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# Diabetes, gray matter loss and cognition in the setting of Parkinson Disease

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## Abstract

**Background and Purpose—**Parkinson disease (PD) is a progressive neurodegenerative disorder affecting motor and cognitive functions. Prior studies showed that PD patients with diabetes (DM) demonstrate worse clinical outcomes compared to non-diabetic PD subjects. Our study aimed at defining the relationship between DM, gray matter volume and cognition in PD patients.

**Materials and Methods—**36 PD subjects (12 with DM, 24 without DM, mean age=66). Subjects underwent high resolution T1 weighted brain MR imaging, 11C-DTBZ PET imaging to quantify nigrostriatal dopaminergic denervation, clinical and cognitive assessments. MR images were post-processed to determine total and lobar cortical gray matter volumes. Cognitive testing scores were converted to z-scores for specific cognitive domains and a composite global cognitive z-score based on normative data computed. ANCOVA, accounting for effects of age, gender, intracranial volume (ICV) and striatal DTBZ binding was used to test the relationship between DM and gray matter volumes.

**Results—**Impact of diabetes on total gray matter volume was significant (p=0.02). Post hoc analyses of lobar cortical gray matter volumes revealed that DM was more selectively associated with lower gray matter volumes in the frontal regions (p=0.01). Cognitive post hoc analyses showed that interaction of total gray matter volume and DM status was significantly associated

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with composite (p=0.007), executive (p=0.02) and visuospatial domain cognitive z-scores (p=0.005). These associations were also significant for the frontal cortical gray matter.

**Conclusions—**DM may exacerbate brain atrophy and cognitive functions in PD with greater vulnerability in the frontal lobes.

## INTRODUCTION

Numerous epidemiologic studies show increased risk of dementia in diabetic subjects compared to non-diabetic individuals. A recent meta-analysis of 16 prior studies (5706 people with diabetes and 36191 without diabetes) estimated a relative risk of 1.5 for clinically defined Alzheimer disease and 2.5 for vascular dementia in diabetic persons compared to non-diabetic individuals[1]. Furthermore, a recent prospective study showed that elevated blood glucose in the absence of diabetes (DM) increases dementia risk[2].

In patients with Parkinson Disease (PD), associations between DM and more severe motor symptoms and increased levodopa requirements are described[3]. More specifically, DM in the setting of PD is associated with more severe postural instability and gait difficulty (PIGD) features of PD [4]. The effects of DM on cognition in the setting of PD are less well described, despite a well-established association between PIGD motor phenotype and cognitive impairment in PD[5, 6]. A recent historical cohort study showed more pronounced postural impairment as well as greater incidence of cognitive impairment in diabetic PD patients within a three-year follow up period compared to non-diabetic PD subjects[7]. We recently reported that the presence of greater cognitive deficits, especially with executive and attentional functions, in PD patients with DM was independent of the degree of disease-specific neurodegeneration, suggesting an independent mechanism of DM-related brain injury in PD[8]. Volumetric MR imaging studies may be particularly useful in non-invasive delineation of extra-nigral disease pathophysiology in PD patients with DM. A number of studies showed cortical atrophy in the setting of DM in the elderly[9–12]. To our knowledge, there are no published imaging studies delineating the effects of DM on gray matter and assessing the relationship between gray matter imaging metrics and cognitive measures in the setting of PD. The aim of our study was to define the role of DM on total and regional gray matter volumes and to assess the relationship between these imaging measures and cognitive parameters in patients with PD. We hypothesized that PD patients with co-morbid DM would exhibit greater gray matter loss with more pronounced deficits in executive and attentional functions.

## MATERIALS AND METHODS

### Subjects and clinical test battery

This cross-sectional study included 36 PD subjects, 12 of which had DM and 24 of which had no history of DM. Groups were matched at a 2:1 ratio based on age and sex. Diabetes status was defined by self-report during a standardized interview. The group comprised of 32 men and 4 women, with a mean age of 66 years. Clinical characteristics of the subjects in each group are shown in Table 1.

All subjects met the UK Parkinson's Disease Society Brain Bank Research Center clinical diagnostic criteria for PD[13]. Striatal [$^{11}$C]dihydrotetrabenazine (DTBZ) PET denervation findings were consistent with the diagnosis of PD in all subjects. No subjects had evidence of prior large arterial stroke on MRI.

