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ORIGINAL ARTICLE

Disproportionate Decline of Executive Functions in Early Mild Cognitive Impairment, Late Mild Cognitive Impairment, and Mild Alzheimer's Disease

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Background and Purpose Many literatures indicate that executive dysfunction exists in mild cognitive impairment (MCI) as well as Alzheimer's disease (AD). However, there are few studies that found how early the deficits of the executive function (EF) exist in MCI. The present study investigated the presence of executive dysfunctions in the earliest stage of MCI, and the sub-domains of EF which are disproportionately impaired earlier than others.

Methods The participants were 41 normal elderly (NE), 86 with amnestic multi-domain MCI, and 41 with mild AD. The MCI group was further sub-divided into two groups: Early MCI (EMCI, *n*=45) and late MCI (*n*=41), based on the Clinical Dementia Rating-Sum of Boxes. All participants were given neuropsychological tests to assess the sub-domains of EF, such as verbal fluency, psychomotor speed, inhibitory control, and mental set-shifting.

Results Impairment of semantic fluency was observed in EMCI, with gradual worsening as cases approached mild AD. Phonemic fluency and psychomotor speed were also impaired at the early stage of MCI relative to the NE, but maintained at the same level up to mild AD. EMCI exhibited the same degree of performance with NE for inhibitory control and mental set-shifting; however, they progressively worsened from EMCI to mild AD.

Conclusions These results suggest that impairments of EF exist even in the earliest stage of the MCI, with a disproportionate decline in the sub-domains of EF.

Key Words mild cognitive impairment, Alzheimer's disease, executive function, verbal fluency, psychomotor speed, inhibitory control, mental set-shifting.

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INTRODUCTION

Executive function (EF) refers to "higher-level" cognitive functions involved in the control and regulation of "lower-level" cognitive processes and goal-directed, future-oriented behaviors.[1] EFs include planning, abstract reasoning, processing speed, working memory, cognitive flexibility, set-shifting, inhibitory control, and generative fluency.[1] Executive dysfunction is a crucial feature of several neurodegenerative disorders such as fronto-temporal dementia (FTD), Parkinson's disease (PD), and progressive supranuclear palsy (PSP).[2]

For many years, Alzheimer's disease (AD) had been known to have memory dysfunction as an initial and prominent symptom, with the executive function being relatively spared in the early stage of the disease.[3] In recent years, however, researchers reported that even mild AD patients exhibit impairments in a variety of EF tests, and over a 2-year period, mild

AD with dysexecutive clinical phenotype progresses more rapidly than AD with amnestic phenotype.[4] Previous studies have also shown that deficits in EF are common even in amnestic mild cognitive impairment (aMCI).[5-9] A growing body of evidence has shown that aMCI combined other cognitive deficits leads to greater risk for conversion into AD, than in the case of memory dysfunction alone.[10] Rozzini et al.[11] found that aMCI patients with worsening of EF and functional status but not of memory, were more likely to progress to AD at a 1-year follow up.

Some researchers demonstrated that the Clinical Dementia Rating-Sum of Boxes (CDR-SB) is a more detailed quantitative general index for staging of severity of dementia than the CDR-Global Score (CDR-GS), and is more accurate for tracking changes across time.[12,13] O'Bryant et al.[14] suggested that CDR-GS of 0.5 does not represent a homogeneous group, and CDR-SB score of 2.5 may have potential for discriminating between MCI (questionable impairment) and very early AD with CDR-GS of 0.5. Moreover, the Alzheimer's Disease Neuroimaging Initiative (ADNI Go and ADNI 2) sub-categorized MCI into early MCI (EMCI) and late MCI (LMCI), to predict conversion into AD and to develop intervention strategies for the earliest stages of the disease.[15]

Although the aforementioned literatures consistently indicate the relationship between executive dysfunction and aMCI as well as AD, there is a lack of research that indicates how early the deficits of EF exist in aMCI. The present study investigated whether executive dysfunctions occur in the earlier stage of aMCI (EMCI), and which sub-domains of EF are disproportionately impaired earlier than others.

