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ORIGINAL RESEARCH

Internet gaming disorder: deficits in functional and structural connectivity in the ventral tegmental area-Accumbens pathway

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Abstract

Dopamine projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) and from the substantia nigra (SN) to the dorsal striatum are involved in addiction. However, relatively little is known about the implication of these circuits in Internet gaming disorder (IGD). This study examined the alteration of resting-state functional connectivity (RSFC) and diffusion tensor imaging (DTI) -based structural connectivity of VTA/SN circuits in 61 young male participants (33 IGD and 28 healthy controls). Correlation analysis was carried out to investigate the relationship between the neuroimaging findings and the behavioral Internet Addiction Test (IAT). Both the NAc and medial orbitofrontal cortex (mOFC) showed lower RSFC with VTA in IGD subjects compared with controls. Moreover, the RSFC strength of VTA-right NAc and VTA-left mOFC correlated negatively with IAT in IGD subjects. The IGD subjects also showed lower structural connectivity in bilateral VTA-NAc tracts compared with controls, but the connectivity did not correlate with IAT in IGD. We provide evidence that functional and structural connectivity of the VTA-NAc pathway, and functional connectivity of the VTA-mOFC pathway are implicated in IGD. Since these pathways are important for dopamine reward signals and salience attribution, the findings suggest involvement of the brain DA reward system in the neurobiology of IGD. The association of functional but not structural connectivity of VTA circuits with IAT suggests that while lower structural connectivity might underlie vulnerability for IGD, lower functional connectivity may modulate severity. These results strengthen the evidence that IGD shares similar neuropathology with other addictions.

Keywords Internet gaming disorder · Resting-state functional connectivity · Substantia nigra · Ventral tegmental area circuit · White matter tracts

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Introduction

Internet game disorder (IGD) is a serious and growing public health problem, especially in adolescents (Murali and George 2007; Young 1998; Yuan et al. 2011). In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (American Psychiatric Association), IGD has been identified as a condition warranting more research before it might be considered for inclusion as a formal disorder (Petry and O'brien 2013; Zastrow 2017; Markey and Ferguson 2017). Growing evidence has demonstrated that IGD and substance use disorder (SUD) share similar symptoms, including craving, compulsivity, withdrawal and cognitive control deficits (Yuan et al. 2017b). Furthermore, similar neural mechanisms underlying SUD and IGD have been described, particularly for dopaminergic (DA) dysfunctions and reward, i.e., reduced availability of striatal DA D2 receptors (Kim et al. 2011) and

DA transporters (DAT) (Hou et al. 2014). It is still an active debate as to whether IGD is a brain disorder (Weinstein et al. 2017; Markey and Ferguson 2017), hence more research is necessary to improve our understanding of IGD.

DA projections from the ventral tegmental area (VTA) to the striatum especially the nucleus accumbens (NAc) and the prefrontal cortex especially the medial orbitofrontal cortex (mOFC) are implicated in reward processing and motivation (Wise 2009; Volkow et al. 2011). Another major DA circuit that projects from the substantia nigra (SN) to the dorsal striatum is involved in conditioning and habit formation in addiction (Drui et al. 2014; Tomasi and Volkow 2012; Wise 2009; T. Mori et al. 2016; S. Zhang et al. 2016; Everitt and Robbins 2016). Brain imaging studies have provided evidence of dysfunction of fronto-striatal circuits in IGD (Yuan et al. 2017b; Hong et al. 2013), including structural and functional impairments (Cai et al. 2016; Yuan et al. 2017b; Jin et al. 2016; Yuan et al. 2013a). However, there is limited knowledge on the involvement of structural or functional disruption within the midbrain dopamine nuclei (VTA and SN) -centered circuits in IGD.

Resting state functional connectivity (RSFC) may provide insight into the brain's functional organization by assessing spontaneous activity including intra-regional and inter-regional levels, and has been applied in studies on addiction and other brain disorders (Yuan et al. 2016; Yuan et al. 2017b; Bi et al. 2015). Recently, Zhang et al. observed decreased RSFC between the VTA and right NAc in IGD subjects compared with healthy controls (HC) (J. Zhang et al. 2015). However, they failed to investigate RSFC changes in SN, which may be as important as the VTA, and structural connectivity of these circuits. Diffusion tensor imaging (DTI) has provided a method to assess microstructural qualities of specific white matter (WM) tracts (Yuan et al. 2016). Previous DTI studies revealed damage of WM tracts not only within the salience network but also between the thalamus and the prefrontal cortex in IGD (Xing et al. 2014; Dong et al. 2012).

