

## Original Article



# A Comparison Between the Performances of Verbal and Nonverbal Fluency Tests in Discriminating Between Mild Cognitive Impairments and Alzheimer's Disease Patients and Their Brain Morphological Correlates

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## ABSTRACT

**Background and Purpose:** Verbal and nonverbal fluency tests are the conventional methods for examining executive function in the elderly population. However, differences in impairments result in fluency tests in patients with mild cognitive impairments (MCIs) and Alzheimer's disease (AD) and in neural correlates underlying the tests still necessitate concrete evidence.

**Methods:** We compared the test performances in 27 normal controls, 28 patients with MCI, and 20 with AD, and investigated morphological changes in association with the test performances using structural magnetic imaging.

**Results:** Patients with AD performed poorly across all the fluency tests, and a receiver operating characteristics curve analysis revealed that only category fluency test discriminated all the 3 groups. Association, category, and design fluency tests involved temporal and frontal regions, while letter fluency involved the cerebellum and caudate.

**Conclusions:** Category fluency is a reliable measure for screening patients with AD and MCI, and this efficacy might be related to morphological correlates that underlie semantic and executive processing.

**Keywords:** Mild Cognitive Impairment; Alzheimer's Disease; Gray Matter; Language; Executive Function; Neuropsychological Tests

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**Conflict of Interest**

The authors have no financial conflicts of interest.

**Author Contributions**

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**INTRODUCTION**

Decline of executive function has been reported to occur in the early stages of Alzheimer's disease (AD),<sup>1,2</sup> and executive dysfunction is associated with accelerated progression of the disease and severe burden of caregiver.<sup>3</sup> Executive function cannot be defined as a unitary concept and is understood as a complex of various cognitive processes.<sup>4,5</sup> It encompasses abilities to plan strategies for goal attainment and problem solving, to organize in given circumstances, and to flexibly adjust behaviors/actions. Based on a literature review, the major executive function domains are inhibition, working memory, planning, set-shifting, and fluency<sup>6</sup>; fluency refers to the ability to generate words or visual information under specific constraints such as a fixed time.<sup>5,7</sup> Impairments in fluency distract the capability of flexible planning by delaying the time performance for achieving a given goal and solving a problem through inefficient means, consequently, giving rise to adaptive deficits in daily lives.

In the elderly and low-educated population, fluency tests are frequently used to examine executive dysfunction due to their applicability.<sup>6,8,9</sup> On the other hand, in the clinical field, the Controlled Oral Word Association Test (COWAT) is the most commonly employed verbal fluency test; the test consists of category and letter fluency tasks.<sup>10</sup> In the category fluency task, participants are asked to orally produce as many items as possible from a given category (for example, animals and fruits) in one-minute, and require basic semantic knowledge (attribute relationships). In the letter fluency task, participants are instructed to say words beginning with a given letter of the alphabet in one minute, and the task performance reflects phonological abilities. Additionally, an association fluency test in which participants are asked to produce as many associating items as possible with a given item in one-minute may be also used; the test performance mirrors semantic abilities (coordinate relationships). Notably, verbal fluency task performances are known to decrease in amnesic mild cognitive impairments (MCIs) and AD. The Ruff figural fluency test is a widely used nonverbal (design) fluency task in clinical settings; the test measures the ability to make geometric designs by connecting arrays of dots in a one-minute time trial.<sup>11</sup> The design fluency indicates the visuospatial flexibility of a subject, which is also known to deteriorate in MCI and early stages of AD. While the aforementioned measures are aimed at testing executive processes, some argue that the fluency dysfunction relies greatly on semantic organizations and may reflect deficits in semantic memory rather than executive function. Most studies of AD have reported relatively greater semantic fluency deficits than phonemic fluency deficits as evidenced by neocortical temporal lobe neuropathology,<sup>12,14</sup> and inconsistent results on fluency deficit patterns in amnesic MCI have been reported.<sup>15,16</sup>

Previous brain imaging demonstrated that verbal fluency primarily involves the frontal lobe in the language dominant hemisphere, while the other brain regions differentially cooperate for semantic and phonological processes of verbal and nonverbal fluency.<sup>8,17</sup> Most functional neuroimaging studies propose that the frontal lobe is more involved in phonologically driven word retrieval, whereas the temporal lobe is crucial for semantically driven word retrieval.<sup>18,19</sup>

In this study, we aim to investigate the differences in performance between the verbal (category, letter, and association fluency) and nonverbal (design) fluency tasks in older adults with normal cognition, MCI, and AD in the Korean elderly population. Furthermore, we investigated the neuroanatomical correlates of the current measures using structural magnetic resonance imaging.

