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Bupropion Sustained Release Treatment Decreases Craving for Video Games and Cue-Induced Brain Activity in Patients With Internet Video Game Addiction

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Bupropion has been used in the treatment of patients with substance dependence based on its weak inhibition of dopamine and norepinephrine reuptake. We hypothesized that 6 weeks of bupropion sustained release (SR) treatment would decrease craving for Internet game play as well as video game cue-induced brain activity in patients with Internet video game addiction (IAG). Eleven subjects who met criteria for IAG, playing StarCraft (>30 hr/week), and eight healthy comparison subjects (HC) who had experience playing StarCraft (<3 days/week and <1 hr/day). At baseline and at the end of 6 weeks of bupropion SR treatment, brain activity in response to StarCraft cue presentation was assessed using 1.5 Tesla functional MRI. In addition, symptoms of depression, craving for playing the game, and the severity of Internet addiction were evaluated by Beck Depression Inventory, self-report of craving on a 7-point visual analogue scale, and Young's Internet Addiction Scale, respectively. In response to game cues, IAG showed higher brain activation in left occipital lobe cuneus, left dorsolateral prefrontal cortex, and left parahippocampal gyrus than HC. After a 6 week period of bupropion SR, craving for Internet video game play, total game play time, and cue-induced brain activity in dorsolateral prefrontal cortex were decreased in the IAG. We suggest that bupropion SR may change craving and brain activity in ways that are similar to those observed in individuals with substance abuse or dependence.

Keywords: bupropion, Internet video game addiction, craving, functional MRI, dorsolateral prefrontal cortex

Although there is debate regarding the definition of Internet addiction within the field of addictive disorders, it has been suggested to be an inability of individuals to control their Internet use, resulting in marked distress and functional impairment of general life such as academic performance, social interaction, occupational interest, developmental stage, and behavioral problems (Ha et al., 2006; Yang, Choe, Baity, Lee, & Cho, 2005; Young, 1996). The Korea Agency for Digital Opportunity & Promotion (KADO) reported in South Korea approximately two million individuals (8.8% of the national population) would meet these criteria. Notably, the prevalence of adolescents with Internet addiction (14.3%) was twofold higher than that observed in the adult population (6.3%) (KADO, 2010).

Neuroimaging studies have suggested that brain activation in response to Internet video game cues is similar to that observed in patients

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with substance dependence in response to substance-related cues (Han et al., 2008; Ko et al., 2009). In a functional MRI (fMRI) study of patients with online game addiction who played Internet video games >30 hr/week, Ko et al. (Ko et al., 2009) reported that the patient group showed increased activity in dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, anterior cingulate, nucleus accumbens, and caudate nucleus in response to game stimuli, relative to a healthy comparison group. In a cohort of healthy volunteers, excessive Internet video game players who do not meet criteria for addiction demonstrated significantly greater activity in right medial frontal lobe, right and left frontal precentral gyrus, right parietal postcentral gyrus, right parahippocampal gyrus, and left parietal precuneus gyrus, compared to general players (Han et al., 2008). In addition, the activity in left inferior frontal gyrus, left parahippocampal gyrus, and right thalamus in response to game cues was correlated with the craving for Internet video game play (Han et al., 2008).

Bupropion Treatment in Substance Abuse

Antidepressants are often used in patients with substance abuse disorders to treat depression, which is frequently comorbid (Nunes, Donovan, Brady, & Quitkin, 1994; Thase, Salloum, & Cornelius, 2001), and for the effects of these drugs on the underlying mechanisms of addiction in patients with alcohol, cocaine, or nicotine dependence (de Lima, de Oliveira Soares, Reisser, & Farrell, 2002; Pettinati, Kranzler, & Madaras, 2003; Thase et al., 2001). Among a number of antidepressants, bupropion has been applied to the treatment of patients with cocaine dependence (Poling et al., 2006), nicotine dependence (de Lima et al., 2002; Hays et al., 2009; Pettinati et al., 2003; Thase et al., 2001), and pathologic gambling (Dannon, Lowengrub, Musin, Gonopolski, & Kotler, 2005) because of its weak inhibition of dopamine and norepinephrine reuptake (Cooper, Hester, & Maxwell, 1980; Cooper et al., 1994). Bupropion is thought to promote smoking cessation by way of reducing craving, nicotine withdrawal syndrome, and negative affect (Durcan et al., 2002; Shiffman et al., 2000). More recently, bupropion sustained release (SR) has also been reported to prevent delayed relapse to smoking in smokers and in alcohol dependent patients who also smoke (Hays et al., 2009; Hays et al., 2001). In a comparison of the effects of bupropion SR and naltrexone for the treatment of patients with pathologic gambling, Dannon et al. (Dannon et al., 2005) showed that both medications were effective in decreasing the frequency of gambling behavior and the amount of money spent on gambling. There were no differences in effectiveness between bupropion SR and naltrexone.