Here we extended these studies to investigate both functional and structural connectivity of the VTA- and SN-centered circuits in IGD and HC by using RSFC and DTI deterministic tractography, respectively. Correlation analysis was carried out to examine the relationship between the neuroimaging findings and severity of IGD. To our knowledge, this is the first neuroimaging study that combines RSFC and structural connectivity of VTA and SN circuits in IGD. We hypothesized lower RSFC of VTA and SN circuits in IGD subjects compared with HC, and that group differences would be associated with the severity of IGD symptoms. Furthermore, we expected that the WM structural integrity of these circuits would be impaired in IGD subjects compared with HC. Finally, assuming that greater WM coherence facilitates the transmission of functional information (Leong et al. 2016), we hypothesized positive correlations between structural and functional connectivity of these circuits in both IGD subjects and HC.

Materials and methods

Ethics statements

All research procedures were approved by Ethical Committee of Xi'an Jiaotong University and were conducted in accordance with the Declaration of Helsinki. All participants and their legal guardians gave written informed consent after a detailed explanation of the study procedures and goals.

Subjects

Thirty-three male individuals with IGD (19.08 ± 1.36 years old) and 28 male age- and education-matched HC (19.63 ± 1.99 years old) were recruited from the Xi'an Jiaotong University. Participants were screened using diagnostic criteria of IGD in DSM-5 and were included in the IGD group if they met at least five or more of the nine criteria in the last 12 months. In addition, we chose IGD participants who primarily played League of Legends to control for potential effects of other video games on neuroimaging and behavioral findings. We confirmed the reliability of self-reports from the IGD participants by talking to their parents, roommates and classmates. Exclusion criteria for both groups included: (1) any DSM-IV axis I disorders (other than IGD in IGD group); (2) any positive breath alcohol levels or positive drug urine screens on the days of screening; (3) expiratory carbon monoxide (CO) levels >3 ppm measured using the Smokerlyzer System (Bedfont Scientific, Ltd., Rochester, UK); (4) any physical illness or use of any prescription medication in the past 6 months; (5) IQ < 90 (measured by Wechsler intelligence Scale). All participants were right handed (determined by the Edinburgh Handedness Inventory) and native Chinese speakers.

The severity of the IGD was measured by Young's online Internet Addiction Test (IAT) (Chinese version) (Young 1996). The IAT consists of 20 items with a scale of 1–5 and assesses Internet use in the following domains: psychological dependence, compulsive use and withdrawal-related problems in work or life. Sum scores over 50 indicate occasional or frequent Internet-related problems and scores >80 indicate that Internet-game is causing severe problems. Clinical characteristics of subjects with IGD are shown in Table 1.

MRI data acquisitions

Brain images were acquired using a 3-Telsa MRI system (EXCITE, General Electric, Milwaukee, Wisc.) at the First

Table 1 Subjects demographic information

Variable	IGD ($n = 33$)	HC ($n = 28$)	t-value	p value
Demographics				
Age (years)	19.12 ± 1.19 (16~21)	19.79 ± 1.85 (16~22)	1.69	0.096
Education (years)	13.00 ± 0.90 (12~14)	12.89 ± 0.85 (12~14)	−0.634	0.529
Online				
Days per week	3.64 ± 1.78 (1~4)	2.48 ± 2.10 (1~7)	−2.297	0.025
Hours per day	5.36 ± 2.13 (0.5~7)	2.45 ± 1.91 (2~10)	−5.585	<0.001
Duration (years)	5.58 ± 2.83 (2~8)	4.14 ± 1.72 (2~12)	−2.431	0.018
IAT	61.76 ± 10.16 (0~37)	20.38 ± 13.70 (50~87)	−13.607	<0.001

Mean±SD (range) are shown

SD, standard deviation; *IGD*, Internet gaming disorder; *HC*, health controls; *IAT*, internet addiction test

Affiliated Hospital of the Medical College, Xi'an Jiaotong University in China. 3D T1-weighted images were acquired with the following parameters: TR = 8.5 ms, TE = 3.4 ms, FA = 12°, FOV = 240 mm × 240 mm, data matrix = 240 × 240, slices = 140, voxel size = 1 × 1 × 1 mm^3. Resting state functional images were obtained with an echo-planar imaging (EPI) sequence with the following parameters: 35 contiguous slices with a slice thickness = 4 mm, TR =2000 ms, TE =30 ms, flip angle =90°, FOV =240 mm × 240 mm, data matrix =64 × 64, and total volume = 185. Finally, diffusion sensitizing gradients were applied along 32 non-linear directions (b = 1000 s/mm^2) together with an acquisition without diffusion weighting (b = 0 s/mm^2). The imaging parameters were 68 continuous axial slices with a slice thickness of 2 mm and no gap, FOV = 240 mm × 240 mm, TR = 6800 ms, TE = 70 ms, acquisition matrix = 120 × 120 and NEX = 2.

