Published in final edited form as:

Parkinsonism Relat Disord. 2014 December ; 20(12): 1394–1398. doi:10.1016/j.parkreldis.2014.10.008.

Diabetes mellitus is independently associated with more severe cognitive impairment in Parkinson disease

Nicolaas I. Bohnen, MD, PhD^{1,2,3}, Vikas Kotagal, MD, MSc², Martijn L.T.M Müller, PhD¹, Robert A Koeppe, PhD¹, Peter J.H. Scott, PhD¹, Roger L. Albin, MD^{2,3,4}, Kirk A Frey, MD, PhD^{1,2}, and Myria Petrou, MA, MB, ChB, MS¹

¹Department of Radiology, University of Michigan, Ann Arbor, MI

²Department of Neurology, University of Michigan, Ann Arbor, MI

³Neurology Service and GRECC, VAAHS, Ann Arbor, MI

⁴Michigan Alzheimer Disease Center, Ann Arbor, MI, USA

Abstract

Background—There is increasing interest in interactions between metabolic syndromes and neurodegeneration. Diabetes mellitus (DM) contributes to cognitive impairment in the elderly but its effect in Parkinson disease (PD) is not well studied.

Objective—To investigate effects of comorbid DM on cognition in PD independent from PD-specific primary neurodegenerations.

Methods—Cross-sectional study. Patients with PD (n=148; age 65.6±7.4 years, Hoehn and Yahr stage 2.4±0.6, with (n=15) and without (n=133) comorbid type II DM, underwent [¹¹C]methyl-4-piperidinyl propionate (PMP) acetylcholinesterase (AChE) PET imaging to assess cortical cholinergic denervation, [¹¹C]dihydrotetrabenazine (DTBZ) PET imaging to assess nigrostriatal denervation, and neuropsychological assessments. A global cognitive Z-score was calculated based on normative data. Analysis of covariance was performed to determine cognitive differences between subjects with and without DM while controlling for nigrostriatal denervation, cortical cholinergic denervation, levodopa equivalent dose and education covariates.

Results—There were no significant differences in age, gender, Hoehn and Yahr stage or duration of disease between diabetic and non-diabetic PD subjects. There was a non-significant trend toward lower years of education in the diabetic PD subjects compared with non-diabetic PD subjects. PD diabetics had significantly lower mean (±SD) global cognitive Z-scores (−0.98±1.01) compared to the non-diabetics (−0.36±0.91; F=7.78, P=0.006) when controlling for covariate

© 2014 Elsevier Ltd. All rights reserved

Corresponding author: Nicolaas I. Bohnen, MD, PhD, Functional Neuroimaging, Cognitive and Mobility Laboratory, Departments of Radiology and Neurology, University of Michigan, 24 Frank Lloyd Wright Drive, Box 362, Ann Arbor, MI 48105-9755, USA. TEL: 734 936 5388; FAX: 734 998 8403. nbohen@umich.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors declare no conflict of interest relevant to this work.

effects of education, striatal dopaminergic denervation, and cortical cholinergic denervation (total model $F=8.39$, $P<0.0001$).

Conclusion—Diabetes mellitus is independently associated with more severe cognitive impairment in PD likely through mechanisms other than diseasespecific neurodegenerations.

Keywords

Acetylcholine; cognitive impairment; diabetes mellitus; dopamine; Parkinson disease; PET

Introduction

Diabetes mellitus (DM) contributes to cognitive impairment in the elderly (1, 2) and constitutes a risk factor for dementia, possibly including Alzheimer disease (3, 4). The effect of DM on the cognitive impairments of PD is not well understood. A recent historical cohort study reported global cognitive outcomes using the Mini-Mental State Examination (MMSE) in a cohort of 50 PD subjects with DM and 50 non-diabetic PD subjects. PD subjects with DM developed lower MMSE scores at 3 year follow-up compared to non-diabetic PD subjects (5). Although this observation suggests a detrimental effect of DM on cognitive functions in PD, this study did not control for effects of primary neurodegenerations in PD, in particular the degree of nigrostriatal and cholinergic denervations that may influence cognitive decline in PD (6). Hyperglycemia and DM might contribute to cognitive impairment in PD by exacerbation of the primary neurodegenerative processes, as has been suggested for Alzheimer disease (7). Alternatively, DM could cause other forms of brain injury to exacerbate cognitive impairment in PD. It remains unclear whether DM-related cognitive effects are due to aggravation of the primary neurodegenerative processes in PD or to distinct and independently occurring pathological mechanisms.

