Heading Disorientation in Amnestic Mild Cognitive Impairment is Correlated with Hypometabolism in the Posterior Cingulate Cortex

by

Seong-Joon Lee

Major in Medicine

Department of Medical Sciences

The Graduate School, Ajou University

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Supervised by

So Young Moon, M.D., Ph.D.

Major in Medicine

Department of Medical Sciences

The Graduate School, Ajou University

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This certifies that the dissertation of Seong-Joon Lee is approved.

SUPERVISORY COMMITTEE

Kyun Huh

Byung Gon Kim

So Young Moon

The Graduate School, Ajou University

November, 29th, 2012

- ABSTRACT -

Heading Disorientation in Amnestic Mild Cognitive Impairment is Correlated with Hypometabolism in the Posterior Cingulate Cortex

Introduction: A lesional study showed that three patients with right retrosplenial lesions had intact performance in the part A of the card-placing test (CPT) but impaired performance in the part B of the CPT. It was insisted that the part A of the CPT assesses egocentric disorientation whereas part B examines heading disorientation. However, the test has not yet been used in any larger population. In addition, neural substrates of the test have not yet been replicated in other studies. In our study, using statistical parametric mapping (SPM) analysis we aimed to investigate anatomical correlates of both part A and B of the CPT in FDG-PET studies of patients with amnestic mild cognitive impairment (aMCI).
Methods: A total of 15 aMCI patients were enrolled into the study. Patients underwent standardized neuropsychological tests and part A and part B of the CPT. The CPT scores and K-MMSE scores of 29 cognitively normal people were used for comparison. FDG-PET was performed in the same patients. We used the SPM correlation analysis to extract the regions whose changes in regional cerebral metabolism correlated significantly with part A and B of the CPT with adjustment of age and sex of patients. **Results:** Controlling for age, sex, and education years, the K-MMSE score and CPT B score was significantly lower in the aMCI group (26.0±2.0 vs. 28.2±1.4, $p<0.001$, and 16.3±4.4 vs. 19.7±3.7, $p=0.011$). However, CPT A scores did not significantly differ between the two groups (25.5±3.5 vs. 27.7±2.7, $p=0.055$). The SPM analysis showed that decrease in scores of part A correlated with hypometabolism in bilateral precuneus, posterior cingulate gyri, right crus cerebelli, cerebellar vermis, right anterior and middle cingulate gyri, right superior and middle frontal gyri, left inferior parietal region, and the left angular gyrus. (uncorrected $p<0.05$). Decrease in scores of part B correlated with hypometabolism in bilateral precuneus, middle and posterior cingulate gyri (uncorrected $p<0.005$). **Conclusion:** The test scores of part B of the card placing test correlated well with hypometabolism of the posterior cingulate gyrus and its surrounding areas whereas part A correlated with hypometabolism in more various areas.

Normal part A but impaired performance in the part B of the CPT may reflect dysfunction of the posterior cingulate gyrus and predict aMCI patients at risk of progression to Alzheimer's disease.

Key word: Heading disorientation, topographical disorientation, card placing test, mild cognitive impairment, Alzheimer disease, posterior cingulate cortex

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I. Introduction

The question of which deficits can be taken as early predictors of Alzheimer's disease (AD) has been a topic of consistent interest. So far, the greatest attention has been paid to verbally-mediated memory disorders, especially episodic and semantic memory that are traditionally considered the earliest and deepest deficits.(Fox et al., 1998) Visuospatial deficits, especially topographical disorientation, have long been recognized even in early stages of AD but studied much less closely.(Martin et al., 1986; Mendez et al., 1990; Braak and Braak, 1991) The term topographical disorientation (TD) refers to an individual's inability to orient in the environment. As reported in a current taxonomy,(Aguirre and D'Esposito, 1999) TD may occur following lesions in different parts of the brain including medial temporal regions such as the hippocampus and parahippocampal cortex, the fusiform gyrus, and more-posterior temporo-occipital regions including the lingual gyrus, posterior cingulate gyrus, and posterior parietal cortex. Lesions in these selective brain regions may result in specific cognitive impairments such as anterograde disorientation,(Habib and Sirigu, 1987) landmarks agnosia,(Pallis, 1955) heading disorientation,(Takahashi et al., 1997) or egocentric disorientation,(Kase et al., 1977) which severely affect the individuals' ability to orient in familiar or unfamiliar surroundings.

