Shape Features as Biomarkers in Early Parkinson's Disease

R. Prashanth, *Student Member*, *IEEE*, S. Dutta Roy, *Member*, *IEEE*, S. Ghosh, and Pravat K. Mandal

***Abstract*— *In vivo* dopaminergic imaging through [123I]FP-CIT Single Photon Emission Computerized Tomography (SPECT) provide useful information which enhances the accuracy of diagnosis of PD. Such imaging techniques have given rise to new class of subjects termed scans without evidence of dopaminergic Deficit (SWEDD) subjects, who are clinically diagnosed as PD but show normal dopaminergic scans. Although it is now established that the appearance of striatal uptake patterns, as seen in the SPECT images, change in shape during PD as compared to Normal or SWEDD subjects, as per our knowledge, there have been no studies on the quantification of the shape of these uptake regions. We in our study, use the [123I]FP-CIT SPECT data from 20 Normal, 20 SWEDD and 20 Early PD subjects from the Parkinson's Progression Markers Initiative (PPMI) database to segment, followed by quantification of these regions. It is observed that the quantification parameters show good amount of variation in PD as compared to Normal or SWEDD subjects. Hence, it is inferred that these parameters may be useful biomarkers for the early diagnosis of PD.**

I. Introduction

Parkinson's disease (PD) is a progressive neuro-degenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to striatal dopamine depletion [1].

Currently, the diagnosis of PD is based on the presence of cardinal motor signs of tremor at rest, rigidity, bradykinesia and postural instability [1]. The clinical diagnosis is clear-cut in the advanced stages of the disease, however, in the early stages when incomplete syndromes or subtle signs are present, a proper diagnosis of individual patients may be difficult [2-5]. For instance, the Parkinson's Progression Markers Initiative (PPMI), which is the first large-scale study to explore and identify PD progression markers, points out that the early diagnosis of PD in *de novo* (newly diagnosed) subjects, like those being recruited for PPMI, is difficult as characteristic signs and symptoms have not yet fully emerged and patients may present atypical signs and symptoms (Study Protocol, http://www.ppmi-info.org/study-design/research-documents-and-sops/).

R. Prashanth is with the Department of Electrical Engineering, Indian Institute of Technology Delhi, New Delhi 110016, India (corresponding author, email: eez108051@ee.iitd.ac.in, Ph: +91-9891279885).

S. Dutta Roy is with the Department of Electrical Engineering, Indian Institute of Technology Delhi, New Delhi 110016, India (sumantra@ee.iitd.ac.in).

Pravat K. Mandal is with the Neurospectroscopy and Neuroimaging Laboratory, National Brain Research Centre, 122050, India and with the Department of Radiology, Johns Hopkins Medicine, Baltimore, Maryland, USA (pmandal4@jhmi.edu).

S. Ghosh is with the Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA (shantanu@nmr.mgh.harvard.edu).

Early and accurate diagnosis of PD is crucial for several reasons: early management, avoidance of unnecessary medical examinations and therapies and their associated financial costs, side-effects and safety risks [3]. Correct diagnosis is also critical for patients being recruited for clinical trials. Recent studies with [123I]FP-CIT (DaTSCAN™, GE Healthcare) Single Photon Emission Computerized Tomography (SPECT) imaging of the dopamine transporter (DAT) have shown that by depicting the presynaptic dopaminergic deficits in the striata (which is composed of caudate nucleus and putamen), it increases the diagnostic accuracy of PD, even in the early stages of PD [6], and hence, are becoming a valuable tool for the clinician [4, 7-10]. For instance, in several studies on early PD, about 10-15% of the newly diagnosed PD subjects had an *in vivo* dopaminergic scans (SPECT scans) in the normal range, termed as Scams Without Evidence of Dopaminergic Deficit (SWEDD) [11, 12]. Subsequent follow-up on these subjects have shown that they are unlikely of having PD [13-15].

The assessment of SPECT images can be carried out by visual inspection or by region of interest (ROI) analysis [8]. In visual inspection, the specialist (nuclear physician) classifies the images into normal and abnormal based on the appearance of uptake patterns, by assessing the extent (as indicated by shape) and intensity of the striatal signal. In the latter method, the uptake value in the striata is quantified using stereotactic atlas through manually defined ROIs. As per our knowledge, there have been no studies on quantification of the shape features in PD. Quantification of the shape features help better understand the changes in shape during diseased condition, thereby it may help in the diagnostic process. As per the GE report [16], normal scan (Fig. 1(a)) is one in which the striatal activity is bilateral and distinct, and is seen as two comma crescent-shaped focal regions of activity that are largely symmetric. In an abnormal scan (Fig. 1(e)), the striatal activity is reduced and can be asymmetric resulting in a comma or crescent shape in one and a circular or oval focus in the other (where activity may be reduced in at least one striatum); or it can be relatively symmetric forming two roughly circular or oval foci (where activity is reduced in both right and left striatum).