## MATERIALS AND METHODS

### Participants

Participants were recruited from Seoul Metropolitan Government-Seoul National University Boramae Medical Center, they were older than 60 years of age and native Korean speakers. All the participants' level of education was greater than 6 years and provided informed consent forms before completing a questionnaire. Diagnosis of MCI and AD was made by a psychiatrist using the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations<sup>20</sup> and Petersen's criteria.<sup>21</sup> The exclusion criteria included structural brain lesions unrelated to MCI or AD on brain imaging, a history of other neurological disorders or physical illnesses that may affect the cognitive function, a history of alcohol or drug abuse in the past 10 years, visual or hearing difficulties or motor impairments that could affect the test performance, and inadequate or uncooperative attitude during the test. All the participants were administered the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR). Finally, 27 normal older adults (healthy elderly controls [HC]), 28 subjects with MCI, and 20 subjects with AD were included in the study. The demographic and clinical features of the subjects are summarized in **Table 1**. The study was approved by the Boramae Medical Center Institutional Review Board (IRB No. 10-2018-60), and all the procedures were completed under the guidance of the Helsinki Declaration.

### Administration of fluency tests

Administration of the Korean version of fluency tests to the cognitively normal, MCI, and AD subjects was conducted by trained psychologists. The category and letter fluency tests were based on the COWAT originally invented by Benton (1969).<sup>10</sup> In the category fluency test, 2 categories 'Animals' and 'Fruits' were adapted, whereas the letter fluency used Korean letters 'Ga' and 'Ma' instead of English letters. In the association fluency test, 2 items 'Desk' and 'Fox' were given in the task. The nonverbal fluency task was based on the Ruff figural fluency test<sup>11</sup> and consisted of arrays of 9 dots to generate as many different geometric designs as possible.

To avoid exhaustion and shortage of attention in the older adults, the test duration was shortened to 30 seconds for each trial. The whole test consisted of association fluency (2 trials), category fluency (2 trials), letter fluency (2 trials), and design fluency (1 trial), thereby the total running time taken was 3 minutes and 30 seconds.

### Screening assessments

#### MMSE

MMSE is a practical neurocognitive screening test in the form of a 5–10 minutes long questionnaire that is designed to examine cognitive aspects of mental state and estimate

**Table 1.** Demographic and clinical features of HC, MCI, and AD groups

Characteristic	HC (n=27)	MCI (n=28)	AD (n=20)	$\chi^2$ or F	ANOVA p-value	p-value for pairwise comparison		
						HC vs. MCI	HC vs. AD	MCI vs. AD
Gender (Man:Woman)	8:19	9:19	9:11	1.324 <sup>‡</sup>	0.562 <sup>‡</sup>	-	-	-
Age	72.6±5.4	74.8±4.7	78.9±6.2	8.050	0.001*	0.380	<0.001 <sup>†</sup>	0.034*
Year of education	11.8±3.7	9.7±3.2	9.1±4.0	3.862	0.026*	0.102	0.038*	1.000
MMSE	27.7±2.2	24.4±2.6	18.6±3.8	58.231	<0.001 <sup>†</sup>	<0.001 <sup>†</sup>	<0.001 <sup>†</sup>	<0.001 <sup>†</sup>
CDR global	0.2±0.2	0.5±0.1	0.75±0.3	44.805	<0.001 <sup>†</sup>	<0.001 <sup>†</sup>	<0.001 <sup>†</sup>	0.001
CDR sum of boxes	0.4±0.7	1.8±1.1	4.4±2.1	49.633	<0.001 <sup>†</sup>	0.001*	<0.001 <sup>†</sup>	<0.001 <sup>†</sup>

Values are mean ± standard deviation. Comparisons were conducted using ANOVA with *post hoc* Bonferroni correction, unless otherwise indicated.

HC: healthy elderly controls, MCI: mild cognitive impairment, AD: Alzheimer's disease, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating, ANOVA: analysis of variance.

\*Significant at  $p < 0.05$ ; <sup>†</sup>Significant at  $p < 0.001$ ; <sup>‡</sup>Chi-square test.

the severity of cognitive impairments.<sup>22</sup> The test was further developed and adjusted to fit the Korean elderly populations. The Korean version of the MMSE consists of orientation (10 points), short-term memory registration and recall (6 points), attention (5 points), naming (2 points), following verbal commands (4 points), judgment (2 points), and copying a double pentagon (1 point). The MMSE score equal to or greater than 25 out of 30 indicates a normal cognitive function, whereas below 25 indicates cognitive impairment.

