REVIEW

Neuroimaging in Glucocerebrosidase-Associated Parkinsonism: A Systematic Review

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ABSTRACT: Background: Mutations in the *GBA* gene cause Gaucher's disease (GD) and constitute the most frequent genetic risk factor for idiopathic Parkinson's disease (iPD). Nonmanifesting carriers of *GBA* mutations/variants (GBA-NMC) constitute a potential PD preclinical population, whereas PD patients carrying some *GBA* mutations/variants (GBA-PD) have a higher risk of a more aggressive disease course. Different neuroimaging techniques are emerging as potential biomarkers in PD and have been used to study GBA-associated parkinsonism.
Objective: The aim is to critically review studies applying neuroimaging to GBA-associated parkinsonism.
Methods: Literature search was performed using PubMed and EMBASE databases (last search February 7, 2022). Studies reporting neuroimaging findings in GBA-PD, GD with and without parkinsonism, and GBA-NMC were included.
Results: Thirty-five studies were included. In longitudinal studies, GBA-PD patients show a more aggressive disease than iPD at both structural magnetic resonance imaging and 123-fluoropropylcarbomethoxyiodophenylnortropane single-photon emission computed tomography. Fluorodeoxyglucose-positron emission tomography and brain perfusion studies reported a greater cortical involvement in GBA-PD compared to iPD. Overall, contrasting evidence is available regarding GBA-NMC for imaging and clinical findings, although subtle differences have been reported compared with healthy controls with no mutations.
Conclusions: Although results must be interpreted with caution due to limitations of the studies, in line with previous clinical observations, GBA-PD showed a more aggressive disease progression in neuroimaging longitudinal studies compared to iPD. Cognitive impairment, a "clinical signature" of GBA-PD, seems to find its neuroimaging correlate in the greater cortical burden displayed by these patients as compared to iPD.

Key Words: 123-fluoropropylcarbomethoxyiodophenylnortropane-SPECT; glucocerebrosidase; magnetic resonance imaging; multiomics; Parkinson's disease; parkinsonism; positron emission tomography; prodromal stage; single-photon emission computed tomography; transcranial sonography

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by multiple motor and nonmotor symptoms.[1] In the past decades, more than 20 genes have been related to parkinsonism.[2] Following the observation of higher risk of developing parkinsonism in patients affected by Gaucher's disease (GD), a lysosomal disorder

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caused by mutations in the *GBA* gene (which encodes for lysosomal glucocerebrosidase -GCase-), *GBA* mutations have been found to constitute the greatest risk factor for sporadic PD, although with variations in mutation frequency based on the characteristics of the observed population.[3] The molecular mechanisms that lead to increased PD risk in *GBA* mutation carriers are multiple and not fully elucidated yet; they include α-synuclein aggregation, lysosomal-autophagy dysfunction, and endoplasmic reticulum stress.[4] *GBA* mutations can be distinguished based on the classification in use for GD: mild mutations are those that cause GD type I (nonneuronpathic), severe mutations are those that cause GD types II and III (neuronpathic)—however, some mutations that are linked to PD are nonpathogenetic in GD.[5] Moreover, dysfunction of GCase has been demonstrated in PD without *GBA* mutations, suggesting its interaction with other pathogenic mechanisms.[6,7]

PD with *GBA* mutations/variants (GBA-PD) does not present pathognomonic features that distinguish it from "idiopathic" PD (iPD). However, depending on the mutation, GBA-PD is associated to an earlier onset; more aggressive disease course and reduced survival; and an increased risk of dementia, motor disability, dysphagia, and autonomic dysfunction.[8,9]

Nonmanifesting carriers of *GBA* mutations/variants (GBA-NMC) and GD patients without parkinsonism constitute a potential preclinical population to study the pathophysiology of the disease and to target in case of development of neuroprotective therapies. In particular, drugs that target GCase pathways are currently under investigation in clinical trials as neuroprotective therapies in PD.[10]

Considering the potential relevance of *GBA* mutations/variants for prognostic and therapeutic applications, the search for GBA-related biomarkers is becoming essential.

In clinical practice, conventional imaging techniques are used to support the diagnosis of PD and to investigate specific clinical features.[1] Other techniques, such as advanced structural magnetic resonance imaging (MRI) or functional MRI (fMRI), are used in research settings (for review, see references 11-13). The focus is on the potential role of neuroimaging as biomarkers for diagnosis, to assess disease progression and monitor therapeutic interventions and to understand the pathophysiology of the disease.[14] In the past years, several studies applied imaging techniques in GBA-PD, GD patients with (GD-p) and without parkinsonism, and GBA-NMC to elucidate aspects of pathogenesis in GBA-PD and to identify at-risk populations.

The aim of the present systematic review is to critically summarize evidence from these studies, to update a previous review on the topic,[15] and to analyze and discuss the emerging controversies in the field, trying to address apparent discrepancies.

Patients and Methods

Search Strategy

Literature search was performed using PubMed and EMBASE (last search: February 7, 2022). Methods and search string are provided in Supplementary Material. The PRISMA flowchart is shown in Supplementary Figure S1. The details of the studies (number of participants, methods, etc.) are presented in Supplementary Table S1 and Tables 1–5. As the definition of "iPD" and "controls" differs across studies, we invite the reader to search for details in Supplementary Table S1.

Results

Structural MRI

Six studies were included (Supplementary Table S1 and Table 1).

PD is not associated with alterations in conventional structural imaging scans.[1] However, advanced MRI techniques allow the quantification of iron accumulation in the substantia nigra (SN) using neuromelanin-sensitive MRI, structural gray matter (GM) changes (eg, GM volume or cortical thickness), and microstructural white matter (WM) integrity. Diffusion tensor imaging (DTI), in particular, allows the assessment of microstructural tissue integrity; the most commonly used DTI indices include fractional anisotropy (FA)—a measure of the directionality of water diffusion—and mean diffusivity—a measure of the absolute magnitude of diffusion (for review, see references 13 and 14).

In GBA-NMC, no structural GM differences have been reported compared to controls[16,19] or to nonmanifesting carriers of *LRKK2* mutations (LRRK2-NMC).[19]

In GD patients (including 2 GD-p patients) a negative correlation between SN echogenicity—a sonographic feature considered to reflect iron accumulation (see later)—and iron-sensitive MRI-T2 hypointensity of SN pars compacta has been reported: the authors suggested that this finding might be related to disturbance in iron metabolism involving deep brain structures in GD.[21]

In a study, GBA-PD patients showed a left-sided prevalent pattern of cortical thinning involving mainly temporal, parietal, and occipital regions compared to iPD and controls.[18] Longitudinal follow-up of this cohort showed a greater cortical thinning of posterior regions and additional greater involvement of frontal and orbitofrontal lobes in GBA-PD compared to iPD, whereas the pattern of subcortical GM atrophy was similar in the two PD groups. After 5 years, iPD patients reached a similar pattern of cortical thinning to GBA-PD at baseline. These imaging findings were in line with clinical observations demonstrating a more rapid trajectory of motor and cognitive impairment in GBA-PD compared to iPD.[18] Also a study conducted

TABLE 1 *Magnetic resonance imaging studies*

Structural MRI

Studies	MRI method	Sample	Clinical features	Cognition	Clinical findings	Imaging findings	Conclusions
Sezgin et al[16]	Whole-brain analysis	18 GBA-NMC, 17 CTRL	Age GBA-NMC = 43.7 ± 7.8, CTRL = 44 ± 9.2 UPDRS III GBA-NMC = 0.2 ± 0.9, CTRL = 0 ± 0	MMSE GBA-NMC = 28.8 ± 1.2, CTRL = 29.6 ± 0.7	GBA-NMC = no differences (vs. CTRL)	No differences in GM (vs. CTRL)	No *GBA*-specific patterns
Caminiti et al[17a]	ROI-based analysis	46 GBA-PD, 339 iPD (281 LO-iPD, 58 EO-iPD), 59 CTRL	Age GBA-PD = 58.9 ± 9.6, EO-iPD = 47 ± 4.8, LO-iPD = 64.8 ± 7.1, CTRL = 59.2 ± 10.7 UPDRS III GBA-PD = 28.9 ± 10.2, EO-iPD = 21.7 ± 10.8, LO-iPD = 26.7 ± 12.2 HY GBA-PD = 1.9 ± 0.3, EO-iPD = 1.6 ± 0.5, LO-iPD = 1.8 ± 0.6	MoCA GBA-PD = 26.9 ± 2.5, EO-iPD = 28.1 ± 2.3, LO-iPD = 27 ± 2.3, CTRL = IC > 26	GBA-PD = ↑ HY, UPDRS III, UPDRS total, SCOPA-AUT, ↓ MoCA (vs. EO-iPD); ↑ RBDSQ (vs. EO-iPD and LO-iPD)	GBA-PD = ↓ GM volume of whole left putamen, whole right putamen, left anterior putamen, right anterior putamen, right posterior putamen, left ventral striatum, right ventral striatum, right thalamus, left hippocampus, right hippocampus, left amygdala, right amygdala (vs. EO-iPD) and left posterior putamen, right caudate nucleus, right thalamus (vs. LO-iPD)	GBA-PD = more aggressive disease (vs. EO-iPD)
Leocadi et al[18b]	Whole-brain/ROI-based analysis	10 GBA-PD, 20 iPD, 22 CTRL	Baseline Age GBA-PD = 62.1 ± 4.9, iPD = 62.4 ± 5.2, CTRL = 62.1 ± 5.6 UPDRS III GBA-PD = 15.4 ± 6.5, iPD = 15.5 ± 4.3 HY GBA-PD = 1.1 ± 0.2, iPD = 1.0 ± 0.1 5-year follow-up UPDRS III GBA-PD = 46.8 ± 3.7, iPD = 30.7 ± 11.0 HY GBA-PD = 2.8 ± 0.7, iPD = 2.1 ± 0.5	MMSE GBA-PD = 28.1 ± 1.7, iPD = 28.9 ± 1.2, CTRL = 29.8 ± 0.5 GBA-PD ↑ motor and cognitive deterioration[c] (vs. iPD)	GBA-PD = no differences (vs. iPD); ↓ MMSE (vs. CTRL)	GBA-PD = ↑ cortical thinning of left temporal, parietal, and occipital gyri (vs. CTRL and iPD) GBA-PD = ↑ cortical thinning of posterior regions, frontal and orbitofrontal cortices; similar pattern of subcortical, hippocampal, and amygdala volume loss (vs. iPD)	GBA-PD = faster cortical disease progression, similar topographic trajectories of brain damage, similar subcortical progression (vs. iPD)
Thaler et al[19]	ROI-based analysis	12 GBA-PD, 9 LRRK2-PD, 57 iPD, 14 GBA-NMC, 41 LRRK2-NMC, 49 CTRL	Age GBA-PD = 65.5 ± 11.4, LRRK2-PD = 60.4 ± 12.5, iPD = 65.3 ± 9, GBA-NMC = 49.3 ± 8.9, LRRK2-NMC = 49 ± 10.9, CTRL = 47.5 ± 11.5 UPDRS III GBA-PD = 42 ± 20.9, LRRK2-PD = 50.7 ± 29.9, iPD = 34.1 ± 18.2, GBA-NMC = 1.3 ± 1.8, LRRK2-NMC = 1.9 ± 2, CTRL = 1.8 ± 1.6	MoCA GBA-PD = 24.8 ± 4.6, LRRK2-PD = 26.6 ± 2.9, iPD = 25.5 ± 2.6, GBA-NMC = 26.8 ± 2.3, LRRK2-NMC = 26.3 ± 2.8, CTRL = 26.7 ± 2.2	GBA-PD = no difference (vs. iPD); GBA-PD and iPD = ↓ disease duration, motor symptoms, depression, ↑ hyposmia (vs. LRRK2-PD) No differences between NMC groups	PD (all) = ↓ subcortical volumes and cortical thinning (vs. CTRL); no difference related to genetics	No *GBA*-specific patterns
Agosta et al[20]	Whole-brain/ROI-based analysis	15 GBA-PD, 14 iPD, 16 CTRL	Age GBA-PD = 64 ± 8, iPD = 64 ± 7, CTRL = 64 ± 8 UPDRS III GBA-PD = 40 ± 18, iPD = 32 ± 9 HY GBA-PD = 2.8 ± 1, iPD = 2.7 ± 0.8	MMSE GBA-PD = 28 ± 3, iPD = 27 ± 2	3 GBA-PD had dementia (MDS criteria) vs. 0 in other groups No other differences between GBA-PD and iPD	GBA-PD = ↓ FA olfactory tracts, corpus callosum, and anterior limb of the internal capsule bilaterally, right anterior external capsule, and left cingulum, parahippocampal tract, parietal portion of the superior longitudinal fasciculus, and occipital white matter (vs. CTRL); external capsule bilaterally and left SLF (vs. iPD); body and genu of the corpus callosum, olfactory tract, anterior limb of the internal capsule, cingulum bilaterally (vs. iPD and CTRL) No differences in GM volumes between GBA-PD, iPD, and CTRL	GBA-PD = widespread WM alterations (vs. iPD)

