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Decreased frontal lobe function in people with Internet addiction disorder

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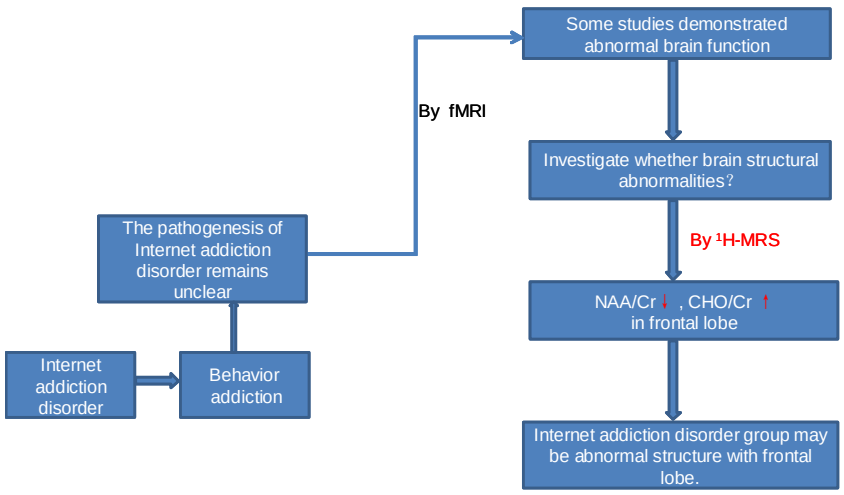
Graphical Abstract



Abstract

In our previous studies, we showed that frontal lobe and brainstem functions were abnormal in on-line game addicts. In this study, 14 students with Internet addiction disorder and 14 matched healthy controls underwent proton-magnetic resonance spectroscopy to measure cerebral function. Results demonstrated that the ratio of N-acetylaspartate to creatine decreased, but the ratio of choline-containing compounds to creatine increased in the bilateral frontal lobe white matter in people with Internet addiction disorder. However, these ratios were mostly unaltered in the brainstem, suggesting that frontal lobe function decreases in people with Internet addiction disorder.

Key Words

neural regeneration; Internet addiction disorder; internet gaming addiction; magnetic resonance imaging; magnetic resonance spectroscopy; N-acetylaspartate; choline-containing compounds; creatine; grants-supported paper; neuroregeneration

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Conflicts of interest: None declared.

Ethical approval: This study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University in China.

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INTRODUCTION

Internet addiction disorder is defined as the inability of an individual to control his or her use of the Internet. This inability eventually causes psychological, social, and work difficulties, and even physical and mental disorders[1-4]. The use of the Internet has increased considerably over the last few years. Data from the China Internet Network Information Center, as of June 30, 2012, showed that 538 million people had gone online, of which approximately 60% were under 30 years old[5]. With this increasing number of Internet users, Internet addiction disorder has attracted considerable attention from psychiatrists, educators, and the public. As the world's fastest growing "addiction", Internet addiction disorder is considered a serious global public health issue[1, 6-7]. Chou and Hsiao[8] reported that the incidence of Internet addiction disorder among Taiwan college students was 5.9%. Cao and Su[9] reported that the incidence of Internet addiction disorder was 2.4% in China. Wu and Zhu[10] identified 10.6% of Chinese college students as Internet addicts. Thus, Internet addiction disorder is becoming a serious mental health problem among Chinese adolescents. Internet addiction disorder is also considered a behavioral addiction and may share similar neuropsychological characteristics (*i.e.*, development of euphoria, craving, and tolerance) and personality characteristics with other addictions[11], especially behavioral addiction, for example, gambling addiction[12]. Compared with other subtypes of Internet addiction disorder, internet gaming addiction, the most important subtype of Internet addiction disorder, exhibits some specific features such as role-playing in the virtual world. The pathogenesis of Internet addiction disorder, however, remains unclear. As far as we know, few studies have addressed brain structure changes in people who are addicted to internet games.

