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REVIEW ARTICLE

# Abnormal structural alterations and disrupted functional connectivity in behavioral addiction: A meta-analysis of VBM and fMRI studies

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**ABSTRACT**

*Background:* Altered large-scale brain systems, including structural alterations and resting-state functional connectivity (rs-FC) changes, have been demonstrated as effective system-level biomarkers for revealing potential neural mechanism of multiple brain disorders. However, identifying consistent abnormalities of large-scale brain systems in behavioral addictions (BA) is challenging due to varying methods and inconsistent results. Therefore, the aim of this study was to identify the significantly abnormal large-scale brain systems in BA. *Method:* PubMed, OVID Embase, OVID Medline, and Web of Science were searched with relevant keywords to identify potential studies. A total of 52 studies including 35 rs-FC studies and 17 structural studies were examined by extracting the coordinates of seeds and target brain regions. The seeds were then categorized into predefined seven networks by their locations based on previous parcellations in rs-FC studies, followed by pooling the results in those networks. *Results:* The rs-FC findings illustrated that BA were characterized as abnormal networks in response to inhibition, salience attribution, self-referential mental process, and reward-driven behaviors. Meanwhile, meta-analysis of structural studies showed decreased gray matter volume in the anterior cingulate cortex, extending to the middle cingulate cortex and the superior frontal gyrus. Importantly, overlapping regions in the cingulate cortex and anterior thalamus projections extending to caudate regions exhibited both dysfunctions in structure and rs-FC. *Conclusions:* This study highlighted substantial dysconnectivity in BA, which might result in impaired response to inhibition and salience attribution. Therefore, this study might provide novel insights of neural biomarkers for clinical diagnoses and treatment targets for BA.

**KEYWORDS**

meta-analysis, behavioral addiction, frontoparietal network, ventral attention network, insula

## INTRODUCTION

Behavioral addictions (BA) are characterized by repetitive and compulsive addictive behaviors despite the presence of disadvantageous consequences (Derevensky, Hayman, & Lynette, 2019; Petry, Zajac, & Ginley, 2018). Those addictive behaviors include pathological gambling (PG), internet gaming disorder (IGD), mobile phone addiction, shopping addictions, and sex addiction, among others. Although numerous similarities exist between substance use disorder (SUD) and BA, the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-5) workgroup maintains that neurobiological basis of BA is independent of that of SUD, based

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on growing neuroscientific evidence (Derevensky et al., 2019). More importantly, prevalence rates of BA have been profoundly increasing over the past ten years, with rates for IGD increasing from 2.38% to 3.91% and rates for PG increasing from 0.1% to 6.0% (Abbott, 2020; Stevens, Dorstyn, Delfabbro, & King, 2021). BA is associated with a set of explicit symptoms, including addictive activities, mood modification, tolerance, withdrawal symptoms, conflict with other things, relapse, and a tendency of suffering from psychiatric disorders (Derevensky, 2019). In addition, BA is also associated with impaired cognitive functions, such as sensation seeking, inhibitory control, attentional bias, and intertemporal choice (Gao, Jia, Zhao, & Zhang, 2019; Morris & Voon, 2016; Müller, Dreier, Beutel, & Wölfling, 2016; Weinstein, Abu, Timor, & Mama, 2016). These altered symptoms or cognitive impairments have been clearly linked to abnormal large-scale brain systems. Those systems are demonstrated by distinct brain regions (i.e., nodes) and inter-regional connectivity (i.e., edges) (Park & Friston, 2013). In particular, it is essential to examine disrupted large-scale brain systems including structural alterations and functional connectivity changes, which can serve as an effective systems-level biomarker to fully understand neural mechanisms of BA. Therefore, significantly abnormal large-scale brain systems in BA will be inspected in present work by using a multi-modal meta-analysis approach based on the presently available results.

More interestingly, with the advancement of neuroimaging tools and advanced analysis methods, abnormalities in physiology, structure, functional connectivity could be revealed at both microscopic and macroscopic levels (Buchbinder, 2016; Zeng, 2018). In particular, combination of magnetic resonance imaging (MRI) and voxel-based morphometry (VBM) has been broadly accepted to detect alterations in gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) associated with various brain disorders (Nemoto, 2017). For example, Han, Lyoo, and Renshaw (2012); Jin et al. (2016); Lin, Dong, Wang, and Du (2015); Seok and Sohn (2018) have identified decreased gray matter volume (GMV) in the left anterior cingulate cortex (ACC), right supplementary motor area (SMA), temporal gyri, and occipital gyrus in BA. Meanwhile, Ko et al. (2015); Lin et al. (2015); Zhou et al. (2011) also demonstrated increased GMV in the right ventral striatum, right prefrontal cortex (PFC), hippocampus, and amygdala. Additionally, Qin et al. (2020) investigated brain GMV alterations in BA, demonstrating decreased GMV in the left ACC, right putamen, and right SMA. Despite of discrepancy between decreased and increased GMV, those subcortical nuclei and PFC are considered as crucial and dominant regions responsible for disrupted brain structures and functions in individuals with BA.

It is important to note that while neural correlates of BA and SUD share similarities, there are also distinct differences between BA and SUD. Unlike SUD, some brain regions of BA were not directly altered by the specific neurotoxic profiles and neurotransmitter systems of consumed substance, such as thalamus (Pando-Naude et al., 2021). However, the neural underpinnings of BA share three core similarities with SUD, including: 1) the ventral striatum engaged in compulsive seeking sensation and impaired reward circuity, 2) the PFC involved in unstoppable control behaviors, and 3) the amygdala associated with negative stressful emotions.

