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Disrupted inter-hemispheric functional and structural coupling in Internet addiction adolescents

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ABSTRACT

Rapid progress had been made towards the effect of Internet addiction (IA) on the adolescents’ brain, relatively little is known about the alterations in inter-hemispheric resting state functional connectivity (RSFC) changes. In the current study, voxel-mirrored homotopic connectivity (VMHC) was used to examine inter-hemispheric RSFC in IA adolescents (n=21) and controls (n=21). The integrity of the fibers connecting the regions, which showed aberrant inter-hemispheric functional connectivity, was assessed by fiber tractography analysis. In addition, the coupling of inter-hemispheric functional and structural connectivity was investigated. Relative to controls, IA adolescents showed decreased VMHC of dorsolateral prefrontal cortex (DLPFC) and reduced fractional anisotropy (FA) values in the genu of corpus callosum (CC). The decreased VMHC of DLPFC was significantly negative correlated with the duration of IA. Moreover, the VMHC of DLPFC showed significant correlations with the FA of CC in healthy controls, which was disrupted in IA. Our findings provided more scientific evidence for the involvement of DLPFC in IA. It is hoped that multimodal imaging methods can provide deeper insights into the IA effects on the brain.

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1. Introduction

Internet addiction (IA) is usually characterized by an individual’s inability to control his or her use of the Internet. IA has drawn scientific attention around the world (Aboujaoude, 2010; Block, 2008). Previous studies had detected the association of IA with academic performance, social interaction, and even criminal activity (Young, 1998; Yuan et al., 2013a). Recently, the most important subtype of IA—Internet gaming disorder, which refers to the use of electronic games only (online and/or offline, regardless of the platform used) and is not to be applied on other forms of computer or internet use, has been included in the appendix of the Statistical Manual for Mental Disorders (DSM-5) (Association, 2013). For the first time, DSM-5 introduces non-substance addictions as psychiatric diagnoses, which makes clear that more researches are needed on this phenomenon to collect evidence for its clinical relevance and underlying mechanisms. By employing neuroimaging methods, couples of studies have shown IA-related structural and functional alterations in several brain regions, such as the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, anterior cingulate cortex, supplementary motor area, parahippocampal gyrus, some of which were found to be correlated with the duration of IA (Yuan et al., 2013a, 2013b, 2011). Taken together, these findings revealed the prefrontal cortex (PFC) dys-function and suggested that the IA shared partially similar pathology of substance abuse (Brand et al., 2014; Meng et al., 2014). However, the treatment of IA is not so satisfied (Winkler et al., 2013; Young, 2009) and more comprehensive studies are needed to carry out.

Among previous findings, it is worthy to note that diffusion tensor imaging (DTI) method had revealed the reduced fractional...
anisotropy (FA) of corpus callosum (CC) in IA adolescents (Lin et al., 2012; Weng et al., 2013). CC provides the main route of communication between the two hemispheres of the brain and facilitates inter-hemispheric communication (Caminiti et al., 2009; Hofer and Frahm, 2006). The abnormal integrity of CC probably result in impaired inter-hemispheric functional connectivity, however, relatively little is known about the alterations in inter-hemispheric resting state functional connectivity (RSFC) changes in IA adolescents, and even less is known about its association with the abnormalities of the CC. Functional homotopy, the high degree of synchrony in patterns of spontaneous activity between homotopic regions in each brain hemisphere, is a fundamental characteristic of the brain's intrinsic functional architecture (Salvador et al., 2005). Altered inter-hemispheric RSFC had also been found in several brain disorders including autism, cocaine abuse and migraine (Anderson et al., 2011; Kelly et al., 2011; Yuan et al., 2012). Although resting state methods had been used to investigate the IA (Ding et al., 2013; Hong et al., 2013; Yuan et al., 2013b), few studies examined the functional connectivity between homotopic regions within bilateral hemispheres.

To address these issues, voxel-mirrored homotopic connectivity (VMHC) (Kelly et al., 2011; Yuan et al., 2012) was used to investigate the alterations of inter-hemispheric RSFC, which quantifies the RSFC between each voxel in one hemisphere and its mirrored counterpart in the opposite hemisphere. In addition, fiber tractography analysis was used to assess the fiber integrity of the part of CC connecting the bilateral regions which showed abnormal VMHC values. Finally, the coupling of the corresponding inter-hemispheric functional-structural connectivity was also examined in both groups. Based on the PFC dysfunctions in previous IA studies (Brand et al., 2014; Meng et al., 2014), we hypothesize that the VMHC values of PFC and the integrity of the fiber connecting the bilateral hemisphere would be abnormal and these changes would be correlated with duration and severity of IA. In addition, the coupling of the inter-hemispheric functional and structural connectivity was disrupted in IA.

