J. Biomed. Eng. Res.
Vol.26, No.1, 1-7, 2005

An fMRI Study of Cognitive Function during Hyperoxia

Soon-Cheol Chung[1], Ik-Hyeon Kim[1], Gye-Rae Tack[1],
Soo Yeol Lee[2], Jin-Hun Sohn[3]

[1]Department of Biomedical Engineering, College of Medicine, Konkuk University, Choongjoo, S. Korea
[2]Graduate School of East-West Medical Science, Kyunghee University, Soowon, S. Korea
[3] Department of Psychology, Institute for Brain Research, Chungnam National University, Daejon, S. Korea
(Received September 21, 2004. Accepted November 17, 2004)

Abstract: This study aimed to investigate the hypothesis that administration of the air with 30% oxygen compared with normal air (21% oxygen) enhances cognitive functioning through increased activation in the brain. Seventeen college students (right-handed, average age of 24.3) were selected as subjects for this study. An oxygen supply equipment that provides 21% and 30% oxygen at a constant rate of 8L/min was developed. In order to measure the performance level of visuospatial and verbal cognition, two psychological tests were developed. The experiment consisted of two runs, one for cognition task with normal air (21% oxygen) and the other for cognition task with hyperoxic air (30% oxygen). Visuospatial and verbal tasks were presented while brain images were scanned by a 3 T fMRI system using the single-shot EPI method. The results showed that there was an improvement in performance and also increased activation in several brain areas in the higher oxygen condition. These results suggest that while performing cognitive tasks, high concentrations of oxygen administration make oxygen administration sufficient, thus making neural network activate more, and the ability to perform cognitive tasks increase.

Key words: fMRI, Cognitive function, Visuospatial and verbal tasks, Hyperoxia

INTRODUCTION

The brain is the most metabolically active organ in the body. This almost exclusively consists of the oxygen-dependent breakdown of glucose. A number of brain imaging techniques have identified that there is an enhanced intake of glucose and oxygen into brain areas that are differentially active depending on the types of cognitive tasks involved [1]. Sufficient glucose and oxygen can improve cognitive functioning while hypoglycemia and hypoxia results in reversible cognitive impairments [2,3]. Similarly, an aging-related cognitive decline is attributed to the compromised delivery of oxygen and glucose through the cerebral vasculature [4].

This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health and Welfare, Republic of Korea (02-PJ3-PG6-EV07-0002)
Corresponding Author: Soon-Cheol Chung
Dept. of Biomedical Engineering College of Medicine, Konkuk University, 322 Danwall-dong, Chungju, Chungbuk, 380-701, Korea
Tel. 82-43-840-3759 Fax. 82-43-851-0620
E-mail. scchung@kku.ac.kr

The administration of a glucose drink has been found to enhance memory performance [5]. This phenomenon is observed in all ages and is greater in the elderly [6]. Like glucose, oxygen is also reported to enhance the cognitive performance. Oxygen inspiration for 1 min prior to the presentation of a word list resulted in a significant increase in the number of words recalled 10 min or 24 hr after the presentation [7,8]. From these results, it is concluded that external oxygen administration has positive effects on memory formation. Furthermore, reaction time is much faster with external oxygen administration when responding to previously presented words [8]. Oxygen administration is found to improve the aspects of everyday memory, including shopping list items and matching names to faces [9]. The studies on the effects of oxygen administration have focused on cognitive functioning and not the direct effects on the brain. As a result, research is necessary to identify the underlying brain mechanism that accounts for these behavioral effects produced by increased oxygen administration.

We hypothesized that transient administration of highly concentrated oxygen activates energy production, and enhances neural activation in the brain during a cognitive task, which in turn improves performance. To test this hypothesis, we simultaneously measured the level of visuospatial and verbal performance and neural activation in the brain with functional Magnetic Resonance Imaging (fMRI). In the late 1980s, functional imaging started to be used to study brain activity using electroencephalogram and Positron Emission Tomography (PET). FMRI as measured by the changes in the blood oxygenation level-dependent (BOLD) signal was introduced as a noninvasive method with an accurate spatial and relatively high temporal resolution [10]. Therefore, this study was designed to investigate the effect of a 30% oxygen administration on the visuospatial and verbal cognitive performance using fMRI.

