Predictors And Patterns of Cognitive Decline Differ between Mild Cognitive Impairment in Parkinson’s Disease (PD-MCI) And Alzheimer’s Disease (AD-MCI)

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Introduction

Mild cognitive impairment (MCI) represents a transitional state between normal cognitive ageing and dementia. Although MCI was initially conceptualized with an emphasis on memory impairment, it is now recognised to be heterogeneous in terms of etiology and prognosis. As such, the focus on MCI has broadened beyond the scope of Alzheimer’s disease (AD), and is now increasingly recognised as an early symptom of other neurological conditions, such as Parkinson’s disease (PD) [1].

Although PD is traditionally known for its characteristic motor impairments, non-motor symptoms such as cognitive deficits are increasingly being recognised for their important implications on prognosis and poorer clinical outcomes such as lower quality of life [2], higher rates of institutionalization [3], and early mortality [4]. At any given time, about one in every four PD patients (27%) meets the criteria for PD-MCI [5-6], and approximately 20-60% of non-demented PD patients developed Parkinson’s disease dementia (PDD) over two to five years [5]. As such, greater efforts are being made to elucidate the early cognitive impairments in PD patients.

The literature on the cognitive profile of PD-MCI has thus far been inconclusive. Relative to healthy controls, impairments across a range of cognitive domains has been reported, including memory, attention, executive functions, language and visuospatial functioning [5-7]. While some studies demonstrate that executive dysfunctions are
a prominent feature of PDD, there are contrasting findings suggesting memory and visuospatial deficits to be the predominant cognitive deficits in PD [6,7]. The increased risk of dementia accompanying MCI warrants greater investigations to elucidate the early-stage characteristics and trajectory of cognitive decline.

Given the neuropathological differences between the degenerative processes of AD and PD, the profiles and progression of early cognitive impairment in the two diseases may manifest differently. However, little is known about the predictors of cognitive decline between these different MCI subtypes. As such, this present study investigates not just the differences in profiles and progression of cognitive impairment between AD-MCI and PD-MCI, but is also the first known study comparing the factors predicting cognitive decline in the two groups. We hypothesize that greater frontal-based cognitive functions such as attention and executive function, as well as visuospatial functions, would be more severely impaired, and see greater decline over time in PD-MCI, as compared to AD-MCI, which we expect to display mainly amnestic deficits. Further, we hypothesize that cognitive decline in each MCI subtype will be associated with differing predictors, whereby AD-MCI will be more heavily influenced by age and apolipoprotein E4 (APOE4) status, compared to PD-MCI.

Neuropsychological Assessment

Global cognitive function was evaluated using the Mini Mental State Examination (MMSE) [11] and Montreal Cognitive Assessment (MoCA) [12]. Episodic memory was measured using the immediate and delayed 10-word recall tasks from the Alzheimer’s Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) [13]. Attention was assessed using the Color Trails Test 1 (CTT1) [14], and Digit Span. Executive functions was measured using the Frontal Assessment Battery (FAB) [15], and Color Trails Test 2 (CTT2) [14]. Visuospatial function was assessed using the Sunderland’s Clock Drawing Test [16] and the constructional praxis task from ADAS-Cog [13]. Language was assessed using the ADAS-Cog naming task [13] and semantic fluency. The standardized battery was administered both at baseline and follow-up by trained psychologists, following established guidelines.

APOE Genotyping

Blood samples were collected from participants, and DNA was extracted using QiAamp® DNA Blood Maxi Kit (Qiagen GmbH, Hilden, Germany). APOE genotyping was performed using TaqMan SNP genotyping assay and ABI 7900HT PCR system (Applied Biosystems, Foster City, GA).