Resting-state functional connectivity (rs-FC) denotes another crucial aspect of large-scale networks that quantifies brain activity of different brain areas at rest. Therefore, rs-FC has been widely adopted to reveal difference in large-scale intrinsic functional connectivity associated with various brain disorders (Briley et al., 2022; Lv et al., 2018). In particular, seed-based connectivity analysis is the most commonly used rs-FC analysis method, which measures the correlations between time series of region-of-interest (ROIs) and target regions (Smitha et al., 2017). Interestingly, findings from rs-FC studies have illustrated multiple altered functional connectivity networks within BA, including the default mode network (DMN), frontoparietal networks (FPN), affective networks (AN), and their connections with other networks (Bae, Han, Jung, Nam, & Renshaw, 2017; Kim et al., 2021; Liu et al., 2018). However, findings on BA's functional connectivity at rest are still mixed. For example, some studies have identified strong functional connectivity within the DMN (Chen et al., 2014; Ding et al., 2013), while others have reported the opposite pattern (Zhang et al., 2015). Additionally, the locations, sizes, and properties of seed ROIs in previous rs-FC studies have been inconsistent, and the confounding effects of factors have varied across studies, such as age, gender ratio, addiction type, and sample size. For instance, previous studies have found age is negatively correlated with functional connectivity of orbital frontal cortex (OFC) among BA (Chen et al., 2020), and gender ratio might also have an impact on brain functions of BA (Zeng et al., 2021). Consequently, it is challenging to comprehensively depict and characterize the functional connectivity and structural information alterations associated with BA. To date, no meta-analysis has been carried out to inspect the dysfunctions of rs-FC and structural changes in patients with BA.

In this study, seed ROIs were categorized into the fitted functional network based on their locations (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015; Radua et al., 2012). And then meta-analysis was performed based on the parcellated functional networks in both positive and negative directions. Several functional networks that might exhibit abnormalities in addictions were examined (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Choi, Yeo, & Buckner, 2012; Yeo et al., 2011), including the DMN, FPN, ventral attention network (VAN), dorsal attention network (DAN), AN, somatosensory network (SSN), and visual network. In particular, to gain a better understanding of large-scale brain system, anisotropic effect-size version of seed-based mapping (AES-SDM) and multi-model analysis were adopted for the present work by converting the seed-based functional connectivity into consistent patterns of impairments among predefined networks (Radua & Mataix-Cols, 2012). To the best of our knowledge, this study is among the largest and first meta-analysis studies to:

1) explore the rs-FC changes in patients with BA as compared to those of health controls (HC), 2) examine the joint alterations from both rs-FC and GMV, and 3) inspect the relationships between brain network dysfunctions and relevant demographic (age, gender) and clinical variables (depression, anxiety, severity degree of BA, sub-types of BA) in patients with BA.

## METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009).

### Search strategies

A comprehensive search was carried out to identify studies exploring the rs-FC networks or GMV in individual with BA, which were published in English up to June 2021 in four electronic databases including PubMed, OVID Embase, OVID Medline, and Web of Science. The keywords were set as BA ("behavioral addiction" OR "internet gaming disorder" OR "pathological gambling") and structural or functional MRI ("magnetic resonance imaging" AND "resting-state" OR "functional connectivity" OR "grey matter" OR "voxel-based morphometry" OR "VBM"). The full search strategy was presented in Supplementary Materials and additional meta-analysis databases, such as Brainmap and Neurosynth, were also provided as supplements. Besides, reference lists of studies contained in the final full-text paper consensus list were thoroughly reviewed for additional relevant studies.

### Inclusion criteria and study selection

Studies included in this meta-analysis were original case-control MRI studies adopting seed-based rs-FC or VBM to make comparisons between BA patient groups (diagnosed according to the DSM-5, or ICD-10 criteria) and HC with reported coordinates in Montreal Neurological Institute (MNI) space or Talairach space (TAL). Studies should be excluded if they used samples with the same seed ROIs as other studies (Gao, Shuai, et al., 2019). In particular, publications that included the same sample yet adopted different seed ROIs were coded as separate datasets. Two researchers (ZX and HX) reviewed studies independently based on aforementioned criteria and reached a consensus in the end. In cases where conflicts arose between the two researchers during study selection, they resolved them through discussion and consensus, with a third-party arbiter's (ZY) consultancy in rare cases when disagreements persisted.

### Data extraction

Relevant variables were extracted from eligible studies, including the coordinates of the center of each seed ROI mass, peak effect in fMRI studies, coordinates of GMV alterations in VBM studies, participant characteristics (e.g., sample size, age, gender), clinical measurements (e.g., depression, anxiety, severity of addiction), and parameters of MRI acquisition. In particular, the seed ROIs in fMRI studies were categorized into seven predefined resting-state functional networks, which included the DMN, FPN, VAN, DAN, AN, SSN, and visual network, according to their corresponding MNI or TAL coordinates (Buckner et al., 2011; Choi et al., 2012; Yeo et al., 2011). Meanwhile, the strengths of connectivity between seed ROIs and target brain regions were categorized into hyperconnectivity and hypoconnectivity conditions based on the connectivity analysis results. Hyperconnectivity was denoted as increased positive or decreased negative connectivity of rs-FC of BA group compared to HC, whereas hypoconnectivity was defined as decreased positive and increased negative connectivity of rs-FC. Besides, findings that did not show significant differences in seed-to-whole brain rs-FC between BA and HC groups were also included in the meta-analysis.

