Chapter 3
Structural Brain Imaging and Internet Addiction

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Abstract In recent years, neuroimaging techniques have increasingly been used to study Internet addiction disorder (IAD), with the aim of identifying functional and structural changes in the brain, which may constitute the neurological/psychiatric causes of IAD. This chapter reviews current neuroimaging findings concerning brain structural changes associated with IAD. To aid readers in understanding these findings, the commonly used structural imaging methodologies—primarily, magnetic resonance imaging (MRI)—are also outlined. The literature review clearly demonstrates that IAD is associated with neuroanatomical changes involving prefrontal cortex, thalamus, and other brain regions. At least some of these changes appear to correlate with behavioral assessments of IAD. More importantly, these data suggest that the pattern of IAD-related structural differences in the brain resemble, to some extent, those changes observed in substance addiction.

3.1 Introduction

Internet addiction disorder (IAD) was originally proposed as a mental disorder in a satirical hoax by Ivan Goldberg in 1995. It commonly refers to one's inability to control his or her urge to be online, resulting in uncontrolled use of the Internet and adverse consequences in life, such as marked distress, impaired social interaction, and loss of educational/occupational interests (Aboujaoude 2010; Douglas et al. 2008; Kuss et al. 2013). IAD, or pathological Internet use, may be caused by a spectrum of online activities including gaming, shopping, gambling, viewing pornography, and social networking. Clinical studies have demonstrated that subjects with uncontrolled use of the Internet, not only share core symptoms with

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substance addiction such as tolerance, withdrawal symptoms and relapse (Beard and Wolf 2001; Young 1998), but also frequently have psychiatric comorbidity, including attention deficit/hyperactivity disorder, anxiety disorders, sleep disorders, and obsessive-compulsiveness (Bernardi and Pallanti 2009; Ko et al. 2012; Yen et al. 2007).

Although the concept of IAD is well received by the general public and has attracted extensive popular media coverage, controversy exists among the scientific community regarding whether IAD constitutes a standalone illness (Chakraborty et al. 2010; Morahan-Martin 2005). Currently, IAD is not officially recognized as a psychiatric disorder in most parts of the world. In the newly released Diagnostic and Statistical Manual of Mental Disorders Edition V (DSM-V), Internet gaming disorder, which constitutes a major subtype of IAD, is listed as one of the "conditions for further study" (http://www.dsm5.org/Pages/Default.aspx).

With reference to the criteria defining pathological gambling and substance addiction, psychometric tools have been constructed for IAD assessment, among which the Young's Internet addiction scale (YIAS) (Young 1996) and Young's diagnostic questionnaire for Internet addiction (YDQ) (Young 1998), both developed by Dr. Kimberly Young, are the most widely used. Although discrepancy and controversy still exist around such criteria, they nonetheless provide a common ground for communication and research on IAD, and have been widely used in practice.

As with many other psychiatric disorders, the fiercest debates swirling around IAD concern the problem of defining the condition scientifically. Entering the era of DSM-V, more and more neurologists, psychiatrists, and researchers would agree that defining a psychiatric/mental disorder, such as addiction, solely based on symptomatology (or psychometric assessment) may not be sufficient. More objective biomarkers, such as genetic risk factor, biochemical profile, and functional/structural changes of the brain, need to be uncovered to help achieve better understanding, diagnosis and treatment. Undoubtedly, neuroimaging can play a crucial role in this regard.

Because of their noninvasiveness and capability of providing functional/structural information on the brain in high spatial resolution, neuroimaging approaches, especially magnetic resonance imaging (MRI), have been increasingly used over the last two decades to study the neural mechanisms underlying psychiatric disorders. Through neuroimaging research, many psychiatric disorders originally thought to have no clear anatomical pathology are now known to be associated with functional/structural abnormalities of the brain at the neural circuit/network level. For example, subjects addicted to substances were consistently shown to have prominent functional as well as structural changes in the prefrontal cortex (PFC), and such PFC abnormalities are known to play crucial roles in the development of craving, compulsive use, and relapse (Goldstein and Volkow 2011).

IAD is believed by some to be a form of so-called behavioral addiction, which is expected to share similar neural mechanisms, at least in part, with substance addiction. However, there are also researchers who disagree with this concept;

skeptical about whether non-drug stimuli, such as repetitive, high-frequency and highly rewarding behaviors/experiences, could be potent enough to generate neuroadapation similar to that found in substance addiction (Holden 2001). One way to settle this disagreement and lead to a better understanding/definition of IAD is to see whether the functional/structural abnormalities known to be associated with substance addiction, as revealed by neuroimaging approaches, are also present in subjects with IAD (as defined by psychometric assessments). In fact, an increasing number of such studies have been done in the past few years. In this chapter, we shall focus on neuroimaging findings on the brain structural abnormalities associated with IAD. Literature results are reviewed, and the implications of the findings are discussed.

3.2 Methodologies for Assessing Structural Changes of the Brain

3.2.1 Three-Dimensional Anatomical MRI

Among the existing neuroimaging approaches, MRI is probably the most powerful and widely used for assessing structural changes of the brain. Three-dimensional (3D) T_1-weighted imaging (T_1WI) is the most commonly used technique for anatomical MRI, because it is fast in terms of acquisition speed, and is capable of providing high-resolution images with clear contrast among gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Moreover, 3D acquisition enables reconstruction of brain slices in any arbitrary orientation. With the state-of-art technology, a 3D-T_1WI dataset covering the whole human brain can be acquired in less than 10 min on the 3 T clinical scanners with an isotropic spatial resolution of 0.5 mm. With different image processing methods, volumetric and morphormetric measures could be derived from the whole-brain 3D-T_1WI dataset, and such measures are often used to assess structural changes of the brain.