In this paper, we study the shape features by performing segmentation followed by quantification of the regions of activity in Normal, SWEDD and Early PD using the [123I]FP-CIT SPECT images obtained from the PPMI database.

II. MATERIALS

A. Database

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. The PPMI [17], which mainly recruits early-untreated PD subjects and age-matched controls, is a comprehensive, observational, international, multi-center study to identify PD progression biomarkers. For our study, we use the [123I]FP-CIT SPECT image data from 20 early PD subjects (Hoehn and Yahr (HY) stage I and II [18] with mean HY of 1.8), 20 healthy controls and 20 SWEDD subjects (Hoehn and Yahr (HY) stage I and II with mean HY of 1.55) from the PPMI database.

B. Shape Analysis in early PD, SWEDD and Normal

The PPMI Central SPECT Core Lab, which performed the reconstruction of the image from raw projection data, including attenuation correction based on phantoms acquired on the day the subject was imaged, also performed the spatial normalization of images to create consistent orientation (2012 PPMI Annual Meeting, http://www.ppmi-info.org/wp-content/uploads/2013/03/2012-PPMI-Annual-Meeting-Presentations.pdf). Among the 91 slices in each 3D image, the 42nd slice was chosen as it clearly showed the high activity region corresponding to the striata making it suitable for further analysis. The shape analysis is carried in 3 steps as explained below.

1) Preprocessing

Preprocessing of the images was necessary to make a consistent intensity range for each input image in order to establish comparisons between subjects. This was carried out by image normalization in which each image is converted in the range [0,1].

$$I_{new} = \frac{I - I_{min}}{I_{max} - I_{min}} \quad (1)$$

where I_{new} is the normalized intensity, I is the input value of intensity, I_{min} is the minimum intensity, I_{max} is the maximum intensity.

2) Binarization and image segmentation

Followed by preprocessing, image segmentation was carried out, to extract the high intensity regions in both the right and left striatum, through image binarization. A threshold was selected such that it best segmented the high intensity region. Based on our experiments, a threshold value in the range of 0.6 to 0.75 worked for all the images.

3) Quantification

The segmented regions were quantified using the parameters as shown in Table I. Each parameter is computed for both the regions of activity segmented corresponding to the right and left striatum (on the right side and left side corresponding to both the hemispheres) and the average is taken for each subject.

TABLE I. QUANTIFICATION PARAMETERS AND DESCRIPTION

Parameter	Description and Computation
Area	The number of pixels in the region.
Roundness	A measure of circularity. It is 1 for circle and < 1 for any other shape. It is computed as $4 * pi * Area/Periemter$
Major Axis Length	The length (in pixels) of the major axis of the ellipse that has the same normalized second central moments as the region.
Minor Axis Length	The length (in pixels) of the minor axis of the ellipse as mentioned above.
Aspect Ratio	Ratio of lengths of the major axis to the minor axis. An aspect ratio of 1 indicate circle.
Orientation[#]	The angle (in degrees ranging from -90 to 90 degrees) between the x-axis and the major axis of the ellipse that has the same second-moments as the region.
Equivalent Diameter	The diameter of a circle with the same area as the region which is computed as $\sqrt{4 * \text{Area/pi}}$
Eccentricity	The eccentricity of the ellipse that has the same second-moments as the region. The eccentricity is the ratio of the distance between the foci of the ellipse and its major axis length. A value of 0 indicates a circle.

[#]As the segmented regions on the right side and left side had almost opposite orientation, we took the negative of the orientation corresponding to the right side region and then computed the average orientation as (Orientation of the left side region - Orientation of the right side region)/2.

III. RESULTS AND DISCUSSION

Fig. 1 depicts the results of the image analysis carried out in the study. Fig. 1(a) shows a normal image and Fig. 1(b) the corresponding binary image obtained after image segmentation which clearly shows the two near symmetric comma shaped region corresponding to the left and right striatum. Similarly, Fig. 1(c) shows the SPECT image from a SWEDD subject and Fig. 1(d) the corresponding binary image after segmenting the regions of activity in both the right and left striatum. Almost similar comma shaped region is seen for SWEDD subjects as depicted in Fig.1 (c and d) which shows that there is no dopaminergic deficit for these subjects. Fig. 1(e) shows the image from an early PD patient, and Fig. 1(f) shows the corresponding binary image which clearly shows the reduction in the dopamine transporter density in PD. It shows that the activity in both the striatum has reduced leading to a circular or oval like appearance.

