소아청소년정신의학 제19권 제1호 2008
J Kor Acad Child Adolesc Psychiatry 19 : 13~18

□원 저□

Brain Neuroadaptative Changes in Adolescents with Internet Addiction : An FDG-PET Study with Statistical Parametric Mapping Analysis

Young Jin Koo, M.D., Ph.D.[1], Jin Chul Paeng, M.D.[2], Eun Jeong Joo, M.D., Ph.D.[1], Hyejin Kang, M.A.[2], Youn Seok Im, B.A.[3], Ju Won Seok, M.D.[4] and Ung Gu Kang, M.D., Ph.D.[5]

[1]Department of Neuropsychiatry, Eulji University School of Medicine, Daejeon, Korea
[2]Department of Nuclear Medicine, Seoul National University College of Medicine, Seoul, Korea
[3]Department of Nuclear Medicine, Eulji General Hospital, Seoul, Korea
[4]Department of Nuclear Medicine, Chung-Ang University Hospital, Seoul, Korea
[5]Department of Psychiatry and Institute of Human Behavioral Medicine, Seoul National University College of Medicine, Seoul, Korea

Objectives : Internet addiction or pathologic internet use is one of the major mental health problems in children and adolescents in Korea. Internet addiction is defined as uncontrollable, markedly time-consuming internet use, which lasts for a period of at least six months. Internet addiction results in poor academic performance and negative parent-child relationships. By using ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET), we investigated the effects of internet addiction on functional changes occurring in the adolescent brain.

Methods : Adolescent patients with an internet addiction (4 boys and 2 girls ; 15.6±1.2 years) participated in this study. Eight healthy young adults (5 males and 3 females ; 18−30 years old) with no previous history of psychiatric illness also participated as normal controls. Brain FDG-PET data was obtained with the participants in the resting condition and with no addictive stimuli.

Results : Statistic parametric mapping analysis of the brain FDG-PET data revealed hypometabolic changes in the visual information processing circuits and hypermetabolic changes in the prefrontal areas in the adolescents with internet addiction, as compared with normal controls ($p<.001$).

Conclusion : These results suggest a neuronal adaptation to excessive visual stimulation and synaptic plasticity due to internet addiction.

KEY WORDS : Internet addiction · Adolescents · Brain glucose metabolism · FDG-PET.

Introduction

Internet addiction or pathologic internet use is one of the major mental health problems among children and adolescents in Korea. ADHD, depression, school refusal and aggravated parent-child relationship are common comorbid conditions associated with internet addiction during childhood and adolescence.[1] Internet addiction, first proposed by Goldberg in 1996, has also been described as 'pathologic internet use' or 'problematic internet use'.[2] In the present study, Internet addiction was defined as a) uncontrollable, b) markedly time-consuming internet use, c) resulting in academic, relational, or financial difficulties, d) not solely present during hypomanic or manic symptoms.[2]

Behavioral scientists regard all kinds of addiction as a behavioral disorder that is a powerful contributing factor to the narrowing of behavioral repertoire.[3,4] One of the most important perspectives in addiction research may prove to be the neurobiology of learning and memory that characterizes addiction as a habit, a particularly strong habit, marked by compulsivity and chronicity.[5,6] It has been suggested that some neural circuits and molecular mechanisms would be involved in the persistent and compulsive behavioral features associated with addictions. Brain responses to addiction have implicated neuronal adaptations to excessive stimulation and

접수완료 : 2007년 8월 9일 / 심사완료 : 2007년 9월 28일
Address for correspondence : Young Jin Koo, M.D., Ph.D., Department of Neuropsychiatry, Eulji University School of Medicine, 280-1 Hagye-1-dong, Nowon-gu, Seoul 139-711, Korea
Tel : +82.2-970-8303, Fax : +82.2-949-2356
E-mail : zelkoba@eulji.ac.kr
This study was supported by Eulji Research Grant(EJRG-04-004-11E15).

synaptic plasticity for the association of addiction-related stimuli with specific learned behaviors.[3)]

Postnatal brain maturation processes result from complex interactions between genetic, epigenetic, and environmental factors.[7)] Gray matter volume reductions due to synaptic pruning and white matter volume increases due to myelination have been consistent findings in studies on normal brain maturation during childhood and adolescence.[7-9)] The synaptic pruning and myelin formation during childhood and adolescence are not random processes but are rather based on activity-dependent mechanisms.[9-13)] Environmental learning and experience induced long-term neuroadaptations and synaptic changes play a crucial role in the brain maturation processes during childhood and adolescence. Therefore, we hypothesized that internet addiction, a type of repeated environmental exposures, during childhood and adolescence would exert influence on the brain maturation processes in both structural and functional aspects, which changes could be detected by measuring the regional cerebral glucose metabolism using ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET).

