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Visual processing capacity and cognitive decline in Parkinson's disease

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ABSTRACT

Background Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by motor symptoms. However, approximately half of patients with PD exhibit signs of dementia within a decade of diagnosis. While deficits in working memory and visuospatial abilities are recognised as hallmarks of cognitive decline in PD, these populations are rarely studied using detailed cognitive tools that link cognitive impairments to formal theoretical models, such as the theory of visual attention (TVA).

Methods This cross-sectional study addresses this gap by employing the TVA whole report paradigm to assess visual processing in a cohort of patients with PD, both with and without cognitive impairment. Participants were divided based on their Montreal Cognitive Assessment (MoCA) scores into two PD groups (n=25 each) and a healthy control group (n=25).

Results Our principal finding is that the visual processing speed (C) and visual short-term memory capacity (K) are significantly diminished in patients with PD with MoCA scores below 26 (Analysis of variance, p=0.016 for C and p<0.001 for K), while no notable differences were observed between controls and patients with PD with MoCA scores of 26 or above. Using a generalised linear model to assess the impact of factors such as age, gender and disease duration, we discovered that the C-parameter was significantly influenced by age, while the K-parameter was notably affected by gender.

Conclusion TVA parameters demonstrate their suitability for detecting cognitive deficits in PD. Given their independence from motor and non-motor symptoms, TVA parameters may prove to be valuable tools for early diagnosis and longitudinal monitoring of cognitive deficits in individual patients with PD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The theory of visual attention (TVA) is well established in other neurodegenerative disorders and offers certain advantages for cognitive assessment in Parkinson's disease. These include independence from motor impairment and the targeting of visuospatial function as a key indicator of cognitive decline.

WHAT THIS STUDY ADDS

⇒ This study demonstrates that the TVA parameters can detect cognitive impairment in Parkinson's disease: Patients with cognitive impairment showed significantly reduced visual processing speed C and diminished visual short-term memory capacity K compared with both cognitively unimpaired patients and healthy controls. Furthermore, the correlation of TVA parameters with clinical parameters underscores their potential value in understanding and assessing cognitive function in Parkinson's disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ TVA-based assessment may serve as a valid tool for detecting and monitoring cognitive deficits in patients with Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease, characterised by motor symptoms such as bradykinesia, tremor and rigidity. Partly, PD is caused by the loss of dopamine-producing neurons in the midbrain, resulting in decreased dopamine in the basal ganglia, a region of the brain deeply connected to the prefrontal cortex.[1] Consequently, in addition to motor impairments, cognitive deficits are common in PD and tend to worsen over time. Longitudinal studies have shown that 10 years after PD diagnosis, dementia prevails in around 46% of patients.[2]

Cognitive impairment in patients with PD varies and can comprise heterogeneous symptom clusters. According to the 'dual syndrome hypothesis',[3] deficits in executive function and working memory are related to dopaminergic depletion within frontal-striatal networks, whereas impairments in anterograde memory and visuospatial functions are related to cholinergic deficiencies in posterior cortical regions and the temporal lobes. While the 'frontal-striatal' deficits seem to remain relatively stable during the course of PD, the 'posterior' deficits are associated with a more rapid cognitive decline and the development of dementia.[3] This has also been shown in more recent longitudinal studies.[4 5] Therefore, the posterior symptom

cluster seems to bear predictive value for estimating the risk of dementia.

From a neuropsychological perspective, deficits of visuospatial perception are the hallmark of posterior cortical dysfunction.[3 5] Thus, it is not surprising that tasks tapping this cognitive domain have shown great potential for predicting cognitive decline. For example, tests of lower level visual function, such as contrast sensitivity and visual acuity, have shown that deficits on these tests are strongly associated with cognitive performance in PD.[6] Furthermore, Weil *et al* found that despite having similar cognitive scores, patients with PD performed worse than healthy controls (HC) on a task of identifying briefly presented cat and dog images.[7] Poorer performance on this task has been found in patients with PD at high risk for dementia[8] and poor visual performance was linked to cognitive decline and white matter damage.[9] While the sensitivity of visual tasks for evaluating cognitive decline or dementia risk in PD is well established, the underlying mechanisms hampering visual processing in PD are incompletely understood.

The theory of visual attention (TVA) offers the possibility of separately assessing the underlying components of visual processing capacity within the same task (for a more detailed theoretical background, see the online supplemental material). The mathematical TVA model provides parameter estimates for visual processing speed and visual short-term memory (VSTM) capacity.[10] The TVA-based assessment of these parameters is largely independent of motor status, making it particularly suited for patients with PD where motor impairments can confound cognitive assessments. In previous studies, we have successfully applied this method in early Alzheimer's disease[11 12] and in patients with Huntington's disease, where TVA-based analyses showed associations of TVA parameters with the degree of the genetic defect[13] and with impaired simultaneous perception of visual objects.[14] Thus, future studies can build on this approach and enhance our understanding by relating TVA parameters to specific neuropathological and behavioural aspects of PD.

In the current study, our aim was to assess the efficiency of visual information uptake in patients with PD based on the application of the TVA. Given the known relationship between short-term maintenance of information with the dopaminergic system,[15] and between visual processing speed and the cholinergic system,[16] we hypothesised that both TVA parameters reflecting these cognitive components would be reduced in patients with PD with cognitive impairment compared with those without cognitive impairment and the HC. As a secondary objective, we assessed the association of TVA-derived parameters with clinical features relevant to PD, such as age, disease duration, gender and disease severity. We aimed to show how TVA parameters relate to PD progression, providing valuable insight into their clinical significance.