The segmented regions were quantified and the values of the quantification parameters in terms of mean ± standard deviation is shown in Table II. It is observed that all parameters showed good amount of variation in PD as compared to Normal, but none showed much deviation in SWEDD as compared to Normal. These variations are evident from the box plot of each parameter and is shown in Fig. 2. Following are the important observations from the Fig.1, Fig. 2 and Table II.

- The area of the regions of activity is reduced in PD, but remained almost similar for SWEDD as compared to Normal.
- The major axis length, minor axis length, aspect ratio and equivalent diameter is reduced in PD, but is almost unchanged for SWEDD as compared to Normal.

- The orientation is greatly reduced in PD, and is almost similar for SWEDD as compared to Normal.
- The roundness and aspect ratio becomes close to 1, and eccentricity becomes close to 0 indicating that the shape becomes more circular/oval-shaped in PD.

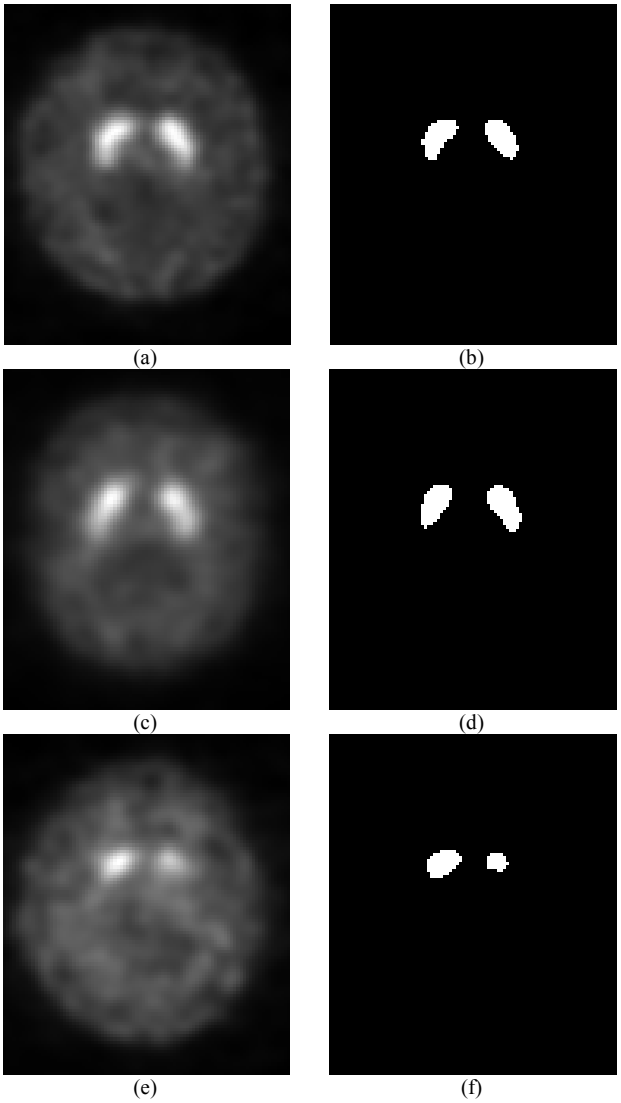

Figure 1. Input images and the binarized image for (a and b) Normal subject (c and d) SWEDD subject (d and e) Early PD subject. The shape change of the high intensity region corresponding to striatum, in PD, is clearly visible in the the images.

TABLE II. QUANTIFICATION PARAMETER VALUES

Parameter	SWEDD	Normal	Early PD
Area	87.23 ± 10.25	84.05 ± 4.34	54.60 ± 10.34
Roundness	0.83 ± 0.06	0.86 ± 0.07	1.02 ± 0.10
Major Axis Length	15.17 ±1.13	14.60 ± 0.80	10.13 ± 1.46
Minor Axis Length	7.74 ± 0.63	7.69 ± 0.60	6.96 ± 0.63
Aspect Ratio	1.97 ± 0.18	1.92 ± 0.24	1.45 ± 0.19
Orientation	51.33 ± 4.79	50.11 ± 4.79	18.15 ± 20.49
Equivalent Diameter	10.51 ± 0.65	10.34 ± 0.27	8.21 ± 0.82
Eccentricity	0.85 ± 0.03	0.84 ± 0.05	0.69 ± 0.10