Magnetic resonance spectroscopy (MRS) is an MRI technique that can be used to measure biochemical or metabolite concentrations in specific brain regions *in vivo*. Typical compounds that can be measured in proton (^{1}H) MRS include N-acetylaspartate (NAA), choline-containing compounds (Cho) and creatine (Cr). NAA localizes mainly in neurons and is thought to be a marker of structural integrity[13]. Cr is a reactant in the creatine kinase phosphate reaction and is often used as a reference standard for expressing concentrations of other metabolite's signals from ratios[14]. The Cho peak reflects a composite signal from several choline-containing metabolic compounds, including free choline, phosphocholine, and glycerophosphocholine, and to a lesser degree the neurotransmitter acetylcholine and its precursor choline[15].

Previous studies have shown that mental disorders can change spontaneous activity in the brain[16-18]. The MRS method has been successfully applied in selected mental disorders, including autism (autism and autism spectrum disorder), panic disorder, schizophrenia, depression, and bipolar disorder (manic-depressive illness)[19-31]. ^{1}H-MRS was used to evaluate metabolic brain changes in drug abusers. Some research reported the use of MRS to study drug addiction[32-34]. Neural substrates of drug addition, craving, drug interaction, individual abstinence, and drug withdrawal can be studied with functional MRI and ^{1}H-MRS. However, to our knowledge, no research has used this approach for Internet addiction disorder. In previous studies, we found abnormal brain function associated with a task- related functional magnetic resonance method. Specifically, college students, who were online games addicts, showed frontal lobe dysfunction[35-36]. We found that there were abnormalities in regional homogeneity in college students with Internet addiction disorder compared with controls. This suggested that the connections between the enhancement of synchronization among the cerebellum, brainstem, limbic system, frontal lobe, and apical lobe may be related to reward pathways[37]. Thus, in this study, we used MRS to explore brain metabolites in college students with Internet addiction disorder, and to further investigate the pathophysiological mechanism of Internet addiction disorder.

RESULTS

Quantitative analysis of subjects

A total of 14 Internet addiction disorder college students (aged 18–25 years) and 14 age- and sex-matched healthy college students (aged 17–25 years) were enrolled in this study. There was no statistically significant difference in age, gender, years of internet use and educational level between the Internet addiction disorder group and the control group ($P > 0.05$). Weekly computer browsing time was significantly higher in the Internet addiction disorder group compared with the control group ($P < 0.01$). Additionally, Internet addiction disorder subjects were online for a longer period of time per computer session compared with controls ($P < 0.05$; Table 1).

Results of ^{1}H-MRS of the bifrontal lobe and brainstem in college students with Internet addiction disorder

High resolution T1- and T2-weighted MRI showed no significant brain structural abnormalities in any subjects. The bilateral frontal lobes showed lower NAA peaks and higher Cho peaks in Internet addiction disorder subjects compared with controls ($P < 0.01$), and decreased NAA/Cr and increased Cho/Cr ratios. No significant differences in brainstem NAA/Cr or Cho/Cr ratios were found between the groups ($P > 0.05$; Figures 1, 2; Table 2).

DISCUSSION

In our previous study, the regional homogeneity (ReHo) method was used to analyze the differences between the average ReHo in the Internet addiction disorder and control groups. Compared with controls, we found that there were abnormalities in ReHo in college students with Internet addiction disorder and enhancement of synchronization in most encephalic regions[37]. In another study, 19 college students who had internet game addiction and 19 controls were presented video stimuli *via* computer. A 3.0 Tesla MRI was used to record the results of echo planar imaging. Intra-group and inter-group results were obtained. We found abnormal frontal lobe function associated with a task-related functional magnetic resonance method in college students addicted to online games[35-36].

Table 1 Basic information of the participants

Item	Internet addiction disorder group (n = 14)	Control group (n = 14)	t	P
Gender (n, male/female)	8/6	8/6		
Age (year)	20.0±1.1	19.0±1.5	2.012	> 0.05
Education level (year)	15.0±0.6	14.0±2.0	1.791	> 0.05
Weekly time spent online (hour)	49.0±10.8	10.0±2.6	13.136	< 0.01
Years online (year)	4.4±2.2	4.9±1.8	0.876	> 0.05
Longest period online at one time (hour)	38.4±32.7	5.9±3.2	2.165	< 0.05
Beck Depression Inventory (score)	4.4±0.6	2.4±1.2	5.644	< 0.01
Internet Addiction Test (score)	70.4±7.6	16.6±3.1	24.648	< 0.01

Measurement data are expressed as mean ± SD. Intergroup differences were compared using paired t-tests.