The purpose of this study was to explore regional cerebral metabolic changes in adolescents with internet addiction using FDG-PET. The PET data were analyzed by using the statistical parametric mapping (SPM), a powerful technique for the comparison of functional imaging data sets among groups of patients or individuals under different conditions.[14)]

Methods

1. Subjects and psychiatric evaluation

Clinic-referred adolescent patients with internet addiction (4 boys and 2 girls ; 15.6±1.2 years old) participated in this study. In the present study, internet addiction was defined as uncontrollable, markedly time-consuming internet use, resulting in negative influences on academic performance, parent-child relationships, and daily living routine, lasting for a period of at least six months.[2)] A direct clinical interview with the patients and a history taking interview with their parents were performed for the diagnostic evaluation. Comorbid conditions were assessed, based on the DSM-IV classification with the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime-Korean Version (K-SADS-PL-K).[15)] The Korean version of the Wechsler Intelligence Scale for Children-III (K-WISC-III) and electroencephography were also performed. Mental retardation, seizure disorders, bipolar disorders and schizophrenia were ruled out.

A Korean version of the standardized self-rating scale for internet addiction,[16)] a modified and extended form of Young's internet Addiction Test, was also used for the assessment. The scale consists of 40 items rated on a 4-point scale and has 7 subscale domains : disturbance of adaptive functions, addictive automatic thoughts, tolerance, withdrawal, disturbance of reality testing, virtual interpersonal relationship, and deviate behavior. In the study, the cut-off points for the subjects were as follows : total scores >108, or disturbance of adaptive functions subscale scores >26.

2. Normal controls

Healthy young adults (5 males and 3 females ; 18−30 years old) were selected as a normal controls from individuals who visited the center for a periodic medical check-up. All of the control subjects were found to be free of any psychiatric or neurological illness by physical examinations, laboratory tests, the Minnesota Multiphasic Personality Inventory and the internet addiction scale.

3. Image acquisition

PET imaging was performed using a PET/CT scanner (Biograph, Siemens, USA). Approximately 222−370 MBq of FDG was injected intravenously according to the body weight of the patient. Twenty minutes after the injection, a transmission scan for attenuation correction was performed using a CT scanner. An emission scan was then acquired for 10 minutes. The subjects were situated in a dark and quiet room without addictive stimuli, comfortably lying in a resting position with eye closed and ears unplugged from 10 minutes prior to the FDG injection until the end of the PET scan. Brain FDG-PET images were reconstructed from the acquired data using OSEM method.

4. Image analysis by statistical parametric mapping

Statistical parametric mapping analysis was performed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab 5.3 (Mathworks Inc., USA). Spatial normalization and global count normalization were performed under the default setting, and the normalized images were smoothed by convolution with a Gaussian kernel of 16 mm full-width-at-half-maximum (FWHM).

For any difference in regional glucose metabolism, the brain FDG-PET images of the patient group and the normal control group were compared using voxel-by-voxel analysis. The regions with uncorrected p-values less than 0.001 and a cluster of more than 100 contiguous voxels were considered to show a significant metabolic change. The results were displayed on the surface-rendered brain image.

To determine the functional anatomical location of a detected region, the Talairach brain coordinates were estimated by a nonlinear transformation from the Montreal Neurological Institute (MNI, McGill University, Montreal, Canada) space to the Talairach (Talairach Daemon Client. Ver.1.1, Research Imaging Center, University of Texas Health Science Center, San Antonio, USA) space.[17)]

Results

1. Clinical features of the subjects with internet addiction

The demographic and clinical characteristics of the six adolescents with internet addiction are described in Table 1. The mean intelligence of the subjects was 101.66±14.15 on the K-WISC-III full scale scores. Of the six adolescents with internet addiction, two had conduct disorder, two had depressive disorder, and two had ADHD, as comorbid psychiatric conditions.

