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White matter connectivity and Internet gaming disorder

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Abstract

Internet use and on-line game play stimulate corticostriatal-limbic circuitry in both healthy subjects and subjects with Internet gaming disorder (IGD). We hypothesized that increased fractional anisotropy (FA) with decreased radial diffusivity (RD) would be observed in IGD subjects, compared with healthy control subjects, and that these white matter indices would be associated with clinical variables including duration of illness and executive function. We screened 181 male patients in order to recruit a large number ($n = 58$) of IGD subjects without psychiatric co-morbidity as well as 26 male healthy comparison subjects. Multiple diffusion-weighted images were acquired using a 3.0 Tesla magnetic resonance imaging scanner. Tract-based spatial statistics was applied to compare group differences in diffusion tensor imaging (DTI) metrics between IGD and healthy comparison subjects. IGD subjects had increased FA values within forceps minor, right anterior thalamic radiation, right corticospinal tract, right inferior longitudinal fasciculus, right cingulum to hippocampus and right inferior fronto-occipital fasciculus (IFOF) as well as parallel decreases in RD value within forceps minor, right anterior thalamic radiation and IFOF relative to healthy control subjects. In addition, the duration of illness in IGD subjects was positively correlated with the FA values (integrity of white matter fibers) and negatively correlated with RD scores (diffusivity of axonal density) of whole brain white matter. In IGD subjects without psychiatric co-morbidity, our DTI results suggest that increased myelination (increased FA and decreased RD values) in right-sided frontal fiber tracts may be the result of extended game play.

Keywords

Axial diffusivity; diffusion tensor imaging; fractional anisotropy; Internet gaming disorder; myelination; radial diffusivity; tract-based spatial statistics

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Disclosure/Conflict of Interest

All authors have no conflicts of interest.

Authors Contribution

DHHan and PFR were responsible for the study design and writing article. BSJ and SWL were responsible of analysis of data. SMK was responsible for data collection and recruiting for patients. All authors have critically reviewed content and approved final version submitted for publication.

INTRODUCTION

Brain changes in patients with Internet gaming disorder (IGD)

Recent functional magnetic resonance imaging studies have reported that Internet use or on-line game play stimulates corticostriatal-limbic circuitry in both healthy subjects and patients with IGD (Table 1) (Ko *et al.* 2009; Han *et al.* 2010a; Sun *et al.* 2012). The corticostriatal-limbic circuitry, including prefrontal cortex, anterior cingulate, hippocampus, amygdala and striatum, is thought to play an important role in contributing to the pathophysiology of psychiatric disorders (Stein 2008). Han *et al.* (2010a) have reported that inferior frontal cortex, parahippocampal gyrus, parietal cortex and thalamus of healthy university students were activated in response to on-line game cue presentation. Similarly, in response to on-line game cues, the orbitofrontal cortex, anterior cingulate, dorsolateral prefrontal cortex, caudate nucleus and hippocampus of patients with IGD were more activated than those of a healthy comparison group (Ko *et al.* 2009; Sun *et al.* 2012).

Additionally, structural brain imaging studies have suggested that game play of IGD subjects is associated with reduced volumes of gray matter (GM) within the corticolimbic circuit (Table 1) (Zhou *et al.* 2011; Weng *et al.* 2013) while healthy on-line game users had increased GM volume of brain regions within the corticolimbic circuit. The life time amount of video game play has been positively correlated with the GM volumes of parahippocampal regions (entorhinal cortex), inferior parietal lobe, posterior parietal cortex, DLPFC and cingulate in healthy on-line game players (Han, Lyoo & Renshaw 2012; Tanaka *et al.* 2013; Kuhn & Gallinat 2014). Conversely, Weng *et al.* (2013) reported a decreased volume of GM in right frontal cortex and supplementary motor areas in IGD subjects. Zhou *et al.* (2011) reported that GM density within the anterior and posterior cingulate cortices, insular and lingual gyrus decreased in IGD subjects. Yuan *et al.* (2011) reported that the GM volumes within dorsolateral prefrontal cortex, supplementary area, orbitofrontal cortex, cerebellum and left rostral anterior cingulate decreased in IGD subjects.

