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REVIEW

Shared gray matter alterations in subtypes of addiction: a voxel-wise meta-analysis

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Abstract

Background Numerous studies based on voxel-based morphometry (VBM) have revealed gray matter (GM) alterations in multiple brain regions for addiction. However, findings are poorly replicated, and it remains elusive whether distinct diagnoses of addiction are underpinned by shared abnormalities. Our aim was to conduct a quantitative meta-analysis of structural neuroimaging studies investigating GM abnormalities in two main categories of addiction: substance use disorders (SUD) and behavioral addictions (BA).

Method A systematic database search was conducted in several databases from Jan 1, 2010, to Oct 23, 2020, to identify eligible VBM studies. Meta-analysis was performed with the seed-based d mapping software package to compare alternations between individuals with addiction-related disorders and healthy controls (HC).

Results A total of 59 VBM studies including 2096 individuals with addiction-related disorders and 2637 HC met the inclusion criteria. Individuals with addiction-related disorders showed shared GM volume decrease in bilateral prefrontal cortex, bilateral insula, bilateral rolandic operculum, left superior temporal gyrus, and right Heschl gyrus and GM increase in right lingual gyrus and right fusiform gyrus comparing with HC ($p < 0.005$). Subgroup analysis found heterogeneity between SUD and BA mainly in left inferior occipital gyrus and right striatum ($p < 0.005$). Meta-regression revealed that GM atrophy in right anterior cingulate ($r = 0.541$, $p = 0.03$ (uncorrected)) and left inferior frontal gyrus ($r = 0.595$, $p = 0.015$) were positively correlated with higher impulsivity.

Conclusions This meta-analysis identified a concordance across subtypes of addiction in terms of the brain structural changes in prefrontal and insula areas, which may relate to higher impulsivity observed across addiction diagnoses. This concordance provides an organizing model that emphasizes the importance of shared neural substrates in addiction.

Keywords Substance use disorders · Behavioral disorders · Voxel-based morphometry · Gray matter · Meta-analysis

Introduction

Addiction is a growing mental health issue, though no consensus exists on whether behavioral addictive disorders (BA) fall into the same category as substance use disorders (SUD) (Potenza 2014). SUD are defined as a chronic relapsing disorder characterized by diminished control over substance intake related to neurobiological changes (Unterrainer et al. 2019). Lifetime prevalence of SUD has been estimated at up to 3% for the general population in the European Union (Alonso et al. 2004; Rehm et al. 2005), imposing a significant burden on society and healthcare systems. BA, on the other hand, known as non-substance addiction, are characterized by distress or interference with personal functions that develop as a result of repetitive rewarding behaviors other than the use of dependence-producing substances (Alabdulsalam et al. 2014). The estimated 12-month prevalence of BA in US adults is between 2% (Internet addiction) and 10% (work addiction), causing disruptions to daily functioning (Sussman et al. 2011). More evidence is thus needed

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to understand the structural and functional abnormalities of BA, especially in relation to SUD.

Addiction-related disorders share common characteristics in clinical and epidemiological samples and frequently co-occur with two or more disorders. Recently, DSM-V classifies gambling disorders as a separate non-substance-related disorder from other substance-related disorders (although they fall under the same category). This is due to the absence of the potent pharmacological effects of drugs of abuse in behavioral addictions, although similar neurobiological mechanisms have been proposed to underlie BA and SUD (Fauth-Bühler et al. 2017). In fact, the reinforcers present in behavioral addictions like gambling have been proposed to act on the dopaminergic system similarly to the SUD (Linnet et al. 2011; Joutsa et al. 2011), which may illustrate the common pathway in BA and SUD. Moreover, both disorders have deficits in impulse control which is based on impulsivity, poor control, and compulsion of addiction (Fineberg et al. 2014). Impulsivity and compulsivity are multidimensional constructs. They cover a variety of disruption within a wide range of neural processes, involving coordination of motor or cognitive responses (Robbins and Roberts 2007; Brewer and Potenza 2008). Several strands of evidence suggest that impulsivity may be an endophenotypic marker for addiction risk (Wit 2009). Nevertheless, it remains unknown whether this similarity is mediated by shared or distinct neurobiological substrate because few structural magnetic resonance imaging (MRI) studies have directly compared the two disorders.

With the quick development of high-resolution MRI and the technology of voxel-based morphometry (VBM), subtle GM alterations can also be detected, which has been widely applied in mental disorders to find evidence of gray matter (GM) changes between patients and healthy controls (Ashburner and Friston 2001). In SUD, meta-analyses of different substances using conducted by voxel-based morphometry (VBM) studies of gray matter volume (GMV) have been reported almost consistent GMV reduction relative to healthy controls in the bilateral insula, dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), superior frontal gyrus, middle frontal gyrus, and superior temporal gyrus (Yang et al. 2020; Klaming et al. 2019; Hall et al. 2018). Moreover, a meta-analysis of region of interest (ROI) found that a decrease GMV in the insula was correlated with duration of substances using (Yang et al. 2020; Hall et al. 2018). In BA, VBM studies comparing with healthy controls reported GMV reduction in the left ACC extending to the left medial superior frontal gyrus (mSFG) and bilateral orbitofrontal gyrus (OFG), right putamen, and right supplementary motor area (SMA) (Qin et al. 2020), including internet gaming disorder (IGD), pathological gambling (PG), problematic hypersexual behavior (PHB), and mobile phone dependence (MPD). In addition, Qin's results also showed that higher BIS-11(Barratt Impulsiveness Scale-11) scores in BA were positively associated with lower GMV in the ACC (Qin et al. 2020). But there has been few comprehensive meta-analysis investigating brain structural changes in distinct subtypes of addiction including both SUD and BA.