### Meta-analysis

Separate meta-analysis in VBM and fMRI were respectively performed via an anisotropic effect-size version of signed differential mapping software package (AES-SDM, 5.15 version, https://www.sdmproject.com/software/). Firstly, the coordinates and statistics ($T$, $Z$, and $p$ values were converted to $T$ values) of the cluster peaks were selected and prepared. And then effect-size maps in structural and functional neuroimaging alterations in BA group were recreated respectively for each study via an anisotropic unnormalized Gaussian kernel, such that voxels were assigned a high value if they were close to the peak coordinates (Radua et al., 2014). Further, meta-analytic computation was applied to each individual map, which was influenced by sample size, intra-study variance, and inter-study heterogeneity (Salimi-Khorshidi, Smith, Keltner, Wager, & Nichols, 2009). In addition, to reduce false positive rate (FDR), a more conservative threshold was chosen, in which only abnormality with a voxel-level (height) threshold of $p < 0.001$ with peak $Z > 1$ and a cluster-level (extent) threshold of 100 voxels was able to be reported (Radua et al., 2012; Tang et al., 2018). The effect networks were also categorized based on the spatial correlation between the clusters of meta-analysis results and predefined seven networks mentioned above. To improve accuracy of network classification, the networks from previous studies (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012; Smith et al., 2009) were also offered to compare the clusters from meta-analysis with their predefined networks as supplements.

More importantly, a conjunction analysis was conducted to examine the regions of shared abnormalities across structures and rs-FC in BA group as compared to those in HC group. The $p$ values of union alterations were calculated using the two probability maps of separated meta-analysis in each group within each voxel: $p_{UNION} = p_{rs\text{-}FC} + p_{VBM} - p_{rs\text{-}FC}{}^{*}p_{VBM}$. To account for noise in the estimation of meta-analytic $p$ values, the voxel level threshold was decreased to

0.0001 and the cluster level threshold was set to 100 voxels (Radua, Romeo, Mataix-Cols, & Fusar-Poli, 2013).

### Control analysis

To assess the reliability, robustness, and potential confounding moderators of results, six complementary analyses were respectively carried out for each seed-based network. 1) Subgroup analysis: to explore the alterations of large-scale brain systems among sub-types of BA, a subgroup analysis of IGD was conducted, as this subtype had a sufficient number of studies. 2) Heterogeneity: inter-study heterogeneity was calculated by using $Q$ value. Clusters were considered as heterogeneous if the studies showed significant heterogeneity ($I^2$ > 50%) when the results were extracted for comprehensive meta-analysis. 3) Meta-regression: The potential effects of several demographical (age, gender) and clinical data (depression, anxiety, impulsivity, severity degree) on large-scale brain systems were explored by meta-regression. The meta-regression analyses were done respectively if more than eight studies had reported those variables (Radua & Mataix-Cols, 2009). Considering the significant difference among various scales, the normalized score was adopted to recalculate the scales according to the lowest and highest scores (Rogers & De Brito, 2016). The normalized score = (primary score – the minimum score)/(the maximum score – the minimum score). Still, to reduce FDR, the voxel-level threshold of $p < 0.0001$ and cluster-level threshold of 100 voxels were chosen. 4) Potential bias from MRI parameters: to examine this effect, a contrasting analysis was adopted with $p < 0.0001$ and cluster-level over 100 voxels exhibiting group difference. 5) Reliability of all analyses: jackknife sensitivity analysis was used to examine the reliability of all analyses (Radua & Mataix-Cols, 2009). The results would be replicable if previous significant findings still remained keeping significant in all combinations of studies or with one or two exceptions. 6) Publication bias: the bias associated with studies with positive outcomes being more likely to be published, as compared to those reporting negative outcomes, was tested by using Egger's test with a threshold of $p < 0.05$.

## RESULTS

### Search results and characteristics of included studies

The initial electronic search yielded 1,067 studies from the four datasets, which were reduced to 721 studies after removing 346 duplicates. Additional 669 studies were screened out based on titles, abstracts, and full-texts, resulting in 35 rs-FC studies and 17 GMV studies for formal analysis (Fig. 1). The rs-FC studies consisted of 39 datasets comparing the differences between BA and HC groups, while four studies included comparisons of three groups. A total of 1,143 patients and 1014 HC participants were included in the rs-FC studies, with an average age of 22.14 and 22.03 years old, respectively. The GMV studies included 423 patients and 481 HC participants, with an average age of 28.43 and 28.88 years old, respectively. There were no significant differences in age or gender ratio between BA and HC groups in rs-FC and GMV studies (Table S2 and Table S3).

In addition, 66 seed ROIs were extracted from the 39 BA datasets for further meta-analysis (Table S1), with DMN involving 21 seeds, FPN 16 seeds, AN 24 seeds, and VAN 13 seeds. The MRI acquisition parameters in rs-FC and GMV analysis were listed in supplementary tables (Table S4 and Table S5), which showed overall satisfactory consistency.

### Rs-FC alterations in BA

Relative to the HC group, the BA group exhibited hyperconnectivity within the FPN and between the FPN seeds and the right SFG. Meanwhile, the AN showed increased connectivity with the FPN and VAN, whose cluster centers were located along the right inferior frontal gyrus (IFG) and corpus callosum, respectively. Additionally, hyperconnectivity was identified within the VAN, which showed the highest connectivity strength on the right rolandic operculum cluster and the left median cingulate cluster. Interestingly, BA was also linked to hypoconnectivity between the FPN seeds and areas of the posterior cingulate cortex, which was distributed within the DMN. Further, decreased connectivity between the VAN seeds and the left supplementary motor area was also revealed within VAN (Table 1 and Fig. 2 Panel A).

### GMV alterations in BA

BA group showed decreased GMV on the left anterior cingulate cortex (ACC), extending to the median cingulate cortex (MCC) and SFG as compared to HC group. No brain regions with increased GMV were detected (Table 2 and Fig. 2 Panel B).

### Conjunction analysis in BA

Cluster of the left anterior thalamic projections to the caudate demonstrated increased GMV and decreased rs-FC with the FPN. By contrast, most brain regions exhibited decreased GMV and altered rs-FC patterns jointly for the BA group as compared to those from the HC group. In addition, the cluster of the left ACC, as part of the DMN, showed decreased GMV and reduced hypoconnectivity with the DMN seeds in BA. Meanwhile, the VAN seeds showed hypoconnectivity with the cluster of the MCC extending to the SFG and ACC, and concurrently reduced GMV (Table 3 and Fig. 2 Panel C).

