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Common abnormality of gray matter integrity in substance use disorder and obsessive-compulsive disorder: A comparative voxel-based meta-analysis

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Abstract

The objective of the current study is to determine robust transdiagnostic brain structural markers for compulsivity by capitalizing on the increasing number of case-control studies examining gray matter volume (GMV) alterations in substance use disorders (SUD) and obsessive-compulsive disorder (OCD). Voxel-based meta-analysis within the individual disorders and conjunction analysis were employed to reveal common GMV alterations between SUDs and OCD. Meta-analytic coordinates and signed brain volumetric maps determining directed (reduced/increased) GMV alterations between the disorder groups and controls served as the primary outcome. The separate meta-analysis demonstrated that SUD and OCD patients exhibited widespread GMV reductions in frontocortical regions including prefrontal, cingulate, and insular. Conjunction analysis revealed that the left inferior frontal gyrus (IFG) consistently exhibited decreased GMV across all disorders. Functional characterization suggests that the IFG represents a core hub in the cognitive control network and exhibits bidirectional (Granger) causal interactions with the striatum. Only OCD showed increased GMV in the dorsal striatum with higher changes being associated with more severe OCD symptomatology. Together the findings demonstrate robustly decreased GMV across the disorders in the left IFG, suggesting a transdiagnostic brain structural marker. The functional characterization as a key hub in the cognitive control network and casual interactions with the striatum suggest that deficits in inhibitory control mechanisms may promote compulsivity and loss of control that characterize both disorders.

KEYWORDS
compulsivity, coordinate-based meta-analysis, obsessive-compulsive disorder, substance use disorder, voxel-based morphometry

1 | INTRODUCTION

Obsessive-compulsive disorder (OCD) and substance use disorder (SUD) represent two neuropsychiatric disorders characterized by maladaptive and persistent repetitive behaviors. Typically, OCD involves either hidden or overt ritualistic acts to obtain relief, whereas SUD engages in the consumption of a substance for rewarding effects or relief of distress. Initially, these behaviors serve a specific goal such

as relief from emotional, physical, or social distress or a rewarding experience. However, during the transition into the pathological state of the disorders, the initial goal-directed behavior becomes progressively habitual and ultimately compulsive. Although compulsivity represents a transdiagnostic key symptom of both disorders and overarching models emphasize the contribution of Pavlovian and instrumental learning mechanism to the development of compulsive behavior in both disorders (Robbins, Gillan, Smith, de Wit, & Ersche, 2012; Robbins, Vaghi, & Banca, 2019) the transdiagnostically shared neurobiological mechanisms of the disorders remain to be systematically examined. Also, SUD and OCD often co-occur (Blom et al., 2011; Lochner et al., 2014; Mancebo, Grant, Pinto, Eisen, & Rasmussen, 2009; Ruscio, Stein, Chiu, & Kessler, 2010) and comorbidity has been reported to be a potential source of inefficient treatment (Glazier, Calixte, Rothschild, & Pinto, 2013).

Accumulating evidence from different lines of research suggests shared brain dysregulations between the disorders, such that both disorders have been characterized by dysregulations in central glutamatergic (Blom et al., 2011; Gass & Olive, 2008; Pittenger, Bloch, & Williams, 2011) and dopaminergic signaling which has been associated with key symptoms of both disorders as well as the regulation of behavioral control, associative learning, and compulsivity (Bari & Robbins, 2013; Bellini et al., 2018; Cools, 2008). Moreover, functional neuroimaging studies emphasize an important role of frontocortical circuits in compulsive behavior, and accumulating evidence suggests that neurofunctional dysregulations in specific frontocortico-striatal pathways facilitate the development of compulsive symptoms in both disorders (Gonçalves et al., 2016; Milad & Rauch, 2012; Vollstädt-Klein et al., 2010; Zhou et al., 2019).

Despite evidence from previous meta-analyses suggesting robust brain structural alterations in both, SUD and OCD patients relative to control subjects, shared and separable brain structural alterations between the disorders have not been systematically determined. Previous overarching conceptualizations and neuroimaging studies point to some candidate brain systems that have been identified most consistently, particularly frontostriatal circuits and cortical regions such as the insula (Everitt & Robbins, 2005; Goldstein et al., 2009; Koob & Volkow, 2010). Additionally, quantitative and qualitative voxel-based morphometry (VBM) studies have suggested altered gray matter indices in SUDs (see cocaine; Crunelle et al., 2014; Ide et al., 2014; Rando, Tuit, Hannestad, Guarnaccia, & Sinha, 2013), Cannabis; (Cousijn et al., 2012; Wetherill et al., 2015), Alcohol; (Xiao et al., 2015; Yang et al., 2016), and Nicotine; (Hanlon et al., 2016; Zubieta et al., 2001). Moreover, recent meta-analyses suggest robust changes in gray matter in OCD (Lázaro et al., 2011; Joaquim Radua, Van Den Heuvel, Surguladze, & Mataix-Cols, 2010; Rotge et al., 2010; So et al., 2008), with recent mega-analyses further confirming OCD-associated brain structural changes (Boedhoe et al., 2018; Thompson et al., 2020; van den Heuvel et al., 2020) which may partly overlap with mega-analytically determined brain structural changes in SUD (Thompson et al., 2020), also effects of medication may contribute to some of the reported gray matter alterations in OCD (Boedhoe et al., 2017). However, shared gray matter alterations between the disorders have not been systematically examined determined. The determination of shared structural alterations between the disorders may not only facilitate to ascertain the neurostructural basis of compulsivity but may additionally enable the development of clinical interventions, including the determination of promising targets for invasive or noninvasive brain modulation techniques.

Against this background, the present study aimed at determining shared and robust brain structural markers for the disorders by capitalizing on the increasing number of case-control studies examining gray matter alterations in SUD patients and OCD patients relative to healthy control subjects. To this end, we combined original studies from three prevalent substances abused (Alcohol, Cocaine, and Nicotine) which we individually analyzed in a first step. Next, we investigated the shared brain gray matter alterations between SUDs and OCD via voxel-based meta-analysis. This meta-analytic approach has the potential to address the inconsistencies and lack of replicability that often characterizes the original studies on brain structural alterations in psychiatric disorders (Button et al., 2013; Ioannidis, 2011). Based on previous results from functional imaging studies and overarching models of compulsivity we hypothesized that SUDs and OCD will exhibit shared GMV alterations in frontostriatal regions.