#### CDR

CDR quantitatively measures the severity of dementia.<sup>23</sup> The rating is made by interviewing a patient and a reliable informant such as a family member to obtain a global composite score characterizing 6 domains of cognition: memory, orientation, judgment and problem solving, community affairs, home, hobbies, and personal care. The composite rating denotes stages of dementia: 0 (no cognitive impairment), 0.5 (questionable), 1 (mild), 2 (moderate) and 3 (severe).

#### Statistical analyses for the Fluency tests

Data analysis was conducted using SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL, USA). Demographic and clinical characteristics were compared between groups using analysis of variance for continuous variables and  $\chi^2$  tests for discrete variables. *Post hoc* analyses were also performed by applying Bonferroni multiple comparison corrections. Between-group differences in fluency test scores were also tested using analysis of covariance (ANCOVA) and *post hoc* analyses with Bonferroni adjustments controlling for age effects. Receiver operating characteristics (ROC) curves were plotted to assess the ability of fluency tests to screen for MCI and AD; 1-specificity was plotted on the x-axis and sensitivity on the y-axis. The cut-off values for determining sensitivity and specificity were decided by calculating the Youden index. The area under the curve (AUC) was used to measure the accuracy of the tests in discriminating HC, MCI, and AD subjects. The AUC results are considered perfect for AUC value of 1; 0.9–1, very accurate; 0.7–0.9, moderately accurate; 0.5–0.7, poorly accurate; below 0.5, inaccurate.

#### Structural brain imaging analysis

The participants underwent structural magnetic resonance imaging (3 Tesla, Achieva; Philips, Amsterdam, The Netherlands). The acquisition parameters for structural T1 imaging were as follows: repetition time, 9.9 ms; echo time, 4.6 ms; slice thickness, 1 mm; imaging size, 180×224×224 mm; voxel size, 1.00×0.98×0.98 mm. The image preprocessing steps and statistical analysis for VBM were performed using Statistical Parametric Mapping 12 (SPM12; UCL Queen Square Institute of Neurology, London, UK; <https://www.fil.ion.ucl.ac.uk/spm/>) implemented in MATLAB (2018a; The MathWorks, Inc., Natick, MA, USA; <http://www.mathworks.com>). We used a fully automated preprocessing procedure illustrated in CAT12r1450 (Computational Anatomy Toolbox; Structural Brain Mapping Group, Departments of Psychiatry and Neurology, Jena University Hospital; <http://dbm.neuro.uni-jena.de/cat/>) to apply a standardized analysis pipeline. Segmentation algorithms based on the adaptive maximum a posteriori technique implemented in CAT12, were used to classify brain tissue into gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), and WM hypointensities. Additionally, partial volume estimation was used to create a more accurate segmentation for the 2 mixed classes: GM–WM and GM–CSF. To spatially normalize the GM image into the standard space with enhanced accuracy of inter-subject registration,<sup>24</sup> we used diffeomorphic anatomical registration using exponentiated lie algebra. A customized template was created, and a deformation field was applied to previously segmented GM images to warp non-linear transformation to standardized Montreal Neurological Institute

(MNI) space. During the transformations, the total amount of GM was preserved. All the images were smoothed using an 8-mm full width half-maximum Gaussian kernel.

A multiple regression model was implemented to examine regional correlates of verbal and nonverbal fluency tests in a voxel-wise manner, and age, years of education, gender, and total intracranial volume were added as covariates of no interest. We applied cluster-level multiple comparison adjustments based on familywise error-corrected  $p < 0.05$  with a cluster defining threshold of  $p < 0.001$  ( $Z = 3.09$ ) estimated by the Gaussian random field method implemented in SPM12.

## RESULTS

### Demographic and clinical features of subjects

As described in **Table 1**, the gender distribution was not significantly different among the groups, however, there was a difference in age and year of education ( $p = 0.001$  and  $p = 0.026$ , respectively). A *post hoc* analysis revealed that the AD patients were older than MCI and HC patients ( $p = 0.034$  and  $p < 0.001$ , respectively). The years of education were fewer in the AD group than in the HC group ( $p = 0.038$ ). MMSE and CDR scores showed significant group differences ( $p < 0.001$ , both).