## Cognitive Assessment

Subjects were examined while taking their usual dopaminergic medications to minimize bias in cognitive assessment by motor deficits. The Montreal Cognitive Assessment (MOCA; [14]) was used as a measure of global cognitive integrity. Details on the neuropsychological test battery testing in this population have been reported previously[8]. Composite z scores were calculated for different cognitive domains (memory, executive, attention, and visuospatial functions) based on normative data. Global cognitive performance was calculated as the average z-score for the 4 cognitive domains.

## Imaging Techniques

**DTBZ PET Imaging—**No carrier–added (+)-[$^{11}$C]-DTBZ (250 –1,000 Ci/mmol at the time of injection) was prepared as reported previously[15]. Dynamic PET scanning was performed for 60 minutes immediately after a bolus injection of 55% of 555 MBq (15 mCi) of (+)-[11C]DTBZ dose (containing less than 50 μg of cold DTBZ mass) over the first 15–30 seconds of the study, whereas the remaining 45% of the dose was continuously infused over the next 60 minutes.28 A series of 15 frame sequence of scans over 60 minutes was obtained as follows: 4 × 30 seconds, 3 × 1 minute, 2 × 2.5 minutes, 2 × 5 minutes, and 4 x10 minutes.

**PET Imaging Analysis—**All dynamic PET imaging frames were spatially coregistered in subjects with a rigid body transformation to reduce the effects of subject motion during the imaging session. These motion-corrected PET frames were spatially coregistered to the MRI scan using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK). IDL image analysis software (Research Systems, Inc., Boulder, CO) was used to manually trace volumes of interest (VOIs) on the MRI scan.

Traced VOIs included the striatum (caudate and putamen). Cortical VOI definition used semiautomated thresholding delineation of the cortical gray matter signal on the MRI scans. General cortical area was determined by VOI placement and then was thresholded (based on signal intensity) to filter out any white matter. The entire neocortex was included in the VOI. Time-activity curves for each VOI were generated from the spatially aligned PET frames. DTBZ distribution volume ratio (DVR) was then estimated by using the Logan plot graphical analysis method with the global neocortex as reference tissue[16].

## MR Imaging

All subjects underwent brain magnetic resonance imaging on a 3 Tesla Achieva system (Philips, Best, The Netherlands) utilizing a 15 channel head coil. A standard T1 weighted series of a 3D inversion recovery prepared turbo-field echo was performed in the sagittal plane using TR/TE/TI=9.8/4.6/1041 ms; turbo factor=200; single average; FOV=240 × 200

× 160 mm; acquired Matrix =240 × 200. One hundred and sixty slices were reconstructed to 1 mm isotropic resolution.

### MR Imaging Analysis

MR data were segmented using multi-atlas consensus labeling method based on the DRAMMS deformable registration algorithm[17].

### Standard protocol approvals, registrations and patient consents

The study was reviewed and approved by our Institutional Review Board. Written informed consent was obtained from all subjects.

### Statistical Analysis

Our primary analysis used ANCOVA to test the effect of DM on total gray matter volume accounting for effects of age, sex, intracranial volume (ICV) and striatal DTBZ binding. Post-hoc ANCOVA analyses of the effects of DM on lobar cortical gray matter volumes (frontal, parietal, temporal, occipital) were subsequently performed, again accounting for age, sex, ICV and DTBZ binding. We applied the Holm-Bonferroni correction for multiple post-hoc comparisons (n=4).

We also evaluated the relationship between cognitive z-scores and total gray matter volumes and their interaction with DM status, again accounting for age, sex, striatal DTBZ binding and ICV.

A similar analysis of the relationship of cognitive metrics and lobar gray matter volumes that had showed significant associations with DM was also performed. Holm-Bonferroni correction for multiple comparisons was again applied.

## RESULTS

### Relationship between gray matter volumes and presence of DM in PD

There was a significant association between DM and lower total gray matter volume (p=0.02) after accounting for age, sex, ICV and striatal DTBZ binding. Total adjusted mean gray matter volume in the PD-DM subjects was 8.3 % lower compared to the PD non-DM subjects. Effect of age on total gray matter volume was also significant (p=0.0007).

Post-hoc ANCOVA analyses performed to test the association between lobar cortical gray matter volumes and DM revealed a significant effect of diabetes on frontal cortical gray matter (p=0.01) with a similar independent contribution of age (p=0.004).

Details regarding the different models interrogating the relationship between the presence of DM and total gray matter volume as well as lobar cortical gray matter effects are shown in Table 2.