Brain Change Because of Bupropion Treatment

Functional imaging studies during craving provocation have suggested that decreased brain activity may be associated with improvements in depressed mood or reduced drug craving (Chung et al., 2009; Robertson et al., 2007; Volkow, Fowler, Wang, & Swanson, 2004). In an fMRI study of 10 patients with major depression, 8 weeks of bupropion extended release treatment reduced brain activation, especially, in orbital frontal cortex, cingulate, amygdala/parahippocampal area, and caudate in response to emotionally distracting stimuli (Robertson et al., 2007). In addition, a decrease in amygdala activation was correlated with improvement in mood (Robertson et al., 2007). In positron emission tomography (PET) studies using measures of global and regional brain glucose metabolism (regional cerebral metabolic rates of glucose [rCMRglc]) with [18F]-Fluorodeoxyglucose [FDG]), Weinstein et al. (Weinstein et al., 2009) suggested that 2 months of bupropion treatment reduced craving for smoking and brain metabolic activity in orbitofrontal cortex, anterior cingulate, ventral striatum, middle temporal lobe, hippocampus, insula, midbrain, and thalamus during the presentation of smoking cues (see Table 1).

Hypothesis

Most brain studies of patients with substance dependence suggest that brain activity will decrease in response to substance cues after bupropion treatment (Chung et al., 2009; Robertson et al., 2007; Volkow et al., 2004). In this study, we hypothesized that brain activation of the prefrontal cortex and parahippocampal gyrus in response to video game cues in persons with Internet video

Table 1
The Change of Brain Activation After Bupropion Treatment

Authors	Modality	Disease	Brain regions
(Robertson et al., 2007)	fMRI	Major depression	↓ Orbitofrontal cortex, cingulate, amygdala, hippocampus, caudate
(Little et al., 2005)	PET [18F]-FDG	Major depression	↓ left inferior and medial prefrontal, bilateral insular, and left amygdala, right temporal cortex
(Meyer et al., 2002)	PET [11C]-RTI32	Major depression	↓ Striatal doapmine transporter binding potential
(Weinstein et al., 2009)	PET [18F]-FDG	Smokers	↓ Orbitofrontal cortex, anterior cingulate, striatum, temporal lobe, insula, thalamus, hippocampus, caudate, midbrain
(Brody et al., 2004)	PET [18F]-FDG	Smokers	↓ Perigenual/ventral anterior cingulate

Note. fMRI = functional MRI; PET[18F]-FDG = positron emission tomography using [18f]-Fluorodeoxyglucise; PET[11C]-RTI32 = positron emission tomography using carbon-11-labelled RTI 32 ((–)-2β-Carbomethoxy-3β-(4-tolyl)tropane); ↓ = decreased brain activity or decreased metabolism.

game addiction (IAG) would be similar to that observed after drug cue presentation to individuals with substance dependence. In addition, we also hypothesized that bupropion SR treatment would decrease craving for Internet game play as well as cue-induced brain activity in these regions. We further expected that decreased craving for Internet video game play would be associated with decreased regional brain activity in response to Internet video game cues.