Similar cerebral regions causing TD in patients with acquired brain damage have been shown to be involved in the neurodegenerative process typical of patients affected by mild cognitive impairment (MCI) progressing to AD.(Huang et al., 2002; Trivedi et al., 2006; Seo et al., 2007; Whitwell et al., 2007; Desikan et al., 2008) Due to this neuroanatomical similarity and evidence of MCI patients manifesting with orientation impairment, it has been suggested that TD occurs early in the development of AD and can be used for detecting the disease and monitoring its progression.(Hort et al., 2007) In particular, heading disorientation, a disorder caused by disruption of the exocentric visuospatial frame by lesions in the posterior cingulate cortex, is of much interest because metabolic reduction in the posterior cingulate cortex is seen in very early Alzheimer's disease and its presence has also been proven to predict progression to Alzheimer's disease in mild cognitive impairment.(Minoshima et al., 1997; Huang et al., 2002) Therefore, tests to evaluate heading orientation can be used to discriminate patients with MCI who would convert to AD. However, most of the tests for heading disorientation include virtual reality and have limitation in that the aged have difficulty with manipulating and understanding tests. An easy test to be used in clinical facilities is necessary.

Recently, a lesional study showed that three patients with right retrosplenial lesions had intact performance in the part A of the card-placing test (CPT) but impaired performance in the part B of the CPT.(Hashimoto et al., 2010) The CPT is easy for the examiner to make and for the examinee to take. Part A of the test assesses the ability of a subject to retain information on spatial locations of cards placed on the floor around the subject. Part B examines the subject's ability to integrate information on the spatial locations of similarly arranged cards and that on changes of the body directions. It was insisted that the part A of the CPT assesses egocentric disorientation whereas part B examines heading disorientation. However, the test has not yet been used in any larger population. In addition, neural substrates of the test have not yet been replicated in other studies. In our study, using statistical parametric mapping (SPM) analysis we aimed to investigate anatomical correlates of both part A and B of the CPT in fluorodeoxyglucose positron emission tomography (FDG-PET) studies of patients with amnestic mild cognitive impairment (aMCI).

II. Methods

A. Participants

Patients were 15 individuals (8 men) with aMCI (mean age 65.3, s.d. 5.5 years, mean Mini-Mental State Examination [MMSE] score 26.0, s.d. 2.0, mean years of education 9.2, s.d. 4.7). They fulfilled the criteria proposed by Petersen et al.(Petersen, 2004):1) Subjective memory complaint by the patient or his/her caregiver;2) Normal general cognitive function above the 16th percentile on the Korean version of the Mini-Mental State Examination (K-MMSE);3) Normal activities of daily living (ADL) assessed both clinically and on a standardized scale;4) Objective memory decline below the 16th percentile on neuropsychological tests;5) Exclusion of dementia.

The absence of secondary causes of cognitive deficits was assessed by laboratory tests including complete blood count, blood chemistry, vitamin B_{12}/folate, syphilis serology, and thyroid function tests. Brain magnetic resonance imaging (MRI) scans were performed to confirm the absence of structural lesions such as territorial cerebral infarction, brain tumor, or vascular malformation.

29 healthy volunteers (12 men) in their sixties and seventies (mean age 68.7, s.d. 5.5 years, mean MMSE score 28.2, s.d. 1.4, mean years of education 11.7, s.d. 4.7) also participated in the experiment. All subjects had corrected visual acuity of 20/40 or better, and no other known neurological or ophthalmological conditions. We obtained informed consents from all the patients and controls, and the study was approved by the Institutional Review Board of Ajou University Hospital.

B. CPT

Participants underwent the CPT by a method previously described.(Figure 1)(Hashimoto et al., 2010) In part A of the CPT, a subject stands in the center square of nine, 3X3 squares. The subject is instructed to remember the spatial locations of three different cards randomly placed in one of the eight squares. After 10 seconds, the cards are taken away and the subject is to restore them to their original positions. In part B, immediately after the cards have been removed, the subject is rotated to the right or to the left by 90 or 180°, and then asked to replace the cards. For both part A and part B of the CPT, the subject undergoes 10 consecutive trials, and scores 1 point if the location of a card that the subject has replaced is correct. The full score of each of part A and part B of the CPT is 30 points.

C. Neuropsychological tests

All patients underwent standardized neuropsychological evaluation, the Seoul Neuropsychological Screening Battery. The battery, of which norms are based on 447 healthy controls, includes tests assessing attention, language, praxis, four elements of Gerstmann syndrome, visuoconstructive functions, verbal and visual memory, and frontal/executive function.(Ahn et al., 2010) The Korean version of MMSE was performed in the cognitively normal group.

D. FDG PET studies

Fifteen patients with aMCI took the FDG-PET. PET/CT data were acquired on a Discovery ST scanner (General Electric Medical Systems, USA). After fasting for at least 4 h, patients received 300 MBq of FDG intravenously. We checked serum glucose-levels in all subjects prior to FDG injection, and the subjects whose glucose-level exceeds 150 mg/dl were excluded in this study. All subjects were instructed to rest comfortably for 30 min with their eyes closed and ears unplugged and then image acquisition was started. To reduce head movement during scanning, the patients were positioned and maintained using an individually molded head holder. They first had a CT scan (tube-rotation time of 1 s per revolution, 120 kV, 70 mA, 5.0 mm per rotation and an acquisition time of 11.8 s for a scan length of 150.42 mm) and, subsequently, one frame (8 min per frame) of emission PET data was acquired in a three-dimensional mode. PET images were reconstructed by iterative reconstruction (ordered subsets expectation maximization, with one iteration and 32 subsets), using the CT images for attenuation correction. Also, the random correction by singles and model-based scatter correction were applied.