2. FDG-PET findings

SPM analysis showed a significant reduction of FDG uptake in the bilateral occipital fusiform gyri and parahippocampal regions in the adolescents with internet addiction in the resting condition with no addictive stimuli, as compared with the young adult controls by statistical voxel-based analysis ($p<.001$, uncorrected) (Table 2, Fig. 1). The left parietal precuneus, inferior parietal lobe, middle temporal gyrus, and in the right posterior cingulate also showed significant hypometabolism in the adolescents with internet addiction ($p<.001$, uncorrected) (Table 2, Fig. 1).

Hypermetabolic changes were detected in the prefrontal areas in the subjects with internet addiction, as compared with the control group by statistical voxel-based analysis ($p<.001$, uncorrected) (Table 2, Fig. 2). The right inferior frontal gyrus, left superior frontal gyrus, and bilateral middle frontal gyri in the prefrontal areas showed significantly hypermetabolic changes ($p<.001$, uncorrected) (Table 2, Fig. 2).

Table 1. Demographic and clinical data of adolescent patients with internet addiction

Patients	Sex/Age (years)	K-WISC-III Full IQ (Verbal /Performance)	Cormobid conditions
A	F/16	80(83/ 83)	Conduct disorder with school dropout
B	F/15	88(86/ 96)	Conduct disorder with school dropout
C	M/16	106(96/120)	Depressive disorder with school dropout
D	M/14	113(120/ 98)	Depressive disorder
E	M/16	113(114/109)	Attention-deficit hyperactivity disorder
F	M/14	110(114/103)	Attention-deficit hyperactivity disorder

Table 2. Metabolic changes in the brain FDG-PET in adolescent subjects with internet addiction

Regions	Brodmann area	Talairach			T	Cluster size
		x	y	z		
1) Hypometabolism						
Right parahippocampal gyrus	36	24	−38	−12	7.93	1237
Right occipital fusiform gyrus	19	25	−55	−14	4.85	
Left occipital fusiform gyrus	18	−30	−80	−18	6.8	1090
Left parahippocampal gyrus	36	−24	−38	−10	5.05	
Left parietal, precuneus	31	−10	−58	30	5.98	946
Right posterior cingulate	29	14	−50	16	4.0	
Left middle temporal gyrus	21	−66	−44	−8	5.65	442
Left middle temporal lobe	21	−62	−6	−12	4.62	133
Left inferior parietal lobule	39	−48	−68	42	5.29	412
2) Hypermetabolism						
Right inferior frontal gyrus	47	58	28	−6	5.54	439
Right middle frontal gyrus	10	30	59	24	6.03	233
Left superior frontal gyrus	8	−28	48	40	5.09	176
Left middle frontal gyrus	10	−30	58	26	4.27	

Voxel size=2×2×2mm, Cluster level in voxels >100, Height threshold : T=3.93 ($p<.001$, uncorrected)

