Application of Pattern Recognition Framework for Quantification of Parkinson’s Disease in DAT SPECT Imaging

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Abstract—Dopamine transporter (DAT) SPECT imaging is increasingly utilized for diagnostic purposes in suspected parkinsonian syndromes. Visual classification or quantitative analysis of mean regional uptake has been performed in the past. Our objective is to enable further enhanced clinical utility in the diagnosis as well as tracking of progression in Parkinson’s disease via quantification based on pattern recognition. We developed and implemented two such frameworks: first, we utilized shape/texture metrics that did require registration to a common structure/template; e.g. 3D moment-invariants, Haralick texture features, and multiple others. We also used a surface registration algorithm, which falls under the broad class of Large Deformation Diffeomorphic Metric Mapping (LDDMM). In this latter framework, we obtain a common coordinate system, we then used Principal Component Analysis (PCA) on intensities to obtain sub-regions of voxels inside the structure of interest) with highest variance in SPECT intensities across subjects. We show that the healthy and diseased populations can be subsequently distinguished. Via these methods, we also aimed to assess correlations with different clinical measures (e.g. UPDRS score, disease duration). In addition to enabling enhanced diagnostic task performance, these methods have considerable potential as biomarkers of PD progression.

I. INTRODUCTION

Imaging of the dopaminergic system with SPECT has become widespread in Europe and has entered a new active phase in the US since 123I-iофлупане-dopamine transporter (DAT) SPECT was approved by the FDA in 2011. Visual interpretation is the common assessment approach [1-3]. However, more objective assessment can be performed using quantitative analysis [4] involving manual or automated ROI drawing and analysis [5, 6]. Our proposed approach is based on the observation that SPECT and PET images convey important information at the voxel level, whereas commonly used ROI-averaging vastly oversimplifies the available spatial uptake information. We propose to explore a novel quantification paradigm applied to SPECT neurochemical imaging that utilizes pattern recognition to quantify uptake alterations with disease, expected to detect subtle regional DAT losses: this is especially important as DAT binding can be a marker of PD at the presymptomatic stage [7, 8] and the proposed approach can enhance abilities to discriminate among different populations. Furthermore, we seek to move beyond classification tasks in clinical DAT SPECT imaging [9], to also arrive at enhanced markers of progression. This is a significant step, and is for instance consistent with the aims of the Parkinson’s Progressive Marker Initiative (PPMI) to identity biomarkers of PD progression, a critical step in the development of novel and enhanced treatments for PD [10].

We have in the past pursued pattern recognition techniques, including shape and texture analysis in the context of quantitative brain PET imaging, in studies of PD [11-13] and neuroinflammation [14]. These techniques have the advantage of not requiring normalization/registration of all regions of interest (ROIs) to a common structure. In the present work, we turn our attention to DAT SPECT imaging, given its increasingly popular clinical usage. Furthermore, we have evidence that application of shape and texture metrics can appropriately extend from the higher resolution spectrum of PET imaging to the domain of SPECT imaging [15].

In parallel, we have also utilized a distinct and powerful normalization framework, enabling generation of a population-based template of ROIs, to which individual subject ROIs are mapped, enabling application of other pattern recognition tools, such as principal component analysis (PCA), and generation of sub-structure maps of correlation with clinical manifestations. To do the latter, we investigated the use of surface matching based on Large Deformation Diffeomorphic Metric Mapping (LDDMM) [16], as a method for obtaining a common coordinate system to compare SPECT intensities across subjects. Nonlinear mapping of intensities, commonly known as normalization, is performed in popular neuroimaging analysis packages such as SPM by mapping MRI images to predetermined atlases. Compared to more typical normalization methods, our approach is based on surface matching, as opposed to image matching, which is more robust under noise, since it is not affected by noise once we obtain an...
appropriate segmentation. Furthermore, our method has the advantage of estimating population-based templates for each structure individually rather than using a predetermined collective atlas for all regions, as is customary. We used our LDDMM framework, described in Section II, to first obtain a population-based template from the caudate and putamen segmented from MRI scans, and then obtain non-linear maps between each subject and the template. These mappings are then used to map the SPECT intensities in caudate and putamen to the common coordinate system of the template. We then perform PCA of the intensities in the common coordinate system to obtain low dimensional features, which correspond to regions in the caudate and putamen in which the intensities vary the most across subjects.

