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RESEARCH

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Role of multimodal advanced biomarkers as potential predictors of cognitive and psychiatric aspects of Parkinson's disease

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Abstract

Background The value of biomarker research in Parkinson's disease (PD) exists in the early detection and accurate diagnosis of non-motor neuropsychiatric symptoms with implications for future treatment strategies. The aim of the this work was to assess and predict risk for possible cognitive, psychiatric abnormalities in patients with early stage idiopathic PD using a combination of advanced diagnostic biomarkers for early recognition and intervention.

Methods This cross-sectional case–control study was conducted on 58 eligible idiopathic PD-patients, and 45 age/sex-matched healthy controls. All participants were subjected to neuro-psychiatric-, radiological-, audiological-, and laboratory-evaluations. Cognitive assessment was performed using Montreal Cognitive Assessment, Mattis Dementia, and Parkinson's Disease-Cognitive scales. Depression was evaluated by Hamilton Depression and Beck Depression Inventory-II rating scales. Radiologically, volumetric-MRI, diffusion tensor imaging (DTI), and susceptibility weighted imaging were done. Audiologically, P300 and cortical auditory evoked potentials were elicited. Laboratory investigations included 24 h-urinary 5-HIAA and serum levels of IL6, BDNF, 5-HT, and aberrant cimiRNA 132-3p expression profile.

Results Neuropsychological scales revealed mild depression and mild cognitive impairment, with significant differences in PD group. Volumetric-MRI highlighted that PD-patients had a significant bilateral decrease in the mean cortical thickness and thickness/volume of many brain areas. DTI showed a reduction in fractional isotropy and a significant bilateral increase in mean diffusivity through many areas in PD-patients. Patients also had either absent or diminished amplitude of P300,P1, diminished amplitude of N1,P2,N2 and delayed latency of all previous waves. There was a significant reduction of 24 h-urinary 5-HIAA and serum BDNF, with significant elevation of serum IL6, as well as non-significant reduction of serum 5-HT and microRNA-132-3p(2-ΔCt) in PD-patients.

Conclusions Early stage PD-patients had subtle cognitive impairment and depression as detected by psychometric scales and correlated significantly with the various biomarkers, including advanced neuro-imaging, evoked potential studies, and laboratory markers. The key message of this work include evaluating the high prevalence of cognitive and psychiatric impairment in early idiopathic PD has encouraged research and workup for precision medicine. Proper integration of advanced multimodal biomarkers in this study has led to predict the risk of early mild cognitive and psychiaric affection. This will optimize the health strategies for early proper management to improve quality of life.

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Keywords PD, Cognitive impairment, Psychometric tests, depression, genetic, neurophysiological tests, Brain imaging, Bio-markers

Introduction

Parkinson's disease (PD) is one of the commonest neurodegenerative disorders distinguished chiefly by progressive movement disturbances. Nevertheless, a range of non-motor neuro-psychiatric features (e.g., cognitive decline, depression, anxiety, apathy, and even psychosis) can characterize the earliest phase of the disease. These manifestations are often under-diagnosed by neurologists in > 50% of consultations as the clinician's and/or the patient's attention is mainly paid for the more annoying motor impairment [1, 2].

Mild cognitive impairment (MCI) is one of the prominent non-motor symptoms (NMS) of PD, accounting for about 50% of patients, and can even pre-date other core motor manifestations of the disease. MCI is characterized by a slight turn-down of cognitive abilities, not attributed to other co-morbidities, which if neglected increases over time, ultimately proceeding to the more worried Parkinson's dementia (PDD) [3]. The disturbances in chemical transmitters seem to take a basic role in the evolution of PD–MCI. As well, other NMS such as sleep disorders, autonomic dysfunction and mood troubles may also contribute to PD–MCI [4].

Depression is another overlooked early NMS of PD, with an estimated prevalence of 30–40% across studies[5]. It may be attributed to the emotional distresses that are expectedly driven by living with PD. However, more likely, Parkinson is proposed to affect brain chemistry as both dopamine and serotonin, which are brain chemicals impacted in PD and mood disorders, respectively, sharing the same pathways that are acknowledged to the coupling of mood disorders with PD[6]. Nevertheless, a minority (< 20%) of PD patients with depression seek and receive selective psychiatric treatment. Neglected mood troubles associated with PD can seriously affect quality of life and treatment as it can impact elements of PD managing such as: keeping-on socially connected, maintaining fitness and proactively looking for the required care [7].

Psychometric tests have been widely used, with great success, for the diagnosis of cognitive impairment and psychiatric symptoms among various populations, although, the accuracy of these scales are sometimes doubtful, because they may be affected by the examiner's experience or patient's compliance and honesty. Hence, struggles to find other objective biomarkers to confirm the presence of cognitive impairment and depressive symptoms among PD patients were a stimulus for many researchers to introduce functional MRI, biological laboratory markers and event-related potentials to support the results of conventional neuropsychological scales [8].

Aim of the work

This research was conducted to assess and predict risk for possible cognitive, psychiatric abnormalities in patients with early stage idiopathic PD using a combination of advanced biochemical, genetic, imaging and neurophysiological biomarkers for early recognition and intervention.

Subjects and methods

Subjects

This cross-sectional case–control study was conducted on 58 idiopathic PD patients (illness duration < 5 years) who attended the movement disorder clinic of the Neuropsychiatry Department—Tanta University Hospitals in the period from 1st November 2021 to 30th June 2022. 45 healthy control subjects who matched the patient's age, sex, and educational level were also included for analysis and comparison.

The study protocol was approved by the local institutional ethics committee of the faculty of medicine(Approval No: 35013/11/21), Tanta University, and informed consent was obtained from each participant before enrollment.

Idiopathic PD was diagnosed in accordance to the criteria of the Movement Disorder Society (MDS-PD) [9]. The study protocol was approved by the local institutional ethics committee and informed consent was obtained from each participant before enrolment.

Inclusion criteria

This included the following: (1) Participants (patients and controls) aged 50–77 years with MoCA scoring ≥ 21 at the time of enrollment. (2) Patients presented with an early stage (< 5 years duration) idiopathic PD with the existence of 2 diagnostic features on MDS-PD criteria. (3) Improvement with dopamine therapy. (4) Hoehn and Yahr ranking scale of < 2.5 as well as motor UPDRS < 30 on dopamine therapy.

Exclusion criteria

(1) Participants not fulfilling the above-mentioned inclusion criteria. (2) Patients with early onset PD. (3) Participants < 12 years of education (to be able to participate in psychometric tests). (4) Participants with stroke, other

neurologic diseases, major head trauma or severe organic illness. (5) Significant dyskinesia or high amplitude tremors in the upper limbs and head. (6) History of depression or major psychiatric disorders and/or chronic use of psychotropic drugs. (7) Presence of any contraindication for undergoing MRI scanning (such as: claustrophobia, pacemaker, …..etc.).

Methods

Neuro-psychiatric evaluations

Patients were subjected to history taking (including age of onset and duration of illness), and detailed neurological examination to assess the severity of PD that was graded according to the MDS-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS–UPDRS-III) motor section [10].

All participants were subjected to cognitive assessment using Montreal Cognitive Assessment (MoCA) [11], Mattis Clinical Dementia Rating Scale (CDRS) [12], Parkinson's Disease–Cognitive Rating Scale (PD–CRS) [13], and Scales for Outcomes in Parkinson's disease–Cognition (SCOPA–COG-Version2) [14].

In addition, the Arabic version of Mini International Neuropsychiatric Interview with Mental state examination was applied for all subjects. Moreever, the Arabic form of Hamilton Depression Rating Scale (HDRS) [15] and Beck Depression Inventory II (BDI-II) scale [16] were used to detect depressive symptoms. All psychometric tests were carried out by 2 qualified neuro-psychiatric consultants.

Radiological evaluation

All subjects were submitted to Imaging that included cortical thickness assessment using voxel-based morphometry in MRI, white matter changes and diffusion MRI using diffusion tensor imaging (DTI) and susceptibility weighted imaging (SWI) [17, 18].

Cortical reconstruction and automatic volumetric segmentation were conducted with the Free surfer image analysis suite according to Reuter and colleagues [18], used both intensity and continuity information from the entire three dimensional MR volumes in segmentation and deformation procedures to generate representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface. Procedures for the measurement of cortical thickness have been validated against histological analysis and manual measurements [18].

MR imaging was done at 1.5 T (GE Signa Explorer) by a standard eight-channel head coil. The slice thickness was 4 mm, the matrix was 256×256 and the field of view was 220–240 mm. Axial 3D diffusion tensor imaging was achieved using a single shot spin echo EPI (TR/TE = 7400/60 ms, 56 slices, acquisition matrix of 112×112 with pixel size of $2 \times 2 \times 2\,mm^3$, interpolated to $1 \times 1 \times 2\,mm^3$, 60 diffusion gradient directions with $b = 1000\ s/mm^2$, and three repeats of b = 0). SWI (TR/TE = 6000/20–35 ms), a phase mask that scaled data from the filtered phase images over a 0–1 range to accentuate tissues with different susceptibilities. The magnitude image was digitally multiplied by the phase image [17, 18].

Post-processing was performed using MRI workstation software (ADW 4.7 Vantage, GE Medical Systems) by GE software devised for tractography. The analysis was based on the evaluation of DTI parameters; FA, MD and rADC values were assessed by placing small regions of Interest (ROIs) measuring $2 \times 2\ mm^3$ in different white matter and grey matter areas in both cerebral hemispheres. All values were normalized to the values from the white matter of controlled volunteers to obtain relative values of all parameters [17, 18].

