HHS Public Access

Author manuscript

Mov Disord. Author manuscript; available in PMC 2023 March 01.

Published in final edited form as:

Mov Disord. 2022 March ; 37(3): 629–634. doi:10.1002/mds.28852.

Comparison of transcranial sonography and [^{18}F]-fluorodopa PET imaging in *GBA1* mutation carriers

Daniel P. Eisenberg, MD[1,#], **Grisel Lopez, MD**[2,#], **Michael D. Gregory, MD**[1], **Karen F. Berman, MD**[1], **Ellen Sidransky, MD**[2,*]

[1]Clinical and Translational Neuroscience Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD

[2]Medical Genetics Branch, National Institutes of Health, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

Abstract

Background: Mutations in *GBA1* are a common genetic risk factor for parkinsonism; however, penetrance is incomplete, and biomarkers of future progression to parkinsonism are needed. Both nigral sonography and striatal [^{18}F]-FDOPA PET assay dopamine system health, but their utility and coherence in this context are unclear.

Objectives: To evaluate the utility and coherence of these modalities in *GBA1*-associated parkinsonism.

Methods: Thirty-four patients with *GBA1* mutations (seven with parkinsonism), underwent both transcranial studies for substantia nigra echogenicity and [^{18}F]-FDOPA PET to determine striatal tracer specific uptake (K_i).

Results: Larger nigral echogenic areas and reduced striatal K_i were exclusively seen in parkinsonian subjects. Sonographic and PET measurements showed strong inverse correlations, but solely in individuals with clinical parkinsonism.

Conclusions: Close correspondence between nigral echogenicity and striatal presynaptic dopamine synthesis capacity seen only in *GBA1* carriers with parkinsonism provides validation that these two modalities may conjointly capture aspects of the biology underlying clinical parkinsonism but raises questions about their utility as predictive tools in at-risk subjects.

[*]Corresponding author: Ellen Sidransky, MD, Chief, Medical Genetics Branch, NIH, Bld 35A, Room 1E623, 35 Convent Drive, MSC3708, Bethesda, MD, 20892-3708, Phone: 301-451-0901, sidranse@mail.nih.gov.

Authors' Roles

DPE: Analyzed the PET Data, prepared the figure, wrote first draft of the manuscript.
GL: Recruited the patients, performed the sonography, organized the data, reviewed and critiqued the manuscript.
MDG: Analyzed the PET data, reviewed the manuscript.
KFB: Supervised the PET studies, reviewed and critiqued the work.
ES: Conceived of and organized the study, wrote the mature draft.
[#]These authors contributed equally

Disclosures: The authors have no conflicts of interest or financial disclosures to report.

Keywords

Transcranial sonography; ^{18}F-fluorodopa PET imaging; glucocerebrosidase; parkinsonism; Gaucher disease

Introduction

One anticipated outcome of research identifying genetic variation associated with parkinsonism is an enhanced ability to detect illness at an early stage, when personalized therapeutics or early treatments might be administered.[1] However, many of the identified risk alleles for Parkinson disease (PD) have variable penetrance, especially variants in *GBA1* and *LRRK2*, the genes most strongly associated with PD risk.[2] Pathologic variants in *GBA1*, the gene mutated in the lysosomal storage disorder Gaucher disease (GD), have been identified in 2–29% of patients with PD, yet the vast majority of patients with GD and their carrier relatives never develop parkinsonism.[3,4] Thus, even in genetically at-risk populations, in order to discover and implement disease-altering therapies, there is an urgency to identify early diagnostic tools that may help identify individuals on a trajectory toward developing parkinsonism. While factors including impaired olfaction, REM sleep behavior disorder, autonomic dysfunction or depression may precede motor involvement in some patients destined to develop parkinsonism, most clinical evaluations are fairly non-specific,[5] and hence imaging modalities are being evaluated as potential biomarkers of disease progression.

