

Molecularly distinct neurodegeneration shapes the DOPA-dependent dynamic of large-scale brain connectomics in GBA-associated Parkinson's disease

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Abstract

GBA1-associated Parkinson's disease (GBA1-PD) is a biologically distinct synucleinopathy associated with glucocerebrosidase deficiency, lysosomal dysfunction, and more extensive cortical neurodegeneration. How these molecular abnormalities shape large-scale cortical network dynamics in vivo remains incompletely understood. This study aimed to characterize resting-state EEG functional connectivity and network topology in GBA1-PD and to determine whether GBA1-related molecular pathology is associated with a distinct oscillatory connectome signature and its modulation by dopaminergic treatment. We recorded resting-state EEG in 22 patients with PD (GBA1-PD = 7; LRRK2-PD = 5; sporadic PD = 10) together with 14 age-matched healthy controls. EEG was acquired in OFF and ON dopaminergic states. Functional connectivity was estimated using imaginary coherence (ImCoh) and phase-locking value (PLV) across canonical frequency bands, while network organization was quantified using the graph-theoretical clustering coefficient. Linear mixed-effects models were used to assess therapy- and subtype-specific effects. GBA1-PD exhibited a selective increase in gamma-band clustering coefficient in the ON condition ($p = 0.044$), which was not observed in LRRK2 or sporadic PD. PLV-based analyses highlighted opposite clustering changes in GBA1 and LRRK2 patients. ImCoh analyses further revealed different therapy-related connectivity changes in genetic and sporadic PD across all frequency bands (all $p \leq 0.0035$). Compared with healthy controls, PD was associated with widespread disruption of cortico-cortical connectivity. All significant effects were abolished in surrogate-data analyses, supporting their physiological specificity. Resting-state EEG connectomics may reveal genotype-specific network alterations in GBA1-PD and their modulation by dopaminergic treatment, supporting a relationship between genetic background and large-scale brain network dynamics.

Introduction

Parkinson's disease (PD) associated with heterozygous mutations in the GBA1 gene (GBA1-PD) represents a distinct genetic subtype¹, characterized by faster disease progression², more extensive cortical Lewy body pathology³, and earlier cognitive impairment⁴. GBA1 mutations result in partial deficiency of the lysosomal enzyme glucocerebrosidase (GCase)¹, which promotes lysosomal dysfunction, lipid accumulation, and α -synuclein dysregulation⁵. These alterations can disrupt cellular homeostasis through autophagic, mitochondrial, and endoplasmic reticulum pathways⁵. In addition, neuronal involvement extends beyond the nigrostriatal dopaminergic system. Neuropathological studies have shown atypical Lewy pathology in hippocampal CA2–4 regions^{6,7}, together with more diffuse cortical involvement and a broader distribution of α -synuclein pathology than in idiopathic PD⁸. Similar patterns have also been reported in neuroimaging studies^{9–11}. These distinctive molecular features are mirrored by alterations in the large-scale organization of brain activity¹². To date, network-level changes have mainly been investigated using resting-state fMRI and FDG-PET, which provide indirect measures of neural activity through hemodynamic and metabolic signals, respectively^{13,14}. Evidence in GBA1-PD indicates an abnormally reorganized functional connectome, marked by a maladaptive enhancement of

global network integration^{9,15–17}. By contrast, EEG studies remain extremely limited, leaving a critical gap in our understanding of how genotype-driven molecular pathology influences cortical oscillatory dynamics and translates into distinct neurophysiological phenotypes¹². In this context, quantitative EEG (qEEG) represents a widely accessible and highly reproducible tool to investigate large-scale brain dynamics with high temporal resolution^{18,19}.

Beyond spectral analysis, EEG enables the assessment of functional connectivity, defined as the statistical dependence between spatially distributed neural signals. This provides insight into the organization of large-scale brain networks^{20–24}. Emerging evidence suggests that genetic profile may shape cortical connectivity patterns, although current findings remain limited and heterogeneous^{1,17,25}. Furthermore, whereas dopaminergic therapy is known to modulate cortical oscillatory activity, its effects on large-scale network organization, both in sporadic and genetic PD, remain to be elucidated^{26,27}.

