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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Putaminal γ-Aminobutyric Acid Modulates Motor Response to Dopaminergic Therapy in Parkinson's Disease

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ABSTRACT: Background: Motor response to dopaminergic therapy is a characteristic of patients with Parkinson's disease (PD). Whether non-dopaminergic neurotransmitters contribute to treatment response is uncertain.

Objectives: The aim of this study is to determine whether putaminal γ-aminobutyric acid (GABA) levels are associated with dopaminergic motor response.

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Methods: We assessed putaminal GABA levels in 19 PD patients and 13 healthy controls (HCs) utilizing ultra-high field proton magnetic resonance spectroscopy. Motor performance was evaluated using the Movement Disorder Society—Unified Parkinson's Disease Rating Scale, Part III, in the ON and OFF states. Statistical analysis comprised group comparisons, correlation analysis, and multiple linear regression.
Results: In PD, GABA levels were significantly higher compared to HCs (1.50 ± 0.26 mM vs. 1.26 ± 0.31 mM, $P = 0.022$). Furthermore, GABA levels were independent predictors of absolute and relative dopaminergic treatment response.
Conclusions: Our findings indicate that elevated putaminal GABA levels are associated with worse dopaminergic response in PD, emphasizing the essential role of nondopaminergic neurotransmitters in motor response.

Key Words: Parkinson's disease; magnetic resonance imaging; spectroscopy; y-aminobutyric acid; neuroimaging

Motor symptoms in Parkinson's disease (PD) typically show a considerable response to dopaminergic treatment. Therefore, dopaminergic responsiveness has been included as a key feature in the current diagnostic criteria for PD.[1] However, the magnitude of dopaminergic response varies among PD patients, and individuals showing a limited response to dopaminergic treatment may be difficult to distinguish from those with atypical parkinsonism or essential tremor.[2,3]

Studies on PD patients' dopaminergic treatment response are surprisingly sparse and mainly focused on immutable factors, for example, disease progression and age. Results are heterogeneous, with studies reporting no relation to disease progression[4] and others reporting adverse effects of age[5,6] and disease progression[7,8] on treatment response.

Even though dopamine is the pivotal neurotransmitter facilitating motor execution in the basal ganglia circuitry, other neurotransmitters are involved as well.[9] Indeed, alterations in nondopaminergic brain metabolites are well described in PD.[10] Notably, several animal and human studies have shown that in PD the concentration of γ-aminobutyric acid (GABA) is significantly elevated in selected brain areas.[11,12] As GABA mainly acts as an inhibitory neurotransmitter, its enrichment might counteract dopaminergic signaling.[13]

To investigate the influence of GABA on motor function, we measured GABA levels in the putamen of PD patients using proton magnetic resonance spectroscopy (^{1}H-MRS) at ultra-high field and examined the GABAergic impact on dopaminergic treatment response.

Patients and Methods

Participants and Clinical Assessments

We recruited 22 PD patients and 13 healthy controls (HCs) for this case–control study. The inclusion criteria were as follows: age 50–80 years, Geriatric Depression Scale (GDS-15) ≤ 5, and Montreal Cognitive Assessment (MoCA) ≥ 22. PD patients had to fulfil the Movement Disorder Society (MDS) clinical diagnostic criteria for PD (20 patients met the clinically established and 2 met probable criteria).[1] Exclusion criteria included contraindications for magnetic resonance imaging (MRI) and structural brain lesions and, for HCs, any symptom suggesting a movement disorder. No subject was on any medication that may affect the GABAergic system (ie, benzodiazepines, z-medications, and baclofen). Assessments included demographics and Sniffin' Sticks and, in PD patients, disease duration, the levodopa-equivalent daily dose (LEDD),[14] and Hoehn & Yahr stage. All but one patient were on dopaminergic medication; 1 patient was treatment-naive. PD subtypes were classified according to Stebbins et al. (2013).[15] We classified the clinically more affected body side by the side of symptom onset and by calculating the difference in the right- minus left-sided MDS-Unified Parkinson's Disease Rating Scale, Part III (MDS-UPDRS, Part III) items.[16] PD symptoms were considered lateralized if (1) the difference between the right- and left-sided items was ≥4 points and (2) it matched the side of onset.[16] We evaluated treatment response with the MDS-UPDRS III in the ON and OFF states. ON state was defined as subjects' self-reported individual best motor functional level during the day while taking their regular dopaminergic medication. OFF state was assessed after an overnight medication withdrawal of at least 14 hours. As discrepancies between absolute (total MDS-UPDRS III OFF – total MDS-UPDRS III ON) and relative dopaminergic treatment effects ([1 – total MDS-UPDRS III ON/total MDS-UPDRS III OFF] × 100) were reported,[8] we evaluated both estimates. The local ethical committee approved the study, and all participants provided written informed consent before inclusion.