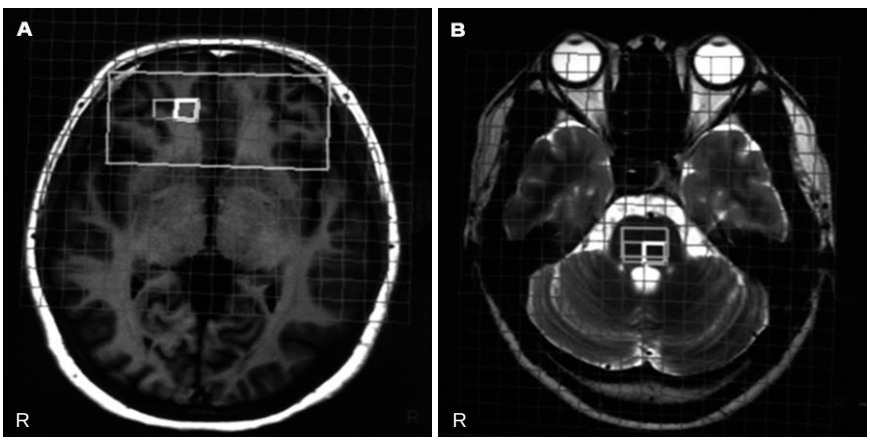

Figure 1 Images of brain spectroscopy positioning.

(A) Bilateral frontal; (B) brainstem. Large box represents the detection range, and the internal small boxes represent the smallest unit which can be detected in brain tissue. R: Right.

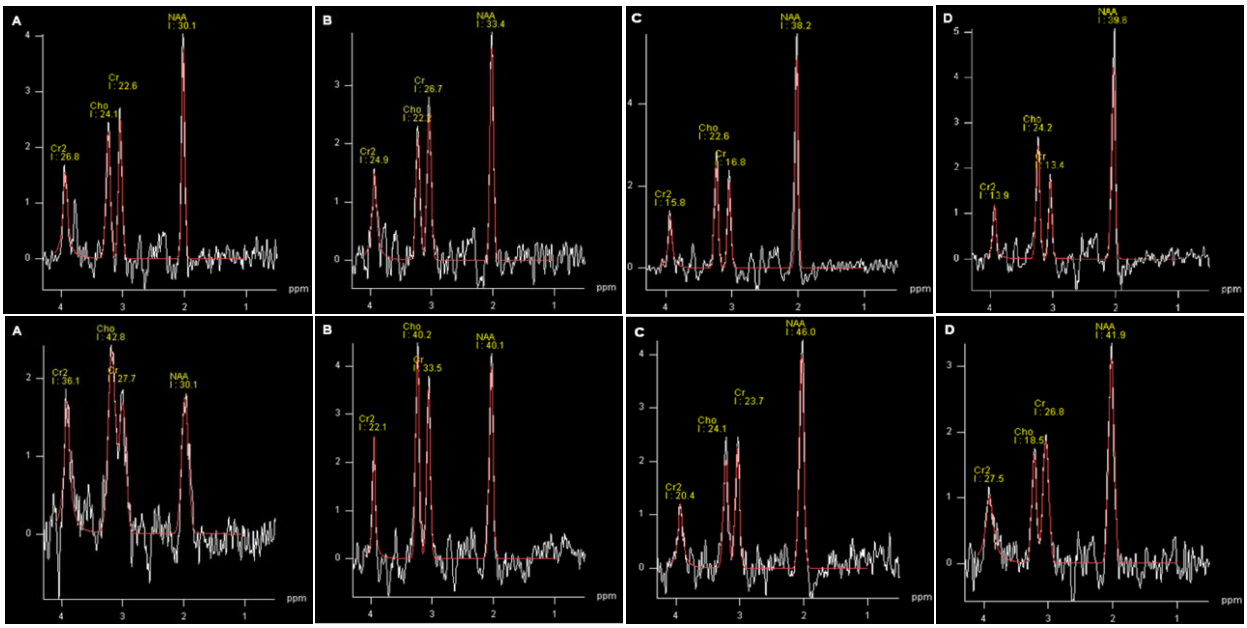

Figure 2 ^{1}H-MRS spectrogram of the frontal lobe and brainstem in the control (upper panel) and Internet addiction disorder (lower panel) groups.

