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
INTRODUCTION

Decline of executive function has been reported to occur in the early stages of Alzheimer’s disease (AD), and executive dysfunction is associated with accelerated progression of the disease and severe burden of caregiver. Executive function cannot be defined as a unitary concept and is understood as a complex of various cognitive processes. 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; fluency refers to the ability to generate words or visual information under specific constraints such as a fixed time. 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. 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. 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 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). 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 amnestic 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. 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, and inconsistent results on fluency deficit patterns in amnestic MCI have been reported.

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. 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.

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\textsuperscript{20} and Petersen’s criteria.\textsuperscript{21} 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).\textsuperscript{10} 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\textsuperscript{11} 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)  | χ\textsuperscript{2} or F  |
| Gender (Man:Woman)         | 8:19                       | 9:19                       | 9:11        | 1.324\textsuperscript{†}  |
| Age                        | 72.6±5.4                   | 74.8±4.7                   | 78.9±6.2    | 8.050                      |
| Year of education          | 11.8±3.7                   | 9.7±3.2                    | 9.1±4.0     | 3.862                      |
| MMSE                       | 27.7±2.2                   | 24.4±2.6                   | 18.6±3.8    | 58.231                     |
| CDR global                 | 0.2±0.2                    | 0.5±0.1                    | 0.75±0.3    | 44.805                     |
| CDR sum of boxes           | 0.4±0.7                    | 1.8±1.1                    | 4.4±2.1     | 49.633                     |
| ANOVA p-value              | 0.652\textsuperscript{†}  | -                          | -           | -                          |
| p-value for pairwise comparison | HC vs. MCI | HC vs. AD | MCI vs. AD |
| HC vs. MCI                 | -                          | -                          | -           | -                          |
| HC vs. AD                  | 0.380                      | <0.001\textsuperscript{†} | 0.034\textsuperscript{*} |
| MCI vs. AD                 | 0.026\textsuperscript{†}  | 0.102                      | 0.038\textsuperscript{*} |
| 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; †Significant at p<0.001; ‡Chi-square test. |
the severity of cognitive impairments. 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. 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-squared 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 posterior 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, 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.
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 \( (p=0.038 \)\).

**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 to 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 \( (p<0.001 \) 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 p-value | p-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\(^\)† | 0.014* | <0.001\(^\)† | <0.001\(^\)† |
| Category fluency | 22.81±4.30 | 17.14±5.07 | 11.45±2.44 | 24.153  | <0.001\(^\)† | <0.001\(^\)† | 0.001* |
| ‘Animal’        | 12.85±3.22 | 9.50±3.36  | 6.35±1.95 | 16.051  | <0.001\(^\)† | 0.005* | <0.001\(^\)† | 0.005* |
| ‘Fruit’         | 9.96±2.31  | 7.64±2.58  | 5.10±1.62 | 16.627  | <0.001\(^\)† | 0.004* | <0.001\(^\)† | 0.005* |
| Association fluency | 12.33±4.22 | 10.86±4.55 | 5.75±3.32 | 9.188   | <0.001\(^\)† | 1.000 | <0.001\(^\)† | 0.001* |
| ‘Desk’          | 7.51±2.56  | 6.14±2.35  | 3.30±1.63 | 11.286  | <0.001\(^\)† | 0.388 | <0.001\(^\)† | 0.001* |
| ‘Fox’           | 4.81±2.59  | 4.71±2.94  | 2.45±2.19 | 3.813   | 0.027*   | 1.000 | 0.070 | 0.033* |
| Letter fluency  | 11.33±4.19 | 7.93±4.75  | 4.75±3.32 | 6.158   | 0.003*   | 0.115 | 0.002* | 0.176 |
| ‘Ga’            | 6.52±2.42  | 6.44±3.00  | 2.35±1.93 | 7.453   | 0.001*   | 0.152 | 0.001* | 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*   | 1.000 | 0.107 | 0.034* |

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.

