이학석사 학위논문

Functional Neural Correlates of the Block Design Test in Older Adult with mild cognitive impairment and Alzheimer's disease

경미한 인지 장애 및 알츠하이머 병을 가진 노령 성인 대상의 토막짜기검사의 기능성 신경 상관 관계

2019년 8월

서울대학교 대학원

협동과정 인지과학 전공

Joung, Hae Jung

이학석사 학위논문

Functional Neural Correlates of the Block Design Test in Older Adult with mild cognitive impairment and Alzheimer's disease

경미한 인지 장애 및 알츠하이머 병을 가진 노령 성인 대상의 토막 짜기 검사의 기능성 신경 상관 관계

2019년 8월

서울대학교 대학원

협동과정 인지과학전공

정 혜 중

Abstract

Functional Neural Correlates of the Block Design Test in Older Adult with mild cognitive impairment and Alzheimer's disease

Joung, Hae Jung
Interdisciplinary Program in Cognitive Science
Seoul Nation University Graduate School

Background: Block design test (BDT) have been widely used in both research and clinical setting as a measure of cognitive decline in the aging population and lesion patients. However, the neural substrates underlying BDT performance has not been widely studied. Furthermore, it has not yet been examined whether the neural substrates of BDT performance reflect the cortical regions associated with cognitive decline in Alzheimer's Diseases (AD). This study aims to identify functional neural correlates of BDT performance using the ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in cognitive impaired population.

Method: The current study includes 213 cognitively impaired middle and old-aged adults. All participants underwent comprehensive clinical and neuropsychological assessments and FDG-PET scan. BDT

performance was assessed using the Wechsler Adult intelligence scale-IV Korean version. Voxel-wise analyses of FDG-Pet images were used to investigate the correlation between regional cerebral glucose metabolism and BDT performance. The same analyses were conducted in the subgroup that was dived by using clinical dementia rating sum of box score in order to reexamine the effects of severity of AD.

Results: The study sample consisted of 213 participants of which had a mean age of 73.1 (*SD* = 7.4) years, mean years of education of 9.8 (*SD* = 4.9), mean BDT score of 20.9 (*SD* = 9.1), and 67.1% were female. Significant positive correlations between BDT performance and regional cerebral glucose metabolism was found bilaterally in the inferior parietal lobule and thalamus and the right superior temporal gyrus and left occipital precuneus.

Conclusion: The results of this study indicate that the neural mechanism of BDT performance is related to both hemispheres, suggesting not only the visuospatial function but also involving somatosensory, motor, executive functions are equally essential in cognitively-impaired patients with AD.

Keywords: Block design test, BDT, FDG-PET, cognitively impaired, neural correlates, Alzheimer's disease

Student Number: 2016 - 25872

Contents

List of Tables

List of Figures

List of Supplementary tables and figures

1. Introduction

The Block Design Test (BDT) is a visuospatial subtest of the Wechsler Adult Intelligence Scale-IV (WAIS-IV) and is a widely used neuropsychological measure to assess visuospatial and constructional ability and perceptual reasoning (Lazarević et al., 2015; Polunina, Bryun, Sydniaeva, & Z Golukhova, 2018; David Wechsler, 1981). It is also known as a good predictor of everyday spatial skills (Groth-Marnat & Teal, 2000) and considered to be the most representative of the non-verbal, performance, or perceptual organization subtest of the WAIS (Matarazzo, 1972; Royer & Weitzel, 1977). The BDT is often used in clinical settings particularly for differentiating cognitive status between cognitively normal with mild cognitive impairment (MCI), dementia as well as other neuropsychological diseases (Machulda et al., 2009; Mukundan, 2013; Yin, Zhu, Huang, & Li, 2015). Furthermore, the BDT is known as a reliable test that correlates highly with general intelligence (Lichtenberger & Kaufman, 2013; Royer & Weitzel, 1977; David Wechsler, 1981). However, despite the frequent use, underling neuronal mechanism of BDT has not been widely studied.

Performance on the BDT relies on visuospatial ability, and motor ability (Groth-Marnat & Teal, 2000; Royer & Weitzel, 1977). Earlier studies on BDT have attributed the performance on the BDT reflects right parietal visuospatial functioning. While diverse neuroanatomical lesions studies associated with poor BDT performance is found, the functional correlation in

patients with AD are still unclear. Early functional neuroimaging studies using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) reported a strong uptake in right parietal regions associated with BDT performance (Chase et al., 1984; Warrington, James, & Maciejewski, 1986). More recent lesion studies on neuroanatomical correlation with BDT performance were conducted on patients with brain lesions or neurological damages. Lichtenberger and Kaufman (2013) suggested that performance on the BDT is vulnerable to cerebral brain damages particularly in the right hemisphere. Studies on patients with lateralized lesion further corroborated the correlation between BDT performance and right parietal regions (Warrington et al., 1986; Wilde, Boake, & Sherer, 2000). These reports over many years helped formulation of a widely accepted understanding that lesions to the right posterior region of the parietal lobes is known to strongly impact BDT performance (Lezak, 2012).

In contrasts, earlier lesion studies reported significant association with lower BDT scores in the left hemisphere as well (Akshoomoff, Delis, & Kiefner, 1989; Benton, Varney, & Hamsher, 1978; Kertesz & Dobrowolski, 1981). A lesion study with split-brain patients indicated that both hemispheres contribute to BDT performance (Geschwind, 1979). Ferreira et al. (2016) reported that BDT performance predicts reduced cortical thickness of the left rostral middle frontal gyrus, left insula, left precentral, right entorhinal, right isthmus cingulate, and right pars opercularis. Taken together, these studies suggest that broader

regions may be associated with BDT performance, which may indicate that visuospatial functioning assessed by the BDT requires complex planning and organization as well.

While there are evidence demonstrating neural basis of the BDT mostly based on lesion studies, given that a cognitive task is not limited by the boundaries of the damaged location of the brain due to the lesions (Adolphs, 2016; Rorden & Karnath, 2004), further examination is needed to better understand the relationship more directly between the BDT and functional neural substrates in cognitively impaired subjects. The parietal cortex is known to be closely related to visuospatial processing, and it has been consistently reported to be involved in process of pathological progression of AD (Kang et al., 2018; Takahashi et al., 2008). There has been only one study on functional neural correlation on the BDT in AD patients. However, this study was conducted was done over 30 years ago with small subjects group with uncharacterized group (Chase et al., 1984). Furthermore, there has been no suggestion of an association between the frontal lobe and the BDT performance in cognitively-impaired and AD patients, although the frontal lobe is responsible for executive functions and known to be pathologically involved in the later stages of AD. Differences in usage of imaging methods or clinical severity of AD maybe the reason for these conflicting reports. Moreover, the brain areas that underline the impaired performance of the BDT in patients with AD and MCI including prodromal state of AD is largely unknown.

