이학석사 학위논문

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Abstract

Functional neural correlates of adult reading test performance

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Background: Adult reading tests (ART) have been widely used in both research and clinical settings as a measure of premorbid cognitive abilities or cognitive reserve. However, the neural substrates underlying ART performance are largely unknown. Furthermore, it has not yet been examined whether the neural substrates of ART performance reflect the cortical regions associated with premorbid intelligence or cognitive reserve. The aim of the study is to identify functional neural correlates of ART performance using ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET) imaging in healthy adults.

Methods: The current study included 271 cognitively normal middle and old-aged adults. All participants underwent comprehensive clinical and neuropsychological assessments, FDG-PET scans, and ^{11}C-labelled Pittsburgh Compound B (PiB)-PET scans. ART performance was assessed using the Korean Adult Reading Test (KART). Voxel-wise analyses of FDG-PET images were used to investigate the

correlations between regional cerebral glucose metabolism and KART performance. The same analyses were performed for a subgroup of individuals without pathological beta-amyloid (Aβ) deposition on PIB-PET (Aβ negative) in order to reexamine the relationship while the influence of Alzheimer's disease (AD) process on ART performance was removed as much as possible.

Results: The study sample consisted of 271 participants of which 51.7% were female and 87.7% were Aβ negative. Participants had a mean age of 69.0 years (*SD* = 8.1) and average years of education of 11.8 (*SD* = 4.8). Voxel-wise analyses revealed positive correlations between glucose metabolism and KART performance in the frontal and primary somatosensory regions, more specifically the lateral frontal cortex, anterior cingulate cortex and postcentral gyrus independent of the effects of age and gender. When conducted again only for Aβ negative individuals, the voxel-wise analysis showed significant correlations in broader areas of the frontal and primary somatosensory regions.

Conclusions: This is the first neuroimaging study directly demonstrating the neural substrates associated with ART performance. The positive correlation found between glucose metabolism and KART in the frontal and primary somatosensory regions serves as important evidence at the neural level that ART predicts premorbid general intelligence and cognitive reserve, as these regions are previously reported to be associated with general intelligence and cognitive reserve.

Keywords: the Korean Adult Reading Test, KART, cognitive reserve, premorbid intelligence, FDG-PET, neural correlate

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I Introduction

Estimation of premorbid cognitive ability is important in both research and clinical settings to quantify and diagnose cognitive impairment. The most widely applied approach to estimating premorbid cognitive function is the use of an adult reading test (ART), which comprises of oral reading of orthographically irregular words. ART provides an estimate of premorbid intelligence based on the rationale that the reading ability of irregular word correlates strongly with measure of IQ in healthy adults (Crawford, Millar, & Milne, 2001; Nelson, 1982; Nelson & Willison, 1991; Spreen & Strauss, 1998; Yi et al., 2017), and is relatively resistant to cognitive declines in patients with neurological or psychiatric disorders (Matsuoka, Uno, Kasai, Koyama, & Kim, 2006; McGurn et al., 2004; Sasanuma, Sakuma, & Kitano, 1992). It is assumed that better performance on ART implies prior knowledge of a word's pronunciation and therefore a higher premorbid intelligence (Lezak & Lezak, 2004). Moreover, numerous studies on Alzheimer's disease (AD) have reported that an ability to pronounce irregular words is a retained skill even in advanced stages of the disease (Matsuoka et al., 2006; McGurn et al., 2004; Sasanuma et al., 1992), suggesting that ART is able to provide a reasonable estimate of premorbid intelligence for AD patients.

ART has also been used as a measure for cognitive reserve (CR)—a theoretical concept referring to the cognitive capacity to cope with brain damages (Franzmeier, Buerger, et al., 2017; Habeck et al., 2003; Habeck et al., 2005; Lo, Jagust, & Alzheimer's Disease Neuroimaging, 2013; McGurn et al., 2004; Osone, Arai, Hakamada, & Shimoda, 2015; Rentz et al., 2010; Rentz et al., 2016; Scarmeas et al., 2003; Steffener, Reuben, Rakitin, & Stern, 2011; Stern et al., 2008; Stern et al., 2003; Vemuri et al., 2011). The concept of CR has been proposed to

account for the discrepancy between the degree of brain damage or pathology and clinical manifestations (Stern et al., 2008; Stern et al., 2003). It is also considered as a contributing factor toward an understanding of individual differences in resilience to brain pathology. In epidemiologic studies, higher intelligence has consistently been shown to be protective against progression of AD (Snowdon et al., 1996; Whalley & Deary, 2001; Yeo, Arden, & Jung, 2011). Moreover, high prevalence of AD-related abnormal biomarkers at a given level of cognitive performance was associated with higher scores on ART, indicating that those with higher ART scores cope better with AD pathology (Alexander et al., 1997; Franzmeier, Buerger, et al., 2017; Lo et al., 2013; McGurn et al., 2004; Osone et al., 2015; Rentz et al., 2010; Rentz et al., 2016; Steffener et al., 2011; Vemuri et al., 2011). Taken together, these findings support that performance on ART reflects CR.