Diffusion tensor imaging (DTI) in IGD subjects

DTI is a technique for studying the role of neural connectivity by exploiting the restricted diffusion of water molecules in white matter (WM) (Catani 2006). Due to long axonal connections that are established in early brain development, the diameter and microtubular structure of axons continue to develop through adulthood (Keshavan *et al.* 2002). During development, both experience and environment can affect the myelination of fibers within a tract (Juraska & Kopcik 1988). Fractional anisotropy (FA) is a DTI metric for measuring the integrity of WM fibers. FA alterations may be related to changes in myelination, axonal density, axonal membrane integrity, axon diameter and fiber crossing (Zatorre, Fields & Johansen-Berg 2012). Several assessments with DTI have suggested that the IGD subjects have increased connectivity of WM tracts. Dong *et al.* (2012a) have reported that IGD subjects showed increased FA values within the thalamus and posterior cingulate cortex. Yuan *et al.* (2011) reported increased FA values within the posterior limb of the internal capsule and decreased FA values within the parahippocampal regions of IGD subjects relative to healthy comparison subjects.

However, to completely characterize more alterations of FA values, both axial diffusivity (AD) and radial diffusivity (RD) may be investigated. Changes in AD reflect the magnitude of diffusivity along the main diffusion direction that is associated with alterations in axonal density or caliber (Kumar *et al.* 2012). Decreases in RD reflect the magnitude of diffusivity perpendicular to the main diffusion direction consistent with increased myelination (Hu *et al.* 2011). Cognitive training provided by remedial reading for 100 hours (Keller & Just 2009) increased FA and decreased RD in poor readers, suggesting that myelination was the predominant process responsible for increased FA. In contrast, 4 weeks of mindfulness meditation led to AD and RD reductions accompanied by increased FA values, indicating the involvement of increased myelin as well as other axonal changes (Tang *et al.* 2012). IGD subjects have typically been gaming for significant time periods, requiring substantial cognitive work. Thus, the FA changes reported in previous DTI studies may reflect changes in axonal morphology, myelination or both, and should be understood in light of parallel changes in RD and AD (Yuan *et al.* 2011; Dong *et al.* 2012a) (Table 1). AD or RD alterations in conjunction with FA changes would provide evidence whether the FA changes in IGD subjects are primarily associated with either axonal morphology or with myelination. Using tract-based spatial statistics (TBSS) (Smith *et al.* 2006), the present study assessed the connectivity of WM including FA, RD and AD in patients with on-line game addiction. TBSS is an approach for comparing group differences that comprise an anatomically based, non-linear registration procedure to project results onto an alignment-invariant tract representation (the ‘mean FA skeleton’) using voxel-wise analysis of multi-subject diffusion data (Smith *et al.* 2006).

Most studies to date have included relatively small numbers of IGD subjects (10–19 subjects) and have not considered the effects of psychiatric co-morbidity (Ko *et al.* 2009; Han *et al.* 2010a; Yuan *et al.* 2011; Zhou *et al.* 2011; Dong *et al.* 2012b; Sun *et al.* 2012; Weng *et al.* 2013). Attention deficit hyperactivity disorder (ADHD), major depressive disorder, obsessive compulsive disorder and schizophrenia are considered to be common co-morbid diseases (Ha *et al.* 2006, 2007). Studies of large numbers of patients and considering the effects of co-morbidity have been suggested as an important direction for future studies by a number of authors (Ko *et al.* 2009; Han *et al.* 2010b; Zhou *et al.* 2011; Sun *et al.* 2012; Weng *et al.* 2013). Thus, in the present study, we assessed 181 patients in order to rule out co-morbidity and recruit a large number of IGD subjects without psychiatric co-morbidity.

Hypothesis

Based on the functional and anatomical brain changes in response to remedial reading and meditation, we hypothesized that increased FA with decreased RD, consistent with myelination, would be observed in IGD subjects compared with healthy control subjects. This pattern of change reflects the results of extensive game play and is likely to be related to clinical variables including duration of illness and executive function.

METHODS

Subjects

One hundred eighty-one male individuals (15–41 years old) with problematic on-line game play who visited the On-line Game Clinic Center in Chung Ang University Hospital were screened. Through advertisements posted at Chung Ang University Medical Center, 26 male healthy control subjects were also recruited to participate in the study. Both patients and healthy controls were screened with the Structured Clinical Interview for DSM-IV (Ha *et al.* 2006; Preuss *et al.* 2010). Questionnaires regarding their pattern of on-line game play (Han *et al.* 2014), the Young Internet Addiction Scale (YIAS) (Young 1996), the Beck Depression Inventory (Beck *et al.* 1961) and the Beck Anxiety Scale (Beck *et al.* 1988) were also completed by all subjects. Parents and main caretakers completed Dupaul's ADHD scale-Korean version (K-ARS) for patients. Internal consistency of the K-ARS has been reported to range from 0.77 to 0.89 (So *et al.* 2002). In addition, all subjects completed a computerized version of the Wisconsin Card Sorting Test (CNT4.0, Maxmedica Inc, Seoul, Korea) for assessment of executive function, including set shifting, working memory and inhibitory control process (Lee *et al.* 2002). The reliability of the computerized version WCST is reported as Cronbach's $\alpha = 0.783$ (Lee *et al.* 2002). Perseverative errors are used to assess set shifting that represents prefrontal cortex function (Pedersen *et al.* 2012).

