Journal of Neurology (2019) 266:2505–2511
https://doi.org/10.1007/s00415-019-09448-0

ORIGINAL COMMUNICATION

Prospective memory in Parkinson's disease: the role of the motor subtypes

Alfonsina D'Iorio[1] · Gianpaolo Maggi[1] · Carmine Vitale[2,3] · Marianna Amboni[3,5] · Diana Di Meglio[1] · Luigi Trojano[1,4] · Gabriella Santangelo[1]

Received: 20 March 2019 / Revised: 18 June 2019 / Accepted: 25 June 2019 / Published online: 29 June 2019

Abstract

Background Prospective memory (PM) is defined as memory for future intentions and it is typically divided into time-based and event-based PM. Deficit of PM has been reported in patients with Parkinson's disease (PD) but no study has yet explored the association between motor subtypes (tremor dominant and rigidity/bradykinesia dominant) and performance on PM tasks. The aim of the study was to explore the role of motor subtypes in the defect of PM.

Methods Consecutive outpatients with tremor dominant (TD-PD) or rigidity/bradykinesia dominant (PIGD-PD) PD and healthy subjects (HCs) were enrolled and underwent a neuropsychological battery assessing PM, verbal memory and executive functions and questionnaires assessing apathy, functional autonomy, and perceived memory disturbances.

Results We enrolled 28 patients with TD-PD, 28 patients with PIGD-PD and 50 HCs. The three groups did not differ on demographic and cognitive variables. Patients with TD-PD performed worse on time-based PM tasks than patients with PIGD-PD and HCs; no significant difference was found among the three groups on event-based PM tasks. Executive dysfunctions contributed to reduced time-based PM scores in TD-PD. Moreover, severe deficit of time-based and more frequency of perceived failures of PM contributed to reduced functional autonomy in TD-PD.

Conclusion The finding of a poorer performance of patients with TD-PD than ones with PIGD-PD and HCs suggests a selective deficit of time-based PM abilities in TD-PD group; therefore, deficit of time-based PM might be considered as a distinctive non-motor symptom of TD-PD and it might affect the functional autonomy in this subtype of PD.

Keywords Parkinson's disease · Prospective memory · Cognitive dysfunctions · Postural instability/gait difficulty subtype · Tremor dominant subtype

Introduction

Prospective memory (PM) is defined as memory for future intentions to be acted at an appropriate time (time-based PM) or at the occurrence of a certain event in the future (event-based PM) [1–3]. While time-based PM involves remembering to perform an intention at a specified time, event-based PM involves remembering to perform an intention at the occurrence of a certain external event.

PM functioning has been poorly investigated in Parkinson's disease (PD). A meta-analytic review on 12 studies [2] revealed an impairment of PM abilities in PD patients when compared to healthy subjects (HCs) and no discrepancy in performance between tasks assessing time-based or event-based PM. However, Ramanan and Kumar [2] suggested caution in interpreting these findings as time-based PM is more cognitively demanding than event-based

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00415-019-09448-0) contains supplementary material, which is available to authorized users.

✉ Gabriella Santangelo
gabriella.santangelo@unicampania.it

[1] Department of Psychology, University of Campania "Luigi Vanvitelli", Caserta, Italy

[2] Department of Motor Sciences and Wellness, University "Parthenope", Naples, Italy

[3] Institute of Diagnosis and Health, IDC-Hermitage Capodimonte, Naples, Italy

[4] Salvatore Maugeri Foundation, Scientific Institute of Telese, Telese Terme, Italy

[5] Department of Medicine, Surgery and Dentistry, University of Salerno, Salerno, Italy