The aim of the current study is to identify the functional neural correlates of the BDT in older adults including cognitively-impaired and AD patients. To achieve this aim, correlations between performance on the BDT and cerebral glucose metabolism was examined. To explore the overall correlation pattern between diverse brain areas and BDT performance without an *a priori* hypothesis, we adopted voxel-based analysis instead of region-of-interest approaches.

2. Materials and Methods

2.1 Subjects

Participants were recruited from the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), an ongoing prospective cohort study to identify novel biomarkers for AD. Total of 213 adults between the ages of 55 and 89 who completed all clinical, neuroimaging, and neuropsychological assessments were included. The inclusion criteria for patients with MCI were: (a) meeting the inclusion criteria based on core clinical criteria for the diagnosis of MCI according to the recommendations of the National Institute on Aging and the Alzheimer's Association (NIA-AA) guidelines (Albert et al., 2011); and, (b) global CDR score of 0.5. The inclusion criteria for patients with AD were: (a) meeting both the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV-TR) criteria for dementia and the NIA-AA diagnostic criteria for probable AD dementia; and, (b) global CDR score of 0.5 or 1. Participants who were unable to undergo neuroimaging scans or complete neuropsychological assessments were not included in the current study.

The Institutional Review Boards of Seoul National University Hospital approved this study protocol. All participants and/or their legal representative provided written informed consents.

2.2 Clinical Assessments

All participants were examined by trained psychiatrists with advanced training in dementia research according to the KBASE clinical assessment protocol (Byun et al., 2017) which incorporates the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment (CERAD-K) (J. H. Lee et al., 2002). Psychiatric, general physical, and neurological examinations were performed along with the routine laboratory tests and MRI. Reliable informants were necessarily interviewed to acquire accurate information regarding the cognitive, emotional and functional changes as well as the medical history of the participants. All comprehensive assessments including brain imaging scans were conducted at a single center. Comprehensive neuropsychological assessments were administered by trained psychometrists.

2.3 Neuropsychological Battery Block Design Test

The BDT is a subtest of the WAIS-IV (D. Wechsler, 2008). It involves subjects to reconstruct the 2-dimensional designs into 3-dimentional renditions using either four or nine, red and white colored blocks. Each trial is timed, and bonus points are given for faster completion. Scores on the BDT range from 0 to 48, with bonus points up to 66. The higher score reflects better visuospatial functioning. In this study, BDT performance was assessed using the WAIS-IV Korean version (WAIS-IV-K) (Hwang, Kim, Park, Chey, & Hong, 2012). BDT performance was scored in a standard manner according to the manual.

2.4 Neuroimaging

Participants underwent PET-MR scanning to obtain multi-modal FDG-PET imaging and 3D T-1 weighted MR, using a 3.0T Biograph mMR (PET-MR) scanner (Siemens, Washington, DC, USA) according to the manufacturer's approved guidelines. The participants fasted for at least six hours and rested in a waiting room for 40 minutes prior to the scans after intravenous administration of 0.1 mCi/Kg of [18F] FDG radioligands. The PET data collected in list mode (5 minutes x 4 frames) were processed for routine corrections such as UTE-based attenuation, scatter, random coincidences and decay corrections. After inspecting the data for any significant head movements, data was reconstructed into a 20-minute summed image using iterative methods (6 iterations with 21 subsets) (Byun et al., 2017). The FDG-PET scans were preprocessed using statistical parametric mapping 12 (SPM 12; Institute of Neurology, University College of London, United Kingdom) implemented in MATLAB 2014a (Mathworks, Natick, MA, USA). First, static FDG-PET images were co-registered to individual T1 structural images, and transformation parameters for the spatial normalization of individual T1 images to a standard Montreal Neurological Institute (MNI) template. The spatially normalized FDG-PET images were smoothed using a 12-mm Gaussian filter. Glucose metabolism in the pons was used as the reference region for intensity normalization.

2.5 Statistical Analysis

Statistical analyses were conducted with statistical package for the social science PC software for window, version 22.0 (SPSS, Cary, N.C., USA) and SPM 12. The demographic and clinical variables were compared across the subgroups using independent sample *t*-test. The effects of demographic and clinical variables on the BDT scores were examined using univariate analysis of variance. In the current study, the norm-based z-scores of the BDT were not used due to limited availability of the normative data for aging Korean population. Covariates were chosen *a priori* on the basis of previous evidence (Albert et al., 2011; Ganguli et al., 2010; Kaufman, McLean, & Reynolds, 1988; Lynn & Dai, 1993; Machulda et al., 2009; Menendez-Gonzalez & Alvarez-Avellon, 2015; Polunina et al., 2018; Ronnlund & Nilsson, 2006; Wahlin, Backman, Wahlin, & Winblad, 1993; David Wechsler, 1981; Yin et al., 2015; Zink, Miller, Caldwell, Bird, & Banks, 2018).

Correlations between the BDT score and cerebral glucose metabolism were examined using voxel-wise analyses with age, education, gender, and CDR SOB as the covariates. Statistical threshold was set at $p < 0.005$ (uncorrected) with application of the cluster size threshold of 1062 voxel based on a cluster correction procedure in Analysis of Functional and Neural image, with 10000 iterations of Monte Carlo simulations on anatomical cerebral mask dataset (Forman et al., 1995).

Family-wise error (FWE) correction was additionally applied to verify

the association more stringently. Visualization of the results were done using the BrainNet viewer (http://www.nitrc.org/projects/bnv/) (Xia, Wang, & He, 2013).

3. Results

3.1 Examination of demographic and clinical variables

The demographic and clinical characteristics are summarized in Table 1. The participants are consisted of 213 older adults, of which 67.1% were female, and had an average education of 9.8 years (*SD* = 4.9). The mean BDT score was 20.9 (*SD* = 9.1) and mini-mental status exam (MMSE) score of 24.8 (*SD* = 4.8).

In order to investigate if age, educational years, gender and CDR sum of boxes (SOB) (O'Bryant et al., 2008) show significant effects on BDT performance, univariate analysis of variance was performed. All variables showed significant main effects; age, $F(65, 576) = 6.06$, $p < .001$, educational years, $F(21, 576) = 3.36$, $p < .001$, gender, $F(1, 576) = 4.85$, $p < .028$, and CDR SOB, $F(15, 576) = 9.00$, $p < .001$ on BDT performance. Interaction effects of the demographic variables were not significant. Hierarchical linear regression analysis was conducted to examine relative effects of the variables. Age and CDR SOB accounted for 27.6% and 23.8%, of the variance, respectively. Education and gender accounted for less than 6% combined.