(A, B) ^{1}H-MRS spectrogram of the left and right frontal lobes in the control group (upper panel): from left to right, Cho, Cr, and NAA appear in a rising pattern, with NAA the peak point; and in the Internet addiction disorder group (lower panel) with ascended Cho peak and descended NAA peak. (C, D) ^{1}H-MRS spectrogram of the left and right brainstem in the control (upper panel) and Internet addiction disorder (lower panel) groups. White line: The actual image out of the curve; the red line: the fitting out of the spectral curve. Each index of MRS was measured three times and averaged before being compared. ^{1}H-MRS: Proton-magnetic resonance spectroscopy; NAA: N-acetylaspartate; Cho: choline; Cr: creatine.

Table 2 Bilateral frontal lobe and brainstem ratios of MRS metabolite levels in the Internet addiction disorder and control groups

	Internet addiction disorder group (n = 14)	Control group (n = 14)	t	P
NAA/Cr				
Right frontal lobe	1.630±0.006	1.841±0.006	93.042	< 0.01
Left frontal lobe	1.506±0.026	1.798±0.008	41.013	< 0.01
Right brainstem	1.648±0.008	1.653±0.005	1.983	> 0.05
Left brainstem	1.598±0.053	1.633±0.042	1.937	> 0.05
Cho/Cr				
Right frontal lobe	1.593±0.035	0.851±0.026	62.018	< 0.01
Left frontal lobe	1.486±0.017	0.849±0.016	102.276	< 0.01
Right brainstem	1.001±0.068	0.968±0.045	1.973	> 0.05
Left brainstem	0.978±0.017	0.965±0.019	1.908	> 0.05

Data are expressed as mean ± SD. Intergroup differences were compared using paired t-tests. Each index of MRS was measured three times and averaged before being compared. MRS: Magnetic resonance spectroscopy; NAA: N-acetylaspartate; Cho: choline; Cr: creatine.

Based on these studies, we found that the frontal lobe and brainstem are dysfunctional. Thus, in this study, we investigated the frontal lobe and brainstem using brain tissue spectroscopy. Findings from the present MRS study showed that the Internet addiction disorder group had a significantly lower NAA/Cr and a higher Cho/Cr ratio in the frontal white matter compared with control subjects.

MRS is widely used to assess both neuronal viability and demyelination. It can detect both NAA and Cr in discrete tissue volumes. NAA is considered a putative marker for neurons; and a decrease in NAA reflects neuronal cell death and/or neuronal dysfunction[38]. A decrease in NAA, which is located in neuronal cell bodies, has been proposed to indicate possible neuronal and axonal damage or loss, with decreases measured relative to the level of Cr, a stable metabolite whose level is constant after neuronal loss[39]. MRS studies of the human brain have also shown a decrease in NAA levels in the frontal cortex of patients with cognitive impairment[40]. In this experiment, the decreased NAA/Cr ratio suggested either

neuronal loss or functional decline of the corresponding neurons. We speculate that this frontal lobe dysfunction is the result of long-term computer exposure, resulting in neuronal loss.

Cho reflects the total Cho content of the brain, including Cho, phosphatidylcholine, and phosphoglycerolcholine, which is the product of phospholipid membrane metabolism and represents the transportation of cytomembrane. The elevated Cho peak and Cho/Cr ratio in the bilateral frontal lobes in Internet addiction disorder subjects suggests altered membrane phospholipid metabolism. Cho constitutes two major components of the cell membrane, phosphosphingolipid and lecithin[41]. Lecithin, a type of second messenger, is a major source of diacylglycerol and participates in intracellular signal transduction. Some authors believe that intracellular changes in Cho can lead to hydrolysis of lecithin, which would then alter the velocity of signal transduction[42]. We speculate that neuronal cell membrane damage or abnormal signal transduction may be present in Internet addiction disorder subjects. However, the specific mechanisms require further exploration.