METHODS

Subjects

In this study, 75 participants were divided into three different groups based on their Montreal Cognitive Assessment (MoCA) scores (table 1): 25 PD-ND (patients with PD with no decline indicated by a MoCA score ≥26; 14 female; age: M=62.5, SD=7.28), 25 PD-CD (patients with PD with cognitive decline indicated by a MoCA score ≤25; 16 female; age: M=66.8, SD=6.99), and 25 HC (14 female; age M=62.7, SD=7.14). We recruited all patients with PD who were undergoing treatment in the Center for Movement Disorders at the Jena University Hospital. HC were recruited via information in local media. Inclusion and exclusion criteria for the study were as follows: all patients with PD were required to have clinically established PD (according to the 2015 Movement Disorder Society (MDS) criteria[17]), and either normal or corrected-to-normal vision. Participants with clinically relevant symptoms of depression, as indicated by the depression subscore of the Hospital Anxiety and Depression Scale (HADS-D) above the cut-off (>10),[18] a prior diagnosis of dementia or other relevant neurological diseases were excluded.

To outline the groups' characteristics and account for potential confounders, we collected relevant clinical parameters: motor disability and disease stage were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III[19] and the Hoehn and Yahr scale.[20] To screen for non-motor symptoms in PD, the non-motor Symptoms Questionnaire[21] and the Hospital Anxiety and Depression Scale (HADS)[18] were employed. Additionally, we assessed impulse control disorders with the Questionnaire for Impulsive-Compulsive Disorders in PD Rating Scale (QUIP-RS)[22] and the quality of life with the Parkinson's disease Questionnaire 8 (PDQ-8).[23] We documented the levodopa equivalent dosage and the disease duration.

To achieve equal group sizes, we initially recruited 60 patients with PD, targeting two groups of 30 patients each based on the MoCA cut-off (PD-ND: MoCA ≥26 and PD-CD: MoCA ≤25). After recruitment, we corrected for demographic and clinical factors such as age, gender and disease duration, forming matched pairs of patients in each PD group. HC were subsequently included from a precollected dataset, matched on demographic factors, resulting in three equally sized groups.[24]

Patient and public involvement

Patients were directly involved in this study as subjects. All received detailed information and consent forms to ensure they understood the aims and procedures of the study and their rights. We spoke to patients and ward staff to explain the study and assess the ability to participate. No members of the public were involved in this study.

Whole report

We conducted the TVA-based whole report paradigm described in detail by Martin *et al*.[25] The experiment was

Table 1 Demographic and neuropsychological data for the three subject groups taking part in the study

PC	Group	Value	Sign.	Statistics
N	HC	25	–	
	PD-ND	25		
	PD-CD	25		
Gender (female/male)	HC	14/11	–	F=2.36 df=72 p = 0.103
	PD-ND	14/11		
	PD-CD	16/9		
Age in years	HC	62.7 (7.14)	–	F=2.65 df=72 p = 0.078
	PD-ND	62.5 (7.28)		
	PD-CD	66.8 (6.99)		
Education (N of more than 12 years of education)	HC	13	–	F=0.63 df=72 p = 0.538
	PD-ND	11		
	PD-CD	10		
MoCA	HC	28.5 (1.62)	+ (*)	F=66.94 df=72 **p = 0.000**
	PD-ND	27.6 (1.60)		
	PD-CD	21.3 (2.10)		
HADS-A	HC	4.7 (3.15)	–	F=0.61 df=72 p=0.549
	PD-ND	4.7 (2.98)		
	PD-CD	5.52 (2.84)		
HADS-D	HC	2.1 (1.74)	+	F=8.09 df=72 **p=0.001**
	PD-ND	4.3 (3.46)		
	PD-CD	6.3 (4.27)		
Disease duration in years	HC	–	–	T=–0.58 df=48 p = 0.563
	PD-ND	7.7 (4.22)		
	PD-CD	8.5 (4.85)		
Hoehn and Yahr (N of disease stages 1/1.5/2.0/2.5/3.0/4.0/5.0)	HC	–	+	T=–2.80 df=48 **p = 0.008**
	PD-ND	0/0/3/16/6/0/0		
	PD-CD	0/0/0/5/20/0/0		
UPDRS III	HC	–	–	T=–1.37 df=48 p = 0.177
	PD-ND	21.3 (11.78)		
	PD-CD	25.4 (09.54)		
PDQ-8	HC	–	–	T=–1.94 df=48 p = 0.059
	PD-ND	7.0 (5.68)		
	PD-CD	9.8 (4.23)		
NMS-Quest	HC	–	–	T=–1.57 df=48 p = 0.124
	PD-ND	8.2 (3.41)		
	PD-CD	10.2 (5.08)		
QUIP-RS	HC	–	–	T=–1.79 df=48 p = 0.081
	PD-ND	9.26 (11.00)		
	PD-CD	16.7 (15.84)		
LD	HC	–	–	T=–1.26 df=48 p=0.216
	PD-ND	680 (449.40)		
	PD-CD	834 (378.80)		