In PD, loss of midbrain dopaminergic neurons and their nigrostriatal projections leads to deterioration of striatal dopaminergic terminals, which can be reliably measured with [^{18}F]-fluorodopa PET.[6] The influx constant, K_i, represents the specific uptake of [^{18}F]-fluorodopa in DOPA decarboxylase-containing cells and reflects presynaptic dopamine synthesis and storage. Marked reduction in striatal K_i has been a well-established, validated indicator of dopaminergic insufficiency in idiopathic PD.[6] In prior work, we performed [^{18}F]-fluorodopa PET studies in a cohort of individuals with mutations in *GBA1*, both with and without clinical evidence of PD, and observed striatal dopamine synthesis deficits in *GBA1*-associated PD closely resembling that in idiopathic PD.[7] A subsequent longitudinal PET study in an overlapping but larger sample again showed significant dopamine loss in those with parkinsonism. However, at baseline and over time, [^{18}F]-fluorodopa specific uptake in at-risk *GBA1* carriers without parkinsonism did not differ significantly from controls,[8] identifying a notable disconnect between genetic risk and the neurochemical risk phenotype, suggesting that *GBA1*-mediated genetic risk alone is not sufficient to alter striatal dopaminergic tone. Additionally, these findings raise questions about whether striatal K_i variation within the normal range might reflect nigral neuronal population strength or vulnerability in genetically high-risk groups.

Alongside the [^{18}F]-FDOPA PET PD literature, accumulated evidence has supported the diagnostic and potentially predictive value of transcranial sonography (TCS) of the substantia nigra in PD.[9] Postmortem evaluations have shown nigral echogenicity is associated with co-localized iron stores,[10] yet the how this measurement relates to

hallmark dopaminergic pathology in PD is incompletely understood. Studies employing both ultrasonography and molecular neuroimaging to examine relationships between nigral echogenicity and dopamine-related parameters have varied in methodology and results. Some studies of PD have identified inverse relationships between nigral echogenicity and monoaminergic transporter SPECT assays,[11, 12] whereas others have not.[13–16] [^{18}F]-FDOPA PET investigations in individuals with incidentally discovered nigral hyperechogenicity,[17] and in *Parkin* mutation carriers,[18] suggest an inverse correlation between presynaptic dopamine synthesis capacity and nigral echogenicity although these studies have limitation in size and design. No prior reports have compared TCS and molecular neuroimaging results in cohorts with *GBA1* mutations. Anticipating that nigral echogenicity would be expanded in individuals with clinical parkinsonism and would be inversely related to striatal presynaptic dopamine synthesis capacity in groups with parkinsonism and at-risk for parkinsonism, we studied a cohort with homozygous and heterozygous *GBA1* mutations with and without clinical parkinsonism using both TCS and [^{18}F]-FDOPA PET.