Table 1. Demographic and clinical characteristics of the participants

Characteristic	Participants	Mildly-impaired group	Severely-impaired group	$p^{\#}$
N	213	111	102	
Age, years, mean (*SD*)	73.1 (7.4)	73.5 (7.1)	72.6 (7.8)	.352
Education, years, mean (*SD*)	9.8 (4.9)	9.9 (4.7)	9.6 (5.0)	.651
Women, *n* (%)	143 (67.1)	69 (62.2)	72 (69.2)	.196
MMSE, raw score, mean (*SD*)	24.8 (4.8)	23.0 (3.1)	17.6 (4.0)	< .001
CDR SOB, mean (*SD*)	2.7 (2.0)	1.2 (0.4)	4.4 (1.7)	< .001
BDT, raw score, mean (*SD*)	20.9 (9.1)	23.4 (8.0)	17.8 (9.3)	< .001

Note. [#]Independent sample *t*-test for mildly-impaired group compared to severely-impaired group, Block design test; CDR SOB, Clinical Dementia Rating Sum of Boxes; MMSE, Mini-mental Status Exam; SD, standard deviation.

3.2 Regional cerebral glucose metabolism and the BDT scores on voxel-wise analysis

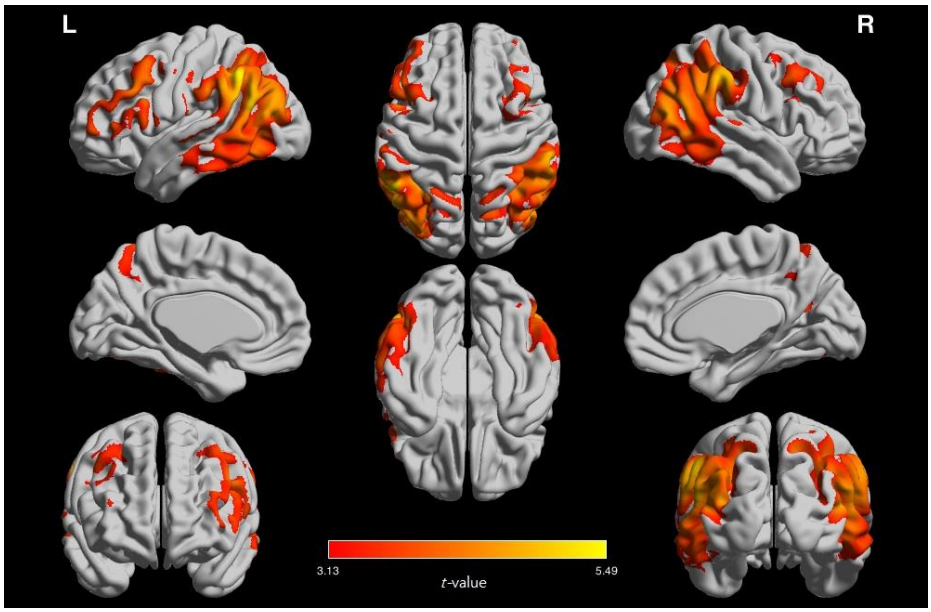
Voxel-wise analysis showed significant positive correlations between the BDT score and regional cerebral glucose metabolism in various cortical regions. Across all participants, positive correlations were observed in the left inferior parietal lobule, right middle frontal gyrus, right superior temporal gyrus and bilaterally in the thalamus. (Table 2, Figure 1). In order to explore the effect of overall severity of cognitive impairment on the relationship between BDT scores and regional cerebral glucose metabolism, participants were divided into two severity subgroups: mildly-impaired group with the CDR SOB ranging from 0.5 to 2.0 (consisted mostly of MCI) and severely-impaired group with the CDR SOB ranging from 2.5 to 9.0 (consisted mostly of AD). In mildly-impaired subgroup, positive correlation was observed in the left middle frontal gyrus and left inferior parietal lobule (Table 3, Figure 2). In severely-impaired subgroup, positive correlations were observed in left inferior parietal lobule, right postcentral gyrus, right thalamus and bilaterally in middle frontal gyrus (Table 3, Figure 3). When more stringent statistical threshold was applied with FWE correction method, the same regions remained and overlapped with the uncorrected results (Supplementary Tables 1 and 2; Supplementary Figures S1 and S2). In general, the correlations with the BDT scores were present bilaterally.

Table 2. Brain areas showing significant positive correlations between the Block Design Test scores and cerebral glucose metabolism in the participants

Brain Regions	BA	Coordinates (mm)			Extent Voxels (*n*)	*T* value	*Z* score	*P* value
		X	Y	Z				
L inferior parietal lobule, parietal suprmarginal gyrus	40	-56	-51	44	353001	5.49	5.30	< .005
R thalamus	-	13	-11	15	11727	4.02	3.94	< .005
R middle frontal gyrus	8	47	13	41	36573	3.97	3.89	< .005
L thalamus	-	-20	-28	11	4165	3.54	3.48	< .005
R superior temporal gyrus	22	51	9	-10	1755	3.22	3.18	< .005
L occipital precuneus	31	-15	-63	17	1199	3.03	2.99	< .005

Note. $p < .005$ (uncorrected) with cluster threshold of k >1062. Adjusted for age, education, gender and CDR SOB. Coordinates are in Montreal Neurological Institute (MNI) space. BA, Brodmann area; L, left hemisphere; R, right hemisphere.

Figure 1. Brain regions showing significant association between increased cerebral glucose metabolism with better BDT performance in the participants.



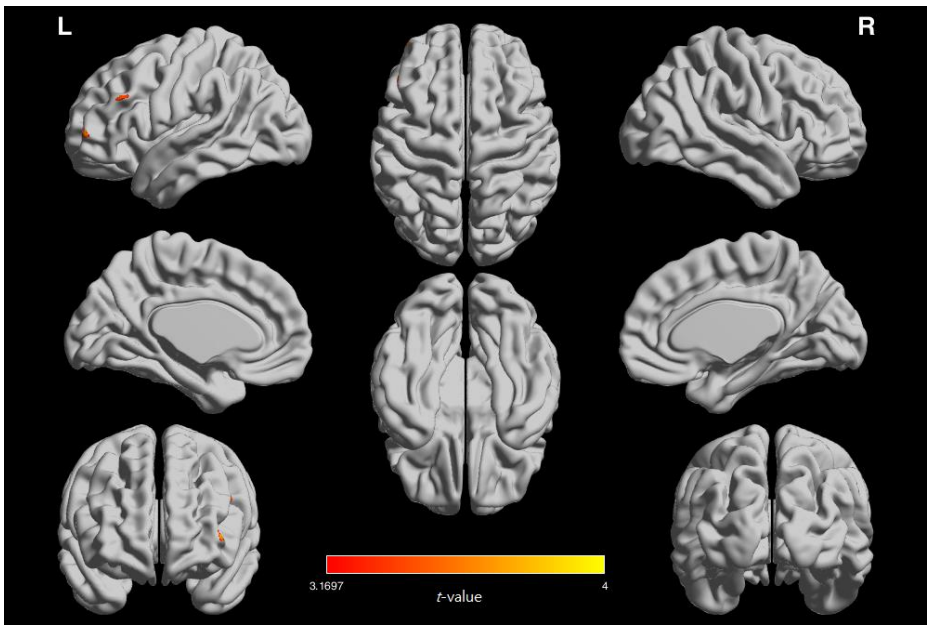
Note. $p < .005$ (uncorrected) with cluster threshold of k >1062. Adjusted for age, education, gender and CDR SOB.

