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CONSCIOUS ATTENTION DEFECT AND INHIBITORY CONTROL DEFICIT IN PARKINSON'S DISEASE-MILD COGNITIVE IMPAIRMENT: A COMPARISON STUDY WITH AMNESTIC MILD COGNITIVE IMPAIRMENT MULTIPLE DOMAIN

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SUMMARY

Background: *Frontal/executive dysfunction commonly occurs in Parkinson's disease - Mild Cognitive Impairment (PD-MCI patients). However, to date, the number of studies comparing PD-MCI and MCI patients of other etiologies are too small. The present study aims at clarifying the attention/working memory and executive dysfunction of PD-MCI patients in comparison to amnestic MCI multiple domain patients with first extended then abbreviated structural brain changes suggesting preclinical Alzheimer's Disease.*

Subjects and methods: *40 PD-MCI patients and 40 amnestic MCI multiple domain (aMCI+) patients were diagnosed according to the International guidelines. 22 healthy subjects were also recruited as control group. The groups were assessed by a wide neuropsychological battery, including measures of attention/working memory (Digit Span and Stroop Test), executive functions (Tower of London-Drexel Version -TOLDX- and Brixton Test), language (Boston Naming Test and Category Fluency), memory (Prose Recall and Pairs Associates Learning), and visuospatial function (Street's Completion Test and Constructive Apraxia Test). Performances were compared by non parametric tests. Spearman correlations were performed to explore association between neuropsychological measures of attention/working memory and executive functions in PD-MCI group.*

Results: *The PD-MCI patients performed worse on Digit Span and Stroop Interference/Error than aMCI+ and controls. AMCI+ patients, in turn, showed a greater deficit on TOLDX Initiation Time and on Violation Time than PD-MCI and controls. Both PD-MCI and aMCI+ patients reported lower scores on Stroop Interference/Time than controls. Moreover, aMCI+ patients performed worse then controls on Brixton Test. Positive correlations between Digit Span and Stroop Interference/Error, Stroop Interference/Error and TOLDX Execution Time, Total Time and Violation Time, Stroop Interference Time and TOLDX Move Score and Total Time were found in PD-MCI group.*

Conclusion: *PD-MCI patients mainly present a conscious attention defect and an inhibitory control deficit than aMCI+. PD-MCI patients with deficits in attention/working memory domain should undergo specific cognitive trainings in order to improve cognitive abilities and prevent Parkinson's Disease Dementia onset.*

Key words: *Parkinson's disease - Mild Cognitive Impairment (MCI) – attention - working memory - planning dysfunction*

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INTRODUCTION

The concept of Mild Cognitive Impairment (MCI) identifies an intermediate phase in the continuum physiological aging-dementia characterized by a slight cognitive impairment in patients that may proceed toward dementing illnesses (Petersen et al. 2014). MCI was introduced as a clinical entity in the 1980s, first systematized by Petersen et al. (1999) and then re-defined by the International Work Group on MCI in a Key Symposium (Winblad et al. 2004). From this last turnover, MCI became a broader construct than first thought and focused not only on amnestic deficits reported by patients but also on impairments in other cognitive domains rather than memory. Based on epidemiological longitudinal studies, the International Work Group on MCI argued that when patients with MCI were followed over time, some progress to Alzheimer's Disease (AD) or other dementing illnesses while others remain stable over time or revert to a normal cognitive status. Many studies have suggested that patients with amnestic MCI multiple domain are more likely to progress to AD whereas MCI patients with non-amnestic cognitive impairment may develop other conditions, such as frontotemporal dementia, vascular dementia, dementia with Levy bodies and even depression (Petersen et al. 2009). Amnestic MCI multiple domain (aMCI+) is considered the most frequent subtype among individuals with MCI and it has been recognized that episodic memory disorder along with executive functions deficits (especially in planning and inhibitory control) constitute the neuropsychological pattern with high risk of conversion into dementia (Petersen & Negash 2008, Cammisuli et al. 2012, 2017). Furthermore, the use of biomarkers may aid researchers in distinguishing MCI due to specific causes. The National Institute of Aging-Alzheimer's Associations (NIA-AA) aimed at developing criteria for the symptomatic pre-dementia stages of AD. They therefore redefined MCI criteria including two main sets

of biomarkers that may help in formulating the clinical judgement of MCI due to AD (i.e. biomarkers of amyloid beta deposition and neuronal injury) with four levels of certainty depending on the presence and nature of biomarkers finding (Albert et al. 2011).

Contrary to the MCI construct, the Parkinson's Disease-Mild Cognitive Impairment (PD-MCI) construct is still recent dating back to 2012. According to the fact that PD is not only defined by characteristic motor hallmarks (i.e. rest tremor, bradykinesia, rigidity and gait impairment) but also by cognitive symptoms, the Movement Disorder Society (MDS) commissioned a task force to provide diagnostic criteria for PD-MCI, including guidelines for the assessment (i.e., Level I: abbreviated assessment and Level II: comprehensive assessment) and subtypes classification (Litvan et al. 2012; Geurtsen et al. 2014, Hoogland et al. 2017).

In PD, there is a wide spectrum of cognitive dysfunction from MCI to Parkinson's Disease Dementia (PDD). MCI is quite common in non-demented PD patients occurring in about 20-50% of patients and it represents a risk factor for the conversion into PDD (Goldman & Litvan 2011). PD-MCI patients usually report some difficulties in functional independence that may be reflected in the quality of life (Federico et al. 2015). PD-MCI is associated to increasing age, low levels of education, later onset of the disease, greater PD severity, longer disease duration and it is more frequent in males than females (Palavra et al. 2013).