METHODS

Participants and Oxygen Administration

Eight healthy right-handed male college students (23.5 ± 3.2 years) participated in the visuospatial cognitive performance study. Nine healthy right-handed male college students (25.1 ± 0.7 years) were selected to participate in the verbal cognitive performance study. None of the participants reported having a history of psychiatric or neurological disorders. The overall procedure was explained to all subjects who released consent for the procedure. All examinations were performed under the regulations of our Institutional Review Committee.

The oxygen supply equipment (OxyCure Co. Korea), providing 21% and 30% oxygen in the air at a constant rate of 8L/min, was developed for this study. In order to maintain the steady flow and constant concentration level of oxygen, oxygen was administrated to the subject through a mask without indicating on the concentration level.

Cognitive Performance Task

We developed two versions of visuospatial and verbal performance tests each with similar difficulty by selecting items from the Korean versions of an intelligence test, an aptitude test, and a general aptitude battery (GATB) [11-13]. From these, we made two subtests (versions A and B) of 45 items each for visuospatial task and made two subtests (versions C and D) of 55 items each for verbal task. The visuospatial task was to be selected from 4 figures which subject selects the same type from 4 given candidates over identical in shape and figure. The verbal task requires the subject to select the word which has the same relationship as one of the two given words or requires the subject to select the word which has a different meaning among 4 words. Group testing of the subtests was administered to 263 college students (77 males and 62 females for Version A and C; 66 males and 58 females for Version B and D), from which 20 pairs of visuospatial items and 28 pairs of verbal items with similar difficulty were selected [20]. From these, we constructed two visuospatial tasks and two verbal tasks of equivalent difficulty.

Procedure

The experiment consisted of two runs of the visuospatial and verbal cognition testing each, one with 21% level of oxygen and the other with 30% oxygen level. Each trial consisted of 4 blocks, each containing control and cognitive items.

The control and cognitive tasks were presented using SuperLab 1.07 (Cedrus Co.). The items were projected onto a screen to a subject pressed a button to respond to the given items. In the control task, subjects were instructed to press the button corresponding to the number (1, 2, 3, or 4) presented on the screen. In the cognitive task, subjects were asked to press the button as quickly as possible to the correct number of the item presented on the screen (5 items for visuospatial task and 7 items for verbal task per block). Image scanning was done during two runs, each consisting of four blocks. It took about two minutes to finish one block. Figure 1 shows the paradigm for the fMRI experiment. Before the experiment started, each subject was asked to carefully listen to the instructions about the procedures and was trained to do the task exactly the same as he would have to do in the scanner. The two cognitive task versions were counterbalanced across high and low oxygen levels. Every subject took 2 runs of cognitive performance tasks according to 21% and 30% oxygen, respectively.

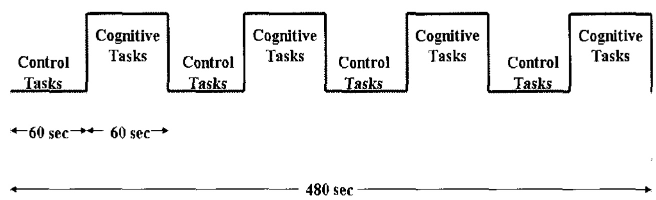

Fig. 1. The fMRI experimental procedure

Imaging Parameters

Imaging was conducted on a 3.0T ISOL Technology FORTE (ISOL Technology, Korea) equipped with whole-body gradients and a quadrature head coil. Single-shot echoplanar fMRI scans were acquired in 35 continuous slices, parallel to the anterior commissure-posterior commissure line. The parameters for fMRI were as follows: the repetition time/echo time [TR/TE] were 3000/35 ms, respectively, flip angle 60, field of view 240 mm, matrix 64 × 64, slice thickness 4 mm, and in-plane resolution 3.75mm. Five dummy scans were removed at the beginning of each run to decrease the effect of non-steady state longitudinal magnetization. T1-weighted anatomic images were obtained with a 3-D FLAIR sequence (TR/TE = 280/14 ms, flip angle = 60, FOV = 240 mm, matrix = 256 × 256, slice thickness = 4 mm).