MRI

MRI data were acquired using a 7-T Siemens Terra scanner. All PD subjects were scanned during the stable ON condition, and no patient reported fluctuations during scanning. A T1-weighted mp2rage sequence (TE/TR = 1.99 millisecond/4.5 second; isotropic voxel size = 0.75 mm^3) was used for anatomical imaging and for positioning the MRS voxel. Before MRS

acquisition, the radiofrequency power was calibrated for each subject, and B0 shim was performed using FASTESTMAP. MRS spectra of a voxel centered in the left putamen (voxel size: 14 [left–right] × 32 [anterior–posterior] × 17 [rostral–caudal] mm^3) were measured using a single-voxel-stimulated echo acquisition mode, with the following parameters: TE = 4 ms, TR = 8000 ms, TM = 28 ms, 72 averages, received bandwidth = 6000 Hz, and vector size = 2048. One extra complete phase cycle was measured without water suppression for eddy-current correction and absolute quantification. All data were preprocessed utilizing the FID-A package[17] in Matlab 2015a and quantification using LCModel (6.3-0I). The details are provided in the Supporting Information. A given spectrum was discarded if the full-width at half-maximum was >0.08 ppm and if the signal-to-noise ratio was <18. This led to the exclusion of 3 PD patients.

The anatomic image was segmented, using FAST[18] for cortical gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) and FIRST[19] for subcortical structures (FMRIB Software Library v6.0.3). The relative amounts of CSF, GM, and WM within the MRS voxel were determined. Metabolite concentrations were corrected for differences in the MRS voxel's CSF content by dividing the concentration value obtained with LCModel by "1-CSF fraction."

Statistics

Data were analyzed using SPSS version 25 and described by means and standard deviations. Distribution was assessed using Shapiro–Wilk tests, Q–Q plots, and box plots. We compared groups with Student's t test, χ^2 test, and Mann-Whitney U tests, as appropriate. Correlations were examined by Pearson's correlation coefficients. Multivariate analysis was performed using stepwise multiple linear regression, including GABA levels, age, LEDD, disease duration, and total MDS-UPDRS III OFF. Significance was accepted at $P < 0.05$ uncorrected.

Results

PD patients and HCs were comparable regarding age, sex, MoCA scores, and GDS-15 values (Table 1). The average disease duration was 5.7 ± 4.2 years, and the mean MDS-UPDRS III OFF score was 36.9 ± 16.4. The mean treatment response to dopaminergic therapy was 26.8 ± 17.5%.

Figure 1 shows a representative voxel placement and MRS spectra. Groups did not differ in MRS quality attributes, and no significant differences were found for GM, WM, and CSF volume fractions (Table 1). The putamen accounted for approximately 65% of the voxel's total GM, and 75% of the putamen was covered by the MRS voxel on average (no difference between groups; both $P > 0.05$). GABA concentrations were significantly elevated in PD patients (1.50 ± 0.26 mM) compared to HCs (1.26 ± 0.31 mM; $t(30) = -2.420$, $P = 0.022$). Averaged Cramer–Rao

TABLE 1 *Demographic data, clinical characteristics, and MR spectroscopy assessment of PD patients and healthy controls*

