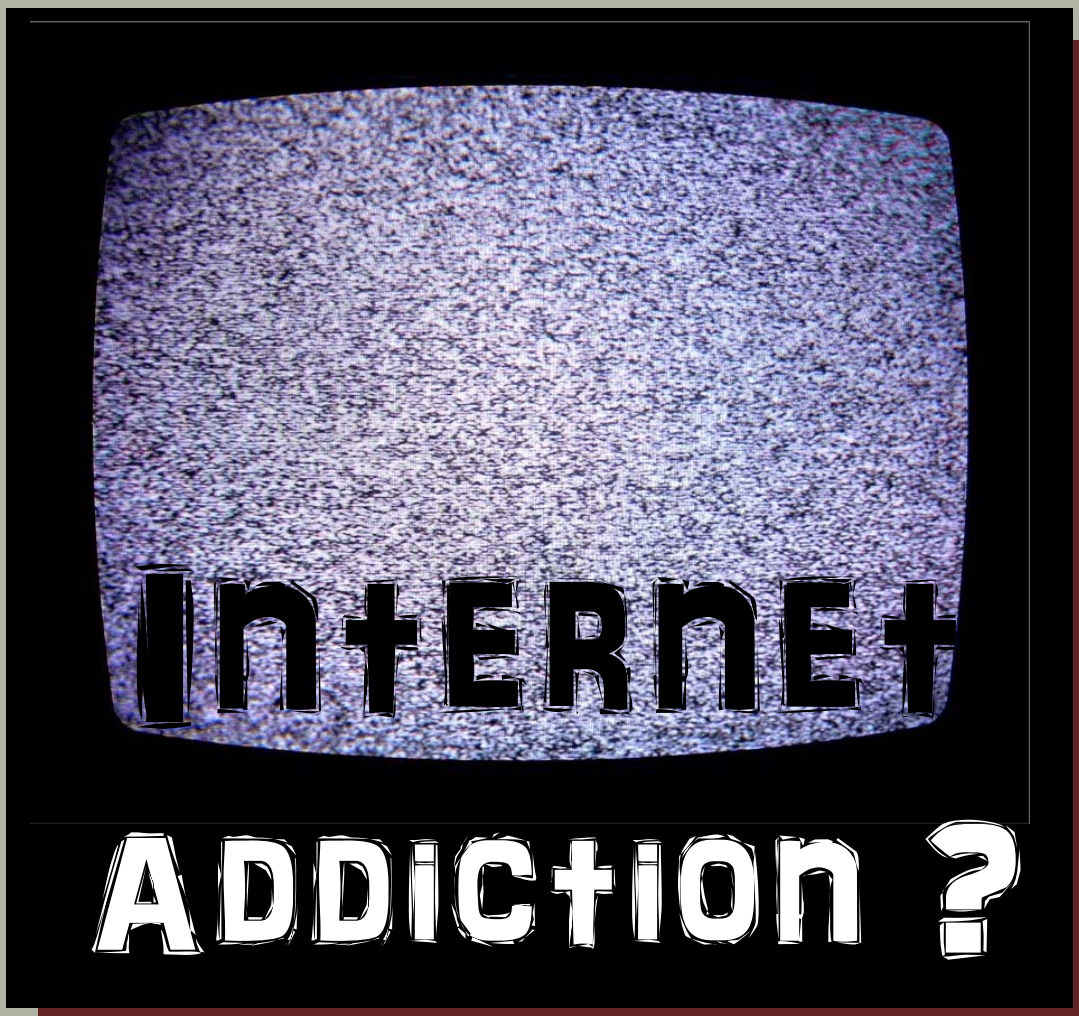
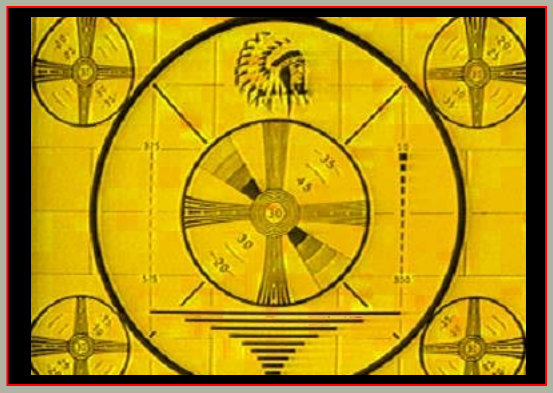


For those of you old enough to remember, the image above depicts “snow” on the TV screen. It appeared when there was no broadcast on any given channel. Turns out that what the television was receiving is the left over signal of the cosmic microwave background radiation; the end result of the “big bang” creation of the universe. It was discovered in 1964 by American radio astronomers Arno Penzias and Robert Wilson and eventually earned them the Nobel Prize in 1978. In retrospect, had they been playing World of Warcraft or multi-tasking while talking to their friends on Facebook, such a discovery might never have been made! And of course you have to be really old to recognize the symbol below.