In this study, there were no obvious abnormalities found in the NAA/Cr and Cho/Cr ratios in the brainstem of Internet addiction disorder and control subjects. The specific reason is unclear. We speculate that the frontal lobe is the brain's executive center and that a prolonged period online has led to frontal lobe dysfunction or neuronal loss. The brain stem is only a part of that pathway, and a prolonged period online only causes changes in frontal function, and not ultrastructural changes in the brainstem.

The strength of the current study is use of a MR system with a 3-T magnetic field to examine brain regions. However, some limitations of the present study exist. Firstly, only the frontal lobe and a partial brain stem segment were used for sampling. As the pathological process of Internet addiction disorder may involve multiple brain regions, having only local brain tissue samples provides greater difficulty in determining the relationship between ^{1}H-MRS and Internet addiction disorder. Secondly, this experiment studied the encephalic spectroscopy characteristics of college students with Internet addiction disorder and chose not to focus on other populations of interest that also have long use of screen times, including high school students. Thirdly, the small sample size is also a limitation affecting the power of this study. A study with a larger sample size may provide more information regarding the association between Internet addiction disorder and metabolic brain changes. Fourthly, although a 3-T field provides good spatial resolution, the voxel size (1 × 1 × 1 cm^3) may have included some gray matter in the frontal or periventricular white matter. Finally, as some researchers may prefer absolute values of biochemical concentrations compared with ratios, more sophisticated methods to quantify the signal from spectra are needed. However, *in vivo* ^{1}H-MRS data revealed the relationship between metabolites seen in Internet addiction disorder and also provides a novel way to explore the pathogenesis of Internet addiction disorder.

The biochemical abnormalities in Internet addiction disorder were found bilaterally in the frontal white matter. The lower NAA/Cr ratio may indicate a neurodegenerative process in the frontal white matter associated with Internet addiction disorder, while high membrane turnover and second messenger systems in the frontal white matter were reflected by a higher Cho/Cr in the Internet addiction disorder group. Internet addiction disorder subjects may have abnormal frontal lobe function due to partial neuronal loss. To a certain extent, the cell membrane function of neurons may be damaged or signal transduction may be abnormal. Follow-up investigation of these abnormalities in association with treatment response and clinical outcomes is also suggested.

SUBJECTS AND METHODS

Design

A non-randomized comparative study of imaging.

Time and setting

This experiment was conducted in the Room of Magnetic Resonance, Second Xiangya Hospital, Central South University, China from July 2010 to December 2012.

Subjects

Internet addiction disorder college students were outpatients initially diagnosed at the Second Xiangya Hospital in China. Control subjects were recruited through advertisements with questionnaires among college students. We used the modified Diagnostic Questionnaire for Internet Addiction criteria by Beard[43] as the inclusion standards for this study. Depression was further assessed using the Beck Depression Inventory[44]. Anyone who scored more than 5 was excluded from the study. All subjects were right-handed as measured by the Edinburgh Inventory[45]. All participants underwent structured psychiatric interviews (Mini-International Neuropsychia-

tric Interview)[46] performed by an experienced psychiatrist with an administration time of approximately 15 minutes. The Mini-International Neuropsychiatric Interview was designed to meet the need for a short, but accurate structured psychiatric interview for multicenter clinical trials and epidemiology studies[47]. The Internet Addiction Test has been shown to be a valid and reliable instrument that can be used in classifying Internet addiction disorder[48]. People who scored greater than 50 were considered to experience occasional or frequent problems because of the internet. Those people who scored greater than 80 were considered to have significant problems in their lives[46]. In the present study, the threshold cut-off we used was 80 in the Internet Addiction Test. Estimates of the size of the group of "addicted gamers" was defined by applying various cut-off points to scales measuring symptoms of internet addiction[49]. The controls were also measured with using the same process. None of the subjects were taking medications that could affect brain excitability nor was there any evidence of current or historical psychiatric or neurological illnesses. No participant had previous experience with cocaine or marijuana. All subjects gave written informed consent for the study.