While there is ample evidence demonstrating that ART provides a good estimate of intelligence and CR at the behavioral level, the neural basis of ART performance is largely unknown. Furthermore, it has not yet been identified whether ART performance reflects the neural function of the regions associated with intelligence or CR. Previous neuroimaging studies on ART focused largely on examining whether CR measured by ART helps to cope against neuropathology in individuals with cognitive impairment (Alexander et al., 1997; Franzmeier, Buerger, et al., 2017; Lo et al., 2013; McGurn et al., 2004; Osone et al., 2015; Rentz et al., 2010; Rentz et al., 2016; Steffener et al., 2011; Vemuri et al., 2011). To our knowledge, however, there are no studies to date that looked directly into the neural substrates of ART performance.

Therefore, the present study aimed to identify the neural correlates of ART performance in cognitively normal adults. To achieve this aim, the correlation between ART performance and regional cerebral glucose metabolism was

examined with ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET), which has been known to provide a reliable index of neural activity associated with cognitive function (Han et al., 2015; D. Y. Lee et al., 2008; J. H. Lee et al., 2015; Melrose et al., 2009; Melrose, Harwood, Khoo, Mandelkern, & Sultzer, 2013; Schonknecht et al., 2011; Shon et al., 2013; Welsh, Hoffman, Earl, & Hanson, 1994; Yun et al., 2011). In addition, the neural correlates were reexamined in individuals without pathological beta-amyloid (Aβ) deposition shown on ^{11}C-labelled Pittsburgh Compound B (PIB)-PET , in order to eliminate the influence of AD process on ART performance as much as possible.

II Materials and Methods

1. Subjects

This study included 271 healthy cognitively normal middle- and old-aged adults who participated in the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's disease (KBASE), which is an ongoing prospective cohort study established in 2014. All subjects underwent comprehensive clinical and neuropsychological assessments and multi-modal brain imaging including brain FDG-PET and PiB-PET. The inclusion criteria for participants with normal cognition were (a) aged 55–90 years (inclusive), (b) Clinical Dementia Rating score of 0, and (c) no diagnosis of mild cognitive impairment or dementia. The exclusion criteria were (a) any present serious medical, psychiatric, or neurological disorder that could affect mental functioning; (b) presence of severe communication problems that would make a clinical examination or brain scan difficult; (c) contraindications for MRI; (d) absence of a reliable informant; (e) illiteracy; and, (f) participation in another clinical trial and treatment with an investigational product. All subjects provided written informed consent prior to study procedure, which used the protocols approved by the institutional review boards of Seoul National University Hospital, Seoul, South Korea.

2. Clinical assessments

All participants received standardized clinical assessments by trained psychiatrists based on the KBASE clinical assessment protocol (Byun et al., 2017) which corresponded with the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) (J. H. Lee et al., 2002). In addition, the KBASE neuropsychological assessments (Byun et al., 2017) incorporating the CERAD-K neuropsychological battery (D. Y. Lee et al., 2004)

were administered to all participants by a trained neuropsychologist or psychometrists.

3. FDG-PET Acquisition and Preprocessing

FDG-PET scans were performed using a 3.0T Biograph mMR (PET-MR) scanner (Siemens, Washington DC, USA) and 3D T1-weighted magnetic resonance imaging was simultaneously performed with PET. Prior to the scan, participants fasted for at least six hours and rested in a dimly lit waiting room for 40 minutes after receiving an intravenous injection of 0.1 mCi/Kg of [18F] FDG radioligand. The PET data collected in list mode (5 min × 4 frames) were processed for routine corrections such as attenuation, scatter, random coincidences and radioactive decay. After inspecting the data for any significant head movements, the data were reconstructed into a 20-min summed image using iterative methods (5 iterations with 21 subsets).

The FDG-PET data were preprocessed using Statistical Parametric Mapping 12 (SPM12; Institute of Neurology, University College of London, United Kingdom) implemented in Matlab 2014a (Mathworks, Natick, MA, USA). In a first step, static FDG-PET images were co-registered to individual T1 structural images. Next, transformation parameters were calculated and used to spatially normalize individual T1 and FDG-PET images to the MNI template. The spatially normalized FDG-PET images were smoothed with a 12-mm Gaussian filter and intensity normalized using the pons as the reference region since glucose metabolism in the pons tends to be relatively preserved in AD (Minoshima, Frey, Foster, & Kuhl, 1995).