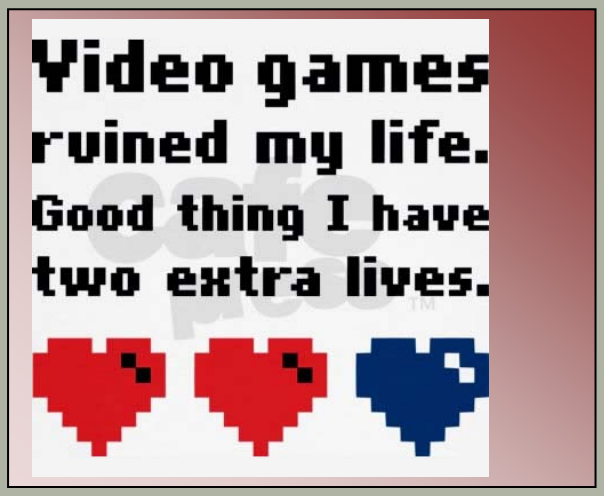


This is what you saw when the station “went off the air.” The broadcast was over for the night. The station usually played the Star Spangled Banner first, then came this symbol, or just plain snow. No more shows. No more talk. Just static.

Not so today. Every form of media in the world is accessible 24 hours a day, 7 days a week, 365 days a year for probably the rest of your life…. So long as there is still electricity and microchips! As such, the internet has become a blessing and a curse for students all around the globe and especially here at IMSA. During our sophomore welcome lecture we talk about how the various activities on the internet have become stress reducers, entertainment and social networking functions for our students. We also mention how these same things have become major time wasters, not just for IMSA students, but for students in general. Many of our kids pride themselves on being multi-taskers: able to write a paper while instant messaging on Facebook or finishing up a problem set for math while video gaming with a group of friends on-line. The question is not really whether or not this internet behavior is a good or bad thing. The question comes down to whether or not it is helpful, efficient or healthy. We find that in many instances the internet is a distraction that absorbs more time than students have to give it. Surfing the web, talking on Facebook or playing video games has become the new procrastination. In the old days we used to stare out into space, bite our pencils or day dream. Now, all we have to do is push keys on a keyboard to get just about anything we can imagine. If we are not careful, hours drift by like sand through an hour glass (Google "hour glass" if you've never seen one) and we can get lost in cyberspace. The funny thing is that a lot of students will tell you that they should spend less time on the computer or on the internet. They already know that it can be a problem and may have been a problem for them in the past, but they continue to use the internet in a way that fosters procrastination and avoidance. Why don't kids just stop? Why don't they just play for an hour rather than for five hours? What is it inside a person that says "I just can't stop?"

There is no formal diagnosis for internet addiction and there is no specialized treatment for people who compulsively use the internet. However, probably everyone knows someone who is "addicted" and spends way too much time on the computer or the X-Box. If you look up "internet addiction" on the internet itself you will get all kinds of conflicting results with not much scientific evidence behind them. And this occurs on both sides of the issue. There are articles that borrow signs and symptoms from other addictive disorders and apply them directly to internet abuse. Other articles poke fun at such a correlation and firmly state that internet addiction does not exist. Still, as you read through these various sources, you get the clear sense that lots of people are having some kind of a problem in controlling the amount of time they spend on the computer and no one really knows why that is. It is assumed that there will always be that small percentage of people who may end up using the internet compulsively, but the

majority of people will use it appropriately…. Except no one can really define what "appropriately" is.



Jane McGonigal, in an article entitled *Video Games: An Hour A Day Is Key To Success in Life* (www.huffingtonpost.com/jane-mcgonigal/video-games) argues that "video games do a better job than ordinary life of provoking our most powerful emotions -- like curiosity, optimism, pride, and a desire to join forces with others to achieve something extraordinary." She insists that computer time and video games are fulfilling genuine human needs that are not being fulfilled by the "real world." She cites a few studies that promote the positive effects of video gaming and claims that playing games up to 21 hours a week can "produce positive impacts on your health and happiness-- especially if you are playing face-to-face with friends and family, or playing cooperative games rather than competitive games." However, the positive effects were very short lived. She considers playing over 28 hours will serve to be more of a distraction. 28 hours?? Even 21 hours is a part-time job! Do we now live in a world where we really believe that spending that much time glued to a computer screen is more enriching and beneficial than real life? The author ends up advocating for playing games at least one hour a day to get a "spill-over effect" that boosts self-confidence in real life. And yes, the author is a video game designer.

In a book entitled Glued to Games (Rigby, Scott & Ryan, Richard. (2011). *Glued to Games: How video games draw us in and hold us spell bound*. New Directions in Media), the authors explore why video games are so compelling to play. Although it is not their intention, one could apply what they have found in their research to a general perspective on why the internet is often over-used by students. (The authors' website is www.gluedtogames.com).