*Significant at \( p<0.05 \); †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

![ROC curve analysis](https://dnd.or.kr)

**Fig. 1.** Receiver operating characteristic curve analysis of verbal and nonverbal fluency performances for screening for AD (A) and MCI (B).

| HC vs. MCI | Characteristic       | AUC | Cut-off value | Sensitivity | Specificity |
|------------|----------------------|-----|---------------|-------------|-------------|
| 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 | Characteristic       | AUC | Cut-off value | Sensitivity | Specificity |
|------------|----------------------|-----|---------------|-------------|-------------|
| 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 |
|--------------|--------------------------------------------------|-------------------|--------------|------------|
|              |                                                  |                   | 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 |
|               | R Superior temporal cortex                       | 5.48              | 7,302         | −48 | −9 | −6 |
|               | L Superior temporal cortex                       | 6.44              | 4,297         | −51 | −54| −23 |
|               | L Insula                                         | 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 | L Ventral insula/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  |
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. 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. Literature documented that category-specific deficits may occur due to different brain systems, although it is still being debated. 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 amnestic 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.\(^{14,31}\) 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,\(^{32-34}\) 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,\(^{8}\) 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 elders, and the involvement of the regions was also proved in patients with AD.\(^{35,36}\) 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.\(^{37}\) 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.\(^{36,39}\) 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.\(^{38}\) 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.\(^{40}\)
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.\textsuperscript{41,42}

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.\textsuperscript{43} 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.\textsuperscript{29,44}

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.\textsuperscript{11,29,44-47} In accordance with this, Possin et al.\textsuperscript{48} 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.\textsuperscript{49} 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.
REFERENCES

1. Lambon Ralph MA, Patterson K, Graham N, Dawson K, Hodges JR. Homogeneity and heterogeneity in mild cognitive impairment and Alzheimer’s disease: a cross-sectional and longitudinal study of 55 cases. Brain 2003;126:2350-2362.

2. Royall DR, Lauterbach EC, Kaufer D, Malloy P, Coburn KL, Black KJ, et al. The cognitive correlates of functional status: a review from the Committee on Research of the American Neuropsychiatric Association. J Neuropsychiatry Clin Neurosci 2007;19:249-265.

3. Grober E, Hall C, McGinn M, Nicholls T, Stanford S, Ehrlich A, et al. Neuropsychological strategies for detecting early dementia. J Int Neuropsychol Soc 2008;14:130-142.

4. Elliott R. Executive functions and their disorders. Br Med Bull 2003;65:49-59.

5. Chan RC, Sham D, Touloupolou T, Chen EY. Assessment of executive functions: review of instruments and identification of critical issues. Arch Clin Neuropsychol 2008;23:201-216.

6. Farba CA, Alves HV, Charchat-Fichman H. The most frequently used tests for assessing executive functions in aging. Dement Neuropsychol 2015;9:149-155.

7. Nutter-Upham KE, Saykin AJ, Rabin LA, Roth RM, Wishart HA, Pare N, et al. Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. Arch Clin Neuropsychol 2008;23:229-241.

8. Peter J, Kaiser J, Landerer V, Köstering L, Kaller CP, Heimbach B, et al. Category and design fluency in mild cognitive impairment: performance, strategy use, and neural correlates. Neuropsychologia 2016;93:21-29.

9. Tallberg IM, Ivachova E, Jones Tinghag K, Östberg P. Swedish norms for word fluency tests: FAS, animals and verbs. Scand J Psychol 2008;49:479-485.

10. Benton AL. Development of a multilingual aphasia battery. Progress and problems. J Neurol Sci 1969;9:39-48.

11. Ruff RM, Allen CC, Farrow CE, Niemann H, Wylie T. Figural fluency: differential impairment in patients with left versus right frontal lobe lesions. Arch Clin Neuropsychol 1994;9:41-55.