### Control analysis

Subgroup analyses of 34 IGD datasets in rs-FC revealed that the results of rs-FC alterations remained largely unchanged (Table S7). Moreover, one additional significant cluster was found where IGD was linked to decreased functional connectivity between FPN seeds and the left putamen. Subgroup analyses of 11 IGD datasets in GMV also revealed that the IGD showed decreased GMV in the ACC cluster, while IGD

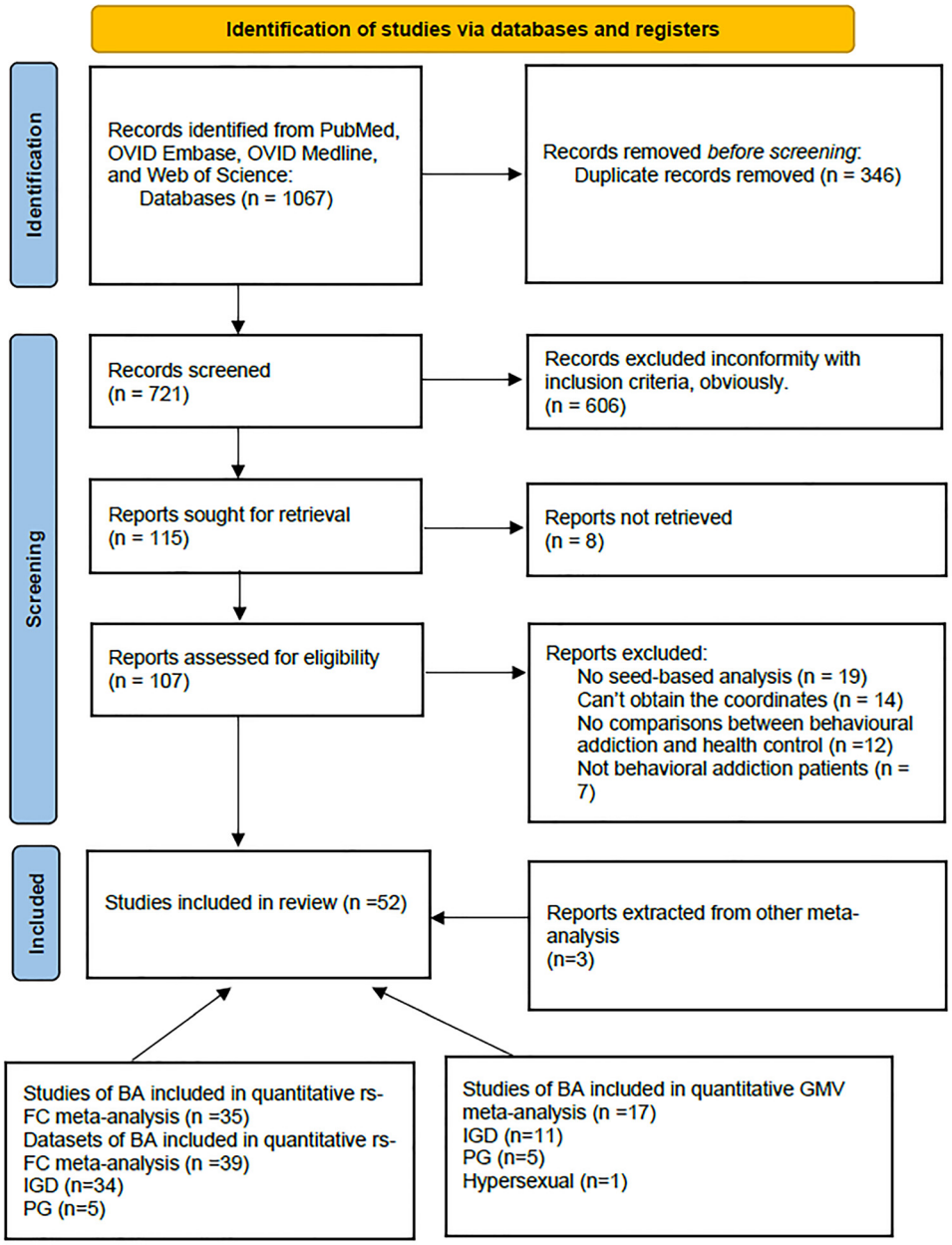


*Fig. 1.* Flow chart for the selection of rs-FC and GMV studies associated with BA

also showed decreased GMV in the SMA and increased GMV in the left caudate nucleus (Table S8).

The results of control analysis suggested that the findings from the meta-analysis have high replicability and reliability according to the jackknife sensitivity analysis. Specifically, all related brain regions from meta-analysis were preserved for all combinations, except for the corpus callosum cluster and the right rolandic operculum cluster which remained significant for the most cases except one combination of datasets (Table S6).

As for the heterogeneity test, most studies showed low heterogeneity with $I^2 < 10\%$, except for the cluster of the left ACC in GMV analysis ($I^2 = 16.216\%$), the left MCC (with $I^2 = 20.8$), and the left SMA (with $I^2 = 31.14$) in rs-FC analysis, implicating moderate heterogeneity.

In addition, all clusters showed no significant publication bias, based on Egger's test ($p > 0.05$), except for the right IFG in BA vs. HC group comparison ($p = 0.019$) (Supplementary figures S1–8). Furthermore, the model of scanner, impact of closed eyes, and duration of resting state were also inspected, and no difference was found between the subgroups.