Audiological evaluation

P300 and cortical auditory evoked potentials (CAEPs) were recorded from both patients and control subjects using Smart EPs of the intelligent hearing system. Regarding P300, it was recorded in the oddball paradigm using speech stimuli/ga/stimuli was used as a standard stimulus and /da/stimuli was utilized as the deviant stimulus. The two stimuli types were presented at second rate of repetition, 15% deviant probability and at 50 dBSL (rePTA average at 500, 1000, 2000 and 4000 HZ) monaurally to each ear in all subjects via an insert-phone. P300 was recognized as the most robust positive wave around 300 ms following N1–P2 complex, and both absolute latency and amplitude were recorded [19].

CAEP components were elicited using speech stimuli CV syllables/da/ using the same electrode montage for P300. Stimuli have been monaurally presented at 90 dBnHL to both ears via ER3A insert phone beginning with the ear of the right side. For identification of the responses, the response consisted of a positive wave at about 50 ms (P1), a large negative wave at about 80–100 ms (N1), and a subsequent positive wave at about 180–200 ms (P2). Classically, the N2 is negativity following the P2. Calculation of the latency and amplitude (peak to peak or baseline to peak) of each wave was performed [19].

Laboratory investigations

Subjects were also submitted to laboratory investigations that included the following:

1. Urine sample: 24 h Urine sample was collected and centrifuged for 20 min, the supernatant was collected and stored at -20 °C for 5- HIAA estimation by Enzyme-linked Immunosorbent Assay (ELISA) Kit, from a fine test (Catalogue No.: EU2582) [20].
2. Blood samples: 3 mL of venous blood was drawn under complete aseptic conditions into a plain tube and separated serum was aliquoted and stored at − 80 °C until used. The serum was used for:
3. Measurement of serum level of serotonin Using ELISA Kit for serotonin, Abcam (catalogue no: ab133053) [20].
4. Measurement of serum IL-6 Using ELISA Kit for human IL-6 from Elabscience (catalogue no: E-EL-H6156) [21].
5. Measurement of serum Brain-Derived Neurotrophic Factor ELISA Kit for Human Free BDNF from R & D system (catalogue no: DBD00) [22]
6. MicroRNA-132-3p expression level by Reverse transcription-quantitative polymerase chain reaction (RT-PCR):

    a) miRNA extraction: total RNA including microRNA was extracted from samples using the miRNeasy Mini Kit (cat. no. 217004, Qiagen, Germany). Detection of RNA purity: by Nanodrop 2000 spectrophotometer (USA).
    b) Reverse transcription for quantitative real-time PCR (1st step): cDNA was produced using the miScriptII RT Kit (Cat.no.217004 QIAGEN, Germany) according to manufacturer instructions.
    c) Real-time PCR for detection of microRNA-132-3p (2nd step): RT qPCR was done using the miScript SYBR Green PCR kit (Qiagen NVcat. no 217004) based on the manufacturer's protocol. Forward and reverse miRNA specific primers were supplied by (Qiagen, Germany). Real-time PCR was done on Real-time PCR cycler Applied Biosystems (USA). Because there is no control available for miRNA in serum, we used the U6B small nuclear RNA gene (RNU6B) as an endogenous control, RNU6B was readily noticeable in the serum and no significant difference was observed in terms of cycle threshold (Ct) values of RNU6B between the controls and other samples. We selected RNU6B as the normalization control because it displayed expression levels of higher stability and less variability. Relative expression of microRNA-132-3p was calculated using $2^{-\Delta Ct}$ formula Where ct = (ctmiRNA−ct control) and Ct is the fractional cycle number at which the fluorescence passes the fixed threshold [23].

Statistical analysis

Statistical analysis was carried out using the SPSS software statistical computer package V17. data was normally distributed. The range and mean ± standard deviation (SD) were measured for quantitative numerical data. For qualitative data, comparison between two or more groups was conducted by Chi-square test (X^2). Correlation analysis was performed by Pearson's correlation test. Significance was adopted at $P < 0.05$ for interpretation of results [24]

Results

This study included 58 PD patients (mean age 58.448 ± 4.87 years, 38 males (65.52%), 20 females), and 45 controls (mean age 62.556 ± 4.98 years, 20 females (44.44%), and 25 males). Patients' had a mean disease duration of 3.000 ± 1.05 years and the mean illness severity was 26.086 ± 2.28 as measured by MDS–UPDRS-III motor section, as well as 1.526 ± 0.517 as assessed by Hoehn and Yahr rating scale.

Neuropsychiatric results

Cognitive and depression rating scales showed a mild decrease of each of MoCA, PD–CRS, and SCOPA–COG-Version2 scales as well as a mild increase of CDRS, HDRS and BDI-II in PD patients than their matched controls, with statistically highly significant differences ($p < 0.001$), as shown in Table 1.

Radiological results

Volumetric-MRI study highlighted that PD patients had a significant bilateral reduction in the mean cortical thickness as well as the thickness and volume of many brain areas compared to controls, as shown in Table 2 and Fig. 1.

Diffusion tensor imaging (DTI) showed a reduction in fractional isotropy with a significant bilateral increase in mean diffusivity (MD) in many areas in PD patients than controls (Table 3) (Fig. 2).

SWI revealed either: not blooming in 39 (67.24%) patients versus 43 (95.56%) in controls, blooming with iron in 16 (27.59%) versus 2 (4.44%) controls, and minute calcification in 3 (5.17%) patients versus no (0%) controls, with statistically significant differences for all previous variables with p value 0.002 (Table 3) (Fig. 3).

The thickness of Insular cortex, precuneus, lingual and parahippocampal areas in both hemispheres were all positively correlated with MOCA, PD–CRS and SCOPA–COG-Version2, but negatively correlated with CDRS in PD patients (Table 5). Thickness of the frontal cortex, temporal, insular cortex, cingulate and

Table 1 Neuropsychological testsin PD patients and control subjects

Type of the studied test	Groups		*T* Test	
	Patients	Controls	*t*	*p* value
MoCA				
Range	21–29	26–30	− 9.467	< 0.001*
Mean ± SD	24.897 ± 2.117	28.156 ± 1.043		
CDRS				
Range	0–1	0–0.5	6.460	< 0.001*
Mean ± SD	0.371 ± 0.332	0.033 ± 0.126		
PD–CRS				
Range	69–120	87–130	− 11.166	< 0.001*
Mean ± SD	83.155 ± 12.881	112.511 ± 13.677		
SCOPA–COG-Version2				
Range	18–38	29–41	− 15.523	< 0.001*
Mean ± SD	24.724 ± 5.129	37.533 ± 2.351		
HDRS				
Range	2–10	0–7	7.542	< 0.001*
Mean ± SD	6.379 ± 2.398	3.200 ± 1.700		
BDI-II				
Range	4–14	0–7	9.732	< 0.001*
Mean ± SD	9.224 ± 2.944	4.378 ± 1.787		

SD standard deviation, *MOCA* Montreal Cognitive Assessment, *CDRS* Clinical Dementia Rating Scale, *PD–CRS* Parkinson's Disease–Cognitive Rating Scale, *HDRS* Hamilton Depression Rating Scale, *BDI-II* Beck Depression Inventory II

*Significant at p < 0.05

parahippocampus in both hemispheres were all negatively correlated with HDRS and BDI-II in patients (Table 6).

The volume of the hippocampus, amygdala and accumbens area in both hemispheres were all directly correlated with MOCA, PD–CRS and SCOPA–COG-Version2, but inversely correlated with CDRS in patients (Table 5). Hippocampal and amygdala volumes in both hemispheres were inversely correlated with HDRS and BDI-II in patients (Table 6).

Mean diffusity (MD) of SOFF, IOFF and temporal subcortical tract in both hemispheres were all positively correlated with CDRS, but negatively correlated with MOCA, PD–CRS and SCOPA–COG-Version2, but also right (RT) temporal subcortical tract FA was positively correlated with PD–CRS (Table 5). MD of SOFF, IOFF and temporal subcortical tract in both hemispheres were all positively correlated with HDRS and BDI-II (Table 6).

Fractional anisotropy (FA) of SOFF, IOFF in both hemispheres and left (LT) parietal subcortical tract were all directly correlated with MOCA, PD–CRS and SCOPA–COG-Version2, but inversely correlated with CDRS (Table 5). FA of SOFF, IOFF and cingulum in both hemispheres were inversly correlated with HDRS and BDI-II (Table 6).

Audiological results

The study showed that P300 was absent in 8.6% and 10.3% of PD patients in right and left ears, respectively. The rest of the patients showed prolongation of P300 latencies than controls in both ears, with non-significant differences (*p* value 0.757 on RT side and 0.782 on the LT side). None of the control group showed absent response. The amplitudes of P300 were significantly diminished in patients than controls in both ears, with a highly significant difference (*p* value < 0.001 on sides). CAEP showed that only P1 was absent in 1.7% of PD patients in both ears. The rest of the patients showed bilateral significantly delayed P1,N1,P2,N2 latencies (except for LT N2 latency showing non-significant delayed latency), with significantly diminished amplitudes than their matched controls (Table 4) (Fig. 4). P300 amplitude was positively correlated with MOCA, PD–CRS and SCOPA–COG-Version2, but negatively correlated with CDRS (Table 5).