Positron emission tomography (PET) methods allow measurement of axon terminal populations, such as nigrostriatal dopaminergic and cortical cholinergic terminals, whose integrity directly reflects the severity of primary neurodegenerative processes in PD. We performed a group comparison study of subjects with PD with and without a history of DM to test our hypothesis that comorbid DM is associated with greater degree of cognitive impairment in PD, independent of the degree of nigrostriatal dopaminergic and forebrain cholinergic degenerations.

Methods

Subjects and clinical test battery

This cross-sectional study involved a retrospective analysis of 148 subjects with PD (109 males, 39 females), mean age 65.6 ± 7.4 and duration of disease of 6.0 ± 4.3 years. The mean Hoehn and Yahr stage was 2.4 ± 0.6 . Fifteen subjects had a history of diabetes (PD-DM) and 133 PD subjects reported no history of diabetes. Diabetes status was determined through subject self-report in a standardized interview. All 15 diabetic patients had type II DM. All diabetic patients took anti-diabetic medications, including metformin ($n=10$), sulfonylureas ($n=6$), insulin ($n=3$), and thiazolidinediones ($n=4$). All diabetic patients were Caucasian. The

majority of subjects were on dopaminergic drugs but none were on anti-cholinergic (trihexiphenidyl, bztropine) or cholinergic drugs. None of the diabetic patients were on tricyclic anti-depressants. Levodopa equivalent dose was calculated using published conversion formulae (8). PD subjects met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (9). Abnormal striatal [^{11}C]DTBZ (DTBZ) PET findings were consistent with the diagnosis of PD in all subjects. No subjects had a history of a large artery stroke or other significant intracranial disease. Subjects on cholinesterase inhibitor drugs were not eligible for the study. Motor differences between groups for a subset of 13 patients from this cohort have been previously reported (10).

Each subject underwent a detailed cognitive examination following an approach previously reported to characterize cognitive impairment in PD (11). These tests included measures of verbal memory: California Verbal Learning Test (12); executive/reasoning functions: WAIS III Picture Arrangement test (13), and Delis-Kaplan Executive Function System Sorting Test (14); attention/psychomotor speed as absolute time on the Stroop 1 test (15); and visuospatial function: Benton Judgment of Line Orientation test (16). Composite Z-scores were calculated for these different cognitive domains based on normative data. A global composite cognitive Z-score was calculated as the mean of the domain Z-scores. The geriatric depression scale (GDS) was also completed (17).

The study was approved by the Institutional Review Boards of the University of Michigan and Ann Arbor Department of Veterans Affairs medical center. Written informed consent was obtained from all subjects.

Imaging techniques

All subjects underwent brain MRI and [^{11}C]PMP AChE and [^{11}C]DTBZ vesicular monoamine transporter type 2 (VMAT2) PET. [^{11}C]DTBZ PET imaging was performed the morning after withholding dopaminergic medications overnight. After completing the [^{11}C]DTBZ PET scan, subjects on dopaminergic medications took their medications and subjects proceeded with the [^{11}C]PMP PET. MRI was performed on a 3 Tesla Philips Achieva system (Philips, Best, The Netherlands) and PET imaging was performed in 3D imaging mode with an ECAT Exact HR+ tomograph (Siemens Molecular Imaging, Inc., Knoxville, TN) as previously reported (18). The imaging studies were generally completed within 1–2 days of the clinical and neuropsychological testing sessions.

[^{11}C]DTBZ and [^{11}C]PMP were prepared as described previously (19). Dynamic PET scanning was performed for 70 minutes using a bolus dose of 15 mCi [^{11}C]PMP dose. A bolus/infusion protocol was used for [^{11}C]DTBZ (15 mCi) in 60 minutes (20).