Data Analysis

The fMRI data were analyzed with SPM99 (Wellcome Department of Cognitive Neurology, London, UK). All functional images were realigned to the image taken proximate to the anatomical study by using affine transformation routines built into SPM99. The realigned scans were coregistered to the participant's anatomical images obtained within each session, and normalized to SPM99's template image that uses the space defined by the Montreal Neurologic Institute (MNI), which is very similar with the Talairach and Tournoux's stereotaxic atlas [14]. The functional map was smoothened with a 7-mm isotropic Gaussian kernel prior to statistical analysis.

Statistical analysis was done individually, and then as a group using the general linear model and the theory of Gaussian random fields implemented in SPM99 [15]. Using the subtraction procedure, activated areas in the brain during cognitive tasks were color-coded by T-score. Finally, the double subtraction method was used to test the effect of the difference between the two oxygen level conditions (i.e., 21% vs 30% of oxygen). The statistical map made was based on the difference-score [cognitive task-control task] in 30% oxygen and 21% oxygen conditions.

RESULTS

Behavioral Performance

The mean accuracy rate of visuospatial task was 50.6 ± 8.6 (mean ± standard deviation) and 62.5 ± 9.6 for 21% and 30% oxygen administration, respectively, with a statistically significant difference between the two oxygen conditions as shown in Figure 2 (p=0.014).

The mean accuracy rate of verbal task was 52.8 ± 5.6 and 63.1 ± 12.5 for 21% and 30% oxygen administration, respectively. The paired t-test showed that there exists a statistically significant difference between two experimental concentrations as shown in Figure 3 (p=0.039).

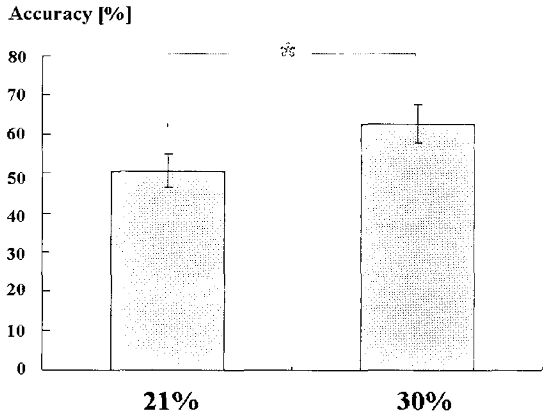

Fig. 2. Accuracy rate of visuospatial task in two conditions (* p<0.05)

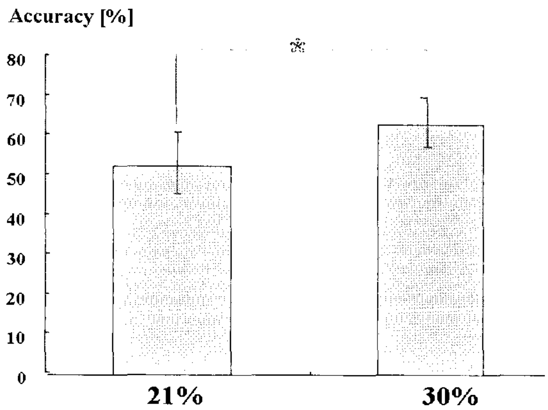

Fig. 3. Accuracy rate of verbal task in two conditions (* p<0.05)

