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Functional Neural Correlates of Semantic Fluency Task Performance in Mild Cognitive Impairment and Alzheimer's Disease: An FDG-PET Study

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Abstract.
Background: Total score (TS) of semantic verbal fluency test (SVFT) is generally used to interpret results, but it is ambiguous as to specific neural functions it reflects. Different SVFT strategy scores reflecting qualitative aspects are proposed to identify specific cognitive functions to overcome limitations of using the TS.
Objective: Functional neural correlates of the TS as well as the other strategy scores in subjects with mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia using Fluorine-18-Fluorodeoxyglucose positron emission tomography (FDG-PET).
Methods: Correlations between various SVFT scores (i.e., TS, mean cluster size, switching (SW), hard switching, cluster switching (CSW)) and cerebral glucose metabolism were explored using voxelwise whole-brain approach. Subgroup analyses were also performed based on the diagnosis and investigated the effects of disease severity on the associations.
Results: Significant positive correlation between TS and cerebral glucose metabolism was found in prefrontal, parietal, cingulate, temporal cortex, and subcortical regions. Significantly increased glucose metabolism associated with the SW were found in similar but smaller regions, mainly in the fronto-parieto-temporal regions. CSW was only correlated with the caudate.

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In the subgroup analysis conducted to assess different contribution of clinical severity, differential associations between the strategy scores and regional glucose metabolism were found.
Conclusion: SW and CSW may reflect specific language and executive functions better than the TS. The SVFT is influenced by brain dysfunction due to the progression of AD, as demonstrated by the SW with larger involvement of temporal lobe for the AD, and CSW with significant association only for the MCI.

Keywords: Alzheimer's disease, dementia, fluorodeoxyglucose F18, mild cognitive impairment, neuropsychological tests, positron emission tomography

INTRODUCTION

Semantic verbal fluency test (SVFT), which assesses the ability to generate as many words as possible from a certain category within a time limit, is a widely used test to assess for language and executive dysfunctions in individuals with Alzheimer's disease (AD) and related cognitive disorders [1]. In addition to language ability and executive functions, the SVFT is considered to tap into other functions such as attention, working memory, and semantic memory [2, 3].

The SVFT total score (TS) (i.e., sum of correctly generated words according to the administration rule) is commonly used in clinical setting. Given that the TS is influenced by numerous cognitive functions, however, it is unclear as to which specific cognitive functions it actually reflects. To overcome such limitation, several strategy scores were developed based on an individual's approaches on clustering or switching such as mean cluster size (MCS), switching (SW), hard switching (HSW), and cluster switching (CSW) [4–6]. Specifically, it was suggested that MCS is associated with verbal memory, SW with cognitive flexibility, HSW with speed of information processing, and CSW with cognitive flexibility [4–6]. The SW and the MCS were shown to be particularly impaired in individuals with AD dementia [7–9].

Investigation on the associations between neuroimaging and cognitive performance helps to understand possible links between brain and behaviors. Compared to normal aging, reduction in glucose metabolism can be identified in AD as well as MCI patients [10, 11], and glucose hypometabolism using FDG-PET imaging represents presymptomatic feature of AD development as well as expression of AD [12]. Thus, significant association between each strategy SVFT score and cerebral glucose metabolism (CMglc) according to the diagnoses may help to identify the affected brain areas and related cognitive functions according to the disease stages. Earlier studies using [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) reported that the SVFT TS was associated with CMglc in various brain regions including the frontal, temporal, parietal, and cingulate cortices in AD dementia patients [13, 14]. However, limited information is available regarding functional neuroanatomical substrates of the scores of clustering or switching strategies. To the best of our knowledge, only one structural MRI study examined and reported the neural correlation of the SVFT MCS, number of clusters, HSW, and CSW in individuals with mild cognitive impairment (MCI) [15]; this report was based on only 20 MCI patients and 30 healthy controls. Confirming the neural basis of the each SVFT score may help clinicians to identify which brain dysfunction is present, and plan interventions accordingly to make up for such cognitive impairments. Therefore, further delineation of the functional neuroanatomical substrates of the scores of clustering or switching strategies in individuals on diverse cognitive impairment spectrum is needed using a larger sample.

In this context, the present study aims to identify the brain regions with regional CMglc correlating with each of the five SVFT scores including the TS and the four strategy scores reflecting qualitative aspects (i.e., MCS, SW, HSW, and CSW) in individuals with MCI and AD dementia. Voxel-wise analysis was used to explore the entire brain regions without *a priori* hypothesis.

