Dement Neurocogn Disord. 2022 Jan;21(1):17-29
https://doi.org/10.12779/dnd.2022.21.1.17
pISSN 1738-1495·eISSN 2384-0757

DND Dementia and Neurocognitive Disorder

Original Article

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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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OPEN ACCESS

Received: Oct 16, 2021
Revised: Nov 28, 2021
Accepted: Dec 1, 2021
Published online: Jan 7, 2022

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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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Funding
This work was supported by a grant from the National Research Foundation of Korea (NRF) grant funded by the Korea Government (MEST; grant No. NRF-2018R1A5A2025964 and NRF-2014M3C7A1046042).

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Kwak S, Shin SA, Ko H, Youn JH, Lee JY; Data curation: Kim H, Oh DJ, Youn JH, Lee JY, Kim YK; Formal analysis: Kwak S, Shin SA; Funding acquisition: Oh DJ, Youn JH, Lee JY, Kim YK; Investigation: Ko H, Kim H, Youn JH, Lee JY, Kim YK; Methodology: Kwak S, Shin SA, Youn JH; Project administration: Kim H, Oh DJ, Youn JH, Lee JY, Kim YK; Supervision: Youn JH, Lee JY; Writing - original draft: Kwak S, Shin SA; Writing - review & editing: Kwak S, Shin SA, Ko H.

INTRODUCTION

Decline of executive function has been reported to occur in the early stages of Alzheimer's disease (AD),[1,2] and executive dysfunction is associated with accelerated progression of the disease and severe burden of caregiver.[3] Executive function cannot be defined as a unitary concept and is understood as a complex of various cognitive processes.[4,5] 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[6]; fluency refers to the ability to generate words or visual information under specific constraints such as a fixed time.[5,7] 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.[6,8,9] 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.[10] 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 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.[11] 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,[12-14] and inconsistent results on fluency deficit patterns in amnestic MCI have been reported.[15,16]

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.[8,17] 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.[18,19]

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[20] and Petersen's criteria.[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).[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[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 shorted 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)	$ 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‡	0.562‡	-	-	-
Age	72.6±5.4	74.8±4.7	78.9±6.2	8.050	0.001*	0.380	<0.001†	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†	<0.001†	<0.001†	<0.001†
CDR global	0.2±0.2	0.5±0.1	0.75±0.3	44.805	<0.001†	<0.001†	<0.001†	0.001
CDR sum of boxes	0.4±0.7	1.8±1.1	4.4±2.1	49.633	<0.001†	0.001*	<0.001†	<0.001†

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.[22] 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.[23] 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 $ 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,[24] 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 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†	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±2.28	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	4.64±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

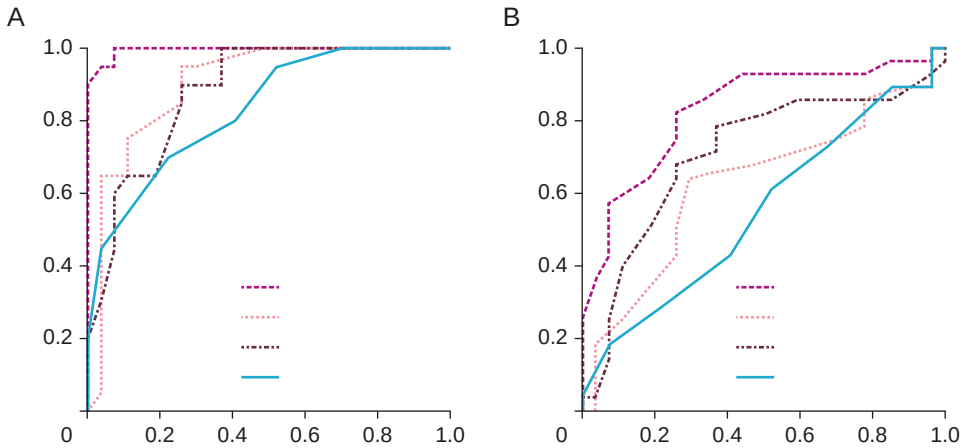

Fig. 1. Receiver operating characteristic curve analysis of verbal and nonverbal fluency performances for screening for AD (A) and MCI (B).
HC: healthy elderly controls, MCI: mild cognitive impairment, AD: Alzheimer's disease.

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.[25,26] 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.[15,27,28] Literature documented that category-specific deficits may occur due to different brain systems, although it is still being debated.[29,30] 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