Original Article

Metabolite changes in prefrontal lobes and the anterior cingulate cortex correlate with processing speed and executive function in Parkinson disease patients

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Background: Processing speed and executive function can be impaired in patients with Parkinson disease (PD). However, the neural factors related to the slowdown in processing speed and dysexecutive function in PD are not completely understood. The objective of this study is to investigate the metabolic changes of the frontal and anterior cingulate cortex (ACC) through the use of ^{1}H magnetic resonance spectroscopy and to explore the association between cognitive function and metabolic ratios.

Methods: In this retrospective case-control study, we conducted neuropsychological assessments of executive function and information processing speed in healthy controls (HCs) and in patients with PD. Chemical information was obtained for the of N-acetyl-aspartate (NAA):creatine (Cr) ratio and the choline-containing compounds (Cho):Cr ratio within the bilateral prefrontal cortex and ACC. Using hierarchical multiple regression analysis, we analyzed the relationship between cognitive function and metabolic ratios in the bilateral prefrontal lobe and ACC in patients with PD.

Results: In all, 59 patients with PD and 30 HCs were recruited. Patients with PD showed worse performance in executive function and processing speed compared with HCs (P<0.001). In patients with PD, the Cho:Cr ratios in the ACC (Z=2.20, P=0.028) and the right prefrontal cortex (t=2.16, P=0.034) were significantly increased. The hierarchical multiple regressions in patients with PD showed that the NAA:Cr ratio in the ACC correlated with the Stroop A completion times (P<0.05) and that the NAA:Cr ratio of the right prefrontal cortex correlated with the scores of the Wechsler Adult Intelligence Scale (WAIS)-Digit symbol test (P<0.05).

Conclusions: Information processing speed and executive function are impaired in patients with PD. Neuronal integrity and membrane turnover in the ACC and the right prefrontal cortex may be important factors in the slowdown of the information processing speed in patients with PD.

Keywords: Parkinson disease (PD); executive function; information processing speed; magnetic resonance spectroscopy (MRS); prefrontal lobe; anterior cingulate cortex (ACC)

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Introduction

Parkinson disease (PD) is one of the most common neurodegenerative diseases. The main pathological feature is degeneration of dopaminergic neurons in the substantia nigra (1). Clinically, typical motor symptoms of PD are characterized by bradykinesia, resting tremor, and rigidity. However, a wide range of nonmotor disturbances can occur in patients with PD. Cognitive impairment, especially impairment of executive function (EF), attention, visuospatial, and memory commonly present in patients with PD who have nonmotor symptoms. Longitudinal studies show that approximately 20% of the patients with PD develop dementia within 5 years of follow-up, which eventually develops to 80% at 20 years of follow-up (2,3).

Cognitive deterioration, especially of the executive dysfunction, has received considerable research attention as it may predict progression to dementia and has a significant impact on the patients' daily life and their quality of life. The main components of EF include the allocation and internal control of attention, planning, inhibition, set shifting, concept formation, dual task performance, decision-making, and social cognition (4,5).

Neuroimaging is an attractive option for identifying biomarkers of cognitive status, especially progression to dementia, and may facilitate prompt interventions to slow cognitive decline. However, results from neuroimaging studies that explore EF and processing speed in patients with PD were not always consistent, which may be related to the vague concept of EF itself and the use of different cognitive assessment scales. In terms of understanding the neuroanatomical substrate of EF, previous studies support the notion that the frontal and parietal cortex play an important role in EF (6,7). However, identifying a clear correspondence between specific brain regions and subcomponents of EFs has remained a challenge in this field.

Structural and functional abnormalities of the anterior cingulate cortex (ACC) and the prefrontal cortex have been found in PD both for patients with mild cognitive impairment (PD-MCI) and for those with dementia. In our previous work, we found that the cortical thickness of the ACC correlated with the atrophy of the Meynert nucleus in patients with PD-MCI (8). Another study found the components of ACC structural covariance networks to be associated with cognitive impairment in patients with mild-to-moderate PD (9). A decrease of the regional cerebral blood flow (rCBF) in the ACC and the dorsolateral prefrontal cortex may reflect cognitive dysfunction in patients with PD (10). Previous studies have reported brain metabolism deficits in the ACC to be correlated with executive performance in patients with PD (11-13). In addition, a functional magnetic resonance imaging (fMRI) study demonstrated that a decline in the memory and visuospatial domains may be associated with stronger coupling between the dorsal caudate and the rostral ACC (14). These findings suggest that PD-related executive deficits and brain changes are heterogeneous; however, the processing speed-related changes remain to be fully elucidated.

Proton magnetic resonance spectroscopy (^{1}H-MRS) is a method used to investigate the biochemical index and metabolic changes through quantification of a range of metabolites, including N-acetyl-aspartate (NAA), choline-containing compounds (Cho), and creatine (Cr), in different brain structures (15,16). NAA is an indicator of neuronal integrity, and the decreased ratio of NAA:Cr indicates neuronal and axonal loss or dysfunction (17). Meanwhile, Cho is an indicator of membrane metabolism, and an increased ratio of Cho to Cr corresponds with increased membrane turnover (17). One study found that, compared with healthy control (HC) subjects, PD-MCI patients showed a reduced NAA:Cr ratio in the occipital lobe and an increased Cho:Cr ratio in the posterior cingulate (18).