In this study, we investigated resting-state cortico-cortical EEG functional connectivity and network topology in people with GBA1-PD, comparing their network features with those observed in LRRK2-PD, sporadic PD, and healthy subjects. We aimed to determine whether GBA1 mutations are associated with a specific and measurable neurophysiological phenotype that may reflect the underlying molecular and neuropathological alterations. Patients were examined in both OFF and ON dopaminergic states to assess whether this putative genotype-specific network signature is sensitive to dopaminergic treatment. These analyses were framed within a molecular connectomics approach, relating GBA1-associated pathology to large-scale oscillatory network organization.

Materials and Methods

Subjects and study design

People with GBA1-PD, LRRK2-PD and sporadic PD (tested negative for known pathogenic mutations)¹⁶ were recruited from the Neurology Department of Padua University Hospital and from the Neurology Unit of San Paolo University Hospital, University of Milan Medical School, Milan. All participants met the Movement Disorder Society clinical diagnostic criteria for PD^{28,29}. Exclusion criteria included dementia (MoCA < 26), major psychiatric disorders, severe tremor interfering with EEG recording, and use of psychoactive medications other than antiparkinsonian therapy^{28,29}. Age- and sex-matched healthy volunteers selected from the hospital communities, with no neurological or psychiatric disorders, were also included as control subjects. Each participant underwent resting-state EEG recording. EEG data were subsequently pre-processed, functional connectivity was estimated using imaginary coherence (imCoh) and phase-locking value (PLV), and graph-theoretical analyses were performed.

Each participant provided a written informed consent before enrollment. The study was approved by the local ethics committees and developed in accordance with the Declaration of Helsinki. Ethical approval

was obtained from the Milan Area 1 Ethics Committee to which ASST Santi Paolo e Carlo refers, with protocol number 0048450/2022 dated 21/11/2022.

Genetic characterization

Genetic PD was defined by the presence of pathogenic or likely pathogenic variants identified through prior genetic testing³⁰. To harmonize genetic classification, variant interpretation and gene selection followed standardized criteria derived from a recent multicentric Italian cohort study³¹. Genetic analyses included the detection of single nucleotide variants (SNVs) and copy number variations (CNVs) using clinically validated techniques, including next-generation sequencing and, when available, multiplex ligation-dependent probe amplification. Genetic reports were considered eligible when they included at least the main genes associated with monogenic PD. Variant pathogenicity was classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines³². Only variants classified as pathogenic or likely pathogenic were considered positive for group assignment.

EEG Acquisition

Patients with PD underwent two EEG recording sessions: OFF medication, after at least 12 hours of dopaminergic washout, and ON medication, 60–90 minutes after intake of the usual levodopa dose. Healthy controls underwent a single resting-state EEG recording. During each session, resting-state EEG was recorded with eyes closed (EC) and eyes open (EO). Each condition lasted approximately ten minutes. EEG signals were recorded using a standard 19-channel system positioned according to the international 10–20 system³³. The ground electrode was positioned at the frontal central channel (FCz), and a mastoid electrode served as a reference. Electrooculogram (EOG) was recorded using a bipolar electrode to mitigate eye artefacts. The contact impedance of each electrode was kept below 10 k Ω and balanced across channels (time constant 0.3 s). The EEG data were collected at a sampling rate of 1024 Hz and digitized using a 16-bit analogue-to-digital converter.

EEG analysis

An overview of the analysis workflow performed on the acquired EEG data is shown in Fig. 1. The EEG analysis pipeline consisted of the following steps:

- *EEG preprocessing.* EEG preprocessing was performed using EEGLAB (MATLAB): band-pass filtering (1–256 Hz), removal of line noise using the CleanLine algorithm, artifact rejection via Independent Component Analysis (ICA), segmentation into 2-second artifact-free epochs and interpolation of noisy channels. Only low-artifact epochs were included in subsequent analyses. To further mitigate the effects of volume conduction and reduce confounding factors related to differences in recording hardware, raw monopolar EEG data were re-referenced to reconstruct 30 bipolar derivations. The

use of bipolar derivations was specifically chosen to minimize common-source artifacts and enhance the physiological interpretability of phase-based connectivity estimates.