Table 3. Brain areas showing significant positive correlations between the Block Design Test scores and cerebral glucose metabolism in the mildly- and severely impaired groups

Brain Regions	BA	Coordinates (mm) X	Y	Z	Extent Voxels (*n*)	*T* value	*Z* score	*P* value
Mildly-impaired group								
L middle frontal gyrus	46	-44	55	6	14581	4.03	3.88	< .005
L inferior parietal lobule, parietal supramarginal gyrus	40	-55	-53	46	5920	3.44	3.34	< .005
Severely-impaired group								
L inferior parietal lobule, parietal supramarginal gyrus	40	-33	-48	37	128147	4.94	4.65	< .005
R postcentral gyrus	2	61	-30	42	147102	4.92	4.64	< .005
R middle frontal gyrus	9	49	11	32	27825	3.93	3.77	< .005
L middle frontal gyrus	9	-51	11	30	3949	3.59	3.46	< .005
R thalamus	-	11	-8	10	2379	3.36	3.26	< .005

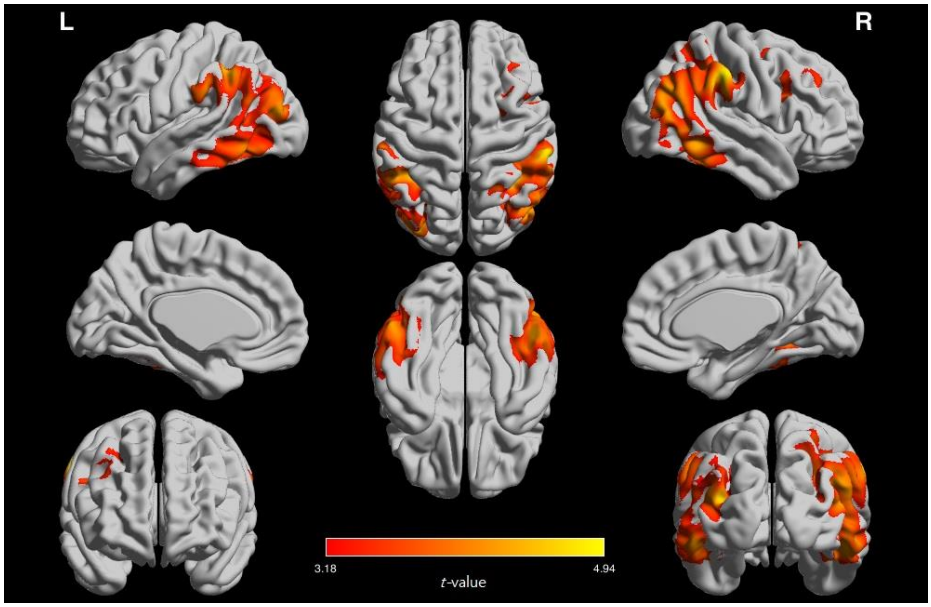
Note. $p < .005$ (uncorrected) with cluster threshold of k >1062. Adjusted for age, education, gender and CDR SOB. Coordinates are in Montreal Neurological Institute (MNI) space. BA, Brodmann area; L, left hemisphere; R, right hemisphere.

Figure 2. Brain regions showing significant association between increased cerebral glucose metabolism with better Block design test performance in the mildly-impaired group.



Note. $p < .005$ (uncorrected) with cluster threshold of k >1062. Adjusted for age, education, gender and CDR SOB.

Figure 3. Brain regions showing significant association between increased cerebral glucose metabolism with better Block design test performance in the severely-impaired group.



Note. $p < .005$ (uncorrected) with cluster threshold of k >1062. Adjusted for age, education, gender and CDR SOB.

4. Discussion

The current study demonstrated the functional neural correlates of the BDT based on the voxel-wise association between BDT performance and regional cerebral glucose metabolism in cognitively-impaired older adults with MCI and AD. Performance on the BDT was positively correlated with regional cerebral glucose metabolism in the inferior parietal lobule, middle frontal gyrus, temporal gyrus, precuneus and thalamus—generally in the somatosensory, motor and dorsolateral prefrontal cortices. This aids our understanding of the complex and hierarchical nature of visuospatial processing, by showing involvement of bilateral hemisphere, indicating of integration various abilities as a required function for successful performance on the BDT. More in-depth examination of the relationship was conducted in terms of age-related cognitive impairments, which yielded positive correlations in a much broader area of the frontal and parietal lobes as the clinical severity increased. These findings suggest that the functional neural correlates of the BDT involve a complex mechanism of visuospatial, sensory input, motor ability and executive functions.

The results of the current study were partially consistent with previous literature—such that not only the right parietal region but also the left posterior parietal region were involved. Earlier studies based on lesion studies suggested a primary involvement of the right hemisphere related to BDT performance (Benton et al., 1978; Chase et al., 1984; Warrington et al., 1986; Zink et al., 2018). Ferreira et al. (2016) reported reduced cortical thickness in frontal as well as temporal regions in association with BDT. There are also reports of left

hemisphere involvement in the performance of the BDT (Ferreira et al., 2016; Machulda et al., 2009). The current study supports the findings of left hemisphere involvement likely indicate more diffuse functional organization required by the BDT.

More specifically, our results show that BDT requires bilateral involvement. The voxel-wise analyses showed a positive correlation in the right superior temporal gyrus, left occipital precuneus, right middle frontal gyrus and bilateral inferior parietal lobule, which are consistent with previous activation study based on amnestic MCI patients (Machulda et al., 2009). Other study also reported weak but significant correlation between BDT and temporal region, suggesting the contribution of perceptual organization role in BDT (O'Hora et al., 2008). Earlier studies results and involvement of the left hemisphere in our results suggests that the BDT is not only associated with the visuospatial ability but also draws from more complicated functions requiring an intricate network of bilateral regions.