Contrary to previous studies in literature, after the introduction of diagnostic criteria for PD-MCI (Litvan et al. 2012), more recent investigations have confirmed that multiple domain impairment seems to predominate in PD-MCI and executive deficits are the most frequent ones that commonly occur (Marras et al. 2013). Executive deficits in planning, sequencing, cognitive flexibility, problem-solving and working memory reflecting frontostriatal circuits dysfunction due to either degeneration of dopaminergic nigrostriatal or mesocortical pathways have been found in PD-MCI patients (Goldman & Litvan 2011; Williams-Gray et al. 2007). Moreover, further investigations have suggested even how memory deficits in PD-MCI may be mainly due to a primary executive dysfunction accounting for strategic encoding and recall difficulties (Weintraub et al. 2011). Impairments of selective and divided attention and inhibitory control have also been reported in PD-MCI (Aarsland et al. 2011). Finally, according to Biundo et al. (2016) an unsolved question regarding the nature and progression of language impairment in PD remains: while some authors suggested that language deficits occur with executive dysfunction or impairment of selective attention or even working memory, other authors showed the presence of specific linguistic deficits without concurrent executive dysfunction.

To date, only one study directly compared performances of PD-MCI patients versus aMCI+ patients for memory domain (Pistacchi et al. 2015) without clarifying the difference about other cognitive abilities, such as attention/working memory and executive functions. The present study sought to differentiate the cognitive profile concerning attention/working memory and executive functions of PD-MCI patients and aMCI+ with structural brain changes "probably" for scientific caution suggesting preclinical AD. Particularly, with regard to executive functions, we investigated planning abilities in detail by focusing on Tower of London-Drexel Version (TOL^{Dx}) Initiation Time and Violation Time evaluating planning accuracy/ task analysis and self-monitoring/rule-bound control, respectively, because they have not been explored by previous studies on MCI in PD (Muslimovic et al. 2005, Hoops et al. 2009, Mamikonyan et al. 2009, Hanganu et al. 2014).

SUBJECTS AND METHODS

Forty PD-MCI patients, forty aMCI+ patients and twenty-two controls constituted the sample of the study. Participants were consecutively recruited by the Neurology Service of Felice Lotti Hospital in Pontedera (Pisa, Italy) from September 2013 to September 2014. PD patients were selected on the basis of patient's medical history, a review of clinical signs and symptoms, and a neurological and physical examination. MRI of the brain and DatScan were used to help rule out other disorders. The aMCI+ patients reported atrophy of the medial temporal lobe structures (i.e. hippocampus and entorhinal cortex) and frontal areas on brain magnetic resonance imaging "probably" for scientific caution, suggesting evidence of structural brain changes of preclinical AD. The severity of clinical symptoms in the PD-MCI group and motor status were assessed by Hoehn and Yahr scale (1967) and Unified Parkinson's Disease Rating Scale Part-III (Goetz et al. 2003), respectively. The PD-MCI patients were all treated with daily doses of Levodopa and Carbidopa. The patients included in the clinical groups were assessed by neuropsychologists of Hospital Psychology Unit (Area Vasta Nord Ovest Toscana, Pontedera, Pisa, Italy) according to Level II criteria of the MDS Task Force (Litvan et al. 2012) for PD-MCI and the International Working Group for aMCI+ (Winblad et al. 2004). The controls were community-dwelling volunteers from the Valdera (Pisa) area without impairment in neuropsychological tests and history of neurological or psychiatric diseases.

All the participants provided written informed consent before clinical examination and neuropsychological assessment. The study protocol was approved by the Ethic Committee of Area Vasta Nord Ovest (Pisa, Italy).

A score below 85.5 in the Milan Overall Dementia Assessment (MODA) (Brazzelli et al. 1994) was defined as the cut-off score for diagnosing a dementia syndrome for clinical groups in which Activities of Daily Living (Katz 1983) and Instrumental Activities of Daily Living (Lawton & Brody 1969) were also administered to evaluate functional impairment. First, we assessed PD-MCI and aMCI+ patients using a wide

neuropsychological battery, including: Digit Span (Spinner & Tognoni 1987) and Stroop Test (Caffarra et al. 2002) for attention/working memory; Tower of London-Drexel Version (TOL^{DX}) (Culbertson et al. 2004), and Brixton Test (Burgess & Shallice, 1997) for executive functions; 60-item Boston Naming Test (BNT) (Kaplan et al. 1983) and Category Fluency (Spinnler & Tognoni 1987) for language; Prose Recall and Pairs Associates Learning (Spinnler & Tognoni 1987) for memory; Street's Completion Test and Constructive Apraxia Test (Spinnler & Tognoni 1987) for visuospatial function.

Raw scores of neuropsychological tests used were transformed into Equivalent Scores (ES) (Capitani & Laiacona 1997, Bianchi & Dai Prà 2008), except for BNT and Brixton Test because of the absence of normative data for Italian population. The raw scores of TOL^{DX} were converted into percentiles according to examinee's age and then transformed into ES by following the correspondence to them (Table 1). To allow a better reading of our findings a comparison between ES and other standardized scores, such as z-scores and T-scores, is provided (Figure 1).

Unpaired sample T-Tests compared sociodemographic characteristics and MODA total scores of groups while a Pearson's chi-square test was used for categorical variables. Statistical Package for the Social Sciences (SPSS) 22.0 software (SPSS Inc, Chicago, IL) was used for data analysis. The distribution of the collected variables did not pass the Kolmogorov-Smirnov Test. Thus, non parametric tests (i.e., Kruskal-Wallis and Mann-Whitney U Tests) were used to compare groups performances on neuropsychological and functional measures. A p value <0.05 (Bonferroni corrected) was set to reach significance. A Spearman Rank correlation was also performed to further investigate the association between neuropsychological measures of attention/working memory and executive functions in the PD-MCI group.

