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Original article

Altered coupling of default-mode, executive-control and salience networks in Internet gaming disorder

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ABSTRACT

Background: Recently, a triple-network model suggested the abnormal interactions between the executive-control network (ECN), default-mode network (DMN) and salience network (SN) are important characteristics of addiction, in which the SN plays a critical role in allocating attentional resources toward the ECN and DMN. Although increasing studies have reported dysfunctions in these brain networks in Internet gaming disorder (IGD), interactions between these networks, particularly in the context of the triple-network model, have not been investigated in IGD. Thus, we aimed to assess alterations in the inter-network interactions of these large-scale networks in IGD, and to associate the alterations with IGD-related behaviors.
Methods: DMN, ECN and SN were identified using group-level independent component analysis (gICA) in 39 individuals with IGD and 34 age and gender matched healthy controls (HCs). Then alterations in the SN-ECN and SN-DMN connectivity, as well as in the modulation of ECN versus DMN by SN, using a resource allocation index (RAI) developed and validated previously in nicotine addiction, were assessed. Further, associations between these altered network coupling and clinical assessments were also examined.
Results: Compared with HCs, IGD had significantly increased SN-DMN connectivity and decreased RAI in right hemisphere (rRAI), and the rRAI in IGD was negatively associated with their scores of craving.
Conclusions: These findings suggest that the deficient modulation of ECN versus DMN by SN might provide a mechanistic framework to better understand the neural basis of IGD and might provide novel evidence for the triple-network model in IGD.

1. Introduction

Internet gaming disorder (IGD) is defined as the inability to control excessive Internet game playing [1–3], and has been shown to share similar neuropsychological processes with drug addictions and pathologic gambling [2–4]. The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) has included IGD as a condition deserving further studies [5] and encouraged more investigations of this disorder for possible inclusion in future editions of the DSM.

Neuroimaging studies of IGD have focused on the identification of regional alterations in structure and function [2,3,6,7]. However, growing evidence demonstrated that this behavioral addiction is associated with system-level alterations between brain regions rather than with the functional breakdown of isolated regions [8–12]. Emerging concepts in cognitive neuroscience suggested that an individual's behaviors are governed by the interaction of multiple brain regions [13]. Functional brain imaging data have revealed that the human brain is topologically organized into a set of coherent spatiotemporal Independent Component Networks (ICNs), which orchestrates disparate cognitive processes [14–17]. Multiple resting-state functional magnetic resonance imaging (fMRI) and structural brain imaging studies have consistently

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found that IGD showed abnormalities in extensive ICNs, such as executive-control network (ECN), salience network (SN) [18,19], default-mode network (DMN) [6], and sensory-motor-related brain networks [8]. Although these ICNs may take charge of distinct cognitive processes, the information that they process needs to be integrated for coherent cognition, perception, and behaviors [15]. Altered interactions between ICNs have been demonstrated to have great potential serving as biomarkers of IGD. For example, the imbalanced functional link between ECN and reward network in IGD can predict their online-gaming behaviors [20], and inefficient functional interactions and reduced fractional anisotropy between ECN and SN were also detected in IGD [19]. Thus, analyses of ICNs and their interactions may help to elucidate impaired network patterns in IGD [21].

Recently, a triple-network model regarding the abnormal interactions between ECN (whose key nodes include the dorsolateral prefrontal cortex [DLPFC], and posterior parietal cortex [PPC]), DMN (which includes nodes of the ventromedial prefrontal cortex [VMPFC] and posterior cingulate cortex [PCC]) and SN (which includes seeds of the ventrolateral prefrontal cortex [VLPFC] and anterior insula (jointly referred to as the fronto-insular cortex; FIC) and the anterior cingulate cortex [ACC]) [22] has been proposed to characterize psychiatric and neurological disorders [23]. This model has also been adapted to understand the mechanism of addictive disorders [24]. SN has been reported to play a critical role in switching between ECN and DMN [22], allocating attentional resources toward ECN and DMN, and therefore facilitating orientation to external versus internal stimuli [23,25–28]. Consistent with the framework, a study on alcohol use disorder suggested that the impaired decision making in alcohol addicts may not only be a deficiency in either the DMN or ECN, but also a deficiency in the switching between those networks, and the key site of this impairment may be the anterior insula [29]. Based on the triple-network model, Lerman & Gu [30] proposed a resource allocation index (RAI) as SN-ECN connectivity subtracting SN-DMN connectivity, reflecting the superiority of modulation of ECN than DMN (or allocating more resources to ECN versus DMN). Using this index, they found that the increased craving for smoking in smokers under acute abstinence was negatively correlated with the reduced RAI, but not with the abnormal SN-ECN or SN-DMN connectivity. Thus, integrating the inter-connectivity between SN and DMN/ECN may offer more comprehensive information about attentional and cognitive control in addiction.