Additionally, we aimed to further characterize the identified common region both on the behavioral and network level. To this end, we employed Neurosynth to identify functional co-activation networks of the identified region and employed Granger causality analysis (GCA) to resting-state data from an independent sample of healthy controls to further map the causal relationship between the identified region and the striatum.

2 | METHODS

The present meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher et al., 2014) and the principles of conducting coordinate-based meta-analysis (Müller et al., 2018). This study has been preregistered on the OSF repository (Registration DOI: 10.17605/OSF.IO/7YG6J). In the initial step, we identified original studies examining brain structural alteration in SUD (Cocaine, Alcohol, and Nicotine) and OCD through MRI-based VBM. For the literature search, four databases (PubMed, Web of Science, Neurosynth, and Scopus) were utilized and original articles were identified based on relevant references in review studies. Titles and abstracts returned by the search results were examined for subsequent full-text screening and inclusion. Only English language studies reporting whole-brain results in terms of coordinates (three-dimensions [*x*, *y*, *z*] and in Talairach or Montreal Neurological Institute stereotactic space) and published between the year 2000–2020 were included. The screening process resulted in original peer-reviewed studies employing case-control designs in SUD and OCD, respectively. The following search terms were applied: "Cocaine" OR "Cocaine use disorder" OR "Alcohol" OR "Alcohol use disorder" OR "Nicotine" OR "Smoking" OR "Obsessive-compulsive disorder" AND (Morphometry OR Voxel-based OR voxelwise). Only articles with case-control

designs reporting differences between the respective diagnostic group and healthy control subjects were included. Additional exclusion criteria were as follows: (a) articles reporting only region-of-interest (ROI) results, (b) articles with poly-drug users and samples with high comorbidities with psychiatric or somatic disorders (e.g., schizophrenia or HIV), (c) articles focusing on parental drug exposure, and (d) articles reporting results from the same dataset from previous studies, five studies including samples lower than $N = 10$ per disorder.

2.1 | Meta-analytic approach

The meta-analysis of VBM studies was performed using the Seed-based d Mapping (formerly "Signed Differential Mapping") (SDM) software version 6.21 (https://www.sdmproject.com/software/). Subsequent functional decoding of the identified regions was conducted via the Neurosynth database (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011; https://neurosynth.org/). The analysis pipeline included the following steps: (a) Extraction of coordinates from peak clusters including their effect sizes (J. Radua et al., 2012; representing the gray matter differences between patients and controls) either *t*-value, *z*-value, or *p*-value (all values in *z* and *p* were converted to *t*-value using the statistical converter; https://www.sdmproject.com/utilities/?show=Statistics); (b) To account for differences between the reported coordinates and the standard space, we created MNI maps of the GM for each study using the anisotropic Gaussian kernel with Full-width at half maximum (FWHM) set at 20 mm and a voxel size of 2 mm. The FWHM is used to assign values to gray matter voxel close to each of the reported coordinates (Albajes-Eizagirre, Solanes, Vieta, & Radua, 2019). It is noteworthy that the kernel is different from the one used to smooth normalized f/MRI original data; (c) To account for potential effects of age in each original study mean of the samples was included as a covariate; and (d) Using the effective size maps and the sample sizes of each study variance maps were obtained. We next performed a voxel-wise computation to derive the mean maps by using the weighted mean study maps (obtained using the sample size, variances, and the between-study difference). In the analysis, we first computed the SDM for each disorder, and next a conjunction map was derived by computing the common regions to identify shared brain structural alterations between the four disorders. All meta-analytic results employed statistical significance testing by thresholding the derived maps by voxel-level uncorrected $p < .001$ and FWE <0.05 (10 voxels) thresholds.

2.2 | Sensitivity analysis

We performed whole-brain, voxel-based jackknife sensitivity analysis to determine the robustness of the results by setting a repetition value equal to the number of studies in each sample. The analysis in each of the groups was systematically repeated for 12, 9, 10, and 30 times, respectively, while discarding a single study each time. The number of repetitions equals the total number of studies in each sample, that is, Alcohol ($n = 12$), Cocaine ($n = 9$), Nicotine ($n = 10$), and OCD ($n = 30$). This process was repeated until the last study was removed and placed back. The analysis was aimed at determining whether the observed findings are driven by single studies and thus testing the robustness of the group-level results.

2.3 | Exploratory analyses of functional characterization: meta-analytic co-activation, causal connectivity, and linear model analysis

To functionally characterize regions exhibiting shared alterations across the disorders a co-activation analysis of the conjunction results across the diagnostic groups was performed. In the co-activation analysis, we used the inferior frontal gyrus (IFG) ROI co-ordinate to search for networks in the Neurosynth database, the result reflects regions extracted from a large database of previous studies that functionally co-activated with our ROI. Next, based on our apriori hypothesis of the importance of frontostriatal circuits in both disorders and compulsivity, we aimed to investigate causal relationships in the intrinsic interaction between the identified prefrontal (IFG) region and the striatum. Accordingly, resting-state fMRI data from $n = 50$ subjects (male; $n = 28$, mean age = 21.60, $SD = 2.01$ and female; $n = 22$, mean age = 21, $SD = 2.24$) all right-handed were included (for standardized resting-state data preprocessing see [Liu et al., 2019]) to examine the causal interaction of the left IFG with the ipsilateral striatum. We employed GCA (GCA derivation similar to [Klugah-Brown et al., 2019]) to investigate the connectivity between the IFG and the targeted areas as it may allow us to explore the interactions between the identified region and the striatum on a causal level. For the technical details of GCA, refer to the manuscript by Zang, Yan, Dong, Huang, and Zang (2012). Based on the meta-analytic determined overlapping GMV alterations between the SUDs and OCD, we defined the IFG as seeds (3 mm-radius sphere) and striatum (left ventral and dorsal, seeds also known as targets), respectively. The striatal target-seeds were obtained from the human connectome atlas (https://atlas.brainnetome.org/bnatlas.html) and used 3 mm radius ROIs for left striatum comprising of the dorsal and ventral striatum, respectively. Furthermore, voxel-wise, residual-based GCA evaluations were made on the mask of the gray matter using the REST toolbox (http://www.restfmri.net).