Therefore, the principal objective of this study is to explore the characteristics of cognitive function changes in patients with PD, especially in terms of the subcomponents of EF and processing speed. Specifically, we used ^{1}H-MRS to investigate the metabolic changes of the frontal lobe and the ACC in patients with PD, and further explored the association between cognitive function and metabolic ratios in the frontal lobe and the ACC. We present the following article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1126/rc).

Methods

Participants

In this retrospective case-control study, patients with PD from the Department of Neurology at Guangdong Provincial Peoples' Hospital in China and age-, sex-, and years-of-education-matched HCs were enrolled in this study from October 2018 to November 2020. All patients with PD fulfilled the following criteria: (I) they met the

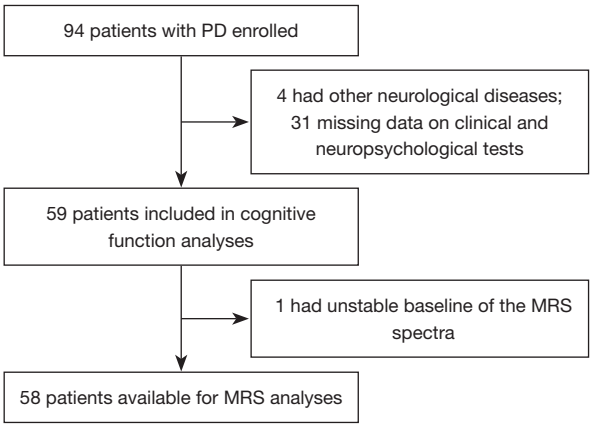

Figure 1 Flowchart of the included patients with PD in this study. MRS, magnetic resonance spectroscopy. PD, Parkinson disease.

Movement Disorder Society (MDS) Clinical Diagnostic Criteria for PD (19); (II) they were not treated with any antidepressant medications; and (III) they did not have other Parkinsonian syndrome or other neurological diseases. The flowchart of the excluded patients with PD can be seen in *Figure 1*. In all, 59 patients with PD and 30 HCs were available for the study for clinical and demographic data. One of the patients with PD was excluded because the baseline of the MRS spectra was unstable. Finally, 58 patients were available for MRS analysis.

Clinical and neuropsychological evaluation

The motor symptoms were measured with the modified Hoehn-Yahr scale (20) and the MDS Unified Parkinson Disease Rating Scale (MDS-UPDRS) part III (21). The severity of depression and anxiety were assessed using the scores of the 24-item Hamilton Depression Rating Scale (22) and Hamilton Anxiety Rating Scale (23). The neuropsychological test battery included the Mini-Mental State Examination (MMSE) (24) and the Montreal Cognitive Assessment (MoCA) (25) for global cognition. The tests to assess EF and processing speed were as follows: verbal fluency test-semantic (26), Wechsler Adult Intelligence Scale (WAIS)-Similarities (27), WAIS-Digit symbol coding (27), Stroop color-word test (28), WAIS-Digit span, and Wisconsin Card Sorting Test (WCST-128) (29). Processing speed was measured using the Stroop A (word naming test) and the WAIS-Digit symbol test. The speed of performance on the color-word trial was subtracted from the speed on the color naming test to calculate interference [Stroop interference effect (SIE)]. The number of completed categories in WSCT is frequently used as a measure of shift and deduction functions. Most prominently, deficits in cognitive flexibility are commonly thought to be reflected in the number of perseverative errors in WSCT. The levodopa equivalent daily dose (LEDD) was appropriately calculated (30). This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent to participate in the study. This study was approved by the Medical Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2019490H[R1]). The demographic and clinical characteristics of the patient and control groups are shown in *Table 1*.

Neuroimaging

Routine MRI and ^{1}H-MRS were performed with a GE Signa Excite 3.0 T scanner (GE Healthcare) with a standard 8-channel head coil. Single-voxel ^{1}H-MRS was used with point resolved spectroscopy sequences (PRESS) with a repetition time (TR)/echo time (TE) of 1,500/144 ms and 128 acquisitions. Spectra were shimmed to achieve a full-width half maximum (FWHM) of <12 Hz, and the percentage of water suppression was higher than 95% to minimize the influence of the signal-to-noise ratio. Volumes of interest (2 cm × 2 cm × 2 cm) were located within the bilateral prefrontal cortex and the ACC (*Figure 2*). The spectra were postprocessed automatically using the Sage 7.0 spectrum processing software system within the magnetic resonance (MR) scanner for filtering and reconstruction, zero filling, phase, and baseline correction. For each patient, the ratios of NAA and Cho relative to Cr were computed.