4. PiB-PET Acquisition and Processing

All participants also underwent 3-dimensional (3D) PiB-PET using the same PET-MR machine as the FDG-PET scans. For each subject, 55 MBq of [11C] PiB radioligand (range, 450-610 MBq) was administered by intravenous injection, and a 30 min emission scan was obtained 40 minutes after injection. The PIB-PET data were collected in list mode and processed for routine corrections, such as uniformity, ultrashort echo time (UTE)-based attenuation, and decay corrections and were reconstructed into a 256 × 256 image matrix using iterative methods (6 iterations with 21 subsets).

Image preprocessing for statistical analyses was performed using SPM 12 implemented in Matlab 2014a. First, the PiB images were coregistered to an individual T1 structural image, and inverse transformation parameters for spatial normalization of the individual T1 image to a standard Montreal Neurological Institute (MNI; McGill University, Montreal, Quebec, Canada) template were calculated. Using IBASPM software, we used the inverse transformation parameters to transform coordinates from the automatic anatomic labeling (AAL) 116 atlas (Tzourio-Mazoyer et al., 2002) into an individual space for each subject (resampling voxel size = 1 × 0.98 × 0.98 mm), and the non-gray matter portions of the atlas were individually masked using the cerebral gray matter segment image from each subject.

Mean cerebral PiB uptake values were extracted using the individual AAL 116 atlas from the T1-coregistered PiB-PET images and quantitative normalization was performed using the cerebellar gray matter as the reference region due to its relatively low Aβ deposition despite severity of disease status (Lopresti et al., 2005). To obtain mean cerebellar PiB uptakes, a probabilistic cerebellar atlas (Institute of Cognitive Neuroscience, UCL; Cognitive Neuroscience Laboratory, Royal Holloway) was transformed into individual space in the same manner as described above and cerebellar lobular regions except the vermis were extracted.

The AAL algorithm (Tzourio-Mazoyer et al., 2002) and a region-combining method (Reiman et al., 2009) were applied to determine regions of interest (ROIs) to characterize the PiB retention level in the frontal, lateral parietal, posterior cingulate-precuneus (PC-PRC), and lateral temporal regions where prominent PiB retention was reported (Klunk et al., 2004). Each participant was classified as Aβ-positive if the SUVR value was > 1.4 in at least one of the four ROIs or as Aβ-negative if the SUVR value of all four ROIs was ≤ 1.4 (Reiman et al., 2009; Villeneuve et al., 2015).

5. The Korean Adult Reading Test (KART)

The Korean Adult Reading Test (KART), the validated Korean version of ART, was administered to all participants (Yi et al., 2017). KART-estimated Wechsler Adult Intelligence Scale—Fourth Edition (WAIS-IV) full-scale IQ (FSIQ) was used as a measure for ART performance.

6. Statistical analyses

Statistical analyses were done with SPSS 22.0 and SPM12. Correlation between KART-estimated FSIQ score and regional cerebral glucose metabolism was examined using voxel-wise regression with age and gender as covariates. Statistical threshold was set at $p < 0.005$ (uncorrected) and a cluster size threshold of 1062 voxels was applied to correct for multiple comparisons. The cluster size threshold was determined based on a cluster correction procedure in Analysis of Functional and Neural image (*i.e.,* 3dClusSim), with 10000 iterations of Monte Carlo simulations on anatomical cerebral mask dataset (Forman et al., 1995). In addition, the mean FDG-PET metabolism SUVR values were extracted from the clusters presenting a significant correlation with KART-estimated FSIQ score. Partial

correlation analysis controlling for age and gender was implemented with the FDG-PET SUVR data to examine the strength of the correlations between KART-performance and FDG uptake. All of the abovementioned analyses were performed again after excluding Aβ-positive subjects

III Results

1. Subject characteristics

Demographic characteristics of the study sample are summarized in Table 1. The sample consisted of 271 participants of which 51.7% (n=140) were female and 86.7% (n=235) were Aβ-negative. Participants had a mean age of 69.0 years (*SD* = 8.1) and average years of education of 11.8 (*SD* = 4.8). The mean KART error score was 5.0 (*SD* = 4.9) and mean FSIQ score estimated from KART error score was 116.0 (*SD* = 9.9).

Table 1. Demographic characteristics

Characteristic	CN
N	271
Age, mean (SD, range)	69.0 (8.1, 55-87)
Female, N [%]	140 [51.7]
Years of education, mean (SD)	11.8 (4.8)
KART error score, mean (SD)	5.0 (4.9)
KART-estimated FSIQ, mean (SD)	116.0 (9.9)
Aβ-negative, N [%]	235 [86.7]

*Notes. Values are mean (SD) or count. CN, cognitively normal; SD, standard deviation; N, count; KART, Korean adult reading test; KART-estimated FSIQ, Wechsler Adult Intelligence Scale Full-Scale IQ estimated using the KART; Aβ, beta-amyloid.

2. Correlation between regional cerebral glucose metabolism and KART performance in all CN subjects

Voxel-wise analysis using age and gender as nuisance covariates revealed significant positive correlations between KART-estimated FSIQ score and regional cerebral glucose metabolism in the frontal and primary somatosensory regions, particularly in the left middle frontal gyrus (MFG), right anterior cingulate gyrus (ACG) and left postcentral gyrus (PCG) (Table 2, Figure 1).