MATERIALS AND METHODS

Subjects

The study subjects were recruited from patients who visited the Dementia and Age-Associated Cognitive Decline clinic of the Seoul National University Hospital in Seoul, South Korea. The study included 219 MCI (179 amnestic MCI and 40 non-amnestic MCI) and 197 AD dementia patients. All MCI subjects were diagnosed according to the criteria of the National Institute on Aging and the Alzheimer's

Association (NIA-AA) guidelines [16] and had global Clinical Dementia Rating (CDR) score of 0.5. AD dementia subjects met the criteria for dementia of the Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition [17] and the criteria of probable AD of the National Institute on Aging and the Alzheimer's Association (NIA-AA) guidelines [16]. The exclusion criteria were as follows: Any present serious medical psychiatric and neurological disorder that could affect mental function; evidence of focal brain lesions on MRI; the presence of severe behavioral or communication problems that would make a clinical or PET examination difficult; or absence of a reliable informant. The Institutional Review Board of the Seoul National University Hospital, South Korea, approved the study protocol (H-1610-125-803), and informed consents were obtained from all patients and their caregivers of the AD patients.

Clinical assessment

All the subjects were examined according to the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) clinical assessment battery [18, 19] by psychiatrists with expertise in dementia research. Psychiatric, general physical, and neurological examinations were performed along with routine laboratory tests and MRI of the brain. Reliable informants were interviewed to acquire accurate information regarding the cognitive, emotional, and functional changes as well as the medical history of the patients. On average, PET data was obtained within 9 days of the clinical and neuropsychological assessments. Psychiatrists referred to the presence of temporal and parietal hypometabolism for evaluating whether the likelihood of AD is high in individuals with probable AD diagnosis. Other neuroimaging findings as well as blood biomarkers such as *APOE* were also considered as supporting factor in diagnoses. Clinical decisions on diagnosis and CDR [20] were made from consensus conferences held with trained psychiatrists and neuropsychologist with expertise in dementia after reviewing all available data.

Neuropsychological assessments

All subjects were administered a comprehensive neuropsychological assessment battery by experienced psychometrists under supervision by a neuropsychologist (DY).

Semantic verbal fluency test and scores

All subjects were required to name words belonging to the animal category in sixty seconds. Five scores were obtained from SVFT performance. The scoring methods used in this study are described below, and more details are provided in the Supplementary Figure 1.

Total score (TS). The TS is the total number of words generated during the time limit, excluding perseverative or intrusive words which are not from the appropriate category (i.e., not from the animal category) [21].

Mean cluster size (MCS). A cluster is defined as words within a subcategory (e.g., 'pets': cat, dog, hedgehog). The cluster size is counted beginning with the second word in each cluster (e.g., 'pets' including cat, dog, and hedgehog represent cluster size two). Several indices for clustering process have been suggested (e.g., number of clusters, etc.). Among them, the MCS is the most commonly used [22]. To obtain the MCS, cluster sizes were summed and divided by the number of clusters. Unlike the TS, errors and repetitions were included in calculations of the cluster size [4].

Switching (SW). The SW is obtained by calculating the number of transitions between multi-word clusters, between a multi-word cluster and a non-clustered word (e.g., 'cat and dog' followed by 'shark and ray' or only 'shark'), or between two non-clustered words (e.g., 'cat' and 'shark') [5]. The SW is considered to reflect strategic searching and ability to shift mental sets [4, 5]. Errors and repetitions were also included in calculation of the SW score [4].

Hard switching (HSW). To clarify the validity of the SW construct, it was suggested to decompose SW into subtypes (i.e., hard switching (HSW), cluster switching (CSW)) [5]. The HSW is defined by transitions between a cluster and non-clustered words (e.g., 'cat and dog' and 'tuna') or between two non-clustered words (e.g., 'cat' and 'tuna'). For the HSW, a non-cluster word is needed; this non-cluster word does not form a cluster and therefore constitutes a cluster size of zero. It is known to reflect speed of information processing and mental productivity [5]. Specifically, as fast switching is more important than constructing a significant cluster, HSW can be more closely associated with speed of information processing [6].

Cluster switching (CSW). The CSW is defined by counting the transitions between clusters, which consists at least two words. For example, the words

sequence 'poodle', 'Maltese', 'dove', 'sparrow' counts as one CSW between dogs and birds. For obtaining the CSW, cluster size equal or greater than one is essential. The CSW is known to reflect more meticulous cognitive strategy and flexibility [5, 6].

Other neuropsychological tests

Six neuropsychological tests included in the CERAD-K neuropsychological battery [19] are 15-item Boston Naming Test (BNT), Word List Memory (WLM), Word List Recall (WLR), Word List Recognition (WLRc), Constructional Praxis (CP), Constructional Recall (CR), the Stroop Color Word Test (SCWT), and the Frontal Assessment Battery (FAB) [23].