- *Functional connectivity analysis.* Functional connectivity was estimated using two complementary phase-based metrics: ImCoh, which selectively captures interactions with non-zero phase lag, thereby reducing spurious connectivity related to volume conduction^{34,35} and PLV, which quantifies the temporal stability of phase differences between signals over time^{34,35}. The use of two complementary analytical approaches (ImCoh and PLV) is motivated by the distinct physiological dimensions captured by these connectivity metrics. PLV quantifies the consistency of phase relationships between signals over time, without distinguishing whether synchronization occurs with or without phase delay. Consequently, PLV is sensitive to any stable phase alignment between regions. While this can reflect genuine functional coupling, it may also arise from shared inputs or common oscillatory generators. In the context of PD, synchronized activity driven by subcortical structures within the basal ganglia–thalamo–cortical system may therefore contribute to PLV-based connectivity patterns, even in the absence of direct cortico-cortical interactions. ImCoh, in contrast, selectively captures interactions characterized by non-zero phase delays. By suppressing instantaneous synchronization, it largely reduces the influence of volume conduction and common sources, making it more sensitive to delayed interactions compatible with information exchange across distributed cortical regions. In intuitive terms, PLV reflects whether two regions oscillate together, whereas ImCoh emphasizes situations in which activity in one region systematically precedes or follows activity in another (Fig. 2).

Connectivity measures were computed for the following frequency bands: delta (1–4 Hz); theta (4–8 Hz); alpha (8–13 Hz); beta (13–30 Hz); low gamma (30–45 Hz); high gamma (60–80 Hz). For each subject and experimental condition, square connectivity matrices ($N \times N$) were generated, where N corresponded to the number of bipolar derivations. From the resulting connectivity matrices, self-connections (diagonal elements) were excluded. Additionally, connections between bipolar derivations sharing a common electrode were excluded to avoid spurious connectivity arising from shared signal components (i.e., non-independent signals due to derivation overlap rather than physiological coupling). To assess the statistical significance of connectivity patterns, a phase-shuffling procedure was applied to the time series data to generate surrogate datasets preserving the spectral properties while disrupting phase relationships. Surrogate connectivity matrices were then constructed and used to build empirical null distributions. Statistical significance at the node and connection level was determined via permutation testing by comparing observed values against the surrogate distributions.

- *Graph-theoretical network analysis.* Connectivity matrices were modelled as weighted, undirected graphs, in which nodes represented bipolar EEG derivations and edges represented the strength of functional coupling between derivation pairs^{36,37}. Graph-theoretical analysis was performed using the Brain Connectivity Toolbox (BCT), a widely validated framework for the quantitative characterization of complex brain networks²⁴. Network topology was characterized using the

“clustering coefficient”, reflecting the degree of local segregation and short-range connectivity within the network.

- *Linear mixed-effects (LME)*. LME models were employed to investigate functional connectivity and network topology while accounting for the repeated-measures structure of the data³⁸. LME models were implemented using MATLAB (fitlme function), including “Subject” as a random intercept to model within-subject variability. Fixed effects included “Group” (GBA1, LRRK2, sporadic PD, and healthy controls), “Region of Interest” (ROI; Frontopolar, Anterior Central, Posterior Central, and Posterior), and their interaction. Age, LEDD, age at onset, disease duration, and UPDRS scores were included as covariates to control for potential confounding effects. Comparisons with healthy controls were performed separately for the OFF and ON medication states, allowing the assessment of disease-related differences under both baseline and treated conditions. Specifically, two separate LME models were fitted, each including PD patients and controls, for OFF and ON states respectively. Subtype-specific effects of dopaminergic therapy were then investigated within the PD cohort (GBA1, LRRK2, sporadic PD) using a separate set of LME models including “Therapy” (OFF vs ON) and “Subtype” as fixed effects, together with their interaction. This three-step analytical approach allowed independent evaluation of disease-related effects and therapy-related modulation, while avoiding confounding between baseline group differences and treatment effects. Separate LME models were fitted for each connectivity metric (imCoh and PLV), network measure (mean connectivity strength and clustering coefficient), and frequency band (delta, theta, alpha, beta, gamma). To confirm significant interactions, post hoc linear contrasts on simple effects were tested using Wald F-tests derived from the linear mixed-effects models. Between-group differences in baseline clinical variables were assessed using Mann–Whitney U tests for continuous variables, as the variables deviated from a normal distribution (Shapiro–Wilk test, $p < 0.05$), and two-sided Fisher’s exact tests for categorical variables, because of the small sample size and low expected cell counts.