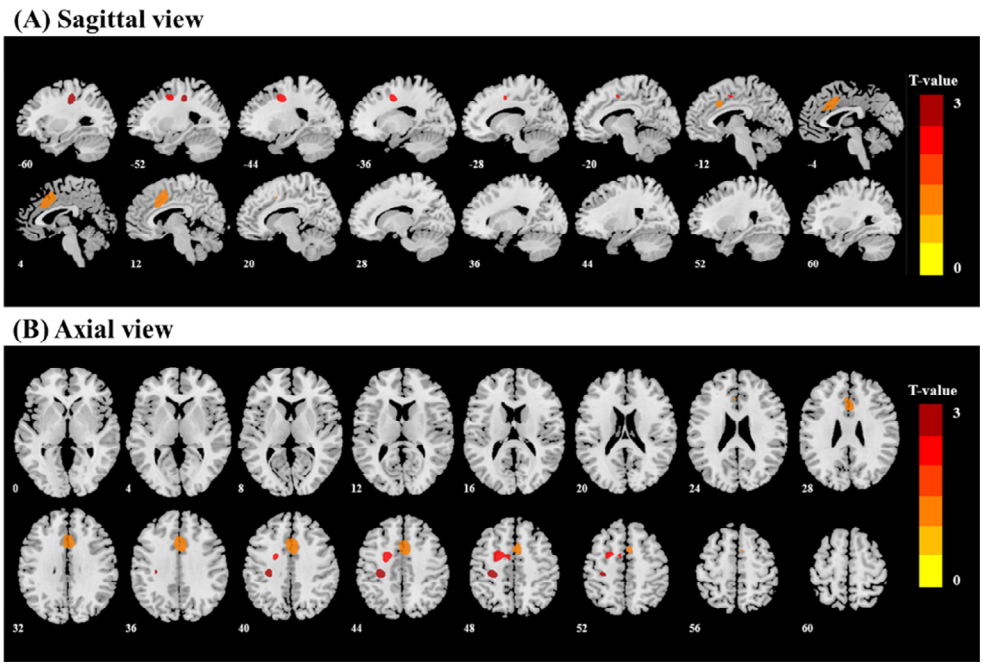
In order to further examine the strength of the correlations, mean FDG-PET SUVR values were extracted from each cluster showing significant association with the KART performance and partial correlation analyses were performed controlling for effects of age and gender. There were positive and moderately significant correlations between KART-estimated IQ score and mean FDG-PET SUVR values in all clusters (left MFG: $r(267) = 0.19$, $p = .001$; left PCG: $r(267) = 0.21$, $p = .002$; right ACG: $r(267) = 0.19$, $p = .002$; whole cluster: $r(267) = 0.18$, $p = .002$) (Figure 2).

Table 2. Positive correlations between regional cerebral glucose metabolism and KART-estimated FSIQ score after adjusting for age and gender in all CN subjects

Regions	BA	Coordinates (mm)			Extent Voxels	T-value
		x	y	z		
L middle frontal gyrus	6/9	-21	-1	46	1990	3.57
R anterior cingulate gyrus	32	5	8	43	5623	3.38
L postcentral gyrus	3	-30	-25	46	1545	3.35

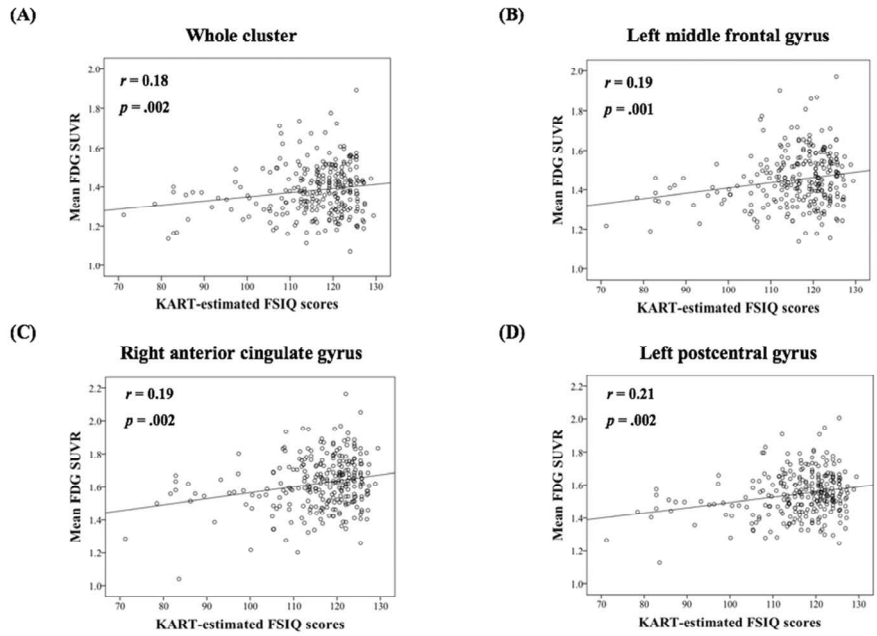
*Note. p <.005 (uncorrected) with significance of k >1062. Adjusted for age and gender. Coordinates are in Montreal Neurological Institute (MNI) space. CN, cognitively normal; BA, approximate Brodmann area; L, left hemisphere; R, right hemisphere.