12. Rinehardt E, Eichstaedt K, Schinka JA, Loewenstein DA, Mattingly M, Fils J, et al. Verbal fluency patterns in mild cognitive impairment and Alzheimer’s disease. Dement Geriatr Cogn Disord 2014;38:1-9.

13. Auriacombe S, Lechevallier N, Amieva H, Harston S, Raoux N, Dartigues JF. A longitudinal study of quantitative and qualitative features of category verbal fluency in incident Alzheimer’s disease subjects: results from the PAQUID study. Dement Geriatr Cogn Disord 2006;21:260-266.

14. Henry JD, Crawford JR, Phillips LH. Verbal fluency performance in dementia of the Alzheimer’s type: a meta-analysis. Neuropsychologia 2004;42:1212-1222.

15. Murphy KJ, Rich JB, Troyer AK. Verbal fluency patterns in amnestic mild cognitive impairment are characteristic of Alzheimer’s type dementia. J Int Neuropsychol Soc 2006;12:570-574.

16. Lonie JA, Herrmann LL, Tierney KM, Donaghey C, O’Carroll R, Lee A, et al. Lexical and semantic fluency discrepancy scores in aMCI and early Alzheimer’s disease. J Neuropsychol 2009;3:79-92.

17. Baldo JV, Shimamura AP. Letter and category fluency in patients with frontal lobe lesions. Neuropsychology 1998;12:259-267.

18. Baldo JV, Schwartz S, Wilkins D, Dronkers NF. Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. J Int Neuropsychol Soc 2006;12:896-900.
19. Mummery CJ, Patterson K, Hodges JR, Wise RJ. Generating 'tiger' as an animal name or a word beginning with T: differences in brain activation. Proc Biol Sci 1996;263:989-995.

20. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology 1984;34:939-944.

21. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, Tangels E. Aging, memory, and mild cognitive impairment. Int Psychogeriatr 1997;9 Suppl 1:65-69.

22. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.

23. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412-2414.

24. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007;38:95-113.

25. Mok EH, Lam LC, Chiu HF. Category verbal fluency test performance in Chinese elderly with Alzheimer's disease. Dement Geriatr Cogn Disord 2004;18:120-124.

26. Isaacs B, Kennie AT. The Set test as an aid to the detection of dementia in old people. Br J Psychiatry 1973;123:467-470.

27. Adlam AL, Bozeat S, Arnold R, Watson P, Hodges JR. Semantic knowledge in mild cognitive impairment and mild Alzheimer's disease. Cortex 2006;42:675-684.

28. Joubert S, Felician O, Barbeau EJ, Didic M, Poncet M, Ceccaldi M. Patterns of semantic memory impairment in Mild Cognitive Impairment. Behav Neurol 2008;19:35-40.

29. Fama R, Sullivan EV, Shear PK, Cahn-Weiner DA, Marsh L, Lim KO, et al. Structural brain correlates of verbal and nonverbal fluency measures in Alzheimer’s disease. Neuropsychology 2000;14:29-40.

30. Ting SK, Hameed S, Earnest A, Tan EK. Dissociative semantic breakdown in Alzheimer’s disease: evidence from multiple category fluency test. Clin Neurol Neurosurg 2013;115:1049-1051.

31. Giffard B, Desgranges B, Nore-Mary F, Lalevée C, Beaulieu X, de la Sayette V, et al. The dynamic time course of semantic memory impairment in Alzheimer’s disease: clues from hyperpriming and hypopriming effects. Brain 2002;125:2044-2057.

32. Duong A, Whitehead V, Hanratty K, Chertkow H. The nature of lexico-semantic processing deficits in mild cognitive impairment. Neuropsychologia 2006;44:1928-1935.

33. Ready RE, Ott BR, Grace J, Cahn-Weiner DA. Apathy and executive dysfunction in mild cognitive impairment and Alzheimer disease. Am J Geriatr Psychiatry 2003;11:222-228.