Continued

Table 1 Continued

PC	Group	Value	Sign.	Statistics

Values are means with SD.
Significant group differences: t-test (independent groups) for two groups, analysis of variance (ANOVA) for three groups, group differences are considered significant a p≤0.05.
*Significant group differences for MoCA: (HC/PD-CD and PD-ND/PD-CD).
HADS-A, Anxiety subscore of the Hospital Anxiety and Depression Scale; HADS-D, Depression subscore of the Hospital Anxiety and Depression Scale; HC, healthy controls; LD, Levodopa equivalent dosage; MoCA, Montreal Cognitive Assessment; NMS-Quest, non-motor Symptoms Questionnaire; PD-CD, patients with PD with MoCA≤25; PD-ND, patients with PD with MoCA≥26; PDQ-8, Parkinson's disease Questionnaire 8; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in PD Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

conducted in a dimly lit room on a 100 Hz computer screen and a viewing distance of 50 cm. It took approximately 20 min to complete and consisted of four practice blocks with 48 trials and four test blocks with 84 trials. Each trial had the same basic design (figure 1). A fixation point in the centre of the black screen initiated the trial and appeared for 1000 ms. Following the fixation point with a delay of 250 ms, six stimuli (red or blue capital letters) appeared on a black background. All stimuli were randomly selected from the alphabet (except for I, Q and Y) and each letter was displayed at most once per trial. The stimuli were arranged in a circle equidistantly at a visual angle of 5.73° around the fixation point. Five different stimulus exposure durations were used across trials. For each participant, these five exposure durations were individually determined, based on the performance in four practice blocks. The aim was to obtain data from the full range of performance, from levels below and close to threshold and at maximum, in order to optimise the fitting procedure's validity. Depending on the trial condition, the stimuli were presented either masked (in five conditions) or unmasked (in two conditions). Masks appeared for 500 ms and were used to better control the presentation time by deleting the visual afterimage.[26] The participant's task was to report as many letters as possible but refrain from guessing. The experimenter recorded the answers.

Based on this performance, the TVA parameters processing speed C and VSTM capacity K were derived. The parameters were fitted and generated in MATLAB (V.9.13.0, R2020a) based on a maximum-likelihood procedure.[27] The relationship between performance accuracy and presentation time is graphically represented by an exponential growth function.[28] Whole report parameters

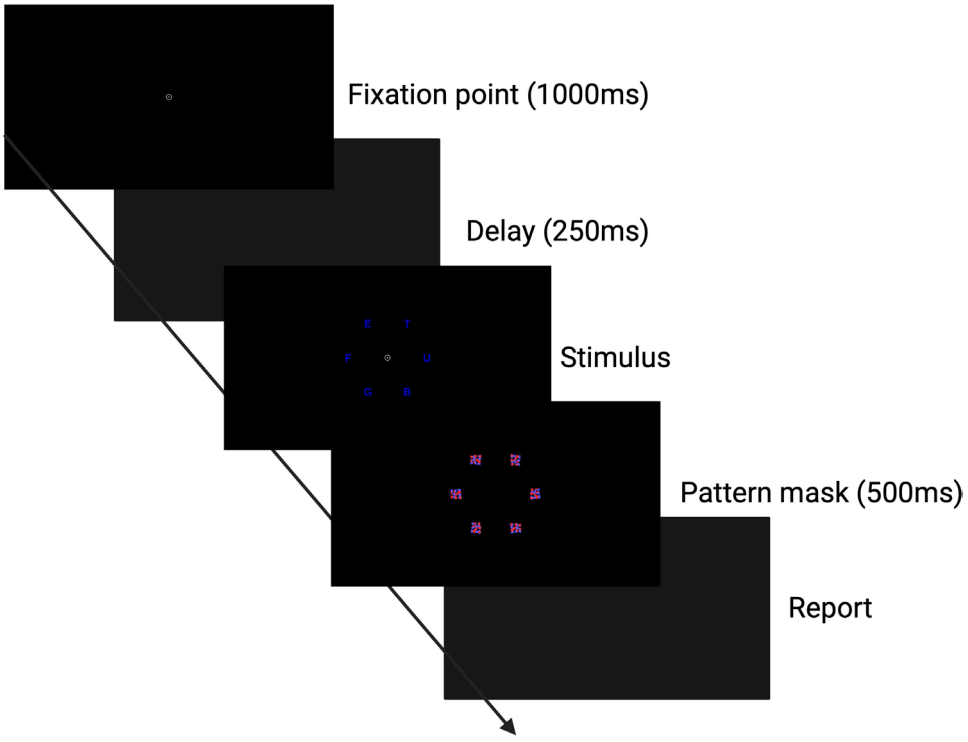

Figure 1 Whole report paradigm: example for one trial. The fixation point initiates the trial, followed by a stimulus display. In the whole report, the stimulus at display consists of six letters and all of them are either red or blue. After the stimulus, in most trials, a pattern mask is presented. The only exceptions to this are two trial conditions where no masking is applied. Finally, the participant reports the recognised stimuli verbally. Figure created with *Biorender.com*

were extracted from this function: The VSTM capacity K is the asymptote of the growth function standing for the number of stimuli that can be simultaneously processed and processing speed C is illustrated by the initial slope of the function representing the rate of stimuli processed per second.[28]

Montreal Cognitive Assessment

The presence of cognitive impairment was assessed by the MoCA,[29] a standard screening test validated to distinguish healthy subjects from patients with mild cognitive impairment and recommended by the MDS PD-MCI Task Force as an economic measure for diagnosing mild cognitive impairment in patients with PD.[30] The MoCA was applied by examiners trained according to the standard guidelines (see www.mocacognition.com). In accordance with the MDS Task Force recommendations, a score <26 was considered as indicating cognitive impairment, while scores ≥26 were considered as normal (maximum score: 30).