Analysis

All image frames were spatially coregistered within subjects with a rigidbody transformation to reduce the effects of subject motion during the imaging session (21). Interactive Data Language image analysis software (Research systems, Inc., Boulder, CO) was used to manually trace volumes of interest (VOI) on MRI images to include caudate nucleus, and putamen of each hemisphere. Total neocortical VOI were defined using semi-automated threshold delineation of the cortical gray matter signal on the MRI scan (18).

[¹¹C]DTBZ distribution volume ratios were estimated using the Logan plot graphical analysis method with the striatal time activity curves as the input function and the total neocortex as reference tissue, a reference region overall low in VMAT2 binding sites, with the assumption that the non-displaceable distribution is uniform across the brain at equilibrium (20). [¹¹C]DTBZ PET imaging estimates of striatal binding provide robust correlates of nigral neuronal counts (22).

AChE [¹¹C]PMP hydrolysis rates (k_3) were estimated using the striatal volume of interest (defined by manual tracing on the MRI scan of the putamen and caudate nucleus) as the tissue reference for the integral of the precursor delivery (23). AChE assessment has been recognized as a reliable marker for brain cholinergic pathways including in the human brain (24, 25). AChE PET imaging assesses cholinergic terminal integrity with cortical uptake reflecting largely basal forebrain neuron integrity. Cortical AChE PET were also classified as normal or below normal range based on the 5th percentile of normative data as previously reported (18).

Standard pooled-variance Student *t*-tests were used for group comparisons. χ^2 testing were performed for comparison of proportions between groups. ANCOVA was performed to determine cognitive differences between the subjects with and without DM while controlling for nigrostriatal VMAT2, cortical AChE, LED and education covariates. Analyses were performed using SAS version 9.2, SAS institute, Cary, North Carolina).

Results

Group comparison findings

Table 1 lists mean ($\pm$ SD) values of demographic, clinical, cognitive, cortical AChE hydrolysis rate (k_3 ; min⁻¹) and striatal [¹¹C]DTBZ VMAT2 distribution volume ratio (DVR) in the patients with PD with and without comorbid DM. There were no significant differences in age, gender, race, Hoehn and Yahr stage, depression scale score, LED or duration of disease between the two groups. There was a borderline non-significant trend toward lower levels of education in the PD-DM subjects compared to the non-diabetic group. There were no significant differences in mean cortical AChE hydrolysis rate (k_3 ; min⁻¹) and striatal [¹¹C]DTBZ VMAT2 distribution volume ratio (DVR) between the two groups (Table 1). There was also no difference in the proportion of patients who had cortical cholinergic innervation below the normal range between groups: 32.3% hypocholinergic patient in the PD compared to 33.4% in the non-DM group ($\chi^2=0.006$, $P=0.93$).

Analysis of covariance of cognitive differences between the PD diabetic and nondiabetic groups

PD-DM subjects had significantly lower mean ($\pm$ SD) global cognitive Zscore (-0.98 ± 1.01) compared to the non-diabetics (-0.36 ± 0.91 ; $F=7.76$, $P=0.0061$) while controlling for covariate effects of education ($F=9.50$, $P=0.0025$), LED ($F=0.08$, $P=0.77$), striatal dopaminergic denervation ($F=8.55$, $P=0.0040$), and cortical cholinergic denervation ($F=8.17$, $P=0.0049$; total model $F=8.39$, $P<0.0001$; table 2).

Post hoc analysis of the cognitive domain Z-scores between the PD-DM and non-diabetic groups

Table 2 lists also results of a *post hoc* analysis for the four different cognitive domain Z-scores. The group effect of DM was most significant for the attention Z-score ($F=9.88$, $P=0.002$) followed by the executive functions Z-scores ($F=4.46$, $P=0.036$). The DM cognitive effects were borderline significant for the visuospatial function Z-score ($F=3.60$, $P=0.06$) and showed a non-significant trend for the verbal learning Z-score ($F=1.94$, $P=0.17$; table 2).