2. Methods

2.1. Ethics statement

All research procedures were approved by the Ethical Committee of Xi’an Jiaotong University and were conducted in accordance with the Declaration of Helsinki. All participants and their legal guardians in our study gave written informed consent.

2.2. Participants

More than three hundreds freshman and sophomore students were screened from the campus over the course of two years using Young’s online Internet addiction test (IAT) (http://netaddiction.com/internet-addiction-test/). The IAT consists of 20 items, which assesses online internet use including psychological dependence, compulsive use, withdrawal, related problems in school or work, sleep, family or time management. For each item, a graded response is selected from 1=“Rarely” to 5=“Always”, or “Does not Apply”. Scores over 50 indicate occasional or frequent internet-related problems (Pawlikowski and Brand, 2011). Accordingly, we chose 50 as the threshold for the inclusion criteria of IA. Healthy controls we selected scored lower than 30 (Dong et al., 2012). Meanwhile, all the participants were told that they were participating in a study assessing the internet usage effects on the brain and that some scales and tests would be needed to assist us to complete. A general survey was made to investigate the participants’ internet usage condition (days spending on internet per week, hours per day, etc.) and some basic information (age, gender, education, handedness, etc.). Also, participants’ school performance was assessed by the question “In general, the mean score of the your major courses is about (1—100 point).” The duration of the IA was estimated via a retrospective diagnosis. We asked the subjects to recall their life-style to answer the question “How long (years) have you been in the current status, for example, you can’t control yourself to play games and prefer to play games than do anything else?” The reliability of self-reports from the IA adolescents was confirmed by talking with their parents and schoolmates via telephone. Meanwhile, the subjects’ sociable ability was assessed by the question “From your observation, does he/she likes to communicate with others in our daily life on a scale from 1 (rarely/never) to 4 (almost always/always)” To exclude the possible effect of different games on our results, all the IA adolescents were League of Legends players, which is a multiplayer online battle arena video game developed and published by Riot Games. Twenty-one IA and twenty-one age-, education- and gender-matched healthy controls participated in our neuroimaging research. They were native Chinese speakers and right-handed adolescents. All the recruited participants never use illegal substances and were free of personal or family history of psychiatric disorders. The exclusion criteria for both groups was (1) existence of a neurological disorder evaluated by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; (2) alcohol, nicotine or drug abuse by urine drug screening; (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. All the participation was voluntary, they could terminate participation at any point.

2.3. MRI data acquisitions

Before scanning, the Barratt Impulsiveness Scale-11 (BIS-11) was used to assess the participants’ frequency of several common impulsive or non-impulsive behaviors. This experiment was carried out on a 3-Telsa MRI system (EXCITE; General Electric; Milwaukee; Wisc.) at the First Affiliated Hospital of the Medical College; Xi’an Jiaotong University in China. A standard birdcage head coil was used, along with restraining foam pads to minimize head motion and to diminish scanner noise. For each subject, a high-resolution structural image was acquired with the following parameters: repetition time (TR)¼8.5 ms; echo time (TE)¼3.4 ms; flip angle¼12○; in-plane matrix resolution¼240×240; slices¼140; field of view (FOV)¼240×240 mm2; slice thickness¼1 mm. Then, the diffusion sensitizing gradients were applied along 30 non-liner directions (b¼1000 s/mm2) together with an acquisition without diffusion weighting (b¼0 s/mm2). The imaging parameters were 45 continuous axial slices with a slice thickness of 3 mm and no gap, FOV¼240×240 mm2; TR¼6800 ms; TE¼93 ms; acquisition matrix¼128×128. Finally, resting-state functional images were obtained using an echo-planar-imaging sequence (TR¼2000 ms; TE¼30 ms; FA¼90○; FOV¼240×240 mm2; data matrix¼64×64) with 30 axial slices (slice thickness¼5 mm and no slice gap, total volumes¼185) in one run of 6 min 10 s. During the functional scan, subjects were instructed to keep their eyes closed, keep still and not to think about anything systematically. After the scan, the subjects were asked whether or not they remained awake during the whole procedure and received 20 dollars as the payment.

