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SHORT COMMUNICATION

Visuo-spatial processing is linked to cortical glutamate dynamics in Parkinson's disease — a 7-T functional magnetic resonance spectroscopy study

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Abstract

Background and purpose: Cognitive decline is a frequent and debilitating non-motor symptom for patients with Parkinson's disease (PD). Metabolic alterations in the occipital cortex during visual processing may serve as a biomarker for cognitive decline in patients with PD.

Methods: Sixteen patients with PD (Unified Parkinson's Disease Rating Scale Part 3, OFF, 38.69 ± 17.25) and 10 age- and sex-matched healthy controls (HC) underwent 7-T functional magnetic resonance spectroscopy (MRS) utilizing a visual checkerboard stimulation. Glutamate metabolite levels during rest versus stimulation were compared. Furthermore, correlates of the functional MRS response with performance in visuo-cognitive tests were investigated.

Results: No differences in static MRS between patients with PD and HC were detected, but a dynamic glutamate response was observed in functional MRS in HC upon visual stimulation, which was blunted in patients with PD ($F_{1,22} = 7.13$, $p = 0.014$; $\eta_p^2 = 0.245$). A diminished glutamate response correlated with poorer performance in the Benton Judgment of Line Orientation test in PD ($r = -0.57$, $p = 0.020$).

Conclusions: Our results indicate that functional MRS captures even subtle differences in neural processing linked to the behavioral performance, which would have been missed by conventional, static MRS. Functional MRS thus represents a promising tool for studying molecular alterations at high sensitivity. Its prognostic potential should be evaluated

Anja Ophey and Ezequiel Farrher contributed equally to this article

in longitudinal studies, prospectively contributing to earlier diagnosis and individual treatment decisions.

KEYWORDS
biomarker, cognitive decline, functional magnetic resonance spectroscopy, visuo-cognition

INTRODUCTION

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder caused by the accumulation of α-synuclein in widespread brain areas [1]. Clinically, PD is characterized by its motor syndrome and a variety of non-motor symptoms [1].

Cognitive decline may be the most debilitating non-motor symptom as it profoundly interferes with the patient's independence and quality of life [2]. The prevalence of mild cognitive impairment in PD is estimated at around 40% [3]. Even in prodromal PD, cognitive alterations, for example in executive functions and visuo-cognition, are reported [4], and up to 80% of patients eventually develop PD dementia (PD-D) [5].

Imaging studies in PD patients with cognitive deterioration showed a cortical hypometabolism, especially in occipital areas, distinguishing PD-D from Alzheimer's dementia [6]. These changes predicted cognitive decline and incipient PD-D [7]. On the metabolic level, a magnetic resonance spectroscopy (MRS) study revealed an association between reduced γ-aminobutyric acid levels in the occipital cortex and visual hallucinations in PD [8]. Visual hallucinations may represent one end of the spectrum of visuo-cognitive impairment in PD, including deficits from early sensory discrimination to higher visual dysfunction [9].

Our study aimed to investigate early metabolic alterations of glutamate metabolism in the occipital cortex during visual processing in PD patients. Functional MRS (fMRS) was performed on a 7-T scanner and the results were compared to those for healthy controls (HC). Furthermore, visuo-cognitive functions were investigated, including visuo-perceptual, visuo-spatial and visuo-constructive abilities, as neuropsychological proxies [10]. Despite a comparable behavioral performance, it was hypothesized that metabolic alterations during visual processing might be revealed in PD patients versus HC.

MATERIALS AND METHODS

Participants and study protocol

Sixteen PD patients and 10 HC were recruited for this case–control study. The inclusion criteria were age 50–80 years, Geriatric Depression Scale score ≤5 and Montreal Cognitive Assessment score ≥22. PD diagnosis was obtained following the current Movement Disorder Society (MDS) clinical diagnostic criteria. Exclusion criteria included contraindications for MR imaging, structural brain lesions and ophthalmological diseases. For HC, any symptom suggesting a movement disorder constituted an exclusion criterion. Participants were comprehensively characterized (Table 1, Supplementary Material 1 in Data S1). The study was approved by the local ethics committee of the Medical Faculty of the University of Cologne (vote no. 18-217), and all participants provided written informed consent before inclusion.