3.2.1.1 Volumetric Analysis

First, the 3D-T_1WI dataset can be used for quantitative volumetric analysis of the whole brain as well as any given brain structure of interest. To measure the volume of the whole brain, the non-brain voxels on the images are removed either manually or automatically using special algorithms. The number of brain voxels can then be counted and used to derive the volume of the whole brain. To derive the volume of a given brain structure, a region-of-interest (ROI) representing the structure under concern is delineated, usually manually and with reference to the landmarks on the images, and the number of voxels in the ROI can then be counted and used to derive the volume. An atlas is often needed to guide the delineation of the ROI. For

example, Makris et al. (2008b) used this method to found out that long-term alcohol users had significantly decreased reward-network (i.e., dorsolateral PFC (dlPFC) and insula) volume than normal controls. However, this method can be laborious, and the results are susceptible to objective bias and cross-subject variations in how the ROI is delineated.

3.2.1.2 Voxel-Based Morphometry

Voxel-based morphometry (VBM) is an unbiased objective technique developed to characterize subtle structural changes in the whole brain, without the need of any a prior knowledge (Ashburner and Friston 2000). The aim of VBM is to identify differences in the local composition of GM and WM at the group level. VBM involves spatially normalizing the anatomical imaging data from individual subjects into the same stereotactic space, segmenting the individual normalized images into GM/WM/CSF compartments, smoothing the segmented images spatially, and performing voxel-wise statistical analyses to localize significant inter-group differences. The output of VBM is a statistical parametric map showing brain regions where GM/WM composition differs significantly at the group level (Ashburner and Friston 2000).

GM (or WM) density and GM (or WM) volume are two frequently used measures of tissue composition in VBM analysis. Although the two are related to each other, they differ conceptually. Within a voxel on the spatially normalized images or an ROI, GM/WM density means the relative concentration of GM/WM tissue (i.e., the proportion of GM/WM to all tissue types), while GM/WM volume means the absolute GM/WM volume. Comparing GM/WM volume within the framework of VBM involves multiplying the spatially normalized GM/WM density by its Jacobian determinants derived from deformation flow information (Mechelli et al. 2005).

VBM analysis has been widely used in neuroimaging studies of addiction (Barros-Loscertales et al. 2011; Liao et al. 2012; Liu et al. 2009; Makris et al. 2008b; Schwartz et al. 2010). Such studies consistently show that subjects who are dependent on stimulant drugs have significantly reduced GM volume in the PFC (Ersche et al. 2013).

3.2.1.3 Cortical Thickness Measurement

In addition to volumetric measures and regional composition of GM/WM, 3D-T_1WI dataset can also be used to derive cortical thickness, a computational neuroanatomy measure defined as the distances between the pial surface (i.e., surface between the cortical GM and CSF) and the interface separating the cortical GM and WM underneath (MacDonald et al. 2000). Measuring cortical thickness involves segmenting the anatomical images into GM/WM/CSF compartments for each individual subject, reconstructing the individual GM/WM surfaces and pial

surface, computing individual cortical thickness, registering the surface-based coordinate system of each individual subject into the same stereotactic space, spatial smoothing, and performing voxel-wise statistics to detect morphometric variations at the group level.

Figure 3.1 explains graphically the steps to measure cortical thickness from the 3D anatomical image data. Cortical thickness is thought to be related to the size, density, and arrangement of cortical cells (MacDonald et al. 2000), and has been shown to change only minimally with brain size and sex (Sowell et al. 2007). Typical cortical thickness values in adult humans are between 1.5 and 3 mm (Salat et al. 2004). Cortical thickness has been used to investigate structural changes of the cortices associated with neurodevelopment and brain diseases. During aging, a decrease (also known as cortical thinning) on the order of about 10 μm per year has been observed (Salat et al. 2004). Cocaine-dependent subjects are known to have lower cortical thicknesses in brain regions involved in executive regulation of reward and attention (Makris et al. 2008a).