(Continues)

TABLE 1 *Continued*

Studies	MRI method	Sample	Clinical features	Cognition	Clinical findings	Imaging findings	Conclusions
Structural MRI							
Böttcher et al[21]	ROI-based analysis	2 GD-p, 6 GD	Age GD-p = 49, 62, GD = 21-66 UPDRS III GD-p = 15.5, GD = 0-1	IC = MMSE ≥ 25	Whole group GD and GD-p = ↑ executive dysfunction and depression (vs. CTRL) GD-p = ↑ hyposmia, UPDRS III, NMS (vs. GD)	GD and GD-p = negative correlation between SN echogenic size and T2—hypointensity of SN pars compacta but not pars reticulata	GD = possible iron metabolism alterations in SN
MRI spectroscopy (MRSI)							
Brockmann et al[22]	Combined proton (1H) and phosphorus (31P) MRSI	13 GBA-PD, 19 CTRL	Age GBA-PD = 56 (30–69), CTRL = 54 (40–71) UPDRS III GBA-PD = 32 (17–43) HY GBA-PD = 2.5 (2–4.5)	NA	NA	GBA-PD = ↓ NAA in the putamen and in the midbrain; ↓ tCho in the midbrain, ↑ GPE in the putamen (vs. CTRL) No difference in ATP, ADP, Pi, and PCr	GBA-PD = altered membrane phospholipid metabolism vs. CTRL No energy dysfunction
Functional MRI (fMRI)							
Sezgin et al[16]	Resting-state fMRI	18 GBA-NMC, 17 CTRL	Age GBA-NMC = 43.7 ± 7.8, CTRL = 44 ± 9.2 UPDRS III GBA-NMC = 0.2 ± 0.9, CTRL = 0 ± 0	MMSE GBA-NMC = 28.8 ± 1.2, CTRL = 29.6 ± 0.7	GBA-PD = no differences (vs. CTRL)	GBA-NMC = ↑ FC between left posterior putamen and left postcentral gyrus, between left caudate and right parietal operculum and planum temporale (vs. CTRL)	GBA-NMC = alterations in striatocortical FC and early impairment of somatosensory system (vs. CTRL)
Greuel et al[23]	Resting-state fMRI (OFF condition)[d]	13 GBA-PD, 42 iPD	Age GBA-PD = 66.7 ± 8.6, iPD = 65.0 ± 10.2 UPDRS III GBA-PD = 25.3 ± 9.8, iPD = 23.7 ± 9.1 HY GBA-PD = 2 (2–3), iPD = 2.5 (1–3)	Dementia was excluded (MDS criteria)	GBA-PD = ↓ global cognition *z* score,[e] ↓ BDI-II (vs. iPD)	GBA-PD = ↓ FC between the caudate nucleus and the occipital cortex and between the right nucleus accumbens and the left superior parietal and right fusiform cortex (vs. iPD)	GBA-PD = more severe alterations vs. iPD, even in carriers without dementia
Bregman et al[24]	Task fMRI = Stroop interference task and N-back working memory task	10 GBA-NMC, 21 LRRK2-NMC, 22 CTRL	Age GBA-NMC = 50.4 ± 2.39, LRKK2-NMC = 47.9 ± 1.79, CTRL = 50.0 ± 2.6 UPDRS III GBA-NMC = 0.7 ± 0.4, LRKK2-NMC = 2.2 ± 0.5, CTRL = 1.3 ± 0.3	IC = MoCA > 23	GBA-PD = no differences (vs. LRRK2-NMC and CTRL)	GBA-NMC = ↑ FC activity in cognitive tasks in the bilateral medial frontal and precentral gyri and ↓ FC activity in cognitive tasks in the lingual gyrus (vs. LRRK2-NMC and CTRL)	GBA-NMC = ↑ activation patterns in the Stroop task, possible compensatory mechanism

Studies are ordered chronologically. If not specified, the studies are cross-sectional. Information on how controls and iPD were selected is provided in Supplementary Table S1. See Supplementary Table S1 for details of classification of GBA mutations/variants. When available, mean ± standard deviation is reported; otherwise, mean, range (separated by –), single values (separated by comma), or IC is reported. If no information is available, NA is reported. If details for the subgroup that underwent imaging study are not available, results for the whole group are reported.

[a]Subjects from the Parkinson's Progression Markers Initiative (PPMI) cohort.

[b]Longitudinal study. The study is divided into two rows for clarity in the table: the second row refers to the longitudinal analysis, 5-year follow-up.

[c]Compared to iPD, GBA-PD showed a greater disease severity progression (HY and UPDRS total and subscores II and III). Compared to iPD, GBA-PD worsened over time in terms of attentive and visuospatial skills and in their ability to inhibit cognitive interference. Group × time interactions also showed that GBA-PD patients progressed in visuospatial deficits more than iPD.

[d]Antiparkinsonian medication was discontinued for a minimum of 12 hours (levodopa) and up to 3 days (dopamine agonists).

[e]A cognitive test battery covered the following domains: executive function, memory, attention, language, and visual–spatial abilities, from which a global cognition *z* score was computed using age- and education-adjusted standard norms. The global cognition *z* score was significantly lower when the BDI-II score was included as a covariate.

Abbreviations: MRI, magnetic resonance imaging; GBA-NMC, nonmanifesting carriers of *GBA* mutations/variants; CTRL, controls; UPDRS III, Unified Parkinson's Disease Rating Scale, Part III; MMSE, Mini-Mental State Exam; GM, gray matter; ROI, region of interest; iPD, idiopathic Parkinson's disease; LO-iPD, late-onset idiopathic Parkinson's disease; EO-iPD, early-onset idiopathic Parkinson's disease; GBA-PD, Parkinson's disease with GBA mutations/variants; HY, Hoen and Yahr score; MoCA, Montreal Cognitive Assessment; SCOPA-AUT, Scale for Outcomes in Parkinson's disease-Autonomic; RBDSQ, REM Sleep Behavior Disorder Screening Questionnaire; LRRK2-PD, Parkinson disease with *LRRK2* mutations; LRRK2-NMC, nonmanifesting carriers of *LRRK2* mutations/variants; FA, fractional anisotropy; SLF, superior longitudinal fasciculus; WM, white matter; GD-p, GD with parkinsonism; GD, Gaucher's disease; IC, inclusion criteria; NMS, nonmotor symptoms; SN, substantia nigra; MRSI, magnetic resonance spectroscopic imaging; NA, not available; NAA, *N*-acetylaspartate; tCho, total choline; GPE, glycerophosphoethanolamine; ATP, adenosine triphosphate; ADP, adenosine diphosphate; Pi, inorganic phosphate; PCr, phosphocreatine; MDS, Movement Disorder Society; BDI-II, Beck's Depression Inventory, II; FC, functional connectivity.

on the Parkinson's Progression Markers Initiative (PPMI) cohort reported significant GM differences in GBA-PD compared with iPD patients.[17] In particular, both GBA-PD and late-onset (LO)-iPD showed greater structural volume reductions compared with the early-onset (EO)-iPD group. The clinical follow-up (up to 6 years) in this cohort showed greater worsening in motor, cognitive, and autonomic functions in GBA-PD versus EO-iPD and in LO-iPD versus EO-iPD but no differences between GBA-iPD and LO-iPD. LO-iPD is associated with a more aggressive form of disease[51]: the findings of this study (see the Nigrostriatal Imaging section) support the hypothesis that *GBA* mutations participate to accelerate the neurodegenerative processes in PD.[17]

Conversely, in other studies, no differences in GM have been reported between GBA-PD, iPD, and controls[20] and between GBA-PD, PD with *LRRK2* mutations (LRRK2-PD), and iPD,[19] although, in the latter study, lower GM volumes were reported in bilateral hippocampus, nucleus accumbens, caudate, thalamus, putamen and amygdala, and the right pallidum in patients with PD (eg, GBA-PD, LRRK2-PD, and iPD) compared to unaffected participants (eg, GBA-NMC, LRRK2-NMC, and controls).