### Group differences in fluency test performances

The means and standard deviations of fluency test scores of HC, MCI, and AD groups are presented in **Table 2**. ANCOVA analysis confirmed the groups' differences on fluency tests, except for the 'Ma' letter fluency. A *post hoc* analysis for category fluency revealed a significant difference in the pairwise group comparisons ( $p < 0.001$  in MCI and AD compared HC,  $p = 0.001$  in AD compared to MCI). Furthermore, both 'Animal' and 'Fruit' categories detected significant impairments in the AD and MCI groups compared to the HC group (Animal:  $p < 0.001$  in AD,  $p = 0.005$  in MCI; Fruit:  $p < 0.001$  in AD,  $p = 0.004$  in MCI). A significant difference was also found in the comparison between the AD and MCI groups ( $p = 0.005$  for both categories). Overall association fluency score showed no fluency impairments in the MCI group, but in the AD group compared to the HC group ( $p > 0.05$  in MCI,  $p < 0.001$  in AD). 'Desk' association fluency test detected impairments in the AD group compared to HC ( $p < 0.001$ ), whereas a significant difference was found in the AD group compared to the MCI

**Table 2.** Means and standard deviations of fluency test scores according to dementia status

Fluency test	HC	MCI	AD	F	ANOVA <i>p</i> -value	<i>p</i> -value for pairwise comparison		
						HC vs. MCI	HC vs. AD	MCI vs. AD
Verbal fluency	46.48±10.10	35.93±11.88	21.95±6.71	18.766	<0.001 <sup>†</sup>	0.014 <sup>*</sup>	<0.001 <sup>†</sup>	<0.001 <sup>†</sup>
Category fluency	22.81±4.30	17.14±5.07	11.45±2.44	24.153	<0.001 <sup>†</sup>	<0.001 <sup>†</sup>	<0.001 <sup>†</sup>	0.001 <sup>*</sup>
'Animal'	12.85±3.22	9.50±3.36	6.35±1.95	16.051	<0.001 <sup>†</sup>	0.005 <sup>*</sup>	<0.001 <sup>†</sup>	0.005 <sup>*</sup>
'Fruit'	9.96±2.31	7.64±2.28	5.10±1.62	16.627	<0.001 <sup>†</sup>	0.004 <sup>*</sup>	<0.001 <sup>†</sup>	0.005 <sup>*</sup>
Association fluency	12.33±4.22	10.86±4.55	5.75±3.32	9.188	<0.001 <sup>†</sup>	1.000	<0.001 <sup>†</sup>	0.001 <sup>*</sup>
'Desk'	7.51±2.56	6.14±2.35	3.30±1.63	11.286	<0.001 <sup>†</sup>	0.388	<0.001 <sup>†</sup>	0.001 <sup>*</sup>
'Fox'	4.81±2.59	4.71±2.94	2.45±2.19	3.813	0.027 <sup>*</sup>	1.000	0.070	0.033 <sup>*</sup>
Letter fluency	11.33±4.19	7.93±4.75	4.75±3.32	6.158	0.003 <sup>*</sup>	0.115	0.002 <sup>*</sup>	0.176
'Ga'	6.52±2.42	4.64±3.00	2.35±1.93	7.453	0.001 <sup>*</sup>	0.152	0.001 <sup>*</sup>	0.052
'Ma'	4.81±2.15	3.29±2.34	2.40±2.04	2.519	0.088	0.281	0.107	1.000
Nonverbal fluency	6.63±2.87	6.04±2.77	3.30±2.11	3.603	0.032 <sup>*</sup>	1.000	0.107	0.034 <sup>*</sup>

Values are mean ± standard deviation. Comparisons were conducted using ANCOVA with *post hoc* Bonferroni correction, adjusting for effects of age and year of education.

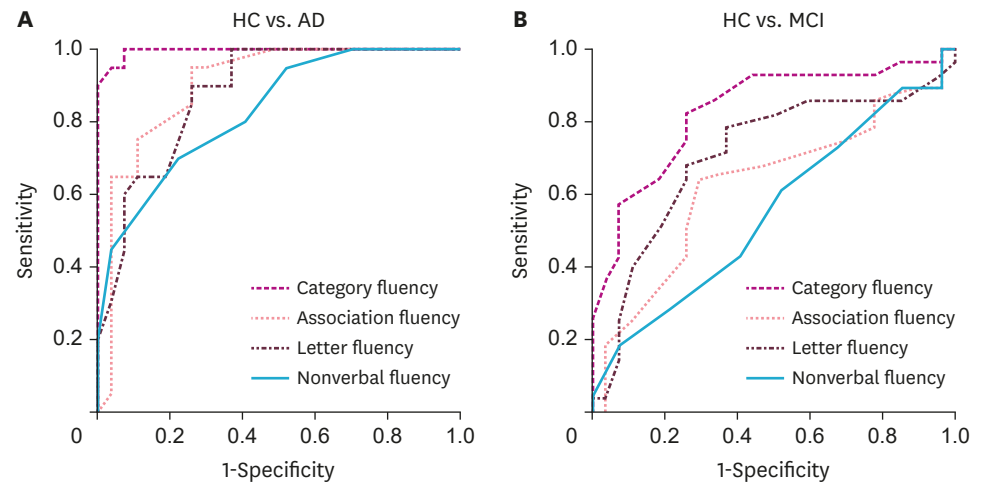
HC: healthy elderly controls, MCI: mild cognitive impairment, AD: Alzheimer's disease, ANOVA: analysis of variance, ANCOVA: analysis of covariance.