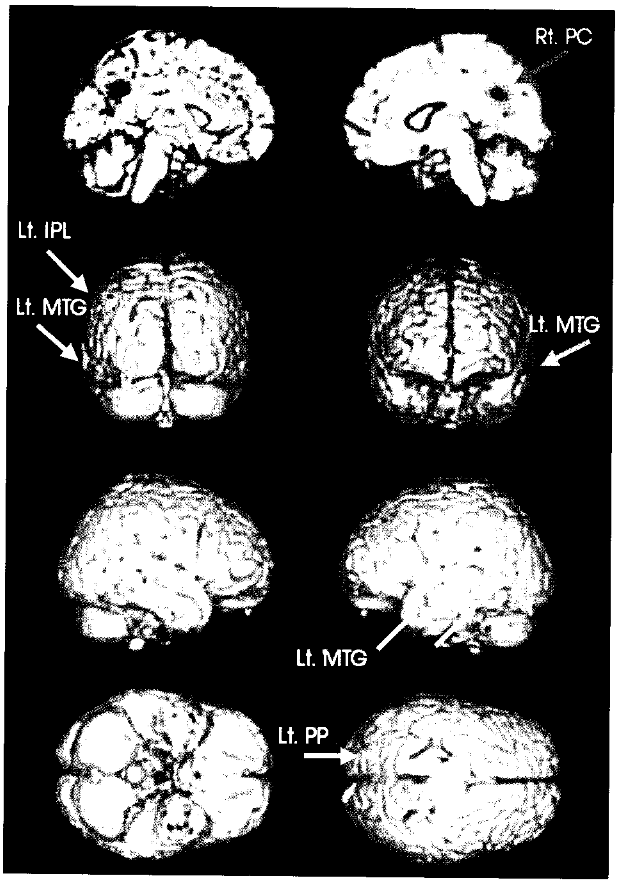

Fig. 1. Hypometabolic brain regions displayed on surface-rendered image in adolescents with Internet addiction (p< .001, uncorrected). IPL : inferior parietal lobule, MTG : middle temporal gyrus, PC : posterior cingulate, PP : parietal precuneus, Lt. : left, Rt. : right.

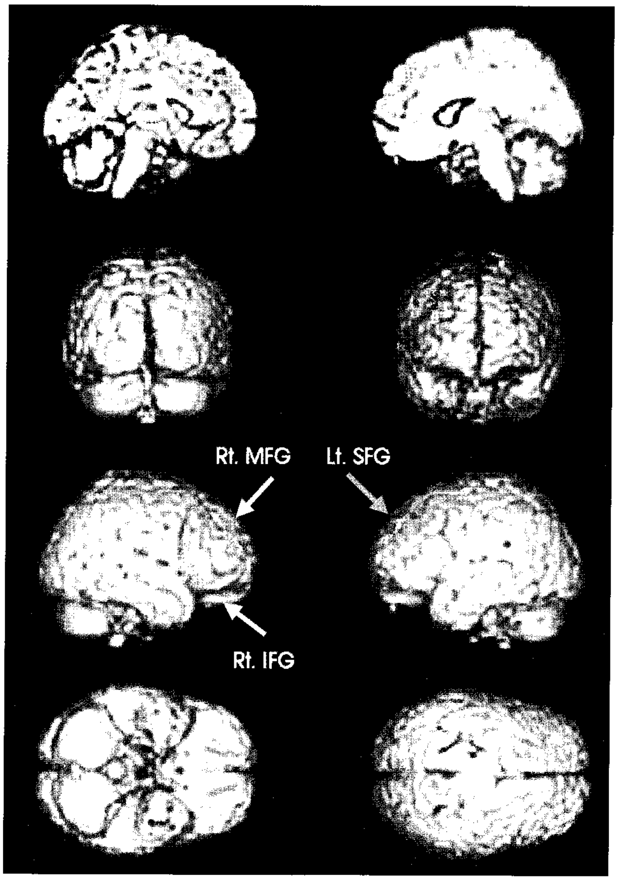

Fig. 2. Hypermetabolic brain regions displayed on surface-rendered image in adolescents with Internet addiction (p< 001, uncorrected). SFG : superior frontal gyrus, MFG : middle frontal gyrus, IFG : inferior frontal gyrus, Lt. : left, Rt. : right.

Discussion

Addiction is a chronic brain disease, modulated by genetic, developmental, experiential, and environmental factors. The understanding of the neurobiological basis of addiction is important not only for the treatment of the illness but also as a model for how experiences modify neural circuitry and thereby behavior.[3-6]

Most neurobiological studies of addiction have concentrated on substance addictions. Previous literature on internet addiction has been primarily focused on the clinical and psychosocial aspects of the condition, because internet addiction is a newly established disease in the field of psychiatry. Thus, the neurobiological changes that accompany internet addiction have yet to be determined. No previous studies have been reported on the metabolic changes in the brains of patients with internet addiction.

The goal of this study was to identify changes in regional glucose metabolism in the brains of adolescents with internet addiction. Regional glucose metabolism in the brain has been interpreted as an indicator of the activity of synapses and dendritic spines.[18] Therefore, glucose metabolic changes observed in the present study may be suggestive of changes in neural connectivity and synaptic activity in the affected brain regions as a result of internet addiction.