E. Data analysis

FDG-PET images were spatially normalized to a standard template provided by SPM2 (Statistical Parametric Mapping 2, Institute of Neurology, University of London, UK) on MATLAB (version 7.1, Mathworks Inc., Natick, MA). A local optimization of the 12 parameters of an affine transformation was applied to spatial normalization. These images were then smoothed with a Gaussian kernel (full-width at half-maximum=16 mm) to minimize noise and improve between-subject spatial alignment. Appropriate voxel-by-voxel statistical tests were used to evaluate differences in glucose metabolism. A correlation analysis was performed to extract regions whose changes in regional cerebral metabolism correlated significantly with part A and part B of the card placing test, controlling for age and sex. Anatomical labeling of significant clusters was performed using automated anatomical labeling SPM toolbox (Tzourio-Mazoyer et al., 2002), which was based on anatomy provided by the Montreal Neurological Institute.

F. Statistical analysis

We used chi square and the student's t-test to compare demographic data and test scores between patients and normal population. A partial correlation analysis was used to show the correlation between the card placing test scores and test scores of SNSB adjusted for age, sex, and education years. P values<0.05 were deemed significant. The statistical analysis was performed using commercially available software (SPSS, version 18.0). In the SPM analyses, regions reaching uncorrected threshold of $p<0.05$ for CPT part A, and $p<0.005$ for CPT part B, were considered to be significant due to the small number of the patient population.

III. Results

A. MCI patients versus controls

The demographics of the patients and the normal population are outlined in table 1. The aMCI patients comprised of 10 (66.7%) single domain aMCI, and 5 (33.3%) multiple domain aMCI patients. 2 (13.3%) were only impaired on visual memory, while 6 (40%) were impaired on verbal memory, and 7 (46.7%) were impaired on both verbal and visual memory. The aMCI patients had significantly lower K-MMSE scores (26.0±2.0 vs. 28.2±1.4, $p<0.001$), CPT A (25.5±3.5 vs. 27.7±2.7, $p= 0.026$) and CPT B scores (16.3±4.4 vs. 19.7±3.7, $p=0.011$) compared to the normal population. Age, education years, and sex did not significantly differ between the groups. Even after controlling age, sex, and education years, the K-MMSE score and CPT B score was still significantly lower in the aMCI group ($p<0.001$, and $p=0.011$). However, CPT A scores did not significantly differ between the two groups after adjusting for age, sex, and education years ($p=0.055$).

B. Correlation analysis between the CPT scores and neuropsychological tests

Table 2 presents the results of partial correlation analysis performed between the neuropsychological test scores and part A and B of the CPT, controlling for age, sex, and education years. Statistically significant correlation was seen between CPT A and calculation score ($r=0.703$, $p=0.011$), RCFT copy score ($r=0.765$, $p=0.004$), RCFT recognition score ($r=0.619$ 4, $p=0.032$), stroop test word ($r=0.649$, $p=0.022$), and stroop test color ($r=0.712$, $p=0.009$). Significant correlation was seen between CPT B and calculation score ($r=0.589$, $p=0.044$) and RCFT copy score ($r=0.616$, $p=0.033$).

C. SPM correlation analysis

Table 3 presents the results of the correlation analysis to evaluate the regions whose changes in regional cerebral metabolism correlated significantly with part A and part B.

Decrease in scores of part A correlated with hypometabolism in bilateral precuneus, posterior cingulate gyri, right crus cerebelli, cerebellar vermis, right anterior and middle cingulate gyri, right superior and middle frontal gyri, left inferior parietal region, and the left angular gyrus (Figure 2., uncorrected $p<0.05$). Decrease in scores of part B correlated with hypometabolism in bilateral precuneus, middle and posterior cingulate gyri (Figure 3., uncorrected $p<0.005$).

IV. Discussion

The results of our study showed that compared to normal population, the scores of CPT B which evaluates heading disorientation tended to be lower in the aMCI group while scores of CPT A that evaluates egocentric disorientation did not differ when controlling for age, sex, and education years. This is in accordance with previous studies that evaluated egocentric orientation and exocentric orientation in MCI and early dementia patients using various tests.(Hort et al., 2007; Guariglia and Nitrini, 2009) In a study by Hort et al., the authors used a four-subtests task that required the subjects to locate an invisible goal inside a circular arena. The patients with AD and multiple domain MCI were impaired on all subtests, while the amnestic single domain MCI group was impaired significantly on tests that focused on allocentric orientation and at the beginning of the real space egocentric subtest.(Hort et al., 2007) In another study by Guariglia et al., AD patients, even with mild dementia, was significantly impaired on most neuropsychological tests the examiners used to evaluate TD except for tests for basic visuospatial tests such as spatial working memory, point localization, three dimension and nonsense figure copy, showing that TD is present even in early AD patients, and the findings are not due to impairments in more elementary spatial functions.(Guariglia and Nitrini, 2009) Our study results and the results of other studies lead us to conclude that while both exocentric disorientation and egocentric disorientation is common in AD patients, heading disorientation, a dysfunction that is caused by disruption of the exocentric perception of the environment, may be more common in aMCI, and occur more early in the disease process.