Image acquisition and preprocessing of FDG-PET

FDG-PET scans were obtained using the ECAT EXACT 47 scanner (Siemens-CTI, Knoxville, TN, USA), which has an intrinsic resolution of 5.2 mm full width at half maximum (FWHM) and the images of 47 contiguous transverse planes with a 3.4-mm thickness for a longitudinal field of view of 16.2 cm. Before administering FDG, transmission scanning was performed using 3 germanium-68 rod sources to correct the attenuation. Static emission scans began 30 min after the intravenous injection of 370 MBq (10 mCi) FDG and were continued for 30 min. All of the [^{18}F]FDG-PET scans were performed in a dimly lit room with minimal auditory stimulation during both the injection and the PET scanning. The patients were in the supine position with their eyes closed during the scanning in order to minimize the confounding effects of any activity. All PET-scans were first assessed and reviewed by neuroradiologists for quality check. The transaxial images were reconstructed using a filtered back-projection algorithm employing a Shepp-Logan filter with a cut-off frequency of 0.3 cycles/pixel as $128 \times 128 \times 47$ matrices with a size of $2.1 \times 2.1 \times 3.4$ mm. Imaging data were preprocessed and statistically analyzed using Statistical Parametric Mapping 12 (SPM12; Institute of Neurology, University College of London, UK) implemented in Matlab (MathWorks Inc, Natick, MA, USA). Before statistical analysis, all the images were spatially normalized to the Montreal Neurological Institute (MNI; McGill University, Montreal, Quebec, Canada) space, in order to correct for interpatient anatomical variability [24]. An affine transformation was performed to determine the 12 optimal parameters, essential for registering the brain on the template. Subtle differences between the transformed image and the template were removed by the nonlinear registration method, using the weighted sum of predefined smooth basis functions used in a discrete cosine transformation. The spatially normalized images with a voxel size of $1 \times 1 \times 1$ mm were then smoothed with a Gaussian filter of 12 mm FWHM, both to accommodate interpatient differences in gyral and functional anatomy and to increase the signal-to-noise ratio in the data set. The glucose metabolism value of each voxel was normalized using the pontine value, which was extracted for each scan, given that glucose metabolism in the pons tends to be relatively preserved in AD [25].

Analysis of demographic, clinical, and neuropsychological data

Differences in demographic, clinical variables, and neuropsychological data between diagnostic subgroups were tested using Student's t test or chi-square test. All analyses were performed using SPSS software, version 25.0 (SPSS, Cary, North Carolina).

Image analysis of FDG-PET

To investigate the relationship between each of the SVFT scores and CMglc, we used voxel-based approach without *a priori* hypothesis. Preprocessed FDG-PET images and each SVFT score of participants were entered into a design matrix using full factorial option of SPM12, with age, gender, and education included as nuisance covariates. For illustration, statistical threshold was applied at $p < 0.001$ (uncorrected) for voxel height ($k > 20$ voxels) (Fig. 1). The MNI coordinates were converted into Talairach coordinates [26] for presentation. For voxel-wise analyses, the results were examined at $p < 0.05$ with correction for multiple comparisons based on cluster-correction procedure using Analysis of Functional NeuroImage (i.e., 3dClustSim, version built on February 10, 2017) with 10,000 iterations of Monte Carlo simulations on dataset using anatomical cerebrum mask with 1,801,748 voxels. The significant clusters after multiple comparisons correction were reported at uncorrected $p < 0.005$ and $k > 1062$ voxels.