GCA: briefly, the analysis is based on the notion that given previous information of $Q(t)$ and $R(t)$, we predict R based on the information of $Q(t)$, such that Q is said to have a causal influence on R. Here, we used the residual version of the GCA, implemented based on auto-regression as follows:

$$R_t = \sum_{k=1}^{p} b_k R_{(t-k)} + \varepsilon_t \quad (1)$$

$$Var(\varepsilon_t) = V_1 \quad (2)$$

$$Q_t = \sum_{k=1}^{p} b'_k Q_{(t-k)} + \varepsilon'_t \quad (3)$$

$$Var(\varepsilon'_t) = W_1 \quad (4)$$

where ε_t and ε'_t are the residuals, V_1 and W_1 represent the variances of the residuals, respectively. Using the joint regression, we obtained V_2 and W_2 as follows:

$$R_t = \sum_{k=1}^{p} X_k R_{(t-k)} + \sum_{k=1}^{p} Y_k Q_{(t-k)} + \mu_t \quad (5)$$

$$Var(\mu_t) = V_2 \quad (6)$$

$$Q_t = \sum_{k=1}^{p} X'_k Q_{(t-k)} + \sum_{k=1}^{p} Y'_k Q_{(t-k)} + \mu'_t \quad (7)$$

$$Var(\mu'_t) = W_2 \quad (8)$$

where μ_t and μ'_t are the residuals of the joint regressive representation, V_2 and W_2 are the variances associated with the residuals. Q_t and R_t indicate the time series of two events at a certain time t whereas $Q_{(t-k)}$ and $R_{(t-k)}$ are the time series at time $t-k$ and p is the number of lagged time points. Finally, the GCA outputs X_k, X'_k, Y_k, and Y'_k as the signed maps and autoregression maps, respectively.

To compute the magnitude of causality to-and-from the two time series a bidirectional and net-direction is derived as follows:

Inflow;

$$M_{q\to r} = \ln\frac{V_1}{V_2} \quad (9)$$

Outflow;

$$M_{r\to q} = \ln\frac{W_1}{W_2} \quad (10)$$

Net-direction:

Netflow;

$$\Delta M = (M_{r\to q}) - (M_{q\to r}) \quad (11)$$

Equations (9) and (10) represent the magnitude of causality of Q or R given the prediction of R or Q. The final step measures the net influence of the direction of causality, that is if ΔM is positive the net direction of causality if from Q_t to R_t, if the ΔM is negative then the net direction of causality is from R_t to Q_t, respectively. The causal parameters; $M_{q\to r}$, $M_{r\to q}$, and ΔM representing the inflow (to seed), outflow (from seed), and out-in-flow (Netflow) were also computed. The inflow (from the striatum to IFG), outflow (from IFG to striatum), and out-inflow (net flow) were also computed. The resultant inflow, outflow, and net flow were further transformed to z-score to improve normality to facilitate the statistical analysis.

To further account for the previously reported effects of disorder duration and medication on brain structural alterations in OCD a linear model analysis with the duration of the disorder and medication (percentage of medicated patients) as our variables of interest was performed in the OCD dataset. Moreover, we performed meta-regression to explore further associations with disorder-relevant indices. To this end associations with duration of substance use in SUD and OCD symptom severity as assessed by the Yale-Brown Obsessive-Compulsive Scale (YBOCs, [Castro-Rodrigues et al., 2018; Goodman et al., 1989]) in OCD, respectively, were examined. Spearman correlation with 95% confidence levels and thresholded at p <.05 were employed.

3 | RESULTS

Literature search performed according to our criteria resulted in a total of 31 original GM VBM studies in SUD (n = 1,191, mean age = 40.03, SD = 10.87) and 31 OCD (n = 1,293, mean age = 29.18, SD = 10.34) that compared brain structure via VBM to controls (SUD: n = 1,585, mean age = 42.63, SD = 14.27, OCD: n = 1,374, mean age = 28.97, SD = 9.96), Figure 1 shows the flowchart of selection procedure. The demographic characteristics of the samples from the included studies are presented in Table 1. There are no significant differences among the four groups (p <.05, F = 8.83). The breakdown of the 31 SUD study group comprising of three diagnostic categories is shown in Table 2.

3.1 | Main GMV results

Results from the disorder-specific SDM-PSI meta-analysis are shown in Figure 2. After FWE correction was performed within each diagnostic category, reduced GMV for each diagnostic category as compared to healthy controls was mainly located in the bilateral anterior insula, except for the nicotine group, in which the reduced GMV was restricted to the left insula. Additionally, all diagnostic categories exhibited GMV reductions in the adjacent inferior frontal gyrus, as well as the dorsal anterior cingulate (dACC), and the adjacent medial frontal gyrus (Figures 2a–d). No regions with increased GMV were observed in any of the SUDs relative to healthy controls. An additional conjunction analysis in the three SUDs additionally revealed convergently decreased GMV in the left insula/IFG and the prefrontal cortex across the SUDs (results displayed in Figure S1). The conjunction analysis revealed that all four disorders exhibited convergently reduced GMV in the left IFG (Figure 3a). The detailed GMV changes in each disorder compared to healthy controls are presented in Tables S1–S4. The results remained robust in the jackknife sensitivity analyses (Table S5).

3.2 | Exploratory analyses: linear model analysis and neural decoding

To functionally characterize the region identified, a functional co-activation analysis was conducted. Co-activation analysis revealed