Statistical analysis

Analyses were carried out using the SPSS v. 20 (IBM SPSS, Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of the data. Between the PD group and HC group, demographic clinical, cognitive, and MRS variables were analyzed with two-sample *t*-tests for normally distributed variables, while the Mann-Whitney test was used for nonnormally distributed variables. The chi-squared test was used to analyze categorical data. The preliminary correlation analysis between processing speed and ratios of metabolite concentration distribution was conducted for the PD group. Hierarchical multiple regressions were applied to assess the association between cognitive function and

Table 1 Demographics and clinical characteristics between the PD and HC groups

Variables	PD (n=59)	HC (n=30)	$t/Z/\chi^2$	P
Male/female	34/25	14/16	0.962	0.373
Age (years)	60.47±8.74	61.10±7.67	−0.332	0.741
Education years	10.67±3.61	11.17±3.57	−0.616	0.539
PD duration (months)	24 [12–36]	–	–	–
Age at PD onset (years)	57.78±8.87	–	–	–
LEDD total (mg/day)	87.5 [0–337.5]	–	–	–
Modified Hoehn-Yahr	2 [2–2.5]	–	–	–
MDS-UPDRS-III	32.27±13.72	–	–	–
HAMD	11 [5–16]	2 [0–3.25]	−6.253	<0.001
HAMA	7 [4–13]	2 [0–5]	−4.461	<0.001
MMSE	28 [27–29]	29 [28–29.25]	−1.628	0.103
MoCA	24 [19–26]	27 [26–28]	−5.041	<0.001

Age, education years, age at PD onset, and MDS-UPDRS-III are expressed as mean ± standard deviation. PD duration, LEDD total, HAMD, HAMA, MMSE, and MoCA are expressed as median [interquartile range]. PD, Parkinson disease; HC, healthy control; LEDD, Levodopa equivalent daily dose, MDS-UPDRS-III, Movement Disorder Society-sponsored Revision of the Unified Parkinson Disease Rating Scale part III; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

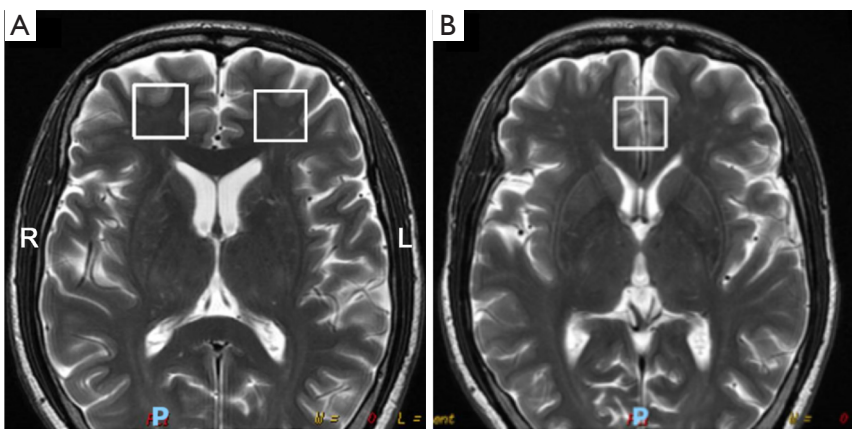

Figure 2 The regions of interest location on MRS images. (A) Bilateral prefrontal lobes. (B) Anterior cingulate cortex. MRS, magnetic resonance spectroscopy; R, right; L, left; P, posterior.

the ratios of metabolite concentrations in the prefrontal lobe and the ACC in patients with PD, with age and MDS-UPDRS-III entered in the first step as control variables, and metabolite ratios entered in the second step. Multiple comparisons were corrected using the Bonferroni procedure with a factor of 6 to account for 3 regions of interest (ROIs) and 2 metabolic measures (P<0.0083). Statistical significance was set at a P value <0.05. Furthermore, in the *post-hoc* analysis, metabolite ratios were compared among the different stages of general cognitive impairment (i.e., MoCA score ≤20, MoCA score =21–25, MoCA score ≥26) from patients with PD using one-way analysis of variance (ANOVA), and the Bonferroni test was used to correct for multiple comparisons in *post-hoc* comparisons.

Table 2 Cognitive performance comparisons between the PD and HC groups

Variables	PD (n=59)	HC (n=30)	*t*/Z	P
Verbal fluency test-semantic	14.98±3.89	20.13±5.23	−4.765	<0.001
WAIS-Similarities	12.37±4.80	19.27±3.95	−6.786	<0.001
WAIS-Digit symbol coding	26.98±10.49	42.43±9.86	−6.701	<0.001
Stroop A times	32 [28–39]	26 [23–30]	−3.786	<0.001
Stroop B times	52 [45–64]	33.5 [30.75–39.5]	−6.147	<0.001
Stroop C times	89 [74–103]	63.5 [59.5–72.5]	−4.758	<0.001
Stroop SIE times	35 [23–49]	30 [20–37]	−1.337	0.181
WAIS-Digit span	12 [10–12]	14 [12.75–16]	−4.958	<0.001
WSCT-completed categories	6 [5–6]	6 [5.75–6]	−1.236	0.216
WSCT-perseverative errors	38.75±19.59	30.23±18.95	1.959	0.053

Verbal fluency test, Similarity test, Digit symbol coding, WSCT-perseverative errors, and WSCT-completed categories are expressed as mean ± standard deviation. Stroop A, B, C, and SIE times, as well as WAIS-Digit span, are expressed as median [interquartile range]. PD, Parkinson disease; HC, healthy control; SIE, Stroop interference effects (SIE = Stroop C time − Stroop B time); WAIS, Wechsler Adult Intelligence Scale; WSCT, Wisconsin Card Sorting Test.