Laboratory results

Laboratory investigations revealed a significant elevation of serum inflammatory marker IL6 with a significant decrease in 24 h-urinary 5-HIAA and BDNF in PD patients than controls. Besides, there were non-significant reduction of serum 5-HT, and relative expression of

Table 2 Volumetric MRI in PD patients and control subjects

Volumetric MRI	Groups: mean ± SD		*T* test	
	Patients	Control	*T*	*P* value
Frontal cortical thickness				
RT	2.041 ± 0.093	2.321 ± 0.202	− 9.344	< 0.001*
LT	2.004 ± 0.076	2.225 ± 0.076	− 14.670	< 0.001*
Temporal cortical thickness				
RT	2.145 ± 0.120	2.409 ± 0.242	− 7.236	< 0.001*
LT	1.956 ± 0.156	2.454 ± 0.199	− 14.254	< 0.001*
Insular cortex thickness				
RT	2.209 ± 0.095	2.582 ± 0.173	− 13.900	< 0.001*
LT	2.248 ± 0.123	2.737 ± 0.180	− 16.322	< 0.001*
Precuneus thickness				
RT	2.104 ± 0.119	2.444 ± 0.103	− 15.254	< 0.001*
LT	2.099 ± 0.123	2.414 ± 0.080	− 14.877	< 0.001*
Lingual thickness				
RT	1.270 ± 0.173	1.845 ± 0.116	− 19.224	< 0.001*
LT	1.558 ± 0.154	1.884 ± 0.075	− 13.042	< 0.001*
Cingulate thickness				
RT	2.024 ± 0.214	2.486 ± 0.219	− 10.743	< 0.001*
LT	2.006 ± 0.165	2.414 ± 0.230	− 10.480	< 0.001*
Parahippocampal thickness				
RT	2.852 ± 0.124	2.937 ± 0.043	− 4.422	< 0.001*
LT	2.076 ± 0.129	2.565 ± 0.237	− 13.372	< 0.001*
Mean cortical thickness				
RT	2.278 ± 0.158	2.441 ± 0.059	− 6.572	< 0.001*
LT	2.278 ± 0.191	2.453 ± 0.075	− 5.805	< 0.001*
Hippocampal volume				
RT	3321.845 ± 135.165	3920.444 ± 291.678	− 13.844	< 0.001*
LT	3192.724 ± 306.639	4120.733 ± 412.457	− 13.099	< 0.001*
Amygdala volume				
RT	1446.707 ± 178.107	2007.000 ± 234.008	− 13.802	< 0.001*
LT	1446.655 ± 151.143	1844.578 ± 129.488	− 14.095	< 0.001*
Accumbens area volume				
RT	344.397 ± 67.129	528.511 ± 74.795	− 13.133	< 0.001*
LT	258.707 ± 53.046	445.511 ± 84.663	− 13.701	< 0.001*
Cerebral WM volume				
Total	340,317.017 ± 1449.507	363,046.089 ± 15,914.589	− 10.834	< 0.001*
Cortical volume				
Total	389,713.138 ± 2456.608	408,564.933 ± 8789.853	− 15.587	< 0.001*
Gray matter volume				
Total	542,201.879 ± 15,146.572	579,925.356 ± 17,505.207	− 11.710	< 0.001*
Caudate volume				
RT	3039.552 ± 277.363	4077.733 ± 229.497	− 20.287	< 0.001*
LT	3160.138 ± 261.459	3832.822 ± 250.058	− 13.199	< 0.001*

SD: standard deviation, *WM* white matter

*Significant at $p < 0.05$

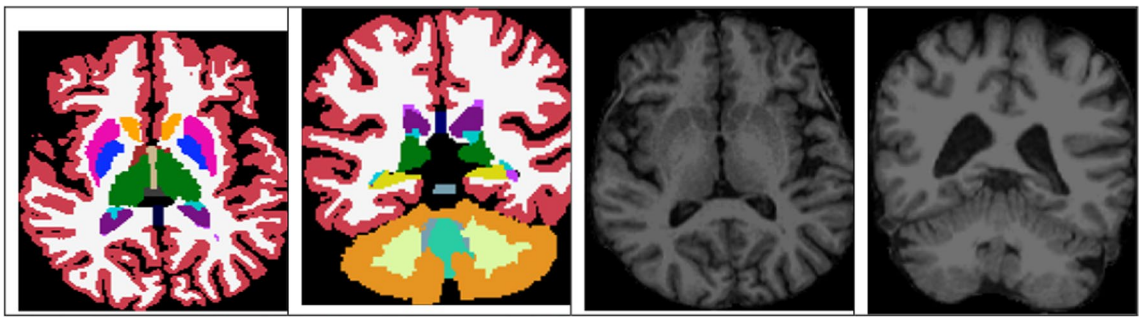

Fig. 1 Brain volumetric MRI study in PD patients with segmented axial, coronal sequences on the RT side, non-segmented axial, coronal sequence on the LT side showing reduction in mean cortical thickness, total cerebral WM volume, total cortical volume and total gray matter volume (original images from patients enrolled in the study)

microRNA-132-3p($2^{-\Delta Ct}$) in PD patients than controls (Table 4).

Serum BDNF and ($2^{-\Delta Ct}$) were positively correlated with MOCA, PD–CRS and SCOPA–COG-Version2, but negatively correlated with CDRS (Table 5). Serum 5-HT and urinary 5-HIAA were negatively correlated with HDRS, BDI-II, meanwhile ($2^{-\Delta Ct}$) was positively correlated with HDRS,BDI-II (Table 6).

Discussion

The spectrum of non-motor neuropsychiatric manifestations of PD can be varied, ranging from mood disturbance to cognitive impairment and even psychosis. A significant number of PD patients ultimately experienced cognitive decline involving several cognitive subdomains. However, great variation exists in the nature and severity of cognitive affection, the most prevailing being the PD–MCI with an estimated prevalence of 15–53% across studies, and a five times increased risk of conversion to PDD. Additionally, longitudinal studies of cognition have documented a more rapid rate of cognitive decline among these early staged PD patients than in healthy populations [25].

Our study proved the presence of significant MCI in our selected early stage PD patients compared to their matched controls. This was in agreement with Aarsland et al. [26] and Yarnall et al. [27] who stated that cognitive impairments were common in patients with PD during the early course of illness. Furthermore, Fengler and colleagues [28] stated that cognitive issues were not uncommon in PD patients even during prodromal stages, which would be in harmony with the evidence in favor of newly diagnosed patients already exhibiting deficits in cognition. Skorvanek et al. [29] deemed that global cognitive scales such as MoCA, CDRS, PD–CRS and SCOPA–COG are reliable, valid, and sensitive to cognitive alterations among PD patients. Our result confirms the relevant role of these psychometric scales in predicting minor cognitive changes in PD, which was supported by, and correlated with the findings of our studied modern biomarkers.

Psychometric assessment also demonstrated significant mild depressive symptoms on the scales of HDRS and BDI-II in PD patients compared to controls. This was in line with Campbell et al. [30] who found that depression was common associated with PDD or even PD–MCI. Weintraub et al. [31] reported depression as symptoms that differentiates patients with early untreated PD from age-matched healthy subjects.

Mood disorders can be treated with several different modalities ranging from medications and lifestyle modifications (such as regular exercise and societal activities) to cognitive behavioral therapy and even non-invasive brain stimulation. It is worth-mentioning that certain antidepressants and Parkinson's drugs may trigger the elderly risk of getting dementia by about 50%, which underlines the importance of the collaboration of qualified psychiatrists and neurologists for creating an appropriate treatment plan that helps alleviate the symptoms of PD without creating other burdens on the patients [32, 33].

In the current study, brain volumetric-MRI revealed significant reduction in the thickness of many areas including frontal-, temporal-, insular-, and cingulate-cortex, as well as parahippocampus, precuneus, lingual gyrus, and mean cortical thickness in both hemispheres in PD patients than controls. The thickness of the former 5 above-mentioned areas in both hemispheres were all negatively correlated with HDRS and BDI-II. In addition, the thickness of the insular cortex, precuneus, lingual, parahippocampal areas in both hemispheres were all positively correlated with MOCA, PD–CRS and SCOPA–COG-Version2, but negatively correlated with CDRS. This was in accordance with Ibarretxe-Bilbao et al. [34] who concluded that PD participants without dementia had more progressive cortical thinning than controls with a bilateral fronto-temporal outline, extending to

Table 3 DTI and SWI in PD patients and control subjects

DTI and SWI	Groups: mean ± SD		*T* test	
	Patients	Controls	*T*	*P* value
SOFF (FA)				
RT	0.314 ± 0.068	0.378 ± 0.026	− 5.967	< 0.001*
LT	0.318 ± 0.070	0.387 ± 0.024	− 6.301	< 0.001*
SOFF (MD)				
RT	5.491 ± 1.034	4.704 ± 0.031	5.096	< 0.001*
LT	7.307 ± 0.696	6.757 ± 0.060	5.282	< 0.001*
IOFF (FA)				
RT	0.295 ± 0.065	0.352 ± 0.013	− 5.722	< 0.001*
LT	0.298 ± 0.061	0.354 ± 0.018	− 6.003	< 0.001*
IOFF (MD)				
RT	8.136 ± 0.704	7.502 ± 0.039	6.023	< 0.001*
LT	5.452 ± 1.024	4.518 ± 0.040	6.103	< 0.001*
Frontal subcortical tract (FA)				
RT	0.146 ± 0.055	0.264 ± 0.018	− 13.791	< 0.001*
LT	0.119 ± 0.053	0.227 ± 0.013	− 13.221	< 0.001*
Frontal subcortical tract (MD)				
RT	6.407 ± 0.715	5.633 ± 0.226	6.990	< 0.001*
LT	5.768 ± 0.625	4.523 ± 0.220	12.754	< 0.001*
Parietal subcortical tract (FA)				
RT	0.146 ± 0.050	0.250 ± 0.013	− 13.682	< 0.001*
LT	0.153 ± 0.052	0.203 ± 0.013	− 6.244	< 0.001*
Parietal subcortical tract (MD)				
RT	6.529 ± 0.792	5.278 ± 0.158	10.419	< 0.001*
LT	6.581 ± 0.822	4.846 ± 0.118	14.035	< 0.001*
Temporal subcortical tract (FA)				
RT	0.150 ± 0.049	0.266 ± 0.018	− 14.930	< 0.001*
LT	0.107 ± 0.036	0.172 ± 0.012	− 11.442	< 0.001*
Temporal subcortical tract (MD)				
RT	4.934 ± 0.499	3.902 ± 0.061	13.788	< 0.001*
LT	8.447 ± 0.530	7.769 ± 0.095	8.461	< 0.001*
Temporal subcortical tract (MD)				
Cingulum (FA)				
RT	0.315 ± 0.080	0.461 ± 0.017	− 12.085	< 0.001*