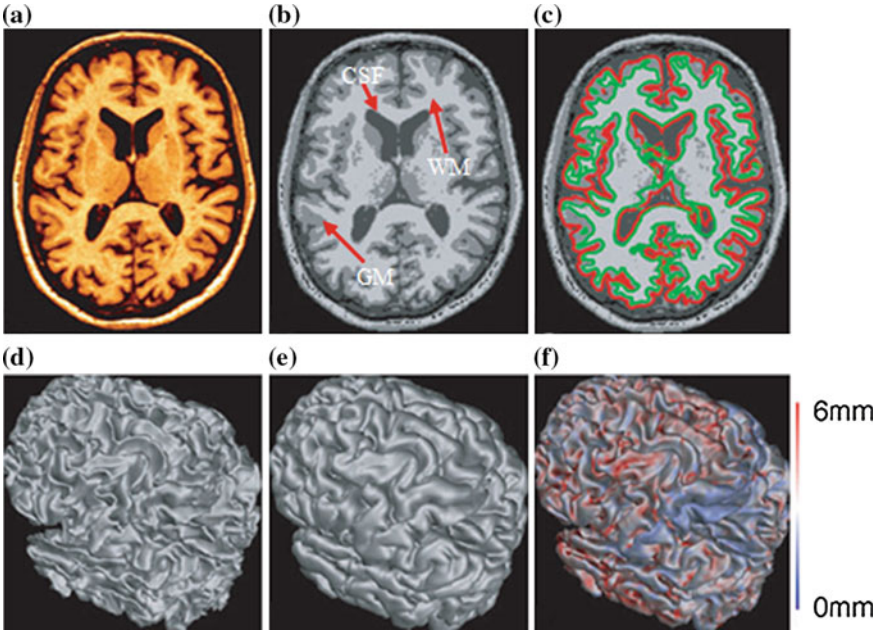

Fig. 3.1 Segmentation and cortical thickness analysis of anatomical images. The raw anatomical images were first corrected for signal intensity nonuniformity and registered into a reference stereotaxic space (**a**), and then segmented into gray matter (*GM*), white matter (*WM*) and cerebrospinal fluid (*CSF*) compartments (**b**). The inner (*green lines* in **c**) and outer (*red lines* in **c**) GM surfaces can then be extracted and fitted into three-dimensional maps using deformable models. Panel **d** shows the resultant inner GM surface, and panel **e** shows the outer GM surface. At a given coordinate in the reference stereotaxic space, cortical thickness is defined as the distance between these two surfaces (**f**). This figure is adapted from a figure from the paper by Lerch et al. (2005) with permission

3.2.2 *Diffusion Tensor Imaging*

Diffusion tensor imaging (DTI) is a noninvasive MRI technique that measures the diffusion properties of water molecules in vivo (Basser et al. 1994a, b; Le Bihan 2003; Pierpaoli et al. 1996). The diffusion of water molecules in a homogenous compartment, such as CSF, is isotropic, and can be characterized simply by a single diffusion coefficient. However, in biological tissues, the diffusion of water molecules is subject to restriction imposed by the microstructural organization of the tissue (e.g., membranes and other biological barriers). For instance, in the WM fibers, the water molecules would diffuse more quickly along the fibers than perpendicular to the fibers. As a result, more complicated models need to be used to characterize the anisotropic diffusion properties of water molecules in the biological tissues.

In DTI, the diffusion behaviors of water molecules are modeled by a zero mean Gaussian distribution, which is fully represented by a second-order diffusion tensor (Basser et al. 1994a, b; Pierpaoli et al. 1996). After measuring the diffusion tensor experimentally, parameterized diffusion indices, such as fractional anisotropy (FA), can be computed (Basser and Pierpaoli 1996). FA is a scalar value between zero and one that describes the degree of anisotropy of a diffusion process. A value of zero represents that the diffusion is isotropic (i.e., it is unrestricted or equally restricted in all directions). A value of one represents that the diffusion occurs only along one axis, and is fully restricted along all the other directions.

Measuring the diffusion indices of water molecules along different directions and the overall anisotropy with DTI may provide important information on the microstructural organization of the underlying tissue (Le Bihan 2003). For example, the FA value of a WM tract is thought to be closely related to fiber density, axonal diameter and myelination, thus often being used as a surrogate for the assessing the microstructural integrity of WM. It has been demonstrated that diffusion indices obtained from DTI can be used to detect tissue microstructural changes that might not be visible with the conventional MRI techniques (Basser et al. 1994a, b; Pierpaoli et al. 1996). Nowadays, DTI has become a widely used tool for revealing the tissue abnormalities associated with neurological/psychiatric diseases. Figure 3.2 shows representative DTI data that are commonly used in the studies on disease-related brain structural changes.

3.2.2.1 Voxel-Based Analysis

Voxel-based analysis (VBA) is an observer-independent voxel-wise analysis method for diffusion indices derived from the DTI data, which can circumvent the problems associated with the more traditional ROI analysis (Jones et al. 2005). The aim of VBA is to assess regional alterations of diffusion indices between groups. VBA includes spatially normalizing the maps of diffusion indices from individual subjects into a standard stereotactic space, smoothing the normalized maps, and

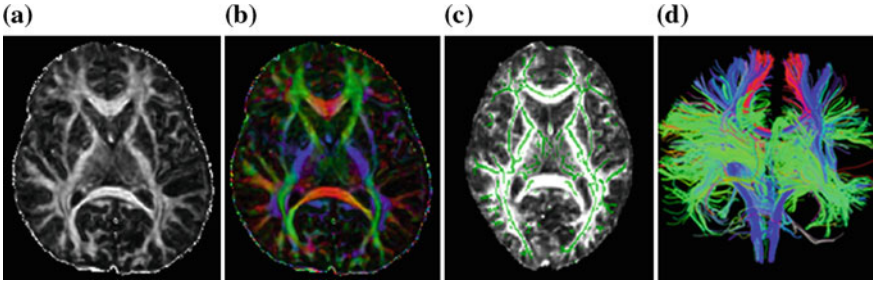

Fig. 3.2 Diffusion tensor imaging (*DTI*) and data analysis. With images acquired with diffusion-weighted gradients applied along different directions and a tensor model, fractional anisotropy (*FA*) maps (**a**), corresponding FA-weighted color directional diffusion maps (**b**), FA skeleton maps (**c**) can be calculated. Whole-brain tractography (**d**) can be performed. The data in **a**–**d** are from the same normal subject

performing voxel-by-voxel statistical comparisons to determine significant inter-group differences. With VBA, the whole brain is tested for control-patient differences without any a priori hypothesis on where the abnormalities should be. The output of VBA is a statistical parametric map showing brain regions where diffusion indices differ significantly at the group level.