	Controls n = 13	PD patients n = 19
Demographic data		
Sex (female/male)	4/9	5/14
Age (y)	68.9 ± 8.0	64.9 ± 8.7
Clinical characteristics		
GDS-15	0.7 ± 0.9	1.1 ± 1.2
MoCA	26.6 ± 1.9	27.8 ± 1.7
Sniffin' Sticks, correct	**9.7 ± 1.6*** **	**5.2 ± 2.3**
PD characteristics		
PD phenotype		
TD (n)/PIGD (n)/I (n)		12/5/2
PD dominant side		
R (n)/L (n)/B (n)		10/5/4
Disease duration (y)		5.7 ± 4.2
Hoehn & Yahr		2.1 ± 0.8
MDS-UPDRS III (OFF)		36.9 ± 16.4
MDS-UPDRS III (ON)		25.5 ± 11.0
Absolute treatment response		10.9 ± 10.0
Relative treatment response (%)		26.8 ± 17.5
Total LEDD (mg/d)		535 ± 448
MR spectroscopy		
Fraction WM	0.34 ± 0.06	0.36 ± 0.06
Fraction GM	0.66 ± 0.06	0.63 ± 0.07
FWHM (ppm)	0.06 ± 0.01	0.06 ± 0.01
SNR	32.9 ± 9.0	28.4 ± 6.5
GABA (mM)	**1.26 ± 0.31***	**1.50 ± 0.26**
CRLB (%)	11.5 ± 2.5	10.8 ± 2.2

Abbreviations: PD, Parkinson's disease; GDS-15, Geriatric Depression Scale; MoCA, Montreal Cognitive Assessment; TD, tremor-dominant phenotype; PIGD, postural instability/gait difficulty phenotype; I, indeterminate phenotype; R, right; L, left; B, bilateral; MDS-UPDRS III, Movement Disorder Society—Unified Parkinson's Disease Rating Scale, Part III; LEDD, levodopa-equivalent daily dose; MR, magnetic resonance; WM, white matter; GM, gray matter; FWHM, full-width at half-maximum; SNR, signal-to-noise ratio; CRLB, Cramer–Rao lower bounds; y-aminobutyric acid.
*$P < 0.05$.
***$P < 0.001$; significant differences are highlighted in bold.

lower bounds for GABA were 10.8 ± 2.2% (PD) and 11.5 ± 2.5% (HCs), $P = 0.414$.

PD patients' putaminal GABA levels inversely correlated with dopaminergic treatment response (relative treatment response: $r = -0.486$, $P = 0.041$, absolute treatment response: $r = -0.578$, $P = 0.012$; Fig. 1C). No significant correlation was found between GABA levels and disease duration or LEDD. Multivariate linear regression revealed GABA levels as independent predictors of absolute and relative treatment response when including age, LEDD, disease duration, and total MDS-UPDRS III OFF scores as covariates (relative treatment response: GABA: $\beta = -0.450$, $P = 0.034$, LEDD: $\beta = 0.458$, $P = 0.032$, $R^2 = 0.445$, and absolute treatment response: GABA: $\beta = -0.412$, $P = 0.008$, LEDD: $\beta = 0.336$, $P = 0.039$, MDS-UPDRS III OFF: $\beta = 0.451$, $P = 0.011$, $R^2 = 0.774$).

Discussion

To the best of our knowledge, our study is the first examining the role of a nondopaminergic neurotransmitter—specifically GABA—and its association to the dopaminergic treatment effect in PD. In this case–control study, we found that GABA levels were increased in PD patients assessed with ultra-high field MRS. Notably, higher GABA levels inversely correlated with dopaminergic response and were an independent predictor of treatment response.