- First and foremost the internet provides ***immediacy***. Everything is readily available. It is there when you need it and you don't have to go anywhere to get it. Students never have to leave their Residence Hall. They don't need a car or a friend to drive them anywhere. They don't have to wait in line at a movie or change their schedule to catch a specific show time. More importantly, there is very little delay in gaining satisfaction. Part of maturing as an adolescent is to develop more frustration tolerance. We have to learn to delay gratification to achieve some higher good or long term goal, like graduating from high school before getting into college. In a world where things are normally frustrating and needs cannot be gratified within a short period of time, the internet fills the need for more immediate satisfaction. This is especially true with two internet favorites: video games and Facebook. They can be accessed by either phone or computer so that the student does not even have to be confined to their room or computer lab to engage in the activity.

- Secondly, the internet provides ***consistency*** in many ways. As the authors point out, "Video games give us clear paths to success and achievement, and treat us fairly. A game doesn't tell us we got passed over for promotion because of office politics or benched during a baseball game unfairly." The same can be said for other forms of internet use. It is consistent in delivering what we want when we want it. Video games are especially good at providing the rewards they promise. They can be counted on time and time again. So internet use can be comforting in a way because it relieves stress by providing some immediate and consistent solace. You can get lost in what you are reading, viewing or playing and delay having to endure frustration in another part of your life.

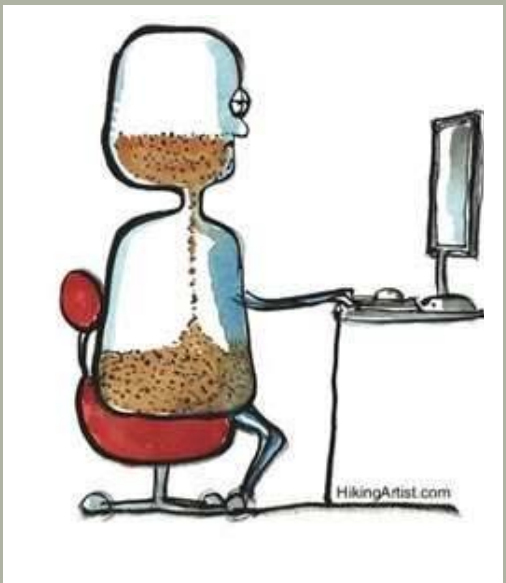
- Finally, a characteristic of internet use that mimics what can be found in video games are what the authors call ***density***. For video games it means that they "provide us with a rich field of opportunities to pursue, activities to undertake, and challenges to conquer." Real life may feel sparse. The games offer a rich field of opportunity that give instant feedback and make us feel effective and even important. Such things come much, much slower in real life. It may take several weeks of listening in class, taking notes, asking questions, doing research, writing outlines, developing a rough draft, and having the teacher proof-read the work before it becomes a final paper to hand in. Then there is the waiting for the final grade. Learning to live and work within that kind of process is how one builds frustration tolerance. It often feels restricting and stressful, but a student has to learn to delay

gratification and channel their frustration into meaningful effort. In some ways, internet use side-steps this process by providing a vast amount of information and entertainment options that are more stimulating and interesting and easier to focus on for long periods of time.

So working or playing on the internet can be a very rich experience that provides many opportunities for learning, entertainment, and social networking. It can also lend itself to compulsive behavior because of the quick access to material, low level of frustration tolerance needed to stay focused, quick rewards (especially in video gaming) and high levels of gratification because there is such a rich and interesting environment to explore. Whether or not someone can become "addicted" is still open to argument in the scientific literature. However, there are compelling references and testimonies on the internet itself that confirm the presence of an addictive quality and how it can influence a student's life in very negative ways. What might be the warning signs of becoming overly-involved with internet use? The warning signs below were taken from a summary article by Rigby and Ryan (http://catholicmom.com/2011/06/16/video-game-addiction-five-warning-signs).

Possible Warning Signs

1) **Do you see a big "satisfaction gap?"** When you think about how needs are satisfied in your "real life" versus on the internet, do gaming and social networking or surfing come out way ahead? Over-involvement on the internet goes hand-in-hand with feeling a lack of basic need satisfactions for competence, autonomy, and relatedness in other areas of life, such as school, work, social relationships, and non-gaming hobbies and activities. People who are not getting these needs filled in their day-to-day interactions are more prone to isolating themselves with on-line activities; either because they lack the social skills necessary to form more meaningful relationships or because they have not experienced a lot of success in initiating and maintaining such relationships. It's just easier to be on-line.
2) **Is your on-line behavior crowding out other important areas of your life?** Do you miss deadlines for assignments or class projects? Do you put off writing papers or doing more difficult assignments by wasting time on the internet? Are you thinking during the day how nice it will be to get back to your room and play video games? Do you know you have a lot of work to do, but you continue to play anyway? Would you rather spend time on-line than take the time to be with people? All of these are warning