Table 3 (continued)

DTI and SWI	Groups: mean ± SD				T test	
	Patients		Controls		T	P value
LT	0.433 ± 0.100		0.6 ± 0.056		− 1.297	0.198
Cingulum (MD)						
RT	4.043 ± 0.471		2.997 ± 0.189		14.031	< 0.001*
LT	4.685 ± 0.701		3.650 ± 0.224		9.527	< 0.001*
Corona radiata (FA)						
RT	0.282 ± 0.038		0.382 ± 0.017		− 16.608	< 0.001*
LT	0.386 ± 0.046		1.663 ± 7.827		− 1.245	0.216
Corona radiata (MD)						
RT	5.939 ± 0.307		5.324 ± 0.190		11.787	< 0.001*
LT	6.448 ± 0.470		5.702 ± 0.094		10.473	< 0.001*
Corona radiata (MD)						
Cerebral peduncle (FA)						
RT	0.610 ± 0.046		0.717 ± 0.035		− 12.999	< 0.001*
LT	1.262 ± 6.111		0.568 ± 0.040		0.760	0.449
Cerebral peduncle (MD)						
RT	5.524 ± 0.565		4.698 ± 0.252		9.125	< 0.001*
LT	7.827 ± 0.515		7.516 ± 0.243		3.741	< 0.001*
Chi-Square Test	***N***	***%***	***N***	***%***	***X^2***	***P value***
SWI						
Not blooming	39	67.24	43	95.56	12.645	0.002*
Blooming with iron	16	27.59	2	4.44		
Minute calcification	3	5.17	0	0.00		

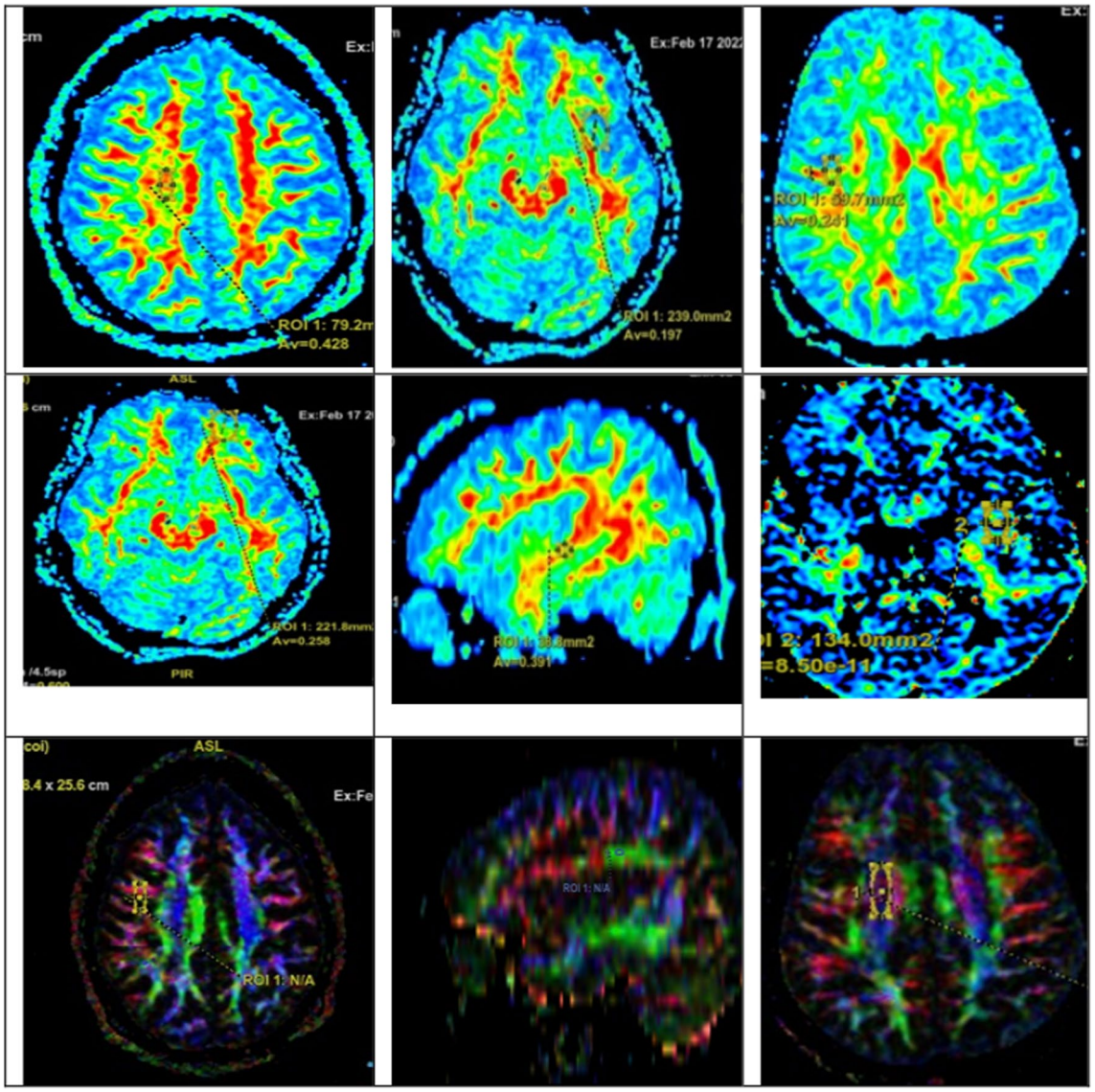

Fig. 2 DTI study in PD patients with upper panel showing reduced FA in the following from RT to LT side: RT corona radiate, Lt temporal subcortical tract, Rt parietal subcortical tract, middle panel showing reduced FA in the following from RT to LTside: Lt frontal subcortical tract, Lt IOFF and increased MD in Lt temporal subcortical tract on the LT side, lower panel showing positioning of the ROI used to measure FA,MD including from RT to LT side: RT parietal subcortical tract, RT SOFF and RT corona radiate (original images from patients enrolled in the study)

the parietal cortex. In the same line, Hanganu and colleagues [35] reported quicker rates of cortical thinning in the frontal and temporal cortices, as well as the insular area in early stage PD. They also, documented a significant association between higher depression scores over time and reduced cortical thickness in the dorsolateral prefrontal cortex, cingulate region, and middle temporal area in PD patients. In addition, our result was in agreement with Mark et al. [36] who found that at the baseline, participants with non-demented PD displayed a significant decrease in cortical thickness in the frontal, parietal and occipital cortices as well as cingulate cortex. Segura et al. [37] also established that precuneus and lingual cortical thinning correlated with cognitive involvement on cognitive tests in early PD.

Brain volumetric-MRI study also demonstrated significant reduction in the volume of each of the hippocampus, amygdala, accumbens, and caudate areas in both hemispheres in PD patients than controls. The volumes of the former 3 areas in both hemispheres were all positively correlated with MOCA, PD–CRS and SCOPA–COG-Version2, but negatively correlated with CDRS.

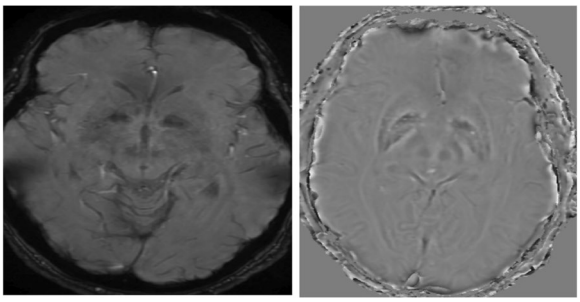

Fig. 3 SWI study in PD patients with minute calcification in the RT image, LT image showing the filter phase of SWAN sequence showing blooming with iron (original images from patients enrolled in the study)

Hippocampal volume and amygdala volume in both hemispheres were also negatively correlated with HDRS and BDI-II. This was in concurrence with Weintraub et al. [38] who recorded significant atrophy of both the caudate nucleus, amygdala and the hippocampus over time in early stage PD particularly PD–MCI. Another study by Hanganu et al. [35] reported that a significant atrophy occurred in the nucleus accumbens eventually in early stage PD particularly PD–MCI. There was also evidence from study carried by Pizzagalli et al. [39] that atrophy of the nucleus accumbens was associated with higher depression scores in non-demented early stage PD.

