

# Volumetric and Shape Analysis of the Subcortical Regions in Schizophrenia Patients: A Pilot Study

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ABSTRACT

**Objective:** Investigation of brain structure in disease has been enhanced by developments in shape analysis methods that can identify subtle regional surface distortions. High-resolution magnetic resonance (MR) imaging was used to compare volumetric and shape analysis in schizophrenia (SCZ) patients and healthy controls (CON). **Methods:** T1-weighted, 1-mm thick MR images were acquired for 15 patients with SCZ and 15 age-matched healthy controls using subcortical volume and shape analysis, which we believe to be complimentary to volumetric measures. **Results:** SCZ patients showed significant shape differences compared to healthy controls in the right hippocampus ( $P < 0.005$ ), left and right putamen ( $P < 0.044$  and  $P < 0.031$ ), left caudate ( $P < 0.029$ ), right pallidum ( $P < 0.019$ ), and left thalamus ( $P < 0.033$ ). **Conclusion:** Our results provide evidence for subcortical neuroanatomical changes in patients with SCZ. Hence, shape analysis may aid in the identification of structural biomarkers for identifying individuals of SCZ.

**KEYWORDS:** Brain structure, high-resolution magnetic resonance imaging, schizophrenia, shape analysis

## INTRODUCTION

Schizophrenia (SCZ), a highly incapacitating complex disorder affecting about 1% of the general population, is associated with substantial morbidity and mortality.<sup>[1,2]</sup> Individuals with SCZ show significant brain morphological abnormalities, but there is considerable heterogeneity in the effect sizes and patterns of brain differences across studies.<sup>[3,4]</sup> The study of structural brain abnormalities in SCZ can help us understand its causes, progression, and even treatment effects.

Volumetric analyses of structural brain imaging data have been a mainstay of brain structure investigations in psychiatry.<sup>[5,6]</sup> The complement data resultant from volumetric and shape analysis methodology have been shown to identify group abnormalities in psychiatry disease.<sup>[7-9]</sup> Since shape analysis methods specifically identify impaired pathways, where the volumetric

analysis did not show the surface abnormalities within the brain supports the revealing of localized deformations more on the surface of a brain structure.<sup>[1,5,6,10]</sup> This is particularly important in the study of brain structures with explicit regional differentiation in function, such as the thalamus or striatum.<sup>[11,12]</sup> Few studies have shown the shape analyses for SCZ.<sup>[1,6,7,9,10,13]</sup>

In the current study, we investigated the volumes and shapes of subcortical structures (i.e., the hippocampus,

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amygdala, caudate, putamen, globus pallidus, nucleus accumbens, and thalamus). We hypothesize that structural abnormalities will exist with SCZ. Abnormalities are expected to be largely trend toward shrinkage and be best captured by shape analysis.

## METHODS

### Participants

Participant groups included as follows: SCZ ( $n = 15$ ) and healthy controls (CON) ( $n = 15$ ) with ages ranged between  $33.14 \pm 9.96$  (mean  $\pm$  standard deviation) years. Participants were enrolled through the local psychiatric clinics, at King Saud University Hospital, whereas the control group were recruited through the health recruitment system. All participants gave written informed consent for participation and study was approved by the Institutional Review Board of King Khalid University Hospital. SCZ and CON participants were all outpatients, and clinically stable for at least 2 weeks.

Participants were excluded if they: (a) met Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for substance dependence or severe/moderate abuse during the prior 6 months; (b) had a clinically unstable or severe general medical disorder; or (c) had a history of head injury with documented neurological sequelae or loss of consciousness.

Table 1 shows the demographic data of participants.

### Clinical assessment

They were diagnosed by a consensus between a research psychiatrist and a trained research assistant who used the structured clinical interview for DSM-IV Axis I Disorders.

Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms was used to assess the psychopathology. Specific subscale scores were summed to develop to measures of positive symptoms (i.e., hallucination and delusion subscales), disorganization (i.e., formal thought disorder, bizarre behavior, and attention subscales), and negative symptoms (i.e., flat affect, alogia, anhedonia, and amotivation subscales).