The largest region showing a positive correlation of BDT performance was inferior parietal lobule—specifically the supramarginal gyrus of parietal lobe. This region had been implicated in previous studies on the BDT (Benton et al., 1978; Chase et al., 1984; Warrington et al., 1986; Zink et al., 2018). The current findings demonstrated that performance of the BDT heavily relies on inferior parietal region indicating the importance of motor control and somatosensory involvement, likely related to the BDT requiring complex motor planning as well as organization leading to visuomotor integration. The inferior parietal lobule is a key location in the brain, connecting somatosensory and

motor cortex allowing simultaneous multimodal processing of visual and sensorimotor input (Dongier, 2002). In addition, the inferior parietal lobule is also involved in visual guidance of hand and arm movements (Singh-Curry & Husain, 2009). Previous studies reported that the inferior parietal lobule utilizes shape information to guide specific hand and arm movements necessary for the appropriate manipulation of visually presented objects. It is therefore possible that this region supports flexible reconfiguration of motor control and visual guidance of the body movement, which in essence required by the BDT for successful performance. Postcentral gyrus, also known as the primary somatosensory cortex, was found additionally to be significantly associated with BDT performance. Somatosensory cortex is involved in processing of somatosensory input and contributes to the integration of sensory and motor signals (Borich, Brodie, Gray, Ionta, & Boyd, 2015). Taken together, as a part of a set of networks with visual somatosensory and limbic movement, each region that showed significant association with the BDT scores may play a key role in perceptual decision making. Thalamus was also positively associated with the BDT scores. Similarly to inferior parietal lobule, this regions functions as a communicator between sensory input and motor control, and therefore explain how BDT performance does not merely rely on visuospatial ability but requires a complex integration of sensory input and motor control (Basso, Uhlrich, & Bickford, 2005).

Additional notable finding from the current study is the involvement of frontal regions, particularly the dorsolateral prefrontal cortex that lies in the middle frontal gyrus. Previous functional connectivity study suggested that left

frontal cortex has significant positive connectivity with somatomotor, visual network and dorsolateral prefrontal cortex (Franzmeier et al., 2017; D. Lee & Quessy, 2003). Executive function, which heavily relies on dorsolateral prefrontal cortex (Lezak, 2012), is a set of cognitive process that is required for the cognitive control of behavior (Diamond, 2013). A widespread network of regions, including bilateral middle frontal gyrus and parietal cortex, is activated during the visuospatial planning task to generate, select and remember appropriate moves over evaluation of specific problem (Ball et al., 2011). Given that the BDT requires visuospatial planning as well as manipulation of 3D visual information, involvement of executive functions relying upon the functions of frontal regions shown in the current results is expected. It is necessary to know the internal relations of the presented models and overall shape to reconstruct the blocks successfully. Therefore, analytical ability and integration of ability are necessary. This study suggests the importance of left hemisphere rather than relying solely on the right parietal lobe as previously suggested by other studies. There are a few consideration that needs to be investigated when an additional technique is required, such as BDT. This is observed through the bilateral activation in the present study. BDT requires physical distinction for orientation of the block. Therefore, a lateralized function is required for the successful execution of the BDT. Our finding indicates the involvement of both visuospatial and executive function as well as highlights of bilateral involvement. The current findings also indicate that the BDT is a useful tool to detect AD-related functional brain impairments, even in a very early stage of the disease process.

In order to delineate complex relationship between BDT performance and age-related neurodegeneration, the current study incorporated a clinical stage-specific approach, separately focusing on groups with varying the clinical severity of AD dementia. Based on the current results, bilateral neural functions affect performance on the BDT in cognitively-impaired individuals especially as clinical severity progresses. A previous study suggested utility of the BDT as an early detector of neural degeneration in subjects at risk for subsequent development of AD (Yin et al., 2015), given that poor performance on the visuospatial tasks indicating a deficit in visuospatial ability is apparent as early as ten years before the diagnosis of dementia (Laukka, Macdonald, Fratiglioni, & Backman, 2012). Backman, Jones, Berger, Laukka, and Small (2005) found that cognitively healthy elderly participants who were later diagnosed as having AD performed more poorly on visuospatial tasks (including the BDT) than those who remained cognitively normal. Given that the patterns of brain metabolic impairment typical of AD begins in the precuneus and posterior cingulate cortex and spreads to parieto-temporal region (Mosconi & Silverman, 2009), it is reasonable to posit that the BDT could be an useful tool in discriminating patients with MCI from dementia (Yin et al., 2015).

5. Conclusion

Thus, this study suggests that functional neural correlates of the BDT are highly dependent on inferior parietal lobule, specifically in supramarginal parietal gyrus. When performing BDT, brain regions are activated bilaterally, which include somatosensory, motor control, and dorsolateral prefrontal cortex. This demonstrates the relevance of the executive function of the complex network, which helps us understand our complex and hierarchical nature of the visuospatial process and suggests various visuomotor integration as a necessary function for successful BDT performance. Depending on the progression, such as MCI and AD severity, which can be observed with BDT performance, it is predictable that the executive function will be lowered and ability to track, observe and transform behavior as its declines. In addition to the previous studies, the present results suggest that BDT is a neuropsychological test that is sensitive to detecting age-related cognitive impairment because it helps to see functional changes in cognitive decline associated with AD progression.

References

Adolphs, R. (2016). Human Lesion Studies in the 21st Century. *Neuron, 90*(6), 1151-1153. doi:10.1016/j.neuron.2016.05.014

Akshoomoff, N. A., Delis, D. C., & Kiefner, M. G. (1989). Block constructions of chronic alcoholic and unilateral brain-damaged patients: A test of the right hemisphere vulnerability hypothesis of alcoholism. *Archives of Clinical Neuropsychology, 4*(3), 275-281. doi:10.1016/0887-6177(89)90018-8

Albert, M. S., Dekosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008

Backman, L., Jones, S., Berger, A. K., Laukka, E. J., & Small, B. J. (2005). Cognitive impairment in preclinical Alzheimer's disease: a meta-analysis. *Neuropsychology, 19*(4), 520-531. doi:10.1037/0894-4105.19.4.520

Ball, G., Stokes, P. R., Rhodes, R. A., Bose, S. K., Rezek, I., Wink, A. M., . . . Turkheimer, F. E. (2011). Executive functions and prefrontal cortex: a matter of persistence? *Front Syst Neurosci, 5*, 3. doi:10.3389/fnsys.2011.00003

Basso, M. A., Uhlrich, D., & Bickford, M. E. (2005). Cortical function: a view from the thalamus. *Neuron, 45*(4), 485-488. doi:10.1016/j.neuron.2005.01.035

Benton, A. L., Varney, N. R., & Hamsher, K. D. (1978). Visuospatial judgment. A clinical test. *Arch Neurol, 35*(6), 364-367. doi:10.1001/archneur.1978.00500300038006

Borich, M. R., Brodie, S. M., Gray, W. A., Ionta, S., & Boyd, L. A. (2015). Understanding the role of the primary somatosensory cortex: Opportunities for rehabilitation. *Neuropsychologia, 79*(Pt B), 246-255. doi:10.1016/j.neuropsychologia.2015.07.007

Byun, M. S., Yi, D., Lee, J. H., Choe, Y. M., Sohn, B. K., Lee, J. Y., . . . Group, K. R. (2017). Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease: Methodology and Baseline Sample Characteristics. *Psychiatry Investig, 14*(6), 851-863. doi:10.4306/pi.2017.14.6.851