PM and this might imply a disproportionate impairment between the two aspects of PM in PD due to dysfunctioning of prefronto-basal ganglia circuitries. The absence of a significant difference between performance on event-based and time-based PM tasks in PD patients might be due to the fact that in the meta-analysis 4/9 primary studies [4–7] exclusively evaluated event-based PM, whereas only 5 studies explored both time-based and event-based PM [8–12]. Therefore, the absence of a significant difference between time-based and event-based PM might depend on the fact that time-based PM seems to be "under-represented" in the meta-analysis. Moreover, another possible factor contributing to the absence of a significant difference might be related to inclusion in all the previous studies of patients with PD, independently from their motor phenotype, i.e., without distinguishing tremor dominant (TD-PD) from rigidity/bradykinesia dominant (postural instability/gait difficulty, PIGD-PD) subtypes. [13]. Taking into account that, besides prefrontal cortex, cerebellum is engaged in PM abilities [14] and that it is damaged in patients with TD-PD subtype rather than in ones with PIGD-PD subtype [15, 16], it might be possible to hypothesize that more severe impairment of PM abilities occurred in TD-PD subtype. However, until now the role of the motor subtype of PD on PM abilities has not yet been investigated.

Considering the abovementioned background, in the present study we evaluated whether deficits in PM abilities are present to the same extent in TD-PD and PIGD-PD subtypes, even when other clinical and neuropsychiatric factors (i.e., apathy) are taken into account, and whether the putative PM defects could be associated with specific neuropsychological features and also with reduced functional autonomy in the two motor subtypes, as the only study investigating functional autonomy in PD [12] did not evaluate the two motor subtypes of PD independently.

Methods

Participants

In the present study, consecutive PD outpatients referred to IDC-Hermitage Capodimonte, Naples, Italy, were screened and enrolled in the study if they met the following inclusion criteria: (1) a diagnosis of idiopathic PD according to the clinical diagnostic criteria (for the reference, see online resource 1); (2) absence of dementia by means of the Italian version of the Montreal Cognitive Assessment (MoCA > 15.5, [17]); (3) absence of major depression according to DSM-5 diagnostic criteria and score < 16 to the Beck Depression Inventory-II (BDI-II); (4) lack of significant cerebrovascular lesion on MRI or CT or severe concomitant disease (i.e., hydrocephalus) which might explain the presence of cognitive or psychiatric disturbances. Patients with diffuse confluent white matter hyperintensity were excluded.

Out of screened outpatients, we selected PD patients according to the motor subtype of PD (i.e., TD-PD and PIGD-PD subtypes) to create two groups matched for demographic variables.

To identify the motor subtype of PD, we employed Jankovic et al. [13] criteria based on the Unified Parkinson's disease Rating Scale (UPDRS). To include PD patients into TD-PD group or PIGD-PD group, we computed a mean score of 9 tremor items (right and left arm tremor by history, lips or chin tremor, tremor in limbs, and both arms action or postural tremor on examination) and a mean score of 5 PIGD items (i.e., falling, freezing, and walking difficulty by history, gait and postural instability on examination). Patients were assigned to the tremor group (TD-PD) if the ratio of the mean tremor score divided by the mean PIGD score was greater than or equal to 1.5 while if this ratio was equal to or less than 1.0 PD patients were included in PIGD-PD group [18].

Demographic features (i.e., gender, age, years of schooling) and clinical aspects (i.e., disease duration, Levodopa Equivalent Daily Dose (LEDD), severity of motor symptoms assessed by both part III of UPDRS and Hoehn and Yahr staging) were recorded.

In addition, we enrolled HCs matched with PD patients for demographic features. HCs were recruited among patients' friends and employees at the university centers. HCs had to meet the following selection criteria: lack of any neurodegenerative or cerebrovascular disorders according to clinical criteria; lack of previous or current psychiatric diseases (e.g., major depression, or psychosis according to DSM-V criteria); absence of dementia or cognitive global dysfunctioning evaluated by of the Italian version of the MoCA (MoCA > 15.5, [17]).