### Post-hoc analysis on the relationship between cognitive test performance and gray matter l[8]oss/regional cortical atrophy

The interaction term total gray matter volume x DM status showed significant association with composite cognitive scores (p=0.007). Cognitive domain specific analyses showed significant associations between visuospatial domain cognitive z-scores (p=0.005) and total gray matter X DM status. Significant associations between frontal cortical gray matter volume and composite and executive domain cognitive z-scores were also present (p- values of 0.01 and 0.002 respectively).

## DISCUSSION

We previously showed that DM is associated with cognitive deficits independent of the disease-specific primary neurodegenerative processes in PD[8]. Our current findings show that comorbid DM is associated with significantly greater global gray matter loss (about 8%) in the setting of PD. Furthermore, in terms of regional lobar cortical gray matter loss, the effects of DM are most pronounced in the frontal region (about 10%). Although there are no published studies examining the effects of DM on gray matter loss patterns in PD, our findings are concordant with previously published data in DM patients without PD, which have shown more prominent DM-related frontal gray matter loss [9, 10]. These previous studies in DM patients without PD have also revealed other areas of preferential cortical gray matter loss, especially in the temporal regions which did not achieve statistical significance in our cohort. Increased vulnerability of the frontal lobe in PD-DM is concordant with our post-hoc analysis of the cognitive data showing more selective executive function cognitive domain effects associated with frontal lobe volume loss. Although we did not find preferential involvement of more posterior cortical structures, more severe global cortical atrophy in PD-DM may explain the visuospatial cognitive domain effects observed in our study.

It is important to note that PD itself is associated with cortical volume loss[18, 19] and it is possible that the interaction between PD-related gray matter injury and DM-related gray matter injury may mask some of the impact of DM via ceiling effects which are difficult to assess especially given that no healthy controls were included in our study.

Our findings point to extra-nigral disease targets in PD and DM. The mechanism responsible for accentuated global gray matter loss as well as preferential involvement of the frontal cortex in DM-associated neurodegeneration is unclear. DM-mediated vascular injury to the white matter causing gray matter loss via retrograde degeneration is a possibility. One large postmortem study reported increased prevalence of vascular pathology, including lacunar strokes, leukoaraiosis lesions, amyloid angiopathy, and microhemorrhages in PD subjects compared to controls[20]. These pathologic findings are also associated with diabetes. A recent paper from our group examining the effects of DM on motor features of PD examined white matter hyperintensities, often ascribed to vascular pathology, in PD patients with and without DM and found no significant difference between the two groups[4].

Similarly, in our study if vascular disruption was the primary mechanism of injury, one might expect greater involvement of longer nerve fibers terminating in the more posterior

aspects of the cortex and resulting in parieto-occipital cortical degeneration as opposed to the observed frontal cortical degeneration. Other potential pathways proposed to link diabetes/the metabolic syndrome and neurodegeneration include tau protein dysregulation, pathologic amyloid precursor protein processing, mitochondrial disruption, or microglial activation. Further research is needed to delineate the mechanisms responsible for increased gray matter loss and cognitive decline accompanying glucose dysregulation in the setting of PD. An important next step is to define whether gray matter injury is a primary effect or the result of white matter injury. Delineation of white matter microstructural disruption using techniques such as Diffusion Tensor Imaging, along with gray matter assessments, would be helpful in this respect.

DM effects follow a similar pattern to the effects of age in our cohort with age having a significant impact on total as well as frontal gray matter volumes. A significant effect of age was also noted in relation to temporal gray matter volumes, which is again consistent with prior published data although the effects of DM on temporal cortical gray matter volumes did not reach statistical significance in our study[21].

Our results may have clinical relevance because of the correlations between total and frontal gray matter volumes and cognitive scores, especially in the executive and visuospatial domains. Intervening in the pathologic effects of DM may be a strategy to retard cognitive decline in PD with comorbid glucose intolerance.

Our study has inherent limitations. The number of patients with PD and DM is small. The determination of diabetes status was made based on self-report. Given the high prevalence of undiagnosed diabetes as well as impaired glucose tolerance in the elderly population[22], we acknowledge that there may be subjects in our non-diabetic group who if tested would meet criteria for diabetes. However, this would only attenuate the association we observed between DM and reduced gray matter volumes. Furthermore, we did not collect information on duration and severity of diabetes in these patients, which could also influence the degree of brain injury and, as a result, gray matter volumes. Larger, prospective longitudinal studies would be useful in delineating the effects of DM on microstructural brain changes in the setting of PD and their effects on cognitive decline.