Brain Activation

Figure 4 shows the areas in the brain significantly activated during the visuospatial tasks with 21% and 30% oxygen administration. Significant activation was observed in the cerebellum, thalamus, pons, occipital lobe, parietal lobe including bilateral superior parietal lobes, bilateral inferior parietal lobes, bilateral precuneus, and bilateral postcentral gyri, and frontal lobe including the bilateral middle frontal gyri, bilateral inferior frontal gyri, bilateral medial frontal gyri, bilateral superior frontal gyri, and bilateral cingulate gyri. Using the double subtraction procedure, activated areas in the brain during performing visuospatial tasks with different levels of oxygen administration (30%-21%) is also shown in Figure 4. These areas were the left precuneus, left cuneus, right postcentral gyrus, bilateral middle frontal gyri, right inferior frontal gyrus, left superior frontal gyrus, bilateral uvula, bilateral pyramis, and nodule, that have already been found to be activated under 30% oxygen administration. More activation in these areas was observed with 30% oxygen administration compared to in that with 21% oxygen condition. The Talairach coordinates (peak of cluster), the corresponding Brodmann area, and t-score of each activated area are shown in Table 1.

Table 1. The Talairach coordinates (peak of cluster), the Brodmann's area, and t-score in the activated areas by the double subtraction (30%-21%) method for visuospatial task.

Region	Brodmann area	Talairach coordinates			T-score
		x	y	z	
left precuneus	7	-16	-66	40	10.76
left cuneus		-20	-70	30	7.44
right postcentral gyrus	7	-20	-50	64	5.31
	7	48	-22	42	9.19
bilateral middle frontal gyri	9	56	18	30	7.99
	6	-22	18	56	7.79
right inferior frontal gyrus	9	58	18	26	8.45
left superior frontal gyrus	6	-20	14	56	6.55
bilateral uvula		0	-66	-28	7.32
		2	-62	-28	7.11
bilateral pyramis		4	-76	-24	6.87
		-2	-76	-24	5.26
nodule		0	-56	-24	5.69

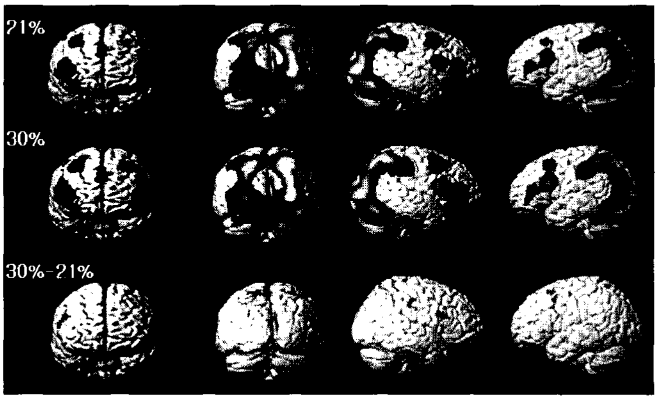

Fig. 4. The brain activation areas of visuospatial task under the administration of the air with 21% and 30% oxygen, respectively (n=8, corrected p<0.05). Activation areas by the double subtraction with 30% oxygen condition subtracted by that of 21% oxygen (30%-21%) (corrected p<0.05)

Figure 5 shows that almost the same areas in the brain were activated during the verbal tasks following both 21% and 30% oxygen administration. The cerebellum, occipital lobe including lingual gyrus and lateral occipital gyrus, parietal lobe including left superior parietal gyrus and left inferior parietal gyrus, temporal lobe including left middle temporal gyrus and fusiform gyrus, and frontal lobe including bilateral middle frontal gyri, bilateral inferior frontal gyri, bilateral superior frontal gyri, bilateral medial frontal gyri, and bilateral cingulate gyri, were almost equally activated. Using the double subtraction procedure, activated areas in the brain during performing verbal tasks with different levels of oxygen administration (30%-21%) is also shown in Figure 5. The right middle frontal gyrus, right inferior frontal gyrus, right superior frontal gyrus, cingulate gyrus, left middle temporal gyrus, and left fusiform gyrus were increased in the condition of 30% oxygen administration compared with that of 21% oxygen condition.