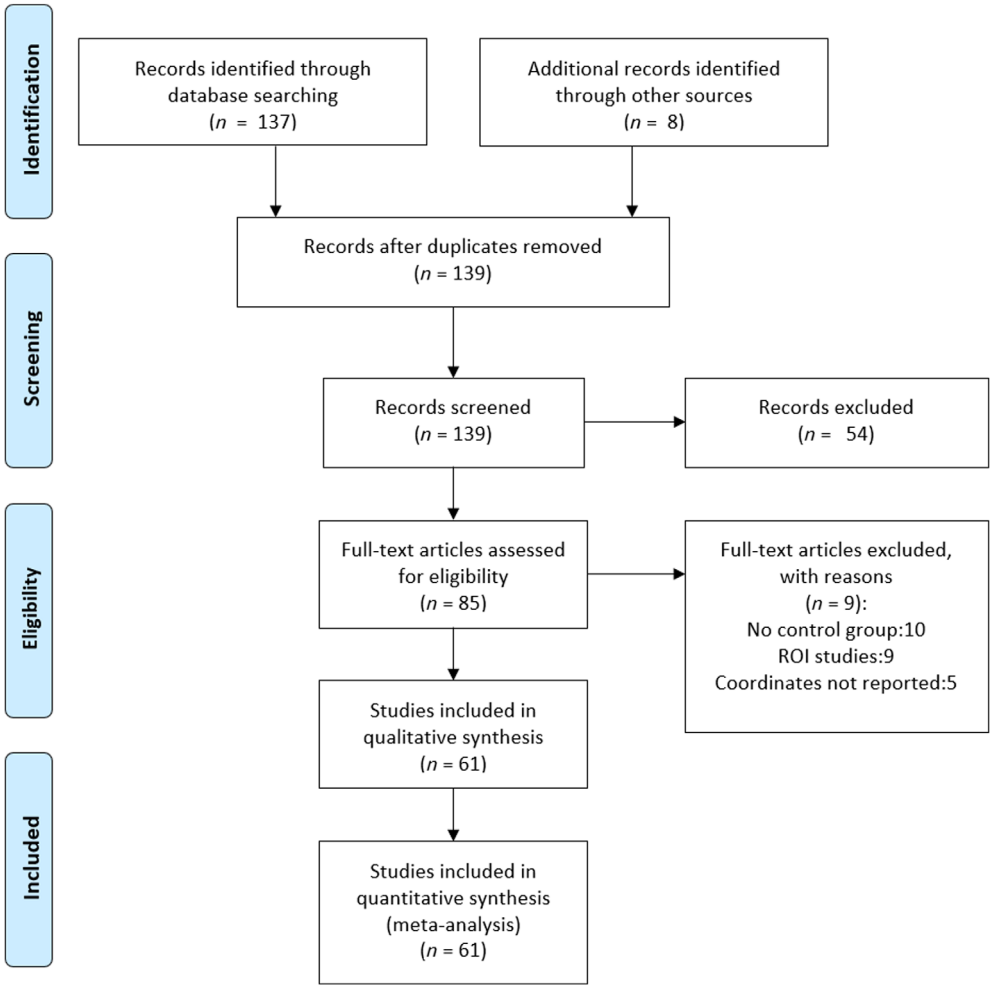

FIGURE 1 PRISMA flowchart of the selection procedure. Number of experiments included in the analysis of interest

that the identified IFG region primarily co-activated with broad regions of the frontal and parietal regions encompassing mainly the frontoparietal control network (Figure 3b). Findings from the GCA in the sample of healthy subjects revealed that causality was observed between the IFG and the striatum, specifically, an inflow pattern from left striatum regions to the IFG except for left dorsal putamen (dPu.L; p <.05; Figure 4a). Generally, the pattern of bidirectional causal flow indicated a higher inflow from the target regions to the IFG (p <.05) with inflow/outflow between IFG and dCa.L showing the highest causality. In these results, we found that there was only positive NetFlow from the seed region to the left ventral putamen (vPu.L), signifying the causal influence from the IFG to this subregion of the striatum (Figure 4b). The meta-regression revealed no significant associations (age, duration of substance use for SUD). The linear model analyses further revealed effects of disorder duration and medication (clinical characteristics of medication use in OCD are displayed in Table S6), with both, increased as well as decreased GMV in OCD. Positive associations between duration and GMV were found in the left calcarine (p = .0009) and right insula (p = .022), whereas negative associations were found in the bilateral superior frontal gyrus, medial frontal (p = .0009), and left putamen/insula (Figure 5a, Table S7). Also, positive associations between medication use and GMV were found in the left postcentral gyrus (p = .0009) and right hippocampus/thalamus (p = .005), whereas, negative associations were found in the bilateral insula (p = .0009), and middle cingulate gyrus (p = .003; Figure 5b, Table S8). Furthermore, the meta-regression revealed a significant positive association between OCD symptom severity in the left dorsal striatum. Specifically, a higher OCD symptom load as assessed by YBOCS scores was associated with increased left putamen GMV in the OCD patients (Figure 6a,b).

4 | DISCUSSION

The present meta-analytic study examined for the first time shared GMV alterations between SUDs and OCD. The disorder-specific voxel-wise meta-analysis revealed widespread medial frontal and insular GMV reductions within the SUD and OCD compared to controls and the conjunction meta-analysis revealed that the disorders are transdiagnostically characterized by reduced GMV in the left IFG. Subsequent exploratory analysis that aimed at functionally characterizing the identified region revealed that the left IFG functionally co-activated with a broad network including bilateral parietal and frontal regions, suggesting that this region represents a core node in the