Results

In all, 59 patients with PD and 30 HCs were available for the study and had clinical and demographic data. In the MRS analysis, one of the patients with PD was excluded because the baseline of the MRS spectra was unstable. No significant statistical difference was found in gender (χ^2=0.962; P=0.373), age (*t*=–0.332; P=0.741), or education (*t*=–0.616; P=0.539). The MoCA scores in general cognition were significantly decreased in the PD group (Z=–5.041; P<0.001). However, the MMSE scores were not significantly different between the 2 groups (Z=–1.628; P=0.103). The detailed results are shown in *Table 1*.

The verbal fluency test (*t*=–4.765; P<0.001) and the similarity test (*t*=–6.786; P<0.001) performances that indicated task fluency and information generation ability, were worse in patients with PD. In the processing speed measurement, patients with PD showed significantly decreased performance, which was reflected by significantly lower scores on digit symbol coding and by the longer completion times in the Stroop word naming and color naming subtests. Compared to HCs, patients with PD showed significantly poorer performance on tests of attention and working memory (WAIS-Digit span; Z=–4.958; P<0.001), but not on set-shifting (WSCT; P>0.05) or response inhibition (SIE; P>0.05). The detailed results of the comparison of cognitive function between the 2 groups are shown in *Table 2*.

Compared to HCs, patients with PD showed significantly increased Cho:Cr ratios in the right prefrontal cortex (RPF; *t*=2.16; P=0.034) and ACC (Z=–2.20; P=0.028) regions (*Table 3*, *Figure 3*). The typical MRS spectra are shown in *Figure 4*. However, these differences did not survive correction for multiple comparisons (P<0.0083).

In the correlation analysis, the NAA:Cr ratio in the RPF was significantly related to the scores of the WAIS-Digit symbol coding test. The relationship between NAA:Cr ratio in the ACC and Stroop A completion times was not significant (P=0.055) (Table S1). The MDS-UPDRS-III score was not correlated with processing speed in the PD group significantly (P=0.062) (Table S2). We performed a correlation analysis between metabolites in the PD group to narrow the independent variables of the regression analysis (Table S3). A strong correlation between the Cho:Cr ratio in the RPF and the ACC was found, and thus the Cho:Cr ratio in the RPF was not included in further regression analysis. Therefore, in the hierarchical multiple regression analysis, age and the MDS-UPDRS-III were included as control variables. In hierarchical multiple regression model 1, age and MDS-UPDRS-III accounted for 4.2% of the variance on step 1. On step 2, metabolite measurements in the ACC accounted for a further 15.6% of the variance in the Stroop A completion times. Examination of β weights suggested that the correlate of Stroop A completion times was NAA:Cr ratio in the ACC (P<0.05), while a positive relationship with Cho:Cr ratio in the ACC was not

Table 3 Comparisons of metabolite ratios for the bilateral prefrontal cortex and anterior cingulate between the PD and HC groups

Metabolite ratios	PD (n=58)	HC (n=30)	*t*/Z	P
ACC				
NAA:Cr	1.40±0.14	1.44±0.16	−1.07	0.285
Cho:Cr	1.09 [1.00–1.15]	1.025 [0.90–1.10]	−2.20	0.028*
RPF				
NAA:Cr	1.66 [1.53–1.85]	1.72 [1.49–1.86]	−0.29	0.768
Cho:Cr	1.09±0.18	1.00±0.18	2.16	0.034*
LPF				
NAA:Cr	1.78±0.27	1.84±0.32	−0.87	0.385
Cho:Cr	1.08 [0.94–1.20]	1.03 [0.86–1.17]	−1.53	0.126

Data are expressed as mean ± standard deviation or median [interquartile range]. *, P<0.05. PD, Parkinson disease; HC, healthy control; ACC, anterior cingulate cortex; RPF, right prefrontal cortex; LPF, left prefrontal cortex; Cho, choline-containing compounds; Cr, creatine; NAA, N-acetyl-aspartate.

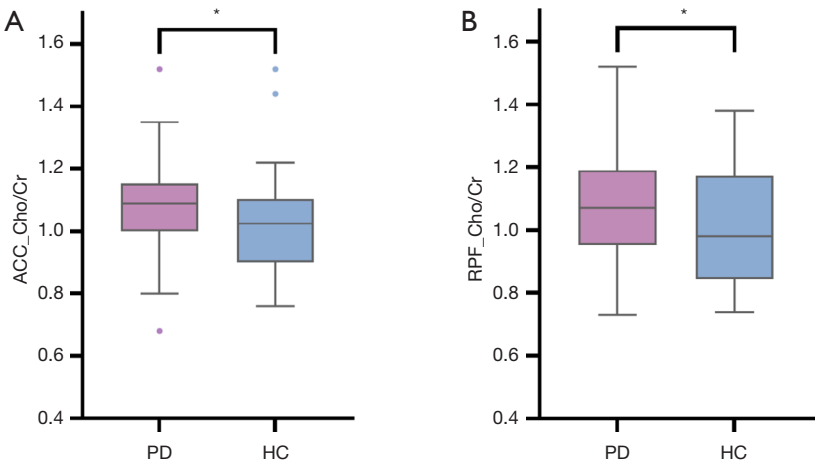

Figure 3 Box plots depicting the ratios of metabolite concentration distribution being significantly different between the PD and HC groups. (A) The Cho:Cr ratios in the anterior cingulate cortex. (B) The Cho:Cr ratios in the right prefrontal cortex. PD, Parkinson disease; HC, healthy control; ACC, anterior cingulate cortex; RPF, right prefrontal cortex; Cho, choline-containing compounds; Cr, creatine. *, P<0.05.