Discussion

Our findings suggest that DM is associated with a greater degree of cognitive impairment in PD. There were no differences in nigrostriatal denervation or cortical cholinergic denervation between PD-DM and non-diabetic PD subjects, and ANCOVA analysis indicated an independent effect of DM on cognitive impairment in PD. Our analysis suggests also that the DM associated exacerbation of cognitive impairments may be linked to mechanisms of neural injury other than disease-specific dopaminergic and cholinergic degenerations.

A recent meta-analysis of cognitive functioning in non-demented adults with type II DM found that diabetic patients performed significantly lower than nondiabetic controls on all cognitive abilities evaluated, with effects size ranging from -0.14 to -0.37 (26). The largest effect sizes were found for attention and processing speeds (26). Our findings in PD-DM subjects also showed the greatest impairments in attentional function, followed by executive function deficits. It is possible that relatively greater PD-specific cognitive deficits in some domains, such as verbal learning, may result in underestimation of independent diabetes effects in our patients. The heterogeneity of cognitive impairments linked to DM, however, may reveal diabetes-specific mechanisms of neuronal injury.

One possible explanation for the association of DM with more severe cognitive impairment in PD is an increase in comorbid microvascular pathology, particularly as DM is an independent risk factor for vascular dementia (3). Leukoariosis, generally thought to be a manifestation of microvascular disease, is common in DM. A large recent large study of cognitively asymptomatic elderly subjects indicated that leukoariosis (white matter hyperintensities) are associated with executive function impairments, suggesting that microvascular injury of subcortical white matter drives this aspect of cognitive impairment (27). Our previous study from a subset of the same DM patients, however, suggest that in vivo MRI findings of leukoariosis do not differ between PD subjects with and without DM (10). Further research is needed to determine whether microstructural rather than macrostructural cerebral changes may play a significant role in the contribution of DM to the cognitive impairment syndrome in PD. For example, a recent MRI study in community-dwelling elderly found evidence of greater cerebral atrophy and reduced fractional anisotropy in the total white matter and greater mean diffusivity for the hippocampus and frontal cortex areas in diabetics compared to non-diabetics (28).

Prior research on the relationships between Alzheimer disease and DM suggests several other plausible mechanisms linking impaired glucose metabolism and neurodegeneration. Insulin resistance, a prominent feature of type II DM, may contribute to dysregulation of tau protein and amyloid precursor protein processing (29). Impaired glucose metabolism may lead to cholinergic system dysfunction (30, 31). Another possibility is that impaired glucose regulation may be linked to mitochondrial dysfunction, a credible mechanism of neurodegeneration in PD. Determining the mechanisms mediating DM effects in PD would be crucial for developing useful interventions.

Our previous report of a smaller study sample showed borderline trends toward worse cognitive performance in PD patients with comorbid DM; however, uncorrected for primary neurodegenerations in PD (10). This study illustrates the importance of controlling for confounder effects of the degree of primary neurodegenerations when assessing cognitive effects of comorbid medical conditions in PD, as these are important determinants of parkinsonian cognitive impairment as previously reported (18).

Our findings of independent DM-related contributions to cognitive impairment in PD adds to the emerging literature that medical comorbidities can aggravate the clinical course of primary neurodegenerative disorders, such as PD (32, 33). Cognitive impairment in PD likely reflects the cumulative effects of heterogeneous processes, including independent effects of nigrostriatal dopaminergic and forebrain cholinergic denervations (18). It is plausible that DM may interact with these primary neurodegenerations and further research is needed to determine whether DM contributes to cognitive impairment in PD not only additively but also multiplicatively.

Limitations of our study include our small number of PD subjects with DM, lack of laboratory assessment of the degree of glycemic control, and crosssectional design, the latter of which allows only for inferences of association rather than causation. Diabetes status was assessed by self-report rather than laboratory testing though recall bias would be expected to be similar amongst cases and controls. The proportion of PD-DM subjects in our PD subject pool was approximately the prevalence of DM (~10%) in elderly Americans, suggesting reasonably good ascertainment of DM. Under-reporting of DM in our control PD subjects, moreover, would only reduce the detection of differences in cognition. Future PD studies collecting in-depth information about comorbid DM, including degree of glycemic control, in both PD and non-PD elderly are needed for better mechanistic understanding of our findings.