TABLE 1 Demography of included studies

	n.p	M_ageP	*SD*	Edu	*SD*	Duration	*SD*	n.c	M_ageC	*SD*	Edu	*SD*	
Alcohol													
van Holst, de Ruiter, van den Brink, Veltman, and Goudriaan (2012)	36	43.2	11.0	NA	NA	11.69	9.7	54	35.3	10.1	NA	NA	
Mechtcheriakov et al. (2007)	22	53.6	NA	9.7	2.6	10	NA	22	53.7	NA	10.1	2.3	
Wang et al. (2016)	20	43.95	6.3	11.6	2.7	NA	NA	20	40.5	8.7	9.15	4.18	
Chanraud et al. (2007)	26	47.7	7.1	7.58	2.96	NA	NA	24	45	6.72	8.7	3.36	
Wiers et al. (2015)	22	42.14	6.2	10.86	1.25	14.82	7.4	21	41.95	6.41	11.62	1.62	
Galandra et al. (2020)	22	45.59	7.99	9.91	2.65	10.11	6.57	18	44.83	8.86	10.11	2.78	
Demirakca et al. (2011)	50	46.6	8.2	NA	NA	12.4	7.4	66	45	10.1	NA	NA	
Chanraud et al. (2009)	24	47.8	7.7	7.75	2.99	NA	NA	24	45	5.6	8.7	3.37	
Nurmedov et al. (2016)	24	40.79	9.8	NA	NA	19	9.19	29	37.45	10.87	NA	NA	
Segobin et al. (2014)	19	44.4	6.07	11.15	1.9	29.05	7.76	20	46.7	4.25	10.6	2.58	
Galandra et al. (2018)	23	45.69	7.82	10	2.62	10.8	7.21	18	44.83	8.86	10.11	2.78	
Jang et al. (2007)	20	43.5	6	14.3	4.2	NA	NA	20	44.5	7.4	15.3	2.6	
Cocaine													
Sim et al. (2007)	40	41.4	6.9	NA	NA	15.3	6.3	41	38.7	8.8	NA	NA	
Vaquero et al. (2017)	30	24	6	NA	NA	NA	NA	30	24	6	NA	NA	
Franklin et al. (2002)	13	42	6.3	12	1.1	13	6.5	16	36.2	1	17	2.6	
Yip et al. (2018)	37	42.43	6.1	12.38	1.11	NA	NA	37	38	11.03	14.38	1.92	
Parvaz et al. (2017)	19	42.58	7.63	12.68	2.75	12.74	7.42	12	39.33	8.66	12.71	1.6	
Hanlon, Dufault, Wesley, and Porrino (2011)	24	38.9	0.9	NA	NA	11.1	1.2	25	36.2	1	NA	NA	
Gardini and Venneri (2012)	14	31.07	5.86	11.21	3.33	13.41	4.94	24	33.21	7.06	12.75	2.47	
Bachi et al. (2018)	24	45.8	7.8	12.7	1.6	16.8	9.5	24	41.9	7.9	14.6	1.9	
Barrós-Loscertales et al. (2011)	20	33.3	6.94	9.2	1.7	NA	NA	16	33.38	9.17	8.53	1.45	
Nicotine													
Brody et al. (2004)	19	39.5	10.3	NA	NA	14.5	NA	17	37.9	12.9	NA	NA	
Franklin et al. (2014)	80	33.85	10.96	14.44	2.22	14.05	10.13	80	32.08	7.4	13.89	2.11	
Gallinat et al. (2006)	22	30.8	7.5	NA	NA	13.9	7.3	23	30.3	7.9	NA	NA	
Hanlon et al. (2016)	58	31.69	NA	20.97	1.02	NA	NA	60	29	NA	21.53	0.88	
Liao, Tang, Liu, Chen, and Hao (2012)	44	28.1	5.5	13.2	2.92	10.4	5.72	44	26.3	5.84	15	2.6	
Morales, Lee, Hellemann, O'Neill, and London (2012)	25	35.4	1.8	14.1	0.3	NA	NA	18	30.1	2.2	14.6	0.4	
Peng et al. (2017)	27	32.26	3.73	19.3	1.32	12.7	8.3	53	30.83	5.18	19.32	1.29	
Wang et al. (2014)	22	22.48	2.48	15.14	1.83	4.95	2.27	20	21.8	1.32	15.2	1.19	
Yokoyama et al. (2018)	50	37.73	7.9	NA	NA	NA	NA	50	35.93	9.08	NA	NA	
Fritz et al. (2014)	315	44.1	11.84	NA	NA	26.8	3	659	51.49	14.45	NA	NA	
OCD													*YBOCS*
Britton et al. (2010)	15	13.5	2.4	NA	NA	4.1	2	20	13.6	2.4	NA	NA	3.34
Carmona et al. (2007)	18	13	2.76	NA	NA	NA	NA	18	13.03	3.04	NA	NA	21.39
Cheng et al. (2016)	30	10.8	2.1	4.6	2.2	NA	NA	30	10.5	2.2	14.4	1.8	5.21

TABLE 1 (Continued)

	n.p	M_ageP	*SD*	Edu	*SD*	Duration	*SD*	n.c	M_ageC	*SD*	Edu	*SD*	
Christian et al. (2008)	21	38	9.6	27	4.2	NA	NA	21	38.9	9.8	27	4.2	27
De Wit et al. (2014)	412	32.1	9.6	13.7	2.8	NA	NA	368	30.2	9.3	13.7	2.8	3.35
Gilbert, Mataix-Cols, et al. (2008)	25	37.5	10.7	NA	NA	NA	NA	20	29.8	7.86	NA	NA	26.9
Gilbert, Keshavan, et al. (2008)	10	12.9	2.7	NA	NA	NA	NA	10	13.4	2.6	NA	NA	26.5
Gonçalves et al. (2017)	15	31.67	11.44	13	3.55	NA	NA	15	30.07	8.22	13	3.55	4.14
Hashimoto et al. (2014)	15	32.5	7.7	13.6	1.8	5.2	2.5	30	32.5	6.7	13.6	1.8	5.61
Van Den Heuvel et al. (2009)	55	33.7	9.19	NA		NA		50	31.4	7.64	NA	NA	22.83
Kim et al. (2001)	25	27.4	7	8.4		8.4		25	27	6.2	15.3	NA	24.2
Kobayashi et al. (2015)	20	31.1	8.5	NA	NA	11.5	7.5	30	31.2	8.5	NA	NA	2.46
Kopřivová et al. (2009)	14	28.6	6.1	NA	NA	15.6	8.3	15	28.7	6.5	NA	NA	5.92
Matsumoto et al. (2010)	16	32.8	7.5	NA	NA	NA	NA	32	32.6	8.7	NA	NA	3.37
Moon and Jeong (2018)	18	27.6	8	14.4	1.8	6.5	5.3	18	30.7	7.5	14.4	1.8	3.71
Moreira et al. (2017)	40	26.28	6.62	13.53	2.25	NA	NA	40	26.45	5.39	13.53	2.25	3.36
Okada et al. (2015)	37	34.4	10.5	13.8	2.1	8.8	6.2	37	36.8	10.8	13.8	2.1	2.52
Pujol et al. (2004)	72	29.8	10.5	13		13		72	30.1	10.2	14	NA	26.7
So et al. (2008)	71	26.61	7.5	NA	NA	8.02	6.1	71	26.68	6.09	NA	NA	3.89
Soriano-Mas et al. (2007)	30	29.8	10.5	11.3		11.3		30	30.1	10.2	13.1	NA	21
Subirà et al. (2013)	30	32.23	9.05	NA	NA	NA	NA	95	33.92	10.53	NA	NA	4.45
Subirà et al. (2015)	71	32.11	8.45	NA	NA	NA	NA	87	32.13	9.57	NA	NA	4.12
Szeszko et al. (2008)	37	13	2.7	NA	NA	NA	NA	26	13	2.6	NA	NA	24.9
Tan et al. (2013)	28	25.35	7.24	13.73	2.99	NA	NA	22	27.88	8.02	13.73	2.99	4.14
Tang et al. (2013)	18	25.5	6.7	NA	NA	11.1	3.9	26	25.2	6.6	NA	NA	4.48
Tang et al. (2015)	26	25.5	4.9	14.1	2.7	4.8	2.55	32	26.2	5.1	14.1	2.7	5.5
Tang et al. (2016)	18	27.3	10.4	13.5	2.4	8.1	5.7	16	26.8	9.8	13.5	2.4	5.4
Togao et al. (2010)	16	32.8	7.5	14	1.6	12.09	8.5	32	32.6	8.7	14	1.6	5.05
Valente et al. (2005)	19	32.7	8.8	18.3		18.3		15	32.3	11.8	10.4	NA	24.6
So et al. (2008)	71	26.6	7.49	NA		8		71	26.68	6.09	NA	NA	22.84

Abbreviations: Duration, mean duration of illness in years; Edu; mean education in years; M_ageP, mean age of patients; NA, not applicable; n.c, the number of controls; n.p, the number of patients; *SD*, standard deviation.