Table 1. Equivalent scores and their psychometric criteria, corresponding percentiles, ability levels and clinical evaluation of performances (Capitani & Laiacona 1997, Bianchi & Dai Prà 2008, Bianchi 2013)

Equivalent Scores	Psychometric criteria	Corresponding percentiles	Ability levels	Clinical evaluation of the performances
4	Sufficient performance or superior to the norm	≥ 50°	Medium – superior	Normal
3	Largely sufficient performance	49°- 36°	Medium – inferior	Modest
2	Sufficient performance	35°- 20°	Medium – inferior	Modest
1	Performances at lower limits of the norm/borderline	19° - 5°	Medium – inferior	Modest
0	Insufficient performance	≤ 4°	Poor	Abnormal

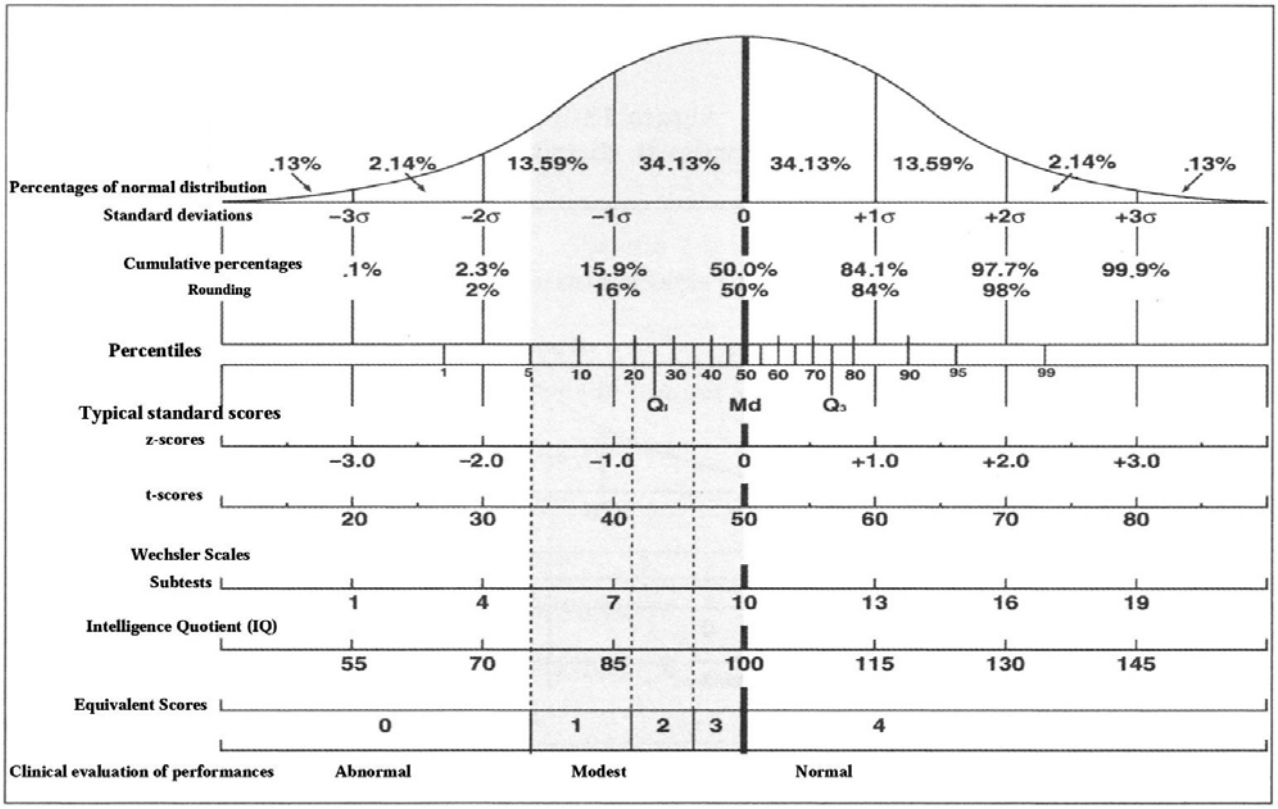

Figure 1. Correspondence between standardized scores and normal distribution. Modified from: Bianchi A: L'esame neuropsicologico dell'adulto (The neuropsychological exam of the adult). Giunti OS Publisher, Florence, 2013

RESULTS

The PD-MCI patients, the aMCI+ patients and controls were demographically matched in terms of age (PD-MCI vs aMCI+: t=1.323, p= n.s.; PD-MCI vs controls: t=1.624, p= n.s.; aMCI+ vs controls: t=1.041, p= n.s.), education (PD-MCI vs aMCI+: t=0.100, p= n.s., PD-MCI vs controls: t=0.018, p= n.s.; aMCI+ vs controls: t=-0.989, p= n.s.) and gender (χ^2=1.728, p=n.s.) (Table 2). No significant difference was found among clinical groups on MODA total score (t=0.353; p=n.s.) while PD-MCI patients and aMCI+ significantly differenced from controls in such overall screening test (PD-MCI vs controls: t=-3.661, p=0.001; aMCI+ vs controls: t=-3.557, p=0.001), as expected. The Kruskal-Wallice detected a significant performance difference for ADL and IADL among the three groups (p<0.001). Therefore, the Mann-Whitney U Test was performed and significant differences among the groups were found, as follows: PD-MCI vs controls for IADL (p=0.001), PD-MCI vs aMCI+ for ADL (p=0.001) and IADL (p=0.006). The other comparisons (i.e., PD-MCI vs controls for ADL; aMCI+ vs controls for ADL and IADL) did not show any significant difference (p= n.s.).