2.4. Functional data processing

Resting state data were preprocessed using Analysis of Functional Neuroimages (AFNI) and FMRIB Software Library (FSL) (Kelly et al., 2011). Scores over 50 indicate occasional or frequent internet addictive behaviors. For each item, a graded response is selected from 1=“Rarely” to 5=“Always”, or “Does not Apply”. Scores over 50 indicate occasional or frequent internet addictive behaviors. For each item, a graded response is selected from 1=“Rarely” to 5=“Always”, or “Does not Apply”. Scores over 50 indicate occasional or frequent internet addictive behaviors.
et al., 2011; Yuan et al., 2012). It is worth to note that previous studies had pointed out that nuisance regression and bandpass filtering alone are often insufficient to control head movement induced noise. Therefore, wavelet despiking was used in the current study to control the head motion effect for the functional connectivity (Patel et al., 2014). Individual VMHC map was derived according to the methods in our previous study (Yuan et al., 2012), then the global VMHC was calculated by averaging VMHC values across all the voxels within a unilateral hemisphere gray matter mask (there is only one correlation for each pair of homotopic voxels), which was created using the MNI152 gray matter tissue prior included with FSL (threshold = 25% tissue-type probability).

2.5. Structural data processing

DTI data preprocessing was carried out using FSL and comprised the following steps: eddy-currents and head motion correction, non-brain tissue and background noise removal, diffusion tensors calculation and individual FA maps construction. According to previous study (Gong et al., 2009), we derived the ROIs for the following fiber tracking from the regions exhibiting significantly different VMHC between groups. In detail, individual T1-weighted structural image was co-registered to its B0 image ($b=0 \text{s/mm}^2$) in the DTI native space; the co-registered structural images in the DTI native space were mapped to the ICBM-152 T1 template in the MNI space to obtain an affine transformation matrix ($T$); the inverse transformation matrix $T^{-1}$ was utilized to warp the AAL atlas from the MNI space to the individual DTI native space. As the ROIs were derived from the normalized MNI space, inverse transformation ($T^{-1}$) was applied to the ROIs in the normalized MNI, resulting in the subject-specific ROIs in the native space of DTI. Because fiber tracking becomes unreliable in gray matter, we ensured that our ROIs extended 2–3 mm into the white matter (Uddin et al., 2011). Subsequently, fiber tracking was performed using Diffusion Toolkit and TrackVis software (Wang et al., 2007). Whole brain fibers were reconstructed along the principal eigenvector of each voxel’s diffusion tensor. The fiber assignment continuous tracking algorithm was used (Mori et al., 1999). Tracking termination criteria were angle $>45^\circ$ and FA $<0.2$ (Mori and Van Zijl, 2002) (individual FA map derived from FSL’s DTIFIT was used as mask image in Diffusion Toolkit). Then, fiber bundles connecting the bilateral ROIs were extracted from the total collection of brain fibers, which were obtained through a two-ROI approach (seed ROI and target ROI) with logical AND concatenation (Wakana et al., 2007). Only fibers that passed both ROIs were included in the reconstructed tract. Obviously spurious fibers were removed from the fiber tract by using an additional avoidance ROI (logical NOT operation). The values of three indexes (Mean FA, Mean length, and number of fibers (FN)) of the remaining fiber bundles connecting each pair of ROIs were extracted.

2.6. Statistical analysis

Group comparisons of global VMHC were performed using two sample t-test ($p < 0.05$). Then, one-sample t-tests were employed to generate group-level VMHC maps for the two groups ($p < 0.05$, family wise error (FWE) corrected), the regional group differences in VMHC were investigated using Permutation-based non-parametric testing with 10,000 random permutations. The statistical procedure produced a threshold for significance of $p < 0.05$ using TFCE method with FWE correction for multiple comparisons. The VMHC values of the brain regions showing abnormal inter-hemispheric functional connectivity were extracted, averaged and correlated with the duration as well as the IAT scores in IA group (Bonferroni correction, $p < 0.0125$). With regard to the DTI analysis, two sample t-test was employed to compare the values of three indexes of the fiber between IA adolescents and healthy controls ($p < 0.05$). Correlation analysis was also carried out to assess the relationship between the mean FA and the duration of IA as well as the IAT scores in IA group (Bonferroni correction, $p < 0.0125$). Finally, correlation analysis was performed between the fiber FA values and VMHC values of abnormal brain regions between IA and controls.

3. Results

3.1. Demographic data results

Forty-six participants were recruited initially. One of which broke up participation, three invalid datasets were excluded because of excessive head motion. According to the survey, all the IA adolescents have bad academic performance, dislike to communicate with others and are more impulsive, while the healthy controls do everything well. More detailed demographic information was given in Table 1.