The criteria for on-line game addiction in the present study have been employed in previous studies (Han *et al.* 2009; Han, Hwang & Renshaw 2010b; Kim *et al.* 2012): (1) excessive on-line game play time (more than 4 hours per day/30 hours per week); (2) YIAS scores > 50 ; (3) irritable, anxious and aggressive behavior when asked to stop on-line game play; and (4) impaired behaviors or distress, economic crisis and maladaptive regular life patterns including disrupted diurnal rhythms (sleeping during the day due to gaming at night, irregular meals and failure to maintain personal hygiene), school refusal and joblessness. Exclusion criteria included (1) participants with other axis I psychiatric diseases; (2) individuals taking psychiatric medications for on-line addiction; (3) IQ < 80 ; (4) substance abuse history except for alcohol or tobacco use; (5) participants with neurological or medical disorders; and (6) participant with claustrophobia. Ultimately, 58 patients with on-line game addiction were included in the study. One hundred fifteen patients with co-morbidities were excluded: 51 ADHD, 33 major depression, nine ADHD + major depression, seven schizophrenia, five obsessive compulsive disorder, four alcohol dependence, four autism spectrum disorders and two mental retardation. Four patients had YIAS < 50 and game playing time < 30 hours/week. Four patients with claustrophobia could not be scanned. The Chung Ang University Hospital Institutional Review Board approved the research protocol for this study. Written informed consent was provided by patients over 18 years of age. In adolescents under 18 years of age, written informed consent was provided by parents and adolescents provided written informed assent.

Image processing and analysis

Multiple diffusion-weighted images, with 32 encoding directions and an additional T2-weighted scan, were acquired using a Philips Achieva 3.0 Tesla TX MRI scanner (Philips, Eindhoven, the Netherlands), with standard single-shot, spin echo, echo planar acquisition

sequence with eddy current balanced diffusion weighting gradient pulses ($b = 600$ seconds/ mm^2 , echo time (TE)/repetition time (TR) = 70 ms/9214 ms; matrix = 124×121 on $250 \text{ mm} \times 250 \text{ mm}$ field of view; slices 2 mm without gap resulting in voxels of $2.02 \times 2.06 \times 2.0 \text{ mm}$). Volumetric T1-weighted anatomic reference images were acquired using a three-dimensional T1-weighted magnetization-prepared rapid gradient echo sequence (TE/TR = 3.8 ms/8.2 seconds; 256×256 matrix for $1.0 \times 1.0 \times 1.0 \text{ mm}$ voxels; 180 slices).

TBSS analysis

Preprocessing for DTI analysis, including skull stripping and Eddy current correction, was performed using FMRIB Software Library (FSL; Oxford, UK; <http://www.fmrib.ox.ac.uk/fsl>). A diffusion tensor model was arranged for each voxel with the generation of FA, mean diffusivity (MD), RD, AD and mode images using FMRIB's diffusion toolbox in FSL. The TBSS tool in FSL was used to analyze tract-based differences in FA values between IGD subjects and healthy control subjects. A common registration target was identified and all subjects' FA images were aligned to this target using nonlinear registration. The aligned FA images were affine-transformed into $1 \times 1 \times 1 \text{ mm}^3$ MNI152 (Montreal Neurological Institute) space and a mean FA image was generated from the transformed FA images. A mean skeleton image was created from the mean FA image. Each subject's aligned FA image was projected onto the mean FA skeleton by filling the structure with FA values from the nearest relevant tract center. Finally, this skeletonized FA image was thresholded using an FA value of 0.2 to reduce inter-subject variability and to represent each tract as a single line running down the center of the tract. Using the transformation matrix produced via the processing of FA images, other DTI metric images consisting of MD, RD, AD and mode were projected onto the skeleton. To identify differences in each diffusion metric between the two groups, voxel-wise statistical analyses were performed based on a non-parametric approach. The FSL randomize command was performed using 10 000 random permutation. The two-dimensional threshold-free cluster enhancement option was used to obtain differences between the two groups at a significance level of $P < 0.05$.