Chase, T. N., Fedio, P., Foster, N. L., Brooks, R., Dichiro, G., & Mansi, L. (1984). Wechsler Adult Intelligence Scale Performance - Cortical Localization by Fluorodeoxyglucose F18-Positron Emission Tomography. *Archives of Neurology, 41*(12), 1244-1247. doi:DOI 10.1001/archneur.1984.04050230026012

Diamond, A. (2013). Executive functions. *Annu Rev Psychol, 64*(1), 135-168. doi:10.1146/annurev-psych-113011-143750

Dongier, M. (2002). Broca's area, wernicke's area and other language-processing areas in the brain. Retrieved from https://thebrain.mcgill.ca/flash/i/i_10/i_10_cr/i_10_cr_lan/i_10_cr_lan.html

Ferreira, D., Bartrés-Faz, D., Nygren, L., Rundkvist, L. J., Molina, Y., Machado, A., . . . Westman, E. (2016). Different reserve proxies confer overlapping and unique endurance to cortical thinning in healthy middle-aged adults. *Behavioural Brain Research, 311*, 375-383. doi:10.1016/j.bbr.2016.05.061

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A.,

& Noll, D. C. (1995). Improved Assessment of Significant Activation in Functional Magnetic-Resonance-Imaging (Fmri) - Use of a Cluster-Size Threshold. *Magnetic Resonance in Medicine, 33*(5), 636-647. doi:DOI 10.1002/mrm.1910330508

Franzmeier, N., Gottler, J., Grimmer, T., Drzezga, A., Araque-Caballero, M. A., Simon-Vermot, L., . . . Ewers, M. (2017). Resting-State Connectivity of the Left Frontal Cortex to the Default Mode and Dorsal Attention Network Supports Reserve in Mild Cognitive Impairment. *Front Aging Neurosci, 9*, 264. doi:10.3389/fnagi.2017.00264

Ganguli, M., Snitz, B. E., Lee, C. W., Vanderbilt, J., Saxton, J. A., & Chang, C. C. (2010). Age and education effects and norms on a cognitive test battery from a population-based cohort: the Monongahela-Youghiogheny Healthy Aging Team. *Aging Ment Health, 14*(1), 100-107. doi:10.1080/13607860903071014

Geschwind, N. (1979). Specializations of the human brain. *Sci Am, 241*(3), 180-199. doi:10.1038/scientificamerican0979-180

Groth-Marnat, G., & Teal, M. (2000). Block design as a measure of everyday spatial ability: a study of ecological validity. *Percept Mot Skills, 90*(2), 522-526. doi:10.2466/pms.2000.90.2.522

Hwang, S., Kim, J., Park, K., Chey, J., & Hong, S. (2012). *Korean-Wechsler Adult Intellignece Scale-IV*. Daegu: Korea Psychology.

Kang, J. M., Lee, J. Y., Kim, Y. K., Sohn, B. K., Byun, M. S., Choi, J. E., . . . Lee, D. Y. (2018). Visual Rating and Computer-Assisted Analysis of FDG PET in the Prediction of Conversion to Alzheimer's Disease in Mild Cognitive Impairment. *Mol Diagn Ther, 22*(4), 475-483. doi:10.1007/s40291-018-0334-z

Kaufman, A. S., McLean, J. E., & Reynolds, C. R. (1988). Sex, race, residence, region, and education differences on the 11 WAIS-R

subtests. *J Clin Psychol, 44*(2), 231-248. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/3360941

Kertesz, A., & Dobrowolski, S. (1981). Right-hemisphere deficits, lesion size and location. *Journal of Clinical Neuropsychology, 3*(4), 283-299. doi:10.1080/01688638108403133

Laukka, E. J., Macdonald, S. W., Fratiglioni, L., & Backman, L. (2012). Preclinical cognitive trajectories differ for Alzheimer's disease and vascular dementia. *J Int Neuropsychol Soc, 18*(2), 191-199. doi:10.1017/S1355617711001718

Lazarević, L. B., Knežević, G., Mitic, M., Jočić, D. Đ., Leposavić, I., Markovic, M., . . . Živanović, M. (2015). *Wechsler Adult Intelligence Scale — Fourth Edition (WAIS – IV).*

Lee, D., & Quessy, S. (2003). Activity in the supplementary motor area related to learning and performance during a sequential visuomotor task. *J Neurophysiol, 89*(2), 1039-1056. doi:10.1152/jn.00638.2002

Lee, J. H., Lee, K. U., Lee, D. Y., Kim, K. W., Jhoo, J. H., Kim, J. H., . . . Woo, J. I. (2002). Development of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K): clinical and neuropsychological assessment batteries. *J Gerontol B Psychol Sci Soc Sci, 57*(1), P47-53. doi:10.1093/geronb/57.1.p47

Lezak, M. D. (2012). *Neuropsychological assessment* (Vol. 5th Edition). New York: Oxford University Press.

Lichtenberger, E., & Kaufman, A. S. (2013). Essentials of WAIS-IV assessment / Elizabeth O. Lichtenberger, Alan S. Kaufman. In A. S. Kaufman (Ed.), *Essentials of Wechsler Adult Intelligence Scale four assessment* (Second edition. ed.): Hoboken, N.J. : John Wiley & Sons.

Lynn, R., & Dai, X. Y. (1993). Sex differences on the Chinese standardization sample of the WAIS-R. *J Genet Psychol, 154*(4), 459-463. doi:10.1080/00221325.1993.9914744

Machulda, M. M., Senjem, M. L., Weigand, S. D., Smith, G. E., Ivnik, R. J., Boeve, B. F., . . . Jack, C. R. (2009). Functional magnetic resonance imaging changes in amnestic and nonamnestic mild cognitive impairment during encoding and recognition tasks. *J Int Neuropsychol Soc, 15*(3), 372-382. doi:10.1017/S1355617709090523

Matarazzo, J. D. (1972). *Wechsler's Measurement and appraisal of adult intelligence* (5th and enl. ed.. ed.). Baltimore: Baltimore : Williams & Wilkins.

Menendez-Gonzalez, M., & Alvarez-Avellon, T. (2015). Editorial: Neuropsychology and Neuropsychiatry of Neurodegenerative Disorders. *Front Aging Neurosci, 7*, 227. doi:10.3389/fnagi.2015.00227

Mosconi, L., & Silverman, D. H. S. (2009). FDG PET in the Evaluation of Mild Cognitive Impairment and Early Dementia. In D. Silverman (Ed.), *PET in the Evaluation of Alzheimer's Disease and Related Disorders* (pp. 49-65). New York, NY: Springer New York.

Mukundan, C. R. (2013). *Computerized Cognitive Retraining Programs for Patients Afflicted with Traumatic Brain Injury and Other Brain Disorders*.