In the correlational analysis performed to extract regions whose changes in regional cerebral metabolism correlated significantly with part A and part B of the CPT, the scores of CPT A was weakly associated with hypometabolism of rather multiple cerebral regions ($p<0.05$), while the scores of CPT B correlated more strongly with hypometabolism of the posterior cingulate region ($p<0.005$). The latter results are in accordance with the results of the case studies that originally mentioned the CPT(Hashimoto et al., 2010) along with other lesional studies.(Takahashi et al., 1997) The core difference between part A and part B of the test is the subjects' rotation in part B just before they replace the cards. The most plausible explanation for the poor achievement in part B is that the patients were unable to integrate information on the registered external spatial locations of objects with that on their body direction.(Hashimoto et al., 2010) In rodents, head direction cells, that are excited when rats are maintaining a certain heading or orientation within an environment, are found in the retrosplenial cortex in addition to several neural structures such as the anterior dorsal nucleus of the thalamus, lateral dorsal thalamus, lateral mammillary nuclei, striatum, and posterior subiculum.(Chen et al., 1994; Taube, 1998) These neural substrates may constitute a functional circuit dealing with directional signals of the self.(Taube, 1998) Thus, the results of our study shows that part B of the CPT is a highly specific test for evaluation of heading disorientation, and its scores correlate well with hypometabolism of the posterior cingulate region. The fact that hypometabolism of the posterior cingulate region is previously known to be seen in very early AD and its presence has also been proven to predict progression to AD in MCI supports the view that the scores of CPT B may be an appropriate screening tool for patients at risk of progression to AD in the MCI population.

The specific regions that were associated with CPT A were bilateral precuneus, posterior cingulate gyri, right crus cerebelli, cerebellar vermis, right anterior and middle cingulate gyri, right superior and middle frontal gyri, left inferior parietal region, and the left angular gyrus. In the correlational analysis between CPT A and the neuropsychological tests, statistically significant correlation was seen with calculation score, RCFT copy score, RCFT recognition score, stroop test word, and stroop test color scores. Hashimoto et al. presumed that for the patients to accomplish part A of the test, they are likely to use an egocentric reference frame.(Hashimoto et al., 2010) Egocentric disorientation with intact visual recognition impairment is currently known to be caused by lesions in the right posterior parietal area.(Aguirre and D'Esposito, 1999) This is in contrast to our results. The hypometabolism patterns observed in our study are somewhat in correspondence with the more fundamental cognitive functions that were proven to be associated with CPT A; attention and frontal executive functions, calculation, and visuospatial functions. To evaluate egocentric disorientation, examiners have classically tested the ability for the patients to point to the objects in the room after their eyes were closed, a method essentially similar to part A of the card placing test.(Takahashi et al., 1997; Guariglia and Nitrini, 2009) Our results suggest that this kind of evaluation method, although it may be sensitive, is not limited to the evaluation of the egocentric frame, and is influenced, or may be compensated by other fundamental cognitive functions. The specific regions that were associated with

CPT B were bilateral precuneus, middle and posterior cingulate gyri. Statistically significant correlation was seen between CPT B and calculation score and RCFT copy score. In contrast to CPT A, scores of part B more selectively correlated with hypometabolism in the retrosplenial region, and fewer fundamental cognitive function scores were associated, proving the validity of CPT B in selectively indicating dysfunction of the retrosplenial region. There have been previous studies that have focused on TD as a predictive marker of AD from MCI patients. Mapstone and colleagues compared healthy subjects with MCI and AD patients in perception of panoramic visual stimuli, showing one third of the patients with MCI, and half the patients with AD showed pervasive impairments of visual motion perception.(Mapstone et al., 2003) Delpolyi and collaborators compared mild AD patients and MCI patients with matched controls on a route learning task, and concluded that while AD and MCI patients recognized landmarks as effectively as controls, they could not find their locations on maps or recall the order in which they were encountered. Patients who got lost had lower right posterior hippocampal and parietal volumes than patients and controls who did not.(deIpolyi et al., 2007) Recently, Lim et al. employed a voxel-based morphometric analysis method to assess the neural substrates underlying TD in MCI patients. TD was assessed clinically in all participants. Presence of TD in MCI patients was associated with loss of gray matter in the medial temporal regions, including the hippocampus and parahippocampal cortex, the fusiform gyrus, the inferior occipital gyrus, the amygdala, and the cerebellum.(Lim et al., 2010) Compared to these studies, the results of our study differ in that while TD, especially heading disorientation, was apparently present in the aMCI patients, using a simple test and cerebral metabolism study, our study results point to the retrosplenial region for the anatomical correlate of this dysfunction rather than the hippocampal regions, and show that the CPT can be a good screening tool for evaluation of the topographical function of these regions.