Methods

MRS procedures

All subjects underwent MRI and ^{1}H-MRS examinations at the Second Xiangya Hospital in China. MRI data were acquired using a Siemens Trio 3T scanner (Siemens, Germany). Participants lay in a supine position with the head snugly fixed by a belt and foam pads to minimize head movement. Multivoxel proton MRS was obtained using a point-resolved spine echo sequence. The structural MRI study ruled out brain lesions and localized the volume of interest for the spectroscopy study, acquiring sagittal T1 images, axial T2 fast spin-echo images parallel to the bicommissural line, and coronal fluid-attenuated inversion recovery images orthogonal to the axial ones. The following parameters were used for T1 anatomical sagittal imaging: 500/12 ms (repetition time/echo time), 256 × 256 matrix, 24 cm field of view, 3 mm section thickness, and 0.9 mm gap. The coronal fluid-attenuated inversion recovery spin echo T2-weighted images (repetition time/echo time = 8 000/91 ms, inversion time = 2 371 ms, 1 excitation, 332 × 512 matrix) and transverse fast spin echo T2-weighted (repetition time/echo time = 4 000/113 ms, 24-cm field of view, 256 × 224 matrix, 1 excitation, 3 mm section thickness and 0.9 mm gap) were acquired sequentially. Bilateral frontal lobe and brainstem imaging was performed with three-dimensional spectroscopy with the following parameters: 1 700/135 ms (repetition time/echo time), 1 × 1 × 1 voxel. The volume of the frontal lobe was 40 cm^3 and that of the brainstem was 4 cm^3. The 1 × 1 × 1 cm voxel size was chosen in a region of interest in the bilateral frontal white matter and brainstem. On the transverse plane, the region of interest was placed symmetrically in order including the bilateral frontal lobe and brainstem. The chosen voxel avoided sulci to prevent contamination from the cerebrospinal fluid. Every subject underwent magnetic resonance shimming before the scan, and the full width of half maximum was less than 10.

Data analysis

All data were analyzed under phase calibration, baseline calibration, and parts per million (ppm) conversions using the Siemens 3.0T workstation. The relative concentrations of NAA, Cr, and Cho were calculated by the area under the curve of certain peak values at 2.0 ppm, 3.02 ppm, and 3.23 ppm. NAA/Cr and Cho/Cr ratio values were evaluated.

We used paired *t*-tests to compare differences in continuous variables between the Internet addiction disorder and control groups. Each index of MRS was measured three times and averaged before being compared. All statistical analyses were performed using SPSS 14.0 software (SPSS, Chicago, IL, USA). A value of $P < 0.05$ was considered statistically significant.

Research background: Previous studies have focused primarily on the field of psychology, but limited to a single isolated study about behavioral traits, not as individual organisms involving human behavior in morbid pathophysiological roles.

Research frontiers: There are few reports concerning functional magnetic resonance changes, but there are no similar reports concerning MRS in college students with Internet addiction disorder at present.

Clinical significance: Through magnetic resonance spectroscopy imaging studies *in vivo*, we found frontal lobe dysfunction in people with Internet addiction disorder, which provides a new way to explore the pathogenesis of Internet addiction disorder.

Academic terminology: Internet addiction disorder, also known as Internet Overuse or Pathological Internet Use, is due to the excessive use of the network that causes significant social and psychological damage.

Peer review: College students with Internet addiction disorder and controls underwent ^{1}H-MRS examination; the authors analyzed metabolite changes in bilateral frontal white matter and brainstem, and found significant differences in MRS in the bilateral frontal white matter in people with Internet addiction disorder. This study revealed that neuronal membrane function and signal transduction may be affected to some degree. This

study will enrich the research in the field of Internet addiction disorder and broaden the clinical application of MRS.

REFERENCES

[1] Young KS. Internet addiction: the emergence of a new clinical disorder. Cyberpsychol Behav. 1998;1(3):237-244.

[2] Davis MR, Votaw JR, Bremner JD, et al. Initial human PET imaging studies with the dopamine transporter ligand 18F-FECNT. J Nucl Med. 2003;44(6):855-861.

[3] Young KS, Rogers RC. The relationship between depression and internet addiction. Cyberpsychol Behav. 1998; 1(1):25-29.

[4] King DL, Delfabbro PH, Griffiths MD, et al. Cognitive-behavioral approaches to outpatient treatment of internet addiction in children and adolescents. J Clin Psychol. 2012;68(11):1185-1195.

[5] China Internet Network Information Center China Internet Development Statistics Report. 2012-07. http://www.cnnic.cn/research/bgxz/tjbg/201207/P020120719489935146937.pdf.