34. Van Der Flier WM, Van Den Heuvel DM, Weverling-Rijnsburger AW, Spilt A, Bollen EL, Westendorp RG, et al. Cognitive decline in AD and mild cognitive impairment is associated with global brain damage. Neurology 2002;59:874-879.

35. Hirshorn EA, Thompson-Schill SL. Role of the left inferior frontal gyrus in covert word retrieval: neural correlates of switching during verbal fluency. Neuropsychologia 2006;44:2547-2557.

36. Katzev M, Tüscher O, Hennig J, Weiller C, Kaller CP. Revisiting the functional specialization of left inferior frontal gyrus in phonological and semantic fluency: the crucial role of task demands and individual ability. J Neurosci 2013;33:7837-7845.

37. Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB; Alzheimer’s Disease Neuroimaging Initiative. What is normal in normal aging? Effects of aging, amyloid and Alzheimer’s disease on the cerebral cortex and the hippocampus. Prog Neurobiol 2014;117:20-40.
38. Grogan A, Green DW, Ali N, Crinion JT, Price CJ. Structural correlates of semantic and phonemic fluency ability in first and second languages. Cereb Cortex 2009;19:2690-2698.

PUBMED | CROSSREF

39. Smith SM, Jenkinson M, Woolrich MW, Behrens TEJ, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 2004;23 Suppl 1:S208-S219.

PUBMED | CROSSREF

40. Biesbroek JM, van Zandvoort MJE, Kappelle LJ, Velthuis BK, Biessels GJ, Postma A. Shared and distinct anatomical correlates of semantic and phonemic fluency revealed by lesion-symptom mapping in patients with ischemic stroke. Brain Struct Funct 2016;221:2123-2134.

PUBMED | CROSSREF

41. Mion M, Patterson K, Acosta-Cabronero J, Pengas G, Izquierdo-Garcia D, Hong YT, et al. What the left and right anterior fusiform gyri tell us about semantic memory. Brain 2010;133:3256-3268.

PUBMED | CROSSREF

42. Birn RM, Kenworthy L, Case L, Caravella R, Jones TB, Bandettini PA, et al. Neural systems supporting lexical search guided by letter and semantic category cues: a self-paced overt response fMRI study of verbal fluency. Neuroimage 2010;49:1099-1107.

PUBMED | CROSSREF

43. Schmidt CS, Nitschke K, Bormann T, Römer P, Kümmerer D, Martin M, et al. Dissociating frontal and temporal correlates of phonological and semantic fluency in a large sample of left hemisphere stroke patients. Neuroimage Clin 2019;23:101840.

PUBMED | CROSSREF

44. Pasquier F, Lebert F, Grymonprez L, Petit H. Verbal fluency in dementia of frontal lobe type and dementia of Alzheimer type. J Neurol Neurosurg Psychiatry 1995;58:81-84.

PUBMED | CROSSREF

45. Benton AL. Differential behavioral effects in frontal lobe disease. Neuropsychologia 1968;6:53-60.

CROSSREF

46. Jones-Gotman M, Milner B. Design fluency: the invention of nonsense drawings after focal cortical lesions. Neuropsychologia 1977;15:653-674.

PUBMED | CROSSREF

47. Miceli G, Caltagirone C, Gainotti G, Masullo C, Silveri MC. Neuropsychological correlates of localized cerebral lesions in non-aphasic brain-damaged patients. J Clin Neuropsychol 1981;3:53-63.

PUBMED | CROSSREF

48. Possin KL, Chester SK, Lalaz V, Bostrom A, Rosen HJ, Miller BL, et al. The frontal-anatomic specificity of design fluency repetitions and their diagnostic relevance for behavioral variant frontotemporal dementia. J Int Neuropsychol Soc 2012;18:834-44.

PUBMED | CROSSREF

49. Gordon EM, Lynch CJ, Gratton C, Laumann TO, Gilmore AW, Greene DJ, et al. Three distinct sets of connector hubs integrate human brain function. Cell Reports 2018;24:1687-1695.e4.

PUBMED | CROSSREF