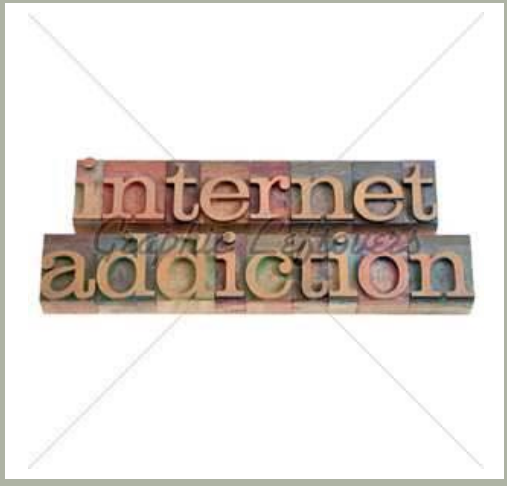
signs in and of themselves. Many of our students fail to hand in work, have extreme difficulty staring larger projects and put off big projects to the last minute. In between time they deal with the anxiety this generates by playing games, watching movies, socializing on the internet, or surfing for interesting information.

3) **Are you feeling personal pressure, guilt or shame around your gaming or other computer activities?** Some students pressure themselves to be on the computer. They feel like they are missing out on something if they do not go on-line. Sometimes they actually feel compelled to play games or do other forms of social networking, even if they don't particularly want to at that moment. It is this pressure that is a warning sign for compulsive behavior. The more students give into the feeling of being compelled to be on-line, the harder it will be to set limits on the behavior. As the compulsion grows, the student may feel a sense of guilt or shame about starting up another game or checking facebook yet again, but will do so anyway despite the negative consequences of having less time to study or neglecting other important parts of their life.
4) **Are you using the internet four or more hours a day for non-academic purposes?** The easiest way to check your own behavior on-line is to keep track of the time you spend on it. Unfortunately, the more time you spend on it the less likely you are to keep track of time. Many of our students lose hours a day checking websites or playing games. A good deal of the stress they feel comes from the pressure of not having enough time to complete all their academic work. Factor in the internet time they are losing and it becomes an uphill battle. Something has to give. The internet has no deadlines, academics do. Part of successful time management in studying involves good time management of on-line behavior.
5) **Is your internet time isolating you from others?** With regard to video games: "if you are immersed in a fantasy world, you aren't in this one." Someone who spends hours on the computer will look tired and

withdrawn. They will have sacrificed time with friends or family for what they were doing on the computer. As this becomes more of a desire and a habit, they become more detached from people in the real world. They don't lose touch with reality. It's just that friends and family activities become less important to them. There is a T-shirt that says "I'd rather be gaming." If that's how you feel, that's a warning sign!

Is there anything you can do?

For people who are suffering from compulsive over-use of the internet, traditional cognitive / behavioral therapy and medication may be used. For now, this is being treated like an addiction similar to gambling. There are physiological components to the compulsion that may be helped by certain antidepressant medications and internet addiction seems to respond well to this. If someone fits the five warning signs, here are some things that can be done to set limits on internet usage:



- Set up some external controls to both monitor and limit your time on the internet. Mac's have a "Self Control" application and Firefox has "Leech Block." Both of these allow the user to enter prescribed amounts of time to be on certain websites. If they exceed the time limits the websites are no longer available.
- Use a simple egg timer. Set it for 45 minutes and dedicate yourself to stopping when the bell goes off. Use the timer along with a written schedule of free time when you can use the internet.
- Ask friends to help you with the goal of limiting your interned time. Let people know that you are struggling with this and need some support.
- Remove any application from your phone or computer that alerts you to new activity on email or social networking sites. Set specific times during the day to check these instead.
- Unplug the internet connection to your computer while working on assignments or turn off the wireless connection until the time you have set aside for internet use arrives.
- Write down your goals for cutting internet use and post them by your computer. You can also post a schedule of when you will use the internet. The external reminders help you remember your commitment to change.

- Spend more time using other forms of relaxation: reading, napping, talking, going outside, and talking with friends.
- Find a new hobby that requires time to learn and practice.
- Exercise is a healthy distraction. Use it instead of the internet to manage anxiety from academic pressures. Using the internet to manage anxiety almost always increases it.
- Reverse the times you normally use the internet. If you get on it right after school, try doing something else and set aside an hour later on. Remember, internet use becomes your routine and the routine can quickly become a habit. Changing times can help break the habit.