MRI data analysis

Functional data processing

Resting state data were preprocessed using Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/) and FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl/index.html). The data preprocessing consisted of the following steps: (1) the first five volumes were discarded to allow for signal stabilization; (2) slice timing correction; (3) rigid-body head motion correction (1.5 mm displacements and 1.5^0 rotations); (4) obliquity transform to the structural image; (5) affine co-registration to the skull-stripped structural image; (6) standard spatial transformation to the MNI152 template; (7) spatial smoothing (6 mm full-width at half-maximum); and (8) intensity normalization. Denoising steps included (9) time series de-spiking (wavelet domain), (10) nuisance signal regression including the 6 motion parameters estimated in (2), their first-order temporal derivatives, white matter, and ventricular cerebrospinal fluid (CSF) signal (14-parameters regression), and (11) a temporal Fourier filter.

Resting state functional connectivity of VTA and SN

The VTA and SN were used as regions of interest (ROIs), and defined using the probabilistic atlas by Murty et al. (2014) (https://web.duke.edu/adcoklab/) (Fig. 1a). The averaged time series of the voxels in each seed were considered as the reference. RSFC analysis was implemented using AFNI's 3dfim + to produce individual-level correlation maps of all voxels that were correlated with the seed's time series. The derived R-value maps were then transformed to approximate Gaussian distribution with a Fisher's z transformation.

DTI data processing and ROIs definition in native space

DTI data preprocessing was carried out using FSL with the following steps: segregation of brain tissue from non-brain tissue, eddy-current distortion and head motion correction, diffusion tensors calculation and individual fractional anisotropy (FA) maps construction (Bi et al. 2015; Yuan et al. 2016). Based on resting state functional connectivity findings, we extracted ROIs from standard space and then transformed them into native diffusion space with the following steps (Fig. 3): (1) FA map - > T1 (FA_2T1): for each subject, the FA map was registered to the T1 image using FSL's Linear Image Registration Tool (FLIRT) (FA_2T1 matrix). (2) T1 - > Standard (T1_2MNI warp): The individual T1 image was normalized into standard space using nonlinear registration tool FNIRT (FSL's Non-linear Image Registration Tool). (3) Inverse transformation (T1_2FA and MNI_2T1): The transformation matrix (FA_2T1) and warp-fields (T1_2MNI warp) were inverted using convert_xfm and invwarp command respectively, which were subsequently applied to the ROIs in standard space to obtain the ROIs in individual diffusion space (Yuan et al. 2017a).

Deterministic tractography

Fiber tracking was performed using Diffusion Toolkit and TrackVis software (http://www.trackvis.org) as described

previously (Xing et al. 2014; Bi et al. 2015). The ROIs were dilated 1–2 mm into the WM to ensure that they were in contact with the fibers. Whole brain fibers were reconstructed along the principal eigenvector of each voxel's diffusion tensor. The fiber assignment continuous tracking algorithm was used with the termination criteria of angle >45° and/or FA < 0.2 (S. Mori and van Zijl 2002). The diffusion values of the tracts (FA and fiber length) of the fiber bundles connecting each pair of ROIs were extracted.

Statistical analysis

Firstly, one sample t-tests within each group of subjects were employed to generate the RSFC maps of the VTA/SN, and independent t-tests were employed to assess group differences for the RSFC maps. All t-tests used permutation-based non-parametric testing with 5000 random permutations. The resulting statistical maps were thresholded at $p = 0.05$, with correction for multiple comparisons (FWE) at the cluster level by using the threshold free cluster enhancement method in the randomize permutation testing tool in FSL. Based on the RSFC results, the FA of the corresponding WM fibers were extracted and compared between the two groups using two independent samples t-tests. Secondly, Pearson's correlation analysis was carried out to assess the relationship between the RSFC and the IAT score (Bonferroni correction, $p < 0.05/6 = 0.0083$), and between structural connectivity and the IAT score (Bonferroni correction, $p < 0.05/4 = 0.0125$) in IGD. Finally, the relationship between structural connectivity and functional connectivity of VTA/SN circuits was investigated in both groups.

Results

Demographic information

There were no significant differences in demographics between IGD and HC (Table 1). The IGD group spent more time (mean = 5.36 ± 2.13 h per day and 3.64 ± 1.78 days per week; $p = 0.025$) on internet gaming than HC (2.45 ± 1.91 h per day and 2.48 ± 2.10 days per week; $p < 0.001$). In addition, IAT scores were significantly higher in the IGD (61.76 ± 10.16) than HC (20.38 ± 13.70) ($p < 0.001$). There was no correlation between the IAT and internet online time in either group.