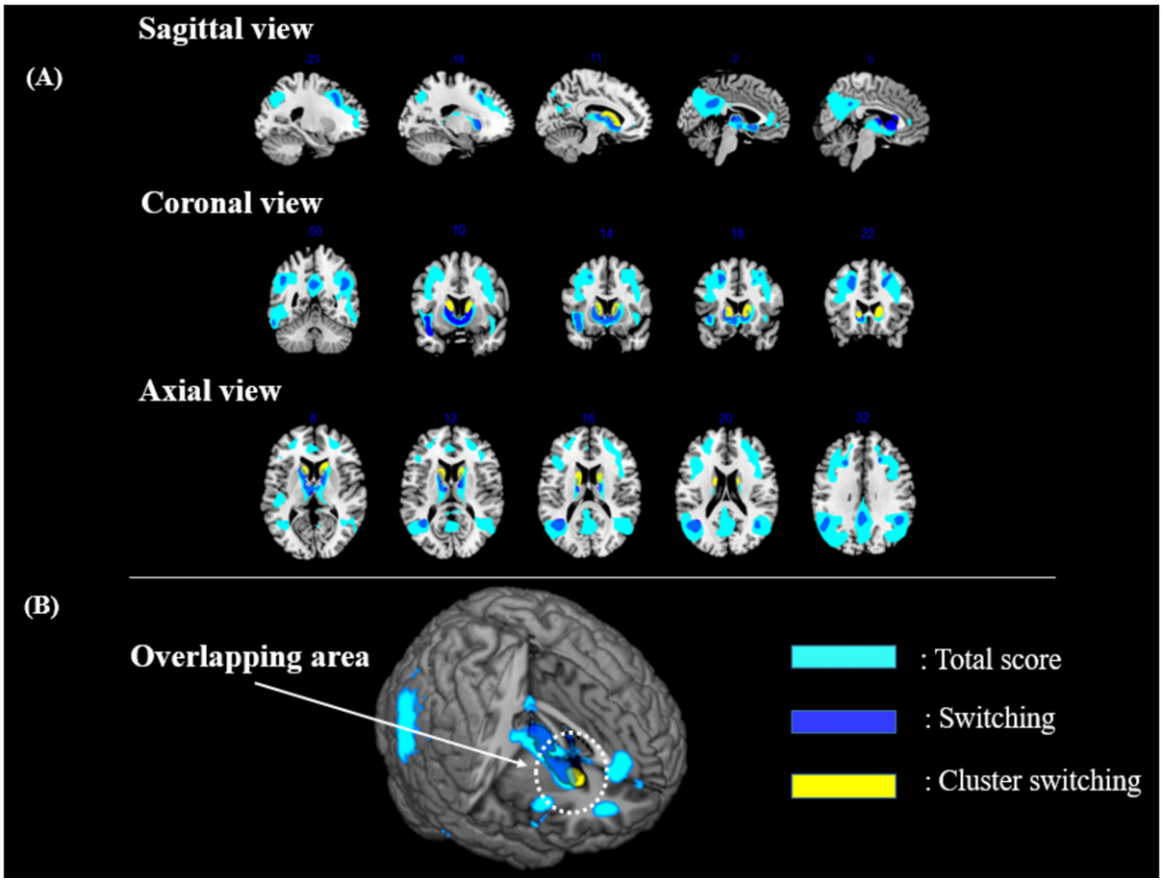

Fig. 1. A) Regions that are positively correlated with each SVFT scores in total group. Only significant correlations between SVFT score and region are represented. ($p < 0.001$ (uncorrected) for voxel height, $k > 20$ for cluster extent). B) A summary of all findings is visualized on a rendered template brain in MRIcron, with different colors for each region to best illustrate overlapping nature (Sky blue, total score; Blue, switching; Yellow, cluster switching).

RESULTS

Demographic and clinical characteristics of the subjects

Demographic and clinical characteristics of the subjects are shown in Table 1. The sample consisted of 416 participants, of which 65.6 % ($n = 273$) were female. Subjects had a mean age of 72.6 years ($SD = 8.4$) and average years of education of 9.7 years ($SD = 5.3$; range = 0–23). The median Global CDR was 0.5. For the whole subjects, the range of Global CDR was from 0.5 to 1.0, and all subjects diagnosed with MCI had Global CDR of 0.5. The mean of Mini-Mental Status Exam (MMSE) score was 20.8 ($SD = 5.0$). To investigate the moderating effect of the disease severity, we investigated the relationship between the SVFT scores and CMglc in each subgroup by diagnosis—MCI and AD (Table 1). There were no significant differences in age or education; gender distribution was statistically significantly different by diagnosis.

SVFT scores and other neuropsychological test scores in overall participants

Regarding the SVFT performance, there were significant differences in four SVFT scores of clustering or switching strategies between the MCI and AD group, except for the MCS (Table 1). With respect to all other six neuropsychological tests, the MCI group performed significantly better than the AD group.

Correlations between SVFT scores and CMglc in overall participants

Significant positive correlations between each of the TS, SW, and CSW and CMglc were found in

Table 1
Demographic characteristics and neuropsychological test results of the participants

Characteristics	Total Patients ($n=416$)	MCI ($n=219$)	AD ($n=197$)	p
Age, y (SD)	72.6 (8.4)	72.2 (7.7)	73.1 (9.1)	0.281[a]
Education, y (SD)	9.7 (5.3)	9.7 (5.0)	9.7 (5.7)	1.000[a]
Sex, *n* (M/F)	143 / 273	64 / 155	79 / 118	0.020[b]
MMSE, raw score (SD)	20.8 (5.0)	23.1 (3.8)	18.1 (5.0)	<0.001[a]
CDR sum of boxes (SD)	2.7 (1.6)	1.5 (0.7)	4.0 (1.4)	<0.001[a]
Semantic fluency (SD)				
Total score	9.8 (4.0)	11.0 (3.8)	8.6 (3.7)	<0.001[a]
Mean cluster size	1.9 (1.6)	1.8 (1.4)	2.0 (1.7)	0.138[a]
Switching	3.4 (2.5)	3.9 (2.4)	2.9 (2.4)	<0.001[a]
Hard switching	2.6 (2.3)	2.9 (2.4)	2.2 (2.2)	0.004[a]
Cluster switching	0.9 (1.0)	1.0 (1.0)	0.7 (1.0)	0.002[a]
Other neuropsychological tests (SD)				
FAB	11.5 (3.9)	12.4 (3.3)	10.4 (4.2)	<0.001[a]
Boston naming test	9.1 (3.1)	9.9 (2.6)	8.2 (3.3)	<0.001[a]
Word list immediate memory	11.5 (4.5)	13.4 (4.0)	9.4 (4.1)	<0.001[a]
Word list delayed recall	2.5 (2.0)	3.3 (2.0)	1.5 (1.5)	<0.001[a]
Word list recognition	6.1 (3.0)	7.2 (2.5)	4.8 (3.1)	<0.001[a]
Constructional praxis	8.7 (2.1)	9.2 (1.9)	8.4 (2.3)	0.004[a]
Constructional recall	2.2 (2.5)	3.0 (2.7)	1.4 (2.0)	<0.001[a]
Stroop color	45.8 (15.1)	50.2 (13.6)	41.1 (15.2)	<0.001[a]
Stroop word	57.3 (20.5)	62.7 (18.0)	51.4 (21.4)	<0.001[a]
Stroop color-word	23.6 (12.1)	25.9 (11.4)	21.1 (12.4)	<0.001[a]

MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; CDR, Clinical Dementia Rating. [a]tested with student *t* test. [b]tested with chi-square test.