Descriptive analysis of the neuropsychological tests was provided (Table 3).

The Kruskal-Wallice did not reveal significant differences between performances of the three groups on Category Fluency, TOL^{DX} Move Score, Execution Time and Total Time, and Constructive Apraxia Test (p= n.s.). On the contrary, the Kruskal-Wallice revealed significant differences on TOL^{DX} Initiation Time (p=0.001) and Violation Time (p=0.001), Brixton Test (p=0.003), Digit Span (p<0.001), Stroop Interference/ Error (p=0.001), Stroop Interference/Time (p=0.001), Boston Naming Test (p<0.001), Pairs Associates Learning (p<0.001), Prose Recall (p=0.006), and Street's Completion Test (p=0.002). The comparisons between groups using the Mann-Whitney U tests (Table 4) showed that PD-MCI patients significantly reported lower scores on Digit Span (p<0.001) and Stroop Interference/Error (p=0.003) than aMCI+ patients. Such differences were corroborated by the comparison between PD-MCI patients and controls on the same tests (Digit Span: p=0.003; Stroop Interference/Error: p=0.001). Both clinical groups reported lower performance than controls on Stroop Interference/Time (PD-MCI+ vs control: p<0.001; aMCI+ vs controls, p=0.001). AMCI+, in turn, performed worse on TOL^{DX} Initiation Time (p<0.001) and Violation Time (p=0.005) than PD-MCI+ patients. Such differences were corroborated by the comparison between aMCI+ patients and controls on the same tests (TOL^{DX} Initiation Time, p=0.016 and Violation Time, p<0.001). Moreover, PD-MCI patients reported lower scores on TOL^{DX} Violation Time than controls, too (p=0.010). A significant difference was found in Brixton Test between aMCI+ patients and controls (p<0.001) but not between PD-MCI vs aMCI+ (p= n.s.) and PD-MCI vs controls (p= n.s.). On BNT, PD-MCI patients and AMCI+ patients performed significantly worse than controls (p=0.008; p≤0.001, respectively) but no significant difference was found between clinical groups (p= n.s.). Finally, aMCI+ patients reported lower performances on Street's Completion Test than PD-MCI (p=0.005) and controls (p=0.001) but no significant difference was found between PD-MCI vs controls (p= n.s.). As expected, aMCI+ patients worse performed than PD-MCI on Pairs Associates Learning (p<0.001) and Prose Recall (p=0.012) as well as than controls on the same tests (Pairs Associates Learning: p=0.001; Prose Recall: p=0.006). The comparison between PD-MCI patients and controls on these memory tests did not revel significant differences (p= n.s.).

A Spearman Rank correlation on attention/working memory and executive measures in PD-MCI group was performed. Significant positive correlations between Digit Span and Stroop Test Interference/Error (ρ=0.434, p<0.01), Stroop Interference/Error and TOL^{DX} Execution Time (ρ=0.374, p<0.05), Stroop Interference/Error and TOL^{DX} Total Time (ρ=0.454, p<0.01), Stroop Interference Error and TOL^{DX} Violation Time (ρ=0.355, p<0.05), Stroop Interference/Time and TOL^{DX} Move Score (ρ=0.336, p<0.05), Stroop Interference/Time and

Table 2. Socio-demographic characteristics of PD-MCI and aMCI+ groups: values in means±SD, sex in ratio

	PD-MCI patients (n=40)	aMCI + patients (n=40)	Controls (n=22)
Age (yrs.)	73.1±7.7	70.8±7.8	69.1±7.8
Education (yrs.)	6.1±2.9	6.2±3.1	6.8±3.2
Sex (M:F)	24:16	19:21	10:12
Onset (yrs.)	2.3±3.6	2.6±3.8	-
Hoehn & Yahr stage	1.3±0.5	-	-
UPDRS-III score	25±9	-	-
MODA total score	91.8±3.5	91.5±3.7	95.2±2.6
ADL score	6±0.0	5.5±1.2	5.9±0.1
IADL score	5.7±1.8	7.2±1.5	7.5±1

Note: PD-MCI: Parkinson's Disease-Mild Cognitive Impairment; aMCI+=Amnestic MCI multiple domain
UPDRS-III: Unified Parkinson's Disease Rating Scale Third Part; MODA= Milan Overall Dementia Assessment;
ADL=Activities of Daily Living; IADL= Instrumental Activities of Daily Living

Table 3. Descriptive analysis of the neuropsychological tests in the three groups