Differences in microstructural WM integrity that may have an impact on the clinical manifestations of the disease, including cognitive impairment, have been reported in GBA-PD.[20] Compared with controls, GBA-PD showed decreased FA bilaterally in the olfactory tracts; genu and body of the corpus callosum; and anterior limb of the internal capsule and in the right anterior external capsule, left cingulum bundle, left parahippocampal tract, left parietal portion of the superior longitudinal fasciculus (SLF), and left occipital WM. Compared to iPD, GBA-PD showed decreased FA in the external capsule bilaterally and left SLF. Compared with both controls and iPD, GBA-PD showed decreased FA in the body and genu of the corpus callosum, olfactory tract, anterior limb of the internal capsule, and cingulum bilaterally. In all PD patients, FA values of the body and genu of the corpus callosum, external capsule, and olfactory tracts correlated with verbal fluency. No differences in WM were reported between iPD and controls.[20]

MR Spectroscopy

One study was included (Supplementary Table S1 and Table 1).

Proton MR spectroscopy of the brain is a noninvasive, in vivo technique that allows investigation into regional chemical environments.[14] Only one study applied MR spectroscopy to the study of GBA-PD.[22] Compared with controls, mesostriatal membrane metabolites (eg, *N*-acetylaspartate [NAA]), but not energy status (high-energy phosphates and low-energy metabolites), were altered in GBA-PD, suggesting that a primary membrane dysfunction, rather than energetic metabolism dysfunction, may underlie the pathogenesis of GBA-PD. It must be considered, however, that lowered NAA has also been detected in the SN and other regions in iPD compared to controls[14]: indeed, in the absence of iPD controls, it is not possible to determine whether these findings are related to the neurodegenerative mechanism underlying PD, in general, or to *GBA* mutations/variants, in particular.[22]

Functional MRI

Three studies were included (Supplementary Table S1 and Table 1).

Two fMRI approaches exist to study brain neuronal activity: resting-state fMRI and task-based fMRI.[11-13] The first method measures the intrinsic fluctuations of the BOLD signal between different brain regions during rest to assess functional connectivity alterations within and between resting-state functional networks. Task-based fMRI includes the performance of a task during the fMRI acquisition, eliciting the activation of task-specific areas (eg, motor, sensitive, and visual). This approach is useful to assess specific patterns of brain activity changes in different conditions or after specific trainings.

A study[16] showed increased resting-state functional connectivity between left posterior putamen and left postcentral gyrus and between left caudate and right parietal operculum and planum temporale in GBA-NMC compared to controls. The authors suggest that an early impairment of the striato-somatosensory network might precede the involvement of the motor system and, thus, the appearance of symptoms in GBA carriers. Another study[24] focused on GBA-NMC and controls, including LRKK2-NMC. Differently from the previous study, the aim was the evaluation of cognitive task performance in the presymptomatic stage of PD. The authors characterized the cognitive profile and functional activation patterns of GBA-NMC in depth while performing two separate fMRI cognitive tasks (Stroop interference task and N-back working memory task). Similar cognitive and task-related performance combined with a higher functional activity in the right medial frontal gyrus and reduced task-related activity in the left lingual gyrus during the Stroop task was found in GBA-NMC relative to LRRK2-NMC and controls. On the N-back task, no whole-brain differences were found between groups. The authors suggest that GBA-NMC present differential cerebral compensatory mechanism that might allow adequate cognitive performance in the preclinical stages of PD.

Only one study explored the resting-state fMRI features in GBA-PD patients in OFF condition.[23] Although

TABLE 2 *Positron emission tomography studies*

Studies	Sample	Clinical features	Cognition	Clinical findings	Imaging findings	Conclusions
2-Deoxy-2-[fluorine-18]fluoro-D-glucose PET						
Greuel et al[23]	12 GBA-PD, 34 iPD	Whole group Age 66.7 ± 8.6 HY 2 (2–3) UPDRS III 25.3 ± 9.8 No data available on subgroups	Dementia was excluded (MDS criteria)	GBA-PD = ↓ global cognition *z* score,[a] ↓ BDI-II (vs. iPD)	GBA-PD = ↑ PDRP expression; trend for higher expression of PDCP; ↓ metabolism in medial and lateral parietal cortex (vs. iPD)	GBA-PD = more severe alterations vs. iPD, even in carriers without dementia
Schindlbeck et al[25]	12 GBA-PD (including 2 GD-p), 14 LRRK2-PD, 14 iPD, 14 CTRL	Age GBA-PD = 56.5 ± 5.9, LRRK2-PD = 58.2 ± 14.4, iPD = 59.6 ± 5.3, CTRL = 58.9 ± 8.6 UPDRS III (OFF) GBA-PD = 20.2 ± 7.2, iPD = 19.5 ± 6.1, LRRK2-PD = 18.3 ± 8.1	Dementia was excluded (IC = MMSE >26 or MDRS >140)	Only akinetic-rigid PD No differences between groups	GBA-PD = ↑ PDRP (vs. LRRK2-PD and iPD) GBA-PD = ↑ PDCP (vs. CTRL) Graph analysis: in GBA-PD ↑connectivity outside the PDRP core, along with ↑ expression of the whole network	GBA-PD = more aggressive disease vs. iPD and LRRK2-PD
Barrett et al[26]	3 GBA-PD	Age 64–69, UPDRS III/HY NA	UPDRS I mentation score = 0–2	NA	GBA-PD = PDRP comparable to iPD; ↑ metabolism in lentiform nuclei; ↓ metabolism in parietal, anteromedial frontal, parieto-occipital, and temporal cortex	GBA-PD = findings consistent with iPD
Kono et al[27]	3 GBA-PD (including 1 GD), 3 GBA-NMC	Age GBA-PD = 44–76, GBA-NMC = 47–74 HY GBA-PD = 3–4 UPDRS III GBA-PD = 16–21	MMSE GBA-PD = 24–30, GBA-NMC = 24–30	Only akinetic-rigid PD All GBA = ↓ FAB scores (vs. normal values)	All = ↓ metabolism in the medial frontal cortex, including the SMA; GBA-PD = ↓ metabolism in parieto-occipital cortex	SMA hypometabolism may be related to the clinical characteristics (akinesia) of GBA-PD
Saunders-Pullman et al[28]	2 GD-p	Age 54–58 UPDRS III/HY NA	Cognitive dysfunction in both patients	Atypical features in both patients[b]	GD-p = ↑ metabolism in the lentiform nuclei, bilateral ↓ metabolism in parieto-occipital, anteromedial frontal, and temporal cortex	GBA-PD = findings consistent with moderately advanced iPD with cognitive impairment
Microglial activation (11C-(R)-PK11195 binding potentials)						
Mullin et al[29]	5 GD, 4 GBA-NMC, 20 CTRL	Age GD = 62.6 ± 2.9, GBA-NMC = 63.3 ± 7 UPDRS III GD = 12.8 ± 10.4, GBA-NMC = 4.5 ± 2.4	MoCA GD = 27.4 ± 1.9, GBA-NMC = 27.8 ± 2.2	NA	GBA-NMC and GD = ↑ binding potential in the SN (correlated with hyposmia), occipital and temporal lobes, cerebellum, hippocampus, and mesencephalon (vs. CTRL); no correlation with 123-FP-CIT SPECT	GD and GBA-NMC = ↑ microglial activity in brain regions susceptible to Lewy body formation—possible cytotoxic or neuroprotective process

Studies are ordered chronologically. If not specified, the studies are cross-sectional. Information on how controls and iPD were selected is provided in Supplementary Table S1. See Supplementary Table S1 for details of classification of GBA mutations/variants. When available, mean ± standard deviation is reported; otherwise, mean, range (separated by –), single values (separated by comma), or IC is reported. If no information is available, NA is reported. If details for the subgroup that underwent imaging study are not available, results for the whole group are reported.

[a]A cognitive test battery covered the following domains: executive function, memory, attention, language, and visual–spatial abilities, from which a global cognition *z* score was computed using age- and education-adjusted standard norms. The global cognition *z* score was significantly lower when the BDI-II score was included as a covariate.

[b]One patient showed medication sensitivity; progressive cognitive deterioration with cognitive fluctuations; and prominent deficits in spatial processing, semantic language, and attention. The other patient showed fluctuations in attention and memory, moderate letter fluency difficulties, mild bradyphrenia, executive dysfunction, and spatial processing deficits.

Abbreviations: PET, positron emission tomography; GBA-PD, Parkinson's disease with GBA mutations/variants; iPD, idiopathic Parkinson's disease; UPDRS III, Unified Parkinson's Disease Rating Scale, Part III; MDS, Movement Disorder Society; BDI-II, Beck's Depression Inventory, II; PDRP, PD-related pattern; PDCP, PD-cognitive pattern; GD-p, GD with parkinsonism; LRRK2-PD, Parkinson's disease with *LRRK2* mutations; CTRL, controls; IC, inclusion criteria; MMSE, Mini-Mental State Exam; MDRS, Mattis Dementia Rating Scale; HY, Hoen and Yahr score; NA, not available; GBA-NMC, nonmanifesting carriers of *GBA* mutations/variants; FAB, frontal assessment battery; SMA, supplemental motor area; GD, Gaucher's disease; MoCA, Montreal Cognitive Assessment; SN, substantia nigra; 123-FP-CIT-SPECT, dopamine transporter 123-I ioflupane single-photon emission computed tomography imaging.

