# Three shape patterns of subcortical structures in medication-naïve first-episode schizophrenia patients revealed by morphometric descriptor and cluster analysis

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**Introduction:**

Schizophrenia has been hypothesized as a subcortical neurotransmitter imbalance syndrome.[1] However, findings from previous volumetric studies on subcortical structures are inconsistent.[2] Both volume increase and decrease in certain structures had been reported. Beside confounders associate with age, illness duration and medication effects, the most possible explanation for the inconsistent findings is the inherent heterogeneity of schizophrenia. Whilst the majority of previous studies have focused on the volume of subcortical structures, the pathological changes in the shape of subcortical structures may not be detected in conventional volumetric test. Thus, current study aims to extract shape descriptors from subcortical structures in a large sample of patients with first-episode medication-naïve schizophrenia and fed into cluster analysis to identify subgroups. We assume that the use of cluster analysis may reveal nature patterns in the shape of subcortical abnormalities in schizophrenia and patients belong to different patterns may also differ in clinical features.

**Method:**

Seventy-eight first-episode right handed schizophrenia patients (42 male, 36 female, age from 18 to 25, mean age 22.8) recruited from outpatient and inpatient units of the Mental Health Center were included in this study. Confirmation of diagnosis was determined by clinical psychiatrists using the Structured Clinical Interview for DSM-IV (SCID). Before MRI scanning, clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). The illness duration of all patients was less than 2 years. Eighty healthy controls (40 male, 40 female, age from 18 to 25, mean age 23.2) were recruited from the local community via poster advertisements. High resolution T1 weighted anatomical images were acquired on a clinical 3T scanner with a 8-channel phase array head coil using 3D spoiled gradient (3D-SPGR) sequence (TR=8.5ms, TE=3.5ms, TI=400ms, Flip angle=12) with 240 x 240 matrix over a field of view of 240 x 240 mm and 156 axial slices of 1mm thickness. The anatomical images were linearly registered to MNI152 standard template with 7 degree of freedom to normalize the head size and subsequently automatically segmented using FSL FIRST[3] with default parameters. The quality of segmentation was visually inspected slice-by-slice for correct location and shape.

The meshes of 14 subcortical structures (bilateral Thalamus, Caudate, Putamen, Pallidum, Hippocampus, Amygdala, Accumbens) of healthy controls generated from segmentation step were used to construct a 3D atlas using the algorithm proposed by Durrleman et al.[4] Before construction, corresponding meshes were rigid registered. 336 control points generated from construction process. Then the atlas was registered to meshes from each schizophrenia patient with same control points location using the same algorithm. The deformation momenta of each control point were treated as the morphometric descriptor of each patient. Before feeding into the hierarchical clustering process, the momenta whose Euclidean norm were less than 0.5 in all subjects were removed to reduce the feature dimensionality (Figure 1). Finally, 136 control points were preserved. The cluster result was validated by homogeneity, separation, Silhouette and Dunn indices. The clinical features were also compared among subgroups using analysis of variance. To further locate the shape abnormalities, Vertex analysis was also performed between each patient subgroup and healthy controls using the utilities provide in FSL package.

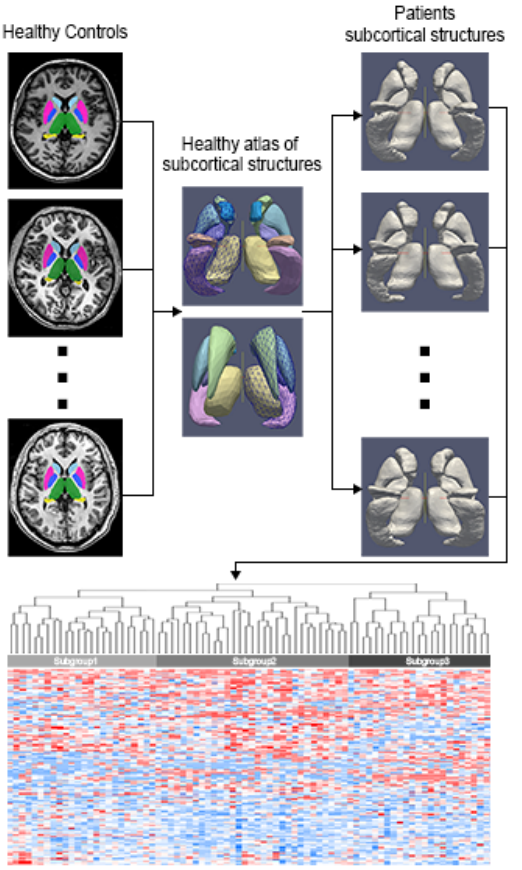


Figure 1. The workflow of morphometric descriptor extraction and cluster analysis

**Result:**

According to the validating indices, the best clustering quality reached when the patient group was partitioned into three subgroups. Twenty-four (30.8%) patients were placed in subgroup1, 31 (39.7%) patients in subgroup2 and 23 (29.5) patients in subgroup3. There is no differ in the age, gender ratio and illness duration among subgroups. However, subgroup1 shows higher PANSS positive scores than another two subgroups and subgroup3 has higher PANSS negative scores when compared with another two subgroups ($p<0.05$). From vertex analysis, subgroup1 showed no significant shape difference when compared with healthy controls in all 14 structures, while subgroup2 showed regional dilatation in bilateral Caudate and left Hippocampus and subgroup3 showed regional atrophy in bilateral Pallidum (Figure 2).

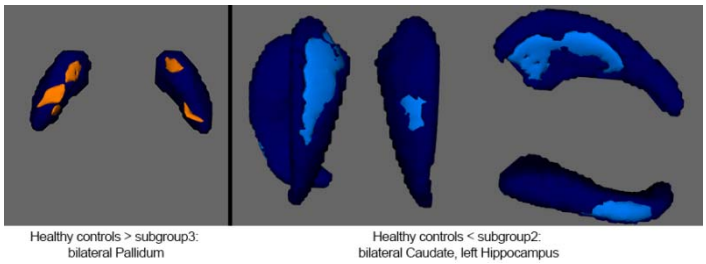


Figure 2. The regional abnormalities revealed by vertex analysis

**Discussion and conclusion:**

The current study firstly revealed three shape patterns of subcortical structures exist at early phase of schizophrenia according to the deformation parameters between patient individuals and the atlas constructed from matched healthy controls. As patients from different subgroups did not differ in age and illness duration and the abnormal regions revealed by vertex analysis did not show significant spatial correlations, the three shape patterns may reflect distinct underlying pathology instead of variations on a continuum of severity of a single disorder. In addition, our results also found that the shape of Pallidum may correlate with negative symptoms. While the dilatation in bilateral Caudate and left Hippocampus could reflect another kind of pathology in patients with mild symptoms. However, whether the shape abnormalities are the primary factor to the disease or a secondary effect cause by deformation of surrounding tissue needs further evidences.

**Reference:**

[1] Carlsson et al., Schizophrenia bull 1990. [2] Arnone et al., Brit J Psychiat 2009. [3] Patenaude et al., NeuroImage 2011. [4] Durrleman et al., NeuroImage 2014