All participants gave their written informed consent to participate to the study, which was approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Neuropsychological and behavioral evaluation

PD patients and HCs underwent the Italian version of the Memory for Intentions Screening Test (MIST, website: https://www.parinc.com/Products/Pkey/233), a neuropsychological test which assesses prospective memory (PM). The MIST is composed of 8 trials consisting of a number of goals, which the subject must keep in mind. Test procedures provide specific instructions to form a conscious intention that must be executed after a delay from the encoding phase. This delay must be filled with a secondary ongoing task

(a word search puzzle). Furthermore, the MIST allows to evaluate several variables as the type of cue (time-based and event-based tasks). There are four time-based trials and four event-based trials. An example of a time-based item from the MIST is "In exactly 15 min please tell me it is time to take a break" while an example of an event-based task is "When I hand you a red pen, please sign your name on your paper". At the end of the testing session, participants undergo a multiple-choice recognition test to evaluate the retrospective component of memory. Finally, the MIST contains a 24-h delayed item to try to approximate the time-span of memory for intentions in daily life. In detail, it provides that participants are instructed to call their examiner and report the length of time they slept the previous night and the quality of their sleep. The MIST is designed to be approximately 30 min in length. Maximum score ranged from 0 to 48 with lower scores indicating more severe prospective memory dysfunctioning.

All participants also underwent a neuropsychological battery to assess verbal memory, by immediate and delayed recall of a short story of Anna Pesenti, and executive functions, by the Trail Making Test (TMT) and the Modified Card Sorting Test (MCST).

Moreover, we also investigated the frequency of prospective memory and retrospective memory failures in all participants by the Italian version of Prospective and Retrospective Memory Questionnaire (PRMQ) and the subjective memory complaints, which can be distinct from objective memory performance, by the Italian version of the multifactorial memory questionnaire (MMQ).

Finally, all the participants completed the Dimensional Apathy Scale (DAS), a self-rated questionnaire assessing apathetic symptoms whereas PD patients completed also the Parkinson's Disease Cognitive Functional Rating Scale (PD-CFRS) to evaluate the functional impact of cognitive impairment in PD (for all tests references, see online resource 1).

Statistical analysis

Demographic, behavioral, cognitive and PM (i.e., subtests of MIST) variables were compared between TD-PD, PIGD-PD groups and HCs by Kruskal–Wallis test. Then, the two-tailed Mann–Whitney *U* test and Quade's rank analysis of covariance (a nonparametric equivalent of analysis of covariance), as appropriate, were used to assess the paired difference between groups.

To investigate a possible difference between scores on time-based PM tasks and scores on event-based PM tasks due to a different complexity between the two types of the tests, we compared *z* scores on event-based and time-based sub-scores of MIST within PD groups by a Wilcoxon signed-rank test. The standardized *z* scores were calculated with reference to control group's means and SD. The *z* scores indicate the relative degree of impairment from normal performance in SD units.

To investigate the possible influence of clinical (i.e., UPDRS, H&Y, LEDD, disease duration), behavioral (DAS) and cognitive variables (i.e., part B-A of TMT, categories sub-score of MCST, a short story) on the raw scores on PM abilities (i.e., time-based and event-based PM sub-scores) within PIGD-PD and TD-PD groups, we performed Pearson' correlational analysis. Then, linear regression analysis (by stepwise method) was performed entering the variables attaining a significant correlation with PM sub-scores at a level of $p < 0.05$ in the Pearson's test as independent variables and time-based and event-based PM sub-scores as dependent variables.

Moreover, to investigate the possible influence of impaired PM abilities on functional autonomy within PIGD-PD and TD-PD groups, Pearson correlational analysis between score on UPDRS, DAS, MMQ, prospective and retrospective sub-scales of PRMQ, time-based and event-based subtests of the MIST and PD-CFRS score was performed. Moreover, we carried out linear regression analysis (by stepwise method), entering variables attaining a significant correlation with PD-CFRS at a level of $p < 0.05$ in the Pearson's test as independent variables and PD-CFRS score as dependent variable.