Table 2 shows the Talairach coordinates (peak of cluster), the corresponding Brodmann area, and t-score of each activated area.

Table 2. The Talairach coordinates (peak of cluster), the Brodmann's area, and t-score in the activated areas by the double subtraction (30%-21%) method for verbal task.

Region	Brodmann area	Talairach coordinates			T-score
		x	y	z	
Right middle frontal gyrus	11	38	44	-8	6.08
	10	40	50	8	8.93
Right inferior frontal gyrus	44	48	44	0	6.36
Left middle temporal yrus	9	-36	-76	18	6.93
	39	-34	-70	28	6.76
Left fusiform gyrus	37	-50	-58	-14	6.14
Right superior frontal yrus	8	6	16	52	5.88
Cingulate gyrus	32	-10	16	40	5.32

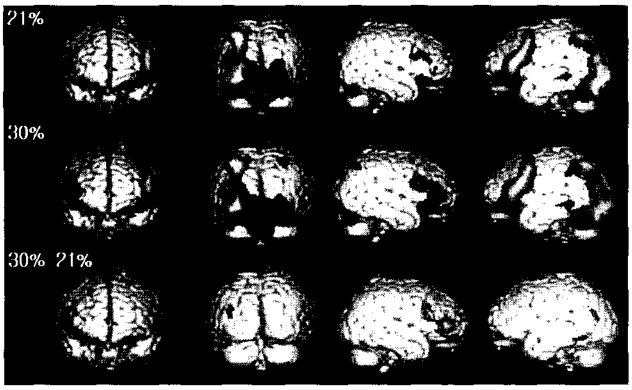

Fig. 5. The brain activation areas of verbal task under the administration of the air with 21% and 30% oxygen, respectively (n=9, corrected $p<0.05$). Activation areas by the double subtraction with 30% oxygen condition subtracted by that of 21% oxygen (30%-21%) (corrected $p<0.05$)

DISCUSSION

Studies of neural networks and brain function related to visuospatial cognition have shown diverse and relatively discrepant results based on the type of visuospatial cognition test, level of difficulty, gender, and the level of personal ability [16-19]. We found in an earlier study that the occipital visual association area, right superior parietal lobe, bilateral cingulate gyri and thalamus become active during performing visuospatial tasks [20]. The result of this study confirmed that the occipital lobe and the parietal lobe including bilateral superior parietal regions are common activation areas in the brain during a visuospatial task. It is reported that the region of the brain activation induced by visuospatial task varies by sex and the degree of difficulty of the tasks [18]. As the visuospatial tasks became more difficult, the brain activation areas turned out to be more one-side oriented and circumscribed. More activation induced by a visuospatial task were observed in the right hemisphere, and there observed differences between sexes. The right hemisphere was activated more than the left in women while the hemispheres were activated equally in men. Our results are consistent with the result of Gur et. al. that both parietal lobes were activated during a visuospatial task, especially in male subjects [18].

Using Positron Emission Tomography (PET), Peterson et al. first carried out the verbal cognition study with functional brain images [21]. After this, many studies such as decoding of stimulus of visual language and auditory language, creation of language, and type of languages are under investigation. It is reported that for verbal processing, many brain regions such as frontal lobe including Broca's area, temporal lobe including Wernicke, cingulate gyrus, parietal lobe, occipital lobe, and cerebellum are activated [22-25]. This study showed that regardless of oxygen concentration verbal processing regions in brain which were similar from previous study were activated. Since this study used visual verbal stimulus, primary and secondary visual cortex in occipital lobe and left lateral occipital gyrus which are related with verbal comprehension, are strongly activated [26]. Middle temporal gyrus and fusiform gyrus in temporal lobe which are related with verbal information processing were also activated [27]. Middle frontal gyrus, superior frontal gyrus in frontal lobe and left inferior frontal gyrus, i.e., Broca's area which is known as a verbal center, showed strong activity [25]. Cingulate gyrus which is related with cognitive information processing, attention separation processing, response-selection processing of verbal and physical activities, and working memory was also activated [28,29]. This study showed that the left parietal lobe was strongly activated and it is believed that this is due to the visuo-perceptive processing of Korean characters [30].