Methods

Thirty-four individuals of European descent with pathological *GBA1* variants (20 with GD and 14 heterozygous carriers) underwent both [^{18}F]-FDOPA PET neuroimaging and TCS nigral measurements. Participants provided informed consent under an NHGRI Institutional Review Board-approved clinical protocol (NCT00302146). Sanger sequencing of *GBA1*, performed on blood samples,[19] confirmed the presence of pathologic variants associated with GD.[20, 21,22] The UK Brain Bank Criteria was used to establish the diagnosis of PD[23] identifying seven individuals, five with GD and two *GBA1* heterozygotes, with parkinsonism. The two imaging assessments were conducted independently by two separate teams during the same patient visit. [^{18}F]-FDOPA PET imaging was performed in a fasting state with a GE Advance tomograph operating in 3D mode as reported.[8] In brief, after tapering any confounding medications, suspending antiparkinsonian medications for at least 12 hours, abstaining from caffeine and nicotine for at least four hours, and receiving a single oral dose of carbidopa 200 mg one hour prior to [^{18}F]-FDOPA injection, participants completed scanning, which included a transmission scan and, immediately after injection, a 90-minute emission scan series. Filtered-back-projection-based reconstruction and corrections, including attenuation correction and realignment for interframe motion, were applied, and data (voxel size 1.5×1.5×1.5mm^3) were spatially warped to an [^{18}F]-FDOPA-specific template, smoothed (10mm Gaussian kernel), and modeled voxelwise in PMOD using a graphical linearization model with cerebellar activity as the input function.[24] TCS was performed using a phased-array ultrasound system with a 2.5 MHz transducer (Acuson Antares; Siemens).[25] Planimetric measurements of the maximal area of echogenicity at the anatomical location of the SN were obtained bilaterally and averaged. Statistical comparisons of TCS group differences (using R software https://www.r-project.org/) and voxelwise associations between neuroimaging measurements (using SPM software https://www.fil.ion.ucl.ac.uk/spm/) were performed using standard general linear models (Student's t-tests/ANOVA for group mean comparisons and linear regression analyses for K_i-echogenicity and K_i-echogenicity-by-group interaction association tests), with $p<0.05$ (FDR-corrected for voxelwise analyses conducted exclusively within the

striatum) considered significant. The striatal search region included the caudate, putamen and subcomissural ventral striatum (including nucleus accumbens) and was delineated with the help of Freesurfer software, which was applied to an MNI space template derived from T_1 weighted MRI data from 240 healthy adults.

Results

Individuals in this study were clinically monitored for up to twelve years after neuroimaging (see Table 1 for demographics, genetic, and clinical information). Only one participant, an N370S carrier without parkinsonism at the time of neuroimaging, developed parkinsonism during the follow-up interval. Relative to a TCS cutoff of 20 mm^2 from prior literature[26] and a putamen K_i reference value of 0.0065 min^{-1} representing two standard deviations below the mean in a previously studied healthy cohort using the same PET methods,[8] this individual's nigral echogenicity (16.7 mm^2) and striatal K_i (mean putamen [^{18}F]-FDOPA K_i 0.00877 min^{-1}) were both unremarkable one year prior to symptom onset. In the entire cohort, most individuals with parkinsonism were outside these thresholds for TCS (5/7) and PET (6/7), whereas most individuals without parkinsonism (4/27 and 0/27, respectively) were not.

The participants with parkinsonism had larger areas of maximal nigral echogenicity than those without parkinsonism ($t(30)=3.92;p<0.0005$). However, neither the effect of *GBA1* status (carrier v. GD; $t(30)=0.66$, $p=0.51$) nor the clinical parkinsonism-*GBA1* status interaction ($t(30)=1.66,p=0.11$) reached significance (Figure 1A). Voxelwise interrogation of the striatum revealed a robust inverse relationship between [^{18}F]-FDOPA specific uptake (K_i) and nigral echogenic areas across individuals with clinical parkinsonism ($p<0.05$, FDR corrected, Figure 1B). However, there was no relationship between K_i and echogenicity in the at-risk *GBA1* mutation carriers without parkinsonism. Direct comparison of K_i-echogenicity relationships in the two groups (with and without parkinsonism) showed these differences to constitute a significant interaction ($p<0.05$, FDR corrected; see Figure 1C, D).

Discussion

The larger echogenic areas observed in the patients with parkinsonism is consistent with the broader literature describing ultrasonography in PD.[27] Based on a reference cutoff of 20 mm^2 from prior literature,[26] TCS measurements from participants without parkinsonism – including one individual who subsequently developed parkinsonism – were largely in the normal range, while most of those with parkinsonism showed abnormally elevated values. The current data do not rule out a subtle statistical increase in overall mean nigral echogenicity in individuals with *GBA1* mutation carriers without parkinsonism relative to healthy genetic controls, as seen in one recent report that did not include post-sonography clinical follow-up;[28] however, they do suggest a paucity of clinically significant TCS-measured pathology in this group. This finding parallels the group differences observed in our prior study with [^{18}F]-FDOPA PET, where significantly reduced striatal dopamine synthesis capacity in the *GBA1* mutation carriers relative to controls was seen exclusively in those with clinical parkinsonism.[8] Despite the hypothesis that TCS and PET assessments might conjointly identify those motorically-intact *GBA1* mutation carriers at greatest risk

