context of early detection.

Two related CTh studies investigated the convexity (Narr et al. 2005a) and the inter-hemispheric surface (Narr et al. 2005b) of the brain. The major differences as compared to the present investigation are larger group sizes with 72 FE and 78 HC subjects. Another study was limited to the prefrontal cortex in 17 FE, 17 affective psychosis patients and 17 HC subjects (Wiegand et al. 2004). These studies did not assess early detection. Previous CTh analyses of at risk subjects are not available. A VBM investigation with a different objective derived subjects from the same study pool

(Borgwardt et al. 2006). In accordance with the present investigation, volumetric differences between groups were present in the insula, amongst other regions. However inclusion criteria and consequently group characteristics were different. We will provide a detailed methodological comparison of CTh versus VBM in identical study samples in a future study.

The discussed previous CTh investigations in schizophrenia report cortical thinning in various regions (Narr et al. 2005a; Narr et al. 2005b; Wiegand et al. 2004; Yoon et al. 2006). Likewise, the majority of previous morphometric studies implementing different methods also report cortical thinning or reduced cortical volume (reviews (Shenton et al. 2001; Vita et al. 2006)). For example, patients with chronic schizophrenia were found to have significant cortical thinning in prefrontal regions (inferior frontal, orbitofrontal, and medial frontal) and temporal regions (inferior temporal, medial temporal, and occipitotemporal) especially on in left hemisphere (Kuperberg et al. 2003). In contrast to these studies, we found no significant difference between groups with regard to the absolute CTh averaged across all ROIs. Changes in CTh might be restricted to certain regions and consequently might be undetectable in average CTh across a whole hemisphere. Another explanation might be a lack of statistical power of our study (i.e., with 20 subjects per group) as compared to the one by Narr (i.e., with 72 FE and 78 HC subjects (Narr et al. 2005a; Narr et al. 2005b)). Additionally, we investigated FE patients at a very early stage and disease-related modifications in the cortex might increase over time. In accordance with our results, other studies also report no significant differences in FE (Wiegand et al. 2004).

In contrast to these previous studies, the focus of our investigation was not the CTh *per se* but *within-subject* cortical asymmetry in corresponding anatomic regions, for reasons discussed above. As expected, ARMS were in-between HC and FE. We found an increasing variability in CTh asymmetry from HC to ARMS to FE. This might suggest a progressive regional cortical disorganization. This assumption is supported by increased variability in gyral shape and cortical surface asymmetry in chronic schizophrenia (Narr et al. 2001). As discussed above, the majority of previous studies reported cortical thinning in chronic schizophrenia. In contrast, previous studies of ARMS showed greater volume in parahippocampal regions (Borgwardt et al. 2006; Goghari et al. 2007), precuneus (Antonova et al. 2005) and anterior cingulate gyrus (Kopelman et al. 2005). Furthermore, healthy relatives of patients with schizophrenia have increased gray matter volume in bilateral parahippocampal gyri and in the left middle temporal lobe despite decreased volume and surface area in the right cingulate gyrus and decreased thickness in bilateral cingulate (Goghari et al. 2007). Data on CTh in ARMS is not available. The observed increased variability in CTh asymmetry might be due to cortical swelling in certain regions in the prodromal and initial phase of psychosis, possibly as expression of ongoing inflammation (Berger et al. 2003) or autoimmune reaction that progresses into atrophy at a later stage of the disease. This process might be aggravated by medication, in particular if long lasting (Dazzan et al. 2005).

Limitations

A general limitation of brain morphometry is the large variation of reported affected brain areas in schizophrenia, as discussed above. There is a substantial inter-individual

variation in CTh even in healthy controls (Haug 1987). In conjunction, this suggests that brain morphometric studies might be substantially influenced by age and gender characteristics of patients and control groups, duration of disease, presence and duration of medication, MR image acquisition and data analysis. This should be considered as a caveat in particular when using brain morphometric measures as an early detection tool.

A major specific limitation of the presented study is the small sample size of the study groups. On the other hand, the highly significant differences despite the small sample size underline the high sensitivity of the presented novel cortical asymmetry analysis.

Another limitation is the time-consuming post processing. The brain scan, in contrast, requires less than five minutes with modern MR scanners and parallel imaging. Furthermore, the individual brains must be related to a reference group. The known age and gender related differences in CTh (Im et al. 2006; Salat et al. 2004) in conjunction with putative differences related to comorbiditiy, ethnical group or medication / drug use implies that a large control sample is necessary. Moreover, the white and grey matter segmentation and consequently the CTh analysis presumably depend on the MR scanner and MR protocol details. This suggests that each institution and each MR scanner requires its own reference group. Increasing computer hardware performance and the possibility to parallelize data analysis on the one hand, and the possibility to standardize MR parameters using appropriate phantoms and / or sequences on the other hand, might significantly increase the clinical applicability of CTh analysis in the near future.