Resting state functional connectivity

For both groups, the VTA and SN exhibited significant RSFC with the main DA target subcortical regions (bilateral striatum, hippocampus, amygdala, thalamus), and frontal cortical regions (prefrontal cortex including medial OFC) (FWE corrected, $p < 0.01$) (Fig. 1), which was consistent with previous findings (S. Zhang et al. 2016; Gu et al. 2010; Murty et al.

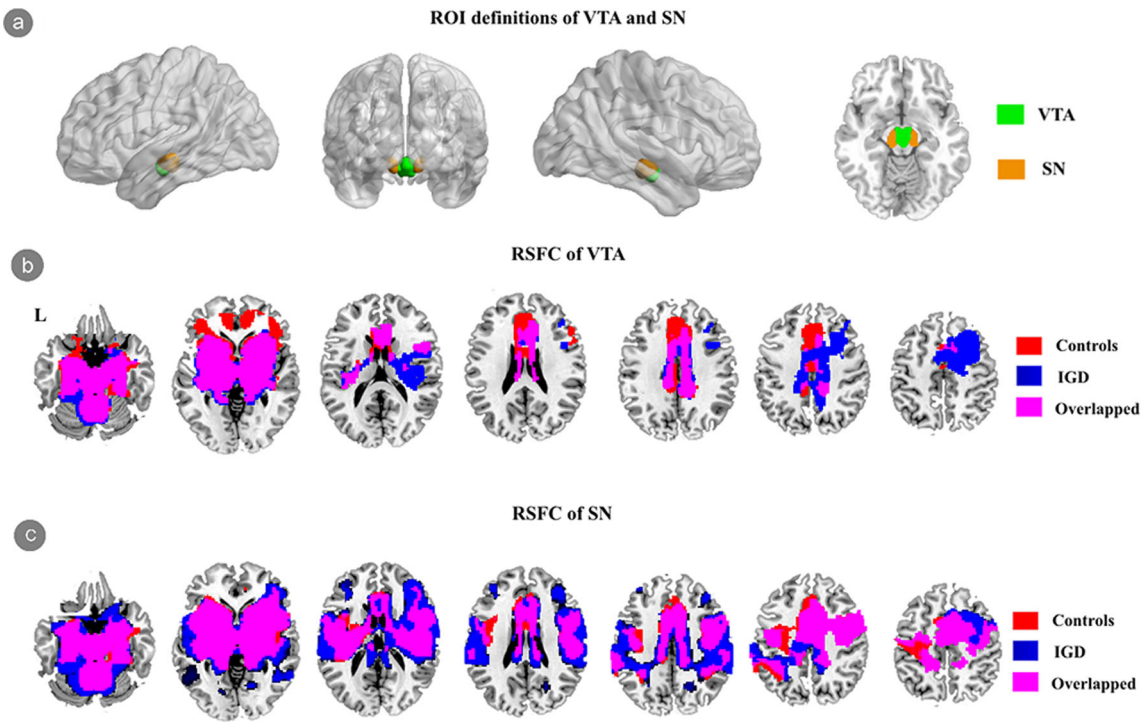

Fig. 1 (**a**) Schematic of the ventral tegmental area (VTA) and substantia nigra (SN). (**b**) Resting-state functional connectivity (RSFC) of VTA in internet gaming disorder (IGD) individuals and healthy controls (HC) (FWE corrected, $p < 0.05$). (**c**) RSFC of SN in IGD individuals and HC (FWE corrected, $p < 0.05$). FWE = family wise error