Results

Sample characteristics

Sample demographic and clinical characteristics are summarized in Table I. A total of 22 patients with PD were included in the analysis: 12 genetic PD (7 GBA1, 5 LRRK2) and 10 sporadic PD. The fourteen healthy volunteers (7 males and 7 females) included as control subjects had a median age of 65 years (IQR 56.5–73), which was comparable to that of the overall PD cohort (median 65 years, IQR 57.25–72.75).

Pairwise comparisons of demographic and clinical characteristics among the three groups (GBA1, LRRK2, and sporadic PD) revealed several significant differences (Table I). Patients carrying GBA1 variants showed a significantly younger age at diagnosis compared with sporadic patients (median 51 [IQR 46–54] vs 67 [59.25–69] years; Mann–Whitney U test, $p = 0.013$, $r = 0.62$), as well as an earlier age at

disease onset (49 [45.5–51.5] vs 65 [57.75–67.5] years; $p = 0.021$, $r = 0.57$). In addition, GBA1 patients had a longer disease duration than LRRK2 patients (8 [6–9.5] vs 3 [2.25–3.75] years; $p = 0.034$, $r = 0.63$) and were treated with significantly higher levodopa equivalent daily doses (LEDD; 700 [587.5–957.5] vs 400 [325–478.75] mg/day; $p = 0.015$, $r = 0.73$). No significant differences were observed among the groups in chronological age, MDS-UPDRS Part III scores in the ON and OFF medication states, or in any other pairwise comparisons (all $p > 0.05$). Effect sizes for significant comparisons ranged from 0.57 to 0.73, indicating moderate to large effects.

Table I. Demographic and clinical characteristics of the Parkinson's disease subgroups.

Variable	GBA1 (n = 7)	LRRK2 (n = 5)	Sporadic (n = 10)	*pValue		
				GBA1 vs LRRK2	GBA1 vs Sporadic	LRRK2 vs Sporadic
Sex (M)	3	5	6	0.08	0.64	0.23
Age (years)	57 (55.5–59.5)	63 (60–68)	72 (65.25–73)	0.27	0.06	0.30
Age at diagnosis (years)	51 (46–54)	47 (40.5–64)	67 (59.25–69)	0.06	0.01	0.54
Age at onset (years)	49 (45.5–51.5)	46 (40.25–62.25)	65 (57.75–67.5)	0.06	0.02	0.58
Disease duration (years)	8 (6–9.5)	3 (2.25–3.75)	6.5 (3.25–7.75)	0.03	0.13	0.42
LEDD (mg/day)	700 (587.5–957.5)	400 (325–478.75)	562.5 (425–741.25)	0.02	0.22	0.10
MDS-UPDRS III ON	29 (22.5–32.5)	17 (7.5–25.75)	20.5 (17.25–30.75)	0.94	0.44	0.90
MDS-UPDRS III OFF	42 (38–46.5)	20.5 (9.5–39)	34 (30.25–50.75)	0.81	0.43	1.000

Data are presented as median (interquartile range, IQR), except for sex, which is reported as the number of male participants. M = male; LEDD = levodopa equivalent daily dose; MDS-UPDRS III = Movement Disorder Society–Unified Parkinson's Disease Rating Scale, Part III. *Mann–Whitney U tests for continuous variables and two-sided Fisher's exact tests for sex.

Parkinson's vs healthy controls.