significant (P=0.058). In model 2, with the WAIS-Digit symbol coding test score as the dependent variable, the significant correlate at P<0.05 was the NAA:Cr ratio of the RPF. Overall, model 2 accounted for 22.4% of the variance in the WAIS-Digit symbol coding test score (*Table 4*). These correlations were not found in the HC groups (Table S4).

In the *post-hoc* analysis among the different stages of cognitive impairment from patients with PD, a significant reduction in the metabolite ratios of NAA:Cr in the right prefrontal cortex was observed in PD group A (MoCA score ≤20) compared to the PD group C (MoCA score ≥26) (P=0.044, Bonferroni corrected; *Table 5*).

Discussion

The present study comprehensively investigated the executive profiles and processing speed in patients with PD, who in turn showed worse performance in EF and processing speed compared with HCs. The Cho:Cr ratios in the ACC and the right prefrontal cortex were significantly

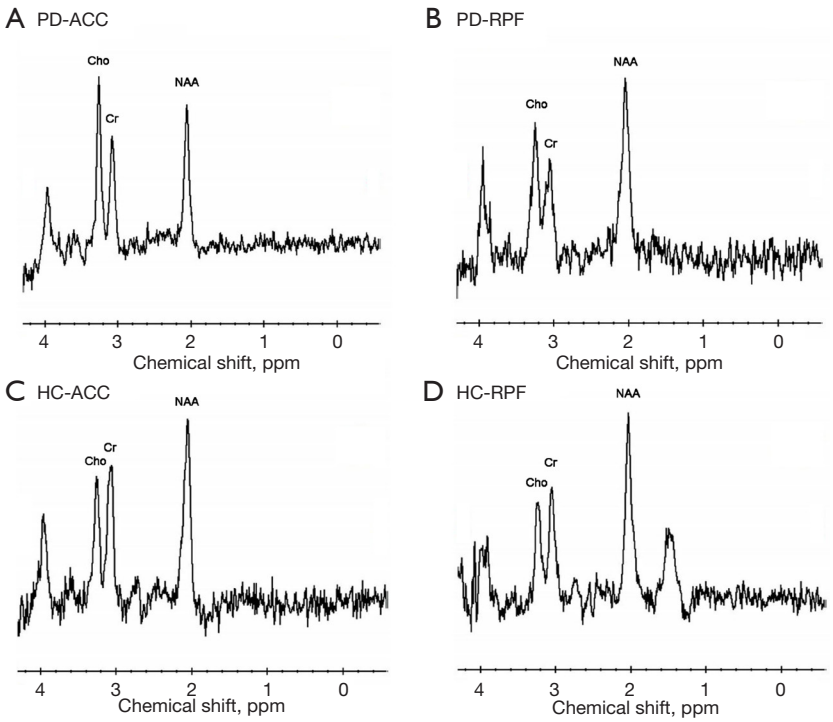

Figure 4 The representative graphs of MRS spectra. (A) Anterior cingulate cortex of a patient with PD. (B) Right prefrontal cortex of a patient with PD. (C) Anterior cingulate cortex in an HC. (D) Right prefrontal cortex in an HC. PD, Parkinson disease; HC, healthy control; ACC, anterior cingulate cortex; RPF, right prefrontal cortex; Cho, choline-containing compounds; Cr, creatine; MRS, magnetic resonance spectroscopy; NAA, N-acetyl-aspartate.

increased in patients with PD compared to HCs. Hierarchical multiple regressions showed that the metabolic ratios in the ACC of patients with PD correlated with the Stroop A completion times, while the NAA:Cr ratios of the right prefrontal cortex correlated with the scores of the WAIS-Digit symbol substitution subtest.

The scores for the processing speed test were significantly decreased in patients with PD compared with those in HCs. Furthermore, the performance of multiple executive domains, such as attention and working memory tests, were poorer in patients with PD compared with HCs. However, selective domain-specific tests for set-shifting and response inhibition were not found to be significantly worse in the PD group compared to HCs. The decline in information processing speed can be manifested as impairment of the initiation ability and reaction speed, which is related to the ability to detect and react to stimuli in order to maintain attentional and motivational status (31,32). Therefore, processing speed plays a role in executive dysfunction. To date, the most influential neuropsychology and cognitive test models in cognitive science are the processing speed theory (33) and the prefrontal executive theory (34). Processing speed theory contends that age-related cognitive declines can be accounted for by a single or global slowing of cognitive processing. The generalized slowdown is thought to be due to a disruption of white matter integrity throughout the whole brain. In contrast, the prefrontal executive theory states that cognitive declines, specifically in executive abilities, lead to more general cognitive deficits and may be attributed to local structural and functional changes in the frontal cortex areas. However, the respective roles of processing speed and EF in age-related cognitive decline have not yet been fully elucidated (35). EF can represent a combination of established cognitive abilities, such as reasoning and perception speed (35). Previous studies have revealed that the differences in age-related central EF can be eliminated by controlling for the processing speed (36). However, there is also evidence that the decline in age-related EF is not only in processing speed (37). It is worth noting that the patients with PD in this study were mainly at Hoehn-Yahr stage 2–2.5. The different states of the disease may be important influencing