Figure 1. Brain regions presenting significant positive correlations between cerebral glucose metabolism with KART-estimated FSIQ score after adjusting for age and gender in all CN subjects



*Note. p <.005 (uncorrected) with significance of k >1062. Adjusted for age and gender. CN, cognitively normal.

Figure 2. Scatterplots demonstrating the strength of correlations between KART-estimated FSIQ score and regional glucose metabolism after adjusting for age and gender in all CN subjects



*Note. Mean FDG-PET SUVR values were extracted from the clusters of voxels showing a significant association with KART performance and examined the correlation with KART performance with using partial correlation analysis adjusted for age and gender. CN, cognitively normal; SUVR, standardized uptake value ratio.

3. Correlation between regional cerebral glucose metabolism and KART performance in Aβ-negative CN subjects

For Aβ-negative subsample (n=235), the voxel-wise analysis showed positive correlations in more widespread clusters of the bilateral frontal and primary somatosensory regions including the bilateral MFC, bilateral ACG, bilateral PCG and right inferior frontal gyrus (IFG) (Table 3, Figure 3). Particularly, additional positive correlations were found in the right lateral frontal cortex (LFC; middle and inferior frontal gyri), left ACG and right PCG after Aβ-positive subjects were excluded.

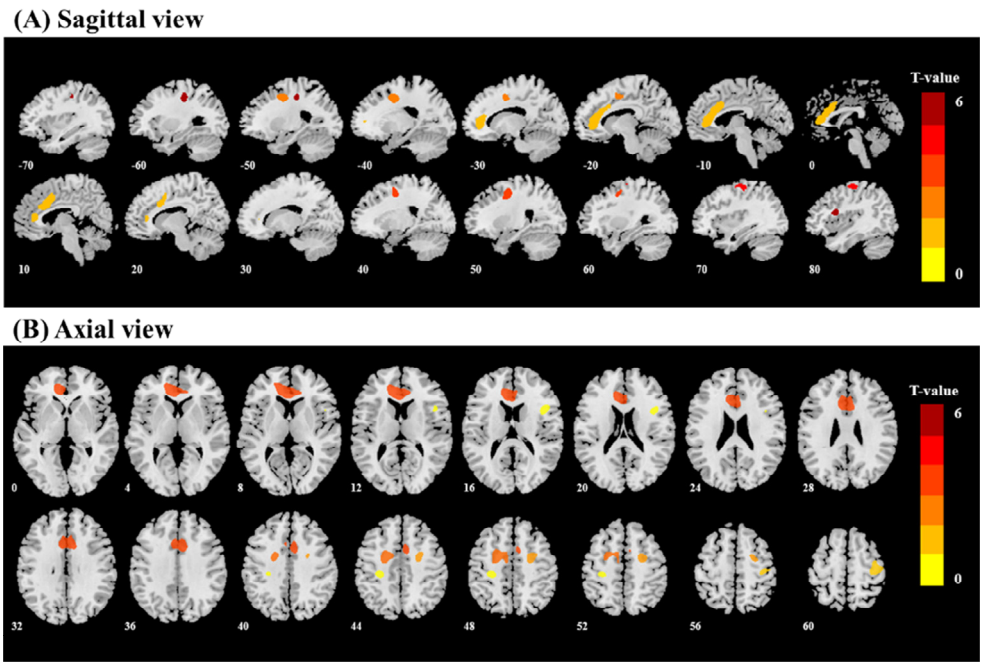
Partial correlation analyses adjusted for age and gender were repeated to see the strength of the correlations with the mean FDG-PET SUVR values from these significant clusters and the KART performance. Relatively modest and significant correlations were found in all clusters (right MFG: $r(231) = 0.20$, $p = .002$; right IFG: $r(231) = 0.19$, $p = .004$; right ACG: $r(231) = 0.21$, $p = .001$; right PCG: $r(231) = 0.19$, $p = .004$; left MFG: $r(231) = 0.21$, $p = .001$; left ACG: $r(231) = 0.21$, $p = .001$; left PCG: $r(231) = 0.19$, $p = .003$; whole cluster: $r(231) = 0.23$, $p = .001$) (Figure 4).