We first examined PD in relation to healthy controls. Comparisons were initially performed separately within each PD subtype, both in ON and OFF levodopa conditions, revealing a highly consistent pattern of network disruption across PD subtypes, characterized by reduced connectivity and altered topological organization relative to healthy controls, with prominent region-specific effects involving frontopolar and posterior regions. Importantly, these alterations were largely comparable across sporadic, GBA1, and LRRK2 PD, supporting the presence of a common disease-related connectomic signature. Based on this convergence, a pooled model including all PD patients was subsequently fitted, confirming the same effects. More specifically, at the network level, the clustering coefficient derived from imCoh showed significant differences in the ON medication state, with group effects in the low gamma ($F(1,120) = 10.10, p = 0.0019$) (Fig. 3-A) and beta bands ($F(1,120) = 4.98, p = 0.028$), as well as additional region-specific effects reflected by significant group by ROI interactions in the beta ($F(3,120) = 3.25, p = 0.024$) and theta bands ($F(3,120) = 4.41, p = 0.0056$) with main effect in frontopolar and posterior regions. PLV-based analyses revealed a convergent pattern of altered network organization, with significant group and group-by-region effects in both the OFF and ON states, particularly in the delta and gamma bands. In the delta band, a significant group effect was observed in the OFF condition ($F(1,128) = 4.29, p = 0.040$), together with a significant group-by-region interaction ($F(3,128) = 15.59, p < 0.001$). In the ON condition, the group effect was no longer significant ($F(1,140) = 1.71, p = 0.193$), whereas regional effects and interactions remained robust ($F(3,140) = 12.99, p < 0.001$) (Fig. 3-B). Similar results were observed in clustering coefficient, with significant group effects in the OFF condition ($F(1,128) = 4.55, p = 0.035$), together with strong group-by-region effects in frontopolar and posterior regions ($F(3,128) = 15.62, p < 0.001$). In the ON condition, the group effect was not significant ($F(1,128) = 3.74, p = 0.055$), while group-by-region interactions ($F(3,128) = 12.89, p < 0.001$) remained significant.

In the gamma band, significant group-by-region interactions were observed in both OFF ($F(3,140) = 16.01, p < 0.001$) and ON states ($F(3,140) = 12.99, p < 0.001$) (Fig. 3C). These findings were confirmed for the clustering coefficient derived from PLV connectivity in the gamma band, with a significant group effect in the OFF state ($F(1,128) = 4.07, p = 0.046$), together with a strong group-by-region interaction ($F(3,128) = 22.44, p < 0.001$). In the ON condition, the group effect was no longer significant ($F(1,128) = 2.98, p = 0.087$), although the group-by-region interaction remained significant ($F(3,128) = 15.67, p < 0.001$).

GBA1-mutation vs other PD subgroups (sporadic, LRRK2).

Having established a common pattern of PD-related network disruption, we next examined subtype-specific responses to dopaminergic therapy, focusing on GBA1-PD.

GBA1-PD showed a distinct therapy-related network profile compared with LRRK2-PD and sporadic PD (Table II). These subtype-specific effects differed between ImCoh- and PLV-derived measures and are detailed below. In imCoh, no significant between-group differences were observed at baseline (OFF) or in the ON state. However therapy interaction emerged across all frequency bands (gamma: $F(1,180) = 9.42, p = 0.0025$; beta: $F(1,180) = 9.84, p = 0.0020$, alpha: $F(1,180) = 8.74, p = 0.0035$, theta: $F(1,180) = 10.08, p = 0.0018$; and delta bands: $F(1,180) = 11.19, p = 0.0010$). Post-hoc analyses consistently showed a