3.2. Functional analysis results

The global VMHC was not significantly different between IA adolescents and healthy controls ($p=0.9316$). Regional comparisons revealed the IA adolescents exhibited reduced VMHC of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Participant Demographics.</th>
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<tbody>
<tr>
<td>Control ($n=21$)</td>
<td>IA ($n=21$)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.29 ± 2.239 (15–23)</td>
</tr>
<tr>
<td>Gender</td>
<td>5F, 16M</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.33 ± 1.494 (10–15)</td>
</tr>
<tr>
<td>School performance</td>
<td>85.90 ± 4.538(78–93)</td>
</tr>
<tr>
<td>Sociable interaction</td>
<td>3.24 ± 0.768(2–4)</td>
</tr>
<tr>
<td>BIS-11</td>
<td>51.57 ± 4.864 (43–59)</td>
</tr>
<tr>
<td>Online</td>
<td></td>
</tr>
<tr>
<td>Hours per day</td>
<td>3.024 ± 1.9396 (0.5–7)</td>
</tr>
<tr>
<td>Days per week</td>
<td>2.786 ± 1.9911 (0.5–7)</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>N/A</td>
</tr>
<tr>
<td>IAT score</td>
<td>25 ± 5.85 (20–30)</td>
</tr>
</tbody>
</table>

All controls and IA adolescents were matched for age, gender ($t^2 = 0.233$, df = 1) and education years. Values are mean ± SD (range). All variables were compared between groups with two-sample t-test except for chi-square which was used for gender comparison.

Abbreviation: SD = standard deviation; F = female; M = male; IA = Internet addiction; IAT = Internet addiction test; ES = effect size; BIS-11 = Barratt Impulsiveness Scale-11.
Fig. 1. Voxel-Mirrored Homotopic Connectivity (VMHC) results. Internet addiction (IA) adolescents exhibited decreased VMHC in the dorsolateral prefrontal cortex (DLPFC) ($p < 0.05$, family-wise error corrected) relative to the healthy controls. No brain regions showed increased VMHC in IA adolescents.

Fig. 2. Correlation analysis results. (a) The duration of Internet addiction (IA) were found to be negatively correlated with the decreased VMHC values of the dorsolateral prefrontal cortex (DLPFC) in IA group. (b) The decreased Voxel-Mirrored Homotopic Connectivity (VMHC) values of the DLPFC were found to be positively correlated with decreased fractional anisotropy (FA) values of the genu of corpus callosum (CC) in the healthy controls; no correlations were found in IA adolescents.
DLPFC than controls (Fig. 1b, effect size (ES) = 1.6872). No brain regions showed increased VMHC in IA. The correlation analysis indicated that the VMHC of DLPFC was negatively correlated with the duration of IA. Besides, a negative tendency was found between VMHC of DLPFC and IAT (Fig. 2a).

### 3.3. Structural analysis results

Relative to healthy controls, IA adolescents showed decreased FA (ES = 0.6878) and increased length (ES = 0.768) in the genu of CC. No significant difference of FN (ES = 0.1925) was found (Fig. 3). Neither the duration ($r = 0.1762$, $p = 0.4450$) nor the IAT scores ($r = -0.144$, $p = 0.5334$) of IA showed correlations with the FA values of the genu of CC in IA group.

### 3.4. Functional-structural coupling results

The VMHC of DLPFC showed no correlations with the FA of the genu of CC in IA adolescents, whereas a significant positive correlation was found in healthy controls (Fig. 2b).