Brain volumetric-MRI study also revealed significant reduction in total cerebral white matter (WM) volume, total cortical volume, total gray matter volume in both hemispheres in PD patients than controls. This was in harmony with Lee et al. [40] who reported that the volume of the WM of PD subjects was significantly smaller than that of controls early in the disease course, but they also concluded that the volume of the gray matter of patients with PD, athough smaller, had no significant difference from that of the control group. The reason of the inconsistency among these outcomes remains uncertain. However, the findings of their study showed that there were regional variations in the loss of volume of brain structure in PD.

In the present work, DTI has illustrated significant FA reduction and MD increase in the superior occipito-frontal fasciculus, inferior occipito-frontal fasciculus, frontal subcortical tract, parietal subcortical tract, temporal subcortical tract, cingulum, corona radiate, and cerebral peduncle in both hemispheres in PD patients than control. In cross-sectional DTI studies pertaining PD [41, 42], considerable WM changes were recognized in non-demented PD, where signs of grey matter atrophy were so far unremarkable. Such WM changes included FA decrease and MD increase in the inferior and superior longitudinal fasciculi and inferior fronto-occipital fasciculus. The changes in grey matter were only noticeable in patients with dementia. This advocates that DTI might be more perceptive to alterations in white matter microstructure as an early indicator of cognitive affection in PD when compared to measures of atrophy. However, further longitudinal studies will be required to ascertain the temporal sequence [41, 42]. Another study carried by Duncan and colleagues [42] reported that MD of parietal and frontal subcortical tracts is higher in early stage PD patients with mild affection of global cognitive tests.

Scarce researches have been carried on to establish the relationship of cerebral peduncles and FA values, and none of them have reported any evidence for using cerebral peduncles as a predictable marker of early stage PD. Thus, further studies on larger scale of population have to be planned to assess the usefulness of using cerebral peduncle as an early PD biomarker [43]. Conversely, Kotianet al [44] found, in their study regarding DTI parameters, a statistically significant differences between the PD and controls in Genu and body of the corpus callosum, and cerebral peduncles. Morever, the study done by Gattellaro et al. [45] gave proof for microstructural aberrations expanding beyond the basal ganglia in non-demented PD patients occurring in the genu of the corpus callosum, corticospinal tract at the level of corona radiate and cerebral peduncle, the superior longitudinal fasciculus, and in the cingulum. These changes were comparable between the two hemispheres, although the FA was not significantly decreased, the MD was significantly increased.

Selective neuronal liability that predisposes to PD and cognitive decline coupling may be attributed to oxidative stress caused partly by excessive brain iron deposition [46]. SWI was a fairly modern MRI technique that showed promise as proxy for regional cellular vulnerability due to iron accumulation. In the present study, SWI revealed blooming with iron in the basal ganglia (27.59% of patients versus 4.44% in controls) and minute calcification (5.17% of patients versus 0% in controls). This was in accordance with a longitudinal SWI study carried by Rossi et al. [47] who reported a follow-up change compatible with increased iron content in numerous basal ganglia structures that were partially connected to cognitive dysfunction.

Our study showed that P300 was absent in 8.6% and 10.3% of PD patients in the right and left ears, respectively. The rest of the patients showed prolongation of P300 latencies than controls in both ears. The amplitudes of P300 were significantly diminished in patients than controls in both ears. This matched with the results of Patel et al. [48] who found that patients with early stage PD had reduced "P300" amplitude, and this could also

Table 4 CAEP and laboratory investigations in PD patients and control subjects

CAEP and laboratory	Groups Mean ± SD		*T* test	
	Patients	Controls	*t*	*P* value
CAEP				
P1 latency (ms)				
RT	51.591 ± 11.560	45.576 ± 2.048	3.446	0.001*
LT	49.347 ± 8.968	44.953 ± 2.828	3.163	0.002*
P1 amplitude (uv)				
RT	1.955 ± 0.567	2.249 ± 0.068	− 3.461	0.001*
LT	2.101 ± 0.456	2.338 ± 0.054	− 3.469	0.001*
N1 latency (ms)				
RT	98.672 ± 18.342	90.089 ± 4.833	3.055	0.003*
LT	99.638 ± 16.674	88.333 ± 5.304	4.375	< 0.001*
N1 amplitude (uv)				
RT	− 3.729 ± 1.653	− 4.789 ± 0.855	3.912	< 0.001*
LT	− 3.699 ± 1.789	− 5.167 ± 0.693	5.205	< 0.001*
P2 latency (ms)				
RT	195.931 ± 16.768	187.733 ± 5.683	3.140	0.002*
LT	197.310 ± 18.118	183.244 ± 9.018	4.766	< 0.001*
P2 amplitude (uv)				
RT	3.205 ± 1.698	4.106 ± 0.794	− 3.288	0.001*
LT	2.800 ± 1.247	4.190 ± 0.950	− 6.208	< 0.001*
N2 latency (ms)				
RT	258.310 ± 30.170	237.556 ± 21.808	3.891	< 0.001*
LT	255.241 ± 31.641	247.044 ± 17.242	1.566	0.121
P2 amplitude (uv)				
RT	− 3.000 ± 1.695	− 4.814 ± 1.409	5.790	< 0.001*
LT	− 2.874 ± 1.548	− 5.362 ± 1.402	8.426	< 0.001*
P300 latency (ms)				
RT	293.397 ± 97.361	288.867 ± 8.220	0.311	0.757
LT	284.914 ± 103.238	289.222 ± 15.158	− 0.277	0.782
P300 amplitude (uv)				
RT	2.422 ± 1.608	3.846 ± 0.825	− 5.409	< 0.001*
LT	2.668 ± 1.704	4.791 ± 0.855	− 7.639	< 0.001*
Laboratory				
IL-6 (pg/ml)	6.978 ± 2.027	5.100 ± 0.875	5.805	< 0.001*
BDNF (ng/ml)	17.955 ± 11.561	27.298 ± 7.960	− 4.633	< 0.001*
5-HT (ng/ml)	123.672 ± 57.050	134.089 ± 36.471	− 1.067	0.289
5-HIAA (mg/urinary 24 h)	4.488 ± 2.554	5.947 ± 1.515	− 3.394	0.001*
CT control	26.597 ± 0.921	25.835 ± 1.048	3.922	< 0.001*
Ct miRNA	29.965 ± 3.673	26.813 ± 1.511	5.408	< 0.001*
2-A Ct	0.765 ± 2.277	1.268 ± 2.380	− 1.091	0.278

SD standard deviation, *CAEP* cortical auditory evoked potential, *BDNF* brain derived neurotrophic factor, *HIAA* hydroxyl indol acetic acid

*Significant at $p < 0.05$

be used for objective judgment of the progression of PD cognitive decline. In another study carried by Tokic et al. [49], the P300 of the participants with PD had no systematic dissimilarity regarding amplitude; although, a prolongation of latency was elicited when compared to healthy controls. Based on the results of Yilmaz et al., [50] prolongation of P300 latency was more detected among newly diagnosed PD patients with MCI-PD when compared to control group. Tokic et al. [49] also revealed that PD patients presented a lengthened latency