Statistical analysis

Data analysis was performed using the Konstanz Information Miner (KNIME: V.5.1.2).[31] All groups were matched for age, gender and years of education. Participants who could not be matched or who had missing data were excluded. To identify group differences in both clinical characteristics and TVA parameters, we compared the three groups using an analysis of variance. To explore differences between the PD groups, pairwise comparisons using t-tests were performed. Levene's test for equality of variances was applied to ensure homogeneity of variance across these comparisons.

Associations between TVA parameters and clinical characteristics were analysed using Pearson correlation. To identify potential clinical confounders affecting the TVA parameters, a generalised linear model (GLM) was performed.

Finally, to assess the predictive power of TVA parameters in distinguishing between PD-ND and PD-CD, a logistic regression classifier was employed to determine whether TVA parameters could effectively predict the grouping of patients with PD based on their cognitive status as indicated by the MoCA scores.

Results were considered significant if p≤0.05. A more detailed description of the statistical methods is provided in the online supplemental material.

RESULTS

Demographic and clinical characteristics of participants

The demographic and clinical characteristics of the groups are summarised in table 1. Groups did not differ in terms of gender distribution (F=2.36, p=0.103), education (F=0.63, p=0.538) and age (F=2.65, p=0.078). MoCA scores differed between the groups (F=66.94, p<0.001): while HC (M=28.5, SD=1.62) and PD-ND (M=27.6, SD=1.60) did not differ from each other, PC-CD (M=21.3, SD=2.10) had lower scores compared with both HC (T=14.57, p<0.001) and PD-ND (T=9.36, p<0.001). The PD groups differed in some clinical aspects, with PD-ND having a milder disease stage (T=−2.80, p=0.008) and lower depression scores (F=8.09, p=0.001). There were no further statistical differences in the other collected clinical parameters.

TVA parameters and comparative group analysis

Our analysis of the TVA parameters revealed notable differences in visual processing between the groups (table 2 and figure 2). In summary, main effects for the whole report parameters indicated lower visual processing speed C and VSTM capacity K in PD-CD compared with HC and PD-ND. Post hoc t-tests revealed no significant difference between HC (M=27.46, SD=9.53) and PD-ND (M=27.76, SD=11.62) in the C-parameter (T=−0.9; p=0.925). However, the C-parameter was significantly lower in PD-CD (M=20.45, SD=10.64) compared with the HC and PD-ND (T=2.22; p=*0.031* for PD-ND vs PD-CD and T=2.35; p=0.023 for HC vs PD-CD). Similarly, VSTM capacity K did not differ between HC (M=2.85, SD=0.67) and PD-ND (M=2.88, SD=0.64) (T=−0.15; p=0.880). However, PD-CD exhibited a significantly lower K-parameter (M=2.12, SD=0.5), compared with both HC (T=4.22; p<0.001) and PD-ND (T=4.50; p<0.001).

The effect sizes (Cohen's d) for the reduction in C in the PD-CD group were 0.69 (PD-CD vs HC) and 0.66 (PD-CD vs PD-ND), indicating moderate effects. For K, the effect sizes were 1.24 (PD-CD vs HC) and 1.33 (PD-CD vs PD-ND), indicating large effects. These values underscore the relatively greater deviation observed for the K-parameter.

TVA parameters and demographic and clinical features

We then analysed the relationship between various demographic and clinical parameters and TVA parameters in all patients with PD (n=50) without distinguishing between PD-ND and PD-CD using pairwise Pearson's correlation analyses and GLM.

Correlation analysis

The correlation analysis (figure 3 and online supplemental table S1) revealed significant correlations (p≤0.05, false discovery rate corrected) that link demographic and clinical features to TVA parameters. Significant negative correlations were found between age and the C-parameter (r=−0.59, p<0.001), with higher age being related to lower processing speed in patients with PD. Furthermore, the C (r=0.33, p=0.021) and K (r=0.37, p=0.008) parameters showed positive correlations with MoCA scores, indicating that better cognitive function is associated with better processing speed and VSTM capacity.

The Hoehn and Yahr scale was moderately correlated with MoCA scores (r=−0.55, p<0.001) and the C-parameter (r=−0.33, p=0.017). This implies that

Table 2 Fitted TVA parameters

	Groups (N=25)	Mean	SD	SE mean	Min	Max	Sign.	Group statistics
Visual processing speed C	HC	27.46	9.525	1.986	12.786	46.114	+	ANOVA: **p=0.016**, F=4,42, df=68
	PD-ND	27.755	11.615	2.422	10.61	66.54		HC/PD-ND: p=0.925, t=−0.9, df=44
	PD-CD	20.453	10.64	2.219	6.618	44.785		HC/PD-CD: **p=0.023**, t=2.35, df=44, Cohen's D 0.69 PD-ND/PD-CD: **p=0.031**, t=2.22, df=44, Cohen's D 0.66
VSTM capacity K	HC	2.852	0.666	0.139	1.803	4.27	+	ANOVA: **p=0.000**, F=14.68, df=68
	PD-ND	2.882	0.64	0.133	1.908	4.647		HC/PD-ND: p=0.880, t=−0.15, df=44
	PD-CD	2.121	0.5	0.104	1.066	3.401		HC/PD-CD: **p=0.000**, t=4.22, df=44, Cohen's D 1.24 PD-ND/PD-CD: **p=0.000**, t=4.50, df=44, Cohen's D 1.33

Mean values and metrics for groups: HC (healthy controls), PD-ND (PD patients, MoCA≥26), PD-CD (PD patients, MoCA≤25). Group differences tested with t-test for two groups and analysis of variance (ANOVA) for three groups; significance set at p≤0.05. Pairwise comparisons provided for significant ANOVA results.
MoCA, Montreal Cognitive Assessment; VSTM, visual short-term memory.

as the clinical severity of PD increases, the general cognitive status and visual processing speed decrease.