METHODS

Participants

Forty-one community-dwelling elders [normal elderly (NE)], without subjective memory complaints, voluntarily participated in the study from July 2015 to September 2015. All were screened based on Christensen's health screening criteria[16] and a total score on the Korean-Mini Mental State Examination (K-MMSE)[17] higher than the 16th percentile. The patients with cognitive impairments were selected from the patients who visited the Department of Neurology at Hallym University Sacred Heart Hospital from July 2013 to April 2015. Patients who had a stroke, significant ischemic changes on brain MRI, movement problems, or salient personality changes, were excluded. Eighty-six patients with amnestic multi-domain MCI (aMCI) met Petersen's criteria for MCI,[18] and 41 patients with mild AD, met the clinical criteria for probable AD proposed by the NINCDS-ADRDA.[19] All patients underwent brain MRI. Additionally, based on the CDR-SB, 86 aMCI patients with a CDR-GS of 0.5 were classified into EMCI (n=45, CDR-SB: 0.5–2.0) and LMCI (n=41, CDR-SB: 2.5–4.0) subgroups.

Materials and procedure

All participants were administered the Seoul Neuropsychological Screening Battery, 2nd Edition (SNSB-II)[20] by trained neuropsychologists, which included measures of attention, language, visuospatial, memory, and frontal/executive functions, as well as the K-MMSE and CDR. We adopted the subtests of frontal/executive function in the SNSB-II for the present study: Go-No go Test, Korean-Color Word Stroop Test (K-CWST), Controlled Oral Word Association Test (COWAT: Semantic and phonemic fluency), Digit Symbol Coding (DSC), and Korean-Trail Making Test-Elderly's version (K-TMT-E). The score on each test was converted to a standardized z-score, except for the Go-No go test and K-CWST: Word, where raw scores were used.

Statistical analysis

An ANOVA and chi-square test were used to detect group differences for demographic variables such as age, education, and sex. We performed a multivariate analysis of variance (MANOVA) on the z-scores of each test measure. In addition, we did post-hoc analyses with *Bonferroni* correction for multiple comparisons to analyze group differences. All p-values were two-tailed, and statistical significance was accepted at $p<0.05$.

RESULTS

Characteristics of demographic variable, K-MMSE and CDR-SB

Demographic variables, K-MMSE score and CDR-SB of the NE, aMCI, and mild AD are presented in Table 1. There were no significant group differences among the NE, aMCI, and mild AD with regards to age, sex, and education. However, significant group differences were observed in the total score of K-MMSE ($F_{(3, 164)}=52.73$, $p<0.001$) and CDR-SB ($F_{(2, 124)}=54.56$, $p<0.001$). Results of the post-hoc analysis indicated mild AD with the lowest score on the K-MMSE, and the highest score on the CDR-SB. Post-hoc analysis also revealed significant differences between the EMCI and LMCI; the LMCI exhibited poorer performance on the K-MMSE and had a greater score on the CDR-SB than the EMCI, respectively. The NE showed significantly higher score on K-MMSE than the EMCI.

Profile of executive functions

The EF performances of the four groups included in the

study are shown in Table 2. MANOVA revealed a significant difference among groups on EF tests (λ=0.41, $F_{(3, 164)}$=6.04, p<0.001). Significant group differences were observed in COWAT: Animal ($F_{(3, 164)}$=18.86, p<0.001), COWAT: Supermarket ($F_{(3, 164)}$=24.61, p<0.001), COWAT: Phonemics ($F_{(3, 164)}$=12.00, p<0.001), DSC ($F_{(3, 164)}$=10.14, p<0.001), Go-No go Test ($F_{(3, 164)}$=9.78, p<0.001), K-CWST: Color ($F_{(3, 164)}$=10.69, p<0.001), and K-TMT-E: Part B ($F_{(3, 164)}$=14.45, p<0.001), but not for K-CWST: Word and K-TMT-E: Part A.

Results of the post-hoc analysis for the COWAT: Animal and Supermarket showed that EMCI was more impaired than the NE, although there were no differences between the EMCI and LMCI. Also, mild AD exhibited worse performance than the EMCI, whereas there were no significant differences between the LMCI and mild AD. With regard to COWAT: Phonemics and DSC, all patient groups revealed significant impairments compared to the NE, but all patient groups were impaired similarly. For the Go-No go Test, K-CWST: Color and K-TMT-E: Part B, there was no difference between the NE and EMCI; however, the LMCI exhibited worse performance than the NE. Although the LMCI revealed no significant difference compare to the EMCI and mild AD, the latter showed poorer performance than the NE and EMCI. There were no significant differences for all groups in the K-CWST: Word and K-TMT-E: Part A.