3.2.2.2 Tract-Based Spatial Statistics

Tract-based Spatial Statistics (TBSS) is another observer-independent voxel-wise method for analyzing whole-brain DTI data (Smith et al. 2006). TBSS involves co-registering the FA maps from all individuals included in the study, to a standard stereotactic space, averaging the co-registered individual FA maps to create a mean FA map, thinning the mean FA map to obtain a mean FA skeleton, projecting co-registered individual FA maps onto the mean FA skeleton to create a skeletonized FA map, and finally performing voxel-wise statistics across subjects on the skeletonized FA data. TBSS retains the strengths of VBA while addressing some of its drawbacks, such as the arbitrariness of the choice of spatial smoothing.

3.2.2.3 Tractography-Based Analysis

DTI data can also be used to trace WM tracts by performing tractography according to the principal directions of neighboring diffusion tensors. The main feature of DTI tractography is that it can be used to reconstruct WM pathways in vivo, and provide information about the shape, location, and topology of fiber tracts as well as anatomical connectivity between distant brain areas (Basser et al. 2000; Conturo et al. 1999; Mori et al. 1999). Tractography is a useful tool for measuring WM deficits, and has been applied in a wide range of clinical and basic studies

(Dell'Acqua and Catani 2012). In tractography-based analysis, the fiber tract under concern is first reconstructed using fiber tracking algorithms, and the diffusion indices of the tract can then be analyzed by considering the fiber tract as a 3D ROI (McIntosh et al. 2008) or by parameterizing the fiber tract (Lin et al. 2006).

3.3 Brain Structural Abnormalities Associated with IAD

Unlike the case for substance addiction, only a limited number of structural neuroimaging studies have been performed on IAD so far, mostly by Chinese and Korean researchers. Table 3.1 lists all the structural neuroimaging studies on IAD that can be found in the literature, and summarizes the major findings from these studies. We shall also give a brief review of these results in Table 3.1.

3.3.1 Results from Anatomical MRI

3.3.1.1 VBM Analysis

Zhou et al. (2011) were among the first to use a neuroimaging approach to assess structural abnormalities in the brain associated with IAD. They acquired 3D-T_1WI data from 18 adolescents (i.e., 17.2 ± 2.6 years) who were considered to be addicted to the Internet based on the criteria of the modified eight-item YDQ (Beard and Wolf 2001), and 15 age- and gender-matched healthy controls. VBM analysis was used to compare regional GM density (GMD) between the two groups. It was reported that the IAD group had significantly reduced GMD in the left anterior cingulate cortex (ACC), left posterior cingulate cortex (PCC), left insula and left lingual gyrus. The major online activities of the IAD subjects were not specified in this study.

There have been three studies that investigated structural abnormalities in the brain of adolescent/young subjects (i.e., 16–21 years) who were specifically addicted to online games (Han et al. 2012; Weng et al. 2013; Yuan et al. 2011). YDQ or YIAS was used in these studies to screen for online game addiction (OGA). Additionally, it was confirmed that playing online game was the primary activity for the addicted subjects when they used the Internet (i.e., on average around 10 h of online game playing per day). Two studies showed similar results in that, compared to normal controls, the subjects with OGA had significantly reduced GM volume (GMV) in the orbitofrontal cortex (OFC) and supplementary motor area (SMA). OGA was also found to be associated with reduced GMV in the left rostral ACC (rACC), bilateral dlPFC, and cerebellum by Yuan et al. (2011); and with reduced GMV in the bilateral insula by Weng et al. (2013). In contrast to the observations in these two studies, Han et al. (2012) reported that the subjects with OGA had reduced GMV in the bilateral inferior temporal gyri, right middle

Table 3.1 A summary of the structural brain imaging studies on Internet addiction disorder (IAD) available so far

Studies	Subjects	Diagnosis criteria	Methodology	Main results
Zhou et al. (2011)	18 addicts (16 M/2F),17.2 ± 2.6 years old 15 controls (13 M/2F), 17.8 ± 2.5 years old	Modified young diagnostic questionnaire for internet addiction by Beard and Wolf (MYDQ)	Scanner: 3.0T Philips Achieva Acquisition: three-dimensional (3D) T_1-weighted anatomical imaging Analysis: Voxel-based morphometry (VBM) to assess gray matter density (GMD)	Compared to the controls, the addicts showed decreased gray matter density (GMD) in: Left anterior cingulate cortex (ACC) Left posterior cingulate cortex (PCC) Left insula Left lingual gyrus
Yuan et al. (2011)	18 addicts (12 M/6F), 19.4 ± 3.1 years old 18 controls (12 M/6F), 19.5 ± 2.8 years old	MYDQ Self-rating anxiety scale and the self-rating depression scale Subjects pending 19.4 ± 3.1 h per day playing online games	Scanner: 3.0T Siemens Allegra Acquisition: 3D T_1-weighted anatomical imaging + diffusion tensor imaging (DTI) Analysis: VBM to assess gray matter volume (GMV) + tract-based spatial statistics (TBSS)	Compared to the controls, the addicts showed decreased gray matter volume (GMV) in: Bilateral orbitofrontal cortex (OFC) Bilateral supplementary motor area (SMA) Bilateral dorsolateral prefrontal cortex (dlPFC) Left rostral ACC (rACC) Cerebellum and reduced fractional anisotropy (FA) in: White matter within the right parahippocampal gyrus and increased FA in: Left posterior limb of the internal capsule (PLIC) GMVs of the right dlPFC, left rACC, and right SMA in the addicts correlated negatively with the duration of addiction FA of the left PLIC correlated positively with the duration of addiction

(continued)

Table 3.1 (continued)