**Table 1: Anthropometric data of schizophrenia and control group**

Parameters	Control ( $n=15$ )	Schizophrenia ( $n=15$ )
Age	28.8 $\pm$ 8.9	33.9 $\pm$ 9.9
Height	170 $\pm$ 7.1	154 $\pm$ 45
Weight	74 $\pm$ 15	77 $\pm$ 29

Vales are presented in Mean $\pm$ SD

### Image acquisition

A Siemens Magnetom Verio 3T magnetic resonance imaging (MRI) clinical scanner (Siemens AG, Healthcare Sector, Erlangen, Germany) and 12-channel phased-array head coil were used to acquire: (1) T1-weighted three-dimensional magnetization-prepared rapid gradient-echo imaging: Repetition time (TR) = 1600 ms, echo time (TE) = 2.19 ms, inversion time = 900 ms, flip angle = 9°, acquisition plane = sagittal, voxel size = 1 mm  $\times$  1 mm  $\times$  1 mm, field-of-view (FOV) = 256 mm, acquired matrix = 256  $\times$  256, acceleration factor (iPAT) = 2; (2) Fluid-attenuated inversion recovery : TR = 9000 ms, TE = 128 ms, inversion time = 2500 ms, flip angle = 150°, acquisition plane = axial, slice thickness = 5 mm, FOV = 220 mm, acquired matrix = 256  $\times$  196, acceleration factor (iPAT) = 2.

### Data analyses

#### Shape of subcortical regions

#### Segmentation of subcortical regions

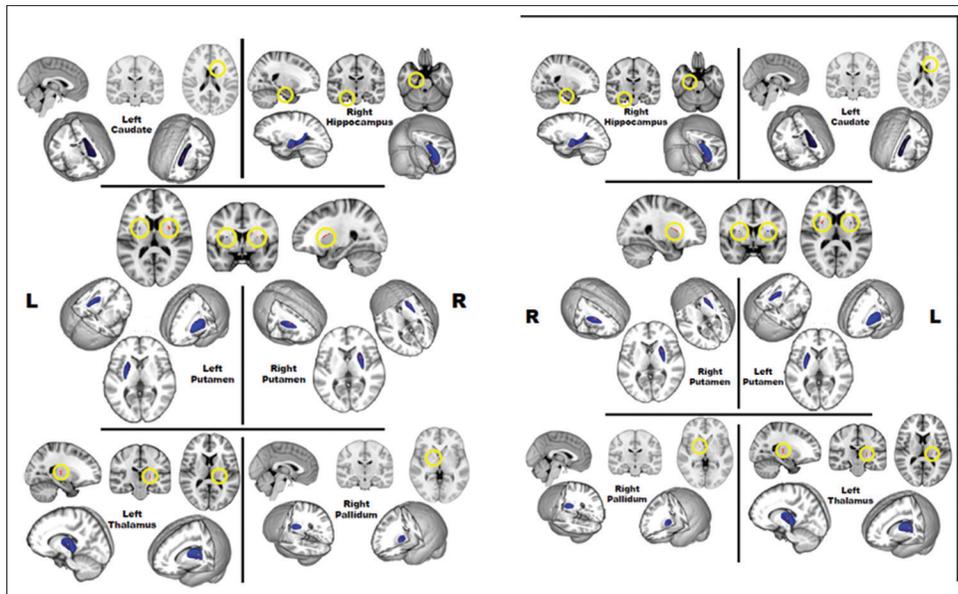
The anatomical T1 data (DICOM format) of each subject was converted into compressed NIfTI format using MRICron (<https://www.nitrc.org/projects/mricron>). Using FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST> Oxford University, Oxford, United Kingdom), the following tools were applied sequentially: brain extraction by the BET tool (Smith, 2002) to clear noncerebral voxels; automated segmentation by the FIRST tool of the subcortical regions.<sup>[14,15]</sup> Voxel-based thresholding, corrected, for multiple comparisons was adopted. The significance level with the family-wise error corrected was set at  $P = 0.05$ . Statistical analyses were performed using SPSS (for MAC, Rel 20.0. 2016. SPSS Inc., Chicago, IL, USA). Group comparisons of fractal dimensions (FD) were performed using Student's independent  $t$ -test.