We recognize that there are some limitations to our study. First, because of the limited number of the patients, we used uncorrected P values for the correlational analysis between the PET images and CPT scores. Also because of the limited number of patients, we could not identify the group of patients that selectively had low CPT B scores, a population that is likely to be of most importance when the test is actually used as a screening tool in aMCI patients. These limitations remain to be appreciated in further studies including a larger number of patients.

V. Conclusion

In conclusion, the card placing test is a valuable tool in MCI patients, for it seems to be sufficient for the evaluation of hypomatabolism in the retrosplenial region, and accordingly, the patients with low scores on part B of the CPT may have a higher possibility of progression to AD.

Table 1. Demographic findings and test results of normal population and aMCI patients.

	aMCI patients (n=15)	Normal population (n=29)	P value
Age, years	65.3±5.5	68.7±5.5	0.066
Sex, male (%)	8 (53.3%)	12 (41.4%)	0.450
Education, years	9.2±4.7	11.7±4.7	0.111
K-MMSE*	26.0±2.0	28.2±1.4	<0.001
Part A, CPT*	25.5±3.5	27.7±2.7	0.055
Part B, CPT*	16.3±4.4	19.7±3.7	0.011

aMCI, amnestic mild cognitive impairment; K-MMSE, Korean version of Mini-Mental State Examination; CPT, card placing test. *ANCOVA test was performed with age, sex, and education years as covariance factors.

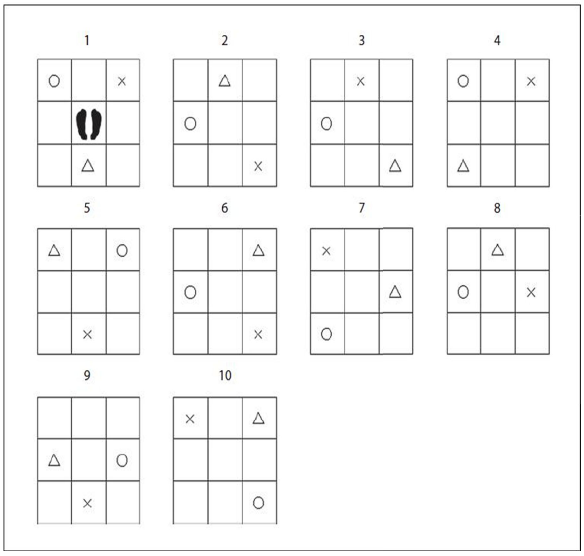
Table 2. Partial correlation analysis to show the correlation between the card placing test scores and sub-scores of SNSB.

	Part A correlation coefficient	significance	Part B correlation coefficient	significance
Attention				
digit span forward	0.426	0.167	0.290	0.361
Working memory				
digit span backwards	0.496	0.101	0.171	0.595
Language and related functions				
Boston naming test	0.180	0.575	-0.130	0.687
praxis	-0.364	0.245	-0.556	0.061
calculation	0.703	0.011	0.589	0.044
Visuospatial functions				
copy of RCFT	0.765	0.004	0.616	0.033
Memory functions				
SVLT-immediate recall	0.156	0.628	0.141	0.662
SVLT-delayed recall	0.368	0.239	0.542	0.069
SVLT-recognition	0.049	0.880	-0.331	0.293
RCFT-immediate recall	0.264	0.408	0.139	0.666
RCFT-delayed recall	0.266	0.403	0.115	0.721
RCFT-recognition	0.619	0.032	0.568	0.054
Frontal functions				
COWAT-A	-0.272	0.393	-0.265	0.406
COWAT-S	0.049	0.881	0.165	0.608
COWAT-phonemic	0.150	0.641	0.116	0.720
Stroop test Word	0.649	0.022	0.249	0.436
Stroop test color	0.712	0.009	0.210	0.513

RCFT, Rey Complex Figure Test; SVLT, Seoul Verbal Learning Test; COWAT, Controlled Oral Word Association Test.

Table 3. SPM correlation analysis between CPT Test scores and regional hypometabolism.