As well as the distinct clinical features in different addictions, important confounding factors such as comorbidity and medication can no doubt contribute to the inconsistency. Moreover, the lack of statistical power is also a major problem, resulting from the typically small sample size in single study. The aim of our study was to conduct a voxel-based meta-analytic comparison of all published whole-brain structural MRI studies of GMV abnormalities to explore (a) shared GM abnormalities and common neurobiological substrate for individuals with addictions, (b) heterogeneity of these findings in subgroup analysis, and (c) the association between some common addiction-related variants and GM alterations by meta-regression. We focused on studies of tobacco use disorder (TUD), alcohol use disorder (AUD), cocaine dependence (CD), pathological gambling (PG), and internet gaming disorder (IGD). Tobacco, alcohol, and cocaine use disorders were part of the SUD group, while PG and IGD formed the BA group. For the VBM meta-analysis, we hypothesized that patients with addictions would show disorder-specific GMV decrease primarily in the prefrontal and insula regions, while we expected that addiction-related variants would be associated with GMV in the prefrontal areas.

Methods

Selection of studies for meta-analysis

We searched PubMed, Web of Science, and Medline for all studies from Jan 1, 2010, to Oct 23, 2020. Studies include patients with PG, AUD, CD, IGD, and TUD. The several search terms were as follows: "internet addiction," "internet gaming disorder," "video game addiction," "cocaine-related disorders," "cocaine addiction," "alcohol addiction," "Alcohol Dependence," "Alcohol Use Disorder," "smoking," "nicotine," "tobacco," and "cigarette" coupled with "VBM," "gray matter," "voxel based morphometry," and "voxel-wise." The reference lists of studies and some details can be found in Table 1.

Studies were selected if (1) diagnoses of each study were based on DSM/ICD, quantitative assessment tools, or both; (2) they used VBM to analyze gray matter; (3) they included healthy control participants; (4) they performed a whole-brain analysis; (5) they reported coordinates in a defined stereotaxic space (e.g., Talairach space or Montreal Neurological Institute space); (6) they used consistent

Table 1 Demographic, clinical, and methodological characteristics in the included studies

Study	Patients		Controls		Diagnosis	Clinical characteristics			
	Sample size (female)	Mean age (years)	Sample size (female)	Mean age (years)		Diagnostic criteria	Duration of illness (years)	BIS-11	BDI
Bu et al. 2016	26 (0)	21.4	26 (0)	20.6	TUD	DSM-V	4.3	NA	NA
Franklin et al. 2014	80 (39)	33.8	80 (39)	32.0	TUD	Consumption of cigarettes	14.0	NA	NA
Fritz et al. 2014	315 (167)	44.1	669 (426)	51.5	TUD	Consumption of cigarettes	26.8	NA	NA
Liao et al. 2012	44 (NA)	20.0	44 (NA)	20.0	TUD	DSM-IV	NA	NA	NA
Morales et al. 2012	25 (12)	35.4	28 (18)	30.1	TUD	DSM-IV	9.0	NA	NA
P. Peng et al. (2015)a (Peng et al. 2017)	26 (NA)	29.4	53 (NA)	30.8	TUD	ICD-10	11.0	NA	NA
P. Peng et al. (2015)b (Peng et al. 2017)	27 (NA)	32.3	53 (NA)	30.8	TUD	ICD-10	13.0	NA	NA
Qian et al. 2019	44 (NA)	38.5	41 (NA)	39.0	TUD	DSM-IV	19.0	NA	NA
Stoeckel et al. (2015) (Stoeckel et al. 2016)	16 (4)	37.9	16 (5)	34.1	TUD	DSM-IV	17.6	NA	NA
Peng et al. 2018	26 (NA)	29.4	53 (NA)	30.8	TUD	ICD-10	11.0	NA	NA
Peng et al. 2018	27 (NA)	32.2	53 (NA)	30.8	TUD	ICD-10	13.0	NA	NA
Wang et al. 2014	22 (NA)	22.4	20 (NA)	21.8	TUD	DSM-IV	5.0	NA	NA
Wetherill et al. 2015	21 (9)	34.0	21 (7)	31.0	TUD	DSM-IV	NA	NA	NA
Yu et al. 2011	16 (NA)	41.6	16 (NA)	39.2	TUD	DSM-IV	21.1	NA	NA
Zhang et al. 2011	48 (24)	31.4	48 (24)	31.1	TUD	Consumption of cigarettes	12.8	NA	NA
Draps et al. 2020	26 (NA)	33.2	25 (NA)	34.5	PG	ICD-10	NA	NA	NA
Koehler et al. (2013) (Koehler et al. 2015)	20 (0)	33.7	21 (0)	39.2	PG	KFG	NA	NA	NA
Mohammadi et al. (2015) (Mohammadi et al. 2016)	15 (0)	36.7	15 (0)	36.8	PG	KFG + DSM-IV	NA	NA	NA
Zois et al. (2016) (Zois et al. 2017a)	60 (NA)	36.7	98 (NA)	36.1	PG	DSM-IV	11.2	NA	13.9
Yip et al. (2017) (Yip et al. 2018)	35 (9)	38.4	37 (9)	38.0	PG	DSM-IV	NA	70.1	NA
van Holst et al. 2012a	40 (NA)	36.5	54 (NA)	35.3	PG	DSM-IV-TR	12.2	NA	NA
Takeuchi et al. 2017	23 (NA)	36.3	36 (NA)	35.9	PG	DSM-V	13.2	NA	NA
Takeuchi et al. 2017	13 (NA)	35.6	36 (NA)	35.9	PG	DSM-V	12.9	NA	NA
Lee et al. 2018	20 (NA)	23.9	20 (NA)	22.7	IGD	DSM-V	NA	51.6	11.7
Mohammadi et al. 2020	29 (0)	23.6	29 (0)	22.7	IGD	Playing time	6.6	NA	NA
Choi et al. 2017	22 (0)	29.5	24 (0)	27.2	IGD	DSM-V	NA	NA	NA
Du et al. 2016	25 (0)	17.3	27 (0)	17.5	IGD	YDQ + IAT	NA	68.6	NA
Han et al. 2012	20 (0)	20.9	18 (0)	20.9	IGD	DSM-IV	4.9	61.5	NA
He et al. 2020	26 (6)	20.7	26 (6)	20.5	IGD	Playing time	8.1	NA	NA
Jin et al. 2016	25 (9)	19.1	21 (7)	18.8	IGD	DSM-V + IAT	6.0	NA	NA
Ko et al. 2015	30 (0)	23.6	30 (0)	24.2	IGD	DCIA	NA	78.5	NA
Lee et al. (2018) (Lee et al. 2019)	31 (0)	24.0	30 (0)	23.0	IGD	DSM-V + IAT	9.9	54.4	14.8
Lin et al. 2015	35 (0)	22.2	36 (0)	22.3	IGD	IAT	NA	NA	NA
Seok and Sohn 2018	20 (0)	21.7	20 (0)	22.4	IGD	DSM-V	NA	56	12.4
Sun et al. 2014	18 (3)	20.0	21 (3)	22.0	IGD	YDQ	NA	63.9	NA
Weng et al. 2013	17 (4)	16.3	17 (2)	15.5	IGD	YDQ	NA	68.9	NA
Yoon et al. 2017	19 (0)	22.9	25 (0)	25.4	IGD	IAT + playing time	6.3	70.1	19.4