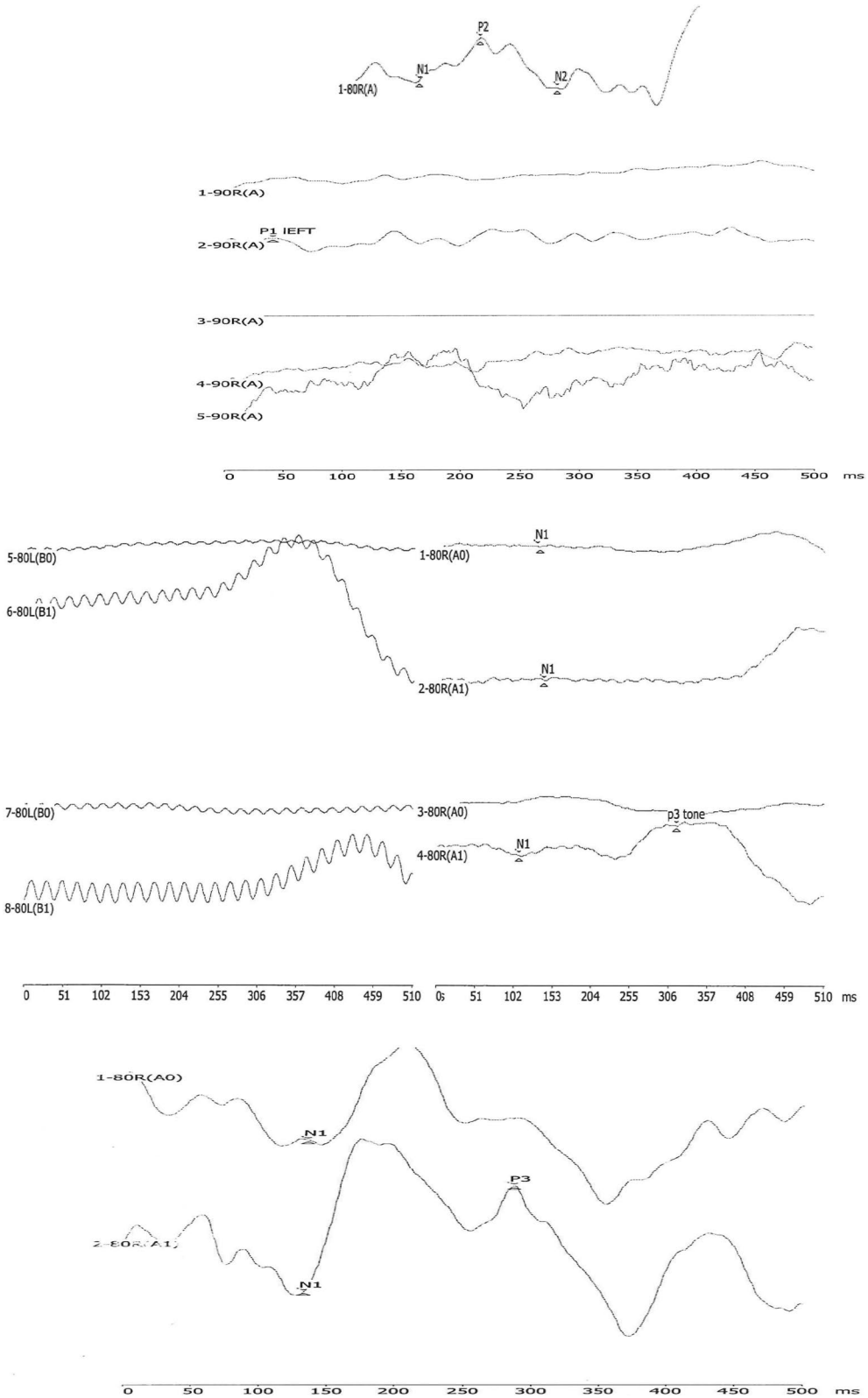

Fig. 4 P300 and CAEP study in PD patients with upper panel showing absent p wave, the second panel showing absent CAEP waves (P1,N1,P2,N2), the third panel showing absent most waves of CAEP, prolonged latency and diminished amplitude of P300, the fourth panel showing normal latency and amplitude of P300 (original images from patients enrolled in the study)

Table 5 Correlation of the global cognitive scales with MRI volumetry, DTI, P300, BDNF and 2—Δ Ct in PD patients

Variables	MoCA		CDRS		PD–CRS		SCOPA–COG-version2	
	r	*P* value	r	*P* value	r	*P* value	R	*P* value
Volumetric-MRI								
Insular cortex thickness								
RT	0.425	0.001*	− 0.143	0.284	0.160	0.230	0.689	< 0.001*
LT	0.411	0.001*	− 0.128	0.338	0.107	0.423	0.732	< 0.001*
Precuneus thickness								
RT	0.453	< 0.001*	− 0.140	0.295	0.156	0.241	0.681	< 0.001*
LT	0.462	< 0.001*	− 0.138	0.300	0.167	0.209	0.672	< 0.001*
Lingual thickness								
RT	0.444	< 0.001*	− 0.164	0.220	0.105	0.432	0.753	< 0.001*
LT	0.448	< 0.001*	− 0.114	0.396	0.188	0.157	0.677	< 0.001*
Parahippocampal thickness								
RT	0.426	0.001*	− 0.094	0.481	0.220	0.098	0.575	< 0.001*
LT	0.484	< 0.001*	− 0.180	0.176	0.221	0.096	0.693	< 0.001*
Hippocampal volume								
RT	0.427	0.001*	− 0.122	0.360	0.095	0.480	0.763	< 0.001*
LT	0.469	< 0.001*	− 0.156	0.243	0.159	0.234	0.728	< 0.001*
Amygdala volume								
RT	0.477	< 0.001*	− 0.158	0.236	0.185	0.163	0.727	< 0.001*
LT	0.472	< 0.001*	− 0.171	0.201	0.152	0.255	0.724	< 0.001*
Accumbens area volume								
RT	0.454	< 0.001*	− 0.117	0.382	0.188	0.158	0.656	< 0.001*
LT	0.456	< 0.001*	− 0.128	0.337	0.152	0.254	0.710	< 0.001*
DTI								
SOFF (FA)								
RT	0.169	0.205	− 0.036	0.787	0.031	0.819	0.321	0.014*
LT	0.165	0.214	− 0.019	0.886	0.007	0.961	0.305	0.020*
SOFF (MD)								
RT	− 0.421	0.001*	0.185	0.164	− 0.196	0.140	− 0.375	0.004*
LT	− 0.368	0.004*	0.184	0.167	− 0.088	0.509	− 0.401	0.002*
IOFF (FA)								
RT	0.294	0.025*	− 0.136	0.310	0.082	0.539	0.512	< 0.001*
LT	0.227	0.087	− 0.074	0.580	0.035	0.794	0.415	0.001*
IOFF (MD)								
RT	− 0.386	0.003*	0.121	0.366	− 0.162	0.224	− 0.300	0.022*
LT	− 0.327	0.012*	0.243	0.067	− 0.135	0.311	− 0.339	0.009*
LT Parietal subcortical tract								
FA	0.336	0.010*	− 0.210	0.114	0.153	0.253	0.438	0.001*
MD	− 0.334	0.010*	0.030	0.825	− 0.364	0.005*	− 0.093	0.486
Temporal subcortical tract (MD)								
RT	− 0.144	0.281	0.139	0.298	− 0.131	0.327	− 0.456	< 0.001*
LT	− 0.176	0.186	0.150	0.262	− 0.112	0.401	− 0.186	0.163
CAEP								
P300 amplitude								
RT	0.400	0.002*	− 0.174	0.191	0.206	0.120	0.702	< 0.001*
LT	0.476	< 0.001*	− 0.145	0.276	0.220	0.097	0.675	< 0.001*
Laboratory								
BDNF (ng/ml)	0.144	0.280	− 0.037	0.783	0.071	0.597	0.135	0.313
$2^{-\Delta Ct}$	0.075	0.575	− 0.133	0.318	0.184	0.167	0.011	0.932

*Significant at $p < 0.05$, *r*: Pearson correlation coefficient

Table 6 Correlation of the psychiatric scales with MRI volumetry, DTI, 5-HT and 5-HIAA in PD patients

Studied variables	HDRS		BDI-II	
	R	*P* value	r	*P* value
Volumetric MRI				
Frontal cortical thickness				
RT	− 0.492	< 0.001*	− 0.590	< 0.001*
LT	− 0.575	< 0.001*	− 0.541	< 0.001*
Temporal cortical thickness				
RT	− 0.454	< 0.001*	− 0.514	< 0.001*
LT	− 0.617	< 0.001*	− 0.545	< 0.001*
Insular cortex thickness				
RT	− 0.493	< 0.001*	− 0.560	< 0.001*
LT	− 0.544	< 0.001*	− 0.548	< 0.001*
Cingulate thickness				
RT	− 0.454	< 0.001*	− 0.556	< 0.001*
LT	− 0.513	< 0.001*	− 0.559	< 0.001*
Parahippocampal thickness				
RT	− 0.405	0.002*	− 0.492	< 0.001*
LT	− 0.551	< 0.001*	− 0.582	< 0.001*
Hippocampal volume				
RT	− 0.597	< 0.001*	− 0.548	< 0.001*
LT	− 0.577	< 0.001*	− 0.579	< 0.001*
Amygdala volume				
RT	− 0.574	< 0.001*	− 0.581	< 0.001*
LT	− 0.582	< 0.001*	− 0.577	< 0.001*
DTI				
SOFF (FA)				
RT	− 0.400	0.002*	− 0.395	0.002*
LT	− 0.361	0.005*	− 0.369	0.004*
SOFF (MD)				
RT	0.305	0.020*	0.385	0.003*
LT	0.313	0.017*	0.437	0.001*
IOFF (FA)				
RT	− 0.539	< 0.001*	− 0.545	< 0.001*
LT	− 0.481	< 0.001*	− 0.481	< 0.001*
IOFF (MD)				
RT	0.324	0.013*	0.282	0.032*
LT	0.353	0.007*	0.417	0.001*
Temporal subcortical tract (MD)				
RT	0.477	< 0.001*	0.275	0.036*
LT	0.249	0.059	0.326	0.012*
Cingulum (FA)				
RT	− 0.489	< 0.001*	− 0.380	0.003*
Cingulum (MD)				
LT	0.142	0.286	0.337	0.010*
Laboratory				
5-HT (ng/ml)	− 0.079	0.557	− 0.031	0.820
5-HIAA (mg/24 h)	− 0.014	0.916	− 0.205	0.122
2-A Ct	0.186	0.163	0.072	0.590

Table 6 (continued)

*Significant at $p < 0.05$, *r:* Pearson correlation coefficient

and diminished amplitude to P300 target and frequent stimuli. These changes supported that patients with PD have frequent cognitive dysfunctions, as the two key neurophysiological indicators of cognitive performance are latency and amplitude [51].

CAEP showed that only P1 was absent in 1.7% of PD patients in both ears. The rest of the patients showed bilateral significantly delayed P1,N1,P2,N2 latencies with significantly diminished amplitudes than controls. Li et al. [52] reported that the affection of parameters of CAEP components including N1, N2, P1, P2 latency prolongation and amplitude reduction were found in early PD patients. Matsui et al. [53] also reported that P1,N1,P2,N2, and P300 were correlated with different cognitive functions**,** thus their abnormalities reflected early cognitive affection in early PD patients**.**

Laboratory investigations revealed a significant elevation of serum inflammatory marker IL6 in PD patients than controls. In the same line, Shen et al. [54] described an immunosensing platform for in-vivo electrochemical monitoring of the pro-inflammatory cytokines interleukin IL6 seeking for future identification of PD in its early stage. Morever, they stated that microglial cells, following dopaminergic neuron cell death, secreted inflammatory cytokines. In addition, Yu et al. [55] found that elevated levels of inflammatory biomarkers such as IL-6, 10 could be found in both the blood and CSF of PD patients at the beginning of the illness and are linked to cognitive decline.