Table 4 Hierarchical multiple regression models testing the association between the ratios of metabolite concentrations and cognitive performance in the PD group

Models	β	*t*	P	R^2	R^2 change	F change	F change P value
Model 1 (DV: Stroop A completion times)							
Step 1				0.042	0.042	1.213	0.305
Age	0.147	1.108	0.273				
MDS-UPDRS-III	0.156	1.181	0.243				
Step 2				0.156	0.114	3.568	0.035*
Age	0.221	1.687	0.098[a]				
MDS-UPDRS-III	0.207	1.618	0.112				
ACC_NAA/Cr	−0.292	−2.238	0.029*				
ACC_Cho:Cr	0.259	1.938	0.058[a]				
Model 2 (DV: WAIS-Digit symbol coding test)							
Step 1				0.151	0.151	4.908	0.011*
Age	−0.272	−2.181	0.033*				
MDS-UPDRS-III	−0.301	−2.418	0.019*				
Step 2				0.224	0.072	1.617	0.197
Age	−0.305	−2.407	0.020*				
MDS-UPDRS-III	−0.270	−2.147	0.036*				
ACC_NAA/Cr	−0.005	−0.040	0.968				
ACC_Cho:Cr	−0.130	−1.003	0.321				
RPF_NAA/Cr	0.257	2.032	0.047*				

[a], trend-level, 0.05<P<0.1; *, P<0.05. β, standardized coefficient; DV, dependent variable; PD, Parkinson disease; MDS-UPDRS-III, Movement Disorder Society-sponsored Revision of the Unified Parkinson Disease Rating Scale part III; ACC, anterior cingulate cortex; RPF, right prefrontal cortex; LPF, left prefrontal cortex; Cho, choline-containing compounds; Cr, creatine; NAA, N-acetyl-aspartate; WAIS, Wechsler Adult Intelligence Scale.

Table 5 Comparison of metabolite ratios among the different stages of cognitive impairment from patients with PD

Metabolite ratios	PD group A (MoCA score ≤20) (n=19)	PD group B (MoCA score =21–25) (n=21)	PD group C (MoCA score ≥26) (n=18)	ANOVA		*Post-hoc* analyses (Bonferroni corrected)		
				F	P	PD-group A *vs.* PD-group B	PD-group A *vs.* PD-group C	PD-group B *vs.* PD-group C
ACC_NAA:Cr	1.384±0.162	1.390±0.124	1.439±0.131	0.867	0.426	1.000	0.715	0.826
ACC_Cho:Cr	1.029±0.119	1.085±0.152	1.132±0.152	2.462	0.095	0.657	0.093	0.906
RPF_NAA:Cr	1.582±0.221	1.723±0.239	1.770±0.216	3.510	0.037*	0.161	0.044*	1.000
RPF_Cho:Cr	1.056±0.200	1.090±0.126	1.121±0.198	0.625	0.539	1.000	0.807	1.000
LPF_NAA:Cr	1.689±0.254	1.784±0.275	1.869±0.278	2.070	0.136	0.813	0.141	0.987
LPF_Cho:Cr	1.066±0.270	1.069±0.176	1.172±0.218	1.349	0.268	1.000	0.470	0.473

Data are expressed as mean ± standard deviation. Bonferroni-corrected for multiple comparisons. *, P<0.05. PD, Parkinson disease; MoCA, Montreal Cognitive Assessment; ANOVA, analysis of variance; ACC, anterior cingulate cortex; RPF, right prefrontal cortex; LPF, left prefrontal cortex; Cho, choline-containing compounds; Cr, creatine; NAA, N-acetyl-aspartate.

factors of inhibitory function. A previous study found reactive inhibition but not proactive inhibition to be more impaired in patients with PD at Hoehn-Yahr stage 1 compared to HCs (38). Early dopaminergic medication could increase the dopaminergic level of the dorsal striatum to improve the function of the dorsal frontal lobe-striatum circuit and ameliorate the related cognitive functions, such as planning and set shift ability (39). Cognitive function impairment may also be associated with limbic and orbitofrontal circuits, such as conditional associative, reverse learning, and reward learning (40,41).

We compared the PD cognition-related prefrontal cortex and ACC metabolic profile alteration between PD and HC groups using ^{1}H-MRS. The increase in Cho:Cr ratios was evident within the right prefrontal cortex and the ACC in the PD group compared with the HC group. However, as the data did not survive Bonferroni correction, this finding should be interpreted with caution. The Cho signal, which mainly includes membrane phospholipid derivatives, is considered to be a marker of cell membrane turnover and breakdown (42,43). Increased Cho:Cr ratios might be the result of membrane structure damage of neurons (44). Furthermore, Cho levels may also be related to an early neuroinflammatory condition in PD (45).