significant reduction in connectivity from the OFF to the ON state in sporadic patients across all frequency bands (gamma: $\beta = -0.362$, $p = 0.009$; beta: $\beta = -0.378$, $p = 0.0048$; alpha: $\beta = -0.374$, $p = 0.0066$; theta: $\beta = -0.393$, $p = 0.0090$; delta: $\beta = -0.331$, $p = 0.0049$), whereas both GBA1 and LRRK2 patients exhibited stable connectivity profiles across conditions. At the topological level, in clustering coefficient on imaginary, the Group-by-Therapy interaction was again significant across all frequency bands: gamma ($F(1,164) = 9.36$, $p = 0.0026$), beta ($F(1,164) = 9.42$, $p = 0.0025$), alpha ($F(1,164) = 8.48$, $p = 0.0041$), theta ($F(1,161) = 8.74$, $p = 0.0036$), and delta ($F(1,161) = 11.38$, $p < 0.001$) (Fig. 4-A). GBA1 patients showed a selective gamma-band increase in the ON state ($\beta = 0.057$, $p = 0.044$). Sporadic patients showed a significant reduction in connectivity from the OFF to the ON state across all bands (gamma: $\beta = -0.445$, $p = 0.005$; beta: $\beta = -0.452$, $p = 0.0032$; alpha: $\beta = -0.452$, $p = 0.0039$; theta: $\beta = -0.470$, $p = 0.0054$; delta: $\beta = -0.407$, $p = 0.0028$). LRRK2 patients showed neither a reduction comparable to sporadic PD nor the gamma-band increase observed in GBA1 patients ($\beta = -0.040$, $SE = 0.038$, $t = -1.07$, $p = 0.291$) (Fig. 4-B). PLV-based clustering coefficient further separated GBA1-PD from the other groups. A significant Therapy-by-Subtype interaction was present across frequency bands (γ : $F(2,175) = 12.04$, $p = 1.26 \times 10^{-5}$; β : $F(2,175) = 16.33$, $p = 3.14 \times 10^{-7}$; α : $F(2,175) = 12.13$, $p = 1.17 \times 10^{-5}$; θ : $F(2,175) = 4.89$, $p = 0.0086$) (Fig. 4-C). Post-hoc results showed that GBA1 patients exhibited a significant reduction in clustering coefficient in the gamma, beta, alpha, and theta bands under therapy (γ : $\beta = -0.018$, $p = 0.026$; β : $\beta = -0.030$, $p = 0.0067$; α : $\beta = -0.020$, $p = 0.0168$; θ : $\beta = -0.020$, $p = 0.0168$). Sporadic patients did not exhibit significant therapy-related changes in clustering coefficient in any frequency band (all $p > 0.15$). LRRK2 patients showed an opposite therapy-related direction of change relative to GBA1, with increased clustering coefficient under therapy, reaching significance in the gamma and beta bands (γ : $\beta = 0.0195$, $p = 0.032$; β : $\beta = 0.0281$, $p = 0.0037$) and showing trend-level increases in the alpha and theta bands (α and θ : $\beta \approx 0.014$, $p \approx 0.051$). This indicates that the therapy effect in GBA1 was distinct from both the sporadic and LRRK2 patterns, supporting the specificity of the GBA1-associated connectomic findings (Fig. 4-D).

Control analysis

To assess the specificity of these findings, all analyses were repeated using phase-shuffled surrogate datasets. No significant effects were observed at either the connectivity or network topology level.

Table II. Therapy-related changes in ImCoh- and PLV-derived clustering coefficient across frequency bands and Parkinson's disease subtypes.

Frequency band	GBA1	LRRK2	Sporadic
<i>ImCoh</i>			
Gamma	↑ (p = 0.044)	n.s.	↓ (p = 0.005)
Beta	n.s.	n.s.	↓ (p = 0.0032)
Alpha	n.s.	n.s.	↓ (p = 0.0039)
Theta	n.s.	n.s.	↓ (p = 0.0054)
Delta	n.s.	n.s.	↓ (p = 0.0028)
<i>PLV</i>			
Gamma	↓ (p = 0.026)	↑ (p = 0.032)	n.s.
Beta	↓ (p = 0.0067)	↑ (p = 0.0037)	n.s.
Alpha	↓ (p = 0.017)	↑ trend (p ≈ 0.051)	n.s.
Theta	↓ (p = 0.017)	↑ trend (p ≈ 0.051)	n.s.
Delta	n.s.	n.s.	n.s.

Arrows indicate the direction of significant ON–OFF changes (↑ increase; ↓ decrease); n.s. = not significant. Reported p values refer to post hoc simple-effects tests from the corresponding linear mixed-effects models.