of developing parkinsonism, no genetically at-risk individuals without parkinsonism in the current study had both abnormally larger nigral echogenic areas and relatively lowered striatal K_i. Thus, excepting the possibility no non-parkinsonism participants in the sample had a heightened risk (at odds with the one converter identified), parkinsonism risk in this group may not necessarily be captured by the conjunction of these two imaging metrics.

Furthermore, the close correspondence of nigral echogenicity and striatal presynaptic dopamine synthesis capacity in subjects with parkinsonism, but not in those without, suggests that pathologic *GBA1* variants alone do not necessarily confer strongly coherent neuroimaging indicators of dopaminergic system aberrancy. Rather, interindividual variability of presynaptic dopamine synthesis capacity in the at-risk group is likely driven by factors unrelated to mesencephalic iron-bound stores associated with PD. Identifying these additional factors may help refine and amplify the diagnostic and prognostic utility of molecular imaging in high-risk groups and poses an important challenge ahead.

Prior longitudinal studies of TCS in PD have reported relative stability of nigral echogenic areas in affected adults,[29] though significantpu-related effects have been noted.[30] If largely stable, hyperechogenicity associated with parkinsonism may be more valuable as a trait marker of disease, rather than for tracking nigral health at any given timepoint. Some reports suggest a correlation between echogenicity and clinical symptoms burden,[29, 30] hypothesizing that TCS measurements may have prognostic value with respect to severity,[29] although this is controversial.[31] In contrast, striatal K_i is directly dependent on the cumulative dopamine synthetic capacity of nigral cell populations, and shows clear decline with disease progression in both sporadic PD[32] and *GBA1*-associated parkinsonism.[8] If nigral hyperechogenicity is exclusively a trait measure of illness, the demonstrated association with striatal K_i deficit in those with clinical parkinsonism may reflect interindividual differences in disease aggressiveness or other characteristics, as opposed to both neuroimaging measures equivalently indexing illness course *per se*.

As discussed in the longitudinal [^{18}F]-FDOPA PET study,[8] one limitation in our cohort is the dearth of individuals who developed parkinsonism during our period of follow-up. On one hand, this ensures that findings in the at-risk group were not substantially confounded by an imminent premorbid parkinsonian state. On the other hand, this makes it challenging to determine whether the observation that our at-risk group did not show unequivocally convergent imaging indications of parkinsonism across modalities reflects an inherent limitation of these complementary tools as long-term predictive measures or is due to the very low penetrance of parkinsonism in this population. Longer follow-up and larger dual-imaging longitudinal studies in *GBA1* mutation carriers are needed to disambiguate these possibilities and further elucidate disease pathology.

Acknowledgements

This work was supported by the National Institutes of Health Intramural Research Programs of the National Human Genome Research Institute and the National Institute of Mental Health (ZIAMH002652). Some of this work utilized the computational resources of the NIH HPC Biowulf cluster (http://hpc.nih.gov).

Financial Disclosures

The Sidransky lab has received funding from the Michael J Fox Foundation, the Aligning Science Across Parkinson's Initiative and from F.Hoffmann-La Roche Ltd. under a Cooperative Research and Development Agreement with the NHGRI and NCATS. The other authors have nothing to disclose.

Funding sources:

This work was supported by the intramural research programs of the National Human Genome Research Institute, the National Institute of Mental Health and the National Institutes of Health.