Although IGD shows similar pathogenetic processes with substance use disorders as well as pathological gambling [2–4]; as a behavioral addiction, it is relatively free from the pharmacological effects of substance use [31]. Whether and how the interactions between these ICNs (especially the modulation of ECN versus DMN by SN) are disrupted in IGD remains unexplored. In the current study, we aimed firstly to identify DMN, ECN and SN in adolescents with IGD and HCs. Second, given the hypothesized role of SN in toggling resources between the ECN and DMN, we explored the inter-connectivity between SN and DMN/ECN, and then examined the alterations in the modulation of DMN and ECN using the RAI introduced by Lerman & Gu [30]. Finally, we assessed the association of altered coupling and the severity of addiction/craving for Internet gaming within IGD.

2. Materials and methods

2.1. Participants' inclusion criteria and clinical assessments

This study was approved by the Institutional Review Board of the State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University. Prior to the study, written informed consent was signed by all participants.

Given the higher incidence of IGD in male than female [32], a total of 432 males (319 individuals potential to have IGD [who play Internet gaming frequently] and 113 potential HCs [who play Internet gaming occasionally]) were recruited for initial screening via the Internet and advertisements posted at local universities. The diagnosis criteria of IGD contained: score $\geq$ 67 [32] of the Chinese Internet Addiction Scale (CIAS)[33]; spent more than half of the online time on Internet gaming [34]; and $\geq$ 14 hours spent on Internet gaming per week (with at least 2 hours spent on Internet gaming every day) as assessed by a semi-structured interview [9]. However, the participants with score of CIAS $\leq$ 60 and never having or spent $\leq$ 2 hours per week on Internet gaming were classified as healthy control (HC) [9]. Participants were excluded if they are younger than 18 or older than 30 years, left handed; score of the Fagerstrom Test for Nicotine Dependence (FTND) [35] > 6; score of the Alcohol Use Disorder Identification Test (AUDIT-C) [36] > 9; any history of other psychiatric or neurological illness, or current or previous use of illegal substances or gambling, or currently taking any psychotropic medications; not suitable for MRI scanning, or with excessive head motion. The data in this study consisted of 39 subjects with IGD and 34 matched healthy controls.

The Beck Anxiety Inventory (BAI) [37], Beck Depression Inventory (BDI) [38], and subjective craving of Internet (gaming) adapted from the Questionnaire of Smoking Urges (QSU-brief) [39], were conducted to assess the clinical situation of the subjects.

2.2. Image acquisition

Magnetic resonance imaging (MRI) was conducted with a Siemens Trio 3-Tesla scanner (Siemens, Erlangen, Germany). The resting-state fMRI data comprised 200 continuous echo-planar imaging (EPI) whole-brain functional volumes: repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle (FA) = 90°; slice number = 33; field of view (FOV) = 200 $\times$ 200 mm; matrix size = 64 $\times$ 64; voxel size = 3.1 $\times$ 3.1 $\times$ 3.5 mm^3; gap = 0.7 mm. The subjects were instructed to look at a black screen, staying awake and motionless, and not to think of anything in particular.

2.3. Preprocessing of fMRI images

Image data were preprocessed using DPARSF version 3.0 ([40]; http://rfmri.org/DPARSF]. Slice timing was applied to correct for within-scan acquisition time differences between slices, then images were realigned to the first volume. Subject whose head motion exceeds 3.0 mm in translation or 3 in rotation was excluded. Friston's 24-parameter model [41] were conducted to reduce the confounds of head motion. Besides, signals from the cerebrospinal fluid and white matter were regressed out [42]. The data were normalized to the MNI space by Dartel [43], and smoothed with a full width at half maximum (FWHM) Gaussian kernel of 8 mm [44–47].