The comparisons of mean diffusion metrics using individual fiber tracts

The skeleton, representing a single line running down the center of the tract, arises from different fiber tracts, especially in WM areas that include crossing tracts, across subjects. Thus, the diffusion metrics were analyzed for each individual fiber tract that passed through the volume of interest (VOI) showing significant group differences in diffusion metrics in TBSS. VOIs were selected on the directionally encoded tensor maps described in previous studies (Concha, Gross & Beaulieu 2005; Vernooij *et al.* 2007). To do this, major fiber tracts showing group differences in TBSS analyses were defined using the Johns Hopkins University DTI-based WM (JHU-WM) tractography atlas (Hua *et al.* 2008). Second, the four-dimensional FA skeleton image based on TBSS analysis was deprojected to a space that was located at one step before the projection onto the mean skeleton. Then, to measure diffusion metrics in major fiber tracts that passed through the VOI, the deprojected four-dimensional skeleton was masked by the JHU-WM tractography atlas. To exclude the skeleton located within GM, the tracts provided by the atlas were threshold at a 30 percent probability level.

Statistical analysis

Using independent *t*-tests, mean age, years of education, YIAS scores, on-line game playing time and IQ were compared between two groups. ANCOVA analyses controlling for age, education years, K-ARS, BAI and BDI scores were performed for five diffusion metrics of each major fiber tract. Then, controlling for age, education, FSIQ, K-ARS, BAI and BDI scores, partial correlations were performed to analyze the relationship between diffusion metrics showing significant group difference and the duration of illness and WCST scores in IGD subjects. To correct for multiple comparisons (six tracts with five diffusion metrics) in partial correlations, α was set at $P = 0.002$ (0.05/30).

RESULTS

Demographic characteristics

There were no significant differences in demographic data including age, sex ratio or full-scale IQ between IGD subjects and healthy control subjects. The YIAS scores ($t = 15.9$, $P < 0.01$) and game playing time ($t = 26.1$, $P < 0.01$) in IGD were higher than those values in healthy controls. The BDI scores in IGD subjects were higher than those in healthy controls ($t = 3.1$, $P < 0.01$). There were no significant differences in the K-ARS scores ($t = 0.09$, $P = 0.34$) and BAI scores ($t = 1.9$, $P = 0.07$) between the two groups. Perseverative responses ($F = 2.2$, $P = 0.03$) and perseverative errors ($F = 2.2$, $P = 0.03$) in the IGD subjects were higher than those observed in the healthy comparison subjects (Table 2).

TBSS results

In TBSS of whole WM with ANCOVA analyses controlling for age, education years, K-ARS, BAI and BDI scores, IGD subjects had significantly increased regional FA values of WM including bilateral orbitofrontal; corpus callosum; association fibers with the involvement of bilateral inferior fronto-occipital fasciculus (IFOF) and the bilateral anterior cingulum; projection fibers consisting of the bilateral anterior, superior and posterior corona radiation; bilateral anterior limb of the internal capsule; bilateral external capsule; and right precentral gyrus, compared with healthy control subjects ($F = 32.05$, $P < 0.0001$) (Figs. 1 & 2) (Table 3). The significant changes in RD overlapped with WM regions for which group differences in FA were found. In TBSS with ANCOVA controlling for age, education, K-ARS, BAI and BDI scores, the mean RD of white matter including right external capsule and right anterior cingulum in IGD subjects was lower than values observed in healthy controls ($F = 33.04$, $P < 0.0001$) (Fig. 1) (Table 3). There was no significant difference in MD, AD or mode between the two groups.

Comparison of mean diffusion metrics from individual fiber tracts

Using JHU-WM tractography atlas, we found six major fiber tracts showing significant differences in FA value in TBSS. In tract tracing of these seven tracts with ANCOVA controlling for age, education years, K-ARS, BAI and BDI scores, IGD subjects showed increased mean FA values within forceps minor (4.0 percent, $F = 22.73$, $P < 0.0001$), left anterior thalamic radiation (4.9 percent, $F = 13.91$, $P < 0.0001$), right corticospinal tract (3.9 percent, $F = 21.17$, $P < 0.0001$), right inferior longitudinal fasciculus (ILF) (4.7 percent, $F =$

10.92, $P = 0.0014$), right cingulum to hippocampus (4.7 percent, $F = 12.67$, $P = 0.0006$) and right IFOF at a trend level (5.1 percent, $F = 9.54$, $P = 0.0027$) compared with healthy comparison subjects (Table 3). There was no significant correlation between game play time and FA values in the six fiber tracts in healthy control subjects.