Unfortunately, there is no magic to maintaining reasonable internet use. It really is all up to the user. Changing a habit will require admitting that something needs to change, bringing others into the change process, putting external controls in place, asking for help when necessary, setting short term goals and sticking to them. When people say, "I've tried to stop but I can't" what they really mean is they have just stopped using the computer for a specified amount of time without putting anything else in place. For a compulsive behavior it is always better when taking away something to replace it with something else. Just trying to "hold on" and "not do it" usually doesn't work for very long. Of course, when it is apparent that things are really out of control, prolonged periods of abstinence may be the only solution. At that point you may have to get a friend to enter passwords so that you directly cut off your access to the internet. After that you could try using the internet only with supervision. The question that has to be answered is "how bad is it?" and "Can I make a few small changes to help solve the problem?"
The earlier you start this process the better!!

<u>Appendix One:</u> Comprehensive list of Video Gaming Addiction symptoms

<u>Appendix Two</u>: Article on brain changes observed in adolescent video game addicts.

Appendix One: Signs of Video Game Addiction

Psychological Symptoms

- Lowered interest in school achievement
- Feelings of anger and frustration when not allowed access to the video game.
- Feeling depressed or anxious when not playing the game (especially for a prolonged period.
- Thinking about the next gaming session when not online.
- Dreaming about the game
- Experiencing calmness, peacefulness, or euphoria while playing.
- Loss of interest in previously enjoyed activities
- Downplaying the impact of the excessive habits (“It’s not as bad as a drug addiction”)
- Justifying excessive use (“Other people play more than I do”)
- Distorted perception of time (suddenly realizing that several hours have passed in what seemed like just one hour)
- Excessive frustration or anxiety when the serve is down
- Difficulty abstaining from video games for more than a few days
- Feelings of guilt or regret after spending much more time than intended with the game

Physical Symptoms

- Sleep difficulties or significant change in sleep patterns
- Decreased personal hygiene
- Poor or irregular eating habits
- Headaches
- Dry or red dyes
- Sore fingers, neck, or back
- Carpal tunnel syndrome

Behavioral Symptoms

- Decreased academic performance
- Less time spent on homework and studying
- Decreased work performance
- Aggression towards those who prevent or attempt to limit access to the video game

- Frequently playing the game while neglecting important responsibilities
- Spending more and more time with the video game
- Playing at the first available opportunity (as soon as getting home from school)
- An inability to quit despite attempts to do so
- Staying up late into the night to play
- Eating meals while playing or skipping meals entirely
- When not playing, discussing the video game in online forums
- Large amounts of money spent on new games, expansion packs, and computer upgrades.
- Occasional gaming “binges” of 10 or more hours nonstop

Relational Symptoms

- Lying to others about how much time is spent with the game
- Declining social invitations so that game playing can continue
- Less time spent with family and friends
- Increased concern expressed by others at the amount of gaming time
- A loss of real world friends, but an increase in virtual world friends
- Blaming others for the problem

Appendix Two: Article

Microstructure Abnormalities in Adolescents with Internet Addiction Disorder

Background

Recent studies suggest that internet addiction disorder (IAD) is associated with structural abnormalities in brain gray matter. However, few studies have investigated the effects of internet addiction on the microstructural integrity of major neuronal fiber pathways, and almost no studies have assessed the microstructural changes with the duration of internet addiction.

Methodology/Principal Findings

We investigated the morphology of the brain in adolescents with IAD (N = 18) using an optimized voxel-based morphometry (VBM) technique, and studied the white matter fractional anisotropy (FA) changes using the diffusion tensor imaging (DTI) method, linking these brain structural measures to the duration of IAD. We provided evidences demonstrating the multiple structural changes of the brain in IAD subjects. VBM results indicated the decreased gray matter volume in the bilateral dorsolateral prefrontal cortex (DLPFC), the supplementary motor area (SMA), the orbitofrontal cortex (OFC), the cerebellum and the left rostral ACC (rACC). DTI analysis revealed the enhanced FA value of the left posterior limb of the internal capsule (PLIC) and reduced FA value in the white matter within the right parahippocampal gyrus (PHG). Gray matter volumes of the DLPFC, rACC, SMA, and white matter FA changes of the PLIC were significantly correlated with the duration of internet addiction in the adolescents with IAD.

Conclusions

Our results suggested that long-term internet addiction would result in brain structural alterations, which probably contributed to chronic dysfunction in subjects with IAD. The current study may shed further light on the potential brain effects of IAD.