Vitouch et al. reported that those with a higher visuospatial ability used less cerebral cortex while performing a visuospatial task [31]. But Larson et al. performed a PET study to examine cortical activation as a function of the degree of difficulty. They selected people with high scores and those with low scores on the Raven's Advanced Progressive Matrices test [32]. Cortical activation of each subject was measured forward and backward digit span. As task difficulty increased (i.e., from forward to backward digit span), activation in the brain areas of those with high Raven's scores increased, while activation of the cerebral cortex of those with low scores decreased. Similarly, we reported that those with better visuospatial ability showed more increased activation at the right superior parietal lobe and bilateral cingulate gyri [20].

The degree of activation represented by the number of activated voxels in the brain by the two oxygen conditions turned out to be different. All the brain areas were much more activated under the condition of 30% oxygen than in that of 21% oxygen. There was an increase of activation, especially in the parietal lobe and frontal lobe, that is believed to be responsible for visuospatial perception and cognition [16,17,19]. Activity in right frontal lobe (middle frontal gyrus, inferior frontal gyrus, and superior frontal gyrus), left temporal lobe (middle temporal gyrus and fusiform gyrus), and cingulate gyrus was increased with 30% oxygen concentration compared with 21% oxygen concentration during verbal cognition. It is reported that among these regions, right inferior frontal gyrus is closely related with verbal formation [33]. It is also known that the temporal lobe is related with verbal information processing and cingulated gyrus is related with versatile cognitive information processing. It is good to see the increased activities in the regions which are related with verbal information processing.

The mean behavioral accuracy rate increased with a statistically significant difference in the condition of 30% oxygen administration. In particular, activation areas which are believed to be responsible for visuospatial and verbal cognition, increased substantially. This is a very interesting result when comparing previous results, which showed that while performing cognition tests, activation areas in the cerebrum of the higher cognitive level group increased much more than those of the lower cognitive level group [20,32]. Even if the cognitive ability of each individual were the same, it may be concluded that sufficient oxygen administration would help subjects concentrate and pay attention to given tasks, resulting in improving cognitive ability in individuals. This also suggests that while performing cognitive tasks, higher concentrations of oxygen administration make oxygen supply sufficient, thus allowing neural networks to be activated more, and the ability to perform cognitive tasks increases.

This study tried to investigate variations of visuospatial and verbal performance during 21% and 30% oxygen concentration administration as well as observe changes of activities in the brain where the region of cognitive information processing occurs itself using fMRI. Through this study the positive effect of oxygen on visuospatial and verbal performance was made objectively and confidently. It is believed that various effects of highly concentrated oxygen on human cognitive abilities including learning, reasoning, perception, and emotion can be investigated successfully using fMRI. Since more than 50% oxygen administration might be harmful for the subjects, in this study arbitrarily chosen 30% oxygen was used for comparing with 21% oxygen in the normal air. With consideration of both the cognitive ability and harmful limit, it is necessary to study about what the optimal oxygen concentration is.

REFERENCES

[1] B. Horwitz, A. R. McIntosh, J. V. Haxby, and C. L. Grady, "*Network analysis of brain cognitive function using metabolic and blood-flow data*", Behavioural Brain Research, Vol. 66, pp. 187-193, 1995.

[2] P. E. Gold, K. M. Macleod, I. J. Deary, and B. M. Frier, "*Hypoglycaemic-induced cognitive dysfunction in diaberes mellitus: Effect of hypoglycaemic unawareness*", Physiology & Behavior, Vol. 58, pp. 501-511,1985.