<sup>\*</sup>Significant at  $p < 0.05$ ; <sup>†</sup>Significant at  $p < 0.001$ .

group for ‘Fox’ association fluency ( $p=0.033$ ). *Post hoc* analysis results on the letter fluency test showed that the AD group was impaired on overall letter fluency and ‘Ga’ letter fluency when compared to HC ( $p=0.002$  and  $p=0.001$ , respectively), but no statistical significances were observed for the ‘Ma’ letter fluency. Notably across all the groups, subjects displayed poor performances on ‘Fox’ association fluency and ‘Ma’ letter fluency. Lastly, a *post hoc* analysis on nonverbal fluency test showed impairment in AD when compared to MCI ( $p=0.034$ ).

**ROC curve analysis**

A ROC curve analysis was performed to validate the fluency tests for discrimination of MCI and AD. The AUC, cut-off value, sensitivity, and specificity of the tests are summarized in **Table 3** and **Fig. 1**. In the discrimination of AD from HC, all fluency measures showed a moderate to high accuracy with reasonable sensitivity and specificity. The category fluency was the most superior with sensitivity and specificity greater than 0.90 for both overall and individual category items. Overall, association fluency outperformed letter fluency and nonverbal fluency measures. Moreover, ‘Desk’ association fluency was more accurate in discriminating between the groups than did the overall association fluency. However, ‘Fox’ association fluency, letter fluency (both overall score and individual scores), and nonverbal fluency achieved a moderate accuracy in discriminating AD from HC. ROC curve analysis results for discrimination of MCI and HC revealed that the overall category fluency displayed the highest accuracy in discriminating among the fluency measures, while Individual



**Fig. 1.** Receiver operating characteristic curve analysis of verbal and nonverbal fluency performances for screening for AD (A) and MCI (B).  
 HC: healthy elderly controls, MCI: mild cognitive impairment, AD: Alzheimer’s disease.

**Table 3.** AUC of ROC curve, cut-off value, sensitivity, and specificity of fluency tests

Pairwise comparison	Characteristic	AUC	Cut-off value	Sensitivity	Specificity
HC vs. MCI	Verbal fluency	0.765	37.5	0.643	0.852
	Category fluency	0.830	20.5	0.821	0.741
	Association fluency	0.626	11.5	0.643	0.704
	Letter fluency	0.707	9.5	0.679	0.741
	Nonverbal fluency	0.550	3.5	0.179	0.926
HC vs. AD	Verbal fluency	0.982	32.5	0.950	0.926
	Category fluency	0.995	17.5	1.000	0.926
	Association fluency	0.902	10.5	0.950	0.741
	Letter fluency	0.880	9.5	0.900	0.741
	Nonverbal fluency	0.831	4.5	0.700	0.778

AUC: area under curve, ROC: receiver operating characteristics, HC: healthy elderly controls, MCI: mild cognitive impairment, AD: Alzheimer’s disease.



category scores had moderate accuracy. Letter fluency achieved a better discrimination accuracy, especially when overall letter fluency was used than the association fluency (both overall and individual scores), and nonverbal fluency.

**Brain imaging analysis**

Positive correlates of GM volume with fluency measures are reported In **Table 4** and **Fig. 2**. Several regions including the medial prefrontal cortex, temporal pole, superior temporal cortex showed spatially overlapping correlation with 4 of the fluency tests. A correlating pattern of association fluency and category fluency was observed in the medial and inferior prefrontal cortex. Category and letter fluency were both associated with GM volume in the entorhinal cortex, dorsal anterior insula, while category and design fluency reflected the volume of the anterior insula. The association fluency score uniquely correlated with the caudate nucleus and left inferior prefrontal cortex, and the category fluency score showed a widespread correlation with the left superior temporal, rolandic operculum, and insular cortex.