[6] van den Eijnden RJ, Spijkerman R, Vermulst AA, et al. Compulsive internet use among adolescents: bidirectional parent-child relationships. J Abnorm Child Psychol. 2010; 38(1):77-89.

[7] Dong G, Lu Q, Zhou H, et al. Precursor or sequela: pathological disorders in people with IAD. PLoS One. 2011;6(2):e14703.

[8] Chou C, Hsiao MC. Internet addiction, usage, gratification, and pleasure experience: the Taiwan college students' case. Comput Educ. 2000;35(1):65-80.

[9] Cao F, Su L. Internet addiction among Chinese adolescents: prevalence and psychological features. Child Care Health Dev. 2007;33(3):275-281.

[10] Wu HR, Zhu KJ. Path analysis on related factors causing IAD in college students. Zhongguo Gonggong Weisheng. 2004;20(11):1363-1364.

[11] Grant JE, Potenza MN, Weinstein A, et al. Introduction to behavioral addictions. Am J Drug Alcohol Abuse. 2010; 36(5):233-241.

[12] Potenza MN, Leung HC, Blumberg HP, et al. An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. Am J Psychiatry. 2003; 160(11):1990-1994.

[13] Urenjak J, Williams SR, Gadian DG, et al. Proton nuclear magnetic resonance spectroscopy unambiguously identifies different neural cell types. J Neurosci. 1993;13(3): 981-989.

[14] Kato T, Inubushi T, Kato N. Magnetic resonance spectroscopy in affective disorders. J Neuropsychiatry Clin Neurosci. 1998;10(2):133-147.

[15] Ross B, Kreis R, Ernst T. Clinical tools for the 90s: magnetic resonance spectroscopy and metabolite imaging. Eur J Radiol. 1992;14(2):128-140.

[16] Peng DH, Jiang KD, Fang YR, et al. Decreased regional homogeneity in major depression as revealed by resting-state functional magnetic resonance imaging. Chin Med J (Engl). 2011;124(3):369-373.

[17] Paakki JJ, Rahko J, Long X, et al. Alterations in regional homogeneity of resting-state brain activity in autism spectrum disorders. Brain Res. 2010;1321:169-179.

[18] Wu T, Long X, Zang Y, et al. Regional homogeneity changes in patients with Parkinson's disease. Hum Brain Mapp. 2009;30(5):1502-1510.

[19] Friedman SD, Shaw DW, Artru AA, et al. Regional brain chemical alterations in young children with autism spectrum disorder. Neurology. 2003;60(1):100-107.

[20] Tang CY, Friedman J, Shungu D, et al. Correlations between Diffusion Tensor Imaging (DTI) and Magnetic Resonance Spectroscopy (^{1}H MRS) in schizophrenic patients and normal controls. BMC Psychiatry. 2007;7:25.

[21] Stanley JA, Vemulapalli M, Nutche J, et al. Reduced N-acetyl-aspartate levels in schizophrenia patients with a younger onset age: a single-voxel ^{1}H spectroscopy study. Schizophr Res. 2007;93(1-3):23-32.

[22] Steen RG, Hamer RM, Lieberman JA. Measurement of brain metabolites by ^{1}H magnetic resonance spectroscopy in patients with schizophrenia: a systematic review and meta-analysis. Neuropsychopharmacology. 2005;30(11): 1949-1962.

[23] Dager SR, Corrigan NM, Richards TL, et al. Research applications of magnetic resonance spectroscopy to investigate psychiatric disorders. Top Magn Reson Imaging. 2008;19(2):81-96.

[24] Lock T, Abou-Saleh MT, Edwards RH. Psychiatry and the new magnetic resonance era. Br J Psychiatry Suppl. 1990;(9):38-55.

[25] Dager SR, Steen RG. Applications of magnetic resonance spectroscopy to the investigation of neuropsychiatric disorders. Neuropsychopharmacology. 1992;6(4):249-266.

[26] Lyoo IK, Renshaw PF. Magnetic resonance spectroscopy: current and future applications in psychiatric research. Biol Psychiatry. 2002;51(3):195-207

[27] Dager SR, Marro KI, Richards TL, et al. Preliminary application of magnetic resonance spectroscopy to investigate lactate-induced panic. Am J Psychiatry. 1994;151(1): 57-63.