Moreover, the investigations revealed non-significant reduction of serum 5-HT, but a significant reduction of 24 h-urinary 5-HIAA in PD patients than controls. Serum 5-HT and urinary 5-HIAA were negatively correlated with BDI-II. This was in accordance with Tong et al. [56] who stated that the consequence of dopaminergic, serotoninergic and noradrenergic neurotransmission damage monitored during the development of the disease is partly responsible for such correlations, with depressed PD patients having lower plasma levels 5-HT and its metabolite 5-HIAA compared with controls according to HDRS.

The study also established a significant drop of BDNF in PD patients than controls. This was in agreement with Scalzo et al. [57] who emphysized that BDNF contributes to the regulation of synaptic plasticity and cognition and hinders apoptosis-directed cell death. Reduced levels in blood and CSF have been discovered in the early phases of the illness, offering a promising early diagnostic biomarker for cognitive decline [57].

Besides, this study showed non-significant reduction of relative expression of microRNA-132-3p in PD patients than controls. Serum BDNF and microRNA-132-3p were positively correlated with MOCA, PD–CRS and SCOPA–COG-Version2, but negatively correlated with CDRS. The study conducted by Schulz et al. [58] and Yang et al. [59] reported that serum miRNA-132-3p was decreased in non-demented PD patients and it was associated with cognitive affection in PD, with or without adjustment for age or disease duration. Li et al. [60] suggested that BDNF gene was probably the most crucial gene implicated in the pathophysiology of major depressive disorder (MDD). It was revealed that miR-132-3p, which decrease BDNF production, was upregulated in MDD patients. The present work reported a direct correlation between serum microRNA-132-3p and BDI-II scores, which was in line with previous studies that revealed comparable results [23, 60]. Su et al. determined elevated peripheral blood miR-132-3p levels and reduced peripheral blood BDNF levels in MDD [23].

The strength of the present article lies in its comparative profile as a control group was applied, which we thought crucial for differentiating age-related cognitive and psychiatric troubles from those associated with PD. Furthermore, it is distinguished by linking 3 different types of advanced objective biomarkers with the results of psychometric tests on a homogenous sample of population.

Its worth mentioning that this study should be regarded in the perspective of a number of shortcomings. First, the restricted number of participants which was attributed to limited study duration, strict selection criteria and the high costs of neuro-imaging and assay kits. Second, the study did not pertain other PD–NMS that may impact the results. In addition, the study could be more informative if we could do follow-up of our patients and evaluate the long-term impact of the disease on our investigated biomarkers. Therefore, future longitudinal prospective researches on a larger scale of participants are fundamental to identify the initial cognitive/psychiatric symptoms and sequential pattern of changes and neural progression predictive of outcomes.

Conclusion

Patients diagnosed with early stage PD may have cognitive alternation and depressive symptoms which could be approached properly by global cognitive and psychiatric scales even if not manifested clinically or mildly. These neuropsychiatric affections can be predicted and correlated with the results of various biomarkers including: advanced neuro-imaging, evoked potential studies and laboratory markers for the prospect of proper treatment and improving quality of life.

By applying and collecting all available clinical, biological, genetic, neurophysiological and functional brain imaging markers in clinical practice, the treated team will be offered with additional objective tool for optimization the choice of pharmacological and/or non-pharmacological approaches for the treatment of cognitive decline and psychiatric troubles even at early stages of PD on an individual basis.

Abbreviations

PD	Parkinson's disease
PDD	Parkinson's disease dementia
MCI	Mild cognitive impairment
DTI	Diffusion tensor imaging
SWI	Susceptibility weighted imaging
CAEP	Cortical auditory evoked potential
BDNF	Brain derived neurotrophic factor
5-HT	5-Hydroxy tryptamine
HIAA	Hydroxyl indol acetic acid
MOCA	Montreal Cognitive Assessment
PD–CRS	Parkinson's Disease–Cognitive Rating Scale
CDRS	Clinical Dementia Rating Scale
HDRS	Hamilton Depression Rating Scale
BDI-II	Beck Depression Inventory II
FA	Fractional anisotropy
MD	Mean diffusity
SOFF	Superior occipito-frontal fasciculus
IOFF	Inferior occipito-frontal fasciculus

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Author contributions

MB conceptualized the study. RA, MK, SS and AR have given inputs in study design. All authors shared in collecting the data. MB analysed the data and wrote the first draft of the manuscript and all co-authors contributed in the critical review of data analysis and manuscript writing. MB will act as a guarantor for this paper. All authors have read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article [and its Additional information files].

Declarations

Ethics approval and consent to participate

The study protocol was reviewed, approved by theResearch Ethics Committee of Faculty of Medicine, Tanta University and hastherefore been performed in agreement with the ethical standards laid down inthe 1964 Declaration of Helsinki. A comprehensive clarification about the studywas given by the researchers after which they provided consent for publication.All subjects enrolled in this study gave written informed consent to publishthe data contained within this study. All ethical standards were maintained. Anyunexpected hazards appeared during the research will be clarified to thesubjects and the ethical committee on time. There were adequate measures tokeep the privacy of participants and confidentiality of the data. Ethics approval code: 35013/11/21.

Consent for publication
Not applicable.

Competing interests
The researchers declared that they have no knowncompeting financial interests or personal relations that could affect the workreported in this study.

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References

1. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol. 1999;56(1):33–9.
2. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol. 2006;5:235–45.
3. Halliday GM, Leverenz JB, Schneider JS, Adler CH. The neurobiological basis of cognitive impairment in Parkinson's disease. MovDisord. 2014;29(5):634–50.
4. Palavra NC, Naismith SL, Lewis SJG. Mild cognitive impairment in Parkinson's disease: a review of current concepts. Neurol Res Int. 2013. https://doi.org/10.1155/2013/576091.
5. Rihmer Z, Gonda X, Döme P. Depression in Parkinson's disease. Ideggyogy Sz. 2014;67(7–8):229–36.
6. Latif S, Jahangeer M, Maknoon Razia D, Ashiq M, Ghaffar A, Akram M, El Allam A, Bouyahya A, Garipova L, Ali Shariati M, Thiruvengadam M, Azam AM. Dopamine in Parkinson's disease. Clin Chim Acta. 2021;522:114–26. https://doi.org/10.1016/j.cca.2021.08.009.
7. Tan LC. Mood disorders in Parkinson's disease. Parkinsonism Relat Disord. 2012;18(Suppl 1):S74–6. https://doi.org/10.1016/S1353-8020(11)70024-4.
8. Delgado-Alvarado M, Gago B, Navalpotro-Gomez I, Jiménez-Urbieta H, Rodriguez-Oroz MC. Biomarkers for dementia and mild cognitive impairment in Parkinson's disease. Mov Disord. 2016;31(6):861–81. https://doi.org/10.1002/mds.26662.
9. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30:1591–601. https://doi.org/10.1002/mds.26424.
10. Fahn S, Elton RL. Unified Parkinson's Disease Rating Scale. In: Fahn S, Madsen CD, Calne DB, Goldstein M, editors. Recent developments in Parkinson's disease. Florham Park, NJ: Macmillan Helathcare Information; 1987.
11. Nasreddine ZS, Patel BB. Validation of Montreal cognitive assessment, MoCA, alternate French versions. Can J Neurol Sci. 2016;43(5):665–71.
12. Sanhaji S, Elargoub I, Lemaréchal C, Benabdeljlil M, Faris ME. Moroccan version of the Mattis Dementia Rating Scale: the effects of age, education, and gender. World J Neurosci. 2018;8:90–7. https://doi.org/10.4236/wjns.2018.81008.
13. Pagonabarraga J, Kulisevsky J, Llebaria G, García-Sánchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. Mov Disord. 2008;23(7):998–1005. https://doi.org/10.1002/mds.22007.
14. Marinus J, Visser M, Verwey NA, Verhey FR, Middelkoop HA, Stiggelbout AM, van Hilten JJ. Assessment of cognition in Parkinson's disease. Neurology. 2003;61(9):1222–8. https://doi.org/10.1212/01.wnl.0000091864.39702.1c.
15. Obeid S, Abi Elias Hallit C, Haddad C, Hany Z, Hallit S. Validation of the Hamilton Depression Rating Scale (HDRS) and sociodemographic factors associated with Lebanese depressed patients. Encephale. 2018;44(5):397–402. https://doi.org/10.1016/j.encep.2017.10.010.
16. Ghareeb AG. Manual of the Arabic BDI-II. Cairo, Egypt: Angle Press; 2000.
17. Deng B, Zhang Y, Wang L, Peng K, Han L, Nie K, et al. Diffusion tensor imaging reveals white matter changes associated with cognitive status in patients with Parkinson's disease. Am J Alzheimers Dis Other Demen. 2013;28:154–64.
18. Reuter M, Schmansky NJ, Rosas HD, Fischl B. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage. 2012;61(4):1402–18.
19. Solís-Vivanco R, Rodríguez-Violante M, Rodríguez-Agudelo Y, Schilmann A, Rodríguez-Ortiz U, Ricardo-Garcell J. The P3a wave: a reliable neurophysiological measure of Parkinson's disease duration and severity. Clin Neurophysiol. 2015;126(11):2142–9.
20. Tong Q, Zhang L, Yuan Y, Jiang S, Zhang R, Xu Q, Ding J, Li D, Zhou X, Zhang K. Reduced plasma serotonin and 5-hydroxyindoleacetic acid levels in Parkinson's disease are associated with nonmotor symptoms. Parkinsonism Relat Disord. 2015;21:882–7.
21. Yu SY, Zuo LJ, Wang F, Chen ZJ, Hu Y, Wang YJ, Wang XM, Zhang W. Potential biomarkers relating pathological proteins, neuroinflammatory factors and free radicals in PD patients with cognitive impairment: a cross-sectional study. BMC Neurol. 2014;14:113–9.
22. Scalzo P, Kümmer A, Bretas TL, Cardoso F, Teixeira AL. Serum levels of brain-derived neurotrophic factor correlate with motor impairment in Parkinson's disease. J Neurol. 2010;257:540–5.
23. Su M, Hong J, Zhao Y, Liu S, Xue X. MeCP2 controls hippocampal brain derived neurotrophic factor expression via homeostatic interactions with microRNA132 in rats with depression. Mol Med Rep. 2015;12(4):5399–406. https://doi.org/10.3892/mmr.4104.
24. Dawson B, Trapp RG. Basic and clinical biostatistics. Lange Medical Book/ McGraw-Hill, Medical Publishing Division. 2001;3(7–9):161–218.
25. Cholerton BA, Zabetian CP, Wan JY, Montine TJ, Quinn JF, Mata IF, Chung KA, Peterson A, Espay AJ, Revilla FJ, Devoto J, Watson GS, Hu SC, Leverenz JB, Edwards KL. Evaluation of mild cognitive impairment subtypes in Parkinson's disease. Mov Disord. 2014;29:756–64.
26. Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, Burn D, Barone P, Pagonabarraga J, Allcock L, et al. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. Neurology. 2010;75:1062–9.
27. Yarnall AJ, Breen DP, Duncan GW, Khoo TK, Coleman SY, Firbank MJ, Nombela C, Winder-Rhodes S, Evans JR, Rowe JB, et al. Characterizing mild cognitive impairment in incident Parkinson disease: The ICICLE-PD study. Neurology. 2014;82:308–16.
28. Fengler S, Liepelt-Scarfone I, Brockmann K, Schنffer E, Berg D, Kalbe E. Cognitive changes in prodromal Parkinson's disease: a review: cognitive changes in prodromal PD. Mov Disord. 2017;32(12):1655–66. https://doi.org/10.1002/mds.27135.
29. Skorvanek M, Goldman JG, Jahanshahi M, Marras C, Rektorova I, Schmand B, van Duijn E, Goetz CG, Weintraub D, Stebbins GT, et al. Global scales for cognitive screening in Parkinson's disease: critique and recommendations. Mov Disord. 2018;33:208–18.
30. Campbell MC, et al. Parkinson disease clinical subtypes: key features and clinical milestones. Ann Clin Transl Neurol. 2020;7(8):1272–83. https://doi.org/10.1002/acn3.51102.
31. Weintraub D, Simuni T, Caspell-Garcia C, et al. Parkinson's Progression Markers Initiative: cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. MovDisord. 2015;30:919–27.
32. Schrag A, Trimble M. Poetic talent unmasked by treatment of Parkinson's disease. MovDisord. 2001;16:1175–6.
33. Shulman LM, Taback RL, Rabinstein AA, Weiner WJ. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. Parkinsonism Relat Disord. 2002;8:193–7.
34. Ibarretxe-Bilbao N, Junque C, Segura B, Baggio HC, Marti MJ, Valldeoriola F, et al. Progression of cortical thinning in early Parkinson's disease. Mov Disord. 2012;27:1746–53.
35. Hanganu A, Bedetti C, Degroot C, Mejia-Constain B, Lafontaine A-L, Soland V, et al. Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally. Brain. 2014;137:1120–9.
36. Elijah M, Li S, Williams GB, Firbank MJ, Lawson RA, Yarnall AJ, et al. Baseline and longitudinal grey matter changes in newly diagnosed Parkinson's disease: ICICLE-PD study. Brain. 2015;138:2974–86.