While there was a negative but non-significant correlation between UPDRS III and MoCA scores (r=−0.25, p=0.080), there was almost no correlation between UPDRS III and the TVA parameters (for C, r=0.09, p=0.534; for K, r=−0.15, p=0.289).

Both disease duration (r=−0.30, p=0.035) and levodopa equivalent dosage (r=−0.33, p=0.018) were negatively correlated with the C-parameter, which demonstrated that slower processing speed was associated with longer disease duration and higher medication.

Furthermore, the MoCA was negatively correlated with PDQ-8 (r=−0.40, p=0.004), QUIP-RS (r=−0.35, p=0.013), HADS-A (r=−0.43, p=0.002) and HADS-D (r=−0.33, p=0.020). The TVA parameters only showed a negative correlation between the K-parameter and HADS-D (r=−0.29, p=0.045), indicating lower VSTM capacity in patients with higher depression scores.

The significant linear relationships are further illustrated in scatter plots provided in the online supplemental material (online supplemental figures S1 and S2). These plots depict the relationships between age and visual processing speed C and gender and VSTM capacity K, with individual data points colour-coded to differentiate between groups.

Generalised linear model

The GLM analysis included TVA parameters C and K as dependent variables (table 3). The first model incorporated age, gender, disease duration and levodopa equivalent dosage as independent variables. An extended GLM model, presented in the online supplemental material (online supplemental table S2), also included the grouping variable (0=PD ND, 1=PD CD) and the interaction between group and age.

Visual processing speed (C)

Age and levodopa equivalent dosage were found to have main effects on the C-parameter. In the extended model, the grouping variable did not significantly predict C, indicating that age was the predominant factor influencing processing speed, irrespective of cognitive status (PD-ND vs PD-CD).

VSTM capacity (K)

Gender showed a significant main effect on the K-parameter (coefficient=0.69 indicating higher values in women), with an interaction between age and group also being significant. This suggests that storage capacity in VSTM is influenced by gender and is differently impacted by age in PD-ND and PD-CD.

MoCA score

PD-ND and PD-CD were primarily separated based on their MoCA scores and there was a slight but significant difference regarding their disease stage

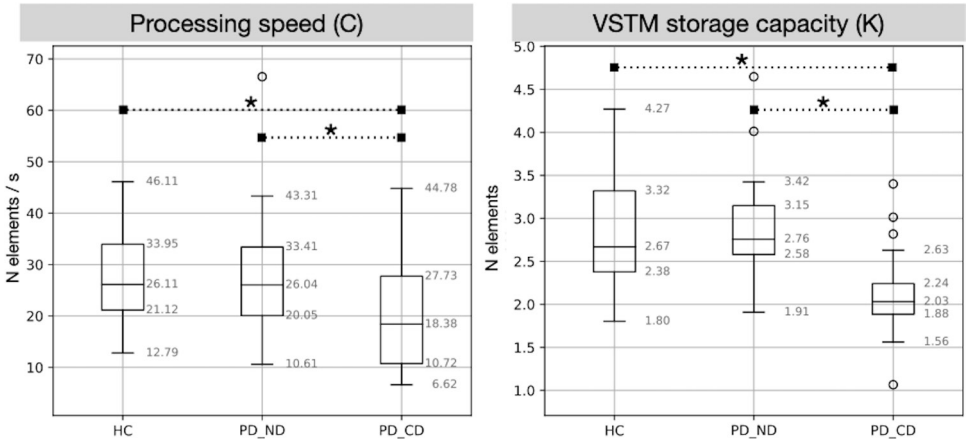

Figure 2 Boxplots of fitted TVA parameters. Groups: HC, healthy controls; PD-ND, patients with PD with MoCA≥26; PD-CD, patients with PD with MoCA≤25. *Significant group differences in t-test for independent groups, differences are considered significant a p≤0.05. MoCA, Montreal Cognitive Assessment; TVA, theory of visual attention; VSTM, visual short-term memory.

with PD-CD being slightly more advanced (table 1). The GLM analysis demonstrated a strong effect of the disease stage[20] on the dependent variable MoCA (coefficient =−4.42, z-score=−2.74). However, disease duration, gender and age did not significantly influence the MoCA scores.

Depression subscore of the Hospital Anxiety and Depression Scale (HADS-D)

As there was a significant difference in depression scores in both PD groups, we performed further GLM analysis including this factor, but it was not significant