Statistical Analysis

Statistical analysis was performed using SPSS (Version 20.0, SPSS, Inc, Chicago, IL, USA). PD-MCI and AD-MCI were compared on demographic characteristics and vascular risk factors using independent t-tests (for normally distributed data), Mann-Whitney U tests (for nonparametric data), and Chi-square tests of independence (for categorical variables). The two groups were compared on baseline cognitive domain scores and cognitive change scores using analysis of covariance (ANCOVA), controlling for the potential confounders of gender, age, ethnicity, years of education, vascular risk factors and duration between testing (for change score analysis), and correcting for multiple comparisons using Bonferroni correction. Predictors of cognitive decline were also compared by performing logistic regression for AD-MCI and PD-MCI separately. Univariate logistic regression analysis was performed for each hypothesized predictor. As earlier work found that the traditional p-value cut-off of 0.05 can fail in identifying predictors known to be important, we adopted a p-value cut-off of 0.20, as suggested by Hosmer and Lemeshow [17]. Significant variables were included in multivariate analysis. Logistic regression was adjusted to control for baseline global cognition. Significance was set at a two-tailed probability value of 0.05.

To compute cognitive domain scores, raw scores of each neuropsychological test were first converted to z-scores based on means and standard deviations derived from a separate cohort of healthy controls (n=66 recruited from the local community; CDR global score of 0; mean age 63.29). The z-scores of the tests in each respective cognitive domain were then averaged to yield composite scores and changes in cognitive functioning in each domain were computed within-subject.

Results

Characteristics of Study Population

A total of 127 participants (AD-MCI: 67, PD-MCI: 60) were
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were significantly more impaired in PD-MCI, namely the CTT1, measures of attention and executive functions observed between AD-MCI and PD-MCI in measures of global factors. Findings demonstrate that no significant differences were comparable in age, years of education, and vascular risk factors. For longitudinal change scores, analysis is also adjusted for duration between testing.

Baseline Cognitiona
Global MMSE 27.03 (1.83) 26.87 (2.8) .601
MoCA 25.43 (2.61) 24.85 (3.56) .171
Episodic Memory ADAS Delayed Recall (-) 2.94 (2.04) 2.69 (2.21) .683
ADAS Immediate Recall (-) 3.42 (1.61) 3.43 (1.68) .817
Attention Color Trails Test 1 (in secs) (-) 69.61 (28.84) 85.65 (42.50) .008*
Digit Span Forward 9.41 (2.09) 10.37 (2.33) .070
Digit Span Backward 7.92 (2.35) 6.19 (2.17) <.001**
Executive Function FAB 16.00 (2.80) 15.53 (2.18) .118
Color Trails Test 2 (in secs) (-) 131.55 (47.54) 160.56 (76.10) .007*
Visuospatial Sunderland Clock 8.72 (2.04) 8.47 (2.27) .548
Constructional Praxis (-) 0.29 (0.58) 0.34 (0.48) .295
Language ADAS-Cog Naming (-) 0.56 (0.77) 0.69 (0.73) .610
Verbal Fluency (Fruits) 13.90 (4.98) 12.48 (3.73) .132

* Chi-square test
a ANCOVA adjusting for gender, age, ethnicity, years of education, and vascular risk factors
b (-) refers to tests whereby a higher score denotes poorer performance

included in the analyses (Table 1). The mean age of the cohort was 66.1 years (SD 7.76), while the mean number of years of education was 10.8 years (SD 3.40). Majority of participants were Chinese (94.4%), and 59.1% were male. For PD-MCI participants, mean H&Y score was 1.94 (SD 0.37). PD-MCI and AD-MCI participants were comparable in age, years of education, cardiovascular risk factors. However, there were a significantly larger proportion of males in the PD-MCI group, compared to the AD-MCI group.

Raw cognitive scores are also presented in (Table 1). ANCOVA was conducted controlling for the potential confounders of gender, age, ethnicity, years of education, and vascular risk factors. Findings demonstrate that no significant differences were observed between AD-MCI and PD-MCI in measures of global cognition, episodic memory, visuospatial function, and language. On the other hand, measures of attention and executive functions were significantly more impaired in PD-MCI, namely the CTT1, Digit Span Backwards, and CTT2.

