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Neurochemical correlates of internet game play in adolescents with attention deficit hyperactivity disorder: A proton magnetic resonance spectroscopy (MRS) study

Sujin Bae [a], Doug Hyun Han [b,*], Sun Mi Kim [b], Xianfeng Shi [c], Perry F. Renshaw [c]

[a] Industry Academic Cooperation Foundation, Chung Ang University, Seoul, South Korea
[b] Department of Psychiatry, Chung Ang University Hospital, Seoul, South Korea
[c] Brain Institute, University of Utah, Salt Lake City, UT, USA

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ABSTRACT

Previous studies have examined the relationship of brain metabolic changes in patients with attention deficit hyperactivity disorder (ADHD) and internet gaming disorder (IGD). However, these studies have been limited by a small number of subjects, a large variance in subject age, and different brain regions of interest. The present study assessed the effects of chronic internet game play in ADHD children. Twenty eight ADHD adolescents with IGD (IGD+ADHD), 27 ADHD adolescents without problematic internet game playing (ADHD only) and 42 healthy comparison adolescents (HC) were included in the study. Magnetic resonance spectroscopy (MRS) was performed on a 3 T MRI scanner. Our results indicate that the levels of NAA in both ADHD groups were lower than those observed in the HC group. The levels of Glu+Gln in the ADHD only group were increased, compared to those observed in the control group. However, Glu+Gln was not increased in the IGD+ADHD group. In addition, the levels of Glu+Gln in the IGD+ADHD group were positively correlated with K-ARS total and inattention scores. ADHD and IGD subjects were both characterized by decreased NAA levels within the frontal lobe, consistent with hypofrontality.

1. Introduction

During the last decade, several community based studies have reported meaningful associations between internet addiction and attention deficit hyperactivity disorder (ADHD) in both adolescents (Cao et al., 2007) and young adults (Yen et al., 2009). Excessive internet game play has been associated with the several ADHD symptoms, including impulsivity and hyperactivity (Chan and Rabinowitz, 2006). ADHD is known to be one of the most frequent comorbid disorders associated with internet addiction in South Korean children (Ha et al., 2006; Yoo et al., 2004). Based on a survey of multi-dimensional correlates in 287 healthy adolescents, Chou et al. (2015) suggested that the amount of internet game play was associated with the severity of internet addiction symptoms in ADHD adolescents.

Neuroimaging provides one means to explore the shared and independent neurobiology of ADHD and internet gaming disorder. The most frequently assessed region in ^{1}H magnetic resonance spectroscopy (MRS) studies of ADHD is the prefrontal cortex (Perlov et al., 2009) and the most frequently measured metabolites assessed with ^{1}H MRS were N-acetyl-aspartate (NAA), glutamate+glutamine (Glu+Gln), creatine+phosphocreatine (Cr), and choline compounds (Cho) (Tafazoli et al., 2013). In a review of sixteen ^{1}H MRS studies of ADHD children, the levels of Cho (increased), NAA (decreased), and Glu+Gln (increased) were reported to be altered, compared to healthy control groups (Perlov et al., 2009). Decreased levels of NAA within frontal lobe have also been reported in more recent ADHD studies (Arcos-Burgos et al., 2012; Tafazoli et al., 2013) (Table 1).

Several studies of ADHD have suggested dysfunction within the right prefrontal frontal cortex (Faraone et al., 2005; Kirley et al., 2002). Moreover, decreased dopamine release within corticostriatal pathways in ADHD adolescents has been linked to right frontal cortex pathology, resulting in impulsivity, inattention, and impaired executive function as well as frequent comorbidities with drug and substance use disorders (Bush et al., 2005; Ohlmeier et al., 2007). Several studies have also reported on dopamine release in response to internet game play (Koepp et al., 1998; Tian et al., 2014). Dysregulation of dopamine D2 receptors within the striatum has been associated with decreased glucose metabolism levels within prefrontal, temporal, and limbic system regions in

* Correspondence to: Department of Psychiatry, Chung Ang University Hospital, 224-1 HeukSeok Dong, Dong Jack Gu, Seoul 156 755, South Korea.
E-mail address: hduk70@gmail.com (D.H. Han).

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Table 1
Studies of brain metabolites using Magnetic Resonance Spectroscopy in ADHD children.

Authors	Design	Regions	Results
MacMaster et al. (2003)	9 ADHD (9.6 yrs) vs. 9 Control (9.4 yrs) children	PFC, striatum	↑Glu/Cr+PCr in PFC, Glu/Cr+PCr in striatum
Sparkes et al. (2004)	8 ADHD (9.4 yrs) vs. 6 Control (9.4 yrs) children	Striatum	→Glx/Cr , →NAA/Cr, Cho/Cr
Courvoisie et al. (2004)	8 ADHD (not presented) vs. 8 Control children (8.9 yrs)	Anterior frontal	↑Glu/Cr, ↑NAA/Cr, Cho/Cr+PCr
Sun et al. (2005)	20 ADHD (12.4 yrs) vs. 10 Control (12.6 yrs) adolescent	Lenticular nucleus	→Glx/Cr, ↓NAA/Cr, →Cho/Cr+PCr
Carrey et al. (2007)	12 ADHD (8.1 yrs) vs. 10 Control (8.4 yrs) children	Striatum, PFC, occipital cortex	↑Glx, →NAA, Cho
Tafazoli et al. (2013)	13 ADHD (12.3 yrs) vs. 13 Control (12.2 yrs) children	Middle frontal gyrus	→Glx, ↓NAA, Cr+PCr, Cho, mIno
Arcos-Burgos et al. (2012)	14 ADHD vs 0.20 Control adults (8–54 yrs)	Striatum	↑Glx/Cr, and Ins/Cr, ↓NAA/Cr,
Jin et al. (2001)	12 ADHD (13 yrs) vs. 10 Control (13 yrs) children , Before and after MTX	*Globus pallidus*	→Glu/Cr, Glx/Cr, ↓NAA/Cr, ↑Cho/Cr
Carrey et al. (2002)	4 ADHD (9.3 yrs) children only, Before and after MTX	Striatum, PFC	↓Glx/Cr in striatum after MTX, ↓Glx/Cr in PFC after atomoxetine →NAA/Cr, Cho/Cr
Carrey et al. (2003)	14 ADHD (7–13 yrs) children only Before and after MTX, atomoxetine, Dexedrine	Striatum	↓Glx/Cr in striatum after medications →NAA/Cr, Cho/Cr+PCr
Hammerness et al. (2012)	10 ADHD (14.2 yrs) vs. 12 Control (12.8 yrs) adolescents Before and after MTX	Anterior cingulate	↑Glu/mIno, ↑Gln/mIno, ↓Glu/mIno, ↓Gln/mIno after MTX