The critical alpha level for all analyses was set < 0.05. Moreover, Bonferroni post hoc test was performed to control for the type I error. All analyses were performed with IBM SPSS-20.

Results

In the present study, we enrolled 56 PD patients and 50 healthy subjects. According to Jankovic et al. [13], 28 patients belonged to TD-PD subtype and 28 patients belonged to PIGD-PD. The three groups did not differ on demographic, cognitive variables and on BDI-II. According to the diagnostic criteria for Mild Cognitive Impairment (MCI) in PD by Litvan et al. [19], none of the patients had a level I diagnosis of PD-MCI. No differences were found on the frequency of prospective memory and retrospective memory failures on PRMQ in daily life (Table 1). A significant difference between the three groups was found on DAS total score: patients with TD-PD and PIGD-PD reported higher score than HCs on DAS (Table 1).

PM abilities

The three groups showed significant differences on the time-based task and on 24-h item of MIST, whereas no significant difference was found on event-based task and on recognition item (Table 2). Post hoc comparisons (Mann–Whitney *U*

Table 1 Comparison between TD-PD, PIGD-PD and HCs groups on demographic, clinical, cognitive and behavioral variables

	TD-PD ($n=28$)	PIGD-PD ($n=28$)	HCs ($n=50$)	χ^2	p	TD-PD versus PIGD-PD	TD-PD versus HCs	PIGD-PD versus HCs
	Mean ± SD	Mean ± SD				p	p	p
Age (ys)	66.6 ± 7.0	64.5 ± 8.1	66.9 ± 5.5	1.263	0.532	0.329	0.992	0.311
Education (ys)	10.5 ± 4.4	11.8 ± 5.1	9.4 ± 4.4	4.457	0.108	0.289	0.284	0.042
Disease duration (ys)	10.9 ± 3.6	9.9 ± 4.4	–	1.043	0.307	0.307	–	–
UPDRS-III	12.1 ± 2.9	12.6 ± 7.4	–	0.156	0.693	0.693	–	–
Hoehn and Yahr	2.1 ± 0.3	2.0 ± 0.5	–	1.448	0.229	0.229	–	–
LEDD	705.3 ± 311.2	724.3 ± 387.0	–	0.022	0.882	0.882	–	–
MoCA	22.2 ± 4.0	21.7 ± 3.0	21.8 ± 3.3	0.360	0.835	0.489	0.742	0.826
MCST—categories	3.9 ± 1.8	4.3 ± 1.7	4.0 ± 1.9	0.615	0.735	0.434	0.774	0.580
MCST—perseverative errors	5.6 ± 4.0	5.2 ± 4.8	5.0 ± 4.4	0.754	0.686	0.459	0.433	0.917
TMT A	65.7 ± 35.3	46.6 ± 19.5	70.9 ± 43.6	6.496	0.039	0.029	0.896	0.020
TMT B	216.4 ± 126.3	162.6 ± 92.0	185.5 ± 96.7	2.894	0.235	0.127	0.330	0.248
TMT B-A	150.7 ± 97.8	115.9 ± 75.2	116.2 ± 67.0	2.142	0.343	0.248	0.164	0.905
Recall of a short story	9.7 ± 5.5	10.3 ± 4.0	10.8 ± 3.8	1.903	0.386	0.496	0.188	0.467
MMQ—ability	56.2 ± 12.2	52.7 ± 13.6	55.5 ± 13.5	1.278	0.528	0.354	0.950	0.292
MMQ—contentment	42.2 ± 14.0	42.2 ± 11.3	47.1 ± 11.4	3.449	0.178	0.600	0.929	0.413
MMQ—strategy	20.8 ± 13.1	18.0 ± 9.8	21.1 ± 14.0	0.643	0.725	0.870	0.179	0.091
PRMQ—prospective	31.0 ± 5.6	30.5 ± 6.5	31.6 ± 4.4	0.489	0.783	0.980	0.514	0.624
PRMQ—retrospective	32.5 ± 4.9	32.6 ± 4.9	34.4 ± 5.4	1.725	0.422	0.844	0.272	0.291
DAS total score	25.4 ± 8.0[a]	25.3 ± 8.2[a]	19.6 ± 7.9	12.991	**0.002***	0.993	**0.003**	**0.003**
BDI-II	7.4 ± 5.4	8.3 ± 5.8	6.4 ± 4.9	2.314	0.314	0.576	0.442	0.127
PD-CFRS	3.5 ± 3.9	3.8 ± 2.9	–	0.737	0.391	0.391	–	–