[3] J. Noble, J. G. Jones, and E. J. Davis, "*Cognitive function during moderate hypoxaemia*", Anaesthesia and Intensive Care, Vol. 21, pp. 180-184, 1993.

[4] F. Eustache, P. Rioux, B. Desgranges, G. Marchal, M. C. Petittaboue, M. Dary, B. Lechevalier, and J. C. Baron, "*Healthy aging, memory subsystems and regional cerebral oxygen consumption*", Neuropsychologia, Vol. 33, pp. 867-887, 1995.

[5] S. Craft, C. Murphy, and J. Wernstrom, "*Glucose effects on complex memory and nonmemory tasks: The influence of age, sex, and glucoregulatory response*", Psychobiology, Vol. 22, pp. 95-105, 1994.

[6] D. Benton, D. S. Owens, and P. Y. Parker, "*Blood glucose influences memory and attention in young adults*", Neuropsychologia, Vol. 32, pp. 595-607,1994.

[7] M. C. Moss, and A. B. Scholey, "*Oxygen administration enhances memory formation in healthy young adults*", Psychopharmacology (Berlin), Vol. 124, pp. 255-260, 1996.

[8] A. B. Scholey, M. C. Moss, N. Neave, and K. Wesnes, "*Cognitive performance, hyperoxia, and heart rate following oxygen administration in healthy young adults*" , Physiology & Behavior, Vol. 67, pp. 783-789, 1999.

[9] R. Winder, and J. Borrill, "*Fuels for memory: The role of oxygen and glucose in memory enhancemen*", Psychopharmacology (Berlin), Vol. 136, pp. 349-356, 1998.

[10] S. Ogawa, D.W. Tank, R. Menon, J. M. Ellermann, S. G. Kim, H. Merkle, and K. Ugurbil, "*Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging*", Proceeding of the National Academy of Sciences of the United States of America, Vol. 89, pp. 5951-5955, 1992.

[11] S. R. Lee, Intelligence test 151-Ga Type (High school students ~ adults). Seoul Korea: Jungangjucksung Press, 1982.

[12] S. R. Lee, and K. R. Kim, Aptitude test 251-Ga (High school students ~ adults), Seoul Korea: Jungang jucksung. Press, 1985.

[13] S. B. Park, GATB (General Aptitude Test Battery): academic, job aptitude test type II (for students of middle schools, high schools and universities, and general public). Seoul Korea: Jungangjucksung Pressm,1985.

[14] J. Talairach, and P. Tournoux, Co-Planar Stereotaxic Atlas of the Human Brain, New York: Georg Thieme Verlag Stuttgart, 1988.

[15] K. Friston, A. Holmes, K. Worsley, J. Poline, C. Frith, and R. Frackowiak, "*Statistical parametric maps in functional imaging: a general linear approach*" , Human Brain Mapping, Vol. 2, pp.189-210, 1995.

[16] P. A. Carpenter, M. A. Just, T. A. Keller, W. Eddy, and K. Thulborn, "*Graded functional activation in the visuospatial system with the amount of task demand*", Journal of Cognitive Neuroscience, Vol.11, pp. 9-24, 1999.

[17] G. R. Fink, J. C. Marshall, P. H. Weiss, and K. Zilles, "*The neural basis of vertical and horizontal line bisection judgments: an fMRI study of normal volunteers*", Neuroimage, Vol.14, pp. 59-67, 2001.

[18] R. C. Gur, D. Alsop, D. Glahn, R. Petty, C. L. Swanson, J. A. Maldjian,B. I. Turetsky, J. A. Detre, J. Gee, and R. E. Gur,"*An fMRI study of sex differences in regional activation to a verbal and a spatial task*", Brain and Language, Vol. 74, pp. 157-170, 2000.

