

## Abnormalities of cingulate cortex in antipsychotic-naïve chronic schizophrenia

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**Target audience:** Radiologists engage in neuroimaging research and psychiatrists with an interest in MRI research.

**Purpose:** Schizophrenia is a complex psychiatric disorder with brain anatomical and functional abnormalities. Among various brain abnormalities, cingulate cortex deficits are considered to be critically implicated in the pathophysiology of schizophrenia. Cingulate cortex is a heterogeneous region and its subdivisions are difference in cytoarchitecture. Gray matter volume is a product of surface area and cortical thickness, either reduced in surface area, cortical thickness or both may lead to a reduction in volume. Antipsychotic medication is known to effect brain structure, previous data suggest it may delay, prevent or reverse the cortical volume loss. In this study, we investigate the sub divisional morphology of cingulate cortex in antipsychotic-naïve schizophrenia. Furthermore, we also investigated the changes of morphology in cingulate cortex and their associations with clinical variables and cognitive performance.

**Methods:** All subjects underwent MRI scans on a 3-Tesla whole body scanner (Signa HDx; GE Medical Systems, Milwaukee, WI, USA). High resolution T1-weighted images were using three-dimensional fast spoiled-gradient recalled acquisition in the steady state (3D-FSPGR) in the coronal plane. The scanning parameters were as follows: acquisition matrix = 256 × 256; TE = 3.9ms; TR = 9.6ms; FOV = 240mm × 240mm; slice thickness/gap = 1.2mm / 0mm. We used the FreeSurfer software (version 5.1.0) for processing of images and measurements of surface area, cortical thickness and gray matter volume. We performed GLM Multivariate analysis of covariance controlling for the effect of age and gender to compare surface area, cortical thickness and volume in rACC (rostral anterior cingulate cortex), cACC (caudal anterior cingulated cortex) and PCC (posterior anterior cingulated cortex) (see Figure1). P value was 0.017 after Bonferroni corrected [i.e. regions=3, P=0.017 (0.05/3)]. Correlations with cognitive domains were computed using partial correlations with age and gender as covariates. All the correlations were performed only in the regions showing deficits, the level of statistical significance was defined as P < 0.05 (two-tailed).

**Results:** Compared to healthy controls, the patients showed significant volume reduction in the left rACC (F=6.988; P=0.013) and left PCC (F=11.147; P=0.002). A strong statistical trend level was found in reduced surface area of the left rACC (F=6.036; P=0.02) and left PCC (F=6.343; P=0.017) in patients (see Figure2). No significant cortical measurements alterations were observed in other regions. The left PCC volume was positively correlated with the working memory in the patients (r=0.597, P=0.019). The left rACC volume did not correlate with any cognitive domains. In the healthy controls, no significant relationships were found between cognitive performances and left rACC and left PCC volume.

**Discussion:** These data could suggest that cingulate cortex volume deficit may be plays a key role in the pathophysiology of the disease. We observed a significant trend level of smaller surface area in left rACC and left PCC in patients, but no differences of the cortical thickness. That might be suggested volume deficit predominantly attributed to a decrease of surface area in the cingulate cortex. The precise cellular basis for surface area reduction in schizophrenia is unknown. Previous study has shown that genetic processes determine the development of surface area [1]. It was suggested that surface area may be determined in the early neurodevelopment and less affected by environmental factors or antipsychotic medications [2]. Therefore, we speculate that alterations of surface area in cingulate cortex can be taken as evidence for neurodevelopmental origin of the disease. In addition, the observed left PCC volume deficit was significantly correlated with working memory impairments in patients, as greater impairments in working memory were associated with a greater degree of left PCC volume deficit. One of the primary functions of the PCC is working memory [3]. Functional MRI data have shown that deficits in working memory were related to abnormalities of the PCC in schizophrenia [4]. Therefore it is possible that the deficits in working memory could be partially attributable to altered in PCC volume in schizophrenia.

**Conclusion:** Our results show that left rACC and left PCC volume reductions in antipsychotic-naïve chronic schizophrenia patients, surface area may be the most important factor in cingulate cortex volume reduction in schizophrenia, and then demonstrated that the left PCC volume deficit may play a role in the working memory of the disorder. Our findings provided evidence that development aberrations in cingulate cortex morphology may be involved in the pathophysiology of schizophrenia.

**References:** [1] Panizzon MS, Fennema-Notestine C, Eyer LT, et al. *Cerebral Cortex* 2009;19(11):2728-35.[2] Habets P, Marcelis M, Gronenschild E, et al. *Biol Psychiatry* 2011;69(5):487-94.[3] Vogt BA, Finch DM, Olson CR. *Cerebral Cortex* 1992;2(6):435-43.[4] Meda SA, Stevens MC, Folley BS, et al. *PLoS One* 2009;4(11):e7911.

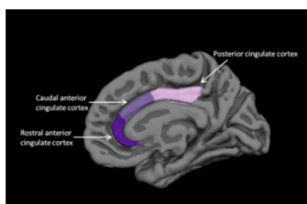


Figure 1. Midsagittal views of the rostral anterior cingulate cortex (rACC), caudal anterior cingulate cortex (cACC) and posterior cingulate cortex (PCC).

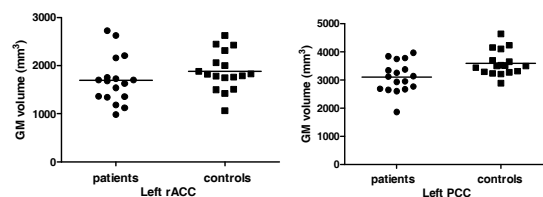


Figure 2. Left rACC and left PCC volume in patients with schizophrenia and healthy controls. Patients had significantly smaller volume than healthy controls.