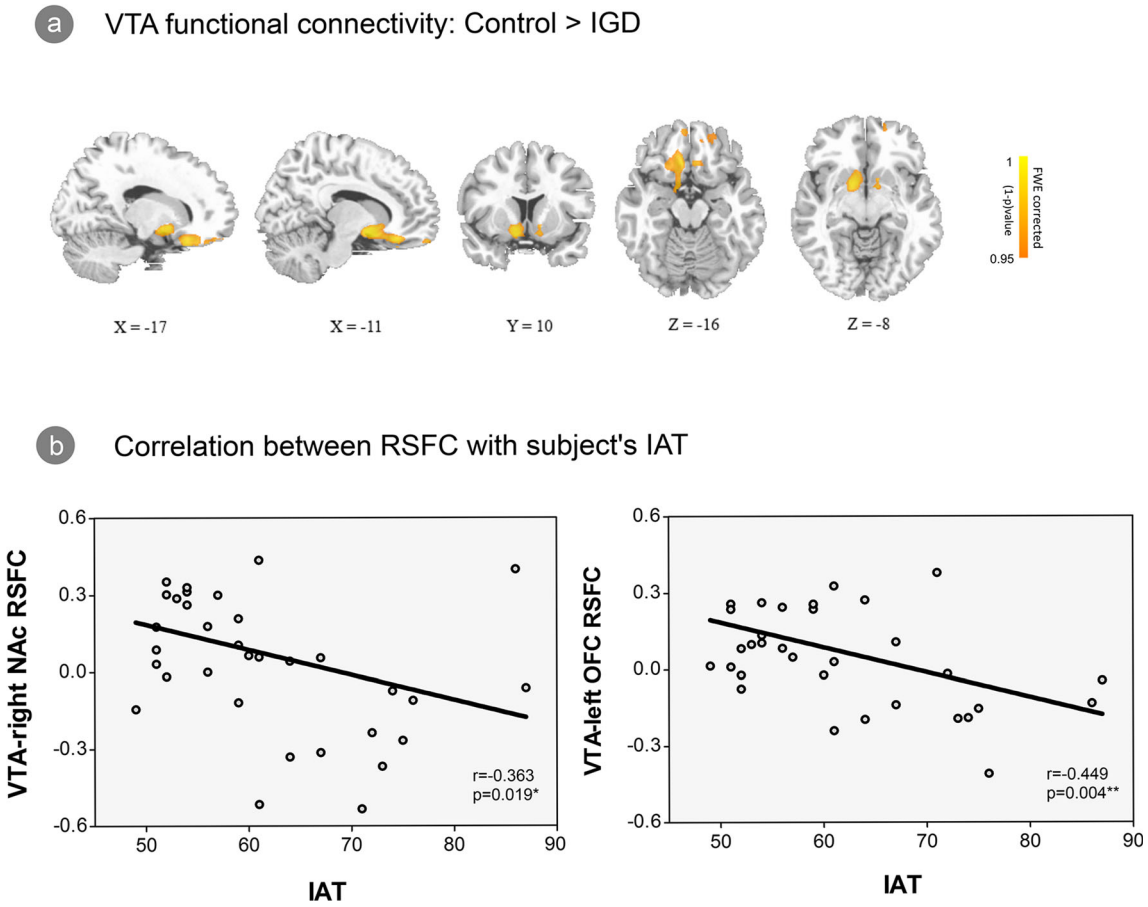

Fig. 2 (**a**) Reduced resting-state functional connectivity (RSFC) of the ventral tegmental area (VTA) in internet gaming disorder (IGD) individuals compared with healthy controls. (**b**) Correlations between VTA RSFC and the internet addiction test (IAT) scores in IGD subjects

2014; Hadley et al. 2014). Additionally, we found significant RSFC of the SN with superior, middle temporal gyrus, calcarine and lingual gyrus, supramarginal gyrus and supplementary motor area (SMA) in both groups (Fig. 1). Importantly, the IGD group showed significant decreases in RSFC of VTA with the bilateral NAc, olfactory tubercle and mOFC, as compared with controls (FWE corrected, $p < 0.05$) (Fig. 2a). In contrast, we found no significant differences in SN RSFC between the groups. Correlation analyses showed that the IAT score correlated negatively with the RSFC strength of VTA-left mOFC ($r = -0.49$, $p = 0.004$) and VTA-right NAc ($r = -0.363$, $p = 0.019$) in IGD (Fig. 2b). However, there was no correlation between the IAT score and the RSFC strength of VTA-olfactory tubercle in IGD.

Structural connectivity

Based on the RSFC results, we extracted fiber tracts connecting the VTA-NAc, as well as the VTA-mOFC in each hemisphere in both groups. Relative to HC, IGD subjects showed lower FA values in bilateral VTA-NAc tracts (left: $p = 0.019$, right: $p < 0.001$) (Fig. 4a and b). In the IGD group, the magnitude of the decrease in FA for the VTA-NAc was 9.32% for the left, and 15.32% for the right hemisphere. There were no group differences in FA of VTA-mOFC (left: $p = 0.092$, right: $p = 0.16$) (Fig. 4d). In addition, there were no group differences in fiber lengths of the VTA-NAc or VTA-mOFC tracts. No significant correlations were found between the structural connectivity of the VTA-NAc and the IAT in IGD individuals.

Correlations between functional and structural connectivity

The correlation between the functional (RSFC) and the structural (FA values) connectivity of VTA-NAc was not significant, although they showed a trend for both the right ($r = 0.26$, $p = 0.072$) and the left pathways ($r = 0.22$, $p = 0.103$) in the IGD group only.