Table 1 (continued)

Study	Patients		Controls		Diagnosis	Clinical characteristics			
	Sample size (female)	Mean age (years)	Sample size (female)	Mean age (years)		Diagnostic criteria	Duration of illness (years)	BIS-11	BDI
Zhou et al. 2011	18 (2)	17.2	15 (2)	17.8	IGD	YDQ	NA	NA	NA
Moreno-Lopez et al. 2012	38 (0)	29.6	38 (0)	31.1	CD	DSM-IV	4.1	NA	NA
Barros-Loscertales et al. 2011	20 (0)	33.3	16 (0)	33.4	CD	DSM-IV	NA	NA	NA
Alia-Klein et al. 2011	40 (0)	45.0	42 (0)	39.0	CD	DSM-IV	19.0	NA	9.0
Crunelle et al. 2014	30 (0)	20–55	33 (0)	20–55	CD	Consumption of cocaine	NA	73.8	11.0
Gardini and Venneri 2012	14 (NA)	31.1	24 (NA)	33.2	CD	DSM-IV	13.4	NA	NA
Hanlon et al. 2011	24 (7)	38.9	25 (13)	36.2	CD	DSM-IV	11.1	NA	20.3
Ide et al. 2014	84 (29)	39.8	86 (39)	38.1	CD	DSM-IV	18.0	NA	NA
Matuskey et al. 2014	14 (10)	41.0	10 (5)	30.7	CD	DSM-IV	21.0	74.0	NA
S. Meade et al. (2019) (Meade et al. 2020)	39 (15)	45.4	40 (16)	43.5	CD	DSM-IV-TR	NA	69.0	NA
W. Yip et al. (2017) (Yip et al. 2018)	37 (12)	42.4	37 (9)	38.0	CD	DSM-IV	NA	64.0	4.0
Galandra et al. 2020	18 (NA)	44.8	22 (NA)	45.6	AUD	Consumption of alcohol	10.1	NA	NA
Li et al. 2019	20 (3)	49.0	15 (2)	49.0	AUD	Consumption of alcohol	NA	NA	NA
Brooks et al. 2014	58 (33)	14.9	58 (33)	14.7	AUD	Consumption of alcohol	2.0	NA	NA
Dalvie et al. 2014	80 (47)	14.9	80 (47)	14.9	AUD	DSM-IV	NA	NA	NA
Heikkinen et al. (2016) (Heikkinen et al. 2017)	35 (20)	24.9	17 (5)	24.6	AUD	AUDIT	NA	NA	NA
Howell et al. 2013	19 (12)	23.0	19 (12)	24.6	AUD	Consumption of alcohol	NA	NA	8.1
Segobin et al. 2014	19 (2)	44.4	20 (0)	46.7	AUD	DSM-IV	29.0	NA	NA
Wang et al. 2016	20 (0)	40.0	20 (0)	40.5	AUD	DSM-IV	25.3	66.9	NA
Wiers et al. 2015	22 (0)	42.1	21 (0)	42.0	AUD	DSM-IV	14.8	NA	NA
Yoon et al. 2017	20 (0)	28.7	25 (0)	25.4	AUD	DSM-IV	5.4	75.4	25.6
Zois et al. 2017b	95 (NA)	45.9	87 (NA)	45.9	AUD	DSM-IV	10.9	NA	11.2

Abbreviations: *BIS-11* Barratt Impulsiveness Scale-11, *BDI* Beck Depression Inventory, *TUD* tobacco use disorder, *AUD* alcohol use disorder, *CD* cocaine dependence, *PG* pathological gambling, *IGD* internet gaming disorder, *ICD* International Classification of Diseases, *DSM* Diagnostic and Statistical Manual of Mental Disorders, *DCIA* Diagnostic Criteria of Internet Addiction, *IAT* internet addiction test, *KFG* "Kurzfrageboge zum Gl€ucksspielverhalten" (German gambling questionnaire), *YDQ* young diagnostic questionnaire, *AUDIT* alcohol use disorders identification test This issue has been revised.

thresholds in different regions; and (7) studies were peer reviewed and published in English as an article. Studies were excluded if (1) the patient group included other diseases such as Parkinson's disease (PD), multiple sclerosis (MS), and mental illness; (2) they did not use VBM; (3) peak coordinates were not reported; (4) only region of interest results were available; and (5) inconsistent thresholds were applied in different regions. Two authors (Zhang and Gao) independently searched, selected, and cross-checked in order to insure our study reliable. Any difference was discussed and settled by consensus.