For consistency, subjects were selected from the PPMI database such that SPECT data were acquired on the same kind of scanner, while having high-resolution 3T MRI images, and age was limited to <70 to minimize further age-related confounds. With this criteria, we analyzed 128 subjects, 48 of which were healthy controls (HCs) while 80 were diagnosed with Parkinson’s Disease (PD). We show in Section V that for this particular population, the uptake in putamen is enough to classify HC from PD using a simple linear classifier in the low dimensional space of principal components. However, what is of greatest interest to us in the present work is the ability to quantify progression and not merely enable classification, as we discuss later in this work.

II. LDDMM FRAMEWORK

In the LDDMM framework, a non-linear map \( \phi \) between two surfaces, say \( S \) and \( T \), is obtained by integrating a time varying vector field \( v_t \) on the underlying Euclidean space \( \mathbb{R}^3 \), so that it is a solution of the differential equation
\[
\frac{d\phi}{dt}(x,t) = v_t \circ \phi(x,t),
\]
with the initial condition \( \phi(x,0) = x \) for all \( x \). The solution to this equation for a given vector field \( v \), is denoted by \( \phi^v \). The optimal mapping is obtained by minimizing the cost functional
\[
\int_0^1 |v|_V dt + |\phi^v(S,1) - T|_W,
\]
where the first term penalizes the size of the vector field in an appropriate norm, which in turn, controls the smoothness of \( \phi \), and the second term penalizes the mismatch between the mapped surface \( \phi^v(S,1) \) and the target surface \( T \). The details of this algorithm can be found in [16].

The template is generated via a Bayesian generative model described in [17], by mapping a hyper-template to a template using a deformation parameterized with a random vector field, as above, and maximizing the joint likelihood of the observed target surfaces, which are considered to be noisy versions of the deformed template.

III. TEXTURE AND SHAPE ANALYSIS METHODS

In parallel to utilization of a normalization (LDDMM) framework, we pursued other pattern recognition tools that do not require normalization. We have elaborated upon these in past application to PET imaging [14], and briefly outline here:

(a) 3D moment invariants (3D-MIs): spatial descriptors designed to be invariant to scaling, translation and rotation, with extensive use in areas such as pattern recognition, and as we have utilized in brain imaging. These metrics included 2\(^\text{nd}\) order J1, J2 and J3 as well as 3\(^\text{rd}\) order B3 and B4 metrics.

(b) Intensity histogram analysis: e.g. standard deviation, skewness and kurtosis. We also performed cumulative histogram analysis leading to the intensity-volume histogram [18].

(c) Neighborhood gray tone difference (NGTD) analysis: which enables quantification of local variations in uptake. Five textural metrics, corresponding to visual properties of texture [19], were computed: (1) energy, (2) entropy, (3) correlation, (4) contrast (also known as inertia [22, 23]), (5) variance, (6) sum mean, (7) agreement [24] (also known as Cohen’s [25] a-statistic), (8) cluster shade, (9) cluster tendency (or prominence), (10) homogeneity, (11) max probability, and (12) inverse variance.

The latter approach (Haralick texture features; d) were utilized in a recent study [9] for automatic detection of PD. We supplement this with other methods, as outlined above (a, b, c), and furthermore move beyond classification tasks, to identify features that best capture progression.

IV. MRI-DRIVEN SEGMENTATION AND MAPPING

Both abovementioned overall frameworks (Sec. II and III) utilized the following MRI-bases analyses:

1. Segment the high-resolution MRI images to obtain the boundaries of the caudate and putamen (both left and right), utilizing a multi-atlas segmentation method [26].

2. Resample the SPECT image on the MRI grid performing rigid mapping, using the FSL utility FLIRT [27].

Figure 1 shows the output of a typical segmentation and resampling of SPECT onto the MRI grid.