**DISCUSSION**

The study aimed to compare accuracy between verbal and nonverbal fluency tests in discriminating dementia status in HC, MCI, and AD subjects. Our results indicated that both verbal and nonverbal fluency performances significantly deteriorate in AD. Among the verbal fluency, category fluency discriminated AD and MCI from HC as well as AD from MCI with the highest specificity and sensitivity. Our results demonstrated that the association fluency was more superior to letter fluency and nonverbal fluency test in distinguishing AD from HC

**Table 4.** Positive neuroanatomical correlates of verbal and nonverbal fluency scores

Fluency test	Brain region	Testing statistics	Cluster size	Coordinate		
		T	k	x	y	z
Category fluency	L Insula	6.57	7,302	-38	18	5
	R Insula	5.09	12,967	42	23	3
	R Entorhinal	6.42	12,967	23	-18	-29
	L Medial prefrontal cortex	6.13	12,967	-2	48	12
	L Rolandic operculum/Postcentral	5.04	7,302	-51	-17	18
	L Superior temporal cortex	5.48	7,302	-48	-9	-6
	L Inferior temporal cortex	6.44	4,297	-51	-54	-23
	L Fusiform	5.40	4,297	-27	-27	-27
	R Middle temporal cortex	5.07	885	63	-15	-11
Association fluency	L Inferior frontal cortex	5.68	602	-50	20	29
	R Temporal pole	5.16	1,030	36	9	-23
	L Temporal pole	4.52	722	-41	8	-18
	R Rolandic operculum/Postcentral/Superior temporal cortex	4.93	2,996	51	-18	17
	L Medial prefrontal cortex/Anterior cingulate cortex/Caudate nucleus	4.77	3,776	0	38	-12
	R Middle frontal cortex	4.43	528	48	30	23
	R Inferior temporal cortex	4.41	574	63	-45	-15
	R Fusiform/Parahippocampal	4.64	1,500	41	-29	-18
	L Middle temporal cortex	4.41	481	-57	-5	-12
	L Posterior cingulate cortex	4.55	1,800	-2	-57	29
R Cerebellum (VIII)	4.99	1,491	29	-74	-50	
R Cerebellum (VII)	4.28	457	29	-80	-50	
Letter fluency	R Entorhinal cortex/Temporal pole	4.73	1,659	20	-20	-29
	L Insula/Superior temporal cortex	4.26	834	-47	-5	-3
	R Rolandic operculum/Postcentral	4.20	498	53	-21	15
Design (non-verbal)	L Ventral insula/Superior temporal cortex	4.61	1,168	-42	9	-11
	R Anterior insula/Inferior frontal cortex/Orbitofrontal cortex	4.20	877	32	21	-20
	R Medial prefrontal cortex	3.93	581	3	45	6