Meta-analysis across all studies

The anisotropic seed-based d mapping (AES-SDM) meta-analytic software (www.sdmproject.com) are employed

widely in recent meta-analysis of addiction disorders or some psychiatric diseases (Yang et al. 2020; Lukito et al. 2020). ASE-SDM can use peak coordinates and effect sizes (*t*-scores) data to calculate signed (positive/negative) effect sizes and variance maps of brain regional differences between patient and control groups by convolving an anisotropic non-normalized Gaussian kernel with Hedges effect size of each peak.

AES-SDM in neuroimaging meta-analysis, maps are combined across studies based on random-effect model, taking sample size, within-study variability, and between-study heterogeneity into account. Correlated datasets (e.g., when the same group of participants completed several cognitive tasks) were included in the meta-analysis as a single set (Norman et al. 2016). Then, modulate it according to shared variance of brain activation or structure across datasets. Here are the following steps: (1) *p* value or *z* value in some studies needed to convert into *t* value online (http://www.sdmproject.com/utilities/?show=Statistics); (2) convert peak coordinates into standardized MNI space; (3) set the full width at half maximum (FWHM) to 20 mm because this will keep balance among sensitivity and specificity and other parameters including voxel $p < 0.005$, peak height threshold > 1, and cluster extent threshold > 10 voxels (Radua and Mataix-Cols 2009); (4) jack-knife sensitivity analysis performed to verify the stability and reliability of the findings by repeating the meta-analysis after excluding one study at a time. If one brain region survives in the most of the repeats, we can get the conclusion that this abnormality is stable (Radua and Mataix-Cols 2009).

Subgroup meta-analysis

To verify the stability and reliability of the findings, we divided individuals into two different subtypes for next subgroup analysis: BA subjects (including PG and IGD) and SUD subjects (including TUD, CD, and AUD), using a random effects model under the same threshold as before. To rule out medication or abstinence effects, studies excluding individuals who received clinical intervention within 6 months prior to scanning formed an intervention-free subgroup. This subgroup meta-analysis can also examine potential confounding factors.

Meta-regression analysis

Meta-regression analysis was conducted to explore the association between GM alterations and clinical features such as BIS-11 score and BDI score which were more typical to be the regressor than other indices. The clinical relevance of impulsivity is frequently highlighted because it impacts many mental and behavioral disorders and BIS-11 assesses core impulsive trait in addictions (Fineberg et al. 2014). The correlation between BDI and addiction-related disorders has been reported in the previous study (Paljarvi et al. 2009). Furthermore, we used a more conservative threshold ($p < 0.0005$) in order to decrease the false-positive rate in this meta-regression analysis (Radua and Mataix-Cols 2009). Egger's test and funnel plots constructing by ASE-SDM assessed potential publication bias in the disorder differences and shared findings (Egger et al. 1997).

Results

Search results and sample features

Searching in various databases, based on the eligible criteria, finally we identified 59 VBM articles in addiction-related studies for meta-analysis comprising 2096 individuals with addiction-related disorders and 2637 healthy controls (Fig. 1). Of these 59 studies, 15 were IGD, 10 were CD, 11 were AUD, 15 were TUD, and 8 were PG. Most of the participants aged between 20 and 45. See Table 1 for more demographic, clinical, and other characteristics.

Regional GM differences by pooled meta-analysis

As demonstrated in Table 2 and Fig. 2, the pooled meta-analysis showed that individuals with addition-related disorders are associated with lower GM volume in bilateral anterior cingulate cortex (ACC) extending to the corresponding medial superior frontal gyrus (mSFG), bilateral superior frontal gyrus medial orbital (OFG), bilateral insula, bilateral rolandic operculum, left superior temporal

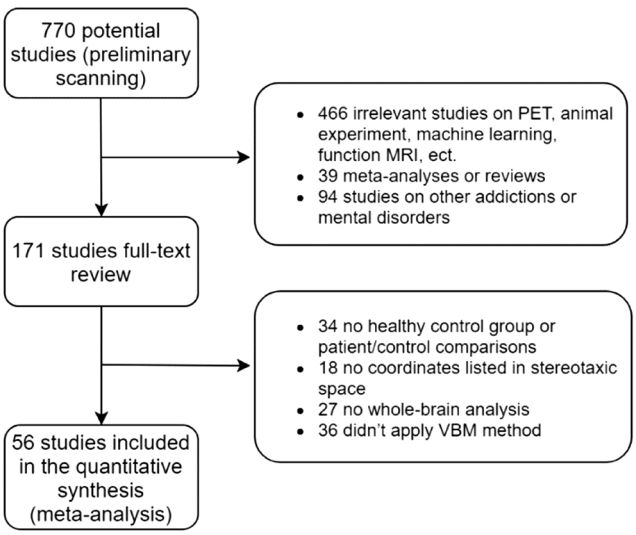

Fig. 1 Procedure for including eligible studies in the meta-analysis. Abbreviations: PET, positron emission tomography; VBM, voxel-based morphometry

Table 2 VBM meta-analysis results across all studies

	Region	Peak MNI	Number of voxels	SDM-Z value	*p* Value	Breakdown (voxels)	Jack-knife sensitivity
HC > patients	R anterior cingulate	2, 42, 8	4040	-4.927	< 0.000001	R anterior cingulate645 L anterior cingulate954 R superior frontal gyrus, medial orbital369 L superior frontal gyrus, medial orbital317 L median cingulate182 R median cingulate364 R gyrus rectus208 L gyrus rectus176 L superior frontal gyrus, medial512 R superior frontal gyrus, medial264 undefined49	55 out of 59 Fritz et al. 2014; Zois et al. 2017a; Galandra et al. 2020; Heikkinen et al. 2017
	L superior temporal gyrus	-40, -16, 0	1639	-3.873	0.000021	L insula569 L superior temporal gyrus244 L inferior frontal gyrus342 L rolandic operculum212 L Heschl gyrus145 undefined127	54 out of 59 Peng et al. 2017; Peng et al. 2018; Zois et al. 2017a; Moreno-Lopez et al. 2012; Galandra et al. 2020
	R Heschl gyrus	48, -8, 8	698	-3.248	0.000274	R rolandic operculum263 R insula258 R Heschl gyrus103 R superior temporal gyrus74	55 out of 59 Peng et al. 2018; Zois et al. 2017a; Moreno-Lopez et al. 2012; Ide et al. 2014
HC < patients	R parahippocampal gyrus	20, -38, -10	535	1.134	0.000010	R fusiform gyrus303 R lingual gyrus232	58 out of 59 Sun et al. 2014

Abbreviations: *HC* healthy controls, *MNI* Montreal Neurological Institute, *SDM* signed differential mapping, *L* left, *R* right

gyrus, and right Heschl gyrus compared with HC. In contrast, the results also showed increased GM volume in right lingual gyrus and right fusiform gyrus.