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## TABLE 1

### Clinical characteristics of study subjects

Mean values and standard deviations for age (in years), Hoehn-Yahr Stage, disease duration (in years) and years of education as well as Montreal Cognitive Assessment (MoCA) scores are provided.

| | PD without DM (N=24, M/F=21/3) | PD with DM (N=12, M/F= 10/2) | Group Comparison |
|---|---|---|---|
| **Age (yrs)** | 66.8 (5.3) | 66.0 (5.2) | p=0.7 |
| **Hoehn-Yahr Stage** | 2.3 (0.6) | 2.6 (0.9) | p=0.3 |
| **PD Duration (yrs)** | 6.2 (4.4) | 5.6 (4.6) | p=0.7 |
| **Education (yrs)** | 15.1(2.9) | 14.3 (2.8) | p=0.5 |
| **MoCa** | 25.6 (2.3) | 25.3 (2.2) | p=0.7 |
| **Sex (% male)** | 86.3 | 83.3 | p=0.8 |

**TABLE 2**

Mean (±SD) total and lobar gray matter volumes in the PD subjects with and without diabetes. ANCOVA F-values (with levels of significance) for the overall models as well as for striatal DTBZ distribution volume ratio (DVR), age, sex, intracranial volume and diabetes group co-variates are also presented. Holm-Bonferroni correction for multiple comparisons was applied for post hoc lobar gray matter analyses.

| | PD without DM | PD with DM | Striatal DTBZ | Age | Sex | ICV | DM | Overall Model |
|---|---|---|---|---|---|---|---|---|
| **Total GM** | 666.8 (58.9) | 611.4(38.3) (−8.3%) | 2.50(0.13) | 15.9(0.0004) | 0.88(0.35) | 69.2(<0.0001) | 5.96(0.02) | 32.7(<0.001) |
| ***Post hoc lobar analyses*** | | | | | | | | |
| **Frontal GM** | 185.8 (19.6) | 165.7(13.6) (−10.8%) | 1.14(0.30) | 9.67(0.004) | 0.09(0.76) | 31.05(<0.0001) | 6.65(0.015) | 16.61(<0.001) |
| **Parietal GM** | 90.5 (9.9) | 83.8 (5.0) (−7.4%) | 1.74(0.20) | 0.94(0.34) | 1.13(0.30) | 32.12(<0.0001) | 0.32(0.58) | 11.74(<0.001) |
| **Temporal GM** | 110.2 (11.6) | 102.2 (7.9) (−7.2%) | 1.74(0.20) | 15.35 (0.0005) | 0.17(0.68) | 0.05(<0.0001) | 2.81(0.10) | 13.16(<0.001) |
| **Occipital GM** | 75.6 (8.3) | 69.6 (6.0) (−7.9%) | 5.0(0.03) | 1.03 (0.36) | 5.65 (0.03) | 51.2(<0.0001) | 0.86 (0.36) | 21.2(<0.0001) |

**TABLE 3**

Results for ANCOVA analysis with cognitive z-scores as the outcome variables and explanatory variables of total gray matter volume x DM status interaction, striatal DTBZ DVR, age, sex and ICV. F-values (with levels of significance) for the overall models as well as individual parameters and associated p-values are presented. Holm-Bonferroni correction for multiple comparisons was applied for post hoc cognitive domain score analyses.

| | Striatal DTBZ | Age | Sex | ICV | Total Gray Matter Volume x DM | Overall Model |
|---|---|---|---|---|---|---|
| **Composite Cognitive Z-score** | 3.91 (0.06) | 0.07 (0.7) | 5.19 (0.03) | 4.48(0.04) | 5.26 (0.01) | 4.10 (0.0047) |
| ***Post hoc cognitive domain analyses*** | | | | | | |
| **Executive Z-score** | 1.99 (0.17) | 0.33 (0.57) | 5.13 (0.03) | 4.47 (0.04) | 4.30 (0.02) | 3.79(0.007) |
| **Visuospatial Z-score** | 0.23 (0.63) | 2.12 (0.15) | 2.54(0.12) | 5.08 (0.03) | 6.40 (0.005) | 3.10 (0.02) |
| **Attention Z-score** | 1.45(0.24) | 0.37 (0.54) | 1.53 (0.22) | 0.89 (0.35) | 1.68 (0.20) | 1.55 (0.20) |
| **Memory Z-score** | 4.67(0.04) | 0 (0.99) | 2.58 (0.12) | 2.93 (0.10) | 2.16 (0.13) | 2.59 (0.04) |