Clinical trials exploring central nervous system-specific therapies aimed at improving glucose metabolism are already underway in Alzheimer disease (34) and may represent a useful therapeutic strategy in the pursuit of neuroprotection in PD and cognitive impairment. More aggressive management of diabetes may ameliorate aggravated cognitive morbidity in PD diabetics though recent trials suggest that aggressive treatment exacerbates cognitive decline and brain injury in Type II DM (35). These results underscore the importance of strategies to prevent or delay onset of DM in the elderly.

Conclusion

We conclude that comorbid diabetes is independently associated with more severe cognitive impairment in PD likely through mechanisms other than disease-specific degenerations.

Acknowledgements

The authors thank all patients for their time commitment and research assistants, PET technologists, cyclotron operators, and chemists, for their assistance with the study. This work was supported by the Department of Veterans Affairs [grant number I01 RX000317]; the Michael J. Fox Foundation; and the NIH [grant numbers P01 NS015655 and RO1 NS070856].

Dr. Bohnen has research support from the NIH, Department of Veteran Affairs, and the Michael J. Fox Foundation. **Dr. Kotagal** has research support from the American Academy of Neurology Clinical Research Training Fellowship. **Dr. Muller** has research support from the NIH, Michael J. Fox Foundation and the Department of Veteran Affairs. **Dr. Koeppe** receives research support from NIH (NINDS, NIA). **Dr. Scott** receives Editorial Royalties from Wiley, is an owner of SynFast Consulting, LLC, and has received research funding from the University of Michigan, GE Healthcare, Bristol-Myers Squibb, Bayer Pharma AG, Eli Lilly, and Molecular Imaging Research. **Dr. Albin** serves on the editorial boards of Neurology, Experimental Neurology, and Neurobiology of Disease. He receives grant support from the National Institutes of Health, CHDI, Michael J. Fox Foundation, and the Dept. of Veterans Affairs. Dr. Albin serves on the Data Safety and Monitoring Boards of the TV7820-CNS-20002 trial. **Dr. Frey** has research support from the NIH, GE Healthcare and AVID Radiopharmaceuticals (Eli Lilly subsidiary). Dr. Frey also serves as a consultant to AVID Radiopharmaceuticals, MIMVista, Inc, Bayer-Schering and GE healthcare. He also holds equity (common stock) in GE, Bristol-Myers, Merck and Novo-Nordisk. **Dr. Petrou** has research support from the Radiological Society of North America.

Abbreviations

AChE	Acetylcholinesterase
DM	diabetes mellitus
DTBZ	dihydropyridine
LED	levodopa equivalent dose
Parkinson disease	PD
PET	positron emission tomography
PMP	methyl-4-piperidinyl propionate
VMAT2	vesicular monoamine transporter type 2

References

1. Tilvis RS, Kahonen-Vare MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE. Predictors of cognitive decline and mortality of aged people over a 10-year period. *J Gerontol A Biol Sci Med Sci*. 2004; 59(3):268–274. [PubMed: 15031312]
2. Yaffe K, Falvey C, Hamilton N, Schwartz AV, Simonsick EM, Satterfield S, Cauley JA, Rosano C, Launer LJ, Strotmeyer ES, Harris TB. Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. *Arch Neurol*. 2012; 69(9):1170–1175. [PubMed: 22710333]
3. Strachan MW, Reynolds RM, Frier BM, Mitchell RJ, Price JF. The relationship between type 2 diabetes and dementia. *British medical bulletin*. 2008; 88(1):131–146. [PubMed: 19029150]
4. Luchsinger JA. Adiposity, hyperinsulinemia, diabetes and Alzheimer's disease: an epidemiological perspective. *Eur J Pharmacol*. 2008; 585(1):119–129. [PubMed: 18384771]