Method

Subjects

To increase the homogeneity of our study subjects, we restricted study enrollment to subjects who were addicted to the specific game, "StarCraft," which is very popular in Korea. Among the patients who were evaluated by the Department of Psychiatry of Chung Ang University Medical Center for IAG and subclinical depression (Beck Depression Inventory [BDI] score <17), 12 subjects agreed to participate in the research study. The criteria for Internet video game (StarCraft) addiction in our research were extensive game play time (>4 hr per day/30 hr per week) (Ko et al., 2009), a score of more than 50 on the Young Internet Addiction Scale (YIAS) (Ha et al., 2006; Young, 1996), and impaired behaviors or distress because of maladaptive pattern of Internet video game play that are consistent with *DSM–IV* criteria for substance abuse. During the most recent 12-month period, Internet video game play in all subjects with IAG had gradually increased. In addition, all IAGs reported a persistent desire for playing Internet game everyday as well as unsuccessful efforts to cut down or control Internet video game play. Academic reports from school or work performance in the office had declined. IAGs also showed disruption of their daily routine (sleeping during the day and gaming at night, irregular meals, and failure to wash face and body) and were irritable, anxious, and aggressive when family members asked them to stop playing Internet video game. Six IAGs were absent from school because of playing Internet video game in Internet cafés for more than 2 months. Two IAGs had been divorced because of excessive Internet use at night. Three IAGs lost their jobs because of frequent absences from work without notice. Because there is a gender imbalance (male $>$ female) in terms of gaming addiction in Korea (Ha et al., 2006), only male gamers were recruited for the current study. Through advertisement at Chung Ang University Medical Center, 12 healthy comparison and all subjects with IAG were recruited. Among the 12 healthy comparison subjects (HC; individuals who play StarCraft <3 days/week and <1 hr/day) who were recruited for this study, two individuals did not appear on the scanning day. One healthy comparison subject reported claustrophobic symptoms during scanning and one subject reported excessive alcohol consumption on the day before scanning. Of the 12 IAG, one subject discontinued bupropion treatment because of nausea on bupropion treatment Day 3. Thus, our final study sample included 19 male subjects (11 IAG and 8 HC).

All subjects were screened with the Structured Clinical Interview for *DSM–IV* and the BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). Exclusion criteria were (a) patients with history or current episode of Axis I psychiatric disease, (b) patients with a lifetime diagnosis of substance abuse except for tobacco and alcohol, and (c) patients with neurological or medical disorders. The Chung Ang University Hospital Institutional Review Board approved the research protocol of this study. Written informed consent was provided by all participants.

Study Procedure

Study processing and statistical analysis. At baseline, the demographic data and problematic behavior for Internet use between IAG and HC were compared. Differences in terms of craving for Internet game play, YIAS, and Internet game play time between IAG and HC were analyzed using a Mann–Whitney *U* test. In addition, craving for Internet use and brain activity between the IAG and HC groups were also compared to find vulnerable brain regions for IAG. The general linear model (GLM) (Weiskopf et al., 2004) and random effects analysis (RFX) (Esposito et al., 2005) were applied to analyze the fMRI signal time-courses on a voxel by voxel basis and to generate individual and group statistical parametric maps of brain activation. For all analyses, we regarded the associations as significant when the False Discovery Rate (FDR) was ≤ 0.05 in 100 adjacent voxels (Heller, Stanley, Yekutieli, Rubin, & Benjamini, 2006). In an initial *F* test, interaction within Factor (video game cue vs. neutral stimuli) $\times$ between factor (IAG vs. HC) at baseline (Ganel et al., 2006), we found three clusters.

As a second-level analysis in IAG, we followed the brain activity of three regions and craving for Internet video game in the IAG group (Carey et al., 2006). The changes in craving for Internet game play, YIAS, and Internet game play time, and the activity of three clusters during 6 weeks of treatment period were analyzed by the nonparametric Wilcoxon's-Signed rank test. Spearman correlations were used to show relationships between the change of mean β value in clusters, craving for playing Internet video game, YIAS, and game playing time.

Video Game Play and fMRI Scanning

This Internet video game, StarCraft (Blizzard Entertainment), is an online, real-time strategy game, which is played with multiple other players at the same time. As a military leader for one of three species, players must gather resources for training and expanding their species' forces. Utilizing various strategies and alliances with other species, players attempt to lead their own species to victory.

At baseline, brain activity in response to StarCraft cue presentation was assessed by 1.5 Tesla fMRI. In addition, symptoms of depression, craving for playing the game, and the severity of Internet addiction were evaluated by BDI (Beck et al., 1961), self-report on a 7-point visual analogue scale (VAS, ranging from 1 = "not at all" to 7 = "extreme") and YIAS (Young, 1996), respectively. All the IAG subjects were asked to take bupropion SR (Wellbutrin SR, Glaxo Wellcome Inc.) daily for 6 weeks. Bupropion SR was started at 150 mg/day during the first week and then increased to 300 mg/day thereafter.

At the end of the 6 week period, brain activity during StarCraft game play cue presentation was assessed again. In addition, symptoms of depression, craving for playing the Internet video game, and the severity of Internet addiction were assessed again with same methods that had been used at baseline.