Table 3. Positive correlations between regional cerebral glucose metabolism and KART-estimated FSIQ score after adjusting for age and gender in Aβ-negative CN subjects

Regions	BA	Coordinates (mm)			Extent Voxels	T-value
		x	y	z		
R middle frontal gyrus	6	23	-4	48	1878	3.38
R inferior frontal gyrus	9	42	12	19	1092	3.01
R anterior cingulate gyrus	32	6	16	33	14444	3.19
R postcentral gyrus	3	38	-20	60	1543	2.95
L middle frontal gyrus	6,8	-21	-2	45	3071	3.66
L anterior cingulate gyrus	32	-6	37	9	14444	3.52
L postcentral gyrus	3	-29	-25	47	1194	3.21

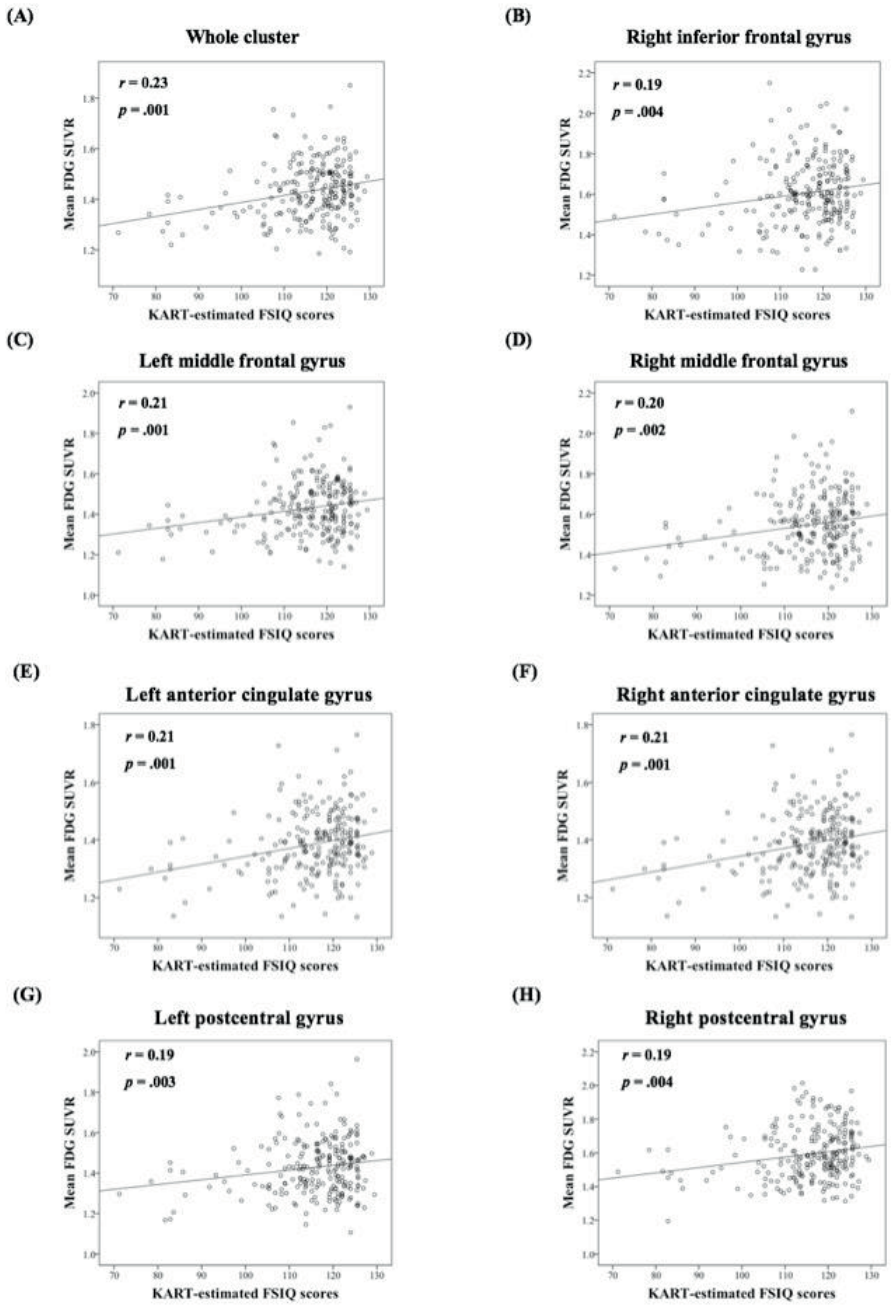
*Note. p <.005 (uncorrected) with significance of k >1062. Adjusted for age, and gender. Coordinates are in Montreal Neurological Institute (MNI) space. Aβ, beta-amyloid; CN, cognitively normal; BA, approximate Brodmann area; L, left hemisphere; R, right hemisphere.

Figure 3. Brain regions presenting significant positive correlations of cerebral glucose metabolism with KART-estimated FSIQ score after adjusting for age and gender in Aβ-negative CN subjects



*Note. p < .005 (uncorrected) with significance of k >1062. Adjusted for age and gender. Aβ, beta-amyloid; CN, cognitively normal.