In hierarchical multiple regression models, a change in metabolic ratios in the ACC and RPF was associated with a poor Stroop A test (word reading) performance and poor scores on the WAIS-Digit symbol coding test in patients with PD. These two tests reflect the processing speed performance of patients. Processing speed has been found associated with functional connectivity of the cingulo-opercular network (C-O), including the anterior insula/frontal operculum and the ACC, which can reflect the functions of attentional initiation, allocation, and behavioral adjustment in response to tasks (46). In one study, the C-O network was activated during perceptual and episodic memory search tasks, which involved trial initiation, target detection, decision-making, and response, indicating its consistent involvement in a broad range of cognitive processes (31). Furthermore, the C-O network is related to the maintenance of performance during tasks (46).

We found that the reduction of NAA levels in the right prefrontal cortex of patients with PD was associated with worse performance in the digit symbol coding test and a slowdown of processing speed. NAA represents the degree of amino acid concentration within neurons and is viewed as a marker of neuronal function. NAA plays a role in mediating osmoregulation and acid-base homeostasis. Reductions of NAA on ^{1}H-MRS are considered as either a depletion of the number of neurons or a loss of neuronal function (47-49). NAA concentrations may be used as one of the earliest neuroimaging markers at the subjective cognitive decline stage (50). Therefore, the loss of the number and function of neurons in the right prefrontal cortex may be important factors that cause processing speed to slowdown. Neuroimaging studies using single-photon emission computed tomography (SPECT) associated processing slowness with a decreased glucose metabolism in the prefrontal cortex (51). Prefrontal Cho/Cr may characterize PD-associated fronto-striatal cognitive syndrome and affect EF. A previous study using data-driven independent component analysis found that reduced connectivity between the dorsal attention network and right fronto-insular regions in PD-MCI patients was related to attention and executive dysfunction (7).

In our post hoc analysis, we examined the MRS metabolite ratios in different stages of general cognitive impairment (MoCA score ≤20, MoCA score =21–25, MoCA score ≥26) from patients with PD: the PD group with MoCA scores ≤20 displayed significantly deceased ratios of NAA:Cr in the right prefrontal cortex. Consistent with the literature, our study found decreased a NAA:Cr ratio in the PD group with the most severe cognitive impairment (MoCA <20). Although not a substitute for comprehensive neuropsychological examination, the MoCA of global screening scales is recommended by the MDS Task Force in their rating scale to assess PD (52). The scale consists of 9 assessment parts: memory, visuo-constructional skills, attention, concentration, EFs, language, conceptual thinking, calculations, and orientation. Generally, cutoffs of 25/26 points for PD-MCI and 20/21 points for Parkinson disease dementia (PD-D) are suggested for screening in clinical practice (52). As mentioned above, when the MoCA scale is weighted toward frontal domains like executive abilities or attention, it may be more likely to be altered in a larger proportion of patients with PD. Indeed, one study found executive, visuospatial, and memory deficits to be associated with a higher risk of dementia conversion, with frontal/executive dysfunction contributing most to the occurrence of PD-D (53).

However, in our study, further multiple linear regression analysis unexpectedly showed that metabolite ratios for the bilateral prefrontal cortex and the ACC were only associated with the processing speed measure, with no correlation with measures of EF, such as semantic fluency, Stroop inhibition, WAIS-Similarities, shift, or deduction functions in the

WSCT test. Therefore, caution should be exercised when using ^{1}H-MRS to serve as a marker of EF. These findings need further confirmation with longitudinal data.

Our study had some limitations. First, we used MRS ratios in reference to Cr but lacked concentration quantification. Second, we only selected 3 ROIs in the PD to analyze focal damage using MRS rather than analyzing more diffuse damage with other functional imaging techniques. The ROI measurements in prefrontal lobes were mainly in the white matter wherein projections with other cortical and thalamic projections might have been involved. Therefore, functional imaging techniques should be explored further to assess the impact of diffuse brain pathology on cognitive impairment in patients with PD. Third, the modified Hoehn-Yahr scale has some limitations, such as the nonlinear relationship with disease progression, more focus on postural instability and mobility problems. However, this scale is widely used to quantify disease severity and functional burden, and may be useful for clinical studies that evaluate therapeutic interventions and prognostic factors in Parkinsonism (54,55). Finally, the effects of antiparkinsonian medications on the current findings cannot be fully ruled out. Future work using multicenter prospective PD cohorts could aim to evaluate the degeneration of the prefrontal lobes and ACC and the effects on cognitive function.

Conclusions

Multiple executive domains and processing speed were impaired in patients with PD. The increase in Cho:Cr ratios was evident within the right prefrontal cortex and the ACC in patients with PD, which may be associated with membrane structure damage of neuronal cells. Loss of the number and function of neurons in the right prefrontal cortex and the ACC may be important factors that cause a slowdown of processing speed in patients with PD.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-1126/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1126/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All participants provided written informed consent to participate in the study. This study was approved by the Medical Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2019490H[R1]).