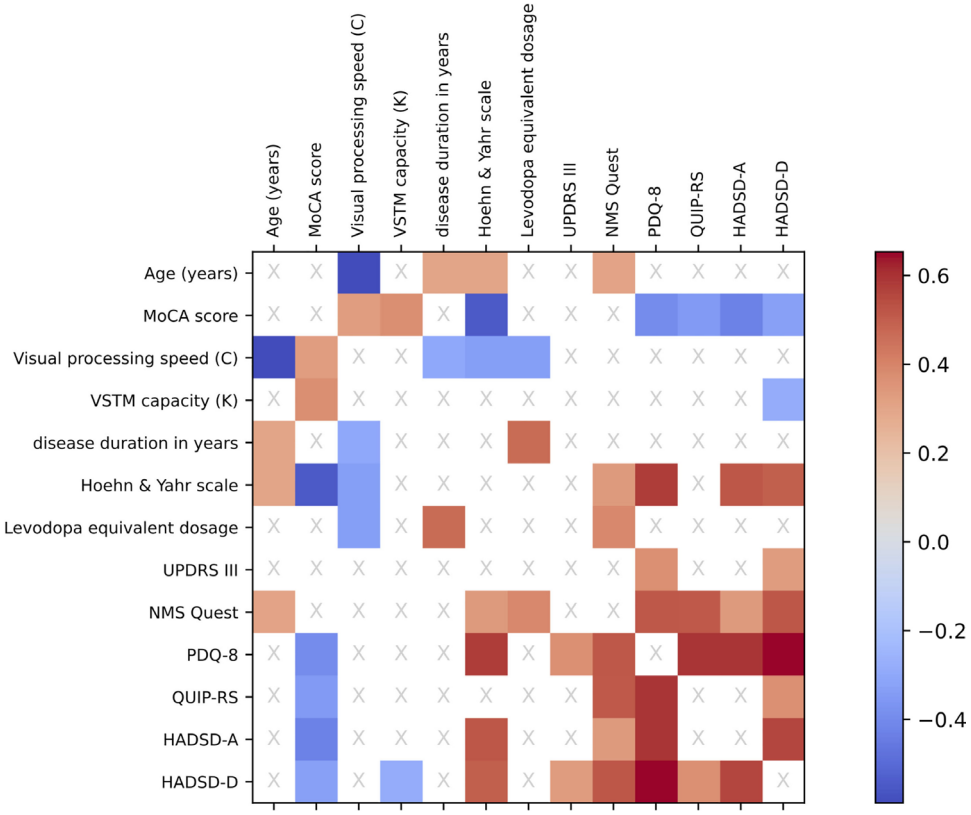

Figure 3 Correlation matrix of TVA parameters and PD-specific clinical scores (N = 50). Pairwise correlations (Pearson's correlation) between clinical markers, scores and TVA parameters, with non-significant correlations marked by an X. Values are considered significant at p≤0.05, after correction for multiple comparisons using the false discovery rate (FDR) method. The intensity of the correlation coefficient is depicted by colour, with red for 1 and blue for −1. MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in PD Rating Scale; NMS-Quest, non-motor Symptoms Questionnaire; PDQ-8, Parkinson's disease Questionnaire 8; TVA, theory of visual attention; UPDRS, Unified Parkinson's Disease Rating Scale; VSTM, visual short-term memory.

Table 3 GLM analysis results for TVA parameters and various clinical factors

Variable/measure	C	K	MoCA
GLM metrics			
Number of observations	50	50	50
Pseudo R^2 (Cox & snell)	0.42	0.35	0.22
Intercept			
Coeff	97.65	4.21	41.75
SE	17.25	1.07	5.67
z	5.66	3.95	7.37
P value	0.000	0.000	0.000
Gender			
Coeff	−1.07	0.69	0.37
SE	3.14	0.19	1.03
z	−0.34	3.59	0.36
P value	0.733	**0.000**	0.721
Age			
Coeff	−0.63	−0.01	−0.09
SE	0.21	0.01	0.07
z	−3.05	−1.09	−1.29
P value	**0.002**	0.275	0.198
Disease duration			
Coeff	−0.09	0.03	0.13
SE	0.35	0.02	0.12
z	−0.26	1.25	1.17
P value	0.799	0.213	0.244
Hoehn and Yahr scale			
Ceff	−9.28	−0.38	−4.42
SE	4.92	0.30	1.62
z	−1.89	−1.27	−2.74
P value	0.059	0.205	**0.006**
Levodopa equivalence dose			
Coeff	−0.01	−0.00	−0.00
SE	0.00	0.00	0.00
z	−2.04	−0.95	−0.99
P value	**0.042**	0.340	0.321

This table presents the outcomes of a generalised linear model (GLM) analysis, employing a Gaussian model family and an identity link function, to assess the influence of multiple factors on TVA parameters. The GLM formula applied was: DEPENDENT_VAR~Age + C(Gender_Code) + disease_duration_years+Hoehn_Yahr+LEDD. Included are the coefficients, SE, z-scores (z) and associated p values for each factor. MoCA, Montreal Cognitive Assessment; TVA, theory of visual attention.

and did not change the significance of the other main effects.

Education

To address the factor of education, we extended the GLM model with the binary variable for education (0–12 years or less, 1—more than 12 years of education); here education did not significantly predict processing speed C (p=0.135), VSTM capacity K (p=0.553) or MoCA scores (p=0.391).

Regression model for grouping PD-ND and PD-CD with TVA parameters and their influencing factors age and gender

To examine the interactions between the TVA parameters C and K and their interaction effects from the GLM (with grouping) and to identify which parameters can predict group membership (PD-ND vs PD-CD), we employed a logistic regression model. The target variable was group membership and the independent variables were visual processing speed C, VSTM capacity K, age, gender and HADS-D. The model revealed a significant effect for K (coefficient=3.14, z=2.83, p=0.005), while C was not significant (coefficient=0.06, z=1.54, p=0.124). The additional covariates, age (coefficient=−0.03, z=−0.48, p=0.631) and gender (coefficient=0.64, z=0.66, p=0.509), and HADS-D (coefficient=−0.20, z=−1.65 p=0.099) were also not significant.