TABLE 3 *Brain perfusion imaging studies*

Studies	Technique	Sample	Clinical features	Cognition	Clinical findings	Imaging findings	Conclusions
Ichinose et al[30]	IMP-SPECT	2 GBA-PD, 5 GBA-NMC	Age GBA-PD = 49,62; GBA-NMC = 49–77 UPDRS III/HY NA	1 GBA-PD = MCI	Only akinetic-rigid PD	1 GBA-PD subject (with MCI) = ↓ perfusion in occipital lobes	GBA-NMC = no abnormal findings; 1 GBA-PD = occipital hypoperfusion
Cilia et al[31a]	Technetium-99m SPECT	35 GBA-PD, 38 iPD, 32 DLB	Whole group Age GBA-PD = 64.3 ± 9.7, iPD = 69.4 ± 10.2, DLB = NA UPDRS III GBA-PD = 22.4 ± 12, iPD = 21.1 ± 11.3, DLB = 23.2 ± 9	MMSE GBA-iPD = 28.6 ± 1.3, PD = 28.6 ± 1.9, DLB = 19.4 ± 3.8	GBA-PD = ↓ age at onset, MMSE, ↑ dementia (vs. iPD)	All GBA-PD = ↓ perfusion in posterior parietal and occipital lobes (vs. iPD); GBA-PD severe mutations = ↓ perfusion in parietal lobes (vs. GBA-PD mild mutations) GBA-PD severe mutations = ↓ perfusion in posterior parietal and occipital lobes (vs. iPD) DLB = ↓ perfusion in posterior parietal, occipital, and dorsolateral prefrontal cortex (vs. GBA-PD mild mutations and iPD) No differences between GBA-PD mild mutations and iPD	GBA-PD severe mutations = similar pattern to DLB; GBA-PD mild mutations = similar pattern to iPD
Oeda et al[32] 2015[b]	IMP-SPECT	12 GBA-PD, 45 iPD	Whole group Age GBA-PD 58.9 ± 3.3, iPD = 61.0 ± 1.3 UPDRS III GBA-PD = 28.5, iPD = 23.6	MMSE GBA-PD = 23.7, iPD = 25.8	GBA-PD = ↑ dementia and psychosis (vs. iPD)[c]	GBA-PD = ↓ perfusion in the bilateral parietal cortex, including the precuneus (vs. iPD)	GBA-PD = greater parietal perfusion dysfunction relative to iPD
Goker-Alpan et al[33]	$H_2{}^{15}O$ PET	7 GD-p, 14 GD, 11 iPD, 7 GBA-NMC, 68 CTRL	Age GD-p = 56.6 ± 9.2, GD = 52.6 ± 12.4, iPD = 62.1 ± 7.1, GBA-NMC = 50.1 ± 18.0, UPDRS-III GD-p = 27.4 ± 8.2, iPD = 27.5 ± 10.5 HY GD-p = 2.4 ± 0.7, iPD = 1.9 ± 0.7	IQ (WAIS) GD-p = 97.3 ± 8.4, iPD = 108.6 ± 35.6	GD-p = ↑ right-sided symptoms than iPD	GD-p = ↓ perfusion in lateral parieto-occipital association cortex and precuneus bilaterally compared to CTRL and iPD	GD-p = greater parieto-occipital perfusion dysfunction relative to iPD

Studies are ordered chronologically. If not specified, the studies are cross-sectional. Information on how controls and iPD were selected is provided in Supplementary Table S1. See Supplementary Table S1 for details of classification of GBA mutations/variants. When available, mean ± standard deviation is reported; otherwise, mean, range (separated by –), single values (separated by comma), or inclusion criteria is reported. If no information is available, NA is reported. If details for the subgroup that underwent imaging study are not available, results for the whole group are reported.

[a]Retrospective-longitudinal study. Technetium-99m SPECT was performed once, after 8.3 ± 4.7 years from disease onset in GBA-PD, 8.3 ± 4.4 years in iPD, and 8.2 ± 3.5 years in DLB.

[b]Retrospective study. IMP-SPECT was performed once, after 7.3 ± 1.5 years from disease onset in GBA-PD and 7.1 ± 0.7 years in iPD.

[c]GBA-PD showed increased hazard ratios for dementia (8.3) and psychosis (3.1) versus iPD.

Abbreviations: IMP-SPECT, *N*-isopropyl-p-[123I]iodoamphetamine single-photon emission computed tomography; GBA-PD, Parkinson's disease with GBA mutations/variants; GBA-NMC, nonmanifesting carriers of *GBA* mutations/variants; UPDRS III, Unified Parkinson's Disease Rating Scale, Part III; HY, Hoen and Yahr score; NA, not available; MCI, mild cognitive impairment; iPD, idiopathic Parkinson's disease; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Exam; PET, positron emission tomography; GD-p, GD with parkinsonism; GD, Gaucher's disease; IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; CTRL, controls.

TABLE 4 *Nigrostriatal imaging studies*

Studies	Sample	Clinical features	Cognition	Clinical findings	Imaging findings	Conclusions
[^{18}F] FDopa PET						
Eisenberg et al[34c]	5 GD-p, 15 GD, 2 GBA-PD, 12 GBA-NMC	UPDRS III GD-p and GBA-PD = 26 ± 13, GD and GBA-NMC = 1 ± 2	NA	NA	Inverse correlation between uptake and SN hyperechogenity in GD-p and GBA-PD	Correspondence between transcranial sonography and [18F]FDopa PET only in GD-p and GBA-PD
Mullin et al[29]	5 GD, 4 GBA-NMC, 9 CTRL	Age GD = 62.6 ± 2.9, GBA-NMC = 63.3 ± 7 UPDRS III GD = 12.8 ± 10.4, GBA-NMC = 4.5 ± 2.4	MoCA GD = 27.4 ± 1.9, GBA-NMC = 27.8 ± 2.2	No patient had parkinsonism	Normal uptake GD and GBA-NMC = ↑ variance in uptake (vs. CTRL)	GD and GBA-NMC = ↑ uptake might be a compensatory mechanism
Lopez et al[35a]	Baseline 11 GD-p, 26 GD, 4 GBA-PD, 16 GBA-NMC, 98 CTRL	Age GD + GD-p = 56 ± 12, GBA-PD + GBA-NMC = 57 ± 12, CTRL = 54 ± 11 UPDRS III/HY = NA	NA	NA	GD-p and GBA-PD = ↓ striatal uptake (>putamen) (vs. GD and GBA-NMC)	GD-p and GBA-PD = findings consistent with iPD; no findings in GD and GBA-NMC
	1.5 to 12 year follow-up 5 GD-p, 15 GD, 2 GBA-PD, 11 GBA-NMC, and 15 CTRL	Age GD + GD-p = 62 ± 9, GBA-PD + GBA-NMC = 58 ± 14, CTRL = 59 ± 7 UPDRS III GD = 0–12, GBA-NMC = 2–9, other NA	NA	Only 1 GBA-NMC developed parkinsonism	GD-p and GBA-PD = ↓ uptake, 4% per year in the caudate, 5% per year in the putamen (vs. baseline)	GD-p and GBA-PD = ↓ uptake GD and GBA-NMC = no ↓ uptake No relationship between ^{18}F-dopa uptake and prodromal features
Greuel et al[23]	7 GBA-PD, 31 iPD	Whole group Age = 66.7 ± 8.6 HY = 2 (2–3) UPDRS III = 25.3 ± 9.8	Dementia was excluded (MDS criteria)	GBA-PD = ↓ global cognition z score,[b] ↓ BDI-II	GBA-PD = ↓ uptake in the bilateral caudate nuclei, anteromedial putamen ipsilateral, and nucleus accumbens contralateral to the more affected body side (vs. iPD)	GBA-PD = more severe alterations vs. iPD, even in carriers without dementia
Barrett et al[26]	2 GBA-PD	Age = 39, 59 UPDRS = III/HY NA	UPDRS I mentation score = 1, 0	NA	GBA-PD = ↓ striatal uptake in the bilateral caudate nuclei	GBA-PD = findings consistent with iPD
Goker-Alpan et al[33]	7 GD-p, 14 GD, 11 iPD, 7 GBA-NMC, 68 CTRL	Age GD-p = 56.6 ± 9.2, GD = 52.6 ± 12.4, iPD = 62.1 ± 7.1, GBA-NMC = 50.1 ± 18.0, UPDRS III GD-p = 27.4 ± 8.2, iPD = 27.5 ± 10.5 HY GD-p = 2.4 ± 0.7, iPD = 1.9 ± 0.7	IQ (WAIS) GD-p = 97.3 ± 8.4, iPD = 108.6 ± 35.6	More GD-p presented with right-sided symptoms than iPD	GD-p, GD, and iPD = ↓ striatal (>putamen) uptake	GD-p = findings consistent with iPD GD = ↓ putaminal dopamine synthesis but effect driven by 2 subjects
Saunders-Pullman et al[28]	2 GBA-PD	Age = 60, 54 UPDRS III/HY = NA	Cognitive dysfunction in both patients	Atypical features in 1 patient[c]	In both = bilateral ↓ striatal uptake	GBA-PD = findings consistent with iPD
Kraoua et al[36]	2 GD-p	Age = 41, 61 UPDRS III/HY = NA	1 had dementia	Atypical features in one patient[d]	In both = bilateral ↓ striatal uptake	GD-p = findings consistent with iPD

(Continues)