TD tremor dominant, *PIGD* rigidity/bradykinesia dominant, *PD* Parkinson's disease, *HCs* healthy controls, *SD* standard deviation, *ys* years, *UPDRS* Unified Parkinson's Disease Rating Scale, *LEDD* levodopa equivalent daily dose, *MoCA* Montreal Cognitive Assessment, *MCST* modified card sorting test, *TMT* trail making test, *MMQ* Multifactorial Memory Questionnaire, *PRMQ* Prospective and Retrospective Memory Questionnaire, *DAS* Dimensional Apathy Scale, *BDI-II* Beck Depression Inventory-II, *PD-CFRS* Parkinson's Disease Cognitive Functional Rating Scale

Significant differences are given in bold

*Significant difference after Bonferroni correction (0.05/21 = 0.0023)

[a]Significant difference between TD-PD and HCs ($U=417.000$; $p=0.003$) and between PIGD-PD and HCs ($U=414.000$; $p=0.003$)

Table 2 Comparison between TD-PD, PIGD-PD and HCs groups on MIST

MIST subtests	TD-PD ($n=28$)	PIGD-PD ($n=28$)	HCs ($n=50$)	χ^2	p
	Mean ± SD	Mean ± SD	Mean ± SD		
Time based	2.1 ± 1.9*	3.6 ± 1.5	3.6 ± 1.8	11.091	**0.004**
Event based	6.4 ± 1.9	5.3 ± 2.0	6.0 ± 1.5	5.337	0.069
Recognition	6.6 ± 1.5	6.4 ± 1.2	6.7 ± 1.2	1.140	0.566
24-h item	0.4 ± 0.8	0.1 ± 0.4^	0.7 ± 0.9	7.512	**0.023**

TD tremor dominant, *PIGD* rigidity/bradykinesia dominant, *PD* Parkinson's disease, *HCs* healthy controls, *SD* standard deviation, *ys* years, *MIST* memory for intentions screening test

Significant differences are given in bold

*Significant difference between TD-PD and PIGD-PD ($U=224.500$; $p=0.005$) and between TD-PD and HCs ($U=409.500$; $p=0.002$)

^Significant difference between PIGD-PD and HCs ($U=494.500$; $p=0.007$)

test) showed that TD-PD group scored significantly worse than both PIGD-PD and HCs groups on time-based task of MIST; moreover, PIGD-PD group had lower scores than HCs group on 24-h item (Table 2). No significant difference

among the three groups was found on the remaining tasks of the MIST. Since TD-PD, PIGD-PD and HCs groups differed on DAS score, we controlled for the possible effect of difference on apathetic symptoms among the three groups using Quade's rank analysis of covariance. This analysis confirmed significant differences on time-based task ($F=4.930$; $p=0.009$).

The Wilcoxon signed-rank test revealed no significant difference between z scores on time-based and event-based sub-scores (time-based z score: 0 ± 0.72 versus event-based score: -0.54 ± 1.34, $Z=-1.748$, $p=0.081$) within PIGD-PD group, whereas z score of time-based PM task was significantly lower than that of event-based PM task within TD-PD group (time-based z score: -0.82 ± 1.02 versus event-based score: 0.18 ± 1.12, $Z=-3.050$, $p=0.002$).