Table 2
Positive associations between rCMglc and semantic fluency in overall group ($N=416$)

Index	Brain Regions	BA	Coordinates (mm)			Extent Voxels (N)	T value	Z score	p (uncorrected)
			X	Y	Z				
Total Score	Bilateral caudate, angular gyrus, PCC, precuneus	–/39/23/7	10	12	6	1598890	5.82	5.70	<0.001
	L middle frontal gyrus	8	–26	28	40	24627	4.71	4.65	<0.001
	R middle frontal gyrus	8	24	32	40	25010	4.48	4.43	<0.001
	L insula	13	–39	14	3	3553	4.07	4.02	<0.001
	L transverse temporal gyrus	41	–45	–24	14	2204	3.86	3.82	<0.001
	L anterior cingulate	32	–5	42	11	3029	3.42	3.40	<0.001
	R insula	13	39	16	5	1826	3.41	3.38	<0.001
Mean cluster size	No regions								
Switching	Bilateral caudate, L thalamus	–	–11	15	5	15940	5.06	4.98	<0.001
	L inferior parietal lobule	40	–37	–51	22	7144	4.44	4.39	<0.001
	R middle frontal gyrus	8	23	30	40	1209	3.76	3.73	<0.001
	L cingulate gyrus	31	–1	–42	32	1932	3.62	3.59	<0.001
	R supramarginal gyrus, angular gyrus	40/39	46	–43	33	2224	3.55	3.52	<0.001
	L insula	13	–40	14	3	1753	3.55	3.52	<0.001
	L middle frontal gyrus	8	–22	27	36	1286	3.51	3.48	<0.001
	L middle temporal gyrus	20	–56	–37	–9	1281	3.44	3.41	<0.001
Hard switching	No regions								
Cluster switching	R caudate	–	12	15	5	2563	4.25	4.20	<0.001
	L caudate	–	–12	7	13	2408	4.08	4.04	<0.001

SPM12 analysis of covariance output for all patients with age, education, and sex as covariates; BA, Brodmann areas; L, left hemisphere; R, right hemisphere; PCC, posterior cingulate cortex.

various cortical and subcortical regions for overall subjects (Table 2 and Fig. 1). The TS was positively associated with CMglc mainly in the bilateral lateral prefrontal and inferior parietal cortices, insula, posterior cingulate cortex (PCC)/precuneus, caudate and left temporal cortex. The SW had significant positive correlations with CMglc in similar, but in much smaller brain regions, mainly including the bilateral

Table 3
Positive associations between rCMglc and semantic fluency in MCI group ($N = 219$)

Index	Brain Regions	BA	Coordinates (mm)			Extent Voxels (N)	T value	Z score	p (uncorrected)
			X	Y	Z				
Total Score	R superior frontal gyrus	10	25	52	24	29623	4.23	4.14	< 0.005
	L middle frontal gyrus	10	–22	56	21	6302	3.88	3.81	< 0.005
	L thalamus	–	–6	–7	11	16222	3.81	3.75	< 0.005
	R supramarginal gyrus	40	46	–43	37	5614	3.73	3.67	< 0.005
	L cingulate gyrus	31	0	–42	33	2903	3.37	3.32	< 0.005
	R inferior temporal gyrus	20	57	–31	–20	2916	3.28	3.24	< 0.005
	L inferior parietal lobule	40	–47	–48	36	7147	3.27	3.22	< 0.005
Switching	L anterior cingulate	24	–1	37	4	10676	3.66	3.60	< 0.005
	L inferior parietal lobule	40	–46	–45	41	3156	3.38	3.33	< 0.005
	L middle temporal gyrus	21	–62	–28	–2	2045	3.32	3.28	< 0.005
	L middle frontal gyrus	10	–17	57	13	1158	3.28	3.24	< 0.005
	R superior temporal gyrus	39	47	–51	18	1113	3.06	3.03	< 0.005
	L superior frontal gyrus	8	–21	21	44	1062	2.99	2.96	< 0.005
Cluster switching	R insula	13	39	–16	4	3880	3.58	3.52	< 0.005
	R caudate	–	9	13	1	7964	3.54	3.49	< 0.005
	R medial frontal gyrus	6	1	30	35	2792	3.41	3.36	< 0.005
	R inferior parietal lobule	40	55	–47	38	6123	3.26	3.21	< 0.005
	R fusiform gyrus	37	46	–45	–14	1086	2.98	2.95	< 0.005
	R middle temporal gyrus	39	55	–56	13	2405	2.96	2.93	< 0.005
	R inferior temporal gyrus	20	52	–26	–14	1948	2.93	2.89	< 0.005

SPM12 analysis of covariance output for all patients with age, education, and sex as covariates; BA, Brodmann areas; L, left hemisphere; R, right hemisphere.