TABLE 2 Details of SUD category

	SUD				Controls		
Category	No. studies	Participants	Mean age	Standard deviation	Participants	Mean age	Standard deviation
Alcohol	12	308	45.4685	8.2472	336	42.9538	9.6344
Cocaine	9	221	38.1661	9.2458	225	35.5804	9.2636
Nicotine	10	662	38.1255	11.5931	1,024	44.0869	15.917

frontoparietal control networks. Based on the consistently reported role of frontostriatal circuits in SUD as well as OCD the intrinsic causal influence of the identified IFG region over the striatum was examined in an independent dataset of healthy subjects and revealed that the causal influence propagated from the left striatum to the left IFG, whereas the IFG exerted causal influence over the ventral putamen. Finally, we found that only OCD exhibited increased GMV, specifically in the left dorsal striatum (putamen) which positively correlated with OCD symptom severity (as assessed by the YBOCs) in OCD. The findings generally remained robust when subjected to

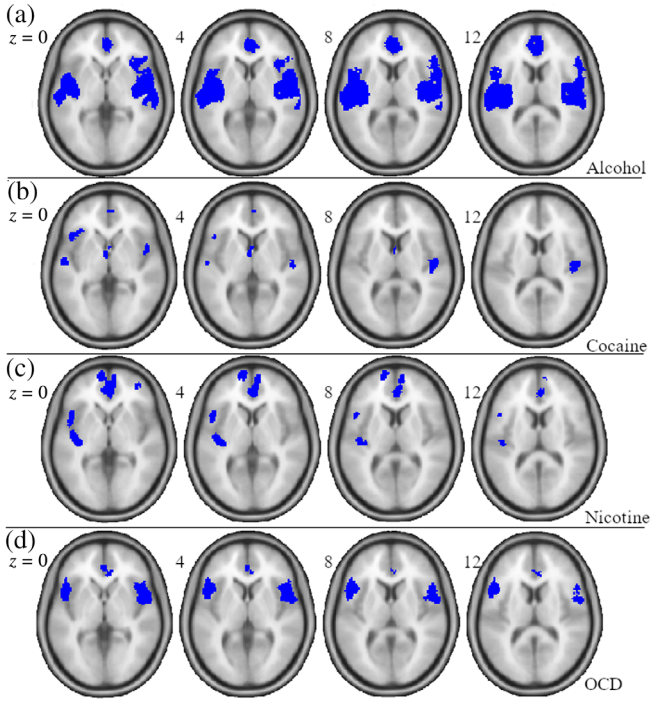

FIGURE 2 Reduced GMV in each of the diagnostic group (patients < controls), corrected at FWE <0.05

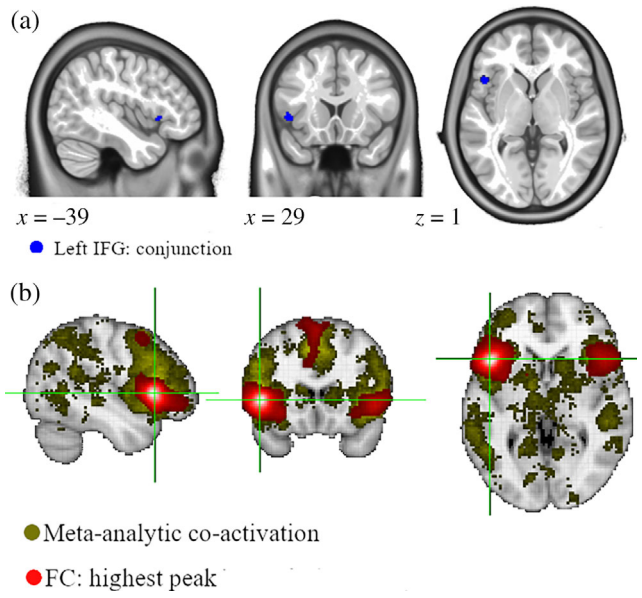

FIGURE 3 Conjunction and meta-analytic co-activation analysis. (a) Reduced GMV overlap among the four groups (Patients < controls), corrected at FWE <.05, (b) the meta-analytic co-activation derived from the Neurosynth database

jackknife sensitivity analyses. Together, the meta-analytic approach allowed us to determine common GMV alterations between SUD and OCD which may underly the shared symptoms on the behavioral level, specifically compulsive behavior and loss of behavioral control which characterizes both disorders.

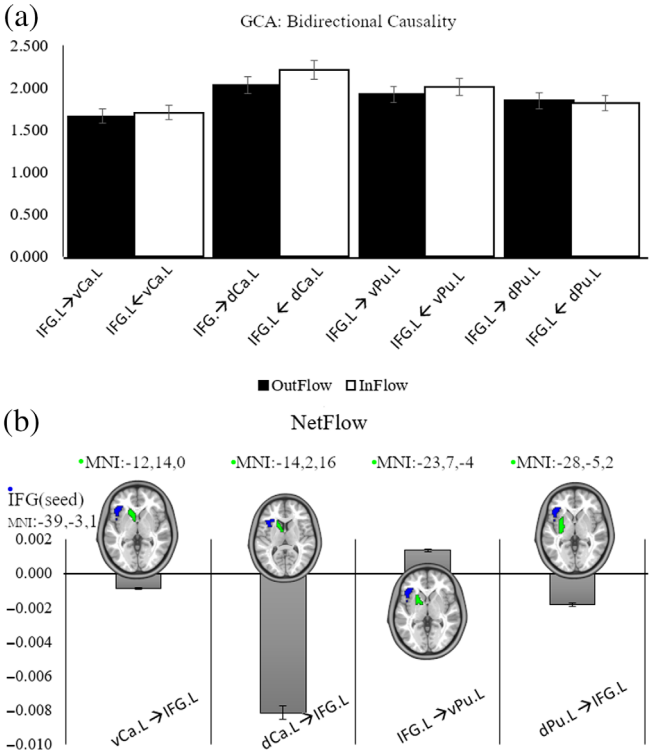

FIGURE 4 Causality between the seed region and target ROIs. (a) Each group of bars represents GCA residual computation from seed region IFG to selected striatal regions and vice versa. (b) the overall causality between the IFG and the striatum regions. Seed region computed from the conjunction GMV of all diagnostic disorders' *y*-axis values are the *z*-scores computed from the residual GCA. Target ROI extracted from Brain connectome project atlas. dCa, dorsal caudate; dPu, dorsal putamen; vCa, ventral caudate; vPu, ventral putamen. The error bar shows the percentage standard error. MNI are the center location of the region