Citation: Yuan K, Qin W, Wang G, Zeng F, Zhao L, et al. (2011) Microstructure Abnormalities in Adolescents with Internet Addiction Disorder. PLoS ONE 6(6): e20708. doi:10.1371/journal.pone.0020708

Editor: Shaolin Yang, University of Illinois at Chicago, United States of America

Received: December 16, 2010; **Accepted:** May 10, 2011; **Published:** June 3, 2011

Funding: This paper is supported by CAS Hundred Talents Program, the National Natural Science Foundation of China under grant nos. 30970774, 60901064, 30873462, 30870685, 81000641, 81000640, 81071217, 31028010, 81071137, the Project for the National Key Basic Research and Development Program (973) under grant nos. 2011CB707700, 2011CB707702, and 863 program under grant no. 2008AA01Z411, the Fundamental Research Funds for the Central Universities. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Introduction

As an important period between childhood and adulthood, adolescence is encompassed by alterations in physical, psychological, and social development [1]. During this developmental stage, more time is spent with peers and adults to face the variant social environment where more conflicts arise [2]. The presence of relatively immature cognitive control [3]–[7], makes this

period a time of vulnerability and adjustment [8] and may lead to a higher incidence of affective disorders and addiction among adolescents [8]–[10]. As one of the common mental health problems amongst Chinese adolescents, internet addiction disorder (IAD) is currently becoming more and more serious [11].

The use of the internet has expanded incredibly across the world over the last few years. The internet provides remote access to others and abundant information in all areas of interest. However, maladaptive use of the internet has resulted in impairment of the individual's psychological well-being, academic failure and reduced work performance [12]–[18]. While not yet officially codified within a psychopathological framework, IAD is growing in prevalence and has attracted the attention of psychiatrists, educators, and the public. The relatively immature cognitive control of the adolescents puts them at a high risk of contracting IAD. Some adolescents cannot control their impulsive use of the internet for novelty seeking and finally become addicted to the internet. Data from the China Youth Internet Association (announcement on February 2, 2010) demonstrated that the incidence rate of internet addiction among Chinese urban youths is about 14%. It is worth noting that the total number is 24 million (http://www.zqwx.youth.cn/).

Numerous IAD studies have been carried out across the world and obtained some interesting findings [11], [15], [19]–[22]. Ko et al. [19] identified the neural substrates of online gaming addiction via evaluation of the brain areas associated with the cue-induced gaming urge, which consisted of the right orbitofrontal cortex (OFC), right nucleus accumbens (NAc), bilateral anterior cingulated cortex (ACC), medial frontal cortex, right dorsolateral prefrontal cortex (DLPFC), and right caudate nucleus. Due to the similarity of the cue-induced craving in substance dependence, they suggested that the gaming urge/craving in online gaming addiction and craving in substance dependence might share the same neurobiological mechanisms. Cao et al. [11] found that Chinese adolescents with IAD exhibited more impulsivity than controls. Recently, Dong et al. [20] investigated response inhibition in people with IAD by recording event-related brain potentials during a Go/NoGo task and showed that the IAD group exhibited a lower NoGo-N2 amplitude, higher NoGo-P3 amplitude, and longer NoGo-P3 peak latency than the normal group. They suggested that the IAD subjects had lower activation in the conflict detection stage than the normal group; thus, they had to engage in more cognitive endeavors to complete the inhibition task in the late stage. In addition, the IAD subjects showed less efficiency in information processing and lower cognitive control [20]. Some researchers also detected gray matter density deficits [21] and resting-state abnormalities [22] in IAD subjects, such as lower gray matter density in the left ACC, left posterior cingulate cortex (PCC), left insula, and left lingual gyrus and increased regional homogeneity (ReHo) in the right cingulate gyrus, bilateral parahippocampus and some other brain regions.

Unfortunately, there is currently no standardized treatment for IAD. Clinics in China have implemented regimented timetables, strict discipline and electric shock treatment, which gained notoriety for these treatment approaches [13]. Developing effective methods for intervention and treatment of IAD will require first establishing a clear understanding of the mechanisms underlying this disease. However, few studies reported the abnormalities of white matter in the adolescents with IAD. Knowledge of the brain abnormalities of gray matter and white matter and association between these abnormalities and cognitive functions in IAD subjects is helpful to

identify possible pharmacotherapies to treat this disorder. Advances in neuroimaging techniques provide us with ideal methods to investigate these issues [23]–[27]. In this study, we investigated the morphology of the brain in adolescents with IAD using an optimized voxel-based morphometry (VBM) technique and studied white matter fractional anisotropy (FA) changes using the diffusion tensor imaging (DTI) method, and linked these brain structural measures to the duration of IAD. We can draw a conclusion from previous IAD studies that the IAD subjects showed impaired cognitive control, and we hypothesized that long-term internet addiction would result in brain structural alterations and these structural abnormalities were associated with functional impairments in cognitive control in IAD subjects [15], [16], [20], [28]. Furthermore, the structural abnormalities of certain brain regions would correlate with the duration of IAD.

Materials and Methods

All research procedures were approved by the West China Hospital Subcommittee on Human Studies and were conducted in accordance with the Declaration of Helsinki.