## RESULTS

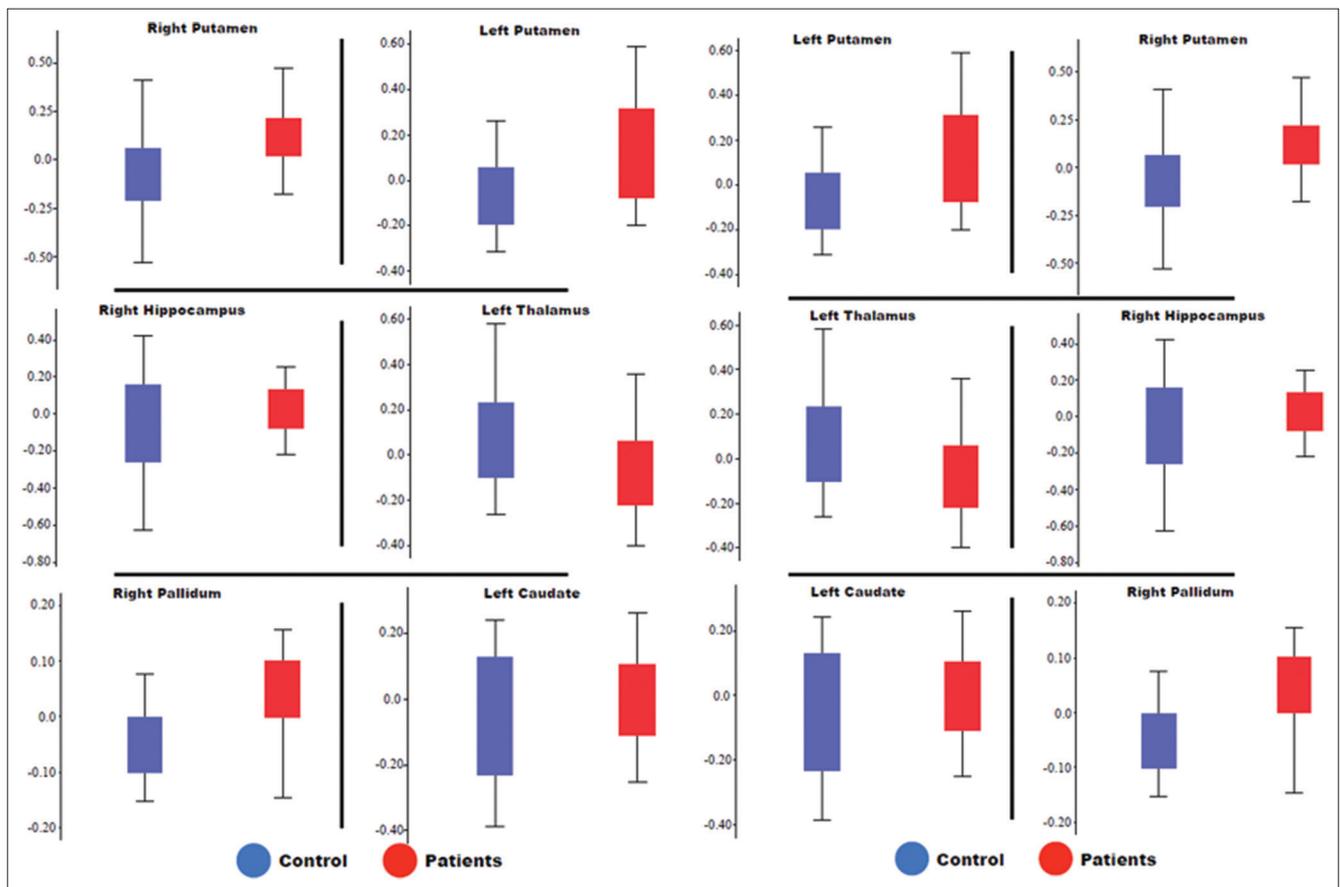
The sociodemographic profile of the sample is shown in Table 1.