DISCUSSION

Summary of key findings

It is well established that visual tasks bear a great potential for evaluating the dementia risk in PD. Object discrimination tasks using brief stimulus presentations and lower level visual function tests assessing visual processing speed and visual memory have been proven as appropriate measures in this regard.[6–9]

Therefore, in this study, we investigated the efficiency of visual information uptake in patients with PD using the TVA-based assessment. Our main findings indicate that patients with PD with cognitive deficits exhibit significantly diminished visual processing speed C and VSTM capacity K. These deficits were not observed in patients with PD without cognitive impairment when compared with HC. Additionally, our correlation and GLM analyses revealed that TVA parameters were significantly associated with demographic and clinical factors such as age, gender, disease severity and medication dosage in patients with PD. These results suggest that the TVA-based assessment can effectively identify early cognitive deficits in PD and may serve as a valuable tool for tracking cognitive decline.

Our findings highlight the added value of TVA-based analysis for the assessment of cognitive decline in PD. This approach provides highly sensitive and specific quantitative parameters (C and K), allowing for a more nuanced characterisation of attentional deficits compared with standard cognitive tests. TVA's robust theoretical framework enhances diagnostic accuracy by linking cognitive impairments to distinct attentional mechanisms, which is particularly important given the heterogeneity of cognitive deficits in PD. In addition, its non-paced performance design mitigates the confounding effects of motor impairments, ensuring more reliable cognitive assessments in this population.

Visual processing speed (C)

The C-parameter is crucial for understanding the efficiency with which patients with PD process visual information. The parameters' observed impairment among patients with PD-CD suggests a reduced ability to quickly and effectively process visual stimuli, which could be linked to dopaminergic deficits in the basal ganglia and its connections with the prefrontal cortex.[1] This finding is consistent with the pathology of PD, where dopaminergic neuron degeneration leads to motor and cognitive impairment. Furthermore, it has been suggested that a cholinergic deficit might lead to impaired processing of visual stimuli.[3 11]

Our findings from the extended GLM analysis indicate that age is the primary predictor of processing speed C and appears to have a stronger influence than cognitive status (PD-ND vs PD-CD). This highlights the significant impact of ageing on visual processing efficiency, potentially overshadowing group-specific effects related to cognitive decline observed in this study.

Additionally, functional connectivity within the cingulo-opercular network, which includes fronto-insular regions, the thalamus and basal ganglia, has been linked to visual processing speed deficits.[32] Disruptions in this network, as seen in PD, may further exacerbate impairments in attentional control and visual information uptake.

VSTM capacity (K)

Similarly, the K-parameter showed an impairment in patients with PD-CD, potentially associated with deficits in the dorsal attention network, which is involved in the allocation of attentional resources and working memory processing.[33] The diminished capacity could result from disruptions in the network due to neurodegenerative changes in PD.

Recent evidence has linked VSTM capacity to structural integrity within key white matter tracts. Chechlacz *et al* showed that individual differences in VSTM are associated with the microstructure of the superior longitudinal fasciculus (II, III) and inferior fronto-occipital fasciculus in the right hemisphere.[34] These tracts are critical for integrating visual information and maintaining attentional focus, both of which are essential for VSTM capacity. In PD, Chen *et al* further established an association between the superior longitudinal fasciculus and global cognitive performance as measured by the MoCA, suggesting that degeneration of these tracts contributes to broader cognitive deficits.[35]

The pronounced reduction in VSTM capacity K in patients with PD-CD compared with the other groups suggests that this parameter may be more sensitive to neurodegenerative changes in PD than visual processing speed C. This is consistent with the role of the dorsal attention network, which is integral to VSTM capacity and may be particularly vulnerable in PD. The larger effect size for K compared with C highlights the potential clinical utility of K as a marker of cognitive impairment in PD.

Clinical cofactors

The strong correlations between the TVA parameters and clinical features such as age, gender and disease severity

highlight the multifaceted nature of cognitive decline in PD. These findings align with previously described predictors for cognitive decline in PD.[2]

To be clear, age and gender are primarily demographic variables, but in the context of neurodegenerative diseases such as PD, they also influence clinical features such as disease progression and cognitive reserve. For example, the negative correlation between age and both C and K-parameters highlights the progressive nature of cognitive decline in ageing patients with PD. Similar age-related declines in these parameters have also been reported in healthy individuals.[36] Nielsen and colleagues provided a more nuanced perspective by demonstrating that processing speed C is more affected by age than VSTM capacity K in a cohort of 112 healthy adults aged 60—75 years.[37] This is consistent with our finding of a strong effect of age on C, suggesting that changes in processing speed may primarily reflect age-related mechanisms. In contrast, K appears to be more sensitive to cognitive decline due to neurodegeneration. We propose that changes in C are largely driven by ageing processes, whereas K reflects cognitive decline associated with progressive neurodegeneration of structures critical for VSTM capacity. This distinction highlights the potential of TVA parameters to discriminate between age-related changes and disease-specific cognitive deficits.

Furthermore, the gender differences observed in the K-parameter in the PD groups may indicate differences in cognitive reserve or disease progression between male and female patients with PD. In our study, female participants had higher K-parameters than their male counterparts, suggesting a more robust functioning of VSTM. Interestingly, the existing literature has not found gender differences in TVA parameters in healthy older adults.[36 37] Thus, our finding seems to be PD-specific and fits to the fact that while the age-adjusted prevalence of dementia is higher in women in the general population,[38] cognitive deficits associated with PD are more common in men.[2] We acknowledge that the observed gender-related effect on the K-parameter has not been previously reported in TVA-based studies and may reflect either a true sex-specific influence in PD or a sample-specific finding. For example, Pourzinal *et al* reported on different mild cognitive impairment subtypes in PD, with male patients being over-represented in the globally impaired subtype, and females belonging more frequently to the cognitively intact subtype.[39] Future studies with larger and more diverse cohorts are needed to replicate and further explore this result.