In tract tracing of three tracts with ANCOVA controlling for age, education years, K-ARS, BAI and BDI scores, IGD subjects showed decreased mean RD values within forceps minor (−3.7 percent, $F = 16.65$, $P = 0.0001$), left anterior thalamic radiation (−7.4 percent, $F = 19.54$, $P < 0.0001$) and right IFOF (−8.3 percent, $F = 18.51$, $P < 0.0001$) compared with healthy comparison subjects (Table 3). There was no significant correlation between game play time and RD values in the six fiber tracts in healthy control subjects.

Significant differences in the other diffusion metrics consisting of AD, MD and mode were not found in both TBSS and VOI analyses.

Correlations between duration of illness, WCST scores and FA and RD values

Controlling for age, education, FSIQ, K-ARS, BAI and BDI scores, the duration of illness in IGD subjects was positively correlated with the FA values within whole WM ($r = 0.48$, $P < 0.001$). Controlling for age, education, FSIQ, K-ARS, BAI and BDI scores, the duration of illness in IGD subjects was positively correlated with FA values within forceps minor ($r = 0.50$, $P < 0.0001$), right corticospinal tract ($r = 0.40$, $P = 0.002$), right ILF ($r = 0.42$, $P = 0.001$) and right IFOF at a trend level ($r = 0.38$, $P = 0.004$).

Controlling for age, education, FSIQ, K-ARS, BAI and BDI scores, the duration of illness in IGD subjects was negatively correlated with RD scores within whole WM ($r = -0.47$, $P < 0.001$). Controlling for age, education, FSIQ, K-ARS, BAI and BDI scores in IGD subjects, the duration of illness in IGD subjects was negatively correlated with the value of RD in the right anterior thalamic radiation tract at a trend level ($r = -0.37$, $P = 0.006$) and right IFOF ($r = -0.45$, $P = 0.001$). Controlling for age, education, FSIQ, K-ARS, BAI and BDI scores, non-perseverative errors in IGD subjects were negatively correlated with the value of mean RD values within whole WM at a trend level ($r = -0.26$, $P = 0.06$). There was no significant correlation between non-perseverative errors and duration of illness.

DISCUSSION

The present results indicate that IGD subjects had increased FA value within forceps minor, right anterior thalamic radiation, right corticospinal tract, right ILF, right cingulum to hippocampus and right IFOF. In addition, IGD subjects had decreased RD values, but not AD values, within forceps minor, right anterior thalamic radiation and right IFOF relative to healthy control subjects. Moreover, the duration of illness in IGD subjects was positively correlated with FA values and negatively correlated with RD scores. Our DTI results suggest that increased myelination occurs in right side frontal fiber tracts that may be the result of extensive game play. This view is supported by the association of DTI measures with duration of illness in IGD subjects.

Increased myelination in the right hemisphere

Most findings of increased myelination in the current study were observed in the right hemisphere except for the left anterior thalamic radiation. Internet video game playing requires an active working memory system, including visual and auditory attention (Dong, Huang & Du 2012b). Moreover, long-duration game play needs sustained attention despite loud background sound and flashy screen (Hyun *et al.* 2013; Song, Han & Shim 2013). During normal brain development, electrophysiological peak changes in response to visuospatial working memory were observed over the right hemisphere in older children (Myatchin & Lagae 2013). In a comparison between StarCraft I and StarCraft II, both of which are popular multi-user and real-time strategy games in South Korea, greater brain activation within the right hemisphere, including frontal and occipital cortices, has also been observed in professional gamers playing StarCraft II, which included three-dimensional images requiring more visuospatial attention than those in StarCraft I (Song *et al.* 2013). Right-sided changes may be accelerated with Internet game play.

Increased FA value in IGD subjects

The present results indicate that FA values in IGD subjects were higher than those observed in healthy control subjects. Duration of illness was positively correlated with FA values. In previous studies, on-line game play has been associated with elevated FA values within the thalamus and posterior cingulate cortex in healthy game users (Dong *et al.* 2012a) and within the posterior limb of the internal capsule in individuals with Internet addiction (Yuan *et al.* 2011). The thalamus is known to play a role in reward systems (Rieck *et al.* 2004; Yu, Gupta & Yin 2010) and action–outcome associations (Corbit, Muir & Balleine 2003). Thalamus is also known to control sensory stimulation including visual and auditory systems (Alitto & Usrey 2003). The anterior thalamic radiation connects the dorsomedial and anterior thalamic nuclei with the prefrontal cortex (Sprooten *et al.* 2009). The cingulum, one of the primary WM tracts within limbic system, connects the anterior thalamus with the hippocampus (Burgel *et al.* 2006). Scantlebury *et al.* (2014) reported increased FA values within corticospinal tract and MD values within IFOF in response to visuomotor information processing. Hu *et al.* (2011) showed that repetitive mental (not chemical) stimulation could change WM connectivity with the finding that mental training (3-year abacus-based mental training) changed the microstructure of brains (increased FA values within corpus callosum, left occipitotemporal junction and right premotor projection) in 25 healthy children. Bengtsson *et al.* (2005) reported that piano playing increased FA values within motor tracts. Therefore, we cautiously suggest that enhanced WM integrity within right frontal regions may arise secondary to repetitive on-line game play (i.e. via experience-dependent changes) (Fig. 3).