### 4. Discussion

Neuroimaging studies have detected brain structural and functional alterations in IA adolescents (Ding et al., 2013; Hong et al., 2013; Yuan et al., 2013a, 2013b, 2011; Zhou et al., 2011). However, IA-related alterations in functional interactions between the cerebral hemispheres and its anatomical basis, especially the relationship between functional and structural deficits during resting state, are rarely examined. In the current study, we found...
that, relative to controls, IA adolescents showed decreased inter-hemispheric functional connectivity of DLPFC. Homotopic RSFC is one of the most salient characteristics of the intrinsic functional architecture of the brain (Salvador et al., 2005; Stark et al., 2008). Regional variation in homotopic RSFC is congruent with the brain’s functional hierarchy (Stark et al., 2008) and the lifespan developmental trajectories of VMHC show regional and hierarchical specificity (Zuo et al., 2010), which likely reflects the importance of inter-hemispheric communication to the integrated brain function underlying coherent cognition and behavior. In the present study, the abnormal VMHC may indicate the underlying mechanism of IA. In addition, the decreased VMHC of bilateral DLPFC was negatively correlated with the duration of IA, which demonstrated that the longer the disorder persisted, the less synchronous fluctuations between the inter-hemispheric DLPFC. This finding suggested that IA may be a progressive disease. Moreover, the negative tendency between the abnormal VMHC and IAT scores of IA may indicate that VMHC of DLPFC can reflect the severity of IA. Taking together, our findings revealed that the information communication between bilateral hemisphere was abnormal in IA, which was associated with the pathophysiological mechanisms of IA. The abnormal DTI properties of CC had also been revealed in the current study, which may be associated with the mechanism underlying these deficits in VMHC. Mounting evidence have demonstrated the important role of CC in maintaining inter-hemispheric coherence of spontaneous BOLD fluctuations (Innocenti, 1986; Zuo et al., 2010). Rationally, the structural deficits of CC have the potential to contribute to the variation of VMHC. Previous lesion studies detected that inter-hemispheric coherence is decreased in acallosal (Nielsen et al., 1993) and callosotomized (Johnston et al., 2008) patients, which demonstrated that CC appears to play a central role in mediating the VMHC. Particularly, Zuo et al. revealed that the lifespan developmental trajectories of VMHC resemble those observed in developmental structural studies, particularly in the CC (Thompson et al., 2000; Zuo et al., 2010), which is an unsurprising observation given the high proportion of CC dedicated to the VMHC (Innocenti, 1986; Johnston et al., 2008). Based on the description mentioned above, we suggested that the mechanism underlying VMHC deficits in IA was associated with FA abnormalities of CC. Besides, we investigated the relationship between functional (VMHC) and structural connectivity (FA) alterations in DLPFC. Our results showed that there were significantly positive correlations between the brain functional connectivity and white matter integrity in the healthy controls. However, no correlations were found in IA adolescents. Considering our findings of the decreased CC integrity, this disruption of the functional-structural coupling may be explained by the reduced constraints that white matter connectivity pose on the brain function in IA, which was consistent with the findings of a previous schizophrenia investigation (Cocchi et al., 2014).

Regardless of whether IA is conceptualized as a behavioral addiction (Holden, 2001), it is speculated to be associated with impaired cognitive control, e.g. longer reaction time (Dong et al., 2011) and more response errors (Xing et al., 2014; Yuan et al., 2013a, 2013b) during incongruent conditions in Stroop task. DLPFC, which showed reduced VMHC in IA adolescents in our present study, has been revealed an crucial involvement in the cognitive control activities (MacDonald et al., 2000; Miller, 2000). The implication of the altered DLPFC activation with cognitive control deficits during cognitive control task had been detected in IA (Liu et al., 2014; Meng et al., 2014). Rationally, we hypothesized that the VMHC abnormalities of DLPFC may be associated with the cognitive control impairments in IA. Besides, it is worth to note that DLPFC was critical to craving in IA. Neuroimaging studies have revealed the DLPFC activation in gaming cue induced craving (Ko et al., 2009; Ko et al., 2013; Sun et al., 2012). Accordingly, we speculated that the VMHC deficits of DLPFC were also associated with craving mechanisms. To test the accurate role of DLPFC in IA, more comprehensive experiment design was needed in the future study.

There are some limitations in our study. Firstly, the present study employed cross-sectional design. We can not make sure whether the abnormalities of the inter-hemispheric structural connectivity were induced by excessive internet gaming and other internet related behaviors or these alterations pre-existed the disorder. Up to date, few studies have addressed this question. Thus, longitudinal study should be considered in the future in order to better understand whether the abnormal DLPFC inter-hemispheric structural connectivity can be used as a predictor of prolonged IA. Secondly, to investigate that the VMHC differences in IA are linear and progressive, we employed duration as the behavior index. Although the duration was retrospective as described in our previous studies (Yuan et al., 2011), it is very difficult to test the accuracy. Finally, although we detected inter-hemispheric functional connectivity of the bilateral DLPFC, which is involved in the executive control processes, our present study did not perform cognitive tasks (e.g. Stroop, Go/No-Go) to investigate the relationship between the neuroimaging findings and the cognitive control ability. It should be considered in the future study.

In the present study, we detected robust effects of IA on the homotopic functional and structural connectivity of bilateral DLPFC. It is hoped that our combination of the functional and structural information may provide deeper insights into the IA effects on the brain.

Contributors

YB, KY, WQ and JT were responsible for the study concept and design. HW, CJ, LX and YL contributed to the acquisition of MRI data. YB, DF, KY, DY and TX performed the data analysis and interpretation of findings. YB and KY drafted the manuscript. All authors critically reviewed content and approved final version for publication.

Conflict of interest

All authors declare that they have no conflicts of interest.

Role of the funding source

The funding sources have no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the article; or in the decision to submit the paper for publication.

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