Systematic whole-brain jack-knife sensitivity analysis demonstrated that there is a significant GM decrease in bilateral ACC (55/59), bilateral OFG (55/59), left insula (54/59), right insula (55/59), left rolandic operculum (54/59), right rolandic operculum (55/59), left superior temporal gyrus (54/59), and right Heschl gyrus (55/59). Besides, the increased brain region in lingual gyrus and right fusiform gyrus could be replicable in 58 datasets.

Neither the funnel plot nor Egger's test showed significant publication bias ($p > 0.05$).

Subgroup analysis

First, we divided individuals into BA group and SUD group, two independent subgroups. The results demonstrated that findings in BA (23 datasets) were substantially consistent with the pooled analysis, apart from the additional significant GM decrease in the left inferior occipital gyrus and right striatum (Table 3). In addition, no significant GM increase regions were found in BA group. The SUD group

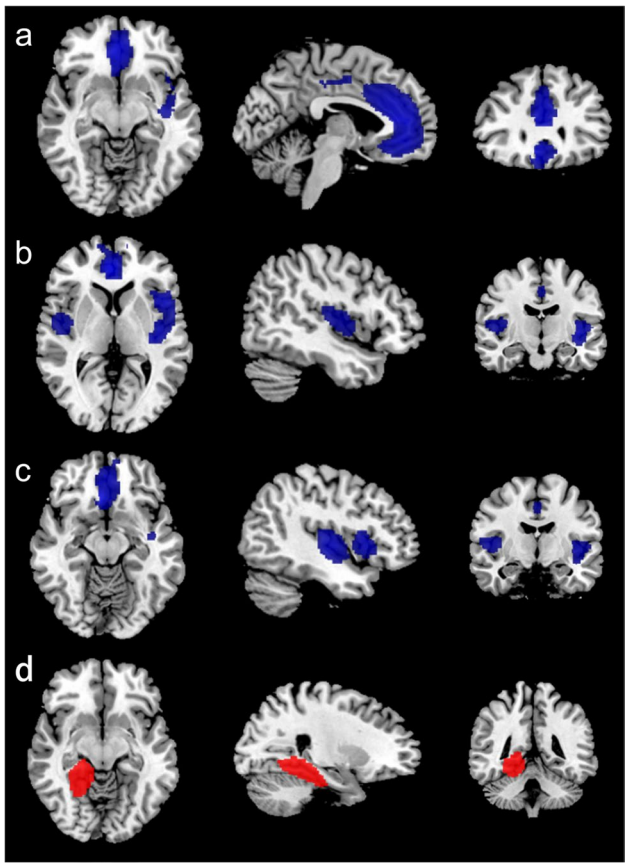

Fig. 2 GM reductions for 2096 individuals with addiction-related disorders compared with 2637 HC. Clusters were shown in the sagittal, axial, and coronal planes. Regions with GM enlargement were shown in red and GM reductions were displayed in blue. **a** GM reduction in the R ACC; **b,c** GM reduction in bilateral insula and L superior temporal gyrus; **d** GM increased in the R lingual gyrus. Abbreviations: ACC, anterior cingulate cortex; GM, gray matter; HC, healthy controls

(36 datasets) consolidated the results of pooled meta-analysis further (Table 4). In order to investigate the heterogeneity of the findings above further, we next performed two group comparation: (i) individuals with BA, relative to SUD, showed lower GM volume in left inferior occipital gyrus, right striatum, and right sMFG, (ii) while, comparing with BA, individuals with SUD had consistently reduced GM volume in left superior temporal gyrus (Table 5 and Fig. 3). The results of the intervention-free subgroup (51 datasets) were substantially consistent with the pooled analysis (Table S1 and Figure S1 in Online Resource 1).

Meta-regression analysis

The variables explored by meta-regression analysis included BIS-11 score and BDI score. The results showed that higher BIS-11 scores (16 datasets) in addictions were positively associated with GM reduction in the right ACC (MNI coordinate, 6, 30, 12; SDM-Z, 3.067; $p = 0.00001$; 67 voxels; $r = 0.541$, $p = 0.03$) (uncorrected), and left inferior frontal gyrus (MNI coordinate, -58, 4, 14; SDM-Z, 3.114; $p = 0.00001$; 253 voxels; $r = 0.595$, $p = 0.015$) (Fig. 4). No significant linear correlations were found with BDI score (12 datasets).

Discussion

To our knowledge, there has been few comprehensive meta-analysis investigating shared structural changes in distinct addictions including both SUD and BA. Our study integrated the findings from 59 VBM studies on five different subtypes of addiction, using the anisotropic seed-based d mapping (AES-SDM) method to explore brain GM alterations compared with HC. Shared GM reduction were found in the prefrontal cortex (PFC), bilateral insula, bilateral rolandic operculum, left superior temporal gyrus, and right Heschl gyrus, stable and replicable under jack-knife sensitivity analysis. In addition, we found heterogeneity between SUD and BA mainly in left inferior occipital gyrus and right striatum. Moreover, meta-regression analysis revealed that higher BIS-11 score was correlated with decreased GMV in the right ACC and left inferior frontal gyrus. These findings reveal potential mechanisms of overlap in SUD and BA and emphasize the importance of shared neural structural biomarker across addiction-related disorders.