More importantly, the results of the present analysis demonstrated that factors including mean age, male proportion, depression, anxiety, and impulsivity were irrelevant to the rs-FC for BA group (Fig. 3). The meta-regression analysis showed that the addiction severity degrees was positively correlated with the left insula (peak coordinate: −30, −6, 12; $Z = 3.875$; $p < 0.0001$; 263 voxels) and VAN as compared to those from the HC group. In particular, the severity of BA was also positively linked to GMV reduction

*Table 1.* Meta-analysis of aberrant intrinsic functional connectivity in BA compared to HC

| Seed network | Effect anatomy | Effect network | MNI coordinate | Voxels | SDM Z-value | *p* value | Breakdown (Main clusters) |
|---|---|---|---|---|---|---|---|
| **BA > HC** | | | | | | | |
| FPN | Right SFG | FPN | 20,18,56 | 142 | 2.158 | <0.0001 | Right SFG (91) |
| AN | Right IFG | FPN | 54,12,26 | 835 | 2.740 | <0.0001 | Right IFG (502)<br>Right precentral gyrus (95) |
| | Corpus callosum | VAN | −48,2,22 | 214 | 2.109 | <0.0001 | Left IFG, BA44 (62)<br>Left FAT (35)<br>Left SLF (27)<br>Corpus callosum (26) |
| VAN | Left MCC | VAN | −12,−14,38 | 265 | 2.469 | <0.0001 | Left MCC (147)<br>Left SLF (40) |
| | Right RO | VAN | 50,−30,22 | 131 | 2.396 | 0.0005 | Right STG, BA42 (58)<br>Right supramarginal gyrus (30)<br>Right RO (15) |
| **BA < HC** | | | | | | | |
| FPN | Corpus callosum | DMN | −2,−32,24 | 176 | −1.892 | <0.0001 | Left PCG (28)<br>Left median network (28)<br>Corpus callosum (28) |
| VAN | Left SMA | VAN | 0,20,48 | 1184 | −1.850 | <0.0001 | Left MCC (297)<br>Left SFG (167)<br>Left SMA (167) |

FAT: frontal aslant tract; IFG: inferior frontal gyrus; MCC: median cingulate cortex; PCC: posterior cingulate cortex; RO: rolandic operculum; SFG: superior frontal gyrus; SLF: superior longitudinal fasciculus; SMA: supplementary motor area; STG: superior temporal gyrus.

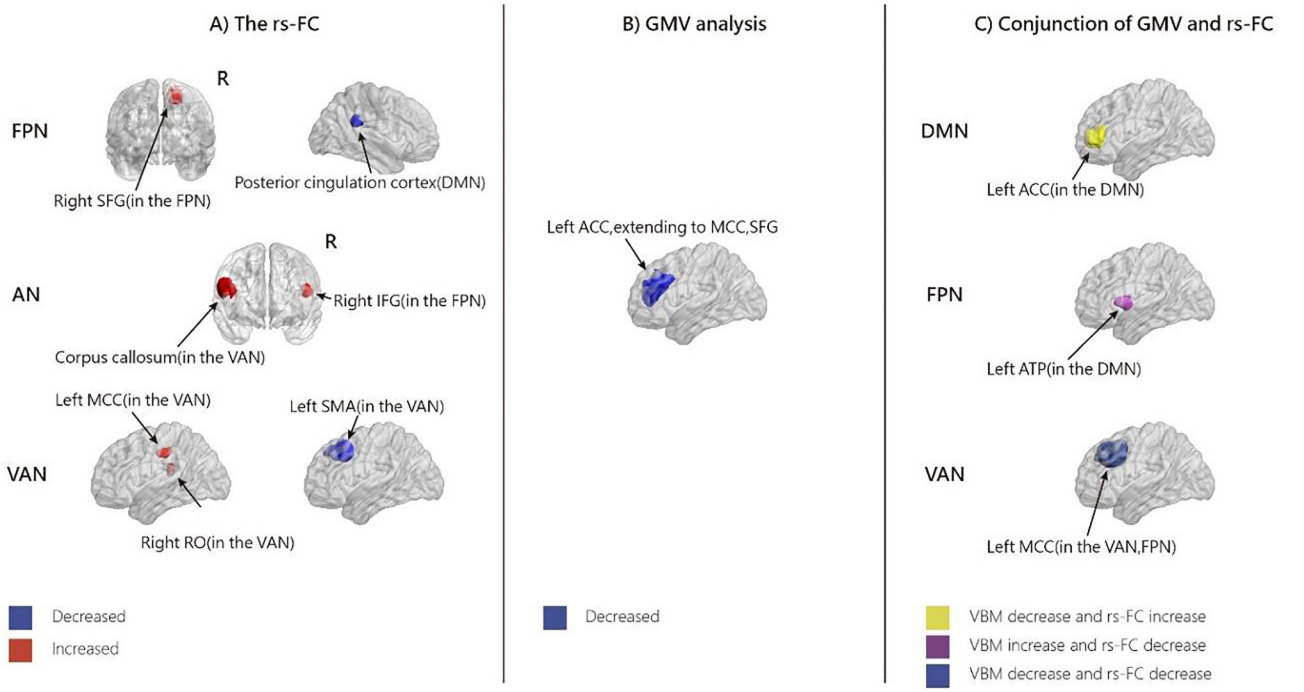


*Fig. 2.* Independent and conjunction analysis of rs-FC and GMV findings. A) Group difference in rs-FC between BA and HC groups. B) BA group showed reduced VBM results as compared to HC group. C) Analysis results based on the conjunction measure of rs-FC and VBM

*Table 2.* Meta-analysis of GMV in BA

| Anatomy | MNI coordinate | SDM Z-value | *p* value | Voxel | Breakdown (Main cluster) |
|---|---|---|---|---|---|
| Left ACC | −2,42,14 | −3.338 | <0.0001 | 1780 | Left ACC (600)<br>Right ACC (351)<br>Left SFG (270)<br>Left MCC (120)<br>Left median network (83)<br>Right MCC (84)<br>Right median network (47) |

ACC: anterior cingulate cortex; MCC: median cingulate cortex; SFG: superior frontal gyrus.