2.4. Group independent component analysis and network identification

The preprocessed data were further analyzed using a standard procedure in group ICA algorithm (GIFT, http://mialab.mrn.org/software/gift, version 3.0a) to identify spatially independent networks [48]. Data from all participants were concatenated into a single dataset and reduced its dimensionality using two stages of principal component analysis (PCA) [49]. Then the data were separated with an infomax algorithm [50] into 23 independent components, determined by the modified minimal description length (MDL) criteria. The analysis was repeated 20 times using ICASSO to assess the stability of Independent Components [51]. A time course for each component and its corresponding spatial map were obtained and then back-reconstructed for each participant [49,52]. The individual subjects' spatial maps of each Independent Component Networks (ICNs) were converted to Z values. Hence the intensities of each spatial map indicated the relative contribution of voxels to distributed and coherent brain activity within that ICN [53]. For the spatial maps of each selected ICN, voxel-wise one-sample t-test was conducted across all subjects to define brain regions that belong to the ICN.

Based on the descriptions available from reference studies [19,30,54,55], the SN/DMN were bilateral spatial maps, but the ECN could split to left and right maps. Referring to the main brain regions of SN/ECN/DMN introduced in Sridharan & Levitin [22], the SN/DMN/right ECN (rECN)/left ECN (lECN) were identified by visual inspection based on the descriptions of these networks of previous studies [19,30,54,55]. Furthermore, spatial sorting with Multiple Linear Regression (MLR) of GIFT was completed to assess correlations between the identified ICNs and templates by Laird (with SN/DMN/rECN/lECN corresponding to IC4 (bilateral anterior insula/frontal opercula and the anterior aspect of the body of the cingulate gyrus), IC13 (medial prefrontal and posterior cingulate/precuneus areas), IC15 (right-lateralized fronto-parietal regions), IC18 (left-lateralized fronto-parietal regions) respectively) [56].

2.5. Analyses of inter-connectivity between SN and DMN/ECN and RAI

The individual time courses for SN/DMN/rECN/lECN, obtained by back-reconstruction for each participant, were used to compute the coupling of these networks. Using the same analysis as developed by Lerman & Gu [30], the inter-network connectivity between SN and ECN ($Z_{SN,ECN}$) and between SN and DMN ($Z_{SN,\ DMN}$) were computed as the correlation coefficients between corresponding component time courses and then converted to z scores via Fisher's r-to-z transform. Finally, based on the crucial role of SN in switching between CEN and DMN and allocating attentional resources [22], we defined an SN centered resource allocation index (RAI), referring to Lerman & Gu [30], to assess the simultaneous interactions of the SN on DMN and ECN. RAI was computed as the difference between SN-CEN connectivity and SN-DMN connectivity (RAI for the left hemisphere was computed as $lRAI = z_{SN,\ lECN} - z_{SN,\ DMN}$, and for the right hemisphere $rRAI = z_{SN,\ rECN} - z_{SN,\ DMN}$). RAI reflects superior modulation of ECN than DMN; a larger RAI indicates that SN is temporally integrated more with ECN while simultaneously dissociated from DMN [25].

2.6. Statistical analyses

One sample t-test was applied across all the subjects to investigate the property of SN-DMN/ECN coupling. Independent sample t-tests were conducted to investigate the group differences in the lRAI/rRAI. To better understand which inter-network connectivity was responsible for the reduced RAI, post-hoc analyses were performed in SN-ECN connectivity ($Z_{SN,lECN}$ or $Z_{SN,rECN}$) and the SN-DMN connectivity ($Z_{SN,\ DMN}$). Although IGD subjects reported significant higher BDI and BAI scores than HC, given concern related to the post-hoc inclusion of covariates [57], and the significant correlations between BDI/BAI scores and hours spent on Internet gaming per week/CIAS scores/craving for Internet (gaming) (see Supplementary material Table S1), including these measures as covariates may remove variance explained by problematic Internet game-playing or IGD severity. Thus, we did not include these variables as covariates in our primary data analyses.

Pearson correlations were performed between the altered RAI and severity of IGD/score of craving within IGD to examine its relationship with clinical assessments.

3. Results

3.1. Participant characteristics

There was no significant differences between the IGDs and HCs in age, education, the proportion of cigarette/alcohol users, or the frame-wise displacement (FD) of head position [58,59]. As expected, IGD individuals had significantly higher scores on CIAS, craving, anxiety, depression, and more hours spent on Internet gaming (Table 1).