Voxel level	Coordinate			Side	Area
P(uncorrected)	X	Y	Z		
Decrease with part A score					
0.001	24	-94	-30	Rt	cerebelum_Crus
0.007	40	-88	-30	Rt	cerebelum_Crus
0.007	2	-46	12	Rt	precuneus
					cinglum_Post
				Lt	precuneus
					cinglum_Post
					vermis
0.036	4	-64	-18		Vermis
				Rt	cerebelum
				Lt	cerebelum
				Rt	lingual
0.009	-60	-54	-46	Lt	inferior parietal
0.026	-56	-54	46	Lt	Angular
					inferior parietal
0.011	0	-60	74	Lt	precuneus
				Rt	precuneus
0.014	-2	-68	68	Lt	precuneus
				Rt	precuneus
0.026	0	-74	62	Lt	precuneus
				Rt	precuneus
0.019	18	30	26	Rt	anterior cingulate
					superior frontal
					middle cingulate
					middle frontal
Decrease with part B score					
0.003	14	-50	28	Rt	precuneus
					middle cingulate
					posterior cingulate
0.003	0	-44	16	Rt	posterior cingulate
					precuneus
				Lt	posterior cingulate
					precuneus



Part B

1) 90° to the right
2) 90° to the left
3) 180° to the right
4) 180° to the left
5) 90° to the right
6) 90° to the left
7) 180° to the right
8) 180° to the left
9) 90° to the right
10) 90° to the left

Figure 1. The card placing test. In part A of the CPT, a subject stands in the center square of nine, 3X3 squares. The subject is instructed to remember the spatial locations of three different cards randomly placed in one of the eight squares. After 10 seconds, the cards are taken away and the subject is to restore them to their original positions. In part B, immediately after the cards have been removed, the subject is rotated to the right or to the left by 90 or 180°, and then asked to replace the cards.

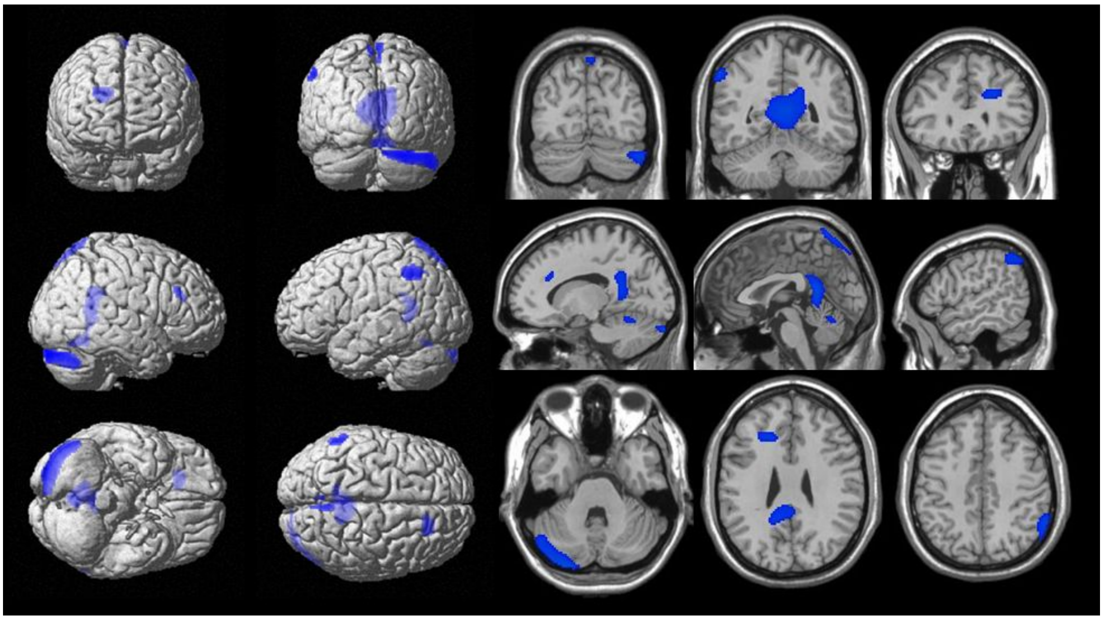


Figure 2. Spatial parametric maps showing areas of hypometabolism that correlate with decrease in scores of CPT A. Decrease in scores of part A correlated with hypometabolism in bilateral precuneus, posterior cingulate gyri, right crus cerebelli, cerebellar vermis, right anterior and middle cingulate gyri, right superior and middle frontal gyri, left inferior parietal region, and the left angular gyrus (uncorrected $p<0.05$).