DISCUSSION

The present study examined whether impairment of EF exists in MCI as well as mild AD, and studied which sub-domains of EF are differentially affected at the earlier stages. The results indicated significant declines of EF in either EMCI or LMCI for 7 out of the 9 measures in 5 EF tests, except in K-CWST: Word and K-TMT-E: Part A.

With regard to the COWAT: Animal and Supermarket, the results indicated that semantic fluency was impaired at the early stage of MCI (EMCI), which gradually worsens up to mild AD. Semantic fluency has been recognized to be dependent not only upon the integrity of semantic memory, but also on executive functioning; semantic fluency is more impaired following focal temporal and frontal lobe damage.[21] Previous studies suggest that semantic memory impairment is often present in aMCI as well as in dementia of the Alzheimer's type. It is said to be associated with injury of the temporal lobe structure.[21] In line with the findings of recent literature, the results of the present study indicated that semantic fluency deficits exist even in the earliest stage of the MCI, with progression through AD, suggesting that semantic fluency is a sensitive measure to detect the early stage of aMCI, and could be a good index to monitor the progression to AD.

Results for post-hoc analysis for the COWAT: Phonemics and DSC showed that phonemic fluency and psychomotor speed were impaired at the early stage of aMCI relative to NE, but were maintained at the same level to mild AD, unlike semantic fluency. Phonemic fluency measures the generating of as many words as possible based on orthographic criteria. It requires effortful self-initiated retrieval processing.[22] In addition, phonemic fluency imposes greater demands on executive skills, than semantic fluency, and many authors have reported that phonemic fluency is more sensitive to frontal, as opposed to non-frontal, lesions.[22] The results of the present study indicated that the effortful self-initiated retrieval processing for words based on lexical representation was already impaired even in the early stage of aMCI. DSC is associated with visuospatial perception, processing speed, sustained attention, visuomotor coordination, and incidental memory. It is especially recognized for use in assessing the psychomotor speed.[23] Several authors have emphasized that the marked characteristic of normal aging is the slowing of processing speed,[24,25] which itself is a very sensitive measure of brain abnormality.[26] Unlike the DSC, however, we could not find any differences on K-TMT: Part A which is a known measure of processing speed among all groups. This result indicated that DSC is a more sensitive test to detect the impairments of psychomotor speed than TMT: Part A. It also showed that psychomotor slowing was already present at the early stage of aMCI. Recent studies reported that psychomotor slowing is a crucial determinant of performance on verbal fluency tests in normal elderly as well

Table 1. Demographic characteristics of the participants, K-MMSE, and CDR-SB

	NE[a] (*n*=41)	EMCI[b] (*n*=45)	LMCI[c] (*n*=41)	Mild AD[d] (*n*=41)	*F or* χ^2	*Post-hoc* (*Bonferroni*)
Age	72.73 (6.19)	70.39 (9.81)	73.95 (7.25)	73.88 (8.21)	2.32	*ns*
Education	9.88 (3.64)	10.52 (4.20)	8.38 (4.80)	8.88 (4.51)	1.88	*ns*
Sex (M:F)	10:31	20:25	11:30	11:30	χ^2=5.31	*ns*
K-MMSE	28.78 (1.39)	26.58 (2.05)	23.86 (2.67)	22.22 (3.66)	52.73*	a>b>c>d
CDR-SB	-	1.24 (0.48)	2.91 (0.73)	4.84 (0.71)	54.56*	b<c<d

*p<0.001.
AD: Alzheimer's disease, CDR-SB: Clinical Dementia Rating-Sum of Boxes, EMCI: early MCI, K-MMSE: Korean-Mini Mental State Examination, LMCI: late MCI, MCI: mild cognitive impairment, NE: normal elderly.

as dementia of the Alzheimer's type.[27] Our results showed the same pattern of decline both in the COWAT: Phonemics and in the DSC, supporting the common role of psychomotor speed for both tests.