Neuropsychological Battery	ES: 0%			ES: 1-3%			ES: 4%			Mean±SD		
	PD-MCI	aMCI+	Controls	PD-MCI	aMCI+	Controls	PD-MCI	aMCI+	Controls	PD-MCI	aMCI+	Controls
Digit Span	18%	0%	9.1%	25%	40%	22.7%	57%	60%	68.2%			
Stroop Test												
Interference/Time	53%	47.5%	0%	30%	32.5%	50%	17%	20%	50%			
Interference/Error	65%	27.6%	6.2%	15%	27.6%	56.3%	20%	44.8%	37.5 %			
Colour reading Total time (sec.)										17.9±10.1	23.4±16.7	5±3.5
Colour naming Total time (sec.)										25.3±13.1	29.2±8.6	21.3±5.9
Interference Total Time (sec.)										50.6±13.1	48±16.6	45.7±15.5
Tower of London Drexel Version												
Move Score	34.2%	25%	11.8%	31.6%	30%	35.3%	34.2%	45%	52.9%			
Initiation Time	22.5%	45%	40.9%	15%	55%	31.8%	62.5%	0%	27.3%			
Execution Time	65.8%	70%	28.6%	23.6%	20%	50%	10.6%	10%	21.4%			
Total Time	63.2%	75%	42.9%	31.3%	20%	35.7%	5.5%	5%	21.4%			
Violation Time	68.4%	100%	28.6%	21.1%	0%	42.9%	10.5%	0%	28.5%			
Brixton Test*										29.8±9.2	32.6±3.4	25.5±7
Category Fluency	2.5%	0%	0%	52.5%	67.5%	42.9%	45.5%	32.5%	57.1%			
Boston Naming Test**										40.1±10.9	33.4±9.5	46.8±10.4
Prose Recall	12.5%	50%	0%	40%	15%	44.4%	47.5%	35%	55.6%			
Pairs Associates Learning	7.5%	60%	11.1%	67.5%	25%	55.6%	25%	15%	33.3%			
Street's Completion Test	7.5%	5.4%	4.8%	40%	78.4%	33.3%	52.5%	16.2%	61.9%			
Constructive Apraxia Test	2.5%	0%	0%	40%	42.5%	19%	57.5%	57.5%	81%			

Note: ES= Equivalent Score; ES: 0 = Abnormal performance; ES: 1-3: Modest performance; ES: 4 = Normal performance; PD-MCI: Parkinson's Disease-Mild Cognitive Impairment; aMCI+=Amnestic MCI multiple domain: *= cut-off 29/33; **cut-off 43/60.

Table 4. Comarison between groups on neuropsychological tests battery

Neuropsychological tests	p values		
Battery	PD-MCI vs aMCI+	PD-MCI vs controls	aMCI+ vs controls
Digit Span	p<0.001	p=0.003	p= n.s.
Stroop Interference/Error	p=0.003	p=0.001	p= n.s.
Stroop Interference/Time	p= n.s.	p<0.001	p=0.001
TOL^{DX} Move Score	p= n.s.	p= n.s.	p= n.s.
TOL^{DX} Initiation Time	p<0.001	p= n.s.	p=0.016
TOL^{DX} Execution Time	p= n.s.	p= n.s.	p= n.s.
TOL^{DX} Total Time	p= n.s.	p= n.s.	p= n.s.
TOL^{DX} Violation Time	p=0.005	p=0.010	p<0.001
Brixton Test	p= n.s.	p= n.s.	p<0.001
Category Fluency	p= n.s.	p= n.s.	p= n.s.
Boston Naming Test	p= n.s.	p=0.008	p<0.001
Prose Recall	p=0.012	p= n.s.	p=0.006
Pairs Associates Learning	p<0.001	p= n.s.	p=0.001
Constructive Apraxia Test	p= n.s.	p= n.s.	p= n.s.
Street's Completion Test	p=0.005	p= n.s.	p=0.001

TOL^{DX} Total Time (ρ=0.329, p<0.05), were found. All the other correlations between attention/working memory and executive measures used were not significant (i.e., Digit Span vs Stroop Interference/Time; Digit Span vs TOL^{DX} sub-scores; Digit Span vs Brixton Test; Stroop Interference/Time vs TOL^{DX} Initiation Time, Execution Time, and Violation Time; Stroop Interference/Time vs Brixton Test; Stroop Interference/Error vs TOL^{DX} Move Score and Initiation Time; Stroop Interference/Error vs Brixton Test).

DISCUSSION

Although it is well known that PPD results in a functional decline, our findings confirm investigations on IADLs impairment also in PD-MCI (Pirogovsky et al. 2014) and the importance to add measures of day-to-day functioning in the clinical evaluation of this category of patients.

Our results demonstrate that attention/working memory and executive dysfunction is specific for PD-MCI and aMCI+ patients and that PD-MCI patients mostly present a major involvement of attention/working memory domain, as shown by the comparisons between groups performances on Digit Span and Stroop Test. The first is a test frequently used as a measure of phonological loop that is assumed to be responsible for maintaining verbal-based information in Baddeley's model of working memory (1992). In order to correctly perform Digit Span, PD-MCI patients would require more attentional resources and control processes than aMCI+ patients. The latter specifically reflects the ability to inhibit a dominant response and it has often been associated to anterior cingulate cortex (Gruber et al. 2002). In comparison to aMCI+, PD-MCI patients show scarce performances in Stroop Test determined by the time needed to discard irrelevant but salient verbal information in favour of a less obvious aspect (i.e. colour naming), known as "interference effect" mostly related to committed errors (i.e. Interference/Error score) than time (i.e. Interference/Time score). Because of their greater inability to restrain interference, PD-MCI patients make more errors than aMCI+ patients in which an impairment of inhibitory control as such and regardless of errors has been shown, too (Traykov et al. 2007). Such results on Digit Span and on Stroop Interference/Error are corroborated by the significant differences between performances of PD-MCI patients and controls. However, PD-MCI patients and aMCI+ patients showed lower performances than controls on Stroop Interference/Time, by suggesting that inhibitory control represents a critical domain more frequently affected in mild cognitive disorders (cfr. Bélanger et al. 2010). Moreover, Santangelo et al. (2015) have recently suggested that among cognitive measures, the Stroop Test may be useful even for identifying patients at high risk of developing PD-MCI at the time of PD diagnosis, by suggesting that an impairment of inhibitory control might represent an early cognitive deterioration in the course of the disease.