Shared GM abnormalities in BA and SUD

Consistent with previous findings, robust GM decrease in the ACC and insula was also observed in the pooled meta-analysis across addiction-related disorders. A lot of single addiction disorders have revealed the abnormalities of ACC and insula such as tobacco, alcohol, and PG (Goldstein and Volkow 2011; Moccia et al. 2017). Researchers found that addiction was caused by an imbalance between unconscious impulsive system and conditional reflex system controlled by consciousness and cognition (Claus et al. 2013). When the balance broken, the inhibitory function would not work effectively, which lead to people could not help to use drugs (David et al. 2005). Cingulate gyrus and insula, the structural basis of the reflex system, which are responsible for impulsive control, decision-making, and emotional regulation (Jastreboff et al. 2015). Moreover, ACC and insula are critical components of salience network (SN). The SN is implicated in cognition and motivation and affects processing and is hypothesized to dynamically allocate cognitive and attentional resources between the default mode (DMN) and executive control (ECN) networks to realize the transformation of different status of the body (Menon 2011; Beissner et al. 2013).

Table 3 VBM meta-analysis results across behavioral addiction studies

HC > BA region	Peak MNI	Number of voxels	SDM-Z value	*p* Value	Breakdown (voxels)
L anterior cingulate	0, 40, 16	3134	-3.308	< 0.000001	L anterior cingulate880
					R anterior cingulate565
					L superior frontal gyrus, medial663
					L superior frontal gyrus, medial orbital247
					R superior frontal gyrus, medial231
					R superior frontal gyrus, medial orbital109
					R median cingulate239
					L median cingulate146
					L gyrus rectus27
					Undefined27
L inferior occipital gyrus	-18, -94, -8	190	-2.02	0.000710	L inferior occipital gyrus95
					L lingual gyrus35
					L calcarine fissure34
					L middle occipital gyrus26
L inferior frontal gyrus, opercular part	-58, 8, 10	170	-2.004	0.000867	L rolandic operculum67
					L inferior frontal gyrus, opercular part103
R striatum	26, -2, -6	152	-2.016	0.000815	R striatum76
					R putamen76

Abbreviations: *HC* healthy controls, *MNI* Montreal Neurological Institute, *SDM* signed differential mapping, *BA* behavioral addictions, *L* left, *R* right

Table 4 VBM meta-analysis results across substance use disorders studies

	Region	Peak MNI	Number of voxels	SDM-Z value	*p* Value	Breakdown (voxels)
HC > SUD	R anterior cingulate	6, 44, 4	1929	-4.33	< 0.000001	R anterior cingulate462
						L anterior cingulate629
						R superior frontal gyrus, medial orbital317
						L superior frontal gyrus, medial orbital187
						R gyrus rectus129
						R superior frontal gyrus, medial123
						L gyrus rectus82
	R Heschl gyrus	56, -10, 8	587	-3.024	0.001677	R rolandic operculum244
						R insula179
						R Heschl gyrus95
						R superior temporal gyrus69
	L superior temporal gyrus	-42, -16, -4	254	-3.694	0.000124	L superior temporal gyrus102
						L insula64
						L Heschl gyrus62
						L rolandic operculum26
	L insula	-44, 14, 2	270	-3.681	0.000139	L inferior frontal gyrus164
						L insula106
HC < SUD		20, -40, -8		1.299	0.000036	R fusiform gyrus205
						R lingual gyrus238

Abbreviations: *HC* healthy controls, *MNI* Montreal Neurological Institute, *SDM* signed differential mapping, *SUD* substance use disorders, *L* left, *R* right

Table 5 VBM meta-analysis behavioral versus substance additions contrast

	Region	Peak MNI	Number of voxels	SDM-Z Value	*p* Value	Breakdown (voxels)
BA (v.HC) > SUD (v.HC)	L superior temporal gyrus	-40, -18, -2	32	1.422	0.002746	
BA (v.HC) < SUD (v.HC)	L inferior occipital gyrus	-18, -94, -8	437	-1.725	0.000361	L inferior occipital gyrus144 L lingual gyrus104 L middle occipital gyrus74 L calcarine fissure 115
	R striatum	22, 2, -2	79	-1.458	0.001063	R striatum79
	R superior frontal gyrus, medial	4, 34, 48	43	-1.356	0.001750	R superior frontal gyrus, medial25

Abbreviations: *HC* healthy controls, *MNI* Montreal Neurological Institute, *SDM* signed differential mapping, *BA* behavioral addictions, *SUD* substance use disorders, *L* left, *R* right