<table>
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<th>Table 1: Demographic characteristics of participants.</th>
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<td>Gender, % Male</td>
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<tr>
<td>Age, Mean ± SD</td>
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<td>Education, Mean years ± SD</td>
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<td>APOE-ε4 status, % Positive</td>
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Cognitive Profile and Changes
PD-MCI and AD-MCI were compared on cognitive domain scores (Table 2). Controlling for potential confounding variables such as gender, age, ethnicity, education, and vascular risk factors, ANCOVA analysis demonstrated that PD-MCI participants performed worse than AD-MCI participants in the domains of attention (p<.010), executive function (p=.002), and visuospatial function (p=.031). Performance in the domains of global cognition, episodic memory, and language were comparable between PD-MCI and AD-MCI (p>.05).

Cognitive domain change scores were also compared, controlling for gender, age, race, education, vascular risk factors, baseline cognitive scores, and duration between baseline and follow-up using ANCOVA analysis. There were no significant differences in change scores in any of the cognitive domains.

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<th>Table 2: Differences in baseline cognitive scores and longitudinal change scores between mild cognitive impairment in Alzheimer’s disease (AD-MCI) and Parkinson’s disease (PD-MCI) Note: ANCOVA controlling for gender, age, ethnicity, years of education, and vascular risk factors. For longitudinal change scores, analysis is also adjusted for duration between testing</th>
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<td>Global Cognitive</td>
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Change in domain z-scores between baseline and follow-up
Global Cognitive 0.11 (1.48) -0.06 (1.33) .456
Episodic Memory 0.25 (1.09) 0.23 (0.70) .996
Attention 0.01 (0.67) -0.08 (0.62) .619
Executive Function 0.03 (1.31) 0.27 (2.20) .514
Visuospatial Function -0.25 (1.28) 0.21 (1.27) .164
Language 0.24 (1.07) 0.09 (0.86) .350

* p < .05, ** p < .01

Predictors of Cognitive Decline
For AD-MCI participants, univariate logistic regression analysis identified older age, presence of the APOE-ε4 allele (APOE4), and history of smoking to be predictive of global cognitive decline (Table 3). These variables were run in a multivariate logistic regression analysis. The resultant multivariate logistic regression model was statistically significant, χ²(3) = 12.41, p=.011. The model explained 30.2% (Nagelkerke R²) of the variance in cognitive decline and correctly classified 75.5% of AD-MCI cases. Older age (OR: 1.11 [1.01, 1.23]) and the presence of the APOE4 allele (OR: 10.00 [1.65, 60.58]) were significant predictors of cognitive decline over one year.

For PD-MCI participants, older age, diabetes, and hypertension were identified by univariate logistic regression analysis as potential predictors of cognitive decline and were included in the multivariate model. However, the multivariate logistic regression model was not statistically significant, χ²(3) = 7.54, p=.057. The model explained 17.2% (Nagelkerke R²) of the variance in
cognitive decline and only correctly classified 62.1% of PD-MCI cases.

**Discussion**

In this longitudinal study, we demonstrated that MCI in PD and AD were distinct in cognitive profiles, and had different predictors of cognitive decline. Compared to AD-MCI, PD-MCI participants displayed greater baseline deficits in attention, executive functions, and visuospatial functions. However, no distinct differences in cognitive change were observed between the two groups during the follow-up period of one year. Importantly, predictors of cognitive decline in AD-MCI, namely age and APOE4, were not similarly predictive of cognitive decline in PD-MCI.

Compared to AD-MCI, the cognitive deficits in PD-MCI were demonstrated to be more subcortical in nature, displaying greater dysfunctions in the domains of attention, executive function, and visuospatial functioning. These findings provide additional support for the position that the deficits in PD-MCI are predominantly in the domain of executive and visuospatial dysfunctions [16, 17]. However, one contrasting study found no differences on measures of attention and executive functions – this could perhaps be attributed to the study’s recruitment from Alzheimer’s Disease Centres (ADC), which typically focus on early cognitive impairment in Alzheimer’s disease. The Braak staging system also describes early pathology in the basal forebrain, which is responsible for selective attention [23-24]. Taken together, these further support the position that executive functions do not rely primarily on the frontal lobes, but may be mediated by connections with other brain regions such as the brain stem [24], and suggest an opportunity to further investigate the neuropathology of executive dysfunctions through comparisons of early cognitive impairments in AD and PD.