Discussion

Our findings suggest that large-scale network organization in PD differs according to the underlying genetic and molecular background. Global connectivity mainly distinguished genetic from sporadic PD, whereas network topology showed different responses to dopaminergic treatment across PD subtypes. In particular, GBA1-PD was characterized by a selective change in gamma-band network topology, while LRRK2-PD showed a different response to treatment. Compared with healthy controls, patients with PD also showed widespread frequency-dependent alterations in cortical functional connectivity and network organization. The partly different results obtained with imCoh and PLV suggest that these measures capture complementary aspects of network dysfunction, from local cortical interactions to broader patterns of synchronization. An important finding of this study is that differences across PD subtypes became more evident when moving from the OFF- to the ON-medication state than in the baseline OFF condition. This suggests that the response of cortical networks to dopaminergic treatment may provide information on the underlying pathological substrate. In this sense, dopaminergic stimulation may act as a functional probe, revealing differences in network responsiveness across PD subtypes. In GBA1-PD, the increase in gamma-band clustering coefficient derived from imCoh may reflect a reorganization of fast, locally organized cortical activity. Conversely, the reduction in PLV following dopaminergic treatment may reflect a decrease in non-specific or pathological large-scale synchronization, possibly related to

common subcortical drivers. Thus, dopaminergic treatment does not appear to affect network organization uniformly across PD subtypes.

Possible genotype-specific engagement of cortico-subthalamic networks in PD

The different network responses observed in GBA1-PD and LRRK2-PD may be related to differences in their underlying neuropathology⁸. Previous evidence suggests that GBA1-PD affects basal ganglia circuitry differently from sporadic PD and other genetic forms^{39,40}. In particular, increased high-beta synchronization and enhanced cortico-subthalamic coupling have been reported in GBA1 mutation carriers¹⁶. Notably, high-beta synchronization between cortex and STN has been identified as a neural signature of pathological hyperdirect pathway engagement in PD⁴⁰. One possible interpretation is therefore that the connectivity changes observed in GBA1-PD partly reflect an altered involvement of cortico-subthalamic networks, including the hyperdirect pathway¹⁶. The uniform changes observed in PLV across frequency bands may reflect a macroscale mechanism, possibly related to subcortical drivers inducing widespread, non-specific cortical synchronization. Previous studies support widespread network involvement in GBA1-PD, with increased global integration and altered hub organization, particularly in frontoparietal and default mode network regions¹⁷. FDG-PET and functional MRI studies have similarly shown greater cortical involvement in GBA1-PD than in idiopathic PD, with patterns resembling those observed in dementia with Lewy bodies¹⁵. These network abnormalities are consistent with the more aggressive clinical course and greater cognitive involvement observed in GBA1 mutation carriers⁹. Direct comparisons of GBA1-PD and LRRK2-PD using graph-theoretical analyses of metabolic imaging have shown different spatial patterns of abnormal connectivity¹⁶. In LRRK2-PD, these changes appear to be more restricted to core network nodes, whereas GBA1-PD shows more widespread alterations extending to cortico-cortical pathways¹⁶.

Hypothetical molecular bases of the observed neurophysiological changes

The present findings may also be interpreted in the context of synaptic dysfunction, without excluding changes in intrinsic membrane excitability⁴¹. The connectivity measures used in this study are mainly sensitive to the temporal coordination of activity across neuronal populations^{34,35}, which depends on synaptic transmission and network synchronization⁴². At the molecular level, GBA1 loss-of-function leads to glucosylceramide and glucosylsphingosine accumulation, α -synuclein misfolding, and altered lysosomal and synaptic trafficking, and may affect fast glutamatergic projections from the frontal cortex to the STN⁴³. Synaptic dysfunction could therefore reduce the temporal precision of neuronal firing and alter synchronization across distributed networks⁴⁴. This may contribute to the functional connectivity changes observed in our study, particularly those detected by imCoh. However, this interpretation

remains speculative, as we did not directly assess the relationship between molecular pathology and large-scale electrophysiological activity.