Studies	Subjects	Diagnosis criteria	Methodology	Main results
Dong et al. (2012)	16 addicts (16 M/0F), 22.2 ± 3.3 years old 15 control (15 M/0F), 21.6 ± 2.6 years old	Young's online internet addiction test Structured psychiatric interviews (M.I.N.I.) Subjects spending > 80% online time playing online games	Scanner: 3T Siemens Trio Acquisition: DTI Analysis: TBSS	Compared with the controls, the addicts showed increased FA in: Bilateral thalamus Left PCC Thalamic FA in the addicts correlated positively with Internet addiction severity scores
Han et al. (2012)	20 addicts (20 M/0F), 20.9 ± 2.0 years old 17 professional gamers (PG) who were not addicted (17 M/0F), 20.8 ± 1.5 years old 18 controls (18 M/0F), 20.9 ± 2.1 years old	Young's internet addiction scale (YIAS) Structured clinical interview for DSM-IV and the beck depression inventory Subjects spending > 4 h per day/30 h per week playing online games	Scanner: 1.5 T Siemens Espree Acquisition: 3D T_1-weighted anatomical imaging Analysis: VBM to assess changes in GMV	Compared to the controls, the addicts showed increased GMV in: Left thalamus and decreased GMV in: Bilateral inferior temporal gyri Right middle occipital gyrus Left inferior occipital gyrus Compared to the PG who were not addicted, the addicts showed increased GMV in: Left thalamus and decreased GMV in: Left cingulate gyrus (CG) GMV of the left CG in the addicts correlated negatively with the YIAS scores and Barratt Impulsiveness Scale total scores GMV of the thalamus in the addicts correlated positively with the YIAS scores

(continued)

Table 3.1 (continued)

Studies	Subjects	Diagnosis criteria	Methodology	Main results
Lin et al. (2012)	17 addicts (15 M/2F), 17.0 ± 2.5 years old 16 controls (14 M/2F), 17.8 ± 2.5 years old	MYDQ Mini international neuropsychiatric interview for children and adolescents	Scanner: 3.0 T Phillips Achieva Acquisition: DTI Analysis: TBSS	Compared to the controls, the addicts showed decreased FA in: Bilateral orbitofrontal white matter Genu of corpus callosum (CC) Bilateral anterior cingulum Bilateral inferior fronto-occipital fasciculus Bilateral corona radiation Bilateral anterior limb of internal capsule External capsule (EC) Left precentral gyrus FA of left genu of CC of the addicts correlated negatively with the screen for child anxiety related emotional disorders FA of the left EC of the addicts correlated negatively with the YIAS scores
Hong et al. (2013)	15 addicts (15 M/0F), 13.3 ± 2.8 years old 15 controls (15 M/0F), 15.4 ± 1.2 years old	YIAS Kiddie-schedule for affective disorders and Schizophrenia-present and lifetime version Subjects self-report to have experienced typical components of addiction to online gaming	Scanner: 3T Siemens Trio Acquisition: 3D T_1-weighted anatomical imaging Analysis: cortical thickness	Compared to the controls, the addicts showed decreased cortical thickness in: Right lateral OFC
Weng et al. (2013)	17 (4 M/13F), 16.3 ± 3.0 years old 17 (2 M/15F), 15.5 ± 3.2 years old	MYDQ Playing online game was the primary activity when the addicts used Internet	Scanner: 3.0 T Philips Intera Acquisition: 3D T_1-weighted anatomical imaging + DTI Analysis: VBM to assess GMV + TBSS	Compared to the controls, the addicts showed decreased FA in: Genu of CC Bilateral frontal lobe white matter Right EC and reduced GMV in: Right OFC Bilateral insula

(continued)

Table 3.1 (continued)

Studies	Subjects	Diagnosis criteria	Methodology	Main results
				Right SMA GMVs of the right OFC and bilateral insula correlated negatively with the YIAS scores FA of the right EC correlated negatively with the YIAS scores
Yuan et al. (2013)	18 addicts (12 M/6F), 19.4 ± 3.1 years old 18 controls (12 M/6F), 19.5 ± 2.8 years old	MYDQ	Scanner: 3.0 T Siemens Allegra Acquisition: 3D T_1-weighted anatomical imaging Analysis: cortical thickness	Compared to the controls, the addicts showed decreased cortical thickness in: Left lateral OFC Left insula Left lingual gyrus Right postcentral gyrus Right entorhinal cortex Right inferior parietal cortex and increased cortical thickness in: Left precentral cortex Left precuneus Left middle frontal cortex Left inferior temporal and middle temporal cortices Cortical thicknesses of the left precentral cortex and precuneus in addicts correlated positively with the duration of addiction Cortical thickness of the left lingual gyrus correlated negatively with the duration of addiction

occipital gyrus, and left inferior occipital gyrus, but increased GMV in the left thalamus, compared to the normal controls. They also compared regional GMV between the subjects with OGA and professional gamers who were not addicted, and found significantly lower left cingulate gyrus GMV in the addiction group (Han et al. 2012).

3.3.1.2 Cortical Thickness Analysis

There have been two studies performed so far to assess the OGA-related abnormalities in cortical thickness. Yuan et al. (2013) showed that, compared to normal controls, subjects with OGA in late adolescence had increased cortical thickness in the left precentral cortex, precuneus, middle frontal cortex, inferior temporal and middle temporal cortices, and decreased cortical thickness in the left lateral OFC, insula, lingual gyrus, right postcentral gyrus, entorhinal cortex, and inferior parietal cortex. Hong et al. (2013) reported decreased cortical thickness in the right lateral OFC of male adolescents who were addicted to online gaming.