O'Bryant, S. E., Waring, S. C., Cullum, C. M., Hall, J., Lacritz, L., Massman, P. J., . . . Texas Alzheimer's Research, C. (2008). Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. *Arch Neurol, 65*(8), 1091-1095. doi:10.1001/archneur.65.8.1091

O'Hora, D., Peláez, M., Barnes-Holmes, D., Rae, G., Robinson, K., & Chaudhary, T. (2008). Temporal Relations and Intelligence: Correlating Relational Performance With Performance on the Wais-III. *The Psychological Record, 58*(4), 569-584. doi:10.1007/bf03395638

Polunina, A., Bryun, E., Sydniaeva, E., & Z Golukhova, E. (2018). Gender differences in cognitive functions: retrospective analysis of the data of 5 neuropsychological studies. *3*, 61-75.

Ronnlund, M., & Nilsson, L. G. (2006). Adult life-span patterns in WAIS-R Block Design performance: Cross-sectional versus longitudinal age gradients and relations to demographic factors. *Intelligence, 34*(1), 63-78. doi:10.1016/j.intell.2005.06.004

Rorden, C., & Karnath, H. O. (2004). Using human brain lesions to infer function: a relic from a past era in the fMRI age? *Nat Rev Neurosci, 5*(10), 813-819. doi:10.1038/nrn1521

Royer, F. L., & Weitzel, K. E. (1977). Effect of perceptual cohesiveness on pattern recoding in the block design task. *Perception & Psychophysics, 21*(1), 39-46. doi:10.3758/bf03199465

Singh-Curry, V., & Husain, M. (2009). The functional role of the inferior parietal lobe in the dorsal and ventral stream dichotomy. *Neuropsychologia, 47*(6), 1434-1448. doi:10.1016/j.neuropsychologia.2008.11.033

Takahashi, M., Sato, A., Nakajima, K., Inoue, A., Oishi, S., Ishii, T., & Miyaoka, H. (2008). Poor performance in Clock-Drawing Test associated with visual memory deficit and reduced bilateral hippocampal and left temporoparietal regional blood flows in Alzheimer's disease patients. *Psychiatry Clin Neurosci, 62*(2), 167-173. doi:10.1111/j.1440-1819.2008.01750.x

Wahlin, T. B. R., Backman, L., Wahlin, A., & Winblad, B. (1993).

Visuospatial Functioning and Spatial Orientation in a Community-Based Sample of Healthy Very Old Persons. *Archives of Gerontology and Geriatrics, 17*(3), 165-177. doi:Doi 10.1016/0167-4943(93)90048-M

Warrington, E. K., James, M., & Maciejewski, C. (1986). The Wais as a Lateralizing and Localizing Diagnostic Instrument - a Study of 656 Patients with Unilateral Cerebral-Lesions. *Neuropsychologia, 24*(2), 223-239. doi:Doi 10.1016/0028-3932(86)90055-2

Wechsler, D. (1981). *Manual for the Wechsler Adult Intelligence Scale-Revised (WAIS-R)*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale—Fourth Edition.* San Antonio, TX: Pearson.

Wilde, M. C., Boake, C., & Sherer, M. (2000). Wechsler Adult Intelligence Scale-Revised Block Design broken configuration errors in nonpenetrating traumatic brain injury. *Appl Neuropsychol, 7*(4), 208-214. doi:10.1207/S15324826AN0704_2

Xia, M., Wang, J., & He, Y. (2013). BrainNet Viewer: a network visualization tool for human brain connectomics. *PLoS One, 8*(7), e68910. doi:10.1371/journal.pone.0068910

Yin, S., Zhu, X., Huang, X., & Li, J. (2015). Visuospatial characteristics of an elderly Chinese population: results from the WAIS-R block design test. *Front Aging Neurosci, 7*, 17. doi:10.3389/fnagi.2015.00017

Zink, D. N., Miller, J. B., Caldwell, J. Z. K., Bird, C., & Banks, S. J. (2018). The relationship between neuropsychological tests of visuospatial function and lobar cortical thickness. *J Clin Exp Neuropsychol, 40*(5), 518-527. doi:10.1080/13803395.2017.1384799

Supplementary

Supplementary table S1. Brain areas showing significant positive correlations between the Block Design Test scores and cerebral glucose metabolism in the participants

Brain Regions	BA	Coordinates (mm) X	Y	Z	Extent Voxels (*n*)	*T* value	*Z* score	*P* value
L inferior parietal lobule / parietal supramarginal gyrus	40	-56	-51	44	7695	5.49	5.30	< .05
R inferior parietal lobule / parietal supramarginal gyrus	40	62	-35	41	1871	5.09	4.93	< .05
L inferior parietal lobule / parietal supramarginal gyrus	40	-34	-48	40	1004	5.08	4.92	< .05
L middle temporal gyrus / occipital gyrus	39	52	-69	17	1372	4.76	4.63	< .05
L middle frontal gyrus	9	-50	13	34	137	4.62	4.50	< .05

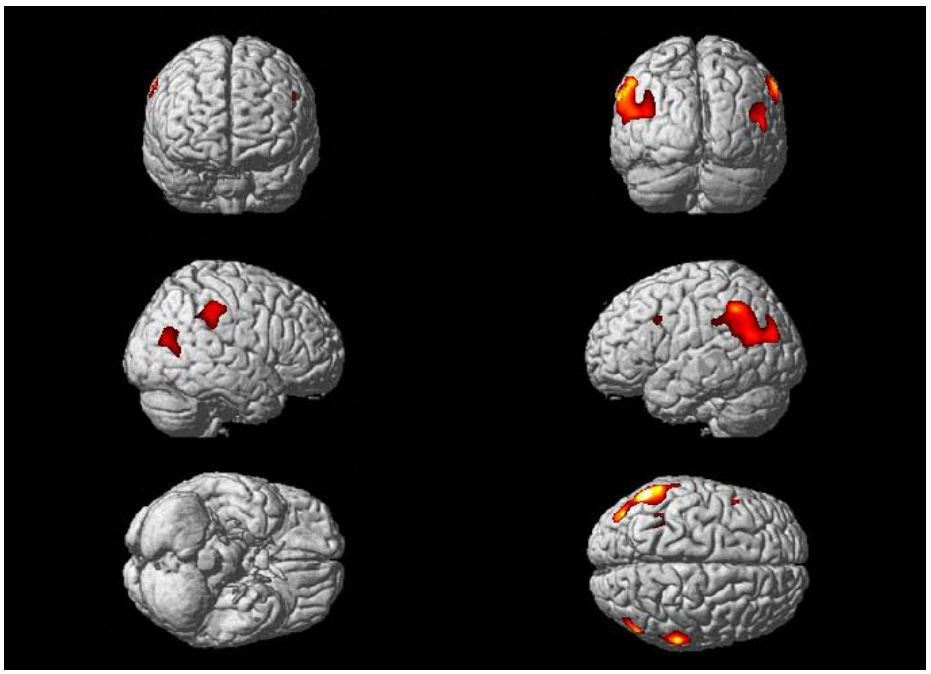
Note. $p < .05$ Family-wise error (FWE) correction. Adjusted for age, education, gender and CDR SOB. Coordinates are in Montreal Neurological Institute (MNI) space. BA, Brodmann area; L, left hemisphere; R, right hemisphere.