Functional MRS

Magnetic resonance data were acquired using a 7-T Siemens Terra scanner running on Syngo VE12U(SP01) (Siemens Healthineers). All PD patients were scanned during the self-reported stable ON condition. A T1-weighted mp2rage sequence was used for anatomical imaging to position the MRS voxel on the visual cortex (Figure 1). A hundred and twenty spectra were acquired utilizing a stimulated echo acquisition mode (STEAM) sequence during the fMRS paradigm. For details on the MR protocol and MRS processing, see Supplementary Material 2 in Data S1. fMRS analysis was focused on glutamate, glutamine and Glx (glutamate + glutamine).

First, a black fixation cross on a grey background was presented during the REST condition. Then, during the stimulation (STIM) condition, a 3.3 Hz alternating checkerboard was presented (Figure 1). Each condition lasted 5 min (block design), and participants were instructed to focus on the cross or the flickering checkerboard. The screen was placed in the back of the scanner's bore (distance to screen 355 cm), and participants viewed the presentation on a mirror installed in the head coil (viewing angle 10° × 5°).

Statistics

Data were analyzed using SPSS 28 and R (https://www.r-project.org). For the comparison between HC and PD patients, independent sample *t* tests or χ^2 tests were performed. 2 × 2 ANCOVA with GROUP (HC vs. PD) as the between-subjects factor and STIMULATION (REST vs. STIM) as the within-subjects factor, as well as age and sex as covariates, were performed for the concentrations of glutamate, glutamine and Glx as dependent variables, respectively. If a significant GROUP*STIMULATION interaction was observed, correlates of the fMRS response defined as the difference in metabolite concentrations between STIM and REST (ΔSTIMULATION = STIM − REST) with performance in visuo-cognitive tests were investigated for the respective metabolite. Correlations were examined per group by

TABLE 1 Descriptive characteristics and comparison between healthy controls and patients with Parkinson's disease concerning demographic, clinical, cognitive and MRS parameters.

Assessment	Healthy controls ($n = 10$)		Parkinson's disease ($n = 16$)		p
Age (years)	68.59 (6.13)		67.44 (7.13)		0.677
Sex					
Female	3 (30%)		5 (31.25%)		0.946
Male	7 (70%)		11 (68.75%)		
Education (years)	13.65 (2.38)		14.75 (3.13)		0.351
MoCA	26.90 (1.60)		27.06 (2.02)		0.831
GDS-15	0.70 (0.82)		1.13 (1.31)		0.369
NMSQ	1.7 (2.45)		6.69 (5.19)		**0.009**
Sniffin' Sticks	10.40 (0.97)		5.38 (2.42)		**<0.001**
Disease duration (years)			8.06 (6.28)		
LEDD			454.69 (268.12)		
MAO inhibitors only			$n = 1$		
Levodopa only			$n = 4$		
Levodopa + dopamine agonists			$n = 11$		
MDS-UPDRS III, OFF			38.69 (17.25)		
Hoehn and Yahr, OFF			2.28 (0.86)		
Visuo-cognition					
BJLO	−0.13 (1.12)		0.23 (1.06)		0.420
ROCFT Figure Copy	0.59 (0.41)		0.72 (0.51)		0.500
LPS50+ 7: Rotation	−0.19 (0.82)		−0.19 (0.86)		0.994
LPS50+ 11: Perception	−0.10 (0.50)		−0.55 (0.70)		0.090
Language					
Impairment in % in the subtest Naming (Aphasia Checklist)	0%		0%		>0.999
HAWIE similarities	0.17 (0.76)		0.16 (0.57)		0.969
Working memory/attention					
Trail Making Test A	1.41 (1.03)		0.66 (0.84)		0.052
Digit Span Backward	−0.38 (1.12)		−0.08 (1.13)		0.515
Executive functions					
Trail Making Test B/A	0.14 (1.04)		−0.05 (0.81)		0.614
RWT Phonemic Verbal Fluency	0.51 (1.33)		−0.38 (0.76)		**0.038**
RWT Semantic Verbal Fluency	0.24 (0.71)		−0.49 (0.72)		**0.016**
Memory					
VLMT Word List Learning	−0.39 (1.38)		−0.13 (1.16)		0.604
VLMT Word List Recall	0.03 (0.98)		0.51 (1.00)		0.249
ROCFT Figure Recall	0.75 (1.26)		1.00 (1.29)		0.631
Metabolite concentration levels					
	REST	**STIM**	**REST**	**STIM**	
Glu (mmol/l)	9.92 (0.98)	9.78 (0.98)	9.87 (1.13)	9.92 (1.17)	**0.014**
Gln (mmol/l)	3.31 (0.52)	3.27 (0.52)	3.35 (0.54)	3.34 (0.58)	0.601
Glx (mmol/l)	13.23 (1.44)	13.05 (1.38)	13.21 (1.54)	13.26 (1.57)	**0.030**