3.3.2 Results from DTI

Yuan and colleagues were among the first to use DTI to assess WM abnormalities associated with IAD. Their results showed that, relative to normal controls, adolescent college students with OGA were associated with significantly increased FA in the left posterior limb of the internal capsule (PLIC), but reduced FA in the WM within right parahippocampal gyrus (Yuan et al. 2011). Higher FA in the bilateral thalamus and left PCC were also reported in the subjects with OGA (Dong et al. 2012).

With the same IAD and control subjects as those reported in the study by Zhou et al. (2011), Lin et al. (2012) reported that IAD is associated with reduced FA in the orbitofrontal WM, corpus callosum (CC), cingulum, inferior front-occipital fasciculus, corona radiation, anterior limb of the internal capsule (ALIC), and external capsule (EC). These findings were largely reproduced in a subsequent study conducted by Weng et al. (2013), showing that adolescents with OGA had decreased FA in the right genu of CC, bilateral frontal WM and right EC, as compared to normal controls.

3.3.3 Correlations Between Brain Structural Alterations and Behavioral Assessments

Some of the studies also assessed the correlations between brain structural alterations and behavioral assessments in Internet addicts. For example, two studies on

OGA showed consistently that the GMV of left CG, right OFC and bilateral insula correlated negatively with the YIAS scores and Barratt impulsiveness scale total scores; while GMV of the left thalamus correlated positively with the YIAS scores (Han et al. 2012; Weng et al. 2013). The studies of Yuan et al. (2011, 2013) on OGA showed that the GMV in right dlPFC, left rACC and right SMA, and the cortical thickness of left lingual gyrus correlated negatively with the duration of Internet addiction. Positive correlation between the cortical thickness of the left precentral cortex and precuneus and the duration of Internet addition was also reported (Yuan et al. 2013).

DTI studies revealed that the addicted subjects had a negative correlation between FA in the EC and YIAS scores (Lin et al. 2012; Weng et al. 2013), and positive correlations between FA in the thalamus and YIAS cores (Dong et al. 2012). A positive correlation between FA of the left PLIC and the duration of Internet addiction was also reported (Yuan et al. 2011). Additionally, Lin et al. (2012) reported a negative correlation between FA of the left genu of CC and the Screen for Child Anxiety Related Emotional Disorders scores.

3.3.4 Synopsis of Structural Abnormalities Associated with IAD/OGA

The structural neuroimaging results summarized in Sects. 3.3.1–3.3.3 consistently demonstrate that IAD and/or OGA is associated with structural abnormalities in the brain, although the exact pattern and characteristics of the abnormalities may appear to vary from study to study. The most consistent findings from the studies available so far are atrophy in the PFC (i.e., OFC, ACC, and dlPFC) and insula. Almost all the studies demonstrate reduced GMD, GMV, or cortical thickness in these two regions, and such changes also appear to be correlated with either the YIAS scores or the duration of Internet addiction.

Thalamus is another brain region frequently reported to show structural abnormalities in subjects with IAD/OGA. But unlike the case for PFC and insula, the findings for thalamus appeared to be less consistent. Increased thalamic GMV and FA have been reported in IAD/OGA, and the increase in thalamic FA was shown to correlate positively with the YIAS scores (Dong et al. 2012; Han et al. 2012). On the other hand, although no structural changes in the thalamus was reported in the paper by Zhou et al. (2011), a trend toward decreased GMD in the bilateral anterior thalamus was found for the subjects with IAD (Fig. 3.3).

Other brain regions found to demonstrate structural changes were mainly visual-related (i.e., occipital gyrus, inferior temporal gyrus, and lingual gyrus) and sensory/motor-related (i.e., SMA, precentral/postcentral cortex, and cerebrullum) areas. DTI abnormalities associated with IAD/OGA were found to be predominately located in or along the WM tracts connecting to PFC and thalamus, such as the genu of the CC, ALIC, EC, and cingulum.