Patients recorded their mean playing game time each week. Parents or spouse also observed patients and checked mean playing game time. At the end of each week, these two groups (patients and parents or spouse) compared their own records and reached a consensus estimate of total game playing time.

Assessment of Brain Activity and Craving for Internet Video Game Play

All MR imaging was performed on a 1.5 Tesla Espree MRI scanner (SIEMENS, Erlangen, Germany). The silent 450-s videotape consisted of five continuous 90-s segments. Each 90-s segment consisted of three 30-s subsegments. A white cross on a black background (B), a neutral control (*N*, humanoid robot animation scenes), and the video game cue (C, StarCraft scence) were included in these 90-s segments. The five segments were ordered as

follows: B-N-C, B-C-N, C-B-N, N-B-C, and C-N-B. This video was presented using an IFIS-SA system (MRI Device Corporation, Waukesha, WI) during a single fMRI scanning session. For the fMRI session, gradient-recalled echo planar imaging (EPI) sequence (37 transverse slices, 5.0 mm thickness, a voxel size of 3.5 × 3.5 × 5.0 mm, TE = 30 msec, TR = 3,000 ms, in-plane resolution = 64 × 64 pixels, field of view [FOV] = 230 × 230 mm) were recorded at 3-s intervals. For anatomical imaging, 3D T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) data were collected with the following parameters: TR = 1,500 ms, TE = 3.00 ms, FOV = 256 × 256 mm, 128 slices, 1.0 × 1.0 × 1.33 mm voxel size.

fMRI Data Analysis

Acquired fMRI data were analyzed using the Brain Voyager software package (BVQX 1.9, Brain Innovation, Maastricht, The Netherlands). The fMRI time series data from each subject was coregistered to the anatomical 3D data sets in the same subject using the multiscale algorithm provided by BVQX. Individual 3D structural images were spatially normalized to standard Talairach space (Talairach & Tournoux, 1988). An identical nonlinear transformation was subsequently applied to the T2*-weighted fMRI time series data. Following preprocessing steps for slice scan time correction and 3D motion correction, the functional data were spatially smoothed using a Gaussian kernel with an FWHM of 6 mm and temporally smoothed using Gaussian kernel of 4 s using algorithms provided by BVQX.

Results

Demographic Characteristics Between Two Groups

There were no differences in terms of age (IAG:21.5 ± 5.6 years, HC: 20.3 ± 4.1 years, $z = 0.23$, $p = .83$), education years (IAG: 11.5 ± 2.5 years, HC: 11.8 ± 2.1 year, $z = 0.33$, $p = .77$), BDI scores (IAG: 6.8 ± 3.7, HC: 8.4 ± 3.4, $z = 1.20$, $p = .24$), and the habits of alcohol drinking (IAG: 7 nondrinking, 4 alcohol drinking [not alcohol dependence by *DSM–IV* criteria], HC: 6 nondrinking, 2 alcohol drinking, $\chi^2 = 1.78$, $p = .78$) and smoking (IAG: 8 nonsmokers, 3 smokers, HC: 6 nonsmokers, 2 smokers, $\chi^2 = 2.50$, $p = .11$) between IAG and HC (see Table 2).

Between the two groups, there were significant differences in terms of craving for playing StarCraft ($z = 2.62$, $p < .01$), total playing game time/total Internet use time ($z = 3.70$, $p < .01$), and YIAS scores ($z = 3.70$, $p < .01$). The mean scores of craving for playing StarCraft in 11 IAG and 8 HC were 5.5 ± 1.0 and 3.9 ± 1.1, respectively. The mean time of playing game (6.5 ± 2.5 hr/day) in 11 IAG, was reported as a consensus estimate from the subject and a parent/spouse. The mean time of Internet use in 8 HC was 1.9 ± 0.6 hr/day. The mean YIAS scores of IAG and HC at baseline were 71.2 ± 9.4 and 27.1 ± 5.3, respectively (see Table 2).

Clusters in the Interaction Between Stimuli and Subject Factors at Baseline

In response to Internet game cue presentation, brain activity within the occipital lobe, DLPFC, and parahippocampal gyrus in patients with IAG was increased relative to healthy comparison subjects. In detail, on an interaction within factor (video game cue vs. neutral stimuli) × between factor (IAG vs. HC), three clusters of activity were identified (FDR corrected $p < .04$, $p < .0009$); Cluster 1 (CL1): Talairach x, y, z; −1, −79, 38, left occipital lobe cuneus, Brodmann area 19; Cluster 2 (CL2): −22, 41, 24, left superior frontal gyrus, Brodmann area 10; and Cluster 3 (CL3): −44, −29, −9, left parahippocampal gyrus, Brodmann area 36 (see Figure 1).