ADHD: Attention deficit hyperactivity disorder, MTX: Methylphenidate, NAA: N-acetyl-aspartate, Glx: glutamate+glutamine+GABA, Cr: Creatine, Cho: Choline compound, mIno: Inositol, PFC: Pre-frontal cortex, ↑ increase, ↓: decreased, →: no change

patients with internet gaming disorder (IGD) (Tian et al., 2014).

Glutamate in frontal cortex is thought to be a crucial regulator of dopamine levels (Carlsson et al., 1999; van Elst et al., 2005). Using ^{1}H MRS, levels of glutamatergic metabolites (Glu+Gln) in ADHD adolescents have been reported to be increased within striatum (MacMaster et al., 2003), anterior cingulate cortex (Moore et al., 2006), and prefrontal cortex (MacMaster et al., 2003), compared to values observed in healthy adolescents. In addition, several studies have suggested that medications with dopamine reuptake inhibition (methylphenidate) decreased glutamate metabolites within prefrontal cortex and striatum in children with ADHD (Hammerness et al., 2012; Wiguna et al., 2012).

However, these previous studies have had a small number of subjects, a wide range of subject ages, and different brain regions of interest. Such factors may contribute to the large variance of metabolic findings that have been reported in ADHD (Table 1). Moreover, Maltezos et al. (2014) reported decreased striatal glutamate levels in adults with ADHD. For these reasons, the study of metabolic differences in a large number of ADHD patients with IGD was undertaken. In this study, we compared three groups (Healthy controls, IGD+ADHD, and ADHD only) with relatively large sample sizes. In addition, neither the ADHD only nor the ADHD+ IGD subjects were being treated with medication.

Based on the biologic characteristics of ADHD and the neural substrates of internet game play, we hypothesized that NAA levels would be decreased in all ADHD adolescents (with or without IGD), compared to healthy adolescents. In addition, we expected that as a consequence of chronic excessive internet game play and associated increased dopamine release, decreased levels of Glu+Gln would be observed in ADHD adolescents with IGD, compared to those with only ADHD.

2. Methods

2.1. Participants

Seventy four adolescents with problematic internet game playing or attention problems who visited the outpatient department of Chung Ang University Hospital from June 2011- July 2013 were screened for the current study. Through advertisements posted at Chung Ang University Hospital, 42 age matched male healthy control adolescents agreed to participate in the study. Ultimately, 28 ADHD adolescents with problematic internet game playing (IGD+ADHD), 27 ADHD adolescents without problematic internet game playing (ADHD only) and 42 healthy adolescent were included in the study. Nine patients with dual diagnoses of ADHD and major depression, six patients with autism spectrum disorders, and two patients with mental retardation were excluded. Two patients could not be scanned due to implants on their teeth. The Chung Ang University Hospital Institutional Review Board approved the research protocol for this study. Written informed consent was provided by parents and adolescents provided written informed assent.

All ADHD adolescent were assessed with the Korean Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Life time version (K-SADS-PL) (Kim et al., 2004) and by clinical interview with a child adolescent psychiatric doctor (DHH). All adolescents were asked to complete questionnaires regarding their patterns of on-line game play, the Young Internet Addiction Scale (YIAS) (Young, 1996), the Beck Depressive Inventory (Beck et al., 1961), and the Beck Anxiety Inventory (Beck et al., 1988). Adolescents' parents were asked to complete the Korean ADHD rating scale, Parents and primary caretakers completed the Korean ADHD rating scale (K-ARS) for patients (So et al., 2002).

The criteria for problematic internet game play in the current study have been employed in previous studies (Han et al., 2010; Kim et al., 2012; Ko et al., 2009); (1) the time of internet game playing (more than 4 h per day or 30 h per week), (2) YIAS score >50, (3) becoming irritable, anxious, and aggressive when stopping internet game play, and (4) impaired behaviors or distress, economic problems, and maladaptive patterns of regular life (disrupted diurnal rhythms with sleeping during the day and gaming at night, irregular meals, and failure to maintain personal hygiene, school truancy, and loss of job) due to internet game play. Exclusion criteria included (1) adolescents with a history of other axis I psychiatric diseases except ADHD, (2) adolescents taking psychiatric medications, (3) IQ <80, (4) substance abuse or dependence, (5) history of neurological or medical disorders, and (6) adolescents with claustrophobia.