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Supplementary

Table S1 Correlation between processing speed and ratios of metabolite concentration distribution in the PD group.

Variables	ACC_NAA:Cr	ACC_Cho:Cr	RPF_NAA:Cr	RPF_Cho:Cr	LPF_NAA:Cr	LPF_Cho:Cr
Stroop A completion times						
Rho	−0.253	0.072	−0.154	−0.055	−0.083	−0.067
P	0.055[a]	0.593	0.247	0.684	0.538	0.619
WAIS-Digit symbol coding test						
Rho	−0.029	−0.067	0.342	0.112	0.110	0.236
P	0.827	0.615	0.009*	0.404	0.409	0.074[a]

[a], trend-level, 0.05<P<0.1; *, P<0.05. PD, Parkinson disease; ACC, anterior cingulate cortex; RPF, right prefrontal cortex; LPF, left prefrontal cortex; Cho, choline-containing compounds; Cr, creatine; NAA, N-acetyl-aspartate; WAIS, Wechsler Adult Intelligence Scale.

Table S2 Correlation between processing speed and clinical characteristics in the PD group

Variables	1. Stroop A completion times	2. WAIS-Digit symbol coding test	3. Age	4. Gender	5. Education years	6. MDS-UPDRS-III	7. Modified Hoehn-Yahr scale
1. Stroop A completion times							
Rho	1						
P							
2. WAIS-Digit symbol coding test							
Rho	−0.386	1					
P	0.003						
3. Age							
Rho	0.094	−0.218	1				
P	0.484	0.100					
4. Gender							
Rho	−0.076	−0.004	0.168	1			
P	0.568	0.975	0.209				
5. Education years							
Rho	−0.083	0.123	0.050	−0.181	1		
P	0.536	0.357	0.712	0.174			
6. MDS-UPDRS-III							
Rho	0.220	−0.247	−0.136	−0.023	0.099	1	
P	0.097[a]	0.062[a]	0.310	0.864	0.462		
7. Modified Hoehn-Yahr scale							
Rho	0.151	−0.190	0.150	0.033	−0.037	0.581	1
P	0.259	0.152	0.260	0.808	0.780	0.000	
8. LEDD total							
Rho	−0.099	−0.054	0.070	0.014	−0.039	0.159	0.273
P	0.462	0.685	0.599	0.916	0.772	0.233	0.038*

[a], trend-level, 0.05<P<0.1; *, P<0.05. PD, Parkinson disease; MDS-UPDRS-III, Movement Disorder Society-sponsored Revision of the Unified Parkinson Disease Rating Scale part III; LEDD, Levodopa equivalent daily dose; WAIS, Wechsler Adult Intelligence Scale.

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Table S3 Correlation between the metabolites in the PD group

Variables	1. ACC_NAA:Cr	2. ACC_Cho:Cr	3. RPF_NAA:Cr	4. RPF_Cho:Cr	5. LPF_NAA:Cr
1. ACC_NAA:Cr					
Rho	1				
P					
2. ACC_Cho:Cr					
Rho	0.214	1			
P	0.107				
3. RPF_NAA:Cr					
Rho	0.218	0.126	1		
P	0.100	0.347			
4. RPF_Cho:Cr					
Rho	0.352	0.441	0.154	1	
P	0.007*	0.001*	0.249		
5. LPF_NAA:Cr					
Rho	0.164	0.006	0.485	0.234	1
P	0.218	0.962	0.000*	0.077[a]	
6.LPF_Cho:Cr					
Rho	0.235	0.281	0.214	0.615	0.505
P	0.076[a]	0.032*	0.106	0.000*	0.000*

[a], trend-level, 0.05<P<0.1; *, P<0.05. PD, Parkinson disease; ACC, anterior cingulate cortex; RPF, right prefrontal cortex; LPF, left prefrontal cortex; Cho, choline-containing compounds; Cr, creatine; NAA, N-acetyl-aspartate.

Table S4 Multiple linear regression models testing the association between the ratios of metabolite concentrations and cognitive performance in the HC group

Models	β	Std. Error	Standardized coefficient beta	*t*	P value
Model 1					
Age	–0.077	0.194	–0.082	–0.396	0.696
ACC_NAA:Cr	–0.574	9.016	–0.013	–0.064	0.950
ACC_Cho:Cr	5.265	8.682	0.123	0.606	0.550
Model 2					
Age	0.199	0.259	0.155	0.769	0.449
ACC_NAA:Cr	–6.428	12.274	–0.103	–0.524	0.605
ACC_Cho:Cr	–9.176	11.563	–0.156	–0.794	0.435
RPF_NAA:Cr	9.349	7.154	0.254	1.307	0.203

In multiple linear regression model 1 and model 2, including age as covariates. Stroop A completion times as dependent variable in model 1. Digit symbol coding score as dependent variable in model 2. HC, healthy control; ACC, anterior cingulate cortex; RPF, right prefrontal cortex; LPF, left prefrontal cortex; Cho, choline-containing compounds; Cr, creatine; NAA, N-acetyl-aspartate.

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