Changes in Maladaptive Behaviors, Craving, and the Mean Beta Value in Cluster 2 After 6 Weeks of Bupropion SR Treatment

After 6 weeks of bupropion SR treatment in the IAG group, maladaptive behaviors because of excessive playing Internet video game were improved. Six IAGs showed improved daily routines to the degree family members found to be acceptable. Four IAGs were no longer absent from school during the treatment period.

Table 2
The Demographic Data, Score of Young Internet Addiction Scale, Playing Game Time, and Craving for Video Game Among GP and IAG

Groups	Age	Sex	Eyr	Alc	Smk	bBDI	6BDI	bYIAS	6YIAS	bUIt/bPGT	6UIt/6PGT	bCr	6Cr
HC1	17	m	10	2	n	7	—	21	—	2	—	4	—
HC 2	17	m	10	n	n	6	—	25	—	2	—	3	—
HC 3	28	m	13	n	n	14	—	35	—	3	—	6	—
HC 4	22	m	12	n	n	7	—	32	—	2	—	3	—
HC 5	24	m	16	1	n	13	—	32	—	1	—	3	—
HC 6	17	m	11	n	3	6	—	26	—	2	—	5	—
HC 7	17	m	10	n	4	9	—	25	—	1	—	4	—
HC 8	20	m	12	n	n	5	—	21	—	2	—	3	—
IAG 1	17	m	10	n	n	3	3	74	77	7	7	4	5
IAG 2	23	m	14	n	n	5	4	83	54	12	2	7	3
IAG 3	17	m	10	n	n	3	4	61	50	5	4	5	6
IAG 4	17	m	8	n	n	5	9	74	70	4	3	6	5
IAG 5	17	m	11	n	n	6	5	76	80	6	6	6	7
IAG 6	29	m	16	4	1	13	9	66	49	6	1	5	1
IAG 7	17	m	10	n	n	12	10	56	54	4	4	5	5
IAG 8	26	m	14	6	n	11	9	76	46	7	2	6	4
IAG 9	16	m	9	n	n	7	6	58	50	4	2	4	4
IAG 10	29	m	11	3	1	7	7	77	55	6	2	5	3
IAG 11	28	m	12	2	1	3	4	82	77	10	8	7	2

Note. HC = Healthy Comparison Subjects; IAG = subjects with excessive Internet video game player; m = male; Eyr = educational years; Alc = alcohol drinking frequency during past 30 days; n = no alcohol drinking/smokers; Smk = smoking, pack years; bUIt = usual Internet using time/day in HC; b/6BDI = baseline/6 weeks BDI scores; b/6YIA = baseline/6 weeks YIAS score; b/6PGT = baseline/6 weeks playing game time (hours) per day in IAG; b/6Cr = baseline/6 weeks craving for playing StarCraft.

After 6 weeks of bupropion SR treatment in the IAG group, there were significant decreases in terms of craving for playing StarCraft (decreased amount: 23.6%, $z = 1.98$, $p = .04$), total playing game time (35.4%, $z = 2.53$, $p = .01$), and YIAS scores (15.4%, $z = 2.45$, $p = .01$) (see Table 2). There was no significant change in BDI scores ($z = 0.67$, $p = .50$).

After 6 weeks of bupropion SR treatment in IAG group, the mean beta value in CL2 was decreased in response to Internet video game stimuli ($z = 2.1$, $p = .04$). There was no significant change in the mean beta values of CL1 ($z = 0.98$, $p = .33$) or CL3 ($z = 0.98$, $p = .33$) (see Figure 2).

The Correlations Between Scales for Internet Addiction, Craving, BDI, and Activity of Brain

At baseline in the IAG group, craving for playing the Internet video game was positively correlated with both YIAS scores (Spearman correlations, $r = .72$, $p = .02$) and mean β value of CL2 (Spearman correlations, $r = .64$, $p = .03$) in response to game stimulation. The YIAS scores at baseline were also correlated with total playing time (Spearman correlations, $r = .82$, $p < .01$). However, there were no significant correlations between craving, YIAS scores, and mean β value of CL2 in HC group.