5. Giuntini M, Baldacci F, Del Prete E, Bonuccelli U, Ceravolo R. Diabetes is associated with postural and cognitive domains in Parkinson's disease. Results from a single-center study. *Parkinsonism Relat Disord.* 2014; 20(6):671–672. [PubMed: 24685342]
6. Klein JC, Eggers C, Kalbe E, Weisenbach S, Hohmann C, Vollmar S, Baudrexel S, Diederich NJ, Heiss WD, Hilker R. Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. *Neurology.* 2010; 74(11):885–892. [PubMed: 20181924]
7. Aviles-Olmos I, Limousin P, Lees A, Foltynie T. Parkinson's disease, insulin resistance and novel agents of neuroprotection. *Brain.* 2013; 136(Pt 2):374–384. [PubMed: 22344583]
8. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord.* 2010; 25(15):2649–2653. [PubMed: 21069833]
9. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathologic study of 100 cases. *J Neurol Neurosurg Psychiatry.* 1992; 55:181–184. [PubMed: 1564476]
10. Kotagal V, Albin RL, Muller ML, Koeppe RA, Frey KA, Bohnen NI. Diabetes is associated with postural instability and gait difficulty in Parkinson disease. *Parkinsonism Relat Disord.* 2013; 19(5):522–526. [PubMed: 23462483]
11. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. *Neurology.* 2009; 72(13):1121–1126. [PubMed: 19020293]
12. Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test Manual, Adult Version. Second ed.. San Antonio: The Psychological Corporation; 2000.
13. Wechsler, D. WAIS III Technical Manual. San Antonio, TX: The Psychological Corporation; 1997.
14. Delis, DC.; Kaplan, E.; Kramer, JH. Delis-Kaplan Executive Function System (D-KEFS): Examiner's manual. San Antonio, TX: The Psychological Corporation; 2001.
15. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol.* 1935; 18:643–662.
16. Benton, AL.; Varney, NR.; Hamsher, K. Judgment of Line Orientation, Form V. Iowa City: University of Iowa Hospitals; 1975.
17. McDonald WM, Holtzheimer PE, Haber M, Vitek JL, McWhorter K, Delong M. Validity of the 30-item geriatric depression scale in patients with Parkinson's disease. *Mov Disord.* 2006; 21(10):1618–1622. [PubMed: 16817205]
18. Bohnen NI, Mueller MLTM, Kotagal V, Koeppe RA, Kilbourn MR, Gilman S, Albin RL, Frey KA. Heterogeneity of cholinergic denervation in Parkinson disease. *J Cereb Blood Flow Metab.* 2012; 32(8):1609–1617. [PubMed: 22569194]
19. Shao X, Hoareau R, Hockley BG, Tluczek LJ, Henderson BD, Padgett HC, Scott PJ. Highlighting the Versatility of the Tracerlab Synthesis Modules. Part 1: Fully Automated Production of [F]Labelled Radiopharmaceuticals using a Tracerlab FX(FN). *J Labelled Comp Radiopharm.* 2011; 54(6):292–307. [PubMed: 21769163]
20. Koeppe RA, Frey KA, Kuhl DE, Kilbourn MR. Assessment of extrastriatal vesicular monoamine transporter binding site density using stereoisomers of [¹¹C]dihydrotetrabenazine. *J Cereb Blood Flow Metab.* 1999; 19(12):1376–1384. [PubMed: 10598942]
21. Minoshima, S.; Koeppe, RA.; Fessler, JA.; Mintun, MA.; Berger, KL.; Taylor, SF.; Kuhl, DE. Integrated and automated data analysis method for neuronal activation studying using O¹⁵ water PET. In: Uemura, K.; Lassen, NA.; Jones, T.; Kanno, I., editors. Quantification of brain function to tracer kinetics and image analysis in brain PET. Tokyo: Excerpta Medica; 1993. p. 409–418.
22. Brown CA, Karimi MK, Tian L, Flores H, Su Y, Tabbal SD, Loftin SK, Moerlein SM, Perlmutter JS. Validation of midbrain positron emission tomography measures for nigrostriatal neurons in macaques. *Ann Neurol.* 2013; 74(4):602–610. [PubMed: 23686841]
23. Nagatsuka S, Fukushi K, Shinotoh H, Namba H, Iyo M, Tanaka N, Aotsuka A, Ota T, Tanada S, Irie T. Kinetic analysis of [(¹¹C)]MP4A using a high-radioactivity brain region that represents an integrated input function for measurement of cerebral acetylcholinesterase activity without arterial blood sampling. *J Cereb Blood Flow Metab.* 2001; 21(11):1354–1366. [PubMed: 11702050]