Figure 4. Scatterplots demonstrating the strength of the correlations between KART-estimated FSIQ score and regional glucose metabolism after adjusting for age and gender in Aβ-negative CN subjects



*Note. Mean FDG-PET SUVR values were extracted from the clusters of voxels showing a significant association with KART performance and reexamined the correlation with KART performance with using partial correlation analysis adjusted for age and gender. Aβ, beta-amyloid; CN, cognitively normal; SUVR, standardized uptake value ratio.

IV Discussion

The current study showed the neural substrates of ART performance by demonstrating voxel-wise associations between KART performance and regional cerebral glucose metabolism in cognitively normal adults. To sum up, in the whole sample including the individuals with and without significant levels of Aβ deposition, KART performance was positively correlated with regional glucose metabolism in the frontal and primary somatosensory areas—more specifically the left MFG, left PCG, and right ACG. After excluding Aβ-positive subjects, positive correlations with KART performance were found in much larger areas of the frontal and primary somatosensory regions including the bilateral MFG, bilateral ACG, bilateral PCG and right IFG. These findings suggest that the neural substrates of ART performance are mainly in the frontal and primary somatosensory areas.

The current observation emphasizes the involvement of the frontal and primary somatosensory areas in premorbid function as estimated by ART. The patterns of brain metabolic impairment typical of AD begins in the precuneus and posterior cingulate cortex, spreads to parieto-temporal regions and finally progresses to frontal and sensory cortices (Mosconi et al., 2007; Mosconi et al., 2008) and the frontal and primary somatosensory regions have been identified to be typically affected in the late stages of AD (Ball, 1977; Braak & Braak, 1991; Mosconi et al., 2007; Mosconi et al., 2008). Indeed, the regional neural functions that are found to be associated with KART performance are relatively less vulnerable in AD. It can be posited that ART can predict premorbid functions by reflecting neuronal functions of the regions that are relatively preserved in AD.

The largest region showing positive correlations of KART performance was the frontal area, particularly the ACC and LFC. The ACC and LFC are parts of the

frontoparietal network (FPN), which has been reported as the neural substrates of general intelligence (Cole, Ito, & Braver, 2015; Cole et al., 2013; Cole & Schneider, 2007; Cole, Yarkoni, Repovs, Anticevic, & Braver, 2012; Margulies et al., 2007; Niendam et al., 2012). The ACC, in particular, is known to support intelligence by handling and processing conflicting streams of information (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Brown, 2009; Cohen, Heller, & Ranganath, 2005). In addition to being recognized as a core region for intelligence, the LFC is functionally responsible for regulating the flow and integration of information between other regions (Cole et al., 2015; Cole et al., 2013; Cole et al., 2012).

The PCG, also known as the primary somatosensory cortex (SSC), was found to be significantly associated with KART performance. While the roles of the SSC pertaining to intelligence are less clear, this observation is line with the previous findings that showed positive association between general intelligence and cortical thickness or gray matter volumes of the SSC (R. Colom et al., 2013; Roberto Colom et al., 2009; S et al., 2009). Given that the SSC is involved in processing somatosensory input and contributes to the integration of sensory and motor signals (Borich, Brodie, Gray, Ionta, & Boyd, 2015), it is therefore possible that this region supports intelligence by working in tandem with frontal area towards high-level cognitive functions such as perceptual decision making (R. Colom et al., 2013; Roberto Colom et al., 2009; Santarnecchi, Tatti, Rossi, Serino, & Rossi, 2015). Taken together, the current findings further substantiate that KART performance provides an estimate of general intelligence by showing its correlations with the neuronal function of the SCC that is reportedly associated with intelligence.

Notably, the LFC, in particular, has also been suggested as a putative neural substrate of CR, in addition to being associated with general intelligence. The neural mechanism underlying CR is largely unclear, but several possible mechanisms have been postulated including the task-invariant networks (TIN)

(Stern, 2006, 2009, 2016; Stern et al., 2005; Stern et al., 2008; Stern et al., 2003). The TIN, which remains active throughout multiple tasks with various levels of processing demands, has been suggested to support CR by serving as a compensatory neural network against brain pathology (Stern, 2006, 2009, 2016; Stern et al., 2005; Stern et al., 2003). The LFC has been reported to have strong connectivity with multiple TINs and is considered as the hub region of the TINs (Cole et al., 2015; Cole et al., 2012; Franzmeier, Duering, et al., 2017; Franzmeier, Gottler, et al., 2017). Given that TIN is reported to support CR and the hub of TIN is thought to reside in the LFC, it can be posited that the LFC subserves CR (Franzmeier, Buerger, et al., 2017; Franzmeier, Duering, et al., 2017; Franzmeier, Gottler, et al., 2017). A recent resting-state fMRI study that showed the association between AD-related biomarkers and lower memory performance was attenuated by the global functional connectivity of the LFC in patients with mild cognitive impairment, provides support for the current findings (Franzmeier, Duering, et al., 2017). Taken together, the current findings further corroborate the possible role of LFC—the region most significantly associated with the KART performance—as the neural substrate of CR.