[28] Dager SR, Richards T, Strauss W, et al. Single-voxel ^{1}H-MRS investigation of brain metabolic changes during lactate-induced panic. Psychiatry Res. 1997;76(2-3): 89-99.

[29] Moore CM, Christensen JD, Lafer B, et al. Lower levels of nucleoside triphosphate in the basal ganglia of depressed subjects: a phosphorous-31 magnetic resonance spectroscopy study. Am J Psychiatry. 1997;154(1):116-118.

[30] Volz HP, Rzanny R, Riehemann S, et al. ^{31}P magnetic resonance spectroscopy in the frontal lobe of major depressed patients. Eur Arch Psychiatry Clin Neurosci. 1998;248(6):289-295.

[31] Chen CS, Chiang IC, Li CW, et al. Proton magnetic resonance spectroscopy of late-life major depressive disorder. Psychiatry Res. 2009;172(3):210-214.
[32] Offiah C, Hall E. Heroin-induced leukoencephalopathy: characterization using MRI, diffusion-weighted imaging, and MR spectroscopy. Clin Radiol. 2008;63(2):146-152.
[33] Salo R, Fassbender C. Structural, functional and spectroscopic MRI studies of methamphetamine addiction. Curr Top Behav Neurosci. 2012;11:321-364.
[34] Sung YH, Cho SC, Hwang J, et al. Relationship between N-acetyl-aspartate in gray and white matter of abstinent methamphetamine abusers and their history of drug abuse: a proton magnetic resonance spectroscopy study. Drug Alcohol Depend. 2007;88(1):28-35.
[35] Du W, Liu J, Gao X, et al. Functional magnetic resonance imaging of brain of college students with internet addiction. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2011;36(8):744-749.
[36] Du WJ, Liu J, Zhou SK, et al. Resting fMRI study of IAD college students based on method of ReHo analysis. Zhonguo Linchuang Xinli Xue Zazhi. 2012;20(4):474-476.
[37] Liu J, Gao XP, Osunde I, et al. Increased regional homogeneity in internet addiction disorder: a resting state functional magnetic resonance imaging study. Chin Med J (Engl). 2010;123(14):1904-1908.
[38] Demougeot C, Marie C, Giroud M, et al. N-acetylaspartate: a literature review of animal research on brain ischaemia. J Neurochem. 2004;90(4):776-783.
[39] van der Knaap MS, van der Grond J, Luyten PR, et al. 1H and ^{31}P magnetic resonance spectroscopy of the brain in degenerative cerebral disorders. Ann Neurol. 1992;31(2):202-211.
[40] Schuff N, Capizzano AA, Du AT, et al. Different patterns of N-acetylaspartate loss in subcortical ischemic vascular dementia and AD. Neurology. 2003;61(3):358-364.
[41] Stanley JA. In vivo magnetic resonance spectroscopy and its application to neuropsychiatric disorders. Can J Psychiatry. 2002;47(4):315-326.
[42] Steingard RJ, Yurgelun-Todd DA, Hennen J, et al. Increased orbitofrontal cortex levels of choline in depressed adolescents as detected by in vivo proton magnetic resonance spectroscopy. Biol Psychiatry. 2000;48(11):1053-1061.
[43] Beard KW, Wolf EM. Modification in the proposed diagnostic criteria for Internet addiction. Cyberpsychol Behav. 2001;4(3):377-383.
[44] Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry. 1961; 4:561-571.
[45] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia. 1971;9(1):97-113.
[46] Widyanto L, McMurran M. The psychometric properties of the internet addiction test. Cyberpsychol Behav. 2004;7(4):443-450.
[47] Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33;quiz 34-57.
[48] Widyanto L, Griffiths MD, Brunsden V. A psychometric comparison of the Internet Addiction Test, the Internet-Related Problem Scale, and self-diagnosis. Cyberpsychol Behav Soc Netw. 2011;14(3):141-149.
[49] Chao-Gan Y, Yu-Feng Z. DPARSF: A MATLAB toolbox for “Pipeline” data analysis of resting-state fMRI. Front Syst Neurosci. 2010;4:13.

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