Education, as included in our analysis as a binary factor (≤12 years or >12 years), did not significantly influence TVA parameters. However, its potential role in shaping cognitive reserve warrants further investigation.

Disease progression, as measured by the Hoehn and Yahr scale, has been identified as a primary risk factor for the emergence of cognitive deficits in PD.[2] Consistent with this observation, our data reveal a detrimental effect of disease progression on both the C-parameter and MoCA scores, underscoring the negative impact of advancing PD on cognitive functions. In comparison to other neurodegenerative diseases, our results align with findings from studies on Huntington's disease[13] and Alzheimer's disease.[11 28] In Huntington's disease, significant reductions in both C and K-parameters have been reported, with a strong correlation to disease duration. Similarly, in Alzheimer's disease and its precursor, mild cognitive impairment, evidence of a staged decline has been obtained. While C and K-parameters are slightly decreased in mild cognitive impairment, they exhibit a marked decline as the disease progresses to manifest Alzheimer's disease.[11]

Non-motor symptoms such as depression, anxiety, fatigue and reduced impulse control are often found in patients with PD and highly affect patients' quality of life. Furthermore, they are often connected to more pronounced cognitive deficits.[40] We found that higher scores in these measures were significantly associated with lower MoCA scores. In contrast, TVA parameters were largely independent of these non-motor symptoms. While there was a slight correlation between depressive symptoms and the K-parameter, the C-parameter was unaffected. This suggests that TVA-based assessments provide a reliable measure of cognitive function in PD that is not confounded by non-motor symptoms.

Clinical implications

As there was no significant difference between HC and PD-ND, but a clear difference between PD-CD and the other two groups, the TVA-based assessment of attentional functions may serve as a valid tool for the early detection of cognitive deficits in PD. Due to its objective nature and minimal habituation effects,[10] the TVA-based assessment could be instrumental in monitoring cognitive decline as the disease progresses. The TVA parameters are mathematically independent measures of separable, relevant attentional components derived from performance in a single task. The lack of correlation between C and K in this study underscores their independence and ability to differentiate distinct facets of cognition. Unlike typical attentional tasks, the TVA-based assessment does not require speeded motor responses, but only non-speeded vocal responses, making this methodology well-suited for patients with severe motor problems.

Additionally, TVA-based parameters may provide a robust framework for tracking longitudinal changes in cognitive decline, offering insights into the trajectory of disease progression and potential treatment effects.

Furthermore, the TVA-based assessment may be effective in evaluating the impact of treatment strategies. For example, cholinergic stimulation has shown promise in enhancing certain TVA parameters in Alzheimer's disease patients,[11] suggesting potential applicability in PD treatment evaluations.

Limitations

This study has limitations. Despite efforts to balance the clinical cofactors such as age, gender, and disease

duration, the PD-CD group was slightly more advanced clinically, as evidenced by higher scores on the Hoehn and Yahr scale.

Participants were selected based on having no diagnosis of dementia, and grouping was based on MoCA scores (cut-off: 26). Using a single cut-off for cognitive impairment may not fully account for potentially confounding factors such as age and education. However, we controlled for these factors by matching groups for age and education, and by using a MoCA cut-off that includes an extra point for education under 12 years, minimising their potential impact on our results. Future studies might benefit from more comprehensive neuropsychological assessments for grouping participants.

The current HC group is a valid neurotypical comparison. Future studies must include a separate, larger group of neurotypical older adults. This is essential to clarify the influence of age on TVA parameters independent of PD-related pathology. This will enhance the statistical power for detecting age-specific versus disease-specific effects on visual processing speed C and VSTM capacity K.

Additionally, future studies might benefit from more comprehensive neuropsychological assessments for grouping participants. Longitudinal studies would also allow insights into how TVA parameters change with disease progression and may help to predict the trajectory of cognitive impairment.

In conclusion, this study contributes significantly to the understanding of cognitive decline in PD through the innovative application of the TVA. We demonstrated that TVA parameters processing speed (C) and VSTM capacity (K) are significantly impaired in patients with PD with early cognitive deficits. These findings highlight the potential of TVA-based assessment methodology as a sensitive tool for detecting and monitoring cognitive impairment in PD.

Importantly, our results suggest that cognitive decline in PD is closely linked to deficits in visual processing capacity, which can be quantitatively assessed using TVA. Critical merits of the TVA-based assessment lie in its ability to measure cognitive deficits independently of motor and non-motor symptoms, making it especially well-suited for patients with PD.

TVA-based assessment shows promise as a valuable tool for early diagnosis and longitudinal monitoring of cognitive deficits in PD. By incorporating TVA into clinical practice, we may enhance early detection and monitor disease progression more effectively.

Contributors KG: research project: conception, organisation; statistical analysis: design; manuscript preparation: writing of the first draft; manuscript revision. PB: statistical analysis: review and critique; manuscript preparation: writing of the first draft, review and critique; manuscript revision. KF: statistical analysis: review and critique; manuscript preparation: writing of the first draft, review and critique. SS: statistical analysis: design, execution. ALR-R: statistical analysis: execution; manuscript preparation: review and critique; manuscript revision. FW: research project: conception, organisation. CK: statistical analysis: review and critique; manuscript preparation: review and critique. SB (guarantor): research project: conception, organisation; statistical analysis: design, execution; manuscript preparation: writing of the first draft; manuscript revision.

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