Conclusions

The novel *within-subject* analysis of CTh makes use of established reversed cortical asymmetry in schizophrenia and successfully avoided larger *between-subject* variation in CTh. We identified seven anatomic regions in which variation of cortical asymmetry differed strongly between groups. The associated score discriminated ARMS versus HC (sensitivity 75% and specificity 65%) in the sense of early detection. At present, the clinical use of CTh analysis for early detection is still limited because the post-processing is time-consuming and difficult to standardize.

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Tables

Table 1

Subjects					
Age at scan	gender	BPRS Score	NL at MRI	NL lifetime	NL duration at scan
HEALTHY CONTROLS - HC					
20	f		0	0	
29	f		0	0	
23	f		0	0	
21	f		0	0	
24	f		0	0	
27	f		0	0	
27	f		0	0	
18	f		0	0	
19	m		0	0	
25	m		0	0	
23	m		0	0	
27	m		0	0	
34	m		0	0	
27	m		0	0	
26	m		0	0	
21	m		0	0	
21	m		0	0	
18	m		0	0	
20	m		0	0	
20	m		0	0	
AT RISK MENTAL STATE - ARMS					
23	f	37	0	0	
20	f	42	0	0	
21	f	26	0	0	
36	f	35	0	0	
19	f	51	0	0	
26	f	40	1	1	less than 1 month
41	f	37	1	1	1-3 months
20	f	36	0	0	
26	m	54	0	0	
28	m	37	0	0	
23	m	30	0	0	
24	m	39	0	0	
19	m	33	0	0	
22	m	40	0	0	
20	m	30	0	0	
34	m	33	0	0	
34	m	58	0	0	

18	m	35	0	0	
19	m	55	0	0	
21	m	34	1	1	1-3 months
FIRST EPISODE - FE					
23	f	54	0	0	-
33	f	49	0	0	-
32	f	43	1	1	less than 1 month
21	f	48	0	0	-
18	f	51	0	0	-
35	f	65	0	0	-
46	f	47	0	0	-
18	f	78	1	1	less than 1 month
28	m	64	0	0	-
24	m	40	1	1	1-3 months
23	m	43	1	1	less than 1 month
35	m	28	1	1	less than 1 month
22	m	44	1	1	less than 1 month
22	m	72	0	0	-
24	m	38	1	1	less than 1 month
26	m	41	0	0	-
27	m	76	1	1	1-3 months
21	m	43	0	0	-
19	m	41	1	1	1-3 months
22	m	50	0	0	-

Table 1: Overview of all 60 subjects included in the present investigation. Age at scan, gender, global BPRS score, neuroleptic (NL) medication at MRI scan, NL in lifetime and duration of NL medication at MRI scan.

Table 2

Absolute *between-subjects* CTh								
	Left hemisphere				Right hemisphere			
	Mean[1]	95%-confidence interval		p-value[2] F-value d.f.	Mean[1]	95%-confidence interval		p-value[2] F-value d.f.
FE	2.95	2.88	3.02	0.06 3.05 2,55	2.90	2.83	2.97	0.26 1.40 2,55
ARMS	2.84	2.76	2.91		2.82	2.75	2.89	
HC	2.85	2.77	2.92		2.84	2.77	2.91	

[1]adjusted for sex and age, [2]group effect in ANCOVA model with cofactor sex and covariate age

Table 2: Adjusted Means and 95% confidence intervals of the average cortical thickness [mm] across all 41 regions for left and right hemispheres and by groups. There was no significant difference between groups.

Table 3

Relative *within-subjects* cortical asymmetry in 7 selected ROIs			
	Group mean of SD(7)	p-value[1]	p-value[2]
HC	0.756	<0.0001	ARMS vs. HC: 0.06 FE vs. ARMS: 0.007
ARMS	0.876		
FE	1.179		

Group means of individual standard deviations of z-standardized asymmetry across 7 ROIs (SD(7)). [1]Jonckheere-Terpstra test for trend; [2]Mann-Whitney-U-test

Figure caption

Figure 1:

Figure 1 visualizes the effect of the cortex-based alignment procedure. Without cortex-based alignment, the inflated average cortical surface of the left hemisphere of all subjects (A) shows blurring of gyri (yellow) and sulci (blue) despite normalization into standard space (Talairach and Tournoux). While major sulci are evident (e.g. central sulcus), sub-sulci have more anatomic variation and consequently appear blurred. The cortex-based alignment (B) improves the alignment of corresponding structures. Sub-sulci and sub-gyri can now be delineated clearly. These inflated, spheric representations of the average left hemispheres (A, B) were folded back to achieve the average surface of the left hemisphere of all subjects before (C) and after (D) cortex-based alignment. The cortex-based alignment improved the detail of the average brain due to improved normalization of corresponding cortical structures.

Figure 2:

Figure 2 illustrates the flow of the essential data analysis steps.