Note: Data are mean (standard deviation) of sum scores or standardized z-values unless indicated otherwise. For comparing healthy controls and patients with Parkinson's disease, p values of independent sample t tests or χ^2 tests are reported as appropriate. For metabolite levels, p values of the ANCOVA GROUP*STIMULATION interaction are reported. Bold values are significant at $p < 0.050$, uncorrected. Details and references for assessments are provided in Supplementary Material 1 in Data S1. Descriptive statistics of other quantified metabolites are reported in Table S2.

Abbreviations: BJLO, Benton Judgment of Line Orientation; GDS-15. Geriatric Depression Scale 15; Gln, glutamine; Glu, glutamate; Glx, glutamate + glutamine; HAWIE, Hamburg–Wechsler Intelligenztest für Erwachsene; LEDD, levodopa equivalent daily dose; LPS50+, Leistungsprüfsystem 50+; MAO, monoamine oxidases; MDS-UPDRS III, Movement Disorder Society Unified Parkinson's Disease Rating Scale Part 3; MoCA, Montreal Cognitive Assessment; NMSQ, Non-motor Symptom Questionnaire; ROCFT, Rey–Osterrieth Complex Figure Test; RWT, Regensburger Wortflüssigkeitstest; VLMT, Verbaler Lern- und Merkfähigkeitstest.