Discussion

Here, we show evidence of reduced RSFC and structural connectivity of VTA-NAc and reduced RSFC of VTA-mOFC in IGD compared to HC. Additionally, the RSFC of both VTA

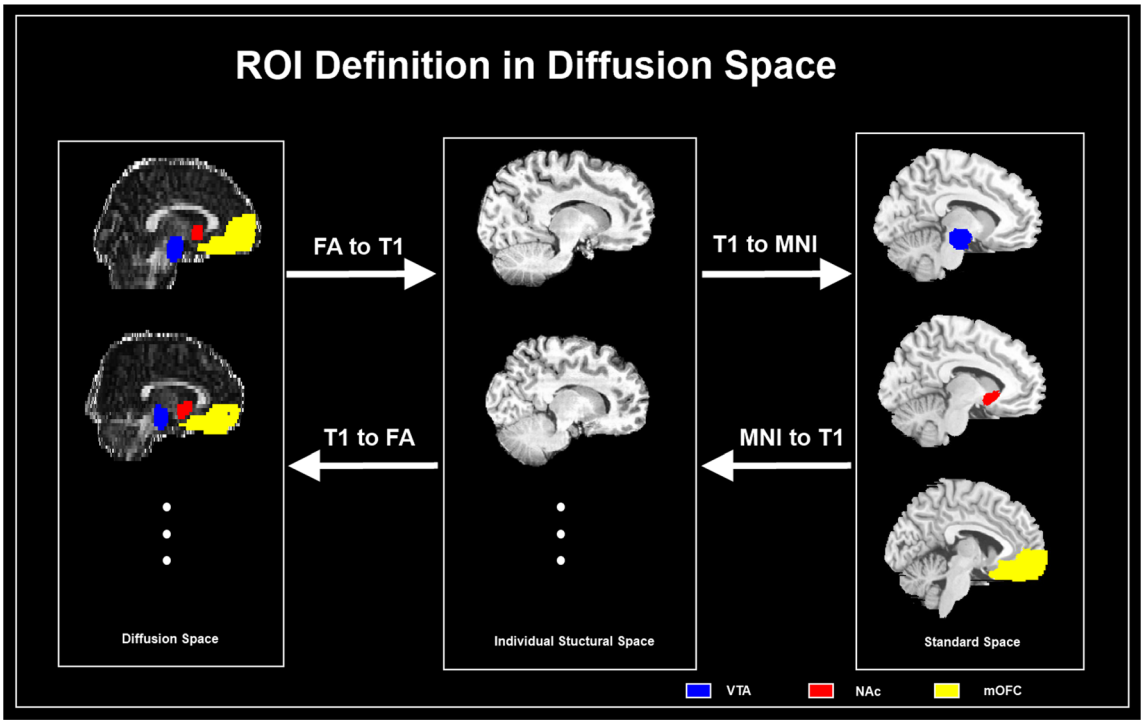

Fig. 3 Regions of interests (ROIs) of the right hemisphere and fiber tracking analysis in diffusion space. The individual DTI image was registered to its T1-weithted structural image. The individual T1 images were normalized into the MNI space. The transformation matrix (FA_2T1) and warp-fields (T1_2MNI warp) were subsequently applied to the ROIs in standard space to obtain the ROIs in individual diffusion space

circuits were associated with IAT scores in IGD. These reduced connectivity patterns were specific to VTA, since there were no group differences in connectivity of the SN. Inasmuch as the VTA contains DA neurons that project to the Nac and mOFC, which are crucial brain regions for processing reward and salience attribution respectively, our findings imply involvement of the DA reward system in IGD. Moreover, the association of reduced VTA connectivity with the severity of IGD symptomatology further strengthens the evidence that VTA connectivity is involved in IGD.

Simulating DA neurons in VTA triggers behavioral hallmarks of addiction (Pascoli et al. 2015; Maskos et al. 2005; David et al. 2006), indicating that DA neurons within the VTA influence drug reward through alterations in DA signaling in the NAc. The central role of the VTA-NAc circuit in addiction has been corroborated in clinical studies (Volkow and Morales 2015). Almost all drugs of abuse increase DA in the NAc either through stimulation of the VTA or by increasing its release from DA terminals in the NAc, which is believed to underlie their rewarding effects (Volkow et al. 2012; Di Chiara et al. 2004; Di Chiara and Imperato 1988). DA increases in the midbrain are also involved with the prediction of reward and drug seeking behavior (Volkow et al. 2010; Wise and Rompre 1989; Schultz et al. 1997). Reduced levels of DA D2 receptor availability and DAT in NAc had been found in IGD individuals (Kim et al. 2011; Hou et al. 2014), which is consistent with findings in chronic drug abusers including tobacco and cocaine (Leroy et al. 2012; Wiers et al. 2017), although lower DAT availability is not a consistent finding in drug users (Volkow et al. 1996). Decreased DAT and D2 receptor availability in NAc in IGD led us to hypothesize that the VTA-NAc circuit would exhibit reduced RSFC connectivity in IGD compared with HC. Our findings, i.e., reduced RSFC of VTA-right NAc in IGD compared with HC, corroborated our hypothesis and were similar with previous findings of the mesocorticolimbic system dysfunction in SUD (Sutherland et al. 2012).