An additional interesting finding of the current study is that the regions associated with KART performance became larger when individuals with high level of Aβ were excluded in the analysis. Considering the fact that accumulated AD pathology generates structural and functional changes in the brain (Bateman et al., 2012; Beason-Held et al., 2013; Hof, Glannakopoulos, & Bouras, 1996; Mattsson et al., 2014; Perl, 2010), the neural correlates related to KART performance may vary due to AD pathology, as also observed in the current analyses. Such variation (*i.e.,* inclusion of much broader regions of functional activity after excluding Aβ-positive) may signify several points. First, this demonstrates that the neuronal functions may be affected by AD neuropathology

even in individuals without clinical manifestation of AD. Second, it may indicate that the much broader regions found after eliminating Aβ positive subjects represent more precise neural correlates of ART performance. Last, given that the associations of the left LFC, left PCG and right ACC—the regions found in the initial analyses with the entire sample—persisted when those with AD pathology were included, it can be inferred that KART performance is indeed resistant against AD.

In conclusion, this is the first functional neuroimaging study describing the neural substrates associated with ART performance. The positive correlation between ART and glucose metabolism in the frontal and primary somatosensory areas indeed corresponds to the regions previously reported to be associated with general intelligence and cognitive reserve. The current study provides support at the neural level for the use of ART as a measure of premorbid functioning to be used in research as well as in clinical settings. Moreover, the identification of the neural correlates of KART helps to gain an understanding of the neural mechanism underlying CR. Future studies using a multimodal approach such as combining FDG-PET with task-fMRI will provide more detailed information on the functional neural substrates underlying ART performance.

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국문 초록

성인읽기검사 수행의 기능적 신경 상관

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성인읽기검사는 병전 지능 및 인지예비능(cognitive reserve)의 추정 도구로 널리 사용되고 있지만, 아직까지 본 검사 수행의 신경 기전에 대해서는 제대로 밝혀지지 않았다. 본 연구의 목적은 인지적으로 정상인 성인을 대상으로 ^{18}F-fluorodeoxyglucose(FDG) positron-emission tomography(PET) 영상을 사용하여 성인읽기검사 수행의 기능적 신경 상관을 탐구하는 것이다.

연구에 포함된 참가자는 271 명의 중년 및 노인 정상인이며, 모든 참가자는 종합적인 임상 및 신경심리평가, FDG PET 영상 촬영, ^{11}C-labelled Pittsburgh Compound B (PiB) PET 영상 촬영을 완료하였다. 성인읽기검사 수행은 한국어 성인 읽기 검사(Korean Adult Reading Test)를 사용하여 측정되었으며, FDG PET 영상의 복셀기반 분석을 통해 국소적인 뇌 포도당 대사와 성인읽기검사 수행 사이의 상관이

조사되었다. 또한 추가적으로 알츠하이머병의 영향을 최대한 제거한 상태에서의 신경 상관을 측정하기 위해 PiB PET 영상을 사용하여 베타 아밀로이드(beta-amyloid, Aβ) 축적이 없는(Aβ 음성) 참가자 만을 따로 분류하여 동일한 분석을 재실시 하였다.

연구 표본 총 271 명 중에 51.7%는 여성이고 87.7%는 Aβ 음성이었다. 참가자의 평균 연령은 69.0 세(*SD* = 8.1)였고 평균 교육 년수는 11.8 년(*SD* = 4.8)이었다. 복셀기반 분석결과, 성인읽기검사 수행은 전두엽 및 체성감각 영역에서의 뇌 포도당 대사와 양의 상관을 보였다. 또한 Aβ 음성인 참가자만을 대상으로 분석을 실시했을 때 결과는 더 넓은 영역의 전두엽 및 일차 체성감각 피질에서 포도당 대사와 성인읽기검사 수행이 유의한 양의 상관 관계를 보였다.

본 연구는 성인읽기검사 수행과 관련된 신경 기전을 직접적으로 보여주는 최초의 신경 영상 연구이다. 본 결과는 성인읽기검사 수행에서 전두엽 및 일차 체성감각 피질의 기능이 매우 중요하다는 것을 시사한다. 또한 본 영역들은 이전 연구에서 지능 및 인지 예비능과 관련이 있다고 보고된 영역과 일치하며, 이는 본 검사 도구가 지능 예측 및 인지예비능의 측정하는 데 있어 유용한 도구임을 신경과학적으로 지지한다.

주요어: 성인읽기검사, KART, 인지예비능, 병전 지능, FDG PET, 신경 상관

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