37. Segura B, Baggio HC, Marti MJ, Valldeoriola F, Compta Y, Garcia-Diaz AI, et al. Cortical thinning associated with mild cognitive impairment in Parkinson's disease. Mov Disord. 2014;29:1495–503.
38. Weintraub D, Doshi J, Koka D, Davatzikos C, Siderowf AD, Duda JE, et al. Neurodegeneration across stages of cognitive decline in Parkinson disease. Arch Neurol. 2011;68:1562–8.
39. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R, et al. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. Am J Psychiatry. 2009;166:702–10.
40. Lee SH, Kim SS, Tae WS, Lee SY, Choi JW, Koh SB, et al. Regional volume analysis of the Parkinson disease brain in early disease stage: gray matter, white matter, striatum, and thalamus. AJNR Am J Neuroradiol. 2011;32:682–7.
41. Hattori T, Orimo S, Aoki S, Ito K, Abe O, Amano A, et al. Cognitive status correlates with white matter alteration in Parkinson's disease. Hum Brain Mapp. 2012;33:727–39.
42. Duncan GW, Firbank MJ, Yarnall AJ, Khoo TK, Brooks DJ, Barker RA, et al. Gray and white matter imaging: a biomarker for cognitive impairment in early Parkinson's disease? Mov Disord. 2015;31:103–10.
43. Meijer FJA, Bloem BR, Mahlknecht P, Seppi K, Goraj B. Update on diffusion MRI in Parkinson's disease and atypical parkinsonism. J Neurol Sci. 2013;332(1–2):21–9.
44. Kotian RP, Prakashini K, Sreekumaran Nair N. Diffusion tensor imaging study to compare normative fractional anisotropy values with patients suffering from Parkinson's disease in the brain grey and white matter. medRxiv preprint. https://doi.org/10.1101/2020.06.09.20126755.
45. Gattellaro G, Minati L, Grisoli M, Mariani C, Carella F, Osio M, et al. White matter involvement in idiopathic Parkinson Disease: a diffusion tensor imaging study. AJNR Am J Neuroradiol. 2009;30:1222–6.
46. Dias V, Junn E, Mouradian MM. The role of oxidative stress in Parkinson's disease. J Parkinson Dis. 2014;3:461–91.
47. Rossi ME, Ruottinen H, Saunamaki T, Elovaara I, Dastidar P. Imaging brain iron and diffusion patterns. A follow-up study of Parkinson's disease in the initial stages. Acad Radiol. 2014;21:64–71.
48. Patel SH, Azzam PN. Characterization of N200 and P300: selected studies of the event-related potential. Int J Med Sci. 2005;2(4):147–54.
49. Tokic K, Titlic M, Beganovic-Petrovic A, Suljic E, Romac R, Silic S. P300Wave changes in patients with Parkinson's disease. Med Arh. 2016;70(06):453–6.
50. Yilmaz FT, Özkaynak SS, Barçin E. Contribution of auditory P300 test to the diagnosis of mild cognitive impairment in Parkinson's disease. Neurol Sci. 2017;38(12):2103–9.
51. Tokic K, Titlic M, Beganovic-Petrovic A, Suljic E, Romac R, Silic S. P300 wave changes in patients with Parkinson's disease. Med Arch. 2016;70(6):453–6.
52. Li M, Kuroiwa Y, Wang L, Kamitani T, Takahashi T, Suzuki Y, et al. Early sensory information processes are enhanced on visual oddball and S1–S2 tasks in Parkinson's disease: a visual event-related potentials study. Parkinsonism Relat Disord. 2003;9:329–40. https://doi.org/10.1016/S1353-8020(02)00094-9.
53. Matsui H, Nishinaka K, Oda M, Kubori T, Udaka F. Auditory event-related potentials in Parkinson's disease: prominent correlation with attention. Parkinsonism Relat Disord. 2007;2006(13):394–8. https://doi.org/10.1016/j.parkreldis.12.012.
54. Shen Z, Huang J, Wei H, Niu H, Li B, Li R, Liu G. Validation of an in vivo electrochemical immunosensing platform for simultaneous detection of multiple cytokines in Parkinson's disease mice model. Bioelectrochem. 2020;134: 107532.
55. Yu SY, Zuo LJ, Wang F, Chen ZJ, Hu Y, Wang YJ, Wang XM, Zhang W. Potential biomarkers relating pathological proteins, neuroinflammatory factors and free radicals in PD patients with cognitive impairment: a cross sectional study. BMC Neurol. 2014;14(113):119.
56. Tong Q, Zhang L, Yuan Y, Jiang S, Zhang R, Xu Q, Ding J, Li D, Zhou X, Zhang K. Reduced plasma serotonin and 5 hydroxyindoleacetic acid levels in Parkinson's disease are associated with nonmotor symptoms. Parkinsonism Relat Disord. 2015;21(882):887.
57. Scalzo P, Kümmer A, Bretas TL, Cardoso F, Teixeira AL. Serum levels of brain derived neurotrophic factor correlate with motor impairment in Parkinson's disease. J Neurol. 2010;257(540):545.
58. Schulz J, Takousis P, Wohlers I, Itula IOG, Valerija D, Rucker G, et al. Meta-analyses identify differentially expressed micrornas in Parkinson's disease. Ann Neurol. 2019;85(6):835–51.
59. Yang ZF, Li TB, Li S, Wei M, Qi HQ, Shen BR, et al. Altered expression levels of microRNA-132 and Nurr1 in peripheral blood of Parkinson's disease: potential disease biomarkers. ACS Chem Neurosci. 2019;10(5):2243–9.
60. Li YJ, Xu M, Gao ZH, Wang YQ, Yue Z, Zhang YX, Li XX, Zhang C, Xie SY, Wang PY. Alterations of serum levels of BDNF-related miRNAs in patients with depression. PLoS ONE. 2013;8(5): e63648. https://doi.org/10.1371/journal.pone.0063648.

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