The significant positive correlation between the Stroop Test and the Digit Span in PD-MCI group might be due to the involvement of some brain areas (i.e. left inferior frontal gyrus and anterior cingulate cortex) in activating conscious attention and mediating inhibitory control (Nee et al. 2007). These brain areas have been found to be of particular interest by neuroimaging studies investigating cognitive impairment in PD-MCI (Lee et al., 2014). Moreover, significant correlations between scores obtained in Stroop Test and in some TOL^{DX} sub-scores support that an underlying attention deficit is present in PD-MCI patients.

Finally, cognitive deficits in PD have been frequently attributed to neurochemical alteration in the dopaminergic system that is crucial for attention and working memory functioning associated to prefrontal

areas (Pillon et al. 2003) instead of a reduced choline acetyltransferase activity in temporal and frontal lobes yielding episodic memory and executive impairment in aMCI+ patients developing AD (Brandt et al. 2009; Reinvang et al. 2012).

Interestingly, despite slow psychomotor speed and resting tremor that may interfere with performance in tests requiring motor abilities such as TOL, PD-MCI patients do not show lower performances than aMCI+ in this test. PD-MCI patients significantly differed from controls in TOL^{DX} Violation Time subtest, by suggesting a weakening of executive planning efficiency but not as severe as that reported by aMCI+ patients. The results of the aMCI+ group on this subtest is in line whit a previous study that pointed out how MCI decliners show a dysfunction in self-monitoring/rule-bound control than stable MCI patients and controls (Rainville et al. 2012). Total Initiation Time, which is the time from the presentation of a test problem by the examiner to the initiation of the first problem-solving move, is more damaged in aMCI+ than PD-MCI patients accounting for a more pronounced deficit in time assumed for planning accuracy/task analysis on the moves sequence. Such a result is corroborated by the significant difference between performances of aMCI+ patients and controls on this TOL^{DX} sub-score. The cognitive planning component of executive problem-solving thought to be the central construct assessed by the TOL^{DX} and brain activity during planning is mainly associated to prefrontal areas, particularly to dorsolateral prefrontal cortex (Lazeron et al. 2000). Other constructs, such as procedural memory, which is recognized to decrease in PD, are considered to have a lesser effect on TOL^{DX} performance (Riccio 2004). Moreover, when compared to controls on Brixton Test, aMCI+ patients present a deficit of cognitive flexibility, which is recognized as a cognitive ability related to the above mentioned brain area (Chan et al. 2008). As expected, aMCI+ patients also present an episodic memory deficit, as shown by groups comparison on Prose Recall and on Pairs Associates Learning. In addition, they have a visual recognition decay, as shown by groups comparison on Street's Completion Test.

Finally, our results highlight that naming is damaged in MCI groups when compared to controls on BNT. Such a result can contribute to clarify the relationship between language and executive impairment and specify the type of linguistic deficit occurring in PD-MCI.

CONCLUSIONS

In comparison to the previous investigation (Pistacchi et al. 2015), we would stress that the present study represents a step forward in specifying the attention/working memory and executive profile of PD-MCI patients in comparison to aMCI+ ones and also contributes to an informative analysis of specificity and validity of the PD-MCI clinical entity. PD-MCI patients may present a defect of conscious attention and an inhibitory control deficit conversely to a scarce self-monitoring/rule-bound and time assumed for planning accuracy that characterize aMCI+ patients. Such differences have been discussed according to neurochemical alterations and neural circuits differently involved in PD and AD.

Neurologists and neuropsychologists are likely to be managing an increasing number of PD-MCI patients in the near future. A reliable testing of attention/working memory and executive functions including Digit Span, Stroop Test, TOL^{DX} should be integrated in clinical practice for the evaluation of MCI patients with different aetiologies.

Currently, non-pharmacological interventions have attracted increasing interest for enhancing cognitive functioning in PD patients without dementia. In the light of our findings, PD-MCI patients with a specific pattern of deterioration in attention/working memory domain should undergo cognitive training which researchers showed to be effective in maintaining and improving cognitive abilities. In a randomized control trial (Petrelli et al., 2014), 65 patients with PD were allocated to one of two cognitive multi-component treatments (a structured training, named "NEUROvitalis" -NV- and a non-structured one, named "Mentally Fit" -MF-, each including 12 group sessions of 90 minutes over 6 weeks) or a waiting list control group (CG). The NV includes individual tasks, group tasks and group games each focusing on specific cognitive functions (i.e., attention, memory, executive functions) whereas in MF cognitive domain training was not addressed in focus sections but over the course of the program and differently from NV. Compared to the CG, patients from NV group improved in short-term memory and working memory. Moreover, the NV group significantly improved more in working memory than MF group. With 1-year follow-up of 45 on 65 original patients (Petrelli et al. 2015), researchers concluded that both cognitive trainings yield a stabilization of overall cognitive functions and a reduced risk of developing MCI.

Our study should be implemented by the collection of more extensive data to let researchers infer more robust conclusions and generalizability of the findings. Moreover, significant statistical differences of groups performances should be interpreted with caution. The use of ES allows the comparability among many neuropsychological tests adopting this kind of scoring net of age, sex and education. However, this statistical model presents some limitations due to large scoring categories (i.e. 0-4) that depend on tolerance limits and inferential error risk, sample size variability and the linear model used for adjusting scoring by considering the effects of age, sex and education.