Values expressed as mean ± standard deviation

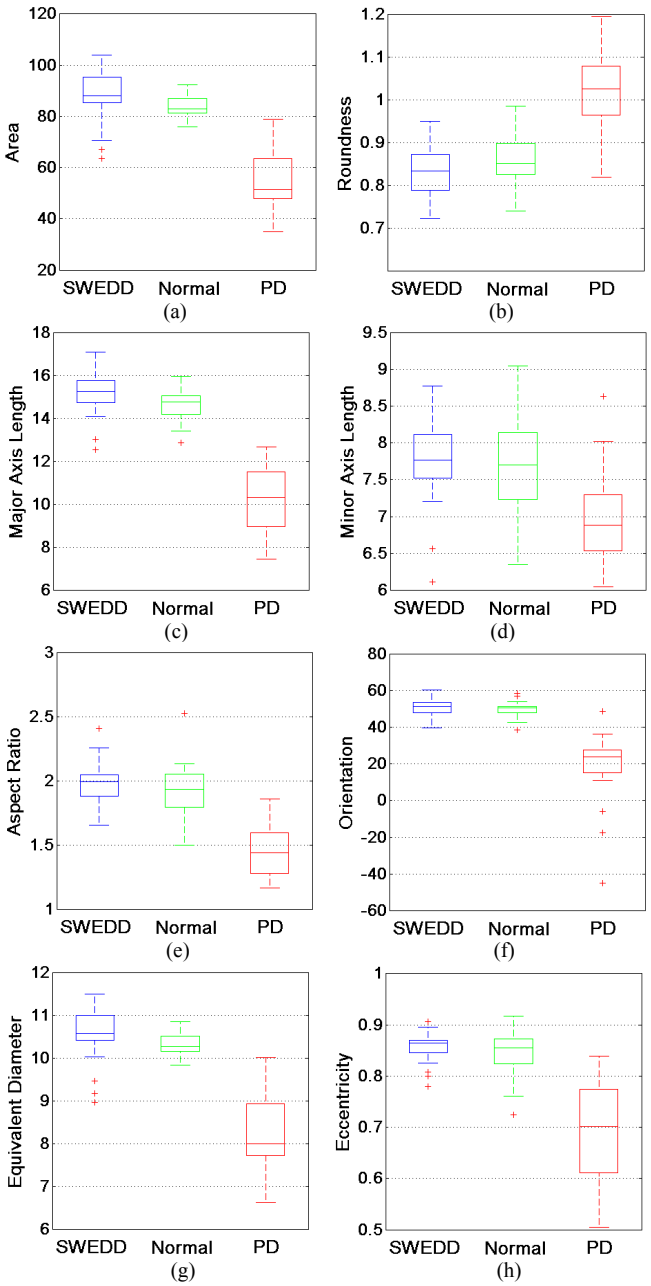

Figure 2. Box plot[1] of the quantification parameters (a) Area (b) Roundness (c) Major Axis Length (d) Minor Axis Length (e) Aspect Ratio (f) Orientation (g) Equivalent Diameter (h) Eccentricity. These box plots indicate that all the parameters show good varaition during PD, almost no variation for SWEDD subjects as compared to Normal subjects.

IV. CONCLUSION

[123I]FP-CIT SPECT imaging have shown to increase the accuracy of PD diagnosis even in the early stages of the disease. Early diagnosis of PD is crucial for early management and effective neuroprotection. The shape of the regions of activity, as observed in the SPECT scan, changes

[1] On each box plot, the central mark is the median (q_2), the edges of the box are the 25th (q_1) and 75th (q_3) percentiles, the whiskers extend to the most extreme data points not considered outliers, and outliers are plotted individually. Points are drawn as outliers if they are larger than $q3 + 1.5*(q3 - q1)$ or smaller than $q1 - 1.5*(q3 - q1)$.

and becomes more like a circular/oval-shaped region/regions during PD. In this paper, we performed segmentation followed by quantification of these regions of activity and studied the shape features corresponding to these regions in Normal, SWEDD and Early PD. As per our knowledge, this is the first time that such a quantification based study of shape features is carried out. It is observed that there is a good amount of variation in the shape features in PD as compared to Normal or SWEDD. It is concluded that such shape features may act as biomarkers and aid in the early diagnosis of PD.

ACKNOWLEDGMENT

PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and funding partners, including [list the full names of all of the PPMI funding partners found at www.ppmi-info.org/fundingpartners].

REFERENCES

[1] S. Fahn, "Description of Parkinson's disease as a clinical syndrome," *Ann N Y Acad Sci,* vol. 991, pp. 1-14, 2003.