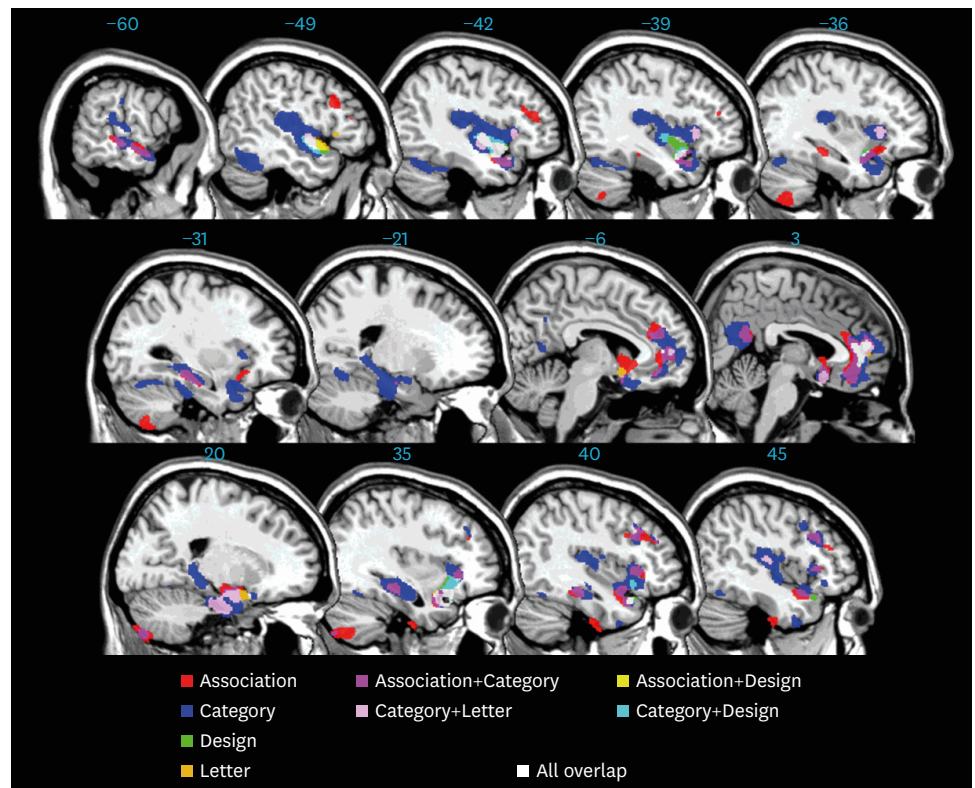


Fig. 2. Brain regions showing positive correlations with fluency test scores. The threshold was set  $p < 0.001$  (uncorrected),  $k > 200$  for a visualization purpose.

and MCI, while letter fluency performed better in the detection of MCI from HC. Nonverbal fluency was severely impaired in AD, but preserved in MCI compared to HC. Neuroanatomical correlation analysis showed that GM density volume in the superior temporal cortex and medial prefrontal cortex were overlappingly associated with the 4 fluency tests. The anterior insula, inferior frontal cortex and the medial temporal lobe regions also showed overlapping association with distinct fluency tests. Our findings demonstrate fluency tests as a powerful method to assess cognitive status in demented or cognitively impaired individuals.

Semantic fluency measures the ability to produce items that have attribute relationships, which requires high integrity of the semantic network and efficient retrieval processes.<sup>25,26</sup> In our study, both the AD and MCI groups showed semantic fluency degradation as a sign of the breakdown of semantic knowledge as expected. Furthermore, the category fluency test presented the highest performance accuracy in discriminating all the 3 groups. Similarly, among various semantic functioning tests, semantic fluency showed the greatest discriminating power in detecting cognitively impaired individuals, which proved its diagnostic utility in the clinical field.<sup>15,27,28</sup> Literature documented that category-specific deficits may occur due to different brain systems, although it is still being debated.<sup>29,30</sup> In our study, we observed comparable accuracy for the 2 categories in the test, suggesting that the animal and fruit categories can be used interchangeably for the detection of AD and MCI. In contrast to semantic fluency which produces items in attribute relationships, association fluency measures the ability to generate semantically associated words that are in coordinate relationships. A previous study reported that in addition to the impairment of semantic memory in both amnesic MCI and mild AD, a semantic association was disturbed



in AD. More specifically, it proposed that in AD with the loss of semantic attributes that define the superordinate concept, the distinction between similar concepts in coordinate conditions becomes more difficult.<sup>14,31</sup> Consistently, in the present study, AD patients had severe impairments in both association and category fluency, while semantic knowledge in coordinate condition was relatively intact in MCI patients. We noticed that the discriminating power when retrieving 'Fox'-associated exemplars had poor accuracy compared to that of 'Desk'-associated word generation. Word generation specifically related to 'Fox' may be difficult even in normal conditions due to limited exposure in a highly urbanized society and infrequent use of relevant words in daily life. The semantic knowledge of 'Fox'-related exemplars is likely to be acquired through education or life experience, leading to the conclusion that living environments may primarily determine the performance rather than dementing conditions. Letter fluency measures the function of retrieval mechanisms based on lexical cues from lexico-semantic memory, and greatly relies on frontal lobe function. In the present study, comparable to deficits in the category and association fluency, patients with AD also showed significant deterioration in letter fluency, corroborating previous findings that both the semantic and executive functions are compromised in AD. Recent studies described executive dysfunction in MCI,<sup>32-34</sup> similarly, our data provide evidence supporting minor impairments in our MCI cohort on a verbal test which greatly depends on executive function, although not as significant as in AD. However, a number of studies indicate that MCI patients are more impaired on intentional access to semantic knowledge and relatively preserved on the frontal function,<sup>8</sup> and thus, a disintegration of the semantic system may account for the declining performance in letter fluency test in MCI. Production of words starting with 'Ma' was more difficult than 'Ga' across the groups. A possible explanation for this may be that the total number of words starting with 'Ga' is twice as many as those starting with 'Ma,' and their utilizing in daily life is more than those starting with 'Ma,' resulting in more difficulty in the 'Ma' letter fluency task. Nonverbal design fluency is non-semantically guided and greatly relies on executive control. The executive dysfunction as mentioned above is a sign of AD pathological progression and it manifested a poor performance in our AD group. On the other hand, impairments in nonverbal fluency were absent in our MCI cohort, possibly implying that executive function is still intact.