*Table 3.* Conjunction analysis of rs-FC and VBM in BA

| Anatomy | MNI coordinate | Effect network | Direction | Voxel | Breakdown (Main cluster) |
|---|---|---|---|---|---|
| DMN | | | | | |
| Left ACC | −2,48,6 | DMN | VBM decrease and rs-FC increase | 159 | Left ACC (130) |
| FPN | | | | | |
| Left ATP | −8,6,4 | DMN | VBM increase and rs-FC decrease | 252 | Left ATP (152)<br>Left caudate (50) |
| VAN | | | | | |
| Left MCC | 0,20,34 | VAN, FPN | VBM decrease and rs-FC decrease | 1485 | Left MCC (203)<br>Right MCC (256)<br>Left SFG (347)<br>Right SFG (167)<br>Left ACC (134)<br>Right SMA (112)<br>Left SMA (174)<br>Right ACC (53) |

ACC: anterior cingulate cortex; ATP: anterior thalamic projections; MCC: median cingulate cortex; SFG: superior frontal gyrus; SMA: supplementary motor area.

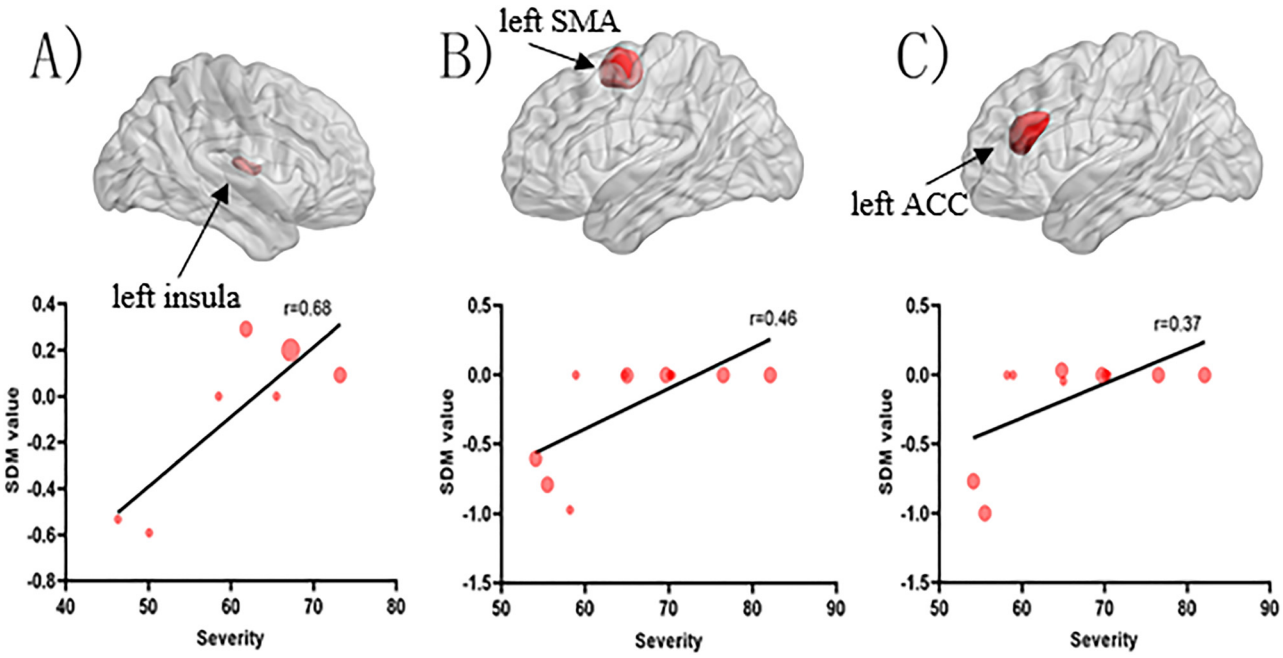


*Fig. 3.* Meta-regression results of BA. A) Positive association was identified between BA severity (the normalized score) and hyper-connectivity within VAN (located in the left insula), B) Positive correlation was revealed between the addiction severity and right SMA GMV reduction, and C) Positive correlation was also detected between the severity degree of BA and left ACC GMV decrease. The small red dots denoted the sample sizes less than 20. Middle dots represented the sample sizes between 20 and 40, whereas large dots defined the sample sizes over 40

in the right SMA (peak coordinate = 6, 4, 60; $Z = 3.048$; $p < 0.0001$; 494 voxels) and left ACC (peak coordinate = −4, 34, 18; $z = 2.605$; $p < 0.0001$; 341 voxels).

## DISCUSSION

The present multi-modal meta-analysis is among the first meta-analysis that examined the large-scale brain system impairments of BA regarding the structure information and functional connectivity as well as their abnormal interactions. Our rs-FC findings were consistent with those of the impaired response inhibition and salience attribution (iRISA) model, demonstrating the deficient core functions of VAN and FPN. The VAN plays an essential role in addiction-related cues, whereas the FPN is responsible for uncontrolled repetitive behaviors. Meanwhile, VBM results exhibited decreased GMV in the ACC, extending to the SFG and MCC. Besides, the conjunction analysis from both the brain structure and rs-FC illustrated the key brain region alterations associated with modality-general and modality-specific abnormalities, thereby suggesting the large-scale brain system biomarkers for BA.