References

1. Schneider SA, Alcalay RN. Precision medicine in Parkinson's disease: emerging treatments for genetic Parkinson's disease. J Neurol. Mar 2020;267(3):860–869. doi:10.1007/s00415-020-09705-7 [PubMed: 31974807]
2. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med. Oct 22 2009;361(17):1651–61. doi:10.1056/NEJMoa0901281 [PubMed: 19846850]
3. Do J, McKinney C, Sharma P, Sidransky E. Glucocerebrosidase and its relevance to Parkinson disease. Mol Neurodegener. Aug 29 2019;14(1):36. doi:10.1186/s13024-019-0336-2 [PubMed: 31464647]
4. Lopez G, Steward A, Ryan E, et al. Clinical evaluation of sibling pairs with gaucher disease discordant for parkinsonism. Mov Disord. Feb 2020;35(2):359–365. doi:10.1002/mds.27916 [PubMed: 31785030]
5. Heinzel S, Roeben B, Ben-Shlomo Y, et al. Prodromal Markers in Parkinson's Disease: Limitations in Longitudinal Studies and Lessons Learned. Front Aging Neurosci. 2016;8:147. doi:10.3389/fnagi.2016.00147 [PubMed: 27445791]
6. Liu ZY, Liu FT, Zuo CT, Koprich JB, Wang J. Update on Molecular Imaging in Parkinson's Disease. Neurosci Bull. Apr 2018;34(2):330–340. doi:10.1007/s12264-017-0202-6 [PubMed: 29282614]
7. Goker-Alpan O, Masdeu JC, Kohn PD, et al. The neurobiology of glucocerebrosidase-associated parkinsonism: a positron emission tomography study of dopamine synthesis and regional cerebral blood flow. Brain. Aug 2012;135(Pt 8):2440–8. doi:10.1093/brain/aws174 [PubMed: 22843412]
8. Lopez G, Eisenberg DP, Gregory MD, et al. Longitudinal Positron Emission Tomography of Dopamine Synthesis in Subjects with GBA1 Mutations. Ann Neurol. Apr 2020;87(4):652–657. doi:10.1002/ana.25692 [PubMed: 32030791]
9. Li DH, He YC, Liu J, Chen SD. Diagnostic Accuracy of Transcranial Sonography of the Substantia Nigra in Parkinson's disease: A Systematic Review and Meta-analysis. Sci Rep. Feb 16 2016;6:20863. doi:10.1038/srep20863 [PubMed: 26878893]
10. Zecca L, Berg D, Arzberger T, et al. In vivo detection of iron and neuromelanin by transcranial sonography: A new approach for early detection of substantia nigra damage. Movement Disorders. 2005/10/01 2005;20(10):1278–1285. doi:10.1002/mds.20550 [PubMed: 15986424]
11. Bártová P, Kraft O, Bernátek J, et al. Transcranial Sonography and 123I-FP-CIT Single Photon Emission Computed Tomography in Movement Disorders. Ultrasound in Medicine & Biology. 2014/10/01/ 2014;40(10):2365–2371. doi:10.1016/j.ultrasmedbio.2014.05.014 [PubMed: 25194454]
12. Weise D, Lorenz R, Schliesser M, Schirbel A, Reiners K, Classen J. Substantia nigra echogenicity: A structural correlate of functional impairment of the dopaminergic striatal projection in Parkinson's disease. Movement Disorders. 2009/08/15 2009;24(11):1669–1675. doi:10.1002/mds.22665 [PubMed: 19514075]
13. Li D-h, Zhang L-y, Hu Y-y, et al. Transcranial sonography of the substantia nigra and its correlation with DAT-SPECT in the diagnosis of Parkinson's disease. Parkinsonism & Related Disorders. 2015/08/01/ 2015;21(8):923–928. doi:10.1016/j.parkreldis.2015.05.024 [PubMed: 26066091]
14. Bor-Seng-Shu E, Pedroso JL, Felicio AC, et al. Substantia nigra echogenicity and imaging of striatal dopamine transporters in Parkinson's disease: A cross-sectional study. Parkinsonism