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Conflict of interest:

The authors declare that they are the investigators for Pisa Italian site of the MDS PD-MCI Study Group and that the study was supported by the Michael J. Fox Foundation for Parkinson's Research and Parkinson Vereeniging (Dutch Parkinson Association).

Contribution of individual authors:

Davide Maria Cammisuli & Marco Timpano Sportiello equally contributed indesign of study, literature searches and analyses, statistical analyses and interpretation of resuls.

References

1. *Aarsland D, Bronnick K, Fladby T: Mild Cognitive Impairment in Parkinson's Disease. J Mov Disord 2011; 11:371–8.*
2. *Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al.: The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's Dement 2011; 7:270–9.*
3. *Baddeley A: Working Memory. Science 1992; 255:556–9.*
4. *Bélanger S, Belleville S & Gauthier S: Inhibition impairments in Alzheimer's disease, mild cognitive impairment and healthy aging: Effect of congruency proportion in a Stroop task. Neuropsychologia 2010; 48:581-90.*
5. *Bianchi A, Dai Prà M: Twenty years after Spinnler and Tognoni: New instruments in the Italian neuropsychologist's toolbox. Neurol Sci 2008; 29:209-17.*
6. *Bianchi A: L'esame neuropsicologico dell'adulto: Applicazioni cliniche e forensi. Giunti OS, Firenze, 2013.*
7. *Biundo R, Weis L, & Antonini A: Cognitive decline in Parkinson's disease: the complex picture. NPJ Parkinsons Dis 2016; 2:16018.*
8. *Brandt J, Aretouli E, Neijstrom E, Samek J, Manning K, Albert MS et al.: Selectivity of executive function deficits in mild cognitive impairment. Neuropsychology 2009; 23:607-18.*
9. *Brazzelli M, Capitani E, Della Sala S, Spinnler H & Zuffi M: A neuropsychological instrument adding to the description of patients with suspected cortical dementia: the Milan overall dementia assessment. Journal of Neurol, Neurosurg & Psychiatry 1994; 57:1510-17.*
10. *Burgess P & Shallice T: The Hayling and Brixton Tests. Test Manual. Thames Valley Test Company, Bury ST Edmunds United Kingdom.*
11. *Cammisuli D, Timpano Sportielo M, Danti S: Impairment of instrumental extra-memory functions in patients suffering from Mild Cognitive Impairment [Danneggiamento delle funzioni strumentali extra-mnesiche in pazienti affetti da Mild Cognitive Impairment]. G Gerontol 2012; 60:255-63.*
12. *Cammisuli D, Innocenti A, Franzoni F & Pruneti C: Aerobic excersise effect upon cognition in Mild Cognitive Impairment: a systematic review of randomized controlled trials. Arch Ital Biopl 2017; 155:54-6.*
13. *Caffarra P, Vezzadini G, Dieci F, Zonato F & Venneri A: Una versione abbreviate del test di Stroop: Dati normative della popolazione italiana. Nuova Rivista di Neurologia 2002; 12:111-15.*
14. *Calleo J, Burrows C, Levin H, Marsh L, Lai E & York MK: Cognitive rehabilitation for executive dysfunction in Parkinson's disease: Application and current directions. Parkinsons Dis 2012; 512892.*
15. *Capitani E & Laiacona M: Composite neuropsychological batteries and demographic correction: standardization based on equivalent scores, with a review of published data. The Italian Group for the Neuropsychological Study of Ageing. J Clin Exp Neuropsychol 1997;19:795-809.*
16. *Chan RC, Shum D, Toulopoulou T & Chen EY: Assessment of executive functions: Review of instruments and identification of critical issues. Arch Clin Neuropsychol 2008; 23:201-16.*
17. *Culbertson W, Moberg P, Duda J, Stern M & Weintraub D: Assessing the executive function deficits of patients with Parkinson's disease: Utility of the Tower of London-Drexel. Assessment 2004;11:27-39.*
18. *Federico A, Maier A, Vianello G, Mapelli D, Trentin M, Zanette G et al.: Screening for Mild Cognitive Impairment in Parkinson's Disease: Comparison of the Italian Versions of Three Neuropsychological Tests. Parkinsons Dis 2015; 681976.*
19. *Geurtsen GJ, Hoogland J, Goldman JG, Schmand BA, Tröster AI, Burn DJ et al.: Parkinson's disease mild cognitive impairment: Application and validation of the criteria. J Parkinsons Dis 2014; 4:131-7.*
20. *Goetz CC: The Unified Parkinson's Disease Rating Scale (UPDRS): Status and recommendations. Mov Disord 2003; 18:738-50.*
21. *Goldman JG & Litvan I: Mild cognitive impairment in Parkinson's disease. Minerva Med 2011; 102:441-59.*
22. *Gruber S, Rogowska J, Holcomb P, Soraci S & Yurgelun-Todd D: Stroop performance in normal control subjects: an fMRI study. Neuroimage 2002; 16:349-60.*
23. *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; 137:1120-29.*
24. *Hoehn M & Yahr M: Parkinsonism: onset, progression, and mortality. Neurology 1967; 57(10 Suppl. 3): S11-26.*
25. *Hoogland S, Boel SA, de Bie RMA, Geskus RM, Schmand BA, Dalrymple-Alford SC, Marras C, Adler CH, Goldman SG, Tröster AL, Burn DS, Litvan I, Geurtsen GS, MDS Study Group „Validation of mild cognitive impairment in Parkinson's disease": Mild cognitive impairment as risk factor for Parkinson's disease dementia. Mov disord 2017; 32:1056-65.*
26. *Hoops BA, Nazem BA, Siderowf AD, Duda JE, Xie SX, Stern MB, Weintraub MD: Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson's Disease. Neurology 2009; 73:1738-45.*