Similar to studies on SUD (Zilverstand, Huang, Alia-Klein, & Goldstein, 2018), our study found that BA exhibited dysconnectivity within the VAN and decreased connectivity between the VAN and FPN. In addition, our study also found that the severity degrees of BA exhibited positive correlation with VAN alterations. VAN as the salience network consists of temporo-parietal junction, anterior insula, and dorsal anterior cingulate cortex (dACC), which are engaged in stimulus-driven attentional control, according to previous findings (Vossel, Geng, & Fink, 2014). Specifically, the insula plays a vital role in integrating external stimulus and interoceptive information, mediating dynamic interactions between other large-scale brain networks involved in externally oriented attention, internally oriented self-related mental processes, and emotional feeling (Menon, 2011; Naqvi, Gaznick, Tranel, & Bechara, 2014). In addition, the dACC and inferior parietal lobe constitute a core area in the allocation of attentional control governed by the FPN (Zhao et al., 2020; Zilverstand et al., 2018). Interestingly, previous studies have found that the activation of the VAN in SUD was correlated with self-rated craving and urgency for intaking substance, indicating an important role of redirecting attentional resources in addiction (Kühn & Gallinat, 2011; Naqvi & Bechara, 2009). Similar phenomenon is also found in BA, in which the repeated excessive addictive behaviors are able to activate the VAN to focus on addiction-related cues, such as internet gaming and gambling dice. This might indicate the altered functions of the VAN. For example, a meta-analysis revealed the hypoactivation of the VAN when BA patients were taking part in response inhibition tasks (Qiu & Wang, 2021). In addition, the VAN also exhibited the same alterations in risky decision making (Lee, Lee, Yoon, Kee, & Jung, 2016) and cue-reactive task in neutral cues (Noori, Cosa Linan, & Spanagel, 2016). These findings demonstrated that BA might be automatically oriented to some salient stimuli even though they did not voluntarily intend to do so. Therefore, being overly focused on addiction-related cues might result in increased interactions between networks relevant to addictive cues (like AN, gaining reward) and blunt response to neutral cues, thus resulting in a vicious circle (Noori et al., 2016; Tsurumi, Aso, Kawada, Murai, & Takahashi, 2020).

More importantly, the FPN comprising the dorsolateral prefrontal cortex (DLPFC) and lateral posterior parietal cortex, plays a primary role in the representation and maintenance of goals during motivated behavior, thereby supporting the selection of behavioral responses based on external and internal information (Marek & Dosenbach, 2018). Importantly, the DLPFC is the core node of the FPN, taking a crucial part in complex cognitive tasks such as decision making, conflict-induced behavioral adjustment, attention, working memory, and inhibitory control (Ge et al., 2017). Besides, the function of FPN is related to making rational decisions that link present sensory experiences to memory of past experiences. However, overloaded and long-lasting reward stimulus might impair the restraining ability of the FPN to the VAN (insula mainly), causing enhanced hypoconnectivity between the VAN and FPN, with BA being impulsive to addictive behaviors with a long time (Cousijn et al., 2012; Lv et al., 2016; Menon, 2011; Zilverstand et al., 2018). For example, during a cue reaction task, IGD exhibited higher engagement in the FPN in response to addiction-related cues as compared to that from neutral cues, implicating high attention allocation to gaming-related stimuli (Ko et al., 2009; Ko, Liu, Yen, Chen, et al., 2013; Liu et al., 2017). It was also found that through the effective intervention in six weeks, the FPN showed decreased activation in gaming-related stimuli (Han, Kim, Lee, & Renshaw, 2012). Besides the potential de-attenuated restraining role in the VAN, the FPN demonstrated the dysfunctions during cognitive control tasks and abnormal activation during response inhibition tasks. For example, in Go/No-go task, the BA group exhibited similar accuracy yet significantly slower reaction time and demonstrated hypoactivation in DLPFC as compared to HC group, indicating a compensatory brain activity to achieve similar performance in response inhibition (van Holst, van Holstein, van den Brink, Veltman, & Goudriaan, 2012), which also provided evidence for the hyperconnectivity within FPN. In addition, BA group manifested impaired learning ability and tended to make more intuitive and risky decisions, which was associated with the hypoactivation in the FPN (Fujino et al., 2018; Trotzke, Starcke, Pedersen, Müller, & Brand, 2015). Taken together, the addictive behaviors induced more activation in the FPN for processing the information from the VAN and compensating to achieve better performance. However, these hyper-active patterns might damage the functions of the FPN and result in deficient connectivity between the FPN and VAN and hyperconnectivity within the FPN, causing reduced self-control and higher risk-taking behaviors among BA (Pyeon et al., 2021).

Moreover, the VAN plays a crucial role in mediating the trade-off between the DMN and FPN. Studies have shown

that the DMN is deactivated during tasks, suggesting involvement in self-monitoring, attention, and introspective thoughts, whereas the FPN is more activated in cognitive control task (Menon, 2011; Sutherland et al., 2013). The conjunction of VBM and rs-FC meta-analysis results revealed increased rs-FC within the DMN (located in the left ACC), showing good agreement with previous studies (Tsurumi et al., 2020). The combined hypoconnectivity between the FPN, VAN, and DMN illustrated that their dynamic switching is impaired, which is in line with the classic triple-network dysfunction model (Menon, 2011). The triple-network dysfunction model proposed that the collection of the DMN, FPN, and VAN plays a unique role in identifying extremely wide range of cognitive tasks and changing responses proportionally according to the task demands. Addictive events detected by the VAN can disrupt the normal engagement of the FPN and DMN. This is because the DMN is responsible for internal mental processes, which can make it harder to focus on external stimuli that are important for the task at hand. As a result, cognitive resources may become impaired. Additionally, hyperconnectivity within the DMN might lead to excessive rumination, a phenomenon observed in individuals with BA who become immersed in addictive scenery they experienced or imagined (Tsurumi et al., 2020). Overly focusing on internal world is more likely to be suffered from psychiatric diseases like depression (Tsurumi et al., 2020). Individuals with IGD and depression had stronger connections within the DMN compared to those with IGD alone or HC (Lee, Lee, Namkoong, & Jung, 2018). Furthermore, the deactivated DMN is related to high task performance (Anticevic et al., 2012), whereas the hyperactivations of DMN are recognized to be related to brain regions in tasks, leading to cognitive dysfunction in addiction (Sutherland et al., 2013).