3.2. Independent component networks in resting state

Referring to the templates in Laird [56], SN was consistent with its ICN4 ($r^2 = .19$), the identified DMN was consistent with their ICN13 ($r^2 = .28$), whereas the rECN and lECN were respectively consistent with their ICN15 and ICN18 ($r^2 = .29$ and 0.17, respectively). The Stability index (Iq) of these components were 0.98, 0.97, 0.98 and 0.97, respectively. These components are displayed at $p_{FWE} = 0.000001$ of the one sample t-test in Fig. 1.

3.3. Differences in RAI/SN-DMN/rECN/lECN connectivity and its correlations with severity of addiction/craving for Internet gaming within IGD

Across all the subjects, SN-DMN connectivity was significantly negative ($t_{(72)} = -2.56$, $P = .013$, $d = -.30$), and SN-rECN connectivity was significantly positive ($t_{(72)} = 9.36$, $P < .001$, $d = 1.10$), however SN-lECN connectivity was not significant different from zero ($t_{(72)} = .85$, $P = .400$, d = 10). Then we focused on the generated rRAI/lRAI from the difference between SN-rECN/SN-lECN and SN-DMN connectivity, the rRAI and lRAI was significantly higher against 0 ($t_{(72)} = 13.12$, $P < .001$, $d = 1.18$; $t_{(72)} = 3.30$, $P = .002$, $d = .39$).

Moreover, rRAI was decreased significantly in IGD compared to HC ($t_{(71)} = -2.42$, $P = .018$, $d = -.58$), but the decrease of lRAI was not significant ($t_{(71)} = -.80$, $P = .426$, $d = -.01$; Fig. 2 A). The post-hoc analyses manifested that IGD showed significantly increased SN-DMN connectivity ($t_{(71)} = 3.36$, $P = .001$, $d = .80$), while there was no significant alteration of SN-rECN connectivity in IGD ($t_{(71)} = 1.32$, $P = .190$, $d = .30$) (Fig. 2 B).

The rRAI was negatively correlated with the scores of craving ($r = -.37$, $P = .020$; Fig. 2 C), but not with severity of addiction (CIAS: $r = -.11$, $P = .513$; hours spent on Internet gaming per week: $r = .000$, $P = .998$) in IGD. Correlation analyses between

Table 1
Participants' characteristics.

Group	IGD(n = 39)		HC(n = 34)		t	df	P
	M	SD	M	SD			
Age	22.26	1.82	22.82	2.22	−1.20	71.00	.234
Education	16.00	2.09	16.24	1.88	−0.50	71.00	.616
CIAS	78.97	8.11	28.56	15.79	16.78	47.72	.000
Craving (QIGU-brief)	39.03	7.06	28.68	18.48	3.08	41.35	.004
Anxiety (BAI)	5.54	5.83	2.56	3.17	2.76	60.24	.008
Depression (BDI)	9.87	5.15	2.47	3.43	7.30	66.64	.000
Hours spent on Internet gaming per week	26.13	10.22	0.36[c]	0.48[c]	4.05[a]	44.00	.000
Number of drinkers	29.00		22.00		0.80[b]	1.00	.370
Number of smokers	2.00		0.00		1.79[b]	1.00	.495
Mean FD Power	0.14	0.07	0.12	0.05	1.38	71.00	.172

SD: standard deviation; IGD: individuals with Internet gaming disorder; HCs: healthy controls; CIAS: Chen Internet addition scale; QIGU-brief: subjective urge of Internet (gaming) questionnaire adapted from the questionnaire of smoking urges; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; Mean FD Power: the mean value of frame-wise displacement (FD) of Power.
[a] Mann-Whitney U Test.
[b] Chi-square test.
[c] Data of 7 HCs were included; other HCs never played Internet games.