Following these steps, texture/shape analysis methods of Sec. III were applied. For the normalization framework (Sec. II), the following steps were also needed:

3. Use the LDDMM method to obtain templates, one for each of the caudate and putamen, and find the optimal mappings from the template to each subjects.

4. Map the SPECT intensities for each subject to the template coordinates using the mapping from 3.

Following this, we performed PCA on the mapped SPECT intensities to obtain the regions with maximum...
variation of the signal across subjects. PCA can be replaced by more sophisticated non-linear dimensionality reduction techniques such as manifold learning. This is a direction we intend to explore in the future.

Figure 1: Same slice of the MRI (left) and SPECT image (right) with the cross-sections of the segmented caudate and putamen surfaces shown by curves.

V. RESULTS

We first demonstrate results for classification of HC vs. PD in Sec. V-A. However, the major goal pursued in the present research effort is to provide methodology to track progression of disease, as pursued in Sec. V-B.

A. Classification

LDDMM normalization framework (Sec. II): Figure 2 shows the two-dimensional spaces obtained from PCA, which best distinguish the diseased from the healthy patients. In the case of the putamen, the first two principal components best separated PDs from HCs. The separation was not successful utilizing the caudate, consistent with routine observations.

We note that in this analysis, we used the more affected side, i.e. with lower uptake, for each subject. This is consistent with the asymmetry of uptake loss in the putamen, and formation of a gradient especially along the putamen. In fact, an approach in past work has been to subdivide the putamen into 2 or 3 sub-regions (anterior, intermediate and posterior). In any case, our technique moves beyond this conventional approach by seeking PCA images that explain the variability between subject populations (Figure 3).

Figure 2: A scatter plot of the putamen in the 2D space of principal components (PC1 and PC3) showing HC (x) and PD (o).

Figure 3: (Left vs. Right) PCA loadings corresponding to the two principal components (PC1 and PC3) plotted in Figure 2 for the putamen. Darker regions show higher loadings in absolute value, and therefore signify regions that correspond to the variance explained by the corresponding principal component.

Shape/texture analysis (Sec. III): An example application of two histogram-based metrics, namely skewness and kurtosis, also showed separation between HC and PD, as seen in Fig. 4.

Figure 4: A scatter plot of two histogram-based features for the putamen (skewness and kurtosis) for PD vs. HC.

B. Progression

It is likely that while utilizing the more affected side (of putman) is preferred for classification/diagnosis, that using the less affected side may be the choice for enhanced tracking of progression. This is because following initial asymmetry in uptake, the less affected side can more severely progress over the years, and as such can provide a higher dynamic range (e.g. as we can seen in Fig. 2-4 of [28]). In the present work, however, we did not detect a significant difference in performance when utilizing more affected side vs. less affected side (thus results are only shown for one case).

In our studies, we correlated image-based metrics against 7 different clinical measures:

1) The unified Parkinson's disease rating scale (UPDRS)
2) Gait
3) Tremor
4) Bradykinesia
5) Rigidity
6) Disease duration (DD) – from diagnosis
7) DD – from symptoms
Items (2-5) are motor sub-scores within the UPDRS motor score.

We found that 16, of the various metrics considered, depicted more substantial correlations against clinical scores than other metrics did, thus we limit our summary to these in what follows. The 16 metrics are as follows:

1) Conventional mean (normalized to mean reference uptake in the occipital cortex).
2) 3D-MIs: B3.
3,4,5) Histogram-based: standard deviation; skewness; Kurtosis.
6,7,8) NGTD: Coarseness; Busyness; Strength.
9,10,11,12) GLSD (haralick): Energy; Homogeneity; Cluster-Shade; Agreement.
13,14,15,16) PCA analysis: First four PC components.

Fig. 5 depicts, for n=128 subjects, the performance of each of the 16 abovementioned metrics in relation to the UPDRS score. On top of each plot three correlation indices are reported: i) Pearson (p), ii) Kendall (k), and Spearman (s). The first one assumes linear correlation, while the latter two are non-parametric.