Likewise, our findings demonstrated increased connectivity between the AN and the IFG regions within the FPN. The AN, mainly including nucleus accumbens (NACC), amygdala, and OFC, is primarily involved in reward, emotion, and motivation processes (Li et al., 2018). The enhanced rs-FC between the AN and the IFG regions implicates the increased synchronization of two systems and the reward-driven behaviors for BA, consistent with previous findings (Contreras-Rodriguez et al., 2016; Kim et al., 2021; Koehler et al., 2013). Additionally, hyperactivation in the AN is responsive to addiction-related stimulus (Golec, Draps, Stark, Pluta, & Gola, 2021; Ma et al., 2019). This brain pattern might suggest a more efficient and convenient activation of reward in BA. Adopting a decision-making task, Wang et al. (2021) found the IGD exhibited riskier behaviors and exaggerated brain activity in AN (located in the NACC and caudate). In particular, it was also suggested that compared to IGD, PG exhibited enhanced resting-state connectivity between the amygdala and dorsal striatum, demonstrating that the AN was significantly correlated with strong sensation and instant feedbacks (Bae et al., 2017).

Further, consistent with previous studies (Jin et al., 2016; Lin et al., 2015), BA exhibited significantly decreased GMV in the ACC, extending to the MCC and SFG. Meanwhile, the degree of BA severity was found to be positively correlated with the decreased GMV in the SMA and ACC cluster. The ACC serves as a key node of brain structure connecting the PCC, PFC, amygdala, striatum, thalamus, and SMA (Rolls, 2019). The ACC consists of the dACC and ventral ACC (vACC). Specifically, the dACC is involved in attention and incentive salience governed by the FPN, whereas the vACC is responsible for emotional, rewarding, and motivational processing, as well as communicating with the DMN and AN (Zhao et al., 2020). In addition, the vACC is the core component of the midline DMN that plays an important role in valuation system, integrating relevant information to evaluate personal relevance and facilitate self-related decision making (Zhang & Volkow, 2019). Given its vital role in addiction, the altered structure of ACC might induce dysfunctions of BA for addictive cue detection, response inhibition, and self-referential process both at rest and during tasks (Dong, Hu, Lin, & Lu, 2013; Ko, Liu, Yen, Yen, et al., 2013; Limbrick-Oldfield et al., 2017).

In our meta-regression analysis, we found that only the degree of BA severity was positively correlated with large-scale brain system alterations, while no other demographic or clinical data showed significant correlations. Structural alterations of the ACC and rs-FC alterations of the VAN were related to stimulus-driven attentional control. Likewise, previous studies have also shown that prolonged addictive behavior leads to continuous brain alterations in VAN during rest and task performance (Hendrick, Luo, Zhang, & Li, 2012). SMA is vitally important in voluntary action and response inhibition (Wolpe, Hezemans, Rae, Zhang, & Rowe, 2022). The positive correlation between reduced SMA and the degree of addiction suggests impaired response inhibition in addiction progression. We did not find any age or gender effect on large-scale brain system alterations when setting age and gender ratio as regressors. This null effect was mainly due to the fact that age variation was not significant (at young ages) in these samples while males constituted the majority of all studies. In addition, we found no significant correlations between alterations in brain and clinical data such as anxiety, depression, and impulsivity. This is mainly due to that the degrees of anxiety, depression, and impulsivity reported in the majority of the included studies were not severe enough to cause significant alterations in the brain. More importantly, the number of included studies reporting demographic data and clinical data was relatively small, and a more conservative threshold was chosen to reduce the FDR.

Several limitations need to be considered in the present meta-analysis. Firstly, only seed-based rs-FC studies were included, whereas other analytic methods were excluded like independent component analysis due to their limited usage to date. As the seeds in the current study focused on the DMN, FPN, VAN, and AN, it is rather impractical to integrate these seeds into the DAN, SSN, and visual network. With more development in these areas, future meta-analyses could test the abnormality of DAN, SSN, and visual network with adequate studies by seed-based or other methods.

Meanwhile, future work can also examine the replicability of rs-FC abnormalities across different analytical methods. Secondly, there is no consensus about the standard protocol of rs-FC analysis. Parameters in data acquisition and processing varied across studies, such as differing size, shapes of seed ROIs, motion correction method, or even instructions for rest (e.g., eyes open vs closed). These factors might generate bias and confounding effects. The present study tested the impact of closed eyes and the duration of resting-state, while it is still impossible to examine the moderating effects of all other variables. Thirdly, there were different parcellations of networks across studies, which might mix some overlapping brain regions in different parcellations ways. Critically, some regions might play a more important role within the same networks. It is therefore important to test the replicability of rs-FC abnormalities across network parcellations with weights. Forth, different types of BA might have their distinct alterations of large-scale brain system. We have found the similarity between IGD and BA is high while there still exists discrepancy. Moreover, due to the limited numbers of studies in other different types of BA, it is difficult to comprehensively explore the impact of BA type. More importantly, there is no unified and widely used scales to measure the severity of different types of BA, thus making it difficult to explore the relations between severity of addiction and large-scale brain system alterations.

## CONCLUSION

This is the first meta-analysis concurrently inspecting the structural and rs-FC patterns of BA. A consistent model of impaired response inhibition, salience attribution, self-referential mental process, and reward-driven behaviors were detected for BA. Therefore, this meta-analysis paves a new avenue for fully understanding the mechanisms of addictive behaviors, and also offers new insight for the recovery and abstention from BA by illustrating the specific function of networks and the effect of network communications.

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*Authors' contribution:* X.Z designed the study; X.Z and X.H searched and screened the literature; X.Z, and Y.H collected the required data for meta-analysis; X.Z and F.G conducted meta-analysis; X.Z write the manuscript; Z.Y and F.G revised the manuscript.

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## SUPPLEMENTARY MATERIAL

Supplementary data to this article can be found online at https://doi.org/10.1556/2006.2023.00025.

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