Supplementary table S2. Brain areas showing significant positive correlations between the Block Design Test scores and cerebral glucose metabolism in the severely-impaired group

Brain Regions	BA	Coordinates (mm)			Extent Voxels (*n*)	*T* value	*Z* score	*P* value
		X	Y	Z				
L inferior parietal lobule / parietal supramarginal gyrus	40	-33	-48	37	520	4.94	4.65	< .05
R postcentral gyrus	2	61	-30	42	735	4.92	4.64	< .05
R inferior parietal lobule / parietal supramarginal gyrus	40	32	-50	39	458	4.87	4.59	< .05
L middle frontal gyrus	19	-37	-84	19	156	4.74	4.48	< .05

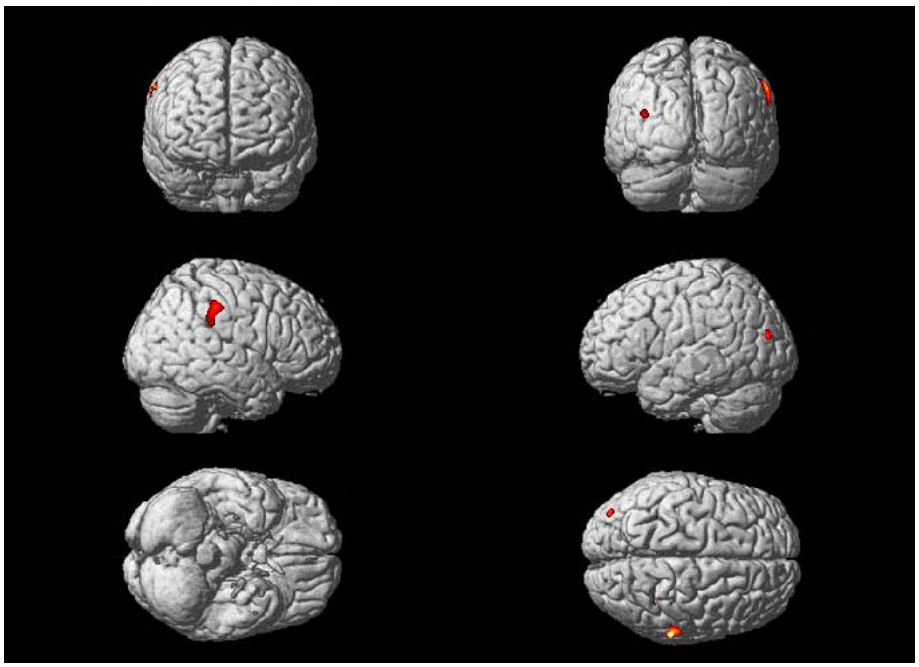
Note. $p < .05$ Family-wise error (FWE) correction. Adjusted for age, education, gender and CDR SOB. Coordinates are in Montreal Neurological Institute (MNI) space. BA, Brodmann area; L, left hemisphere; R, right hemisphere.

Supplementary figure S1. Brain regions showing significant association between increased cerebral glucose metabolism with better BDT performance in the participants.



Note. $p < .05$ Family-wise error (FWE) correction. Adjusted for age, education, gender and CDR SOB.

Supplementary figure S2. Brain regions showing significant association between increased cerebral glucose metabolism with better BDT performance in the severely-impaired group.



Note. $p < .05$ Family-wise error (FWE) correction. Adjusted for age, education, gender and CDR SOB.

국문 초록

경미한 인지 장애 및 알츠하이머 병을 가진 노령 성인 대상의 토막 짜기 검사의 기능성 신경 상관 관계

정 혜 중
협동과정 인지과학 전공
서울대학교 대학원

토막 짜기 검사는 변전 기능 및 노령 인구 기능저하 측정 도구로 흔히 사용되고 있지만 토막 짜기 검사 성능과 연관되는 신경 기질에 대해선 널리 연구되고 있지 않습니다. 또한, 토막 짜기 검사 수행의 신경 기질이 알츠하이머 성 치매의 인지 기능 저하와 관련된 피질 영역을 반영하는지에 대하여 여부는 자세히 조사되지 않았습니다. 본 연구는 인지 기능 장애가 있는 알츠하이머 성 치매 환자에서 ^{18}F-fluorodeoxyglucose (FDG) Positive emission tomography (PET)을 사용해 토막짜기검사의 기능적 신경 상관관계를 확인하기위해 진행되었습니다.

본 연구에 포함된 참가자는 213명의 인지 기능 저하가

있는 중년 및 노인이며, 모든 참가자는 종합적인 임상 및 신경심리 평가와 fdg pet 영상 촬영을 완료하였습니다.

토막짜기 검사 수행은 한국 웩 슬러 성인 지능검사 IV를 사용하여 측정되었으며, fdg pet 영상의 복 셀 기반 분석을 통해 국소적인 뇌 포도당 대사와 토막짜기검사 수행 사이의 상관관계를 조사하였습니다. 알츠하이머 성 치매의 중증도의 영향을 자세히 보기위해 임상 치매 등급 점수 합계를 사용하여 하위집단에서 동일한 분석을 수행했습니다.

연구 표본은 총 213명으로써, 평균 연령은 73.1세 (*SD* = 7.4), 평균 교육은 9.8년 (*SD* = 4.9), 평균 토막짜기검사 점수은 20.9 (SD = 9.1)이였으며, 여성은 67.1%의 참가자로 구성되었습니다. 토막짜기검사 성능과 국소적 포도당 대사 사이의 유의한 양에 대한 상관관계는 양측 뇌 반구에서 관찰되었습니다.

본 연구 결과는 토막짜기검사 수행과 관련된 신경 기전은 양측 뇌 반구 모두 연관성이 있다고 나타내고 있습니다. 본 결과는 토막짜기검사 수행에서 시각, 운동, 집행 기능과 체 감각 피질의 기능이 매우 중요하다는 것을 시사합니다. 또한, 이전 연구에서 시각과 모터에 관련이 있다고 보고된 영역과 일치하며, 토막짜기검사가 지능 및 인지

저하를 측정하는데 있어 유용한 도구임을 신경과학적으로 증명하는 바입니다.

주요어: 토막 짜기 검사, Block design test, FDG-PET, 인지 저하, 신경 기전, 알츠하이머

학번: 2016-25872