TABLE 4 *Continued*

Studies	Sample	Clinical features	Cognition	Clinical findings	Imaging findings	Conclusions
[123]I-FP-CIT-SPECT						
Lee et al[37e,f]	39 GBA-PD, 72 LRRK2-PD, 367 iPD, 213 CTRL (PPMI)[f] + 38 iPD and 71 CTRL (GSH cohort)	PPMI cohort Age GBA-PD = 61.5 ± 11.2, LRRK2-PD = 62.0 ± 8.6, iPD = 60.9 ± 11.3, CTRL = 60.9 ± 11.3 UPDRS III GBA-PD = 26.6 ± 11.2, LRRK2-PD = 20.9 ± 9.2, iPD = 20.8 ± 8.7 GSH cohort Age iPD = 62.3 ± 9.7, CTRL = 59.7 ± 10.3 UPDRS III iPD = 24.9 ± 9.1	NA	GBA-PD = ↑ UPDRS III (vs. iPD and LRRK2-PD), LRRK2-PD, and GBA-PD = ↑ disease duration (vs. iPD)	GBA-PD = estimated models showing ↑ decrease in binding and earlier onset of motor symptom (vs. LRRK2-PD and iPD)	GBA-PD = more rapid deterioration of putaminal dopaminergic function during the premotor phase
Caminiti et al[17f,g]	Baseline 46 GBA-PD, 339 iPD (281 LO-iPD, 58 EO-iPD), 59 CTRL	Age GBA-PD = 58.9 ± 9.6, EO-iPD = 47 ± 4.8, LO-iPD = 64.8 ± 7.1, CTRL = 59.2 ± 10.7 HY GBA-PD = 1.9 ± 0.3, EO-iPD = 1.6 ± 0.5, LO-iPD = 1.8 ± 0.6, CTRL = 0 UPDRS III GBA-PD = 28.9 ± 10.2, EO-iPD = 21.7 ± 10.8, LO-iPD = 26.7 ± 12.2	MoCA GBA-PD = 26.9 ± 2.5, EO-iPD = 28.1 ± 2.3, LO-iPD = 27 ± 2.3, CTRL >26	GBA-PD = ↑ HY, UPDRS III, UPDRS total, SCOPA-AUT (vs. EO-iPD); ↑ RBDSQ (vs. EO-iPD and LO-iPD); ↓ MoCA (vs. EO-iPD)	GBA-PD and LO-iPD = ↓ binding in the globus pallidus, hippocampus, and amygdala (vs. EO-iPD) and ↓ binding asymmetry (vs. EO-iPD); GBA-PD = ↓ binding in the ventral striatum (vs. LO-iPD and EO-iPD)	GBA-PD = widespread dopaminergic damage since the early phases; more aggressive clinical course
	2-year follow-up 22 GBA-PD, 146 iPD (127 LO-iPD, 19 EO-iPD), 59 CTRL	Age GBA-PD = 58.1 ± 7.5, EO-iPD = 47.2 ± 5.1, LO-iPD = 65.8 ± 7.5 HY = GBA-PD = 1.8 ± 0.4, EO-iPD = 1.8 ± 0.4, LO-iPD = 1.9 ± 0.5 UPDRS III GBA-PD = 27.2 ± 8.9, EO-iPD = 25 ± 9.3, LO-iPD = 28 ± 11.2	MoCA GBA-PD = 26.3 ± 3.7, EO-iPD = 27.3 ± 3.4, LO-iPD = 25.7 ± 3.3	GBA-PD = ↑ SCOPA-AUT (vs. EO-iPD)	In 2 years EO-iPD and LO-iPD reached the same dopaminergic damage severity as GBA-PD patients in the ventral striatum	
Chung et al[38f]	54 GBA-PD, 354 iPD	Age GBA-PD = 58.9 ± 9.5 iPD = 62.1 ± 9.6 MDS-UPDRS III GBA-PD = 22.2 ± 10.48 iPD = 20.7 ± 8.6	MoCA GBA-PD = 27.2 ± 2.3 iPD = 27 ± 2.4	GBA-PD = ↑ MDS-UPDRS in the less affected side	No difference in binding (vs. iPD)	GBA-PD = reduced motor reserve (vs. iPD)
Simuni et al[39f]	184 *GBA*-NMC, 208 *LRRK2-NMC*, 194 CTRL	Age GBA-NMC = 61.8 ± 6, LRRK2-NMC = 61.6 ± 7.6, CTRL = 60.8 ± 11.3 MDS-UPDRS III CTRL = 1.2 ± 2.2, LRRK2-NMC = 2.8 ± 3.8, GBA-NMC = 2.5 ± 37	MoCA GBA-NMC = 26.8 ± 2.4, LRRK2-NMC = 26.8 ± 2.4, CTRL = 28.2 ± 1.1	GBA-NMC and LRRK2-NMC = ↑ MDS-UPDRS and SCOPA-AUT (vs. CTRL)	↓ Binding in 3% of GBA-NMC and 11% of LRRK2-NMC; GBA-NMC = ↑ striatal binding ratio (vs. CTRL)	GBA-NMC and LRRK2-NMC = subtle motor and nonmotor signs before dopaminergic function deficit

(Continues)

TABLE 4 *Continued*

Studies	Sample	Clinical features	Cognition	Clinical findings	Imaging findings	Conclusions
Simuni et al[40f]	80 GBA-PD, 158 LRRK2-PD, 361 iPD	Age = GBA-PD = 62.7 ± 9.9, LRRK2-PD = 63.8 ± 9.2, iPD = 63.8 ± 9.7 MDS-UPDRS III (OFF) GBA-PD = 26.2 ± 10.8, LRRK2-PD = 22.1 ± 11.6, iPD = 27.2 ± 11.1	MoCA GBA-PD = 26.1 ± 2.9, LRRK2-PD = 25.9 ± 3.2, iPD = 26.2 ± 3.2	GBA-PD = ↑ QUIP scores (vs. iPD); ↑ RBDSQ (vs. LRRK2-PD) GBA-PD and iPD ↑ MDS-UPDRS III (vs. LRRK2-PD)	LRRK2-PD and GBA-PD = ↑ binding in the side contralateral to the more affected body side (vs. iPD)	GBA-PD and LRRK2 = slower decline in dopaminergic function
Ichinose et al[30]	2 GBA-PD, 4 GBA-NMC	Age GBA-PD = 49, 62; GBA-NMC = 77–51 UPDRS III/HY NA	MCI in 1 GBA-PD	NA	↓ Binding in GBA-PD and in 2 of 4 GBA-NMC	No direct correlation between 123-FP-CIT-SPECT and GCase activity
Chahine et al[41f]	38 GBA-NMC, 88 LRRK2-NMC, iPD = 423, RBD = 39, hyposmia = 26	Age GBA-NMC = 63.6 ± 7.5, LRRK2-NMC = 61.6 ± 7.1, iPD = 61.6 ± 9.7, RBD = 69.6 ± 5.5, hyposmia = 68.1 ± 6.2 UPDRS III/HY NA	MoCA GBA-NMC = 27.6 ± 1.8, LLRK2-NMC = 25.6 ± 2.7, iPD = 27.1 ± 2.3, RBD = 25.5 ± 4.3, hyposmia = 27.3 ± 1.7	GBA-NMC = ↓ MoCA and verbal memory (vs. LRRK2-NMC)	RBD = ↓ binding (vs. hyposmia and NMC) Hyposmia = ↓ binding (vs. NMC) No differences in GBA-PD (vs. other groups)	RBD shows ↓ nigrostriatal function vs. other at-risk cohorts
Huertas et al[42h]	298 PD (48 GBA-PD)	NA	34 "probable dementia" and 25 "possible dementia" (MDS criteria)	NA	GBA-PD (deleterious variants) ↓ binding	GBA-PD (deleterious variants) is associated with ↓ striatal binding and ↑ progression to dementia
Cilia et al[31]	18 GBA-PD, 18 iPD, 14 DLB	Whole group Age GBA-PD = 64.3 ± 9.7; iPD = 69.4 ± 10.2 UPDRS III GBA-PD = 22.4 ± 12; iPD = 21.1 ± 11.3 DLB = 23.2 ± 9.1	Dementia in 34.1% GBA-PD and 19.6% iPD	GBA-PD = younger age at onset (vs. iPD)	Binding iPD < GBA-PD < DLB	GBA-PD (severe mutations) = similar findings to DLB GBA-PD (mild mutations) = similar findings to iPD
McNeill et al[43]	7 GBA-PD, 8 SNCA-PD, 3 LRRK2-PD, 12 PRKN-PD, 7 PINK1-PD	Age GBA-PD = 50 ± 13, SNCA-PD = 47.1 ± 7, LRRK2-PD = 51.5 ± 19.5, PRKN-PD = 44 ± 14, PINK1-PD = 42 ± 17, UPDRS III GBA-PD = 29.8 ± 5, SNCA-PD = 36.2 ± 14, LRRK2-PD = 30 ± 13, PRKN-PD = 28.2 ± 12.7, PINK1-PD = 12.8 ± 6	No participant had cognitive impairment	PINK1-PD = ↓ UPDRS III (vs. other groups)	All groups = ↓ binding (vs. normal values) GBA-PD and LRRK2-PD = ↑ asymmetry (vs. other genetic PD)	DAT asymmetry in GBA-PD and LRRK2-PD due to the need for interactions with additional genetic or environmental factors
C11-Raclopride						
Kono et al[27,44]	1 GD-p, 2 GBA-PD, 3 GBA-NMC	Age GD-p = 38, GBA-PD = 71, GBA-NMC = 47–74, HY GD-p = 4, GBA-PD = 3 and 4 UPDRS III GD-p = 21, GBA-PD = 16 and 36	MMSE GD-p = 24, GBA-PD = 24 and 3 GBA-NMC = 24–30	Only akinetic-rigid PD	Normal binding in all	GD-p and GBA-PD = findings consistent with iPD (see also 11 C-CFT PET)

(Continues)

TABLE 4 *Continued*

Studies	Sample	Clinical features	Cognition	Clinical findings	Imaging findings	Conclusions
Kraoua et al[36]	2 GD-p	Age 41, 61 UPDRS III/HY NA	1 had dementia	Atypical features in one patient[d]	Normal binding in both	GD-p = findings consistent with iPD
11 C-CFT [2β-carbomethoxy-3β-(4-fluorophenyl) tropane] PET						
Kono et al[27,44]	1 GD-p, 1 GBA-PD, 3 GBA-NMC	Age GD-p = 38, GBA-PD 71, GBA-NMC = 47–74 HY GD-p = 4, GBA-PD = 3 and 4 UPDRS III GD-p = 21, GBA-PD = 16 and 36	MMSE 1 GD-p = 24, GBA-PD = 24 and 30 GBA-NMC = 24–30	Only akinetic-rigid PD	GBA-NMC = ↑ caudate uptake GBA-PD and GD-p = ↓ striatal uptake	GD-p and GBA-PD = findings consistent with iPD ↑ Binding in GBA-NMC = uncertain pathophysiological meaning
^{18}F-FP-CIT PET						
Sunwoo et al[45]	1 GD-p, 1 GBA-PD	Age GD-p = 44, GBA-PD = 55 UPDRS III GD-p = 12, GBA-PD = 25	GBA-PD = no cognitive impairment, GD-p = NA	NA	Both = ↓ uptake in the posterior putamen	GD-p and GBA-PD = findings compatible with iPD

Studies are ordered chronologically. If not specified, the studies are cross-sectional. Information on how controls and iPD were selected is provided in Supplementary Table S1. See Supplementary Table S1 for details of classification of GBA mutations/variants. When available, mean ± standard deviation is reported; otherwise, mean, range (separated by –), single values (separated by comma), or inclusion criteria is reported. If no information is available, NA is reported. If details for the subgroup that underwent imaging study are not available, results for the whole group are reported.

[a]Longitudinal study. The study has been divided into two parts for clarity in the table; the second line refers to the longitudinal analysis, range 1.5- to 12-year follow-up.

[b]A cognitive test battery covered the following domains: executive function, memory, attention, language, and visual–spatial abilities, from which a global cognition *z* score was computed using age- and education-adjusted standard norms. The global cognition *z* score was significantly lower when the BDI-II score was included as a covariate.

[c]The patient showed fluctuations in attention and memory, moderate letter fluency difficulties, mild bradyphrenia, executive dysfunction, and spatial processing deficits.

[d]The patient showed minimal response to levodopa and dementia within 3 years of parkinsonism onset with visuoconstructive apraxia and hallucinations.

[e]Longitudinal study (<5-year follow-up). Dopaminergic function before onset of deterioration was estimated by applying a linear model for PD subjects.

[f]Subjects from the PPMI cohort.

[g]Longitudinal study. The study has been divided into two parts for clarity in the table; the second line refers to the longitudinal analysis, up to ∼2-year follow-up (imaging data available).