Relationship between PM and neuropsychological scores within PIGD-PD and TD-PD subtypes

Correlational analysis revealed that, within TD-PD group, time-based sub-score of MIST was associated with categories sub-score of MCST ($r=0.458$, $p=0.014$) and with TMT:B-A ($r=-0.392$, $p=0.039$), whereas performance on event-based PM task was related to disease duration ($r=-0.451$, $p=0.016$) and to categories sub-score of MCST ($r=0.392$, $p=0.039$). Moreover, linear regression analysis showed that in TD-PD lower score on categories of MCST was related to reduced performance on time-based PM tasks ($\beta=0.458$, $t=2.624$, $p=0.014$), whereas longer disease duration was related to poorer performance on event-based PM tasks ($\beta=-0.451$, $t=-2.577$, $p=0.016$).

Within PIGD-PD, correlational analysis showed that the score on time-based PM task was associated with categories sub-score of MCST ($r=0.497$, $p=0.007$), with TMT:B-A ($r=-0.521$, $p=0.004$) and with DAS score ($r=-0.445$, $p=0.018$), whereas no clinical, cognitive and neuropsychiatric variables were associated with event-based PM tasks. Furthermore, linear regression analysis revealed that lower performance on TMT:B-A ($\beta=-0.462$, $t=-2.961$, $p=0.007$) and higher score on DAS ($\beta=-0.372$, $t=-2.383$, $p=0.025$) were related to poorer performance on time-based PM tasks in TD-PD.

Relationship between PM and functional autonomy within PIGD-PD and TD-PD subtypes

Correlational analysis revealed that, within TD-PD, PD-CFRS score was associated with prospective memory sub-scale of PRMQ ($r=-0.468$, $p=0.014$) and time-based PM score ($r=-0.415$, $p=0.031$). Moreover, linear regression analysis showed that within TD-PD group higher score on PD-CFRS was significantly related to lower performance on time-based sub-tasks ($\beta=-0.353$; $t=-2.109$; $p=0.046$) and lower score on prospective memory sub-scale of PRMQ ($\beta=-0.416$; $t=-2.482$; $p=0.020$). Clinical and behavioral variables did not influence functional autonomy in TD-PD.

Within PIGD-PD group, correlational analysis showed that PD-CFRS score was associated with DAS score ($r=0.684$, $p<0.001$). Furthermore, regression analysis revealed that higher score on PD-CFRS was significantly related to higher DAS score ($\beta=0.684$; $t=4.775$; $p<0.001$). Clinical and cognitive variables did not influence functional autonomy in PIGD-PD.

Discussion

The present study investigated PM abilities in the two motor subtypes of PD (i.e., TD-PD and PIGD-PD) compared with HCs. We observed a selective deficit of time-based rather than event-based PM ability in TD-PD when compared to PIGD-PD and HCs groups. Moreover, deficits of time-based PM abilities and subjectively perceived failures of PM resulted to be significantly associated with reduced functional autonomy in TD-PD but not in PIGD-PD.

The selective deficit of time-based PM abilities in TD-PD is confirmed by the significantly lower z score on time-based PM task than on event-based PM task within this group. Several putative cognitive mechanisms might explain the poorer performance on time-based PM task in TD-PD [9, 10, 20–22]. We observed that executive dysfunctions (i.e., impaired cognitive flexibility) and behavioral disturbances related to a frontal damage (i.e., apathy [23]) were significantly associated with a reduced performance on time-based PM tasks in patients with both TD-PD and PIGD-PD subtypes. The present data would thus suggest that performance on time-based PM is related to difficulty in managing two concurrent cognitive demands (i.e., the ongoing task and the time monitoring) [10], and to deficits in executive control, likely to be ascribed to dysfunctioning of prefronto-subcortical circuitries. However, the selective impairment of time-based PM in the TD-PD subgroup would suggest the existence of a further impaired mechanism in this subgroup. Likely, more refined neuropsychological studies might identify the exact correlate of the selective time-based PM impairment, but it would be possible to speculate that on neurobiological grounds this prospective memory defect might be the consequence of an alteration of prefronto-cerebellum circuitry, impaired in TD-PD (but not in PIGD-PD) [15, 16], and thought to be involved in time-based PM abilities [14].