With regard to the Go-No go Test, K-CWST: Color naming, and K-TMT-E: Part B, we found that EMCI performed similarly to NE, though inhibitory control and mental set-shifting progressively worsened from MCI (EMCI and LMCI) to mild AD. Go-No go Test and K-CWST (Stroop test) assess the ability to inhibit the automatized or previously learned responses, and select the appropriate responses.[5,6] Some authors have reported that inhibitory control, which is measured by the Hayling and Stroop tests, was the most frequently and severely impaired in aMCI compared to normal elderly controls, relative to other EF tests.[5] In contrast, other researchers have shown that tests for inhibition of prepotent responses (Go-No go Test and Stroop tests) failed to uncover significant group differences between normal control and aMCI.[6] In our results, we ob-

Table 2. Performance on the executive function tests in NE, EMCI, LMCI, and mild AD

EF Test	NE[a] (*n*=41)	EMCI[b] (*n*=45)	LMCI[c] (*n*=41)	Mild AD[d] (*n*=41)	*F*	*Post-hoc* (*Bonferroni*)
COWAT						
Animal	-0.05 (0.82)	-0.77 (0.94)	-1.04 (0.75)	-1.31 (0.87)	18.86*	a>b=c, a>d, b>d, c=d
Supermarket	0.37 (0.80)	-0.39 (0.91)	-0.68 (0.80)	-1.13 (0.81)	24.61*	a>b=c, a>d, b>d, c=d
Phonemics	0.44 (0.91)	-0.41 (1.06)	-0.31 (0.71)	-0.68 (0.94)	12.00*	a>b=c=d
DSC	0.46 (0.96)	-0.28 (0.84)	-0.43 (0.90)	-0.53 (1.10)	10.14*	a>b=c=d
Go-No go Test	19.78(0.65)	18.67 (3.37)	16.63 (4.93)	15.15 (5.75)	9.78*	a=b, a>c=d, b=c, b>d
K-CWST						
Word	111.41(2.82)	109.98(9.28)	105.54 (11.93)	104.71 (17.36)	1.97	*ns*
Color	0.22 (1.00)	-0.45 (1.06)	-0.71 (1.16)	-1.04 (1.43)	10.69*	a=b, a>c=d, b=c, b>d
K-TMT-E						
Part A	0.31 (0.64)	-0.01 (1.20)	-0.29 (1.23)	-0.15 (0.94)	2.48	*ns*
Part B	0.52 (0.48)	-0.46 (1.30)	-1.39 (2.07)	-2.16 (3.07)	14.45*	a=b, a>c=d, b=c, b>d

*p<0.001.
AD: Alzheimer's disease, COWAT: Controlled Oral Word Association Test, DSC: Digit Symbol Coding, EF: executive function, EMCI: early MCI, K-CWST: Korean-Color Word Stroop Test, K-TMT-E: Korean-Trail Making Test-Elderly's version, LMCI: late MCI, MCI: mild cognitive impairment, NE: normal elderly.

Table 3. Performance on the executive function tests in NE, aMCI, and mild AD

EF Test	NE[a] (*n*=41)	aMCI[b] (*n*=86)	Mild AD[c] (*n*=41)	*F*	*Post-hoc* (*Bonferroni*)
COWAT					
Animal	-0.05 (0.82)	-0.90 (0.86)	-1.31 (0.87)	23.71†	a>b>c
Supermarket	0.37 (0.80)	-0.53 (0.87)	-1.13 (0.81)	33.57†	a>b>c
Phonemics	0.44 (0.91)	-0.36 (0.90)	-0.68 (0.94)	16.74†	a>b=c
DSC	0.46 (0.96)	-0.35 (0.87)	-0.53 (1.10)	13.32†	a>b=c
Go-No go Test	19.78(0.65)	17.70 (4.28)	15.14 (5.75)	12.60†	a>b>c
K-CWST					
Word	111.41(2.82)	107.86 (10.79)	104.71(17.36)	3.42*	a=b, a>c, b=c
Color	0.22 (1.00)	-0.57 (1.11)	-1.04 (1.43)	12.21†	a>b=c
K-TMT-E					
Part A	0.31 (0.64)	-0.14 (1.21)	-0.15 (0.94)	2.96	*ns*
Part B	0.52 (0.48)	-0.91 (1.76)	-2.16 (3.07)	18.62†	a>b>c

*p<0.05, †p<0.001.
AD: Alzheimer's disease, aMCI: amnestic mild cognitive impairment, COWAT: Controlled Oral Word Association Test, DSC: Digit Symbol Coding, EF: executive function, K-CWST: Korean-Color Word Stroop Test, K-TMT-E: Korean-Trail Making Test-Elderly's version, NE: normal elderly.