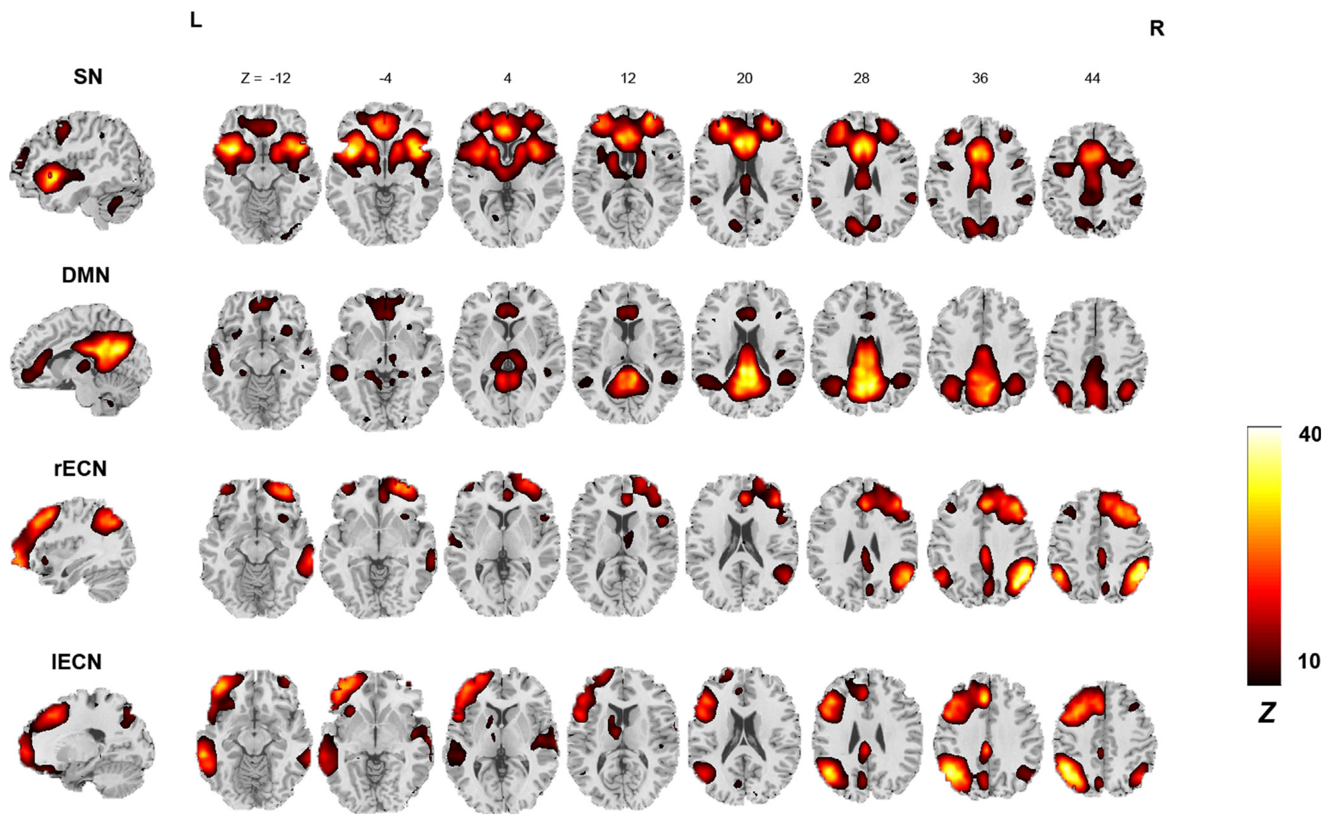

Fig. 1. Brain networks revealed by the group-level independent component analysis (gICA). The salience network (SN), default-mode network (DMN), and left and right executive-control network (lECN/rECN) are shown, at the threshold of $P_{FWE} < 0.000001$ (n =73) and overlaid onto the Talairach standard brain map based on neurological (left = left) convention. Slice coordinates are given in millimeters.

SN-DMN/SN-rECN connectivity ($z_{SN,DMN}/Z_{SN\_rECN}$) and severity of addiction/craving for Internet gaming within IGD were done and the results showed no significant associations ($|r|$'s $\leq$.25, p's $\geq$.125; details in Supplementary material Table S2).

4. Discussion

To the best of our knowledge, this is the first study to investigate the abnormality in network coupling of SN, ECN and DMN in IGD. Our study showed that the rRAI, an index reflecting the extent of superiority of SN-rECN connectivity ($z_{SN,\ rECN}$) versus the SN-DMN connectivity ($z_{SN,\ DMN}$), was decreased significantly in IGD compared with HC, which was mainly caused by significantly increased SN-DMN connectivity; and was negatively correlated with the scores of craving for Internet gaming within IGD.