24. Shute CC, Lewis PR. Electron microscopy of cholinergic terminals and acetylcholinesterase-containing neurones in the hippocampal formation of the rat. *Z Zellforsch Mikrosk Anat.* 1966; 69:334–343. [PubMed: 5973099]
25. Selden NR, Gitelman DR, Salamon-Murayama N, Parrish TB, Mesulam MM. Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. *Brain.* 1998; 121:2249–2257. [PubMed: 9874478]
26. Monette MC, Baird A, Jackson DL. A Meta-Analysis of Cognitive Functioning in Nondemented Adults with Type 2 Diabetes Mellitus. *Canadian journal of diabetes.* 2014 DOI: <http://dx.doi.org/10.1016/j.jcjd.2014.01.014>.
27. Hedden T, Mormino EC, Amariglio RE, Younger AP, Schultz AP, Becker JA, Buckner RL, Johnson KA, Sperling RA, Rentz DM. Cognitive profile of amyloid burden and white matter hyperintensities in cognitively normal older adults. *J Neurosci.* 2012; 32(46):16233–16242. [PubMed: 23152607]
28. Falvey CM, Rosano C, Simonsick EM, Harris T, Strotmeyer ES, Satterfield S, Yaffe K. Health ABCS. Macro- and microstructural magnetic resonance imaging indices associated with diabetes among community-dwelling older adults. *Diabetes care.* 2013; 36(3):677–682. [PubMed: 23160721]
29. Bosco D, Fava A, Plastino M, Montalcini T, Pujia A. Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis. *J Cell Mol Med.* 2011; 15(9):1807–1821. [PubMed: 21435176]
30. Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, de la Monte SM. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. *J Alzheimers Dis.* 2005; 8(3):247–268. [PubMed: 16340083]
31. Umegaki H. Neurodegeneration in diabetes mellitus. *Adv Exp Med Biol.* 2012; 724:258–265. [PubMed: 22411248]
32. Jones JD, Malaty I, Price CC, Okun MS, Bowers D. Health comorbidities and cognition in 1948 patients with idiopathic Parkinson's disease. *Parkinsonism Relat Disord.* 2012; 18(10):1073–1078. [PubMed: 22776043]
33. Williams-Gray CH, Mason SL, Evans JR, Foltynie T, Brayne C, Robbins TW, Barker RA. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. *J Neurol Neurosurg Psychiatry.* 2013; 84(11):1258–1264. [PubMed: 23781007]
34. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, Arbuckle M, Callaghan M, Tsai E, Plymate SR, Green PS, Leverenz J, Cross D, Gerton B. Intranasal insulin therapy for Alzheimer disease and amnesic mild cognitive impairment: a pilot clinical trial. *Arch Neurol.* 2012; 69(1):29–38. [PubMed: 21911655]
35. Launer LJ, Miller ME, Williamson JD, Lazar RM, Gerstein HC, Murray AM, Sullivan M, Horowitz KR, Ding J, Marcovina S, Lovato LC, Lovato J, Margolis KL, O'Connor P, Lipkin EW, Hirsch J, Coker L, Maldjian J, Sunshine JL, Truwit C, Davatzikos C, Bryan RN, investigators AM. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol.* 2011; 10(11):969–977. [PubMed: 21958949]

Highlights

- Diabetes mellitus contributes independently to cognitive impairment in PD.
- This occurs through mechanisms other than PD-specific neurodegenerations.
- Greatest impairments are seen in attentional and executive functions.