served that EMCI performed similarly to NE, but LMCI exhibited a poorer performance than NE on the Go-No go Test and K-CWST: Color. K-TMT-E: Part B measures the working memory, divided attention, and processing speed; however, it mainly requires mental set-shifting ability.[28] Some authors reported that MCI performed similarly to control group on TMT: Part B,[7] whereas other authors found that TMT: Part B was impaired in MCI compared to normal control.[6] In the present study, we found that EMCI performed similarly to NE; in contrast, LMCI was more impaired than NE on the K-TMT-E: Part B. Many reasons could explain the inconsistent conclusions of previous studies indicating the use of different tasks, but we believe it is primarily because of different criteria for the recruitment of aMCI patients. In the current study, we subdivided aMCI patients with a CDR-GS of 0.5 into EMCI and LMCI, according to CDR-SB. As a post-hoc analysis, we re-analyzed after merging the two MCI groups (EMCI and LMCI) into one group (aMCI). We found group differences between the aMCI and NE in the Go-No go Test, K-CWST: Color, and K-TMT-E: Part B (Table 3). Since the EMCI, but not LMCI, still maintained the inhibitory control and mental set-shifting abilities, these results supported that subdividing aMCI into EMCI and LMCI based on CDR-SB would help in understanding the spectrum of impairments of EF in the disease, and to identify the progression of dementia.

To summarize, there were no group differences in simple processing speed among the NE, aMCI, and mild AD. We found that the EMCI performed worse than the NE in verbal fluency and psychomotor speed tests; however, there were no differences between the EMCI and NE in inhibitory control and set-shifting abilities. Also, no differences were observed between the EMCI and LMCI in any of the 9 measures in 5 EF tests; but the LMCI revealed worse performance than the NE in 7 measures. The EMCI exhibited better performance on semantic fluency, Go-No go Test, K-CWST: Color, and K-TMT: Part B than the mild AD; the LMCI did not show any differences with the mild AD on any measures in 5 EF tests.

These results indicated that EF impairments exist even in the earlier stage of the aMCI in several sub-domains, with some sub-domains being similar to NE. This means that the semantic and phonemic fluency and psychomotor speed decline earlier, whereas inhibitory control and mental set-shifting abilities decline later. Functional neuroimaging studies showed that patients with left dorsolateral prefrontal cortex (DLPFC) or inferior frontal gyrus lesions are impaired on verbal fluency,[29,30] whereas psychomotor speed is associated with superior frontal lobe (middle frontal gyrus).[26] It has known that anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) play an important role in Stroop and Go-No go Test performances.[31-33] Set-shifting or cognitive flexibility are also known to be related with increased activation in the DLPFC and medial prefrontal cortex (PFC).[34] In addition, some researchers reported that the most substantial age-related decline is the volume of prefrontal grey matter including both DLPFC and OFC areas.[35,36] Several authors, however, found a relative preservation of the OFC and ACC, although they found the strongest volume reduction within the DLPFC regions.[35,37,38] Taking together these findings from functional and structural neuroimaging with the present study results, we can assume that functions of the PFC which are more related to *lateral* regions decline at earlier stage of aMCI, whereas the EFs associated with the more *orbital* or *medial* part of PFC are impaired at later stage of aMCI.

Our results indicated that executive dysfunction is an important feature of aMCI. Thus, it should be noted that if a clinical setting cannot afford to administer a comprehensive neuropsychological assessment for aMCI, we suggest that at least two kinds of EF tests should be administered for staging aMCI. The results of the present study indicated that the COWAT and DSC are more sensitive for the detection of an early-stage of aMCI, whereas the Go-No go Test, K-CWST: Color, and K-TMT: Part B are useful for the detection of late-stage aMCI.

There are several limitations to the current study. First, this study was retrospective with a relatively small sample size. Second, we could not control the drug effects on each patient group. Third, we did not have biomarker evidences such as hypometabolism, β-amyloid deposition, and cerebrospinal fluid (CSF) proteins which would prove that our aMCI is the prodromal stage of AD, although we excluded patients who had a stroke, significant ischemic changes on brain MRI, movement problems, or salient personality changes. Fourth, all the EF tests included in our study were traditional "paper-and-pencil" tests used in clinical settings. We suggest this study should be replicated using more sensitive experimental tasks that measure the EF in detail. Finally, this study was a cross-sectional study; thus, future research should be conducted as a longitudinal base.

Conflicts of Interest

The authors have no financial conflicts of interest.

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