4.1 | Implications—SUD

The frontocortical GMV decreases in the SUD groups broadly resemble findings from the previous meta- and mega-analysis in subjects with SUD (e.g., [Ersche, Williams, Robbins, & Bullmore, 2013; Mackey et al., 2019; Yang et al., 2016]). Across the SUDs examined, the insula showed marked decreases in the GMV. The insula alteration was functionally shown in our previous study suggesting common neurofunctional alterations in this region across SUDs (Klugah-Brown et al., 2020) as well as between SUDs and OCD (Klugah-Brown - et al., 2021). The insula has increasingly been noted as addiction relevant region, probably via its important role in interoceptive processing, decision making, and/or risky behavior which may promote substance abuse despite being aware of the negative consequences (Naqvi & Bechara, 2009). Structural deficit and/or functional alteration of the insula has been repeatedly described and associated with an increased relapse risk (Paulus, Tapert, & Schulteis, 2009). Moreover, the SUDs were characterized by medial frontal GM decreases, a region involved in decision making, self-awareness, and regulatory control, such that deficits in this region have been shown

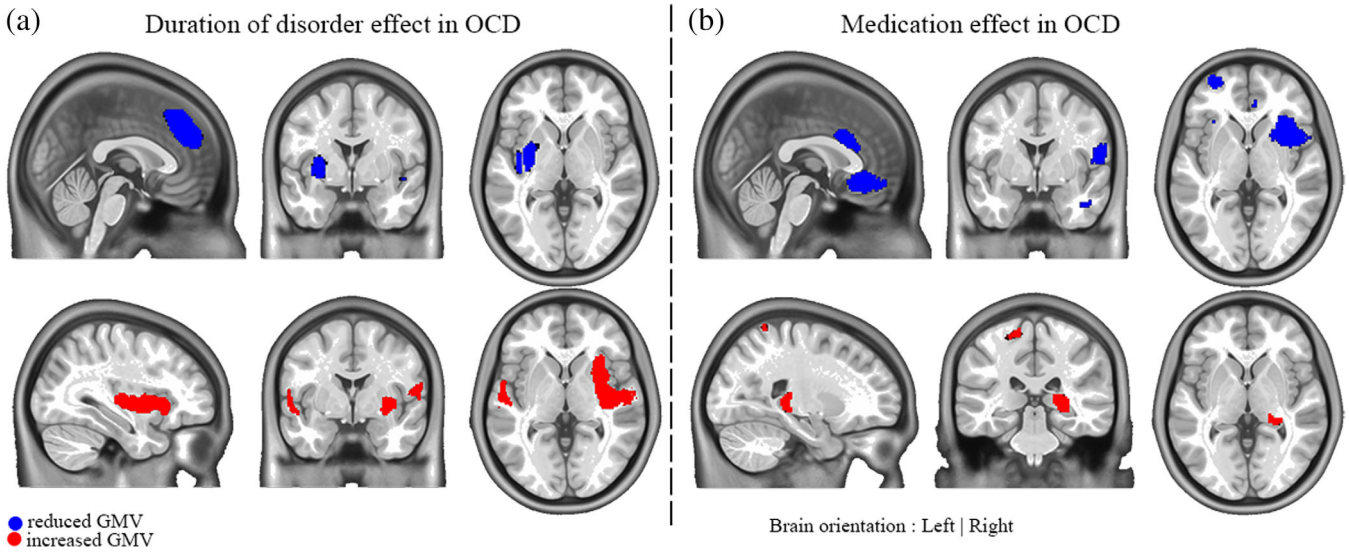

FIGURE 5 linear model analysis of confounding effect. (a) reduced and increased GMV effect due to the duration of disorder in years. (b) reduced and increased GMV effect due to medication, the values taken are the percentage of patients on medication. All images were corrected at FEW<0.05

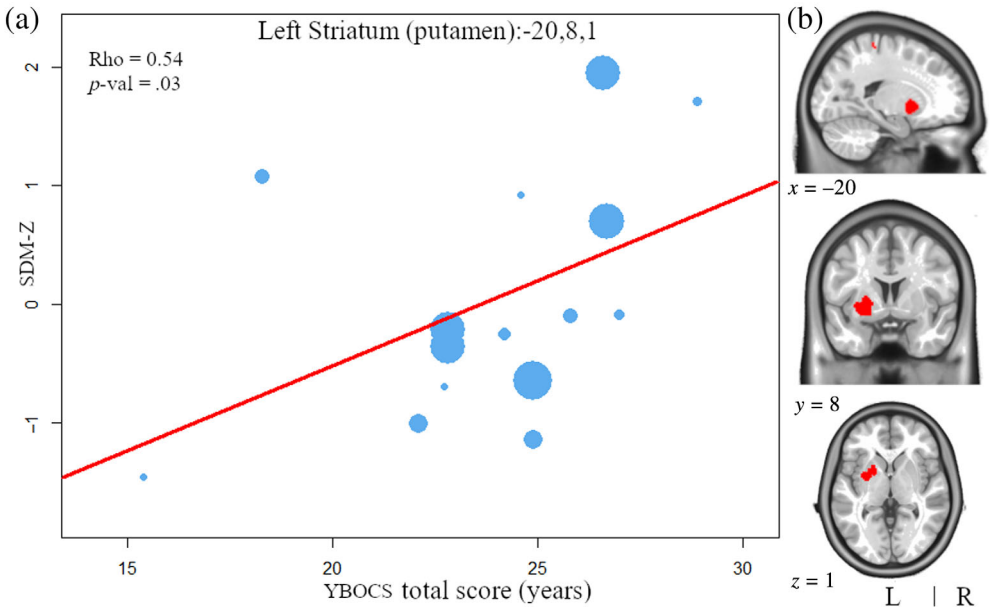

FIGURE 6 Meta-regression. (a) Meta-regression showing a relationship between OCD severity (measured using mean Yale-Brown Obsessive–Compulsive Scale [YBOCS] scale) and GMV in left putamen. Each dot shows studies included in the regression; the different sizes symbolizes greater sample sizes. The meta-regression SDM-Z values indicate the proportion of studies that reported GM alterations close to the voxel. (b) Increase GMV in OCD: L. Putamen, corrected at FWE <0.05. Significant clusters were overlaid on a mni_icbm152 template for display purposes only

to promote dysregulated reinforcement (Bechara, Tranel, & Damasio, 2009; Mackey et al., 2016). Decreased GMV in this network thus may neurally accompany the relationship between maladaptive decision, self-awareness, and deficient regulatory control characterizing addictive disorders.