Elevated GABA levels have been reported in various brain areas of PD patients, including the basal ganglia.[11,12] Yet the biological meaning remains poorly understood. A recent study highlighted that elevated GABA levels within the medial prefrontal cortex were associated with somatic symptom disorder in subjects with and without PD.[20] GABA alterations might also contribute to axial symptoms, which typically show poor response to dopaminergic treatment.[21] On the contrary, van Nuland and colleagues did not find a significant impact of GABA levels on tremor in PD.[22] Instead, they found an inverse correlation of GABA levels in the motor cortex and disease severity.[22] Variations among studies might be explained by various objectives but may also arise due to differences in MRS acquisition and brain regions examined.

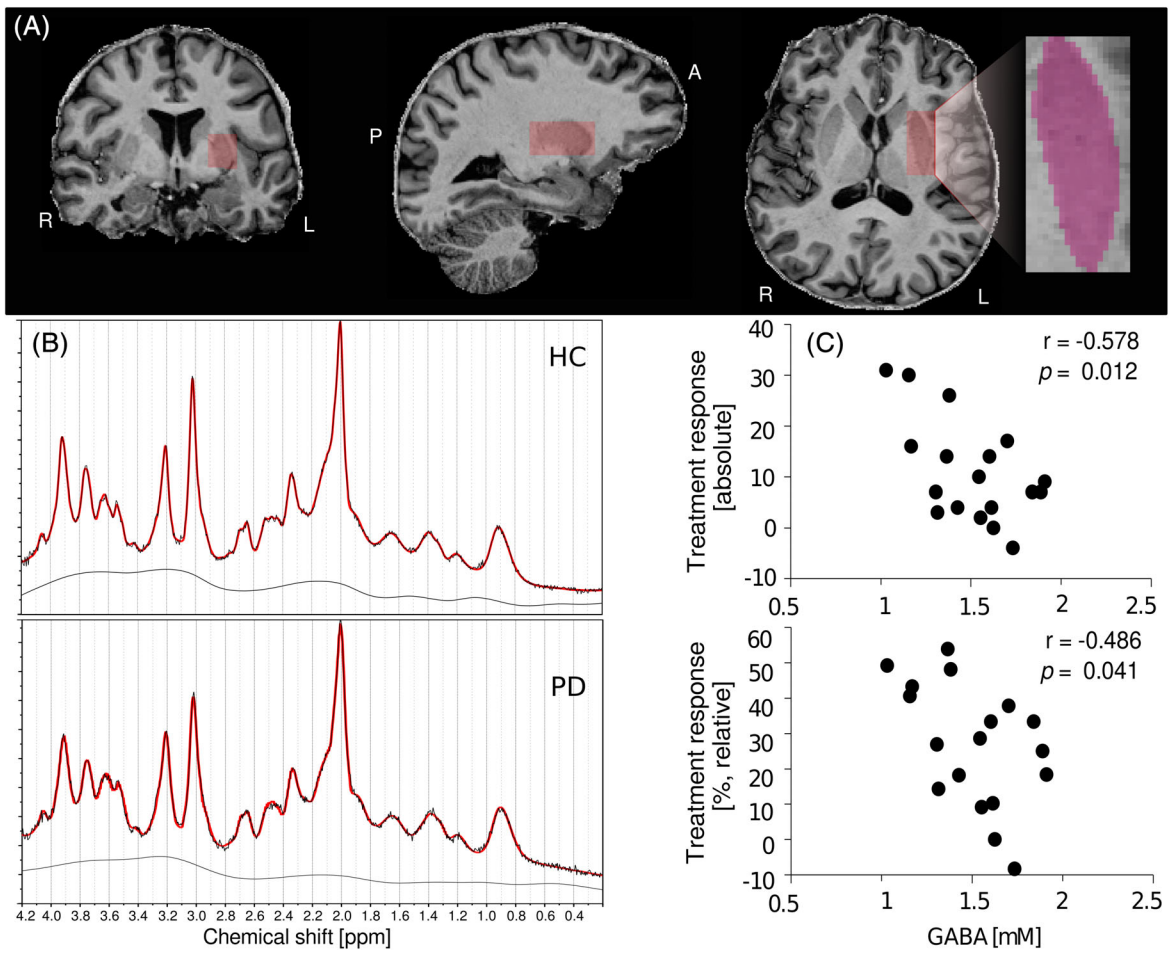

FIG 1. (**A**) Exemplary placement of an MRS (magnetic resonance spectroscopy) voxel on the left putamen. (**B**) ^{1}H-MRS spectra of a healthy control (HC) and a Parkinson's disease (PD) patient. (**C**) Scatter plots of the relation between putaminal GABA levels and dopaminergic treatment response. [Color figure can be viewed at wileyonlinelibrary.com]