The SPM analysis performed in this study showed significant decreases in the activity of the bilateral occipital and parahippocampal regions, the right posterior cingulate, left parietal precuneus, inferior parietal cortex, middle temporal gyrus in the adolescents with internet addiction. The hypometabolic brain regions in this study are reportedly attributed to visuo-spatial information processing and visuo-motor learning circuits.[19-21] The occipital and parahippocampal regions showing hypometabolism in the present study play a critical role in object recognition and memory.[20] The left parietal precuneus, inferior parietal lobule, and middle temporal gyrus seen hypoactive glucose metabolism in this study have been involved in visual search, attentional filtering, and encoding, retention and retrieval of visual representations, along with occipital and parahippocampal cortices.[19,22,23] It has also been reported that the posterior cingulate and left precuneus play a role in visuo-motor sequence learning acquisition and retrieval.[21,22,24] The role of the posterior cingulate has also been associated with monitoring sensory events and orientation.[25]

These changes in the brain seem to occur as a result of neural adaptation to excessive visual stimuli from compulsive internet use and altered synaptic connectivity which leads to altered responses to environmental stimuli. The prolonged excessive saccadic eye movement and visual attention with swift keyboard, mouse button tapping or joystick handling during internet game, chatting or web browsing may be associated with the brain changes observed in the adolescents with internet addiction.

Prior studies suggested that the patterns of glucose metabolism in addiction circuits, which are hypoactive in the absence of substance-related addictive stimuli and hyperactive during intoxication, are similar to the changes seen in epilepsy characterized by an increase in the activity of the abnormal foci during the ictal period and by decreased activity during the interictal period.[6,26] In this study, the hypometabolic changes which observed in the absence of addictive stimuli seem to be consistent with the patterns reported in the literature.

It is well established that the striato-thalamo-orbitofrontal circuits are associated with substance addictions.[5,6] The striato-thalamo-orbitofrontal circuits have been reported to become hypofunctional during withdrawal and without drug stimulation in substance addiction, resulting in a decreased drive for goal-motivated behaviors. In this study, hypermetabolic changes were observed in the dorsolateral and ventral prefrontal areas in the adolescents with internet addiction. The prefrontal areas are reportedly involved in executive functions such as motor response control, decision-making, working memory and attention.[27] The hypermetabolic changes seen in the adolescents with internet addiction may be associated with striving for impulse control or behavioral inhibition under the study condition with no addictive stimuli. It is also possible that the prefrontal hypermetabolism in our results may be based on age-associated differences between the groups. That is why the subjects with internet addiction were younger than the normal controls and the prefrontal brain regions are dynamically changed during adolescence, correlating with synaptogenesis and pruning.[7-9]

Common molecular findings in addiction circuits with those in learning and memory circuits have led to a much more integrative view of the brain regions involved that accounts for the cognitive and behavioral symptoms in addictions.[3,5] It may be possible that the involvement of the visual attention and information processing pathways which play a crucial role in academic activities may contribute to poor academic performance in adolescents with internet addiction. In this study we found hypometabolic changes in the left parietal and middle temporal regions, which are involved in syntactic and semantic understanding in language communication with arithmetic measures.[28,29] These findings may also be associated with poor school work in adolescents with internet addiction.

Limitations of the present study include the small sample size, which was a consequence of the limited PET availability. We did not study age- and sex-matched normal adolescents as controls for ethical reasons in the use of radioisotopes. And we could not exclude comorbid conditions. Considering the above limitations, It is likely that our results may not be specific to internet addiction even though we used p-value $<.001$ in order to diminish type I errors. However, our findings are very suggestive that the neural circuits involved in addiction may rely on the characteristics of the addicted stimuli and that internet addiction during childhood and adolescence may exert negative influence on brain maturation process.

Conclusion

In conclusion, we examined the functional changes in the brains of adolescents with internet addiction using FDG-PET and SPM analysis. The hypometabolic and hypermetabolic changes in the visual information processing circuits and prefrontal areas may contribute to cognitive and behavioral symptoms in adolescents with internet addiction.

References

1) **Yoo HJ, Cho SC, Ha JH, Yune SK, Kim SJ, Hwang J, et al.** Attention deficit hyperactivity symptoms and internet addiction. Psychiatry Clin Neurosci 2004;58:487-494.
2) **Shapira NA, Goldsmith TD, Keck PE, Khosla UM, McElroy SL.** Psychiatric features of individuals with problematic internet use. J Affect Disord 2000;57:267-272.
3) **Berke JD, Hyman SE.** Addiction, dopamine, and the molecular mechanisms of memory. Neuron 2000;25:515-532.
4) **Robbins TW, Everitt BJ.** Drug addiction: Bad habits add up. Nature 1999;398:567-570.