2.1 Subjects

According to the modified Young Diagnostic Questionnaire for Internet addiction (YDQ) criteria by Beard and Wolf [16], [29], eighteen freshman and sophomore students with IAD (12 males, mean age = 19.4±3.1 years, education 13.4±2.5 years) were engaged in our study. The YDQ criteria [16] consisted of the following eight “yes” or “no” questions which were: (1) Do you feel absorbed in the Internet (remember previous online activity or the desired next online session)? (2) Do you feel satisfied with Internet use if you increase your amount of online time? (3) Have you failed to control, reduce, or quit Internet use repeatedly? (4) Do you feel nervous, temperamental, depressed, or sensitive when trying to reduce or quit Internet use? (5) Do you stay online longer than originally intended? (6) Have you taken the risk of losing a significant relationship, job, educational or career opportunity because of the Internet? (7) Have you lied to your family members, therapist, or others to hide the truth of your involvement with the Internet? (8) Do you use the Internet as a way of escaping from problems or of relieving an anxious mood (e.g., feelings of helplessness, guilty, anxiety, or depression)? All of the eight questions were translated into Chinese. Young asserted that five or more “yes” responses to the eight questions indicated an internet-dependent user [16]. Later on, Beard and Wolf modified the YDQ criteria [29], and respondents who answered “yes” to questions 1 through 5 and at least to any one of the remaining three questions were classified as suffering from internet addiction, which was used for screening the subjects in the present study. The addiction was a gradual process, so we investigated whether or not there were any linear changes in the brain structure. The duration of the disease was estimated via a retrospective diagnosis. We asked the subjects to recall their life-style when they were initially addicted to the internet. To guarantee that they were suffering from internet addiction, we retested them with the YDQ criteria modified by Beard and Wolf. We also confirmed the reliability of the self-reports from the IAD subjects by talking with their parents via telephone. The IAD subjects spent 10.2±2.6 hours per day on online gaming. The days of internet use per week was 6.3±0.5. We also verified this information from the roommates and classmates of the IAD subjects that they often insisted being on the internet late at night, disrupting others' lives despite the consequences. Eighteen age- and gender-matched ($p>0.01$) healthy controls (12 males, mean age = 19.5±2.8 years, education 13.3±2.0 years) with no

personal or family history of psychiatric disorders also participated in our study. According to a previous IAD study [19], we chose healthy controls who spent less than 2 hours per day on the internet. The healthy controls were also tested with the YDQ criteria modified by Beard and Wolf to ensure they were not suffering from IAD. All recruited participants screened were native Chinese speakers, never used illegal substances, and were right-handed. Prior to magnetic resonance imaging (MRI) scanning, urine drug screening was performed on all subjects to exclude substance abuse. Exclusion criteria for both groups were (1) existence of a neurological disorder; (2) alcohol, nicotine or drug abuse; (3) pregnancy or menstrual period in women; and (4) any physical illness such as a brain tumor, hepatitis, or epilepsy as assessed according to clinical evaluations and medical records. Furthermore, the Self-Rating Anxiety Scale (SAS) and the Self-Rating Depression Scale (SDS) were used to evaluate the emotional states of all participants on the day of the scans. All patients and healthy controls gave written informed consent. More detailed demographic information was given in Table 1.

Items	IAD N = 18	Control N = 18	*P* value
Age (years)	19.4±3.1	19.5±2.8	>0.05
Education (years)	13.4±2.5	13.3±2.0	>0.05
Duration of internet addiction (months)	34.8±8.5	N/A	N/A
Hours of internet use (/day)	10.2±2.6	0.8±0.4	**
Days of internet use(/week)	6.3±0.5	1.6±0.8	**
Self-Rating Anxiety Scale	28.8±5.3	27.4±4.8	>0.05
Self-Rating Depression Scale	43.2±8.9	28.5±5.2	*

*: $p<0.05$;
**: $p<0.005$.
doi:10.1371/journal.pone.0020708.t001

2.2 Brain Imaging Methodology and Data Analysis

2.2.1 Scanning parameters.

Imaging data was performed on a 3T Siemens scanner (Allegra; Siemens Medical System) at the Huaxi MR Research Center, West China Hospital of Sichuan University, Chengdu, China. A standard birdcage head coil was used, along with restraining foam pads to minimize head motion and to diminish scanner noise. Image sequences were acquired by means of diffusion weighted imaging with single-shot echo planar imaging in alignment with the anterior–posterior commissural plane. Diffusion tensor images were acquired with 2 averages. The diffusion sensitizing gradients were applied along 30 non-linear directions ($b = 1000$ s/mm^2) together with an acquisition without diffusion weighting ($b = 0$ s/mm^2). The imaging parameters were 45

continuous axial slices with a slice thickness of 3 mm and no gap, field of view = 240×240 mm^2, repetition time/echo time = 6800/93 ms, acquisition matrix = 128×128. In addition, the axial 3D T1-weighted images were obtained with a spoiled gradient recall sequence and the following parameters: TR = 1900 ms; TE = 2.26 ms; flip angle = 9^0; in-plane matrix resolution = 256×256; slices = 176; field of view = 256 mm; voxel size = 1×1×1 mm.