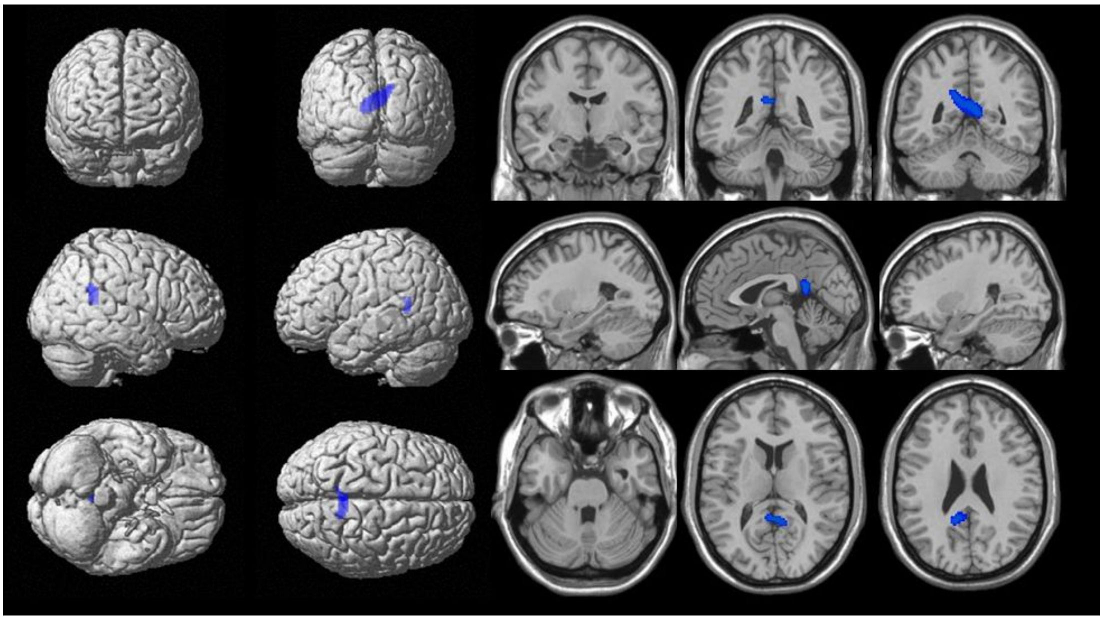


Figure 3. Spatial parametric maps showing areas of hypometabolism that correlate with decrease in scores of CPT B. Decrease in scores of part B correlated with hypometabolism in bilateral precuneus, middle and posterior cingulate gyri (uncorrected p<0.005).

REFERENCES

1. Aguirre GK, D'Esposito M: Topographical disorientation: a synthesis and taxonomy. *Brain* 122 (Pt 9): 1613-1628, 1999
2. Ahn HJ, Chin J, Park A, Lee BH, Suh MK, Seo SW, Na DL: Seoul Neuropsychological Screening Battery-dementia version (SNSB-D): a useful tool for assessing and monitoring cognitive impairments in dementia patients. *J Korean Med Sci* 25: 1071-1076, 2010
3. Braak H, Braak E: Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* 82: 239-259, 1991
4. Chen LL, Lin LH, Green EJ, Barnes CA, McNaughton BL: Head-direction cells in the rat posterior cortex. I. Anatomical distribution and behavioral modulation. *Exp Brain Res* 101: 8-23, 1994
5. deIpolyi AR, Rankin KP, Mucke L, Miller BL, Gorno-Tempini ML: Spatial cognition and the human navigation network in AD and MCI. *Neurology* 69: 986-997, 2007
6. Desikan RS, Fischl B, Cabral HJ, Kemper TL, Guttmann CR, Blacker D, Hyman BT, Albert MS, Killiany RJ: MRI measures of temporoparietal regions show differential rates of atrophy during prodromal AD. *Neurology* 71: 819-825, 2008
7. Fox NC, Warrington EK, Seiffer AL, Agnew SK, Rossor MN: Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease. A longitudinal prospective study. *Brain* 121 (Pt 9): 1631-1639, 1998
8. Guariglia CC, Nitrini R: Topographical disorientation in Alzheimer's disease. *Arq Neuropsiquiatr* 67: 967-972, 2009
9. Habib M, Sirigu A: Pure topographical disorientation: a definition and anatomical basis. *Cortex* 23: 73-85, 1987
10. Hashimoto R, Tanaka Y, Nakano I: Heading disorientation: a new test and a possible underlying mechanism. *Eur Neurol* 63: 87-93, 2010
11. Hort J, Laczo J, Vyhnalek M, Bojar M, Bures J, Vlcek K: Spatial navigation deficit

in amnestic mild cognitive impairment. *Proc Natl Acad Sci U S A* 104: 4042-4047, 2007