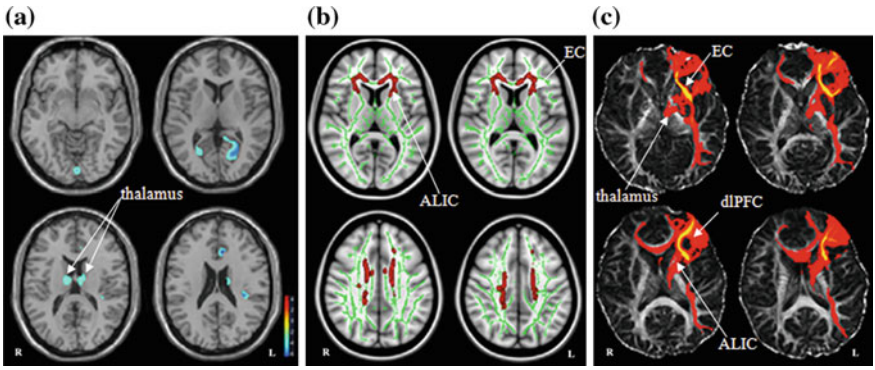

Fig. 3.3 Structural abnormalities associated with Internet addiction disorder (*IAD*) as revealed by voxel-based morphometry (*VBM*) and tract-based spatial statistics (*TBSS*). The data shown in this figure are from the same cohort of subjects reported in the papers by Zhou et al. (2011) and Lin et al. (2012), but analyzed in different ways. Panel **a** shows the brain regions with significantly ($p < 0.001$, uncorrected; voxel size > 200) decreased gray matter density (*GMD*) in IAD subjects, as compared to normal controls. In addition to the regions reported in the original VBM paper (Zhou et al. 2011), decreased GMD was found in the *left* (−14, −9, 19; 822 voxels) and right (10, −7, 14; 962 voxels) anterior thalamus. Please note that a different statistical threshold ($p < 0.05$, with FDR correction) was used in the original paper (Zhou et al. 2011). Panel **b** shows the white matter (*WM*) tracts with abnormal microstructural integrity in IAD subjects. This figure is adapted from Fig. 3.1 of the original DTI paper (Lin et al. 2012). Panel **c** shows the results of probabilistic tractography using the segment of external capsule (*EC*) showing IAD-related FA reduction as the seed. Interestingly, the IAD-related atrophic brain regions revealed by VBM are interconnected via WM tracts showing compromised microstructural integrity. For example, the atrophic thalamus and insula are interconnected to dorsolateral prefrontal cortex (*dlPFC*) via EC and anterior limb of the internal capsule (*ALIC*)

3.3.5 *Comparisons with Brain Structural Abnormalities in Substance Addiction and Pathological Gambling*

Abnormal GMD/GMV in the prefrontal regions (i.e., OFC, ACC, and dlPFC), insula, and thalamus are common findings in smokers (Zhang et al. 2011), heroin-dependent individuals (Yuan et al. 2010), alcoholics (Makris et al. 2008b), opiate-dependent subjects (Lyoo et al. 2006), methamphetamine abusers (Kim et al. 2006) and cocaine-dependent subjects (Franklin et al. 2002). Impaired WM integrity in the orbitofrontal regions, CC, cingulum, ALIC, EC, and corona radiation are also frequently reported in subjects exposed to addictive substances, such as alcohol (De Bellis et al. 2008), cocaine (Lim et al. 2002, 2008; Romero et al. 2010), marijuana (Bava et al. 2009), heroin (Liu et al. 2008), ketamine (Liao et al. 2010), methamphetamine (Alicata et al. 2009; Salo et al. 2009), opiate (Bora et al. 2012; Upadhyay et al. 2010), and tobacco (Lin et al. 2013). Interestingly, we found that the pattern of WM microstructural abnormality in IAD largely resembles that

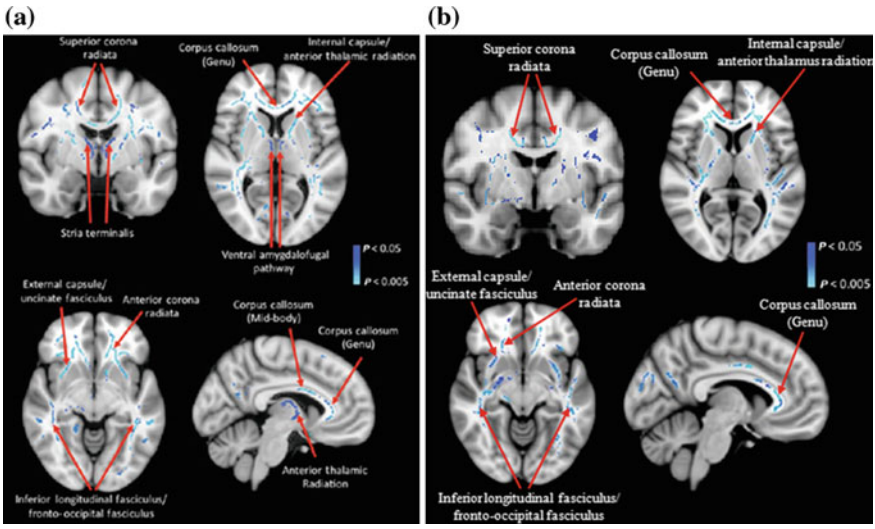

Fig. 3.4 Comparisons between the pattern of abnormal white matter integrity in Internet addiction and that in opiate addiction. The figure in panel **a** is adapted from the paper by Upadhyay et al. (2010) with permission, showing white matter tracts whose fractional anisotropy (*FA*) values were significantly ($p < 0.05$, corrected by cluster-based thresholding with $c > 3$) reduced in opiate addicts ($n = 10$), relative to normal controls ($n = 10$). The figure in panel **b** is modified from Fig. 3.1 of the paper by Lin et al. (2012). This figure is drawn in such a way that it can be directly compared with the figure shown in panel **a** by visual inspection. In this figure, the significance statistical threshold was set to $p < 0.05$ with threshold-free cluster enhancement (*TFCE*) correction. Please note that a different statistical threshold of $p < 0.01$, with TFCE correction, was used in the original paper (Lin et al. 2012). It can be seen from the figure that both the subjects with IAD and those with opiate addiction exhibited impaired microstructural integrity in the white matter tracts connecting to the prefrontal cortex, such as the genu of corpus callosum, cingulum, corona radiate, internal and external capsules. However, reduced FA in stria terminalis and ventral amygdalofugal pathway was observed only in opiate addicts, but not in subjects addicted to the Internet. These findings demonstrate that Internet addiction may, at least to some extent, share similar neural mechanisms with substance addiction

which has been observed in opiate addicts (Fig. 3.4), indicating that Internet addiction may, at least in part, share similar neural mechanisms with other types of substance addiction.

Neuroimaging approaches have also been used to study brain structural changes associated with pathological gambling, a condition originally considered an impulsive-compulsive disorder, but now classified as "addictions and related disorders" in DSM-V (http://www.dsm5.org/Pages/Default.aspx). In subjects with pathological gambling, impaired WM microstructural integrity (i.e., lower FA) was found in the genu of CC, cingulum, ALIC, inferior fronto-occipital fascicle, and anterior thalamic radiation (Joutsa et al. 2011). However, no volumetric differences in regional GM or WM were observed between pathological gamblers and normal controls (van Holst et al. 2012).