It is seen that conventional mean uptake (normalized to reference region) results in high correlation (e.g. p=-0.65), and the two non-conventional metrics comparable to it are skewness (p=0.52) and Cluster-Shade (p=0.59).

Fig. 6 depicts a summary of correlation values (p) for a figure such as Fig. 5, in the case of all seven clinical measures. It is seen that along with conventional mean uptake metric (#1), other texture/shape metrics also show considerable correlations, including metrics #4 and #12, namely skewness and Cluster-Shade.

Fig. 7 is very similar to Fig. 5, except that PD-only subjects (n=80) are only considered. It is seen that the correlations with UPDRS score are substantially dampened. This means that HC vs. PD discrimination plays a considerable role in introducing correlations, and sheds light on the fact that prognosis of PD-only subjects is a difficult task. Similar plots as Fig. 7 for PD-only subjects are shown in Fig. 8, this time correlating imaging to DD (from symptoms), instead of UPDRS. Finally, Fig. 9 summarizes correlation values (p) in the PD-only case for all seven clinical measures.

It is seen that some metrics may outperform conventional mean uptake metric when applied to PD-only subjects in terms of correlation with clinical measures. In any case, the correlations are seen to be weak in this case. We believe this may be enhanced (as we pursue in ongoing work) by performing more effective SPECT to MRI mappings. This is a challenging problem, given the blurred nature of SPECT and the concentrated nature of uptake in DAT imaging.

Another logical step is to consider multi-metric analysis. We performed preliminary analysis in this context, using the multiple correlation coefficient R, in the case of conventional mean vs. feature-of-interest (e.g. cluster-shade) vs. their joint combination. Here are some results:

PD+HC subjects - DD (symptoms): Conventional - 0.65; Cluster-Shade - 0.59; Combined: 0.70.
PD only - DD (diagnosis): Conventional - 0.04; Strength - 0.29; Combined - 0.32.
PD only - DD (symptoms): Conventional - 0.13; Strength - 0.09; Combined - 0.25.
PD only - UPDRS: Conventional - 0.05; Strength - 0.23; Combined - 0.27.

Thus, it is seen that use of multi-metric analysis, incorporating conventional mean uptake in addition to novel shape/texture analysis can enhance the ability to track disease via imaging.
Figure 5: Plots of metric values vs. UPDRS score, for 16 different metrics as described in the text. The first 12 are shape/texture metrics applied to the original patient-space, while the last 4 are PCA components as generated in the normalized/template space. HC+PD subjects were considered.

Figure 6: Plots of correlation (y-axis) vs. metric of interest (16 different metrics on the x-axis) for each of the 7 clinical measures as mentioned in the text. HC+PD subjects were considered.
Figure 7: Plots of metric values vs. UPDRS score, for 16 different metrics as described in the text. Here, PD-only subjects were considered.

Figure 8: Plots of metric values vs. DD (from symptoms), for 16 different metrics as described in the text. Here, PD-only subjects were considered.
VI. MORE DISCUSSION AND CONCLUSION

We also note that the normalization framework enables the performance of an additional kind of analysis. This work is in progress, but we show a sample analysis: since all structures are registered to a common template, it is now possible to ask which voxels correlate most with a given clinical score. An example of this is shown in Fig. 10 for the particular case of bradykinesia (motor subscore within the UPDRS). This approach can be performed for different clinical scores, and also for the caudate, in addition to the putamen, and has the potential to open-up new understandings about sub-regional involvements with clinical manifestations in PD.

Overall, the presented approach of utilizing novel pattern recognition as applied to imaging of PD could have important clinical implications. Potentially enhanced sensitivity to subtle neuroanatomical changes is expected to provide novel insights into the relationship between dopaminergic alterations and PD manifestations, while extending the clinical usefulness of this imaging technique. This approach can also be applied to images from subjects at increased risk of PD (e.g. mutation carriers or subjects with rapid-eye-movement sleep behavior disorder) in an attempt to discern dopaminergic patterns that might be involved in pathogenesis and to assess the impact of novel disease modifying therapies.

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