12. Huang C, Wahlund LO, Svensson L, Winblad B, Julin P: Cingulate cortex hypoperfusion predicts Alzheimer's disease in mild cognitive impairment. *BMC Neurol* 2: 9, 2002
13. Kase CS, Troncoso JF, Court JE, Tapia JF, Mohr JP: Global spatial disorientation. Clinico-pathologic correlations. *J Neurol Sci* 34: 267-278, 1977
14. Lim TS, Iaria G, Moon SY: Topographical disorientation in mild cognitive impairment: a voxel-based morphometry study. *J Clin Neurol* 6: 204-211, 2010
15. Mapstone M, Steffenella TM, Duffy CJ: A visuospatial variant of mild cognitive impairment: getting lost between aging and AD. *Neurology* 60: 802-808, 2003
16. Martin A, Brouwers P, Lalonde F, Cox C, Teleska P, Fedio P, Foster NL, Chase TN: Towards a behavioral typology of Alzheimer's patients. *J Clin Exp Neuropsychol* 8: 594-610, 1986
17. Mendez MF, Mendez MA, Martin R, Smyth KA, Whitehouse PJ: Complex visual disturbances in Alzheimer's disease. *Neurology* 40: 439-443, 1990
18. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE: Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* 42: 85-94, 1997
19. Pallis CA: Impaired identification of faces and places with agnosia for colours; report of a case due to cerebral embolism. *J Neurol Neurosurg Psychiatry* 18: 218-224, 1955
20. Petersen RC: Mild cognitive impairment as a diagnostic entity. *J Intern Med* 256: 183-194, 2004
21. Seo SW, Im K, Lee JM, Kim YH, Kim ST, Kim SY, Yang DW, Kim SI, Cho YS, Na DL: Cortical thickness in single- versus multiple-domain amnestic mild cognitive impairment. *Neuroimage* 36: 289-297, 2007
22. Takahashi N, Kawamura M, Shiota J, Kasahata N, Hirayama K: Pure topographic disorientation due to right retrosplenial lesion. *Neurology* 49: 464-469, 1997

23. Taube JS: Head direction cells and the neurophysiological basis for a sense of direction. *Prog Neurobiol* 55: 225-256, 1998
24. Trivedi MA, Wichmann AK, Torgerson BM, Ward MA, Schmitz TW, Ries ML, Koscik RL, Asthana S, Johnson SC: Structural MRI discriminates individuals with Mild Cognitive Impairment from age-matched controls: a combined neuropsychological and voxel based morphometry study. *Alzheimers Dement* 2: 296-302, 2006
25. Whitwell JL, Przybelski SA, Weigand SD, Knopman DS, Boeve BF, Petersen RC, Jack CR, Jr.: 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. *Brain* 130: 1777-1786, 2007

- 국문 요약 -

기억 상실성 경도 인지 장애 환자에서의 Heading Disorientation 과 뒤쪽 띠이랑 피질의 대사 저하의 연관성

아주대학교 대학원 의학과
이성준
(지도교수: 문소영)

서론: 알츠하이머 병 환자에서 병의 초기부터 뒤쪽 띠이랑 피질의 대사 저하가 동반되며, 위 현상이 경도 인지 장애 환자에서 알츠하이머 병으로의 진행을 예측할 수 있다는 것은 이미 알려진 사실이다. 최근 후측 대상 피질에 병변의 위치한 환자에게서 시행할 수 있는 간단한 검사로서, A part점수는 유지되는 반면, B part의 점수는 감소하여 heading disorientation에 대하여 평가할 수 있는 Card placing test (CPT) 에 대한 보고가 이루어졌다. 따라서 본 연구에서는 기억 상실성 인지기능 환자를 대상으로 이 검사를 시행하고, 동시에 FDG-PET 검사와 statistical parametric mapping (SPM) 을 사용하여, 본 검사의 신경 기질에 대한 평가를 계획하였다. **재료 및 방법:** 총 15명의 기억 상실성 경도 인지 장애 환자를 대상으로, CPT, Seoul Neuropsychiatric Screening Battery (SNSB) 및 FDG-PET 검사를 시행하였다. 첫째, 29 명의 정상 노년 인구를 대조군으로 활용하여 두 군간의 인지 검사 및 CPT 점수를 비교하였다. 둘째, SNSB 세부 항목과 CPT A 및 B와의 상관관계 분석을 통하여, cad placing test 에 영향을 미치는 기초 인지기능에 대하여 분석하였다. 셋째, SPM 상관관계 분석을 통해 국소적인 뇌 대사가 CPT A 및 B점수의 변화와 연관이 있는 부위를 분석하였다.

결과: 정상 노년 군과 비교하여, 기억 상실성 경도 인지 장애 환자군은 나이, 성별, 교육 년수를 통제시 유의하게 더 낮은 K-MMSE (26.0±2.0 vs. 28.2±1.4, $p<0.001$) 및 CPT B (16.3±4.4 vs. 19.7±3.7, $p=0.011$) 점수를 보였으나, CPT A 점수는 차이가 나지 않았다. CPT A점수는 SNSB 중 계산능력, 시공간 능력, 시공간 기억, 및 전두엽 기능과 관련이 있는 반면, CPT B 점수는 계산 능력 및 시공간 능력과만 상관관계를 보였다. SPM 분석 상 CPT A점수의 감소는 보다 다양한 뇌 피질의 대사 감소와 상관성을 보인 반면 (uncorrected $p<0.05$), CPT B점수는 선택적으로 뒤쪽 띠이랑 피질의 대사 저하와 상관성을 보였다 (uncorrected $p<0.005$). **결론:** CPT는 기억 상실성 경도 인지 장애 환자에서 뒤쪽 띠이랑 피질의 대사 저하를 평가하여 본 환자군 중 알츠하이머 치매로의 진행을 예측하는 데에 있어 유용한 검사이다.