[2] J. Booij, and R. J. Knol, "SPECT imaging of the dopaminergic system in (premotor) Parkinson's disease," *Parkinsonism & Related Disorders,* vol. 13 Suppl 3, pp. S425-8, 2007.

[3] J. L. Cummings, C. Henchcliffe, S. Schaier *et al.*, "The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration," *Brain,* vol. 134, no. Pt 11, pp. 3146-66, Nov, 2011.

[4] E. Tolosa, T. V. Borght, E. Moreno *et al.*, "Accuracy of DaTSCAN (123I-Ioflupane) SPECT in diagnosis of patients with clinically uncertain parkinsonism: 2-year follow-up of an open-label study," *Movement Disorders,* vol. 22, no. 16, pp. 2346-51, Dec, 2007.

[5] F. Sixel-Doring, K. Liepe, B. Mollenhauer *et al.*, "The role of 123I-FP-CIT-SPECT in the differential diagnosis of Parkinson and tremor syndromes: a critical assessment of 125 cases," *Journal of Neurology,* vol. 258, no. 12, pp. 2147-54, Dec, 2011.

[6] A. Winogrodzka, P. Bergmans, J. Booij *et al.*, "[123I]FP-CIT SPECT is a useful method to monitor the rate of dopaminergic degeneration in early-stage Parkinson's disease," *Journal of Neural Transmission,* vol. 108, no. 8-9, pp. 1011-9, 2001.

[7] C. Bairactaris, N. Demakopoulos, G. Tripsianis *et al.*, "Impact of dopamine transporter single photon emission computed tomography imaging using I-123 ioflupane on diagnoses of patients with parkinsonian syndromes," *Journal of Clinical Neuroscience,* vol. 16, no. 2, pp. 246-52, Feb, 2009.

[8] T. S. Benamer, J. Patterson, D. G. Grosset *et al.*, "Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group," *Movement Disorders,* vol. 15, no. 3, pp. 503-10, May, 2000.

[9] J. Booij, G. Tissingh, G. J. Boer *et al.*, "[123I]FP-CIT SPECT shows a pronounced decline of striatal dopamine transporter labelling in early and advanced Parkinson's disease," *Journal of Neurology, Neurosurgery & Psychiatry,* vol. 62, no. 2, pp. 133-40, Feb, 1997.

[10] K. D. Seifert, and J. I. Wiener, "The impact of DaTscan on the diagnosis and management of movement disorders: A retrospective study," *Am J Neurodegener Dis,* vol. 2, no. 1, pp. 29-34, 2013.

[11] S. Fahn, D. Oakes, I. Shoulson *et al.*, "Levodopa and the progression of Parkinson's disease," *N Engl J Med,* vol. 351, no. 24, pp. 2498-508, Dec 9, 2004.

[12] J. Seibyl, D. Jennings, R. Tabamo *et al.*, "The role of neuroimaging in the early diagnosis and evaluation of Parkinson's disease," *Minerva Med,* vol. 96, no. 5, pp. 353-64, Oct, 2005.

[13] K. Marek, D. Jennings, and J. Seibyl, "Long-term follow-up of patients with scans without evidence of dopaminergic deficit (SWEDD) in the ELLDOPA study," *Neurology,* vol. 64 (Suppl. 1), pp. A274, 2005.

[14] S. A. Schneider, M. J. Edwards, P. Mir *et al.*, "Patients with adult-onset dystonic tremor resembling parkinsonian tremor have scans without evidence of dopaminergic deficit (SWEDDs)," *Mov Disord,* vol. 22, no. 15, pp. 2210-5, Nov 15, 2007.

[15] P. Schwingenschuh, D. Ruge, M. J. Edwards *et al.*, "Distinguishing SWEDDs patients with asymmetric resting tremor from Parkinson's disease: a clinical and electrophysiological study," *Mov Disord,* vol. 25, no. 5, pp. 560-9, Apr 15, 2010.

[16] "DaTscan (Ioflupane I 123 injection) Prescribing Information," G. Healthcare, ed., 2011.

[17] K. Marek, D. Jennings, S. Lasch *et al.*, "The Parkinson Progression Marker Initiative (PPMI)," *Progress in Neurobiology,* vol. 95, no. 4, pp. 629-635, 2011.

[18] G. Bassotti, D. Maggio, E. Battaglia *et al.*, "Manometric investigation of anorectal function in early and late stage Parkinson's disease," *Journal of Neurology, Neurosurgery & Psychiatry,* vol. 68, no. 6, pp. 768-70, Jun, 2000.