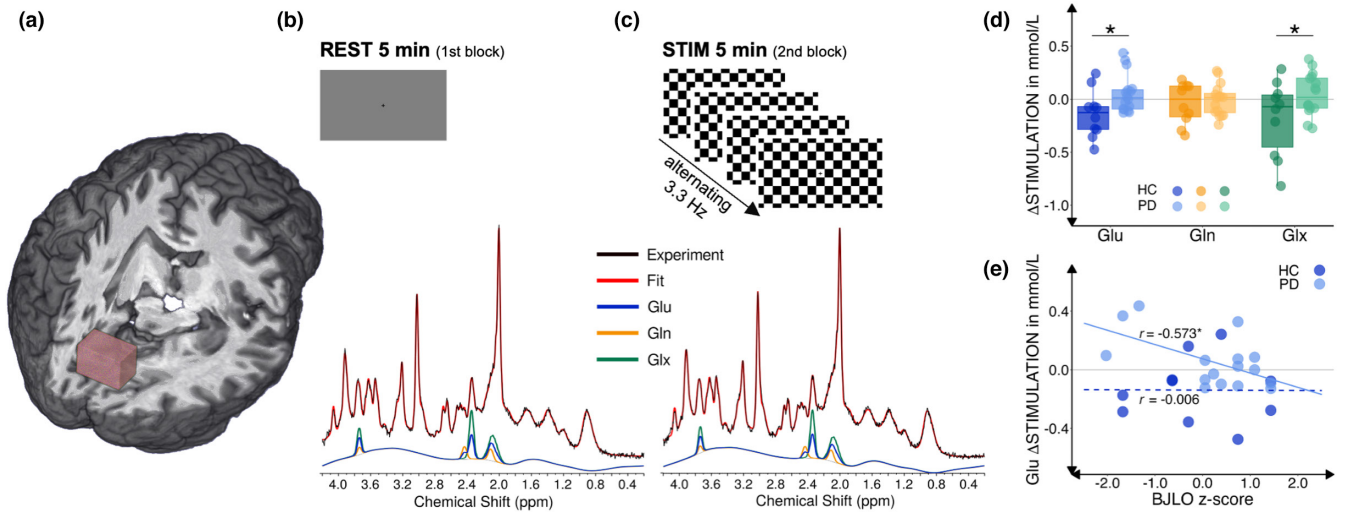

FIGURE 1 (a) Placement of the MRS voxel in the visual cortex in a representative subject. (b) ^{1}H-MRS spectra during the REST condition, that is, whilst watching a black fixation cross on a grey background. (c) ^{1}H-MRS spectra during the STIM condition, that is, whilst watching a 3.3 Hz alternating checkerboard (same representative subject as in (a) and (b)). The blue, orange and green lines in the spectra refer to the individual contributions of Glu, Gln and Glx to the total spectrum. (d) Boxplots of metabolite concentration changes upon visual stimulation in HC and patients with PD for Glu, Gln and Glx. Significant differences are indicated for the ANCOVA GROUP*STIMULATION interaction (Glu, $p = 0.014$; Glx, $p = 0.030$). (e) Correlation between glutamate changes and visuo-spatial function (BJLO) in HC and patients with PD (values at regression lines indicate Pearson's correlation coefficient and asterisk indicates significance: PD, $p = 0.020$). Glu, Gln and Glx concentration levels were computed utilizing the software LCModel. BJLO, Benton Judgement of Line Orientation; Gln, glutamine; Glu, glutamate; Glx, glutamate + glutamine; HC, healthy controls; MRS, magnetic resonance spectroscopy; PD, Parkinson's disease. *$p \leq 0.05$.

Pearson's correlation coefficients. The level of significance was set at $p < 0.05$, uncorrected.

RESULTS

Descriptive statistics are reported in Tables 1, S2 and S3. HC and PD patients were comparable regarding demographic characteristics, depressive symptoms and global cognition. PD patients showed an average MDS Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS-III) OFF score of 38.69 ± 17.25 and a Hoehn and Yahr stage of 2.28 ± 0.86. Compared to HC, PD patients reported significantly more non-motor symptoms ($t_{24} = -2.83$, $p = 0.009$, |Cohen's d| = 1.14) and performed worse on the Sniffin' Sticks examination ($t_{24} = 6.23$, $p \leq 0.001$, |Cohen's d| = 2.51) as well as in the cognitive domain of executive functions (phonemic verbal fluency, $t_{24} = 2.19$, $p = 0.038$, |Cohen's d| = 0.88; semantic verbal fluency, $t_{24} = 2.58$, $p = 0.016$, |Cohen's d| = 1.04). There were no significant group differences in total *N*-acetylaspartate nor in total creatine, considered as surrogate markers for neural damage.

For both glutamate and Glx, the 2 × 2 ANCOVA revealed a significant GROUP*STIMULATION interaction (glutamate, $F_{1,22} = 7.13$, $p = 0.014$, $\eta_p^2 = 0.245$; Glx, $F_{1,22} = 5.37$, $p = 0.030$, $\eta_p^2 = 0.196$), both with large effect sizes: glutamate and Glx (but not glutamine) levels decreased upon stimulation in HC compared to PD patients ($\Delta STIMULATION_{glutamate}$, $t_{24} = 2.40$, $p = 0.025$, |Cohen's d| = 0.97; $\Delta STIMULATION_{Glx}$, $t_{24} = 2.08$, $p = 0.049$, |Cohen's d| = 0.84; Figure 1). Neither the main effects for GROUP nor the main effects for STIM were significant ($p > 0.05$). There were no significant correlations of ΔSTIMULATION with disease duration, levodopa equivalent daily dose and motor symptom severity in PD patients.

As changes in the glutamate concentration mainly drove the effects of Glx, Pearson's correlations of ΔSTIMULATION with performance in visuo-cognitive tests were investigated for glutamate only. For PD patients, the dynamic metabolite response $\Delta STIMULATION_{glutamate}$ inversely correlated with performance in the Benton Judgment of Line Orientation test ($r = -0.57$, $p = 0.020$, Figure 1). This correlation was not observed in HC. No significant correlation of $\Delta STIMULATION_{glutamate}$ with other visuo-cognitive tests was found.