Decreased RD in IGD subjects and postulated mechanisms of action

In our results, RD in IGD subjects decreased in the right external capsule, right anterior cingulum, forceps minor, right anterior thalamic radiation and right IFOF relative to healthy comparison subjects. In addition, the duration of illness in IGD subjects was negatively correlated with RD values. Both increased FA values and decreased RD values can reflect experience-dependent plasticity (increased function of acquired skills over development).

RD values in healthy students were negatively correlated with Preliminary Scholastic Aptitude Test math scores (Matejko *et al.* 2012). Those results were different from the results of a study by Lin *et al.* In Lin *et al.*'s (2012) study, the FA values within the orbitofrontal WM, corpus callosum, cingulum, IFOF and corona radiation, internal and external capsules in IGD subjects were reduced compared with healthy comparison subjects. Moreover, the reduction of FA values in the brain of IGD subjects was associated with an increase in RD, without much change observed in terms of AD (Lin *et al.* 2012). Although FA values are associated with axon numbers (centers of all fiber bundles) (Smith *et al.* 2006), RD is thought to represent the status of myelin (Song *et al.* 2002; Brubaker *et al.* 2009). The divergent findings between the present study and Lin's study may be due to the age differences of subjects between the two studies and the exclusion of co-morbid ADHD. The mean age of subjects in Lin's study was 17.01 ± 2.50 and that in the current research was 21.2 ± 4.8 . Scantlebury *et al.* (2014) has reported that RD decreases with age in the IFOF and corticospinal tract in 27 typically developing children.

Several studies have noted the co-morbidity of ADHD and major depressive disorder in individuals with IGD (Chan & Rabinowitz 2006). The FA values within cingulum, fornix, IFOF and posterior thalamic radiation in adolescents with ADHD decreased relative to healthy comparison subjects (Ashtari *et al.* 2005; Hamilton *et al.* 2008). LeWinn *et al.* (2014) reported that adolescents with major depressive disorder had decreased FA and increased RD values in uncinate fasciculus. However, there was no screening for ADHD and major depression in Lin's study while we assessed possible co-morbidities, including ADHD and major depressive disorder. Therefore, subjects with younger age and (perhaps) co-morbid ADHD or major depressive disorder in Lin's study may show decreased FA values and increased RD values relative to our findings (increased FA value and decreased RD values).

The present results also documented a correlation between decreased RD values and non-perseverative errors at a trend level. Non-perseverative errors on the WCST are thought to represent inefficient set shifting or unsuccessful problem solving during cognitive tasks that are associated with dorsolateral prefrontal cortex function (Greve, Ingram & Bianchini 1998). Functional deficits of prefrontal cortex in IGD subjects have been noted in several studies (Ko *et al.* 2009; Han *et al.* 2010a; Sun *et al.* 2012). In a comparison of GM volumes between IGD and professional gamers who are not patients but excessive players, IGD individuals demonstrated decreased left cingulate GM volumes compared with professional gamers (Han *et al.* 2012). The current study of WM connectivity allowed an estimation of the correlation between duration of illness and increased FA values in IGD subjects. Taken together, we speculate that large amounts of processing data (visual, auditory and working memory) via enhanced tracts (increased FA value of WM) during game play may aggravate processing within dysfunctional prefrontal cortices (Fig. 3).

Limitations

There are several limitations to the current study. First, the recruitment of subjects with excessive on-line game play does not permit an assessment of the effects of other on-line media (social network, browsing etc.) on brain WM. As the current study recruited only

male subjects, it is not possible to comment on gender differences in vulnerability to IGD or related brain changes. In addition, IGD subjects with co-morbid mental illness may demonstrate more substantial brain changes than IGD subjects without psychiatric co-morbidity. Finally, TBSS analysis in the current study used a mask generated from a tractography atlas but did not manually generate brain tracts. Future studies should follow the long-term course of brain changes as well as cognitive alterations associated with excessive game play in IGD subjects and in patients with co-morbid mental illnesses.