Table 4
Positive associations between rCMglc and semantic fluency in AD group ($N = 197$)

Index	Brain Regions	BA	Coordinates (mm)			Extent Voxels (N)	T value	Z score	p (uncorrected)
			X	Y	Z				
Total Score	L superior temporal gyrus/precuneus	22/7	–33	–52	21	20260	4.68	4.55	< 0.005
	R superior temporal gyrus	22	36	–47	21	6131	3.69	3.63	< 0.005
	L insula	13	–42	–15	11	1394	3.24	3.19	< 0.005
	L middle frontal gyrus	8	–23	29	38	2283	2.98	2.94	< 0.005
Switching	R caudate	–	19	19	21	18030	4.02	3.94	< 0.005
	L superior temporal gyrus	22	–33	–48	20	2830	4.02	3.93	< 0.005
Cluster switching	No regions								

SPM12 analysis of covariance output for all patients with age, education, and sex as covariates; BA, Brodmann areas; L, left hemisphere; R, right hemisphere.

prefrontal and inferior parietal cortices, and the left cingulate and temporal cortices, and insula, as well as the left thalamus and caudate. In contrast, significant positive correlations were found between the CSW and CMglc only in the bilateral caudate. The MCS and the HSW did not have any significant correlation with regional CMglc.

Subgroup analyses: Correlations between SVFT scores and CMglc in two diagnostic subgroups

Given that the MCS and HSW did not show presence of correlation in the overall group, subgroup analyses focused on the TS, SW, and CSW. The subgroup analyses revealed that brain regions showing significant positive correlations between each SVFT score and CMglc were different according to the diagnosis (Tables 3 and 4, and Supplementary Figure 2). In the MCI group, significant positive correlations between the SVFT TS and CMglc were predominantly found in the prefrontal, anterior cingulate and inferior parietal cortices, and thalamus, whereas the correlations were observed mainly in the superior temporal gyrus in the AD dementia group. Positive correlations between the SW and CMglc were observed in the anterior cingulate,

Table 5
Positive associations between rCMglc and semantic fluency in aMCI (amnestic MCI) group ($N = 179$)

Index	Brain Regions	BA	Coordinates (mm)			Extent Voxels (N)	T value	Z score	p (uncorrected)
			X	Y	Z				
Total Score	L middle frontal gyrus	10	–23	56	21	1079	4.07	3.97	< 0.001
	R superior frontal gyrus	10	26	52	24	592	4.03	3.94	< 0.001
	R anterior insula	13	38	10	–8	1722	3.90	3.81	< 0.001
	L anterior cingulate	32	–1	40	9	1078	3.74	3.67	< 0.001
	L caudate	–	–5	15	–2	1103	3.55	3.48	< 0.001
	L thalamus	–	–7	–7	11	402	3.54	3.47	< 0.001
	R middle temporal gyrus	21	65	–19	–6	262	3.41	3.35	< 0.001
	R inferior temporal gyrus	20	59	–32	–21	612	3.40	3.34	< 0.001
	L inferior temporal gyrus	20	–48	–5	–34	151	3.34	3.29	< 0.001
Switching	R superior temporal gyrus	38	41	3	–12	1392	3.96	3.87	< 0.001
	R inferior temporal gyrus	20	45	–16	–27	106	3.33	3.28	< 0.001
	L superior frontal gyrus	10	–19	57	14	76	3.28	3.22	< 0.001
	R superior frontal gyrus	10	26	54	22	24	3.22	3.17	< 0.001
Cluster switching	L thalamus	–	–11	–8	13	673	3.73	3.66	< 0.001
	L caudate	–	–10	18	0	244	3.45	3.38	< 0.001
	R Thalamus	–	3	–7	–3	112	3.36	3.30	< 0.001
	R caudate	–	10	16	0	193	3.34	3.28	< 0.001
	R inferior parietal lobule	40	62	–28	38	149	3.33	3.27	< 0.001

SPM12 analysis of covariance output for all patients with age, education, and sex as covariates; BA, Brodmann areas; L, left hemisphere; R, right hemisphere; PCC, posterior cingulate cortex.

Table 6
Positive associations between rCMglc and semantic fluency in naMCI (non-amnestic MCI) group ($N = 40$)

Index	Brain Regions	BA	Coordinates (mm)			Extent Voxels (N)	T value	Z score	p (uncorrected)
			X	Y	Z				
Total Score	No regions								
Switching	R middle frontal gyrus	8	32	10	39	69	3.78	3.44	< 0.001
Cluster switching	R inferior temporal gyrus	36	27	–4	–27	290	3.87	3.51	< 0.001

SPM12 analysis of covariance output for all patients with age, education, and sex as covariates; BA, Brodmann areas; L, left hemisphere; R, right hemisphere; PCC, posterior cingulate cortex.

inferior parietal, temporal, and prefrontal cortices in the MCI group, whereas positive correlations were found in focal regions including the caudate and superior temporal cortex in the AD group. Significant positive correlations were found between the CSW and CMglc in the insula, caudate, and medial frontal and temporo-parietal cortices in the MCI group, whereas no significant correlations were observed for the AD dementia group.