### Volumetric analyses

Vertex analysis was performed to evaluate the shape and volume of 15 subcortical structures in SCZ patients and healthy control groups. Six subcortical regions showed significant localized shape differences, right hippocampus ( $P < 0.005$ ), left and right putamen ( $P < 0.044$  and  $P < 0.031$ ), left thalamus ( $P < 0.033$ ), left caudate ( $P < 0.029$ ), and right pallidum ( $P < 0.019$ ) [Figure 1]. These results revealed an outward movement of vertices in SCZ patients compared to healthy control participants on the medial-inferior part of the right hippocampus (subiculum), the superior-anterior portion of putamen (both hemispheres), the superior-lateral



**Figure 1:** Statistic maps of shape difference in different subcortical regions (the right hippocampus, left and right putamen, left thalamus, left caudate, and right pallidum) between schizophrenia and control. The red color on the three-dimensional mesh and the yellow circle on the sagittal, coronal, and transverse anatomical slices in standard Montreal Neurological Institute space demonstrate the region with shape significant difference between two groups.



**Figure 2:** Box-and-whisker plots showing fractal dimensions of different subcortical regions (the right hippocampus, left and right putamen, left thalamus, left caudate, and right pallidum) for both groups. Red boxes, schizophrenia patients; blue boxes, controls. Boxes enclose 50% of the data and the whiskers show the range.

portion of the left caudate, and the medial-anterior portion of the right pallidum suggesting a volume increase in these regions in SCZ. In contrast, the lateral-medial part of left thalamus showed an inward movement of vertices which express a volume decrease. Figure 2 shows the box-and-whisker plots for both groups' FD values. Significant differences were shown in all six subcortical regions ( $P < 0.05$ ).

## DISCUSSION

Shape analysis complements volumetric analysis and can identify subtle regional abnormalities on brain structures helping to localize specific pathophysiologic pathways. Our study showed differences in the volumes and shapes of multiple subcortical brain structures in SCZ as compared to healthy populations.

The result showed alterations for the right hippocampus is often seen in studies of SCZ patients.<sup>[5,7,8,16]</sup> Our results are consistent about the location of hippocampal shrinkage in the head or anterior region,<sup>[5,6,11,16]</sup> and the body or tail.<sup>[17]</sup> A smaller hippocampus has also been an initiate to be a risk pointer for psychiatry disorder and may indicate an improved vulnerability of the right hippocampus to environmental stress.<sup>[4,18]</sup>

Our results are consistent with some other studies about left and right putamen, left thalamus, left caudate and right pallidum.<sup>[6,11,12]</sup> An outward movement of vertices, medial-inferior part of the right hippocampus (subiculum), superior-anterior portion of putamen (both hemispheres), superior-lateral portion of the left caudate, and the medial-anterior portion of the right pallidum suggesting a volume increase in SCZ.<sup>[19]</sup>

## CONCLUSION

Our results demonstrate deform volumes and shapes of multiple subcortical brain regions in SCZ populations as compared to healthy controls.

These findings may be pertinent to the design and optimization of neurorehabilitation strategies for SCZ patients. However, the present study has several limitations that should be considered when interpreting the results. First, we compared the SCZ with healthy subject making it difficult to draw inference about volume and shape effect directly. Therefore, a longitudinal study would have undoubtedly benefited our predictions of clinical outcomes. The subject group was not homogeneous with respect to SCZ type.

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## Conflicts of interest

There are no conflicts of interest.

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