It therefore appears that IAD/OGA, substance addiction, and pathological gambling are associated with, to some extent, similar structural abnormalities in the brain, which may constitute a neural signature for the three forms of addiction.

3.4 Implications of Brain Structural Abnormalities in Internet Addiction

Overall, Internet addicts appear to have impaired microstructural integrity in the WM tracts involved in the neural circuits underlying emotion generation and processing, executive attention, decision-making, and cognitive control. From the research on substance addiction, we now know that the insula and PFC play crucial roles in addiction. The insula is a brain region that integrates interoceptive states into conscious feelings, and contributes mainly to the motivation or urge to use drugs and to decision-making processes that precipitate relapse (Naqvi and Bechara 2009). Among the complex functions of PFC, one of the most important ones, perhaps, is executive control, such as planning, prioritizing, organizing, and emotion processing (Chan et al. 2008). It is generally accepted that PFC abnormalities are central to the addiction-related behaviors related to executive dysfunction, including maladaptive decision-making and compulsive-repetitive behaviors (Goldstein and Volkow 2011). Subjects with IAD not only show symptoms such as craving and relapse, but also are known to have impaired abilities in impulse control (Whang et al. 2003). Through neuroimaging approaches, IAD subjects are shown to have structural abnormalities in the PFC, insula, and the WM fibers connecting these two regions to other parts of brain. This may be viewed as evidence in support of the notion that impaired decision-making and executive control are important features of IAD.

Thalamus is a key target for dopamine (Sanchez-Gonzalez et al. 2005) and plays an important role in reward processing, goal-directed behaviors, as well as many other cognitive and motor functions (Corbit et al. 2003; Yu et al. 2010). Altered thalamic microstructure may contribute to the development of Internet addiction by disrupting the acquisition of stimulus-reward associations.

The human visual system is very sensitive to subtle details in movements, even to weakened stimuli such as point-light walkers (Blake and Shiffrar 2007). Excessive exposure to visual stimulation (i.e., computer monitor) may lead to neuroplastic changes in the brain regions related to visual/spatial processing, such as MOG, IOG, ITG, lingular gyrus, PCC, and precuneus. Additionally, Internet addicts spend a tremendous amount of time online and become astonishingly skilled and accurate in mouse clicking and keyboard typing (Kuss and Griffithsemail 2012). Such training/overlearning processes may induce neuroplastic changes in the sensorimotor-related areas.

CC is the largest WM fiber tract connecting the neocortex of the two hemispheres (Delacoste et al. 1985). Reduced FA in the CC of the subjects with IAD may be indicative of alterations in the communication between the two

hemispheres. The ALIC is a key region of frontal-subcortical circuits, providing connections between the thalamus/striatum and frontal cortical regions and comprising a system that plays an important role in reward and emotion processing (Mori et al. 2005). EC connects the ventral and medial prefrontal cortex to the striatum, and is involved in emotion generation and processing (Mori et al. 2005). Impaired WM integrity in the ALIC and EC may thus be indicative of alterations in reward and emotion processing in IAD. The corona radiation links the cerebral cortex to the internal capsule and provides important connections between the frontal, parietal, temporal, and occipital lobes (Wakana et al. 2004). The inferior fronto-occipital fasciculus is an association bundle connecting the frontal with the parietal and occipital lobes (Wakana et al. 2004). Impaired WM microstructure in the corona radiation and inferior fronto-occipital fasciculus is likely to be associated with the abnormal GM density/volumes in cerebral cortex.

3.5 Limitations of Previous Studies

Notwithstanding the insightful results on brain structural changes associated with IAD, a number of limitations in the previous studies need to be observed. First, the diagnosis criteria used for IAD and OGA are somewhat different across studies. This may potentially result in error classification in some cases, and limit the ability to draw direct comparisons among different studies. Second, the structural brain imaging studies on IAD/OGA performed so far all constituted relatively small samples. Owing to this limitation, the results summarized in this chapter should to be considered preliminary, and need to be replicated in future studies with larger sample sizes. Generalization of the findings from the available studies should also be undertaken with caution. Third, previous studies often used cross-sectional designs, such that the question of whether brain structural changes are a consequence or a precondition for IAD/OGA cannot be answered. Finally, IAD may have many subtypes (i.e., OGA) depending on the type of online activity one is addicted to. Further studies should compare the brain structural changes across different IAD subtypes to determine whether such changes are specific to online activities, or caused by uncontrolled use of the Internet per se.

3.6 Summary and Perspectives

Taken together, the structural MRI studies available thus far clearly demonstrated that Internet addiction is associated with anatomical abnormalities in the brain involving both GM and WM. Reduced GM density/volume and cortical thickness are consistently observed in the PFC and insula of the subjects addicted to the Internet, who also showed impaired microstructural integrity in the WM tracts that connect to the PFC. The brain regions showing structural changes in IAD are

known to be involved in reward, emotion generation and processing, executive attention, decision-making, and cognitive control. The pattern of IAD-related structural abnormalities in the brain is also shown to be similar, to some extent, to that observed in substance addiction. It therefore may be concluded that Internet addiction may, at least in part, share similar neural mechanisms with substance addiction and pathological gambling. However, only eight structural brain imaging studies on IAD have been published to date. Further studies, especially longitudinal studies with large sample sizes, are needed to elucidate the exact relationship between uncontrolled use of the Internet and plastic structural changes in the brain.

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