4.2 | Implications—OCD

In OCD, widespread regions of the bilateral insula and focused regions in the IFG as well as dorsal anterior cingulate exhibited decreased GMV. On the functional level, the frontocortical and cingulate regions have consistently been found to be disrupted in OCD patients relative to controls in a number of fMRI studies examining resting-state (Y. Cheng et al., 2013; de Vries et al., 2019; Swedo et al., 1989; Yun et al., 2017) and task-based (Friedman et al., 2017; Maltby, Tolin, Worhunsky, O'Keefe, & Kiehl, 2005; Marsh et al., 2014; Yücel et al., 2007) neural activation. Our meta-analysis in OCD patients determined a decreased GMV in a similar network and previous studies have linked the identified network to cognitive control and inhibitory control mechanisms (Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2005; Yücel et al., 2007). Additionally, our meta-regression revealed an association between higher symptom scores in OCD patients and GMV increases of the dorsal striatum (putamen), a region

that has been previously reported in functional neuroimaging studies in OCD (Baxter, Brody, Colgan, et al., 1996; Rapoport & Wise, 1988; Saxena, Brody, Schwartz, & Baxter, 1998).

4.3 | Implications—common decreases in IFG GMV

The principal aim of the present meta-analysis was to determine shared GMV alterations between the disorders to facilitate the identification of brain structural commonalities that may underpin compulsivity, thus representing a key transdiagnostic symptom across SUDs and OCD. The corresponding conjunction analysis revealed that the left IFG exhibited shared volumetric decreases across the disorders. The left insular and adjacent IFG is known to play an important role in regulatory top-down control, particularly response inhibition (Devito et al., 2013), a neurocognitive function that has been found to be impaired in both disorders and may promote the development of compulsive behavior (Chamberlain et al., 2005; Zilverstand, Huang, Alia-Klein, & Goldstein, 2018). Moreover, the subsequent exploratory analysis that aimed at functionally characterizing this region suggests that the identified IFG region co-activates with widespread regions in the parietal and frontal cortex that highly resembles the front-parietal cognitive control network critically engaged in executive functions and behavioral control (Chen et al., 2018; Dixon et al., 2018; Fiske & Holmboe, 2019; Gürsel, Avram, Sorg, Brandl, & Koch, 2018; Reineberg, Gustavson, Benca, Banich, & Friedman, 2018; Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012). Based on previous conceptualizations and studies proposing a critical engagement of the frontostriatal circuits in both, SUD and OCD we employed GCA to examine the causal relationship between the identified IFG region and the striatum. Results confirmed a causal information flow between the two structures, specifically left striatal subregions causally influenced the IFG whereas the IFG controlled the ventral putamen. With respect to SUD, both the ventral striatal and the dorsal striatum have been engaged in maladaptive reward processing and the development of compulsive behavior (Andrews et al., 2011; Patel et al., 2013). Thus, the causal relationships and the main conjunction meta-analytic result support the suggestion that compulsivity and altered response to reward and/or punishment may be linked via these pathways that have been involved in both addiction and OCD. Interestingly previous studies have suggested shared alterations in this circuit between OCD and behavioral addiction (pathological gambling [Scherrer, Xian, Slutske, Eisen, & Potenza, 2015]), or between SUD and obesity (Tomasi & Volkow, 2013), suggesting a potential transdiagnostic marker for compulsivity-related disorders. Moreover, some previous deep-brain stimulation studies have shown that compulsive behavior in OCD and addiction can be significantly attenuated through decreasing frontostriatal connectivity (De Ridder, Vanneste, Kovacs, Sunaert, & Dom, 2011; Dunlop et al., 2016; Figee et al., 2013; Kravitz et al., 2015; Valencia-Alfonso et al., 2012).

Summarizing, shared GMV loss in a region of the IFG which represents a principal node in the cognitive control network and critically interacts with the striatum may characterize addictive disorders and OCD. Together with the shared symptomatologic alterations in compulsivity between SUD and OCD and the involvement of the frontostriatal pathways in compulsivity the present findings may reflect a general neurostructural marker for compulsivity. However, given that a previous meta-analysis revealed decreased GMV in the bilateral anterior insula (Goodkind et al., 2015) across several disorders we cannot exclude that unspecific alteration in mental disorders may have contributed to the robust identification of decreased GMV across OCD and SUD.

It is noteworthy that, despite the important insights that the meta-analytic approach may have allowed, some limitations hindered the full examination of the topic. First, only a limited number of VBM have been conducted in SUD resulting in a comparably low number of studies for the separate SUDs. However, across the separate SUDs convergent changes in the insula and prefrontal cortex were observed suggesting substance-independent GM alterations in SUD and pooling the data for the comparison with OCD increased the statistical power. Nevertheless, findings in the individual SUDs need to be interpreted cautiously. Secondly, since the disorders require different diagnostic symptom assessments, a meta-regression with severity measures could not be conducted across all disorders. Also, studies in each category did not report consistent measures (some studies did not report severity/duration and other measures). We, therefore, encourage researchers to report these measures as it reflects the core relationships between altered regions and symptoms.

5 | CONCLUSION

We capitalized on previous case-control VBM studies in three prevalent SUDs and OCD with the aim to determine shared brain structural alterations across the disorders. The left IFG exhibited decreased GMV across all disorders suggesting a transdiagnostic marker that may underly the key symptomatic feature of compulsivity that characterizes the disorders. The IFG plays an important role in inhibitory control and our findings indicate that this region functionally interacts with both, the cognitive control network and the striatum, suggesting that this region plays a key role in the interaction between frontal regulatory control functions and habitual and reward-driven behavior. The findings emphasize that the symptomatological overlap may be rooted in common brain alterations and may open a new venue toward transdiagnostic treatment approaches that target brain alterations that promote compulsive behavior.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are available from the corresponding authors upon reasonable request.

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SUPPORTING INFORMATION

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