Subgroup analyses: Correlations between SVFT scores and CMglc in MCI subtypes

MCI can be categorized into amnestic (aMCI) and non-amnestic MCI (naMCI) types according to the defining cognitive features and pathological characteristics. Considering that aMCI specifically demonstrates memory impairment with a higher risk of conversion to AD [27, 28], we performed additional subgroup analysis, dividing the MCI group into aMCI and naMCI. Compared to naMCI, the aMCI group showed significant correlation with CMglc in the diffuse brain regions, that are more similar to the brain regions of the association for the MCI group (Tables 5 and 6, and Supplementary Figure 3). Significant positive correlations between the SVFT TS and CMglc were predominantly found in the frontal, anterior cingulate, temporal cortices, as well as insula, caudate, and thalamus in the aMCI group, whereas no significant correlations were found in the naMCI group. Significant positive correlations were found between the SW and CMglc in the temporal and frontal cortices in the aMCI group, whereas significant positive correlations were observed between the SW and CMglc only in the middle frontal gyrus for the naMCI group. Significant positive correlations between the SVFT CSW and CMglc were mainly found in thalamus, caudate as well as parietal lob-

ule in the aMCI group, whereas the correlations were observed only in the inferior temporal gyrus for the naMCI group.

DISCUSSION

In the present study, the SVFT TS was positively correlated with CMglc in the diffuse frontal and posterior regions including bilateral prefrontal cortex (PFC), insula, inferior parietal cortex, PCC/precuneus, caudate, and left temporal cortex. Among the SVFT strategy scores reflecting qualitative aspects, the SW and the CSW scores showed positive correlations with CMglc in the relatively circumscribed areas of the fronto-parieto-temporal cortices or only in the caudate, respectively. The MCS and the HSW, however, did not show significant correlation with CMglc in any brain region.

The positive correlation found between the SVFT TS and CMglc in the lateral PFC and insula, inferior parietal cortex, and PCC/precuneus, and caudate are consistent with the previous reports that showed association between the TS with various and diffuse cortical regions including the prefrontal, parietal, and cingulate cortex, insula, and caudate [13, 14, 29, 30]. The combination of these regions is notable as they are part of the default mode network (DMN), which is known to play a central role in internally based processes and has consistently been associated with both semantic and episodic memory processes [31]. Some regions found to be associated with SVFT TS in the current study, including the PFC, caudate, and PCC/precuneus, are also parts of the fronto-parietal network that is involved in executive functions and is closely linked to the DMN for external goal-oriented tasks [32]. Collectively, the functional neuroanatomical substrates of SVFT TS appears to be the brain regions related with executive functions and semantic/episodic memory processes and to be subserved by the fronto-parietal network and DMN. Furthermore, the association between the left temporal cortex and the SVFT TS strongly support the involvement of language functions; the transverse temporal gyrus, uniquely associated with the TS, is implicated as a region for speech processing as well as processing of abstract semantic concept and word finding [33–35]. While such information about SVFT TS-associated brain regions is helpful, diffuse involvement of brain regions associated with the SVFT TS presents a challenge for making an interpretation on the regional specificity of brain activity based on the SVFT TS alone.

The current results on the SVFT strategy scores of switching help to better understand brain activity when performing the SVFT. The SW score was associated with CMglc of the similar brain regions as the TS but in smaller size. This may indicate that both the TS and the SW reflect generally similar cognitive functions. However, the correlated brain regions of the two scores did not completely overlap. The SW score was uniquely associated with the left thalamus, which was considered to play a role in word generation [36] and to focus on correct lexical word in a broad semantic network [37]. In contrast to the TS and the SW, the CSW was correlated with metabolism only in caudate, which may indicate that the CSW reflects function of highly specific brain region known for its involvement in mental flexibility and goal-directed action [5, 38]. Contrary to our anticipation based on the literature, the MCS and the HSW, did not show functional correlation with brain regions in the overall subjects, indicating that these indices may not be suitable for clarifying cognitive changes due to AD disease severity.

In the present study, differentially associated brain regional CMglc with the SVFT strategy scores of switching by the diagnoses is notable. The SW was associated primarily with the anterior cingulate cortex in the MCI group compared to the caudate and superior temporal gyrus in AD dementia group. In previous studies, the anterior cingulate cortex was reported to be associated with word production and closely linked with the PFC for executive control, specifically being active in controlling incongruent tasks [39–41]. The superior temporal gyrus is known to be involved in semantic memory and language processing, especially word comprehension [42, 43]. The results of the current study, together with the understanding that the SW was devised to measure strategic search and retrieval process [4, 5], indicate that the SW is useful in assessing executive control and active word searching or generation in the MCI stage. As the clinical severity increased, however, semantic and working memory processes may additionally be involved for maintaining animal category and avoiding repetition when retrieving the words. The CSW did not show significant correlation with any brain regions in the AD dementia group compared to the MCI group that showed involvement of more extensive brain regions including the insula, caudate, and fronto-parieto-temporal cortices. This finding suggests that the CSW may sensitively detect subtle dysfunction of multiple brain regions likely related to cognitive strategy and mental flexibility for

word retrieval [5, 6] in the MCI stage; such strategic approach may not be shown in the AD stage due to floor effect.