CONCLUSION

Individuals with IGD showed WM changes including increased FA (increased number of fiber bundle) and decreased RD (increased myelination) within multiple right frontal regions relative to healthy control subjects. This pattern of WM change suggests that IGD subjects have experience-dependent growth of myelin as a consequence of on-line game play.

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Figure 1.

Tract-based spatial statistics (TBSS) analysis. Results of TBSS analysis were calculated with a 10 000 random permutation, two-dimensional threshold-free cluster method. Significantly increased fractional anisotropy (FA) (red-to-yellow) and decreased radial diffusivity (RD) (blue-to-light blue) values were observed in subjects with Internet game addiction. Regions showing significant changes in FA or RD were marked with exaggerated tracts for the purpose of display. The light green color indicates the mean skeletonized FA image. A = anterior; R = right

Figure 2.

Regions showing significant increased fractional anisotropy and decreased radial diffusivity values in subjects with Internet game addiction. R. Ant. Thalamic Radiation = right anterior thalamic radiation; R. IFOF = right inferior fronto-occipital fasciculus; R. ILF = right inferior longitudinal fasciculus

Figure 3.
White matter tracts in response to Internet video game play

Table 1

Brain changes in subjects with Internet gaming disorder.

Authors	Subjects	Modality	Screening/exclusion criteria	Brain regions
Structural changes				
Weng <i>et al.</i> (2013) #11	17 IGD versus 17 HC	VBM-GM↑ TBSS-WM	YDQ/substance abuse, neurologic or medical disorders, anxiety disorder, schizophrenia or psychotic episodes	↓GM within right OFC, bilateral insula, right SMA ↓FA within the right genu of corpus callosum, bilateral frontal lobe, right external capsule
Zhou <i>et al.</i> (2011) #54	18 IGD versus 15 HC	VBM-GM	YDQ/no exclusion criteria appeared	↓GM within left anterior cingulate cortex, left posterior cingulate cortex, left insula and left lingual gyrus
Tanaka <i>et al.</i> (2013) #58	17 expert versus 33 non-experts	VBM-GM↑	Healthy person/neurologic and psychiatric diseases	↑GM in the right posterior parietal cortex in experts compared with non-experts
Yuan <i>et al.</i> (2011) #55	18 IGD versus 18 HC	VBM-GM↑ TBSS-WM	YDQ/neurological disorder, substance abuse, pregnancy or menstrual period in women, any physical and medical illness	↓GM within bilateral DLPFC, SMA, OFC, the cerebellum and the left rostral ACC ↓FA value within the right PHG
Dong <i>et al.</i> (2012a) #60	16 IGD versus 15 HC	DTI-WM	MINI/axis I psychiatric disorders, substance abuse, medication	↑FA within the thalamus and left posterior PCC
Lin <i>et al.</i> (2012) #59	16 IGD versus 16 HC	TBSS-WM	MINI-KID/substance abuse, schizophrenia, depression, anxiety disorder, psychotic episodes	↓FA value within OFC, corpus callosum, cingulum, inferior fronto-occipital fasciculus and corona radiation, internal and external capsules
Functional changes				
Sun <i>et al.</i> (2012) #13	10 IGD versus 10 HC	Game cue-fMRI	CIAS/psychiatric disease history, substance abuse, head trauma	DLPFC, bilateral temporal cortex, cerebellum, right inferior parietal lobule, right cuneus, right hippocampus, PHG, left caudate nucleus
Han <i>et al.</i> (2010a) #56	19 HC	Game cue-fMRI	SCID-IV/axis I psychiatric disease, substance abuse, neurological or medical disease	Right medial frontal lobe, right and left frontal precentral gyrus, right parietal postcentral gyrus, right PHG and left parietal precuneus gyrus
Ko <i>et al.</i> (2009) #34	10 IGD versus 10 HC	Game cue-fMRI	DCIA-C/substance abuse, major depressive episode, current psychotropic medication use, history of bipolar I disorder, psychotic disorder, neurological illness and injury, mental retardation	Right orbitofrontal cortex, right nucleus accumbens, bilateral ACC and medial frontal cortex, right DLPFC, and right caudate nucleus
Lorenz <i>et al.</i> (2013) #103	8 IGD versus 9 HC	Game cue-fMRI	SCID-IV/substance abuse, neurological disorder, social phobia	Medial prefrontal cortex, ACC and lingual gyrus
Hong <i>et al.</i> (2014) #104	12 IGD versus 11 HC	Resting state fMRI	K-SADS-PL/axis I psychiatric diseases	The majority of impaired connections involved cortico-subcortical circuits (24 percent with prefrontal and 27 percent with parietal cortex) Bilateral putamen was the most extensively involved subcortical brain region
Montag <i>et al.</i> (2012) #106	21 experts versus 19 non-experts	Social cue-fMRI	Healthy person/neurologic and psychiatric diseases	Compared with controls, gamers showed a significantly lower activation of the left lateral medial frontal lobe while processing negative emotions