2.2.2 VBM.

Structural data was processed with an FSL-VBM protocol [30], [31] with FSL 4.1 software [32]. First, all T1 images were brain-extracted using the brain extracting tool (BET) [33]. Next, tissue-type segmentation was carried out using FMRIB's automated segmentation tool (FAST) V4.1 [34]. The resulting gray matter partial volume images were then aligned to MNI152 standard space using the FMRIB's linear image registration tool (FLIRT) [35], [36], followed optionally by nonlinear registration using the FMRIB's nonlinear image registration tool (FNIRT) [37], [38], which uses a b-spline representation of the registration warp field [39]. The resulting images were averaged to create a study-specific template, to which the native gray matter images were then non-linearly re-registered. The optimized protocol introduced a modulation for the contraction/enlargement due to the nonlinear component of the transformation: each voxel of the registered gray matter image was divided by the Jacobian of the warp field. Finally, in order to choose the best smoothing kernel, all 32 modulated, normalized gray matter volume images were smoothed with isotropic Gaussian kernels increasing in size (sigma = 2.5, 3, 3.5, and 4 mm, corresponding to a 6, 7, 8, and 9.2 mm FWHM respectively). Regional changes in gray matter were assessed using permutation-based non-parametric testing with 5000 random permutations [40]. Analysis of covariance (ANCOVA) was employed with age, gender effects and total intracranial volume as covariates. Total intracranial volume was calculated as the sum of gray matter, white matter, and cerebrospinal fluid volumes from FSL BET segmentations. Recently, Dong et al. found that depression and anxiety scores were significantly higher after the addiction compared to before the addiction in some college students, and they suggested that these were outcomes of IAD, hence SAS and SDS were not included as confounds [41]. Correction for multiple comparisons was carried out using a cluster-based thresholding method, with an initial cluster forming a threshold at t = 2.0. Results were considered significant for $p<0.05$. For the regions where IAD subjects showed significantly different gray matter volume from the controls, the gray matter volumes of these areas were extracted, averaged and regressed against the duration of internet addiction.

2.2.3 DTI.

We calculated the FA value for each voxel, which reflected the degree of diffusion anisotropy within a voxel (range 0–1, where smaller values indicated more isotropic diffusion and less coherence and large values indicated directional dependence of Brownian motion due to white matter tracts) [42]. FDT software in FSL 4.1 was used for FA calculation [32]. First of all, correction for eddy-currents and head motion was done by means of affine registration on the first no-diffusion weighted volume of each subject. FA images were created by fitting the diffusion tensor to the raw diffusion data after brain extraction using BET [33]. Then, a voxel-wise statistical analysis of the FA data was carried out using the tract-based spatial statistics (TBSS) V1.2 part of FSL [43], [44]. FA imges from all of the subjects (IAD subjects and healthy controls) were realigned into an FMRIB58_FA standard-space image by FNIRT [37], [38] using

a b-spline representation of the registration warp field [39]. The mean FA image was then created and thinned to create a mean FA skeleton (threshold of 0.2) representing the centers of all of the tracts common to the group. Each subject's aligned FA data was then projected back onto this skeleton. White matter FA value changes were assessed using permutation-based non-parametric testing [40] with 5000 random permutations. ANCOVA was employed with age and gender effects as covariates. Correction for multiple comparisons was carried out using a cluster-based thresholding method, with an initial cluster forming threshold of t = 2.0. Results were considered significant for $p<0.05$. For the clusters where internet addiction subjects showed significantly different FA values from the controls, the FA of these brain regions were extracted, averaged and regressed against the duration of internet addiction.

2.2.4 Interaction between gray matter and white matter abnormalities.

To investigate the interactions between gray matter changes and white matter alterations, a correlation analysis was performed between abnormal gray matter volumes and white matter FA values in the IAD group.

Results

3.1 VBM results

Regional gray matter volume changes were assessed non-parametrically using optimized VBM. Correction for multiple comparisons was carried out using a cluster-based thresholding method. VBM comparison between IAD subjects and matched healthy controls indicated decreased gray matter volume in several clusters, i.e. the bilateral DLPFC, the supplementary motor area (SMA), the OFC, the cerebellum and the left rostral ACC (rACC), after controlling for potential confounding variables including age, gender effects and total intracranial volume. Gray matter volumes of the right DLPFC, the left rACC and the right SMA showed a negative correlation with months of internet addiction ($r1 = -0.7256$, $p1 < 0.005$; $r2 = -0.7409$, $p2 < 0.005$; $r3 = -0.6451$, $p3 < 0.005$). No brain regions showed higher gray matter volume than healthy controls as shown in Figure 1 and Table 2.