DISCUSSION

The present study identified metabolic changes in the occipital cortex during basic visual processing in PD patients utilizing a checkerboard stimulation during ultra-high field fMRS compared to HC of similar age, sex and cognitive status. Whereas lower levels of glutamate during STIM than REST were observed in HC, this functional metabolite response was absent in PD patients. There were no behavioral differences in visuo-cognitive assessments between the PD patients and HC. However, the negative correlation between the dynamic glutamate response and performance in the Benton Judgment of Line Orientation in PD patients indicates that a healthier "HC-like" metabolic response correlated with better performance in visuo-spatial abilities.

Visual stimulation has been shown to trigger heterogeneous metabolic responses [11]: in general, visual stimulation of a larger field of vision seems to induce increased neural activity as measured via the blood oxygenation level dependent (BOLD) effect and increased glutamate levels in the occipital cortex in younger adults [12, 13]. In contrast, focused visual stimulation (visual angle of 2°) induces a negative BOLD response and reduced glutamate levels [14]. With a visual angle of 10° × 5° due to technical constraints at our institution, the present study's checkerboard stimulation was comparable to a small central checkerboard stimulation driving a reduction of glutamate levels [14]. Thus, the observed reduced glutamate levels in HC in our study align with previous findings. Interestingly this reduction was blunted in PD patients, indicating distinct metabolic responses in PD patients compared to HC.

Notably, the checkerboard stimulation constitutes a very basic visual stimulation, not requiring additional processing resources [9]. However, higher-order visuo-cognitive functions heavily rely on early sensory discrimination and basic visuo-perception, involving the discrimination of local attributes (e.g., lines, edges) [9]. If higher-order visuo-cognitive functions appear to be preserved in PD patients, this may be partly due to compensational mechanisms [2, 10]. Hence, recognizing visuo-cognitive dysfunction operationalized by early metabolic alterations may serve as a potential prognostic marker of PD-D [9].

Additionally, PD patients tended to perform worse than HC in a test for visuo-perception of fragmented pictures and the Trail Making Test A. Next to psycho-motor processing speed, the latter also involves a visuo-attentional component required for visual search. The most parsimonious explanation for our findings is that dysfunctional basic visual processing in PD patients, uncovered by an altered glutamate response, might subsequently impact such test performance. Striatal glutamate levels correlate with performance in working memory and executive function tasks across the lifespan, suggesting that reduced glutamate availability generally contributes to cognitive decline [15].

Limitations of our pilot study include the small sample size and the simple task condition stimulating very basic visual processing only. However, our data underpin the potential of fMRS to study altered metabolic responses as molecular drivers of cognitive dysfunction in neurodegeneration. Future studies may include more sophisticated paradigms and data on BOLD signal change during the checkerboard stimulation to correlate BOLD changes with the glutamate response. Strengths comprise the clinically and cognitively well-characterized sample, including the elaborate testing of visuo-cognitive functions [10]. Nevertheless, future fMRS studies in patients with PD should aim to investigate subgroups of patients in different PD stages, including more advanced PD and patients with clinically relevant cognitive impairment, to assess possible metabolic changes across disease stages.

In conclusion, our results indicate that fMRS could capture even subtle differences in neural processing that would have been missed using conventional, static MRS and on the behavioral level, making it a promising tool for studying molecular alterations at high sensitivity.

AUTHOR CONTRIBUTIONS

AO: formal analysis (equal), visualization (equal), writing—original draft (equal). EF: formal analysis (equal), methodology (equal), software (lead), data curation (equal), visualization (equal), writing—original draft (equal). NP: project administration (supporting), investigation (supporting), writing—review and editing (equal). AS: project administration (equal), investigation (equal), data curation (equal), writing—review and editing (equal). CEJD: investigation (equal), validation (lead), writing—review and editing (equal). NJS: resources (equal), supervision (supporting), writing—review and editing (equal). EK: supervision (supporting), writing—review and editing (equal). GRF: resources (equal), supervision (supporting), writing—review and editing (equal). MS: conceptualization (lead), formal analysis (equal), methodology (equal), resources (equal), supervision (lead), data curation (equal), visualization (equal), writing—original draft (supporting).

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CONFLICT OF INTEREST STATEMENT

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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 INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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