Deficits in the cholinergic and dopaminergic systems may also further explain the differences in cognitive profiles. The dopamine system is believed to regulate attention, executive functions, and visuospatial functions [25-26]. Given the well-documented reductions in dopamine in PD, but not AD, this might account for the greater deficits in attention and executive functions in PD-MCI. Reduced acetylcholinesterase is also associated with impaired executive functions [26-27]. Consequently, PET studies have found greater cortical and subcortical cholinergic deficits in PD than in AD [28], which may also explain the greater executive and visuospatial dysfunctions in PD-MCI compared to AD-MCI.

This present study is also one of the first to compare the course of cognitive change between AD-MCI and PD-MCI. However, after one year of follow-up, AD-MCI and PD-MCI participants did not display any observable differences in cognitive change scores in any of the domains measured. This was discrepant with findings by Besser and colleagues (2016), where PD-MCI performed better than AD-MCI over time in terms of global cognition, memory, attention, and language [29]. The contrasting findings could be explained by the significantly poorer baseline global cognition and episodic memory in their AD-MCI group, which have been found to be predictive of greater cognitive decline over time [29]. As baseline cognition was not controlled for in their...
study, this could account for the greater cognitive decline in AD-MCI compared to PD-MCI observed.

To our knowledge, this study is the first to compare the predictors of cognitive decline between AD-MCI and PD-MCI. In AD-MCI, older age, the presence of the APOE4 allele, and having a history of smoking were predictive of cognitive decline following one year. However, in multivariate analysis, only age and APOE4 status significantly predicted cognitive decline one year later – this finding has been similarly demonstrated in previous studies [29-30]. That being said, these factors were not able to predict cognitive decline in PD-MCI. Within our PD-MCI sample, age, diabetes and hypertension were identified as significant predictors of cognitive decline in univariate logistic regression analysis. However, in multivariate analysis, none of the studied variables were able to predict cognitive decline, including degree of motor impairment, which was in line with previous findings [31]. The lack of significant predictors of cognitive decline in PD-MCI may stem from the heterogeneity of PD-MCI, and suggests that the factors often used to predict cognitive decline in AD-MCI should not be blindly applied to PD-MCI. Further research should study the different subtypes of PD-MCI separately to shed light on the cognitive profiles, trajectory, and predictors of cognitive decline in the various subtypes.

Strengths of our study include its longitudinal research design, the use of a comprehensive neuropsychological assessment, the well-defined sample of PD-MCI participants diagnosed by neurologists using the criteria recommended by the MDS Task Force, and the use of MRI to support the diagnosis of AD-MCI. Limitations include the modest sample size and relatively short follow-up period which did not allow us to study progression to dementia. The lack of more specific amyloid biomarkers to confirm AD pathology was also a limitation. However, as classifications in this study adhered to well-established diagnostic guidelines and required established PD motor features in PD-MCI and medial temporal atrophy in AD-MCI, we are confident that the two groups represent PD-MCI and AD-MCI respectively. Additionally, due to the motor severity exclusion criteria, we were unable to determine the trajectory and predictors of cognitive decline in cases of advanced PD. Findings of this study can be strengthened by following a larger sample size over a longer duration of time, and the inclusion of various PD-MCI subtypes.

Implications of these present findings include creating a greater understanding of the cognitive profiles and the predictors of cognitive decline that set PD-MCI apart from AD-MCI. These findings may help clinicians come to earlier and more accurate detection of individuals at greater risk of disease progression. Given the heterogeneity of MCI, the accurate characterization of the various etiologies of MCI is vital in informing clinical care and disease management. Findings also emphasize the importance of inquiring about cognitive problems or changes even early in the course of PD. This may also have implications on the development of novel therapeutic interventions to slow or prevent further cognitive deterioration in PD-MCI which substantial affects patients’ quality of life, more so than their motor impairments.

Conclusions

Neuropathological differences in the degenerative processes behind AD and PD suggest that early cognitive impairment in the two diseases may manifest and progress differently. The present study demonstrated a predominance of executive and visuospatial dysfunctions in PD-MCI, surpassing those observed in AD-MCI. Furthermore, the factors predicting cognitive decline in AD-MCI (age and APOE4 status) were not applicable in PD-MCI.