& Related Disorders. 2014/05/01/ 2014;20(5):477–481. doi:10.1016/j.parkreldis.2014.01.015 [PubMed: 24629800]

15. Spiegel J, Hellwig D, Möllers M-O, et al. Transcranial sonography and [123I]FP-CIT SPECT disclose complementary aspects of Parkinson's disease. Brain. 2006;129(5):1188–1193. doi:10.1093/brain/awl042 [PubMed: 16513685]
16. Doepp F, Plotkin M, Siegel L, et al. Brain parenchyma sonography and 123I-FP-CIT SPECT in Parkinson's disease and essential tremor. Movement Disorders. 2008/02/15 2008;23(3):405–410. doi:10.1002/mds.21861 [PubMed: 18067184]
17. Berg D, Becker G, Zeiler B, et al. Vulnerability of the nigrostriatal system as detected by transcranial ultrasound. Neurology. Sep 22 1999;53(5):1026–31. doi:10.1212/wnl.53.5.1026 [PubMed: 10496262]
18. Hagenah JM, König IR, Becker B, et al. Substantia nigra hyperechogenicity correlates with clinical status and number of Parkin mutated alleles. Journal of Neurology. 2007/10/15 2007;254(10):1407. doi:10.1007/s00415-007-0567-y [PubMed: 17934880]
19. Tayebi N, Reissner KJ, Lau EK, et al. Genotypic heterogeneity and phenotypic variation among patients with type 2 Gaucher's disease. Pediatr Res. May 1998;43(5):571–8. doi:10.1203/00006450-199805000-00003 [PubMed: 9585001]
20. Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. Lancet Neurol. Nov 2012;11(11):986–98. doi:10.1016/S1474-4422(12)70190-4 [PubMed: 23079555]
21. Beutler E, Gelbart T, Scott CR. Hematologically important mutations: Gaucher disease. Blood Cells Mol Dis. Nov-Dec 2005;35(3):355–64. doi:10.1016/j.bcmd.2005.07.005 [PubMed: 16185900]
22. Stone DL, Tayebi N, Orvisky E, Stubblefield B, Madike V, Sidransky E. Glucocerebrosidase gene mutations in patients with type 2 Gaucher disease. Hum Mutat. 2000;15(2):181–8. doi:10.1002/(SICI)1098-1004(200002)15:2<181::AID-HUMU7>3.0.CO;2-S [PubMed: 10649495]
23. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. Mar 1992;55(3):181–4. doi:10.1136/jnnp.55.3.181 [PubMed: 1564476]
24. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J Cereb Blood Flow Metab. Dec 1985;5(4):584–90. doi:10.1038/jcbfm.1985.87 [PubMed: 4055928]
25. Walter U How to measure substantia nigra hyperechogenicity in Parkinson disease: detailed guide with video. J Ultrasound Med. Oct 2013;32(10):1837–43. doi:10.7863/ultra.32.10.1837 [PubMed: 24065265]
26. Gaenslen A, Unmuth B, Godau J, et al. The specificity and sensitivity of transcranial ultrasound in the differential diagnosis of Parkinson's disease: a prospective blinded study. Lancet Neurol. May 2008;7(5):417–24. doi:10.1016/S1474-4422(08)70067-X [PubMed: 18394965]
27. Xu R, Chen G, Mao Z, Gao H, Deng Y, Tao A. Diagnostic Performance of Transcranial Sonography for Evaluating Substantia Nigra Hyper-echogenicity in Patients with Parkinson's Disease. Ultrasound Med Biol. May 2020;46(5):1208–1215. doi:10.1016/j.ultrasmedbio.2020.01.019 [PubMed: 32102740]
28. Arkadir D, Dinur T, Becker Cohen M, et al. Prodromal substantia nigra sonography undermines suggested association between substrate accumulation and the risk for GBA-related Parkinson's disease. Eur J Neurol. Jul 2019;26(7):1013–1018. doi:10.1111/ene.13927 [PubMed: 30714262]
29. Berg D, Merz B, Reiners K, Naumann M, Becker G. Five-year follow-up study of hyperechogenicity of the substantia nigra in Parkinson's disease. Mov Disord. Mar 2005;20(3):383–5. doi:10.1002/mds.20311 [PubMed: 15486999]
30. Yu SY, Cao CJ, Zuo LJ, et al. Clinical features and dysfunctions of iron metabolism in Parkinson disease patients with hyper echogenicity in substantia nigra: a cross-sectional study. BMC Neurol. Jan 17 2018;18(1):9. doi:10.1186/s12883-018-1016-5 [PubMed: 29343241]
31. Walter U Substantia nigra hyperechogenicity is a risk marker of Parkinson's disease: no. J Neural Transm (Vienna). Apr 2011;118(4):607–12. doi:10.1007/s00702-010-0564-7 [PubMed: 21190047]