It is well known that dopaminergic signaling in the basal ganglia is not an isolated process but acts in a highly coordinated interplay with other neurotransmitters.[9,23] GABA mediates immediate downstream signaling of dopaminergic neurons in the basal ganglia's direct and indirect pathway (however, with opposing effects depending on the pathway). Yet GABA also modulates dopamine release by axonal GABA receptors on dopamine neurons, providing direct inhibition of striatal dopamine release by GABA receptors.[23] Dopamine neurons may even co-release GABA, regulating postsynaptic dopamine effects.[24] In line with that, Roberts and colleagues showed that striatal dopamine release was reduced by tonic GABAergic inhibition even though dopamine storage capacity was not altered.[13] Therefore, the inverse relationship of GABA levels and dopaminergic treatment response observed in our study might reflect reduced dopaminergic release mediated by GABAergic inhibition, eventually leading to a reduced dopaminergic treatment response. However, MRS cannot distinguish between distinctive compartments, and therefore, we can assess only the "net effects" of putaminal GABA levels.

Our study has several limitations. Due to the small sample size, we could not perform subgroup analyses. Future studies are warranted to further explore the role of GABA on the dopaminergic treatment response in different PD subtypes. In addition, we only assessed MRS of the left putamen and did not integrate laterality of symptoms in our analyses. We did not assess the treatment response by a standardized levodopa test. However, we evaluated the ON state during the patient's best dopaminergic state, reflecting a realistic approximation of the individual treatment response. Nevertheless, our assessment might have underestimated treatment responses and might be prone to variation due to different treatment regimes. Furthermore, all patients were scanned in the ON condition achieved with different treatment regimes.

In conclusion, our findings point toward a significant contribution of nondopaminergic pathways on motor-related dopaminergic function in PD. Future studies are warranted to further explore the interplay of nondopaminergic neurotransmitter systems on dopaminergic function. A better understanding of these complex interactions may eventually facilitate individualized pharmacological treatment strategies for PD patients exhibiting poor motor response to dopaminergic therapy. ■

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Microstructural Abnormalities of the Dentatorubrothalamic Tract in Cervical Dystonia

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ABSTRACT: **Background:** The dentatorubrothalamic tract (DRTT) remains understudied in idiopathic cervical dystonia (CD), despite evidence that the pathway is relevant in the pathophysiology of the disorder.

Objective: The aim of this study was to examine the DRTT in patients with CD using diffusion tensor imaging (DTI)–based tractography.

Methods: Magnetic resonance imaging scans from 67 participants were collected to calculate diffusion tractography metrics using a binary tractography-based DRTT template. Fractional anisotropy and diffusivity measures of left and right DRTT were computed and compared between 32 subjects with CD and 35 age-matched healthy volunteers.

Results: Fractional anisotropy of right DRTT and mean and axial diffusivity of left DRTT were significantly reduced in patients with CD. Similar abnormalities were observed in patients with focal CD and patients with CD without tremor. DTI metrics did not correlate with disease duration or severity.

Conclusions: Significant reductions in DTI measures suggest microstructural abnormalities within the DRTT in CD, characterized by a tractography pattern consistent with decreased axonal integrity. © 2021 International Parkinson and Movement Disorder Society

Key Words: diffusion tractography; cervical dystonia; dentatorubrothalamic tract

Structural and functional imaging studies support broad connectivity abnormalities in adult-onset idiopathic dystonias, including cervical dystonia (CD),[1-4] which are network disorders involving basal ganglia, motor and sensory cortices, thalamic and brainstem