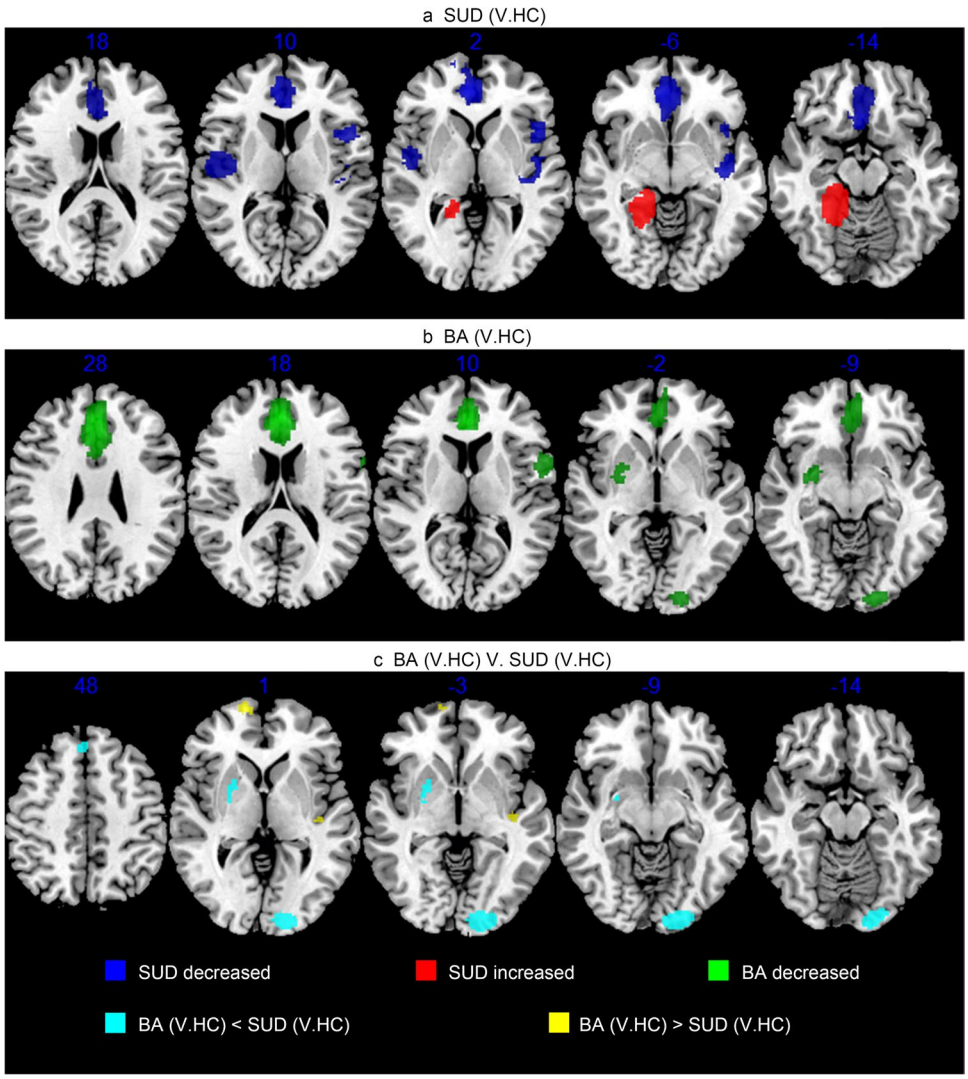

Fig. 3 GM abnormalities in the BA and SUD groups. Rows (i) and (ii) show abnormalities in SUD and BA relative to HC. Abnormalities in BA v. SUD, each relative to HC are shown in (iii). A statistical threshold of $p < 0.005$ with a cluster extent of 20 voxels was used in all analyses

Disruptions of the SN and dysregulated connectivity with other networks, like the DMN, are observed across multiple neuropsychiatric diseases, including SUD (Goodkind et al. 2015). From this meta-analysis, we found GM atrophy in the ACC and insula across addiction diagnoses, which may suggest that such abnormalities lead to poor impulsive control and make people indulge in a certain

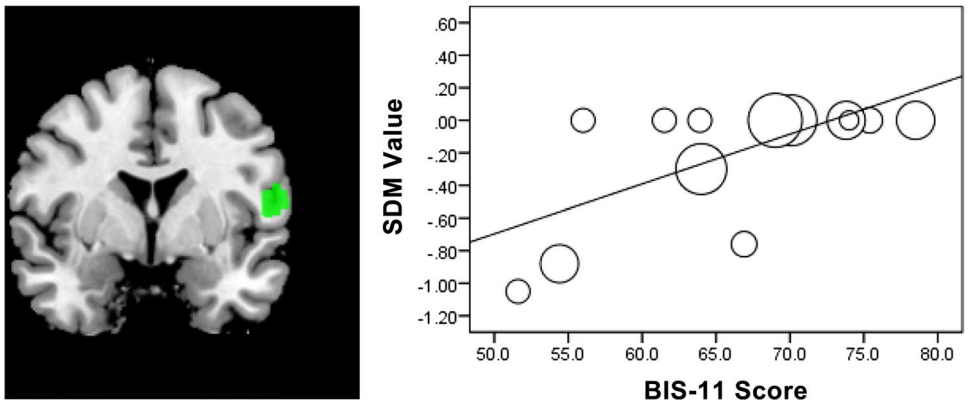

Fig. 4 Results of the meta-regression analysis showing the positive correlation between BIS-11 and regional GM reduction in left inferior frontal gyrus. In this plot, each study is marked as a dot and the size of each dot depends on its sample size. The regression line is presented as a straight line. The SDM values (effect sizes) were extracted from the peak of maximum slope significance. Note that the meta-regression SDM value is derived from the proportion of studies that reported gray matter changes near the voxel, so it is expected that some values are at 0 or near ± 1. Abbreviations: BIS-11, Barratt Impulsiveness Scale-11; SDM, signed differential mapping

status, presented with constantly seeking drugs and repetitive behaviors.

Individuals with addiction-related disorders also demonstrated significant GM decrease in the PFC, specifically in the OFC and superior frontal gyrus compared with HC. Within the prefrontal cortex, the OFC, by its connections with limbic areas, is uniquely positioned to use associative information to project into the future and to use the value of perceived or expected outcomes to guide decisions (Schoenbaum et al. 2006). GM atrophy in the OFC leads to the loss of integrated information, which could account for the propensity of seeking drugs and repetitive behaviors, despite the almost inevitable negative consequences of such behavior. Consistent with our findings, this pattern of deficits in decision-making also existed in addiction animal models (Miles et al. 2003). As the result of the brain structure changes, it might suggest the character of addiction—maladaptive decision-making.