After 6 weeks of bupropion SR treatment in the IAG group, the change of craving for playing Internet video game was positively correlated with the changes in terms of total playing time (Spearman correlations, $r = .78$, $p < .01$) and the mean β value of CL2 (Spearman correlations, $r = .61$, $p = .04$) in response to game stimulation.

Discussion

The present findings suggest that during Internet game cue presentation, brain activity, particularly in DLPFC and parahippocampal gyrus in patients with IAG, is similar to that observed after cue presentation to individuals with substance dependence or pathological gambling. In addition, 6 weeks of bupropion SR treatment decreased craving for Internet video game play

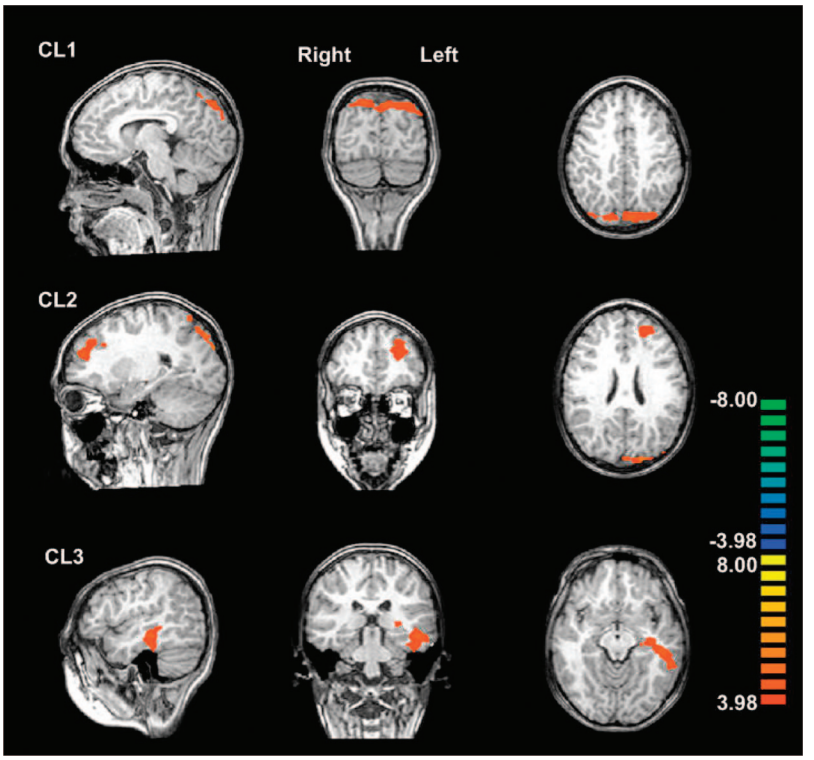

Figure 1. Cluster of regional cerebral blood flow (rCBF) change responding to game stimulation. *F* test, interaction within factor (video game cue vs. neutral stimuli) × between factor (IAG vs. HC), FDR corrected $p < .04$, $p < .0009$; CL1: Talairach x, y, z; −1, −79, 38, left occipital lobe cuneus, Brodmann area 19; CL2: −22, 41, 24, left superior frontal gyrus, Brodmann area 10; CL3: −44, −29, −9, left parahippocampal gyrus, Brodmann area 36.

and activity of DLPFC in response to video game cue stimulation. To the best of our knowledge, this is the first bupropion treatment study in the patients with IAG.

Internet Addiction is Similar to Substance Addiction

In fMRI studies of cue-induced brain activity in patients with substance dependence, most reported addiction brain circuits include the orbitofrontal cortex, DLPFC anterior cingulate cortex, striatum, nucleus accumbens, and amygdala (Franken, 2003; Wilson, Sayette, & Fiez, 2004). In the present study, patients with excessive Internet video game play showed increased activity in DLPFC, parahippocampal gyrus, and occipital lobe during video game cue presentation, relative to healthy comparison subjects. Those regions were also reported in patients with Internet game addiction by Ko et al. (Ko et al., 2009) and in healthy subjects with excessive Internet video game player in our prior study (Han et al., 2008). The DLPFC and the occipital lobe are thought to be associated with visuospatial working memory (Hester & Garavan, 2009). Cocaine dependent subjects who had impaired visuospatial working memory (lower levels of attentional bias in responding to cocaine stimuli) have been reported to experience difficulty in disengaging attention from drug-related stimuli (Hester & Garavan, 2009). Parahippocampal gyrus can reflect the function of amygdala and hippocampus (Kilpatrick & Cahill, 2003). Amygdala and hippocampus, which are important in learning and memory, are thought to play a central role in the main brain circuits responsible for craving for drugs and drug seeking behaviors (Kalivas & Volkow, 2005).