Notwithstanding impaired performance on time-based PM task of the MIST, patients with TD-PD showed scores on prospective memory sub-scale of PRMQ similar to those achieved by PIGD-PD group. These results indicated that TD-PD group is characterized by "objective" deficits of

time-based PM abilities without being aware of their prospective memory failures. This finding would suggest that the occurrence of deficit of time-based PM ability deserves to be evaluated in clinical practice by standardized cognitive tests such as the MIST. The clinical relevance of exploring prospective memory in PD patients is supported by our findings from regression analysis which suggested an association between deficit of time-based PM and more reduced functional autonomy in TD-PD group. Our finding supports the results from a previous study [12] reporting association of time-based rather than event-based PM with functional autonomy, but without distinguishing the two motor subtypes of PD.

The selective nature of impaired time-based PM in TD-PD is underlined by the finding that, instead, the PIGD-PD group performed worse than HCs group on 24-h item, where participants are allowed to use any mnemonic strategies (e.g., a note in their electronic organizer), but are not explicitly prompted to do so [24]. Moreover, more frequent retrospective memory failures were related to poorer performance on event-based PM sub-task in our patients with PIGD-PD rather than in those with TD-PD.

The present study is, to extent, limited by the exiguity of samples which could reduce the generalizability of the findings. Therefore, further studies should be performed to confirm our results on larger samples of PD patients.

In conclusion, our study revealed that selective deficit of time-based PM might be a distinctive feature in TD-PD but not in PIGD-PD. Since PM abilities are associated with functional autonomy, the present findings underline the need of evaluating PM to identify the patients with deficit of PM who might benefit from cognitive trainings [25] aimed at stimulating and improving time-based PM abilities.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards All participants gave their written informed consent to participate in the study, which was approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