Additionally, risk of AD progression is higher for the aMCI than the naMCI [27], and AD patients generally perform worse on SVFT than letter fluency related to the deterioration of semantic knowledge [44]. Thus, it can be inferred that aMCI may demonstrate more decline on SVFT performance in the course of AD progression, and the association between CMglc and SVFT scores could be different between MCI subtypes. Indeed, for the naMCI group, only the SW and CSW—not the TS—showed significant positive correlation in the frontal, and temporal gyrus. For the aMCI group, however, significant positive association between the TS, SW, as well as CSW and CMglc were found in the more extensive brain area. When aMCI group was compared with AD group, involvement of the frontal regions was more prominent for the aMCI group compared to the temporal regions for the AD group. The TS showed significant correlations mainly in the frontal areas for the aMCI group, whereas significant associations were found mainly in the temporal regions for the AD group. Positive correlations between the SW and CMglc were found in temporal and frontal regions in the aMCI group, whereas positive correlations were found in caudate and temporal areas in the AD group. Furthermore, in contrast to the AD group which did not show significant correlation with the CSW, significant correlation were found primarily in the subcortical regions for the aMCI group.

This difference in the pattern of regions showing significant correlations between the aMCI and AD also defines the progression of AD-related pathologies. In the progression pattern of AD, neurofibrillary tangles and neuronal loss initially appear in the medial temporal areas [45], and the prefrontal cortex is affected in the later stage of AD pathology [46, 47]. For compensating the impairment of temporal areas, functional connectivity between brain regions increases. Specifically, aMCI patients often manifest abnormal functional connectivity between the frontal lobe and other brain regions [48]. Indeed, in our study, more involvement of prefrontal cortex was observed in aMCI group. However, as the brain function deteriorates and compensatory frontal activation declines, significant correlation between SVFT performance and CMglc were mainly found in the temporal cortices and subcortical regions in the AD group. The naMCI subgroup showing different metabolic pattern is likely due to different and heterogeneous etiological contributions compared to aMCI. Further delineation with larger number of naMCI participants will be helpful especially given the current finding of absence of cerebral metabolic association with TS.

In conclusion, this study delineated functional neuroanatomical substrates of SVFT TS and the strategy scores based on an individual's approaches on clustering or switching in MCI and AD dementia patients. Our findings suggest that while the SVFT TS reflects the function of wide brain areas associated with executive functions and semantic/episodic memory processes, the scores of switching strategies, particularly the SW and CSW, are more sensitive indices for detecting neural functional activity in more circumscribed regions linked with strategic word generation, sematic processing, or mental flexibility. In addition, the functional neuroanatomical substrates underlying each SVFT score seems to be different according to the clinical severity of AD associated cognitive disability.

Based on the findings, clinicians and researchers may be better informed when interpreting the task results as well as interpreting disease progression by utilizing the strategy scores. Once normative data of these strategy scores are developed from future studies, identifying impairment compared to normal range would be possible and more specifically affected brain areas can be predicted by the SVFT without brain functional PET scans. Furthermore, SVFT strategy scores can be utilized in formulating relevant clinical treatment plans. To manage complex features associated with dementia such as cognition and emotional as well as biological health, a need for integrated multidisciplinary approach that emphasizes cooperative treatment between experts is increasing [49]. If poor performance of SVFT scores and clinical symptoms are confirmed by neuropsychologists and physicians, additional intervention or cognitive rehabilitation therapies may be formulated. For example, since CSW is expected to sensitively detect the executive dysfunction in the pre-AD stage, subjects who demonstrates below-norm on this score may be eligible for intervention by neuropsychologists and occupational therapists to work around cognitive dysfunctions as disease progresses. Based on the data on strategies, it would be helpful to provide intervention programs such as functional task exercise and high-ecological cognitive intervention, given that these are known to improve general cognition, memory and executive function for the cognitively impaired [50, 51].

Our study presents with some limitation. We acknowledge that some regions are overlapping, rather than exhibiting specific regional specificity. However, compared to the total score, which reflects multiple cognitive functions, the SW and CSW have advantage of measuring more specific cognitive functions. From a single test, therefore, it efficiently provides information for comparing multiple cognitive functions as well as identifying localized cognitive-brain function. Comparing SVFT strategy scores with the results of neuropsychological tests that measure specific cognitive function would be meaningful to more clearly understand the state of related cognitive functions. Moreover, the present study did not include cognitively normal group as we gathered data from the Dementia and Age-Associated Cognitive Decline clinic. In addition, the number of naMCI participants were smaller. Therefore, future studies including larger cognitively normal subjects as well as naMCI are needed for investigation of the differences by cognitive state as well as making normative data.

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SUPPLEMENTARY MATERIAL

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