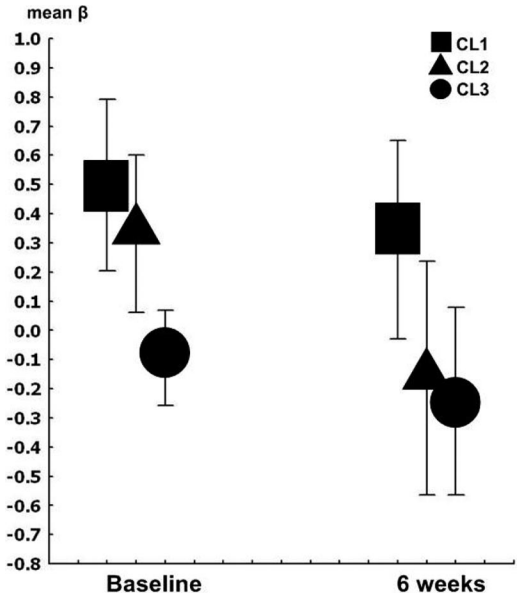

Figure 2. The changes of mean β values during 6 weeks of Wellbutrin SR treatment period. Mean ± 95% CI, CL1: Talairach x, y, z; −1, −79, 38, left occipital lobe cuneus, Brodmann area 19, z = 0.98, $p = .33$; CL2: −22, 41, 24, left superior frontal gyrus, Brodmann area 10, z = 2.1, $p = .04$; CL3: −44, −29, −9, left parahippocampal gyrus, Brodmann area 36, z = 0.98, $p = .33$.

Six Weeks of Bupropion SR Treatment in IAG

In the current study, 6 weeks of bupropion SR treatment improved the maladaptive behaviors of Internet addiction with improved daily routine, attendance of school, as well as decreased craving for Internet video game play and total playing time. In addition, the activity of DLPFC in response to Internet video game cues was also decreased and was positively associated with craving for Internet video game play. The effects of bupropion on smoking, cocaine, and pathologic gambling in terms of decreasing craving and preventing relapse have been reported in several studies (Ascher et al., 1995; Dannon et al., 2005; Durcan et al., 2002; Hays et al., 2009) (see Table 1).

Decreased DLPFC activation in response to video game cues is consistent with the mechanism of action of bupropion. Blocking the reuptake of norepinephrine and dopamine is known to increase extracellular concentrations of these catecholamines (Page & Lucki, 2002) that may prevent stimulation-induced surges in norepinephrine and dopamine release (Dazzi et al., 2002; Dazzi et al., 2001). These results are consistent with an effect of bupropion to decrease craving by reducing DLPFC activity, possibly by modulating norepinephrine or dopamine effects. Additionally, several reports have suggested that bupropion treatment may improve impulsivity and increase concentration in children with attention-deficit/hyperactivity disorder who are thought to have deficits in DLPFC function (Barrickman et al., 1995; Kuperman et al., 2001; Wilens et al., 2001). Han et al. (Han et al., 2009) reported that 8 weeks of methylphenidate treatment reduced Internet use and improved inattention score in subjects with co-occurring attention deficit and hyperactivity disorder and IAGs.

Limitations

There are several limitations to the current study. First, the number of subjects and the duration of treatment may not have been large or long enough to fully document the effects of treatment. In addition, the current sample may not have been representative, as many patients with Internet addiction are known to have various comorbid diseases such as major depression, attention deficit and hyperactivity disorder, and social phobia (Ha et al., 2006; Young, 1996). However, we excluded subjects with comorbid conditions because of the small number of subjects that we were able to include in this study sample. A larger sample and a longer duration of treatment would be important in future studies. In addition, although there was no statistical difference between IAG and HC cohorts, alcohol drinking and smoking in individual subjects could induce a differential effect on the observed changes in brain activity.

Conclusion

Over a 6 week period of bupropion SR treatment, craving for Internet video game play and cue-induced activation in DLPFC of subjects with excessive Internet game play were decreased. These findings are similar to those observed in patients with substance abuse in response to the presentation of substance cues after bupropion treatment. We suggest that bupropion SR may change craving and brain activity in ways that are

similar to those observed in individuals with substance abuse or dependence.

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