Given the critical role of SN in toggling resources between the ECN and DMN, we mainly focused on the inter-network connectivity between SN and DMN/rECN/lECN, and we found that SN had significantly negative connectivity with DMN, and positive connectivity with rECN but not lECN. Previous studies have also demonstrated that the ECN was involved in exteroceptive processes related to cognitive control and goal-directed attention [60], while DMN was implicated in interoceptive processes and self-referential thinking [27]. Our findings were supported by the previous evidences that SN facilitated orientation to external versus internal stimuli and allocating attention [23,26–28], through its positive correlation with ECN and negative correlation with DMN [22,25,61]. The rationale here is that SN and CEN are typically co-activated during cognitively demanding tasks, while SN and DMN are typically anticorrelated [62].

The rRAI, integrating SN-ECN connectivity ($z_{SN,\ rECN}$) and the SN-DMN connectivity ($z_{SN,\ DMN}$), may reflect a predominant resource allocation by SN to externally oriented cognitive and behavioral control than internally oriented processes. The reduced rRAI we found suggested that the homeostatic balance was impaired in IGD, similar with the findings in the abstinent smokers compared with the smoking-sated subjects [30] and in Attention-deficit/hyperactivity disorder (ADHD) compared with HC [54]. Moreover, the only significant group difference in rRAI but not lRAI was consistent with previous results showing the causal outflow hub of the right frontal insular cortex (a key component of SN) to rECN and DMN, but not on the left hemisphere [22]. A possible explanation is that the rECN played a particularly crucial role in the interpretation and modulation of such bodily sensations [63], supported by the reduced craving in cocaine dependent individuals by repetitive transcranial magnetic stimulation (rTMS) over the right, but not the left ECN [64], and the risk-taking behavior induced by a disruption of rECN [65].

IGD showed an increase in SN-DMN connectivity but not in SN-rECN connectivity, suggested the increased resource was allocated to DMN to promote internal mental processes against the cognitive control. In line with this finding, we had found that IGD had higher functional connectivity between anterior insula and areas of DMN [9], and higher task-related activity in the default mode network (DMN) when making the risky decisions [47]. Similarly, cannabis users also showed enhanced of functional anti-correlation between DMN and insula [66], as well as higher functional connectivity between the right anterior insula and components of DMN (e.g., bilateral precuneus, posterior cingulate cortex and left angular gyrus) in substance use disorders [23,67–69]. Furthermore, maladaptive interactions between the insula and DMN have been thought of as a key neural marker underlying the development and maintenance of addiction [24].

We have also found that rRAI was negatively correlated with the higher craving for internet gaming in IGD, consistent with the association between decreased RAI and increased craving for