In the present study, we also found reduced RSFC of VTA-mOFC that correlated with IGD symptoms in IGD (Fig. 2). The mOFC has a specific role in attribution of saliency, reward processing and behavioral flexibility to accommodate for changing needs in the environment (Bechara 2003; Elliott et al. 2000). Reduced cortical thickness and resting state abnormalities of the mOFC have been associated with cognitive-control deficits in IGD (Yuan et al. 2013b). Previous brain imaging studies in drug-dependent populations have revealed that the reduced levels of glucose metabolism (marker of brain activity) in mOFC were associated with decreases striatal D2 receptors (Volkow et al. 2007; Volkow et al. 1993; Volkow et al. 2003), implicating impaired DA signaling in mOFC deficits. The DA mesocortical pathway connecting the VTA to mOFC is implicated in the enhanced motivation and compulsive drug consumption in addiction and in excessive and compulsive food consumption in obesity (Wise 2004; Björklund

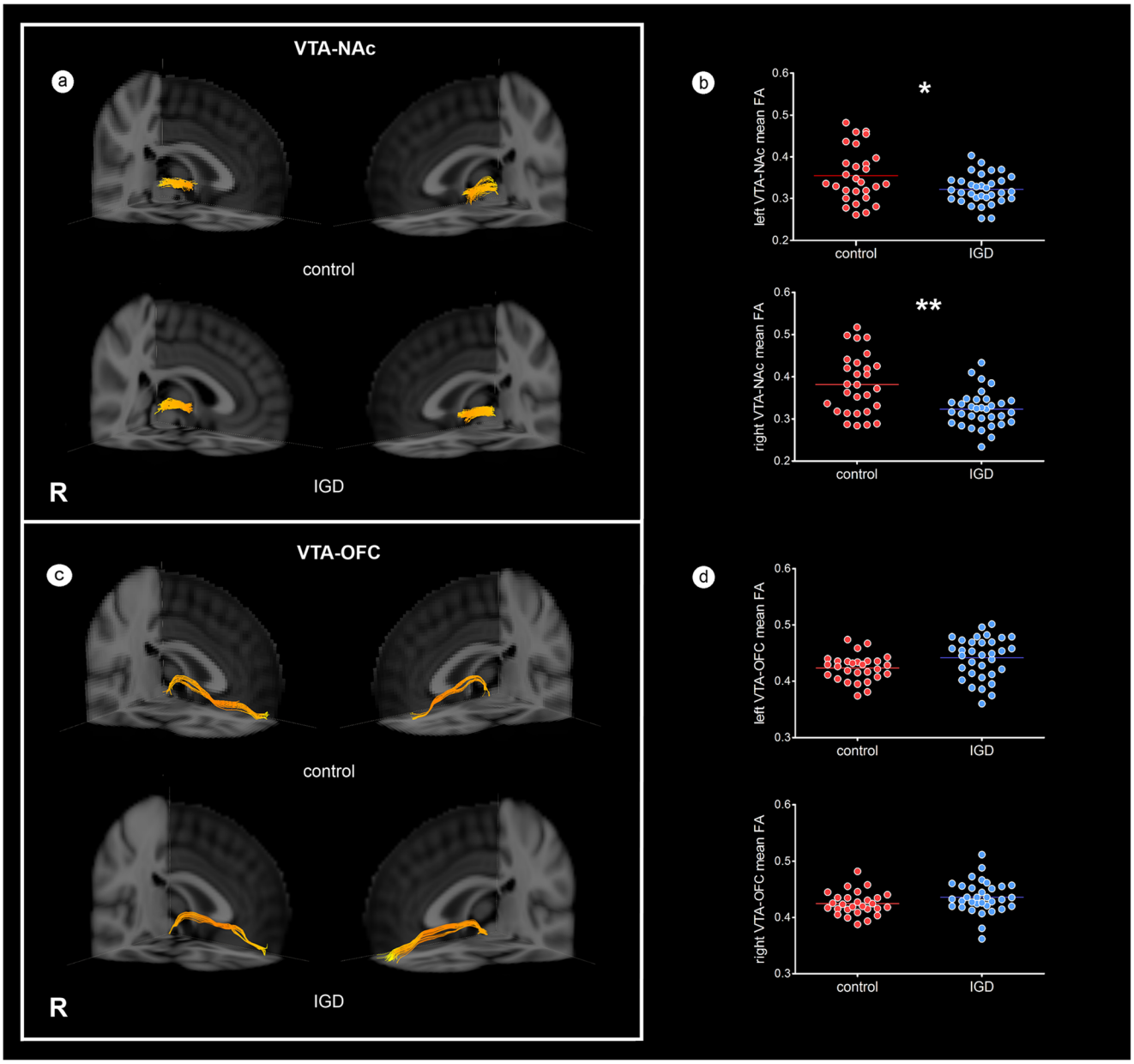

Fig. 4 Fiber tracking analysis in individuals with internet gaming disorder (IGD) and in healthy controls (HC). Relative to HC, IGD showed decreased fractional anisotropy (FA) of the tracts connecting the ventral tegmental area (VTA) and the bilateral nucleus accumbens (NAc), but not difference of the tracts connecting the VTA and the medial orbitofrontal cortex (mOFC)

and Dunnett 2007; Blonder and Slevin 2011; Tomasi and Volkow 2012; Volkow et al. 2017; Volkow et al. 2008). Based on the current findings, we suggest that reduced RSFC between VTA and mOFC is likely to be associated with the enhanced motivation and the compulsiveness to engage in internet gaming in IGD. Previous preclinical lesion studies have reported the emergence of compulsive behaviors in the cases (Volkow et al. 2011). In addition, the negative correlation between the RSFC strength and symptom intensity in IGD provide clinical evidence for the implications of the abnormal VTA-NAc and VTA-mOFC RSFC in the severity of IGD. This inverse association is consistent with previous studies implicating RSFC in VTA-NAc and VTA-mOFC correlated with craving in IGD (J. Zhang et al. 2015) and SUD (Myrick et al. 2004). This may be due to the blunted DA transmission among individuals with both substance and behavioral addictions and the long-time internet gaming modulated the RSFC of these circuits in IGD.

It is worthy to note that the functional repertoire of any system is ultimately determined by its structural composition (Jha et al. 2016). Structural integrity may facilitate functional throughput while the underlying structure is continually being reshaped by function (Yuan et al. 2017a; Hagmann et al. 2010). The mesocorticolimbic pathways (projections from