[h]Retrospective study (11 years), all patients underwent [123I]FP-CIT SPECT after 6 ± 6 years from disease onset.

Abbreviations: GD-p, GD with parkinsonism; GD, Gaucher's disease; GBA-PD, Parkinson's disease with GBA mutations/variants; GBA-NMC, nonmanifesting carriers of *GBA* mutations/variants; DLB, dementia with Lewy bodies; UPDRS III, Unified Parkinson's Disease Rating Scale, Part III; HY, Hoehn and Yahr score; NA, not available; SN, substantia nigra; CTRL, controls; MoCA, Montreal Cognitive Assessment; iPD, idiopathic Parkinson's disease; MDS, Movement Disorder Society; BDI-II, Beck's Depression Inventory, II; IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; SPECT, single-photon emission computed tomography; LRRK2-PD, Parkinson's disease with *LRRK2* mutations; PPMI, Parkinson's Progression Markers Initiative; LO-iPD, late-onset idiopathic Parkinson's disease; EO-iPD, early-onset idiopathic Parkinson's disease; SCOPA-AUT, Scale for Outcomes in Parkinson's Disease-Autonomic; RBDSQ, REM Sleep Behavior Disorder Screening Questionnaire; MDS-UPDRS III, Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale, Part III; LRRK2-NMC, nonmanifesting carriers of *LRRK2* mutations/variants; MCI, mild cognitive impairment; GCase, glucocerebrosidase; RBD, REM sleep behavior disorder; SNCA-PD, Parkinson's disease with SNCA mutations/variants; PINK1-PD, Parkinson's disease with PINK1 mutations/variants; PRKN-PD, Parkinson's disease with PRKN mutations/variants; DA, dopamine transporter; MMSE, Mini-Mental State Exam; ^{18}F-FP-CIT PET, ^{18}F-fluoropropylcarbomethoxyiodophenylnortropane positron emission tomography; GSH, Gangnam Severance Hospital; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease.

no patient presented dementia or hallucinations, reduced functional connectivity in the parieto-occipital cortex was found in GBA-PD relative to iPD, similar to dementia with Lewy bodies (DLB) patients and PD with visual hallucinations.

Positron Emission Tomography with 2-^{18}F-Fluorodeoxyglucose

Five studies were included (Supplementary Table S1 and Table 2).

Fluorodeoxyglucose-positron emission tomography (FDG-PET) is widely used for the evaluation of cortical glucose metabolism in several neurodegenerative disorders. In PD, FDG-PET shows two distinct covariance patterns on resting state: the PD-related-pattern (PDRP), associated with disease progression and motor symptoms, and the PD-cognitive pattern (PDCP), associated with cognitive dysfunction.[14] A study[23] reported increased PDRP scores and a trend for increased PDCP score (in line with a trend in worse cognitive function) in GBA-PD compared to matched iPD. Similarly, in another study,[25] despite matched motor impairment, the GBA-PD group showed higher PDRP scores than iPD and LRRK2-PD. Moreover, GBA-PD was the only group to show elevated PDCP expression compared to controls (despite not having dementia). Using graph theory, the authors found that even though GBA-PD, LRRK2-PD, and iPD express the same disease-specific networks, information flow through these metabolic networks differs across patient groups.[25] LRRK2-PD showed increased functional connectivity within the metabolically active PDRP core zone, and preferential gain in connectivity within the PDRP core was associated with lower disease network expression, indicating less-severe underlying functional pathology in PD patients carrying this mutation. By contrast, in GBA-PD the gains in connectivity extend outside the core, along with increased expression of the whole network. LRRK2-PD showed more connections within the core and GBA-PD within the periphery, suggesting that the PDRP "weather front" has progressed less in LRRK2-PD and more in GBA-PD, over the same disease duration. These findings seem consistent with a more aggressive natural history in GBA-PD.

Some other reports of FDG PET are available, although, due to the small samples, it is difficult to draw any conclusion from the results (Table 2).[26-28]

Microglial Activation Studies

One study was included (Supplementary Table S1 and Table 2).

Inflammation is known to play an important role in the pathogenesis of GD, and it is considered to contribute to the neurodegenerative process in PD.[52] A study,[29] using 11C-(R)-PK11195 PET, demonstrated increased microglial activation in brains of GD patients without parkinsonism and GBA-NMC compared to controls in the SN, occipital and temporal lobes, cerebellum, hippocampus, and mesencephalon. There was a correlation between the degree of hyposmia and nigral microglial activation. The same study evaluated (see later), showing no differences between carriers and noncarriers. The authors suggest that a biphasic trajectory of microglial activation and dopaminergic degeneration might explain the different results.[29]

Brain Perfusion Studies

Four studies were included (Supplementary Table S1 and Table 3).

Cerebral perfusion studies evaluate the metabolic status of brain tissue by quantifying changes in the regional cerebral blood flow using various radiotracers.[14]

In one study,[31] GBA-PD with severe mutations showed reduced posterior parietal and occipital blood perfusion compared to iPD, similar to DLB; conversely, GBA-PD with mild mutations showed a similar pattern to iPD. Additional analysis performed after excluding patients with dementia yielded similar results. This is in line with other findings from this study,[31] which demonstrated that the risk for dementia is influenced by the type of *GBA* mutation/variant. Another study[32] reported reduced regional cerebral blood flow in the bilateral parietal cortex, including the precuneus, in GBA-PD compared to sex-, age-, and disease-duration-matched iPD subjects. Occipital hypoperfusion, resembling the DLB pattern, was reported in a PD member of a family with a gross *GBA* deletion; 6 other individuals (1 GBA-PD and 5 GBA-NMC) displayed normal findings.[30] A study described a reduced regional cerebral blood flow in GD-p in both inferior parietal lobules and the precuneus of both hemispheres but sparing the posterior cingulate gyrus[33]: this pattern is typical of DLB.[53]

Nigrostriatal Imaging

Twenty-one studies were included (Supplementary Table S1 and Table 4).

[^{18}F]FDopa PET is used to assess the density of presynaptic nigrostriatal axons.[14] [123I]N-ω-fluoropropyl-2β-carbomethoxy-iodophenyl nortropane ([123I]FP-CIT) single photon emission computed tomography (SPECT) evaluates nigrostriatal integrity by measuring the density of dopamine transporters (DATs) located at the presynaptic nigrostriatal terminals.[14] Other techniques, such as C11-Raclopride PET, 11 C-CFT [2β-carbomethoxy-3β-(4-fluorophenyl) tropane] PET, and ^{18}F-FP-CIT PET, can be used to investigate the integrity of the nigrostriatal system.[14]

6-[^{18}F]fluoro-L-Dopa ([^{18}F] FDopa) PET

A study compared the [^{18}F]FDopa PET and transcranial sonography (TCS) findings in subjects with

GBA mutations (homozygous and heterozygous) with and without parkinsonism (GD-p and GBA-PD vs. GD and GBA-NMC), showing an inverse relationship between [^{18}F]-FDOPA uptake and nigral echogenic areas only in subjects with parkinsonism.[34] The same authors, in a longitudinal study (1.5–12 years),[35] demonstrated a lack of progression both radiologically and clinically—in terms of parkinsonism—in a cohort of GBA-NMC (even with familiarity for PD or DLB). On the contrary, as expected, GBA-PD and GD-p showed decreased binding over follow-up, especially in the putamina. In the GBA-NMC cohort, only 1 subject aged 60 years (carrying an N370S mutation) developed signs of PD: [^{18}F]FDopa PET scan and TCS performed 1 year before the onset were unremarkable.[35] In a study,[23] compared with iPD, GBA-PD showed a greater reduction in [^{18}F]FDopa uptake in the bilateral caudate nuclei, anteromedial putamen ipsilateral, and nucleus accumbens contralateral to the more affected body side. Together with other findings (see the PET and MRI sections), this led the authors to conclude that GBA-PD has a more aggressive course than iPD. Finally, in another study,[29] GBA-NMC and GD showed a similar mean striatal ^{18}F-dopa uptake to healthy controls, although with a greater variance—with some subjects displaying higher dopamine binding values. Whether this finding represents a compensatory mechanism is not known. A bilaterally reduced uptake in the striatum has also been reported in GD without parkinsonism in one study, although the authors noted that this effect was attributable to 2 patients (of 14) with reduced uptake.[33]

Other reports describe similar findings to iPD in GBA-PD[26,28] or GD-p[33,36] (see Table 4).

[123I]N-ω-fluoropropyl-2β-carbomethoxy-iodophenyl nortropane ([123I]FP-CIT) SPECT

Among a cohort including both GBA-NMC and LRRK2-NMC, a minority of subjects displayed DAT deficit (3% of GBA-NMC vs. 11% of LRRK2-NMC).[39] *GBA*-NMC rather showed increased DAT striatal binding ratios compared with controls in the caudate, putamen, and striatum: this finding was interpreted as a possible compensatory mechanism in the preclinical stage.[39] Clinically, compared with controls, both *GBA-NMC and LRRK2-NMC* showed subtle motor and nonmotor signs (a possible bias in evaluation due to the lack of blinding to the genetic status must be pointed out).[39] A study compared cohorts at risk for PD (namely REM-sleep behavior disorder [RBD], hyposmia, GBA-NMC, and LRRK2-NMC) from the PPMI[41]: a lower mean striatal binding ratio was observed in RBD compared to the hyposmia and NMC cohorts. No difference was observed between GBA-NMC and LRRK2-NMC.[41]

In one study both GBA-PD and LRKK2-PD showed higher (better) striatal binding ratio in the caudate and putamen contralateral to the more affected body side when compared with iPD.[40] As a possible explanation for this finding, the authors suggest a slower rate of decline in DAT in genetic PD compared to iPD or a disruption of dopamine release before the loss of dopaminergic terminals (leading to an overestimation of DAT binding). In this study, GBA-PD showed similar motor and nonmotor symptoms (except for impulse control disorder) to iPD.[40] Conversely, another study reported more pronounced dopaminergic dysfunction in GBA-PD than iPD: age-adjusted analysis showed similar DAT density between GBA-PD with mild mutations and iPD and between GBA-PD with severe mutations and DLB, in line with other findings from the same study.[31] The discrepancy between these two studies could be associated with the different mutations included. In fact, in the study by Simuni et al,[40] most of the cohort carried the N370S mutation, which is a mild mutation: as demonstrated by Cilia et al,[31] and confirmed by a recent meta-analysis,[54] patients with this mutation show similar cognitive features to iPD.