References

1. Scullin MK, McDaniel MA, Shelton JT, Lee JH (2010) Focal/nonfocal cue effects in prospective memory: monitoring difficulty or different retrieval processes? J Exp Psychol Learn 36:736–749
2. Ramanan S, Kumar D (2013) Prospective memory in Parkinson's disease: a meta-analysis. J Int Neuropsychol Soc 19:1109–1118
3. McDaniel MA, Einstein GO (2000) Strategic and automatic processes in prospective memory retrieval: a multiprocess framework. Appl Cogn Psychol 14:127–144
4. Whittington CJ, Podd J, Stewart-Williams S (2006) Memory deficits in Parkinson's disease. J Clin Exp Neuropsychol 28:738–754
5. Altgassen M, Zollig J, Kopp U, MacKinlay R, Kliegel M (2007) Patients with Parkinson's disease can successfully remember to execute delayed intentions. J Int Neuropsychol Soc 13:888–892
6. Foster ER, McDaniel MA, Repovs G, Hershey T (2009) Prospective memory in Parkinson disease across laboratory and self-reported everyday performance. Neuropsychology 23:347–358
7. Pagni C, Frosini D, Ceravolo R, Giunti G, Unti E, Poletti M, McClintock SM, Murri L, Bonuccelli U, Tognoni G (2011) Event-based prospective memory in newly diagnosed, drug naive Parkinson's disease patients. J Int Neuropsychol Soc 17:1158–1162
8. Katai S, Maruyama T, Hashimoto T, Ikeda S (2003) Event based and time based prospective memory in Parkinson's disease. J Neurol Neurosurg Psychiatry 74:704–709
9. Costa A, Peppe A, Caltagirone C, Carlesimo GA (2008) Prospective memory impairment in individuals with Parkinson's disease. Neuropsychology 22:283–292
10. Raskin SA, Woods SP, Poquette AJ, McTaggart AB, Sethna J, Williams RC, Tröster AI (2011) A differential deficit in time- versus event-based prospective memory in Parkinson's disease. Neuropsychology 25:201–209
11. Smith SJ, Souchay C, Moulin CJA (2011) Metamemory and prospective memory in Parkinson's disease. Neuropsychology 25:734–740
12. Pirogovsky E, Woods SP, Filoteo JV, Gilbert PE (2012) Prospective memory deficits are associated with poorer everyday functioning in Parkinson's disease. J Int Neuropsychol Soc 18:986–995
13. Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, Huber S, Koller W, Olanow C, Shoulson I, Stern M, Tanner C, Weiner W, Parkinson Study Group (1990) Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 40:1529–1534
14. Okuda J, Fujii T, Ohtake H, Tsukiura T, Yamadori A, Frith CD, Burgess PW (2007) Differential involvement of regions of rostral prefrontal cortex (Brodmann area 10) in time- and event-based prospective memory. Int J Psychophysiol 64:233–246
15. Zhang J, Wei L, Hu X, Xie B, Zhang Y, Wu GR, Wang J (2015) Akinetic-rigid and tremor-dominant Parkinson's disease patients show different patterns of intrinsic brain activity. Parkinsonism Relat Disord 21:23–30
16. Piccinin CC, Campos LS, Guimarães RP, Piovesana LG, Dos Santos MCA, Azevedo PC, Campos BM, de Rezende TJR, Amato-Filho A, Cendes F, D'Abreu A (2017) Differential pattern of cerebellar atrophy in tremor-predominant and akinetic/rigidity-predominant Parkinson's disease. Cerebellum 16:623–628
17. Santangelo G, Siciliano M, Pedone R, Vitale C, Falco F, Bisogno R, Siano P, Barone P, Grossi D, Santangelo F, Trojano L (2015) Normative data for the montreal cognitive assessment in an italian population sample. Neurol Sci 36:585–591
18. Herman T, Rosenberg-Katz K, Jacob Y, Auriel E, Gurevich T, Giladi N, Hausdorff JM (2013) White matter hyperintensities in Parkinson's disease: do they explain the disparity between the postural instability gait difficulty and tremor dominant subtypes? PLoS One 8:e55193
19. Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, Mollenhauer B, Adler CH, Marder K, Williams-Gray CH, Aarsland D, Kulisevsky J, Rodriguez-Oroz MC, Burn DJ, Barker RA, Emre M (2012) Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. Mov Disord 27:349–356
20. Koch G, Costa A, Brusa L, Peppe A, Gatto I, Torriero S, Gerfo EL, Salerno S, Oliveri M, Carlesimo GA, Caltagirone C (2008) Impaired reproduction of second but not millisecond time intervals in Parkinson's disease. Neuropsychologia 46:1305–1313

21. Perbal S, Deweer B, Pillon B, Vidailhet M, Dubois B, Pouthas V (2005) Effects of internal clock and memory disorders on duration reproductions and duration productions in patients with Parkinson's disease. Brain Cogn 58:35–48
22. Wearden JH, Smith-Spark JH, Cousins R, Edelstyn NMJ, Cody FWJ, O'Boyle DJ (2008) Stimulus timing by people with Parkinson's disease. Brain Cogn 67:264–279
23. Santangelo G, D'Iorio A, Maggi G, Cuoco S, Pellecchia MT, Amboni M, Barone P, Vitale C (2018) Cognitive correlates of "pure apathy" in Parkinson's disease. Parkinsonism Relat Disord 53:101–104
24. Woods SP, Moran L, Dawson MS, Carey CL, Grant I, HIV Neurobehavioral Research Center (HNRC) Group (2008) Psychometric characteristics of the memory for intentions screening test. Clin Neuropsychol 22:864–878
25. Waldum ER, Dufault CL, McDaniel MA (2014) Prospective memory training: outlining a new approach. J Appl Gerontol 35:1211–1234