Clinical implications and future directions

From a clinical perspective, EEG connectivity measures may provide information on the genetic and biological architecture of PD, beyond the simple distinction between sporadic and genetic forms. If confirmed in larger studies, these measures could serve as biomarkers of disease trajectory, distinguishing slowly progressive from aggressive phenotypes, characterizing different disease phenotypes and contributing to more personalized pharmacological and non-pharmacological therapeutic approaches. The present findings also raise the possibility that neuromodulation strategies targeting cortical oscillatory activity may need to take genetic background into account rather than being applied uniformly across PD. This may be relevant to future applications of adaptive deep brain stimulation and brain-sensing technologies ⁴⁵, including approaches supported by artificial intelligence ⁴⁶.

Strengths and limitations

A strength of the present study is the use of a conventional 19-channel EEG montage, which makes the proposed approach more feasible in clinical settings. Standard EEG systems are widely available in routine practice, and our results show that relevant network-level alterations can be detected using this type of recording setup. Given the limited spatial sampling of low-density EEG, we also chose to restrict the analyses to sensor-level connectivity rather than perform source reconstruction, which would have required stronger assumptions about signal localization ⁴⁷.

Nonetheless, some limitations should be acknowledged. First, given the limited spatial sampling provided by a 19-channel montage, analyses were intentionally restricted to sensor-level connectivity measures, which are more appropriate for low-density EEG configurations. Also, the analyses were limited to phase-based linear connectivity measures. Second, the relatively small sample size of GBA1 mutation carriers limits generalizability. Future studies in larger, genetically stratified cohort, comparing other monogenic forms separately, will be necessary to define the neurophysiological biomarkers of specific genetic subgroup of patient. Also, patients were not stratified according to axial motor symptom burden (e.g., UPDRS-III axial subscore), nor according to disease stage defined by the “5–2–1” criteria ⁴⁸. This may be relevant in GBA1-PD, where axial symptoms are often more prominent and may progress more rapidly. We therefore cannot determine whether the connectivity patterns observed here differ according to disease stage or axial symptom severity. However, this choice was intentional and aligned with the primary aim of the study, which was to identify neurophysiological markers of network dysfunction potentially suitable to guide personalized therapeutic strategies, rather than describing some stage or symptom dependent effects; we sought to capture connectivity signatures that are robust across different disease stages, including early forms. Finally, interhemispheric asymmetry was not specifically examined ⁴⁹. PD is characterized by lateralized motor symptoms and asymmetric neural

involvement⁵⁰, but hemispheric analyses were not feasible because measures of clinical lateralization were not available and only total MDS-UPDRS III scores had been collected.

Conclusions

The present study suggests that genetic background and dopaminergic state are associated with different patterns of large-scale cortical network organization in PD. GBA1-PD showed a distinct network phenotype, with frequency-specific changes in network topology and a characteristic response to dopaminergic treatment. The different patterns captured by ImCoh and PLV further suggest that these measures provide complementary information on cortical network organization. By combining phase-based functional connectivity and network topology, our findings support the use of a molecular connectomics approach to investigate the relationship between genetic profile and large-scale brain network dynamics. The detection of these changes using clinically accessible EEG also supports further investigation of network-based electrophysiological measures for patient characterization and, potentially, more personalized therapeutic approaches.

Declarations

Declaration of interest

All authors declare no financial or non-financial competing interests.

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Author Contribution

Conceptualization: T.B., A.G., S.M., M.T.; Methodology: M.T., S.M., F.Z.; Formal analysis: M.T., S.M., F.Z.; Investigation: M.T., V.D., G.L., V.Y., E.S.; Resources: A.G., V.D., A.A., T.B.; Data curation: A.G., V.D., A.A., T.B.; Writing – original draft: M.T., T.B., A.P., V.Y., M.G.; Writing – review & editing: T.B., A.P., S.M., F.Z., A.G., V.D., M.G.; Visualization: M.T., S.M., V.Y.; Supervision: A.A., T.B., A.P. All authors contributed to the editing of the final version of the manuscript and accept responsibility for the decision to submit it for publication.

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Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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