One longitudinal study showed a faster clinical and cognitive deterioration, as well as a more diffuse striatal and extra-striatal damage, in GBA-PD relative to iPD.[17] The clinical and radiological progression in GBA-PD was similar to that in LO-iPD rather than EO-iPD, leading the authors to hypothesize a biological role of *GBA* in the pathogenesis of the "malignant PD phenotype," a more aggressive form of disease associated to LO-iPD[51] (see the MRI section). In another study, the temporal trajectory for putaminal dopaminergic deficit during the premotor period (10 years) in PD patients was modeled using extensive longitudinal PPMI data: according to this model, patients carrying the N370S GBA mutation have more rapid deterioration in dopaminergic function in the premotor phase.[37]

In one study,[43] GBA-PD showed a more asymmetric DAT deficit compared to PD patients carrying other mutations with higher penetrance (eg, *SNCA*). The authors hypothesized that this finding, which resembles what is observed in iPD, suggests that other genetic or environmental factors are needed to drive dopaminergic neuronal loss in GBA-PD.

In another study, despite similar levels of DAT binding compared with other PD patients, GBA-PD showed more severe motor signs in the less-affected side (despite similar levels of DAT availability in the contralateral putamen): this finding has been reconducted to a lower "motor reserve" in GBA-PD that could contribute to a more severe phenotype.[38]

A study[42] investigating the role of genetic variants (*APOE* ε2 and ε4 alleles, *MAPT* H1 and H2 haplotypes, *COMT* Met allele, *SNCA* G allele, and deleterious

TABLE 5 *Transcranial sonography studies*

Studies	Sample	Clinical features	Cognition	Clinical findings	Imaging findings	Conclusions
Eisenberg et al[34]	5 GD-p, 2 GBA-PD, 15 GD, 12 GBA-NMC	UPDRS III GD-p and GBA-PD = 26 ± 13, GD and GBA-NMC = 1 ± 2	NA	NA	GD-p and GBA-PD = ↑ SNh (vs. GD and GBA-NMC)	GD-p and GBA-PD = TCS findings consistent with iPD Normal TCS in the absence of parkinsonism
Lopez et al[46a]	9 GD siblings' pairs discordant for parkinsonism (8 GD-p + 1 GD-DLB, 9 GD)	Age GD-p = 57.2, GD = 57.7 UPDRS III GD-p = 27.18, GD = 5.14	WAIS = no difference (GD-p vs. GD)	GD-p = ↑ UPDRS III, hyposmia, urinary dysfunction (vs. GD)	GD-p = ↑ SNh (vs. GD)	GD-p = TCS findings consistent with iPD Normal TCS in the absence of parkinsonism
Arkadir et al[47]	11 GBA-PD, 130 GD, 68 GBA-NMC, 43 CTRL	Age GBA-PD = 58 (49–74), GD = 51 (40–88), GBA-NMC = 51 (40–77), CTRL = 51 (40–73) UPDRS III/HY NA	NA	NA	GBA-PD, GD, GBA-NMC = ↑ SNh (vs. CTRL)	GBA-PD and NMC = ↑ SNh also in the absence of parkinsonism No correlation with glucosylsphingosine levels
Omrani et al[48]	26 GBA-NMC, 26 CTRL	Age GBA-NMC = 35.6 ± 6.9, CTRL = 34.92 ± 10.14 UPDRS III/HY NA	MMSE GBA-NMC = 29.8 ± 0.6, CTRL = 30 ± 0	NA	GBA-NMC = ↑ SNh (vs. CTRL) GBA-NMC = ↑ third ventricle width (vs. CTRL)	GBA-NMC = ↑ SNh and third ventricle width also in the absence of parkinsonism
Böttcher et al[21]	5 GD-p, 11 GD, 12 iPD, 32 CTRL	Age GD-p = 52.6 ± 8.0, GD = 46.4 ± 11.4, iPD = 60.9 ± 4.1, CTRL = 48.2 ± 11.7 UPDRS III GD-p = 29.6 ± 21.5, GD = 0.3 ± 0.5, iPD = 19.9 ± 8.5, CTRL = 0.5 ± 1.1	Executive dysfunction (TMT-B test) in 44% GD and GD-p, 83% iPD, 3% CTRL	GD-p = ↑ hyposmia, motor signs, NMS (vs. GD), GD and GD-p = ↑ executive dysfunction, motor signs, depression (vs. CTRL), GD and GD-p = ↑ executive dysfunction, motor signs and NMS (vs. iPD)	GD and GD-p = ↑ SNh and ↓ brainstem raphe hypoechogenicity (vs. CTRL), GD and GD-p = ↑ third ventricle width (vs. iPD); no differences between GD-p and GD	GD = ↑ SNh also in the absence of parkinsonism No differences in TCS between GD and GD-p
Kresojević et al[49]	4 GD-p, 12 GD, 18 GBA-PD, 32 iPD, 9 GBA-NMC, 43 CTRL	Age GD-p = 49.0 ± 12.1, GD = 44.7 ± 19.0, GBA-PD = 62.6 ± 8.6, iPD = 61.5 ± 9.3, GBA-NMC = 56.7 ± 11.7, CTRL = 54.9 ± 14.9 UPDRS III GD-p = 47.2 ± 27.7, GBA-PD = 38.6 ± 21.4, iPD = 35.9 ± 15.5, HY GD-p = 2.5 ± 1.2, GBA-PD = 2.7 ± 1.1, iPD = 2.4 ± 0.8	MMSE GD-p = 28.5 ± 1.3, GBA-PD = 27.9 ± 2.6, iPD = 28.5 ± 2.4	GD = ↑ anxiety (vs. GBA-PD and iPD)	GD-p, GBA-PD, iPD = ↑ SNh (vs. GBA-NMC and CTRL) No difference in third ventricle width	GD-p and GBA-PD = TCS findings consistent with iPD
Barrett et al[26]	4 GD-p, 23 GBA-PD, 27 LRRK2-PD, 4 GBA + LRRK2-PD, 32 iPD, 30 CTRL	Age GD-p = 60.2 (50.2–67.6), GBA-PD = 65.0 (59.0–68.2), PD-LRRK2 het = 68.2 (60.6–74.5), PD-LRRK2 hom = 64.4 (62.7–66.2), GBA + LRRK2-PD 65.3 (64.3–68.0), iPD = 64.8 (60.5–73.8), CTRL = 60 (51–68) UPDRS III GD-p = 32 (22–35), GBA-PD = 19 (14–25), PD-LRKK2 het = 12 (6–20), LRRK2 hom = 13 (12–14), GBA + LRRK2-PD = 18 (16–19) iPD = 19 (13–24)	NA	GD-p, GBA-PD, iPD = ↑ UPDRS III (vs. LRRK2)	GD-p, GBA-PD, LRRK2-PD, GBA + LRRK2-PD, iPD = ↑ SNh (vs. CTRL) No difference between GD-p, GBA-PD, LRRK2-PD, GBA + LRRK2-PD, iPD	GD-p, GBA-PD, LRRK2-PD, GBA + LRRK2-PD = TCS findings consistent with iPD

(Continues)

TABLE 5 *Continued*

Studies	Sample	Clinical features	Cognition	Clinical findings	Imaging findings	Conclusions
Brockmann et al[50]	20 GBA-PD, 20 iPD	Age GBA-PD = 62.7 ± 10.4, iPD = 67.6 ± 9.3 UPDRS III GBA-PD = 34.7 ± 14.1, iPD = 27.8 ± 7.5, HY GBA-PD = 2.6 ± 0.9, iPD = 2.3 0.5	MoCA GBA-PD 22.6 ± 6.8, iPD = 26.5 ± 2.2	GBA-PD = ↑ cognitive impairment, psychiatric symptoms, NMS	GBA-PD = ↓ brainstem raphe hypoechogenicity; no difference in SNh	GBA-PD = TCS findings consistent with iPD ↓ Brainstem raphe hypoechogenicity might underlie NMS
Saunders-Pullman et al[28]	3 GD-p, 23 iPD, 40 CTRL	Age GD-p = 54, 58, 65 iPD = 52 (33–79) CTRL = 47.5 (40–70) UPDRS III/HY = NA	Cognitive impairment reported in 3 of 3 GD-p	Atypical features in 2 GD-p patients[b]	GD-p = ↑ SNh (vs. CTRL) No differences between GD-p and iPD	GD-p = TCS findings consistent with iPD

Studies are ordered chronologically. If not specified, the studies are cross-sectional. Information on how controls and iPD were selected is provided in Supplementary Table S1. See Supplementary Table S1 for details of classification of GBA mutations/variants. When available, mean ± standard deviation is reported; otherwise, mean, range (separated by –), single values (separated by comma), or IC is reported. If no information is available, NA is reported. If details for the subgroup that underwent imaging study are not available, results for the whole group are reported.

[a]Longitudinal study (range 1.5–12 year clinical follow-up). TCS was performed cross-sectionally.

[b]One patient showed medication sensitivity; progressive cognitive deterioration with cognitive fluctuations; and prominent deficits in spatial processing, semantic language, and attention; the other patient showed fluctuations in attention and memory, moderate letter fluency difficulties, mild bradyphrenia, executive dysfunction, and spatial processing deficits.

Abbreviations: GD-p, GD with parkinsonism; GBA-PD, Parkinson's disease with GBA mutations/variants; GD, Gaucher's disease; GBA-NMC, nonmanifesting carriers of GBA mutations/variants; UPDRS III, Unified Parkinson's Disease Rating Scale, Part III; NA, not available; SNh, substantia nigra hyperechogenicity; TCS, transcranial sonography; DLB, dementia with Lewy bodies; WAIS, Wechsler Adult Intelligence Scale; iPD, idiopathic Parkinson's disease; CTRL, controls; HY, Hoen and Yahr score; MMSE, Mini-Mental State Exam; TMT-B, Trail Making Test B; NMS, nonmotor symptoms; het, heterozygous; hom, homozygous; LRRK2-PD, Parkinson's disease with LRRK2 mutations; LRRK2-NMC, nonmanifesting carriers of LRRK2 mutations; GBA + LRKK2-PD, Parkinson's disease with GBA mutations/variants and LRRK2 mutations; MoCA, Montreal Cognitive Assessment; IC, inclusion criteria.

and benign variants in *GBA*) in dopaminergic and nondopaminergic degeneration processes (the so-called dual syndrome hypothesis, that distinguishes dopaminergically mediated frontostriatal executive impairment and nondopaminergically mediated visuospatial deficits)[55] found that *GBA* variants were associated with both processes, whereas variants in *APOE*2, *COMT*, and *SNCA* were associated with dopaminergic degeneration and variants in *APOE*4 with nondopaminergic degeneration.