ACC = anterior cingulate cortex; CIAS = Chen's Chinese Internet Addiction Scale; DCIA-C = diagnostic criteria and the screening and diagnosing tool of Internet addiction; DLPFC = dorsolateral prefrontal cortex; DTI = diffusion tensor imaging; FA = fractional anisotropy; fMRI = functional magnetic resonance imaging; GM = gray matter; HC = healthy comparison subjects; IGD = patients with Internet gaming disorder; K-SADS-PL = Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version; MINI = Mini International Neuropsychiatric Interview; MINI-KID =

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Mini International Neuropsychiatric Interview for Children and Adolescents; OFC = orbitofrontal cortex; PHG = parahippocampal gyrus; SCID-IV = Structured Clinical Interview for DSM-IV; SMA = supplementary motor area; TBSS = tract-based spatial statistics; VBM = voxel-based morphometry; WM = white matter; YDQ = Young Diagnostic Questionnaire for Internet addiction; ↑ = increased; ↓ = decreased.

Table 2

Demographic data.

	PGA (58)	Healthy controls (26)	Statistics, post hoc
Age	21.2 ± 4.8	22.5 ± 4.3	$t = 1.2, P = 0.24$
Education (years)	14.2 ± 4.8	15.2 ± 4.5	$t = 0.87, P = 0.38$
IQ	105.0 ± 15.7	106.4 ± 10.3	$t = 0.42, P = 0.67$
YIAS	60.1 ± 7.9	32.0 ± 7.4	$t = 15.8, P < 0.01^*$
Game time (hours/week)	41.9 ± 5.72	2.53 ± 7.61	$t = 26.2, P < 0.01^*$
Duration of illness (years)	7.6 ± 4.8	–	–
BDI	12.8 ± 9.4	7.0 ± 5.3	$t = 3.1, P < 0.01^*$
K-ARS	9.7 ± 6.7	8.1 ± 5.7	$t = 0.09, P = 0.34$
BAI	7.2 ± 6.9	4.2 ± 4.8	$t = 1.9, P = 0.07$
WCST			
PR	15.3 ± 8.5	11.6 ± 4.6	$F = 2.2, P = 0.03^*$
PE	10.4 ± 5.7	8.1 ± 5.7	$F = 2.2, P = 0.03^*$

* Statistically significant. BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; K-ARS = Dupaul's ADHD scale-Korean version; PE = perseverative error; PGA = patients with on-line game addiction; PR = perseverative response; WCST = Wisconsin Card Sorting Test; YIAS = Young Internet Addiction Scale.

Table 3

Diffusion metrics from individual fiber tracts.

	PGA (58)	Healthy controls (26)	Statistics
FA	0.5219 ± 0.0239	0.4829 ± 0.0402	$F = 32.05, P < 0.0001$
Forceps minor	0.6774 ± 0.0197	0.6511 ± 0.0278	$F = 22.73, P < 0.0001$
L. Ant. Thal.	0.6076 ± 0.0353	0.5795 ± 0.0346	$F = 13.91, P = 0.0003$
R. Corticosp	0.7027 ± 0.0293	0.6761 ± 0.0185	$F = 21.17, P < 0.0001$
R. Cingul	0.7366 ± 0.0524	0.7035 ± 0.0564	$F = 12.67, P = 0.0006$
R. ILF	0.6339 ± 0.0373	0.6056 ± 0.0334	$F = 10.92, P = 0.0014$
R. IFOF	0.5634 ± 0.0382	0.5358 ± 0.0385	$F = 9.54, P = 0.0027$
RD	0.000529 ± 0.000032	0.000575 ± 0.000053	$F = 33.04, P < 0.0001$
Forceps minor	0.000614 ± 0.000072	0.000637 ± 0.000095	$F = 16.65, P = 0.0001$
L. Ant. Thal.	0.000594 ± 0.000046	0.000638 ± 0.000057	$F = 19.54, P < 0.0001$
R. IFOF	0.000508 ± 0.000038	0.000550 ± 0.000063	$F = 18.51, P < 0.0001$

FA = fractional anisotropy; IFOF = inferior fronto-occipital fasciculus; ILF = right inferior longitudinal fasciculus; L. Ant. Thal. = left anterior thalamic radiation; PGA = patients with on-line game addiction; R. Corticosp = right corticospinal tract; RD = radial diffusivity.