32. Gallagher CL, Oakes TR, Johnson SC, et al. Rate of 6-[18F]fluorodopa uptake decline in striatal subregions in Parkinson's disease. Mov Disord. Mar 2011;26(4):614–20. doi:10.1002/mds.23503 [PubMed: 21449008]

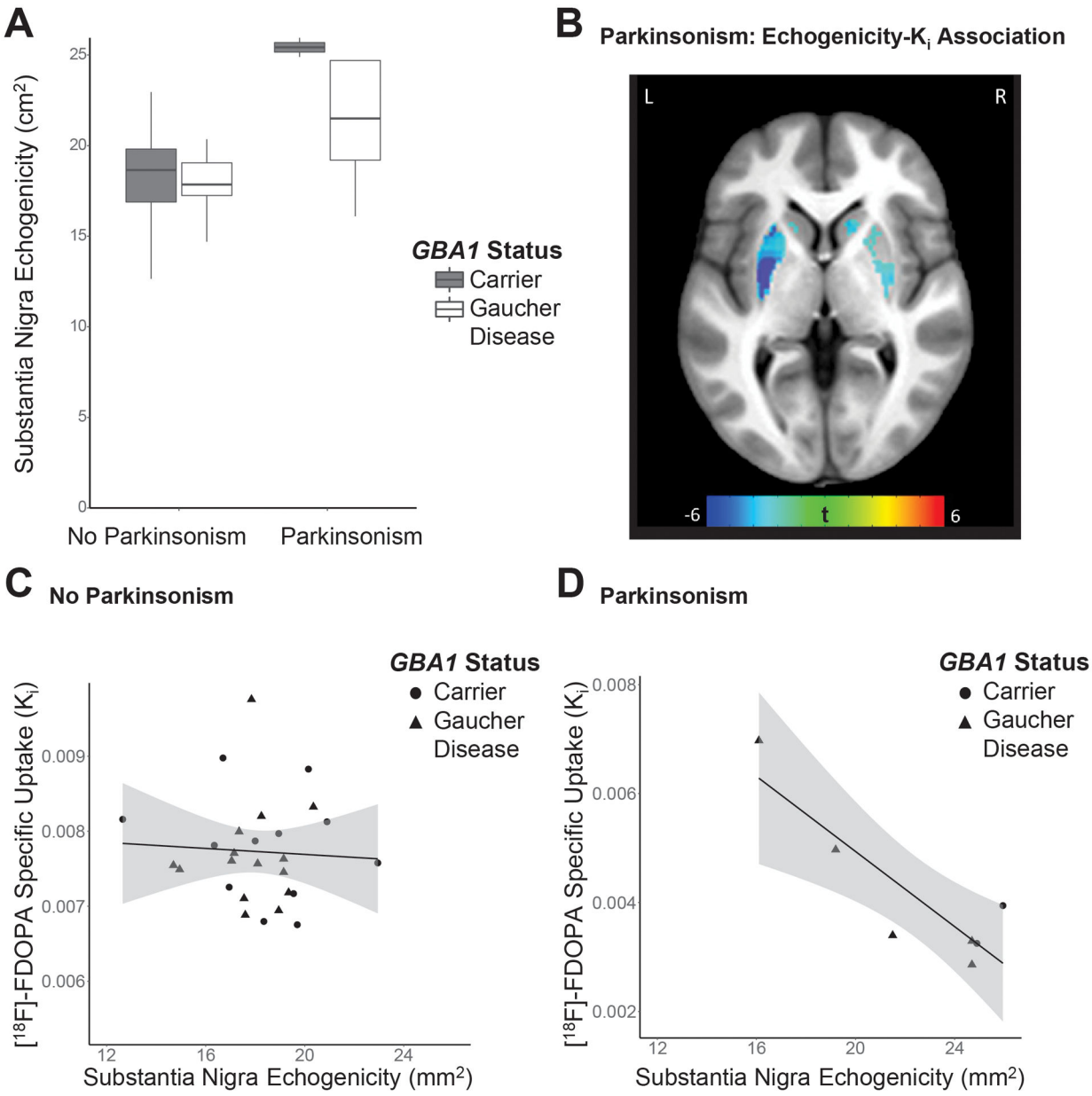

Figure 1.

Substantia nigra echogenicity and striatal presynaptic dopamine synthesis in individuals with *GBA1* mutations. A. Boxplots show size of substantia nigra echogenic area by clinical parkinsonism and *GBA1* mutation group. Centrality lines, hinges and whiskers represent the median, interquartile range, and the farthest datapoint no greater than 1.5 times the interquartile range, respectively. B. Overlying a grayscale anatomical T_1-weighted MRI axial section, a colorized t-value statistical map identifies locales of relationships between average nigral maximal echogenicity area and striatal dopamine synthesis capacity measured with [^{18}F]-FDOPA PET in those with both *GBA1* mutations and parkinsonism. All colored regions meet a voxelwise statistical threshold of $p<0.05$, FDR corrected, and represent two large clusters (peak$_1$ [left posterior putamen]=(−27,−13.5, 6), k_1=1809, t_1=9.59,