Studies using other techniques, that is, C11-Raclopride,[27,36,44] 11 C-CFT PET,[27,44] and ^{18}F-FP-CIT PET,[45] support the notion that GBA-PD and GD-p are similar to iPD: details of these studies are provided in Table 4.

Transcranial Sonography

Nine studies were included (Supplementary Table S1 and Table 5).

TCS can reveal increased echogenicity of the SN, a common and early finding in PD, although the pathogenesis of this finding is not fully elucidated. It must be pointed out that almost 10% of healthy controls display this feature.[14]

Most studies endorse the hypothesis that *GBA*-PD have greater SN echogenicity than non-PD controls but do not differ from PD subjects without *GBA* mutations/variants and that *GBA* mutations/variants in the absence of parkinsonism do not display specific TCS features.[26,28,34,46,49,50] In one study on 18 siblings with GD discordant for parkinsonism, TCS showed greater areas of SN echogenicity bilaterally in the GD-p group but no specific finding in GD patients without parkinsonism.[46] Therefore, in other studies, TCS showed greater areas of SN echogenicity bilaterally in GD-p and GBA-PD but not in GBA-NMC.[34,49] Other studies support the notion that GBA-PD and GD-p show similar TCS findings to iPD.[26,28,49,50]

Conversely, some studies have reported SN hyperechogenicity in patients carrying *GBA* mutations without parkinsonism. In one cross-sectional study,[47] the hyperechogenic area was significantly lower in controls than in subjects with GD without parkinsonism and GBA-NMC. The measurements of hyperechogenic area did not correlate with glucosylsphingosine levels in the untreated patients with GD, in line with the notion that substrate accumulation is not directly related to the pathogenesis of PD. Similarly, in another study,[48] GBA-NMC demonstrated greater hyperechogenicity than controls. The scarceness of information regarding clinical data of the subjects does not allow to generalize these findings. Finally, one study reported that SN hyperechogenicity was more frequent in GD patients, also in the absence of parkinsonism, compared to controls.[21]

One study reported that 69% of subjects with GBA-PD demonstrated an interrupted brainstem raphe compared to 21% of patients with iPD.[50] A reduced echogenicity of the midbrain raphe—reflecting an

alteration in the serotonergic system—is associated with depression and other psychiatric symptoms in PD and other neurological diseases.[56,57] In this study,[50] this result was in line with clinical data, which showed more depression and distinct autonomic disturbances in GBA-PD than iPD, leading the authors to suggest that imaging characteristics assessed with TCS might represent sonographic markers corresponding to some of these clinical findings. In another study, a higher prevalence of abnormal TCS raphe signals was found in GBA-PD compared to iPD (55.6% and 28.6% of patients, respectively), but it did not reach the level of statistical significance.[49]

No study has found any difference in TCS findings based on the type of mutation or heterozygosity/homozygosity.[21,26,34,47,50]

Multiomics Approach to Disentangle the Pathophysiology of GBA-PD

The abnormal aggregation of misfolded neurotoxic proteins, such as α-synuclein, is a key pathological feature of PD. The mechanisms of the deposition of misfolded proteins in the disease epicenter and spread to large-scale network dysfunction through synaptic connections remain unknown; recent advances demonstrated that progression of PD might be a multifactorial process depending on regional vulnerability and cell-to-cell spreading of misfolded proteins.[58] Temporospatial patterns of neuronal dysfunction, consequence of selective regional vulnerability and pathological spreading, might potentially explain different clinical features and progression in the GBA-PD relative to iPD.[58] Using an agent-based epidemic spreading model to integrate structural connectivity, functional connectivity, and regional gene expression to predict sequential volume loss due to neurodegeneration, a recent study demonstrated that regional expression of *GBA*, together with *SNCA*, is a key player in the modulation of local regional vulnerability and is related to the development of atrophy.[59] These findings are in line with biological evidence supporting the role of GCase in influencing α-synuclein synthesis, seeding, and clearance, which underlie the mechanism by which mutations/variants in *GBA* might affect the spread of protein aggregation and, consequently, be associated with faster disease progression.[60,61]

Discussion

The implication of *GBA* mutations/variants in the risk and progression of PD has opened new paths to understanding the mechanisms of PD and design potential therapeutic strategies.[62] Although GBA-PD patients cannot clinically be recognized from patients without *GBA* variants/mutations, they undergo a more aggressive progression and carry a higher risk of cognitive impairment[8]: imaging findings that are able to detect this evolution before its clinical manifestation are critical not only for their prognostic implications but also to elucidate the pathophysiology of the disease.

Summary

Most studies assessing the integrity of the nigrostriatal system failed to find any deficits in GBA-NMC or GD versus controls,[29,33,35,39,41] corroborating the hypothesis that *GBA*-mediated genetic risk alone does not determine an appreciably lower striatal dopaminergic tone. Similarly, no difference in nigrostriatal imaging has been consistently reported between GBA-PD or GD-p and other PD patients[26-28,33,35,36,44,45]; rather contrasting findings—ranging from a diminished[23,31,42] to an augmented[40] dopaminergic tone—have been reported. The differences among the studies, eg, differences in sample sizes, stage of PD, and mutations analyzed, might be accountable for these apparently confounding results although, overall, current evidence does not suggest the existence of a "nigrostriatal signature" of *GBA* mutations/variants in PD.

More insights from longitudinal studies demonstrated that GBA-PD show a more advanced disease at both structural MRI and 123-FP-CIT-SPECT imaging,[17,18] which is reached by iPD after 5 and 2 years, respectively. Importantly, the trajectory of worsening of imaging features corresponded to a more aggressive clinical worsening, in both motor and nonmotor features. Similarly, brain perfusion[31-33] and FDG-PET[23,25] studies suggest a more aggressive underlying disease in GBA-PD, supporting the hypothesis that patients with *GBA* mutations seem to localize midway in the spectrum between PD and DLB, depending on the mutation.[31] The greater involvement of the posterior cortical regions in GBA-PD compared to iPD could represent the neuroimaging counterpart of clinical findings reporting cognitive impairment as a major feature of GBA-PD. On the contrary, it must be noticed that most of these studies also reported worse cognitive function in this population compared to the control group and, thus, this difference might have influenced the imaging results.

Overall, studies in GBA-NMC have yielded highly heterogeneous—if not contrasting—results and overall do not allow to draw firm conclusions. It must be considered that the penetrance of *GBA* mutations is far from complete and depends on many factors,[63] including the type of mutation and other genetic and non-genetic modifiers, most of which are unknown.[64] Therefore, findings in these subjects might represent a mere correlate of their genotype not corresponding to the future development of PD: to effectively distinguish GBA-NMC between "healthy" and "prodromal" carriers and identify the mechanisms of GBA-PD

pathogenesis, longitudinal studies should evaluate the meaning of findings in NMC in relation to the risk of developing PD (eg, use of the MDS prodromal likelihood ratio scores as well as exposure to other environmental factors that contribute to PD in addition to the genetic status[65]).

Limitations

As discussed, only a few studies included in the present review had a prospective design.

Other limitations hinder drawing results from the available studies. First, the variability in the approaches used across the studies to screen *GBA* and other PD-related genes may have significantly influenced the results. The techniques used to analyze genetic alterations were not uniform, with some studies investigating only specific mutations in *GBA* (eg, N370S and L444P, only GD-associated, only non-GD-associated) and other genes (eg, G2019S for *LRRK2*), whereas others assessed several known mutations and performed the sequencing of the entire *GBA* gene. Some studies excluded patients with other known mutations, whereas other studies did not assess other mutations at all. Moreover, a great heterogeneity was present in the control groups, as only in some studies were "controls" or "iPD" groups effectively tested for *GBA* mutations and information on genetic screening was missing, inherently flawing the comparison. Supplementary Table S1 summarizes the heterogeneity of the genetic assessment through the included studies. Other factors that may confound the results of the studies include heterogeneous cohorts with respect to the size, demographic data, and enrollment criteria of patients.

The complexity of interpreting the findings in GBA-NMC is increased by the overlap with other prodromal symptoms. RBD is of particular interest due to the significant risk of developing synucleinopathies that it carries.[65] Neuroimaging findings in RBD have been extensively reviewed elsewhere; we refer the interested reader to a recent review on the topic.[66]

In addition, it must be noted that many studies[17,37-41] used data from the PPMI cohort[67] and analyzed the same subset of patients. Therefore, some data might be redundant rather than adding new information.

Finally, it is considered that "brain reserve"—a construct that combines the structural properties of the brain and cognitive skills and abilities that serve as a hedge against loss of function—influences the progression of PD and other neurodegenerative diseases (for review, see reference 68) but, besides the hypothesis of a reduced motor reserve in GBA-PD,[38] little is known regarding its role in the pathogenesis of GBA-PD. Further research in this direction is warranted in the field of GBA-PD and GBA-NMC (as well as in other preclinical populations) to further elucidate the mechanisms of disease.

Conclusions

In conclusion, so far, in the field of GBA-related parkinsonism and its clinical, neuroimaging, and pathogenetic features, simple solutions have been elusive: in the past decade, the increasing understanding of PD pathogenesis and clinical manifestations, the improvement in neuroimaging techniques, and the advances in basic sciences have led to a vertiginous increase in knowledge in the field of GBA-related PD, increasing the complexity of the problem rather than simplifying it. In parallel with clinical observations, current evidence in neuroimaging suggests a faster progression in GBA-PD, although the details of such progression (eg, the pathogenesis, pattern of progression, which tools are better to capture it, and which patients are at higher risk) must be determined. Cognitive impairment, a "clinical signature" of GBA-PD, seems to find its neuroimaging correlate in the greater cortical burden displayed by these patients as compared to other forms of PD. Undoubtedly, as extensively discussed, these aspects have been systematically investigated, whereas others might have been overlooked, and uneven matching of samples might account for some of these findings. Further studies implementing molecular imaging of protein accumulation, structural and functional connectivity, genetic expression profile, and the activity-related metabolic demand of specific brain regions will play a central role in the definition of vulnerability and understanding the progression of the disease, from the preclinical to the advanced stages, to identify pathogenic processes and cerebral regions implicated in the different and multifarious manifestations of PD.[58] Larger, international, studies with better trail design, exploring more genetic variants, and with a longitudinal design are warranted to achieve a complete scenario of how the most common factors might contribute to the observed clinical and neuroimaging profile of GBA-PD patients, to uncover neurodegeneration mechanisms and to allow the development of new therapeutic strategies. ■

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study

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Supporting Data

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