5) **Kelley AE.** Memory and addiction: shared neural circuitry and molecular mechanisms. Neuron 2004;44:161-179.
6) **Volkow ND, Fowler JS.** Addiction, a disease of compulsion and drive: involvement of the orbitofrontal cortex. Cereb Cortex 2000; 10:318-325.
7) **Lenroot RK, Giedd JN.** Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev 2006;30:718-729.
8) **Huttenlocher PR, Dabholkar AS.** Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 1997; 387:167-178.
9) **Chugani HT.** A critical period of brain development; Studies of cerebral glucose utilization with PET. Prev Med 1998;27:184-188.
10) **Cohen-Cory S.** The developing synapse: construction and modulation of synaptic structures and circuits. Science 2002;298: 770-776.
11) **Ishibashi T, Dakin KA, Stevens B, Lee PR, Kozlov SV, Stewart CL, et al.** Astrocytes promote myelination in response to electrical impulses. Neuron 2006;49:823-832.
12) **Bailey CH, Kandel ER.** Structural changes accompanying memory formation. Annu Rev Physiol 1993;55:397-426.
13) **Lendval B, Stem EA, Chen B, Svoboda K.** Experience-dependent plasticity of dendritic spines in the developing rat barrel cortex in vivo. Nature 2000;404:876-881.
14) **Friston KJ, Holmes AP, Worsley KJ, Poline JB, Frith CD, Frackowiak RSJ.** Statistical parametric maps in functional imaging: A general approach. Hum Brain Mapp 1995;2:189-210.
15) **Kim YS, Cheon KA, Kim BN, Chang SA, Yoo HJ, Kim JW, et al.** The reliability and validity of Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version-Korean version (K-SADS-PL-K), Yonsei Med J 2004; 45:81-89.
16) **Kim CT, Kim D, Park JK, Lee SJ.** Development and Standardization of Korean version of self-rating scale for internet addiction. Korea agency for digital opportunity and promotion, ministry of information and communication;2003.
17) **Friston KJ.** Commentary and opinion. II. Statistical parametric mapping: ontology and current issues. J Cereb Blood Flow Metab 1995;15:361-370.
18) **Chugani HT, Phelps ME, Mazziotta JC.** Positron emission tomography study of human brain functional development. Ann Neurol 1987;22:487-497.
19) **Nobre AC, Sebestyen GN, Gitelman DR, Frith CD, Mesulam MM.** Filtering of distractors during visual search studied by positron emission tomography. NeuroImage 2002;16:968-976.
20) **Serences JT, Schwarzbach J, Courtney SM, Golay X, Yantis S.** Control of object-based attention in human cortex. Cereb Cortex 2004;14:1346-1357.
21) **Tracy J, Flanders A, Madi S, Laskas J, Stoddard E, Pyrros A, et al.** Regional brain activation associated with different performance patterns during learning of a complex motor skill. Cereb Cortex 2003;13:904-910.
22) **Wardak C, Olivier E, Duhamel J.** Saccadic target selection deficits after lateral intraparietal area inactivation in monkeys. J Neurosci 2002;22:9877-9884.
23) **Zubicaray GI, McMahon K, Wilson SJ, Muthiah S.** Brain activity during the encoding, retention, and retrieval of stimulus representations. Learn Mem 2001;8:243-251.
24) **Sakai K, Hikosaka O, Miyauchi S, Takino R, Sasaki Y, Putz B.** Transition of brain activation from frontal to parietal areas in visuomotor sequence learning. J Neurosci 1998;18: 1827-1840.
25) **Vogt BA, Finch DM, Olson CR.** Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. Cereb Cortex 1992;2:435-443.
26) **Saha GB, MacIntyre WJ, Go RT.** Radiopharmacoceuticals for brain imaging. Semin Nucl Med 1994;24:324-349.
27) **Fuster JM.** Frontal lobe and cognitive development. J Neurocytol 2002;31:373-385.
28) **Baldo JV, Dronkers NF.** Neural correlates of arithmetic and language comprehension: A common substrate? Neuropsychologia 2007;45:229-235.
29) **Gold BT, Balota DA, Jones SJ, Powell DK, Smith CD, Andersen AH.** Dissociation of automatic and strategic lexical-semantics: Functional magnetic resonance imaging evidence for differing roles of multiple frontotemporal regions. J Neurosci 2006;26: 6523- 6532.