Most neuroimaging and lesion studies demonstrated the distinct function of the temporal cortex in the semantic fluency and frontal cortex in phonological fluency in normal elderlies, and the involvement of the regions was also proved in patients with AD.<sup>35,36</sup> In our findings, category fluency was associated with GM volume in the left inferior temporal region and hippocampus, which highlights the importance of the temporal lobe in accessing semantic processing. The lateral temporal cortex is the main region that distinguishes normal age-related brain atrophy patterns.<sup>37</sup> A large portion of the loss in the temporal lobe atrophy may lead to degraded performance in retrieving verbal-semantic information. Similar observations were found in the previous structural imaging study showing that category fluency performance was also associated with GM volume in the right frontal cortex (Brodmann area [BA] 10) which has an evident role in memory retrieval and executive control in complex language processes.<sup>38,39</sup> The degree of frontal lobe involvement is category-specific, and a broad category that requires frequent switching between subcategories utilizes more strategic search processes, employing more frontal lobe function.<sup>18</sup> Our findings suggest that more frequent switching and strategic search mechanisms are engaged to generate exemplars (e.g., reptiles, birds, mammals, etc.). The correlation with semantic fluency also showed a large correlating cluster in the left rolandic operculum, which is known to be involved in accessing phonological representations and phoneme selection and production.<sup>40</sup>

For the association fluency task, the left inferior frontal gyrus (BA 44), fusiform gyrus, and temporal gyrus were strong predictors of performance, demonstrating the implications of both frontal lobe function and semantic processing for the task. The involvement of the left fusiform gyrus in semantic processing has been established in a number of studies.<sup>41,42</sup> In the present study 'Desk'-associated word generation was strongly correlated with the left temporal region, while 'Fox'-associated word generation was associated more with the diffuse network including temporal, frontal, occipital, and subcortical regions. From this, it can be assumed that the difficulty of the task challenges more attentional and executive skills, and aggregate a more diffuse network of brain regions to promptly retrieve words for which the availability is very limited. Unlike other types of fluency tests, association and category tests showed a correlation in the anterior cingulate cortex, inferior prefrontal cortex (triangularis), indicating the critical role of the executive-control network regions.

On the other hand, letter fluency was associated with entorhinal, left insula, and superior temporal cortex regions. Previous studies have shown a dissociating pattern that phonological tests more specifically reflect the inferior prefrontal cortex rather than the temporal cortex.<sup>43</sup> However, we found that the correlates of letter fluency largely overlapped with the correlates of other fluency tests, which may be due to heavily weighed AD pathological effects. We did not detect any correlations with frontal regions other than the insular cortex, these findings are similar to previously reported outcomes.<sup>29,44</sup>

Nonverbal design fluency, which was considered as one of the widely used neuropsychological tests for frontal lobe integrity and function, showed that clusters in the left superior temporal cortex and right anterior insula were associated with the test. Emerging evidence reported that a more diffuse network of neocortical regions is engaged for the task since multiple cognitive processes are implicated. On the contrary to the finding that correlates of the verbal fluency are largely observed in the left hemisphere, in the present study the design fluency was correlated with the volumes of the right hemisphere. Based on previous lesion studies, left hemisphere lesions are more associated with verbal fluency deficits, whereas right hemisphere lesions are more involved in nonverbal fluency deficits.<sup>11,29,45-47</sup> In accordance with this, Possin et al.<sup>48</sup> identified bilateral frontal and parietal lobes and right temporal lobe as correlates of design fluency. Moreover, the anterior insula was a region that showed a cross-modal association across fluency tests. Unlike other brain regions that are specialized for processing specific forms of information, the hub regions including the anterior insula are critical in modulating overall integration between multiple network systems.<sup>49</sup> An efficient generation of various responses may require a more flexible shifting and modulation of the macroscale brain network.

Our study has several limitations. The subjects in the AD group were older than those in the HC and MCI groups. However, age was entered as a nuisance variable in the statistical analyses. Also, the relatively small sample size may have led to type II error, and future studies with a larger sample will be needed to ensure the generalizability of our results.

The present study investigated patterns of degradation in verbal and nonverbal fluency in patients with AD and MCI. Category and association fluency tasks were the most accurate in discriminating AD from NA and MCI, and category and letter fluency tasks in discriminating MCI from NA. Nonverbal fluency was well preserved in MCI, while significantly deteriorated in AD.

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