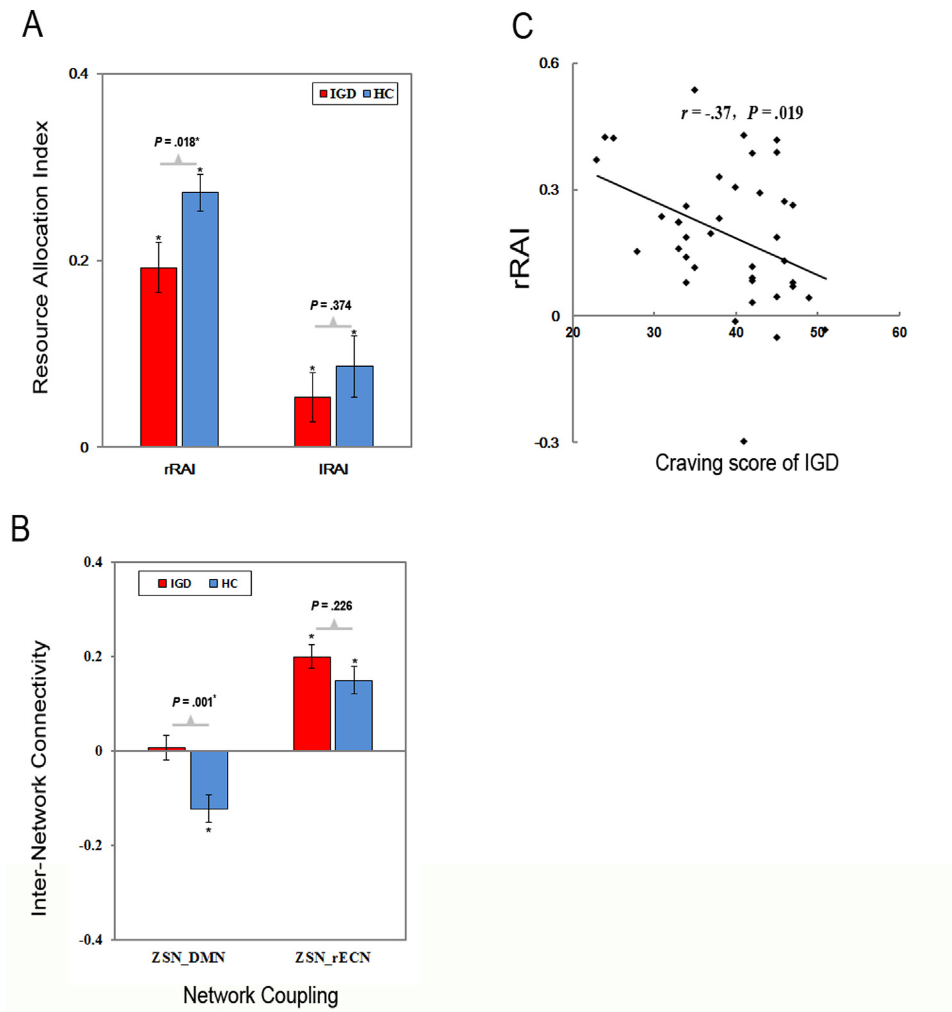

Fig. 2. Group differences in right Resource Allocation Index (rRAI) and its correlations with craving for Internet gaming within IGD, and responsible group differences in inter-network connectivity. (A) Group differences in right and left Resource Allocation Index (rRAI/lRAI). (B) Group differences in inter-network connectivity, responsible for group differences in right Resource Allocation Index (rRAI). SN_DMN: connectivity between salience network and default-mode network; SN_rECN: connectivity between salience network and right executive-control network. Note: * means the result is significant. (C) Negative correlations between Resource Allocation Index for right hemisphere (rRAI) and craving for Internet gaming within IGD. Lines represent the best-fit regression.

smoking by Lerman & Gu [30]. Furthermore, we also examined the relationship between SN-DMN connectivity ($z_{SN,\ DMN}$) and scores of craving within IGD, and results showed no significant associations, suggesting that the dual modulations of DMN and ECN were more sensitive than individual paired network couplings in accounting for IGD, as observed in the previous study of substance addiction and ADHD [30,54]. These findings may be explained by the triple-network model, proposed by Menon [23], that abnormal organizations of the SN, ECN and DMN are prominent characteristics of various psychiatric and neurological disorders, including addiction. The key part in this model is the improper allocation of saliency to external stimuli or internal mental events [23,25]. Thus, in IGD, SN directed more attentional resources towards the internal state via increasing interaction with DMN, despite effort at cognitive control (SN-rECN connectivity) in an attempt to override/inhibit the enhanced craving, the dysfunction of SN in switching from DMN to ECN (decreased rRAI) made individuals perceive more pronounced self-focused thoughts related to craving and withdrawal.

It is important to note that IGD showed significantly higher anxiety and depression scores than HC, which were significantly associated with problematic Internet game-playing. Similar with findings, prior studies have reported elevated anxiety and depression scores among frequent Internet users [70,71], which were positively related with problematic Internet use [72–74]. In addition, among psychological variables considered, depression has been most strongly associated with the development of IGD [75]. Thus, for individuals with IGD, higher depression and anxiety might be representative indicators of problematic Internet game-playing. Actually, we also did additional analyses with anxiety/depression and head motion as covariates, there were still marginal significant decrease in rRAI, and significant increases in SN-DMN connectivity (see Supplementary material Table S3). Further studies explicitly recruiting individuals with IGD that have low levels of anxiety and depression are needed to disentangle the effects of these variables on the coupling of these networks.

One limitation of our study is that only male subjects participated in the study. So further studies with female participants were needed to confirm and/or extend the current results. Another is that RAI is an imaging index reflecting inter-network connectivity of SN, ECN and DMN, and further analyses including other networks (e.g., those reflecting emotions) may have greater potentials to characterize abnormal behaviors in IGD. Moreover, because there was no collection of the physiological data, we can't exclude the effect of cardiac and respiratory fluctuations on our results.

5. Conclusion

In summary, this study provided novel evidence for the triple-network model in IGD, that the interactions between ECN/DMN and SN, especially the deficient modulation of the activity of ECN versus DMN by SN played a critical role in the maintenance of addictive behaviors in IGD. Such large-scale brain network coupling may provide novel insights for understanding the neurobiological mechanisms underlying IGD and for developing effective treatment strategies for the disorder.

Consentment

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

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eurpsy.2017.06.012.

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