p_{FDR}=0.015; $peak_2$ [right caudate head]=(15,16.5,−7.5), k_2=1204, t_2=5.14, p_{FDR}=0.02) C,D. Relationships between substantia nigra echogenicity and bilateral putamen mean K_i are plotted for subjects without (C) and with clinical parkinsonism (D).

Table 1:

Demographic, Genetic, and Clinical Data

	No Parkinsonism, N = 27	Parkinsonism, N = 7
GBA1 Status		
Carrier	12 (44%)	2 (29%)
Gaucher disease	15 (56%)	5 (71%)
Age		
Sex	57 (11, 34–78)	57 (11, 40–72)
Female	13 (48%)	2 (29%)
Male	14 (52%)	5 (71%)
Genotype		
c.84insG/wt	1 (3.7%)	0 (0%)
C342Y/R496H	1 (3.7%)	0 (0%)
L444P/wt	4 (15%)	0 (0%)
N370S/55bpdel	0 (0%)	1 (14%)
N370S/c.84insG	2 (7.4%)	0 (0%)
N370S/L444P	2 (7.4%)	1 (14%)
N370S/N370S	9 (33%)	2 (29%)
N370S/R257Q	0 (0%)	1 (14%)
N370S/V394L	1 (3.7%)	0 (0%)
N370S/wt	6 (22%)	1 (14%)
R120W/wt	0 (0%)	1 (14%)
RecTL/wt	1 (3.7%)	0 (0%)
UPDRS-III	1 (2, 0–8)	26 (13, 7–39)
Duration of Follow-up	6.68 (1.37, 5.26–10.13)	7.43 (1.89, 5.36–11.40)

n (%); Mean (SD, Minimum-Maximum)