[19] V. W. Ng, P. J. Eslinger, S. C. Williams, M. J. Brammer, E. T. Bullmore, C. M. Andrew, J. Suckling, R. G. Morris, and A. L. Benton, "*Hemispheric preference in visuospatial processing: a complementary approach with fMRI and lesion studies*", Human Brain Mapping, Vol.10, pp. 80-86, 2000.

[20] J. H. Sohn, Y. H. Kim, K. H. Lee, S. H. Park, J. M. Lee, and S. C. Chung, "*An fMRI study to identify the brain structure for predicting the level of individual's intelligence*", Neuroimage, Vol. 16, pp. 1024, 2002.

[21] S. E. Peterson, P. T. Fox, M.I. Posner, M. Mintum, and M. E. Raichle, "*Positron emission tomography studies of the cortical anatomy of single word processing*", Nature, Vol. 331, pp. 585-589, 1998.

[22] J. F. Dermonet, F. Chollet, S. Manmsay, D. Cardebat, J. L. Nespoulons, R. Wise, A. Rascol, and R. Frackowiak,

"The anatomy of phonological and semantic processing in normal subjects", Brain, Vol. 115, pp.1753-1768, 1993.

[23] K. Herholz, A. Thiel, K. Wienhard, U. Pietrzyk, H. M. Von Stockhausen, H. Karbe, J. Kessler, T. Bruckbauer, M. Halber, and W. D. Heiss, *"Individual functional anatomy of verb generation"*, Neuroimage, Vol. 3, pp. 185-194, 1996.

[24] F. Jessen, M. Erb, U. Klose, M. Lotze, W. Grodd, and R. Heun, *"Activation of human language processing brain regions after the presentation of random letter strings demonstrated with event-related functional magnetic resonance imaging"*, Neuroscience Letters, Vol. 270, pp. 13-16, 1999.

[25] P. E. Roland, Brain activation. 1st ed, New York: Wiley-Liss Inc, 1993.

[26] S. E. Petersen, P. T. Fox, A. Z. Synder, and M. E. Raichle, *"Activation of extrastriate and frontal cortical areas by visual words and word-like stimuli"*, Science, Vol. 249, pp. 1041-1045, 1990.

[27] A. R. Damasio, H. Damasio, *"The anatomic basis of pure alexia"*, Neurology, Vol. 33, pp. 1573-1583, 1983.

[28] G. Bush, P. J. Whalen, B. R. Rosen, M. A. Jenike, S. C. Mclnerney, and C. L. Rauch, *"The counting stroop: an interference task specialized for functional neuroimaging-validation study with functional MRI"*, Human Brain Mapping, Vol. 6, pp. 270-282, 1998.

[29] O. Devinsky, M. J. Morrell, and B. A. Vogt, *"Contributions of anterior cingulated cortex to behavior"*, Brain, Vol. 118, pp. 279-306, 1995.

[30] Y. H. Kim, D. R. Gitelman, A. C. Nobre, T. B. Parrish, K. S. Labar, and M. M. Mesulam, *"The large scale neural network for spatial attention displays multi-functional overlap but differential asymmetry"*, Neuroimage, Vol. 9, pp. 269-277, 1999.

[31] O. Vitouch, H. Bauer, G. Gittler, M. Leodolter, and U. Leodolter, *"Cortical activity of good and poor spatial test performances during and spatial and verbal processing studied with slow potential topography"*, International Journal of Psychology, Vol. 27, pp. 183-199, 1997.

[32] G. E. Larson, R. J. Haier, and L. Lacasse, *"Hazen K Evaluation of a mental effort hypothesis for correlations between cortical metabolism and intelligence"*, Intelligence, Vol. 21, pp. 267-278, 1995.

[33] G. McCarthy, A.M. Blamire, D. Rothman, R. Gruetter, and R. G. Shulman, *"Echo-planar magnetic resonance imaging studies of frontal cortex activation during word generation in humans"*, Proceeding of the National Academy of Sciences of the United States of America, Vol. 90, pp. 4952-4959, 1993.