Table 1

Mean ($\pm$ SD) values of demographic, clinical, cognitive, geriatric depression scale, levodopa equivalent dose (LED), cortical AChE hydrolysis rate (k_3 ; min^{-1}) and striatal [^{11}C]DTBZ VMAT2 distribution volume ratio (DVR) in the patients with PD with and without comorbid DM. Gender distribution is presented as proportions. Levels of statistical difference between groups are also presented.

	PD subjects with diabetes (n =15)	PD subjects without diabetes (n=133)	Group comparison (significance)
Age (yr)	67.3 $\pm$ 6.1	65.4 $\pm$ 7.5	t=0.95, P=0.35
Gender (M/F)	13/2	96/37	$\chi^2=1.46$, P=0.23
Caucasian	15 (100%)	125 (94%)	$\chi^2=0.95$, P=0.33
Duration of motor PD (yr)	5.8 $\pm$ 4.4	6.1 $\pm$ 4.3	t=0.20, P=0.84
Education (yr)	14.1 $\pm$ 3.1	15.5 $\pm$ 2.8	t=1.85, P=0.07
LED (mg)	890 $\pm$ 756	673 $\pm$ 508	t=1.48, P=0.17
Selegiline use	1 (6.7%)	7 (5.3%)	$\chi^2=0.05$, P=0.82
Hoehn & Yahr stage	2.7 $\pm$ 0.7	2.4 $\pm$ 0.5	t=1.61, P=0.11
Geriatric depression scale	8.8 $\pm$ 7.9	5.9 $\pm$ 5.1	t _{approx} =1.27, P=0.22
Striatal VMAT2 DVR	1.97 $\pm$ 0.38	1.92 $\pm$ 0.28	t=0.60, P=0.55
Cortical AChE hydrolysis rates	0.0247 $\pm$ 0.0036	0.0235 $\pm$ 0.0027	t=1.55, P=0.12

t_{approx}= Satterthwaite's method of approximate t tests.

Mean ($\pm$ SD) global cognitive composite Z-scores in the PD subjects with and without diabetes. ANCOVA F-values (with levels of significance) are listed for the cortical AChE hydrolysis rates (k_3 ; min^{-1}) and striatal VMAT2 distribution volume ratio (DVR), education and LED (levodopa-equivalent dose) co-variables and overall group effect. A *post hoc* analysis of the cognitive domain Z-scores is also presented.

Table 2

	PD with diabetes (n=15)*	PD without diabetes (n=133)*	Striatal VMAT2 DVR	Cortical AChE hydrolysis rates (min^{-1})	Years of education (yr)	LED	Diabetes group effect	Overall model
Global cognitive Z-score	-0.98 $\pm$ 1.01	-0.36 $\pm$ 0.91	F=8.55, P=0.0040	F=8.17, P=0.0049	F=9.50, P=0.0025	F=0.08, P=0.77	F=7.78, P=0.0060	F=8.39, P<0.0001
<i>Post hoc</i> cognitive domain analysis								
Verbal learning Z-score	-0.95 $\pm$ 1.00	-0.57 $\pm$ 1.24	F=4.16, P=0.043	F=7.58, P=0.0067	F=1.06, P=0.39	F=0.51, P=0.48	F=1.94, P=0.17	F=4.44, P=0.0009
Executive functions Z-score	-1.22 $\pm$ 1.31	-0.60 $\pm$ 1.17	F=8.88, P=0.0034	F=5.01, P=0.027	F=10.51, P=0.0015	F=0.77, P=0.38	F=4.46, P=0.036	F=6.90, P<0.0001
Visuospatial function Z-score	-0.77 $\pm$ 1.04	-0.18 $\pm$ 1.14	F=0.49, P=0.49	F=3.05, P=0.083	F=7.43, P=0.0072	F=0.66, P=0.42	F=3.60, P=0.06	F=3.27, P=0.008
Attention Z-score	-1.02 $\pm$ 1.52	-0.09 $\pm$ 1.09	F=10.36, P=0.0016	F=3.64, P=0.058	F=5.92, P=0.016	F=0.00, P=0.96	F=9.88, P=0.002	F=7.59, P<0.0001

* The group means are covariate-adjusted.