the VTA to the NAc and mOFC) play important roles in reward and motivation processing (Bromberg-Martin et al. 2010; Baik 2013). The reduced RSFC of the VTA-NAc has been revealed in IGD (J. Zhang et al. 2015), hence we hypothesized that the bilateral VTA-NAc tracts would also show disrupted structural integrity. This study extracted white-matter tracts connecting the VTA to the NAc and mOFC in both groups and identified decreased structural connectivity between VTA-NAc but not between VTA-mOFC. Neurobiological adaptations of these circuits have been detected in IGD (Han et al. 2007; Hou et al. 2014), and disruptions of related white matter tracts have been observed in IGD (Dong et al. 2012; Xing et al. 2014; Bi et al. 2015). However, as far as we know, here we provide first evidence for decreased FA in the VTA-NAc circuit in IGD compared with HC. Thus, it is possible that reduced structural input from the VTA to the NAc might decrease the sensitivity to reward, making the individual prone to seeking more intense rewards to compensate for this deficit thus making them vulnerable to IGD or other addictions. Although the correlation between the reduced RSFC with the WM integrities (FA) only reached significance at trend level in IGD, the contribution of the decreased functional connectivity to the structural VTA-NAc connectivity cannot be rejected. Future studies with larger sample sizes are needed to replicate these findings.

There were several limitations in our study. Firstly, the cross-sectional design failed to test whether the differences in functional and structural connectivity of the VTA-NAc/mOFC were pre-existing in IGD or were the consequences of IGD. Future longitudinal studies can provide new insight into this issue. Secondly, due to lack of cognitive tasks in the present study, we were not able to investigate the association of our brain findings with executive function including cognitive control. Finally, all participants in the current study were young male university students, which make generalization to a female or older population not possible. Evidently, a more comprehensive experiment design including more participants would be necessary to reveal an accurate role of white matter fibers in the VTA in IGD and to assess if there are gender differences or age effects, which could help explain the higher prevalence of gaming in males and in younger individuals.

Conclusion

Our results showed reduced RSFC and structural connectivity of bilateral VTA-NAc circuit, as well as reduced RSFC of the VTA-mOFC circuit in IGD compared with HC. The RSFC strength of VTA-NAc and VTA-mOFC were correlated with the severity of IGD symptoms implicating the brain DA reward system in the neurobiology of IGD and strengthening the evidence that IGD is a brain disorder that shares similar neuropathology to that of other addictions.

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Compliance with ethical standards

Ethical statements Informed consent was obtained from all individual participants included in the study.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that we have no conflict of interest.

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