27. Kaplan E, Goodglass H & Weintrabs: The Boston Naming Test. Lea & Febiger, Philadelphia, 1983.
28. Katz S: Assessing self-maintenance activities of daily living, mobility, and instrumental activities of daily living. J Am Geriatr Soc 1983; 31:721-7.
29. Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC et al.: Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 2012; 27:349-56.
30. Lazeron RHC, Rombouts SARB, Machielsen WCM, Scheltens P, Witter MP, Uylings HBM et al.: Visualizing brain activation during planning: The Tower of London test adapted for functional MR imaging. Am J Neuroradiol 2000; 21:1407-14.
31. Lawton MP & Brody EM: Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179-86.
32. Lee JE, Cho KH, Song SK, Kim HJ, Lee HS, Sohn YH & Lee PH: Exploratory analysis of neuropsychological and neuroanatomical correlates of progressive mild cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry 2014; 85:7-16.
33. Mamikonyan E, Moberg PJ, Siderowf A, Duda JE, Have TT, Hurting HI et al.: Mild cognitive impairment is common in Parkinson's disease patients with normal Mini-Mental State Examination (MMSE) score. Parkinsonism Relat Disord 2009; 15:226-31.
34. Marras C, Armstrong MJ, Meaney C, Fox S, Rothberg B, Reginold W et al.: Measuring mild cognitive impairment in patients with Parkinson's disease. Mov Disord 2013; 28:626-33.
35. Muslimović D, Post B, Speelman JD & Schmand B: Cognitive profile of patients with newly diagnosed Parkinson's disease. Neurology 2005; 65:1239-45.
36. Nee DE, Wager TD & Jonides J: Interference resolution: insights from a meta-analysis of neuroimaging tasks. Cogn Affect Behav Neurosci 2007; 7:1-17.
37. Palavra NC, Naismith SL & Lewis SJG: Mild cognitive impairment in Parkinson's disease: A review of current concepts. Neurol Res Int 2013; 576091.
38. Petersen RC, Caracciolo B, Brayne C, Gautheir S, Jelic V & Fratiglioni I: Mild Cognitive Impairment: a concept in evolution. J Int Med 2014; 275:214-28.
39. Petersen RC, Roberts RO, Knopman DS, Boeve BF, Yonas E, Ivnik RJ et al.: Mild cognitive impairment: Ten years later. Arch Neurol 2009; 66:1447-55.
40. Petersen RC & Negash S: Mild cognitive impairment: an overview. CNS Spectr 2008;13:45-53.
41. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG & Kokmen E: Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999; 56:303-8.
42. Petrelli A, Kaesberg S, Barbe MT, Timmermann L, Fink GR, Kessler J et al.: Effects of cognitive training in Parkinson's disease: a randomized controlled trial. Parkinsonism Relat Disord 2014; 20: 1196-1202.
43. Petrelli A, Kaesberg S, Barbe MT, Timmermann L, Rosen JB, Fink GR et al.: Cognitive training in Parkinson's disease reduces cognitive decline in the long term. Eur J Neurol 2015; 22:640-7.
44. Phillips LH, Kliegel M, Martin M: Age and planning tasks: The influence of ecological validity. Int J Aging Hum Dev 2006; 62:175-84.
45. Pillon B, Czernecki V & Dubois B. Dopamine and cognitive function. Curr Opin Neurol 2003; 16(Suppl 2):S17-22.
46. Pirogovsky E, Schiehser DM, Obtera KM, Burke MM, Lessig SL, Song DD et al.: Instrumental activities of daily living are impaired in Parkinson's disease patients with mild cognitive impairment. Neuropsychology 2014; 28:229.
47. Pistacchi M, Gioulis M, Contin F, Sanson F & Marsala SZ: Cognitive profiles in Mild Cognitive Impairment (MCI) patients associated with Parkinson's disease and cognitive disorders. Ann Indian Acad Neurol 2015; 18:200-5.
48. Rainville C, Lepage E, Gauthier S, Kergoat M-J & Belleville S: Executive function deficits in persons with mild cognitive impairment: A study with a Tower of London task. J Clin Exp Neuropsychol 2012; 34:306-24.
49. Reinvang I, Grambaite R & Espeseth T: Executive dysfunction in MCI: Subtype or early symptom. Int J Alzheimers Dis 2012; 936272.
50. Riccio CA, Wolfe ME, Romine C, Davis B, Sullivan JR: The Tower of London and neuropsychological assessment of ADHD adults. Arch Clin Neuropsycholog 2004; 19:661-71.
51. Santangelo G, Vitale C, Picillo M, Moccia M, Cuoco S, Longo K et al.: Mild Cognitive Impairment in newly diagnosed Parkinson's disease: A longitudinal prospective study. Parkinsonism Relat Disord 2015; 21:1219-26.
52. Spinnler H & Tognoni G: Standardizzazione e taratura di test neuropsicologici. Gruppo Italiano per lo studio Neuropsicologico dell'Invecchiamento. It J Neurol Sci 1987; Suppl 8.
53. Traykov L, Raoux N, Latour F, Gallo L, Hanon O, Baudic S et al.: Executive functions deficit in mild cognitive impairment. Cogn Behav Neurol 2007; 20:219-24.
54. 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; 68:1562-68.
55. Williams-Gray CH, Foltynie T, Brayne CEG, Robbins TW & Barker RA: Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007; 130:1787-98.
56. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L-O et al.: Mild cognitive impairment-beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004; 256:240-6.

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