GM atrophy in the temporal lobe and rolandic operculum observed in our meta-analysis is a novel structural alteration in addiction. According with our results, previous researches on addiction have demonstrated that the temporal cortex has been observed abnormalities in both SUD (Robbins et al. 2008) and BA (Weinstein and Lejoyeux 2010; Hahn and Kim 2014). Moreover, superior temporal gyrus is associated with urges and craving (Ko et al. 2009) and participated in regulatory control over reward-seeking behavior (Chiamulera 2005), which is an important part of the addiction process. As for rolandic operculum, it has been deeply discussed in previous studies of Parkinson's disease(Bayram et al. 2020) and epilepsy (Dong et al. 2016). Rolandic operculum has been found associated with execution of finger movements (Engel et al. 2012), involved in sensory motor integration in movement (Ciccarelli et al. 2005), and integrated exteroceptive-interoceptive signals related to self-consciousness cooperating with left temporal superior gyrus and supramarginal gyrus (Blefari et al. 2017). However, the exact mechanism of rolandic operculum abnormalities in addiction-related disorders remains to be fully explored, and it should be paid more attention in the future research.

In contrast, this study also observed that addiction-related disorders are linked to higher GM volume in right lingual gyrus and right fusiform gyrus. The fusiform gyrus is regarded as a component part of the temporal and occipital lobes, involved in processing color information, face and body recognition, and word recognition, as well as the perception of emotions in facial stimuli (Parvizi et al. 2012; Weiner et al. 2014). As for right lingual gyrus, it is an important section of the occipital lobe, linked to visual association cortex (Yang et al. 2020). Recent studies found that individuals with major depressive disorder showed increased GMV in lingual gyrus comparing with HC (Du et al. 2014) and the brain activity was also increased during emotion recognition (Scheuerecker et al. 2010). This indicated lingual gyrus may be associated with emotion-related abnormalities. At present, the two of the brain regions have too little discussion to get the conclusion that the lingual gyrus and the fusiform gyrus are the common biomarker in addiction, though there are two researches supporting our results (Yang et al. 2020; Sun et al. 2014). We believe that this finding warrants further investigation to clarify its significance.

Distinct GM abnormalities in BA and SUD

Analyzing by subgroups of addiction, results of SUD group were broadly consistent with the pooled analysis. Evidence from a recent research of polysubstance users has suggested similar prefrontal cortex dysfunction in SUD (Kaag et al.

2018). In contrast to SUD, results in BA subgroup showed more significant GM decrease in the left inferior occipital gyrus, right striatum, and right superior frontal gyrus. Such abnormalities derived from behavior itself without the neurotoxic effect of drugs are inexplicable, indicating subtle dissimilarities between the neural mechanism of BA and SUD (Robbins and Clark 2015). The striatum is anatomically subdivided into the ventral striatum and the dorsal striatum, involved in processing inputs and outputs from numerous brain regions such as prefrontal cortex, ventral tegmental area, and thalamus (Yager et al. 2015). Zhou's study proposed a functional ventral-dorsal shift theory: Ventral striatal reward system was associated with excessive drug using at an early stage while dorsal part dominated after the formation of habitual behaviors (Zhou et al. 2019). Recent studies found that individuals with behavioral addiction showed decreased GMV in putamen comparing with HC (Qin et al. 2020). Moreover, excessive drug using like CD leads to down-regulation of post-synaptic dopamine receptors (Volkow et al. 2014). It may result in putaminal hypertrophy as a compensatory process to produce more dopamine to maintain dopaminergic transmission (Volkow et al. 2014). Therefore, the difference between SUD and BA in the striatum is consistent with such a shift theory and compensatory mechanism of SUD, and the intervention strategies targeting ventral-dorsal shift may prevent high-risk individuals from both SUD and BA.

To eliminate possible medication and abstinence effects, we excluded studies recruiting participants with current intervention therapy. The results were replicable despite the evidence that pharmacotherapy can alter GM volume in other psychiatric conditions (Vita et al. 2015). Moreover, lack of clarity on the confounding effects made it premature to rule out structural effects of medication and abstinence in addictions. As robust our result seems to be, it should be interpreted with caution.

Clinical association with impulsivity

Meta-regression analysis found that the BIS-11 score was positively associated with GM decrease in the right ACC and left inferior frontal gyrus for addiction-related disorders, with smaller ACC in more impulsive individuals. Our results are in line with previous findings of a relationship between ACC volume and impulsivity in IGD (Lee et al. 2018), CD (Meade et al. 2020), and AUD (Crunelle et al. 2014). Such a relationship also existed in animal models (Winstanley 2011), which may suggest that the positive association between impulsivity and lower GMV variation was not related to diagnostic groups. In addition, inhibitory control is the ability to overcome impulsive behavior, and impulse-control deficits represent a risk factor for addiction. As mentioned earlier, dysfunction of the ACC is involved in impaired response inhibition (Holst et al. 2012b), which is the core cognitive function of addiction. Our study demonstrated the homogeneity cross diagnostic and further benefit clinical assessment and treatment of addiction-related disorder.

Limitation

This meta-analysis sheds new light on shared structural abnormalities in distinct addictions including both SUD and BA. However, we need to point out several limitations in our study. First, the causality between GM decrease and development of addiction is still inexplicable by means of the integration of cross-sectional studies. According to causal network of structural covariance (Zhang et al. 2017), we will go a step further to investigate the causation in the future. Second, a number of other types of addiction were lacking; we therefore could only select five typical addiction-related disorders in our meta-analysis. Third, we can hardly get rid of the inter-study heterogeneity in methodology (including software, thresholds, diagnostic criteria, magnetic field strength), which may influence our results. Future research should focus on these aspects.

Conclusion

In summary, evidence in our pooled meta-analysis was able to support the idea that prefrontal and insula regions might be a common neurobiological substrate for addiction-related disorders. Besides, subgroup and meta-regression analysis further explored brain structural changes in SUD and BA as well as association with clinical information, which could pave a way for future treatment. Nevertheless, the fact that common brain structural alterations are seen despite potentially differing etiologies raises the possibility that these brain regions could be used as potential therapeutic neurotarget across various addictions. Future large-scale and longitudinal studies using multimodal methods would further prove and supplement our findings.

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Declarations

Conflict of interest The authors declare no competing interests.

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