Published in final edited form as:

Addict Biol. 2018 January ; 23(1): 394–402. doi:10.1111/adb.12492.

Gray-matter relationships to diagnostic and transdiagnostic features of drug and behavioral addictions

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Abstract

Alterations in neural structure have been reported in both cocaine-use disorder and gambling disorder, separately, suggesting similarities across addiction diagnoses. Individual variation in neural structure has also been associated with impulsivity, a dimensional construct implicated in addictions. This study combines categorical (diagnosis-based) and dimensional (transdiagnostic) approaches to identify neural structural alterations linked to addiction subtypes and trait impulsivity, respectively, across individuals with gambling disorder (n=35), individuals with cocaine-use disorder (n=37) and healthy comparison individuals (n=37). High-resolution T1-

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Author contribution: Neuroimaging data were collected as part of ongoing research protocols being conducted by Drs. Potenza, Carroll, Malison and Constable. Drs. Yip and Potenza are responsible for the study design. Drs. Yip, Worhunsky, Morie and Xu collaborated on image quality and pre-processing steps. Dr. Yip conducted the primary statistical analyses and drafted the manuscript. All authors have provided critical feedback on data interpretation and manuscript presentation

Funding and Disclosures:

This study was supported by R01 DA019039, R01 DA020908, R01 AA017539, P20 DA027844, P50 DA09241, T32 DA022975, T32 DA007238, K01DA039299, the National Center for Responsible Gaming and the National Center on Addiction and Substance Abuse. The views presented in the manuscript are not necessarily those of the funding agencies who did not have input into the content of the manuscript outside of funding the proposed research.

The authors report that they have no financial conflicts of interest with respect to the content of this manuscript. Dr. Potenza has received financial support or compensation for the following: Dr. Potenza has consulted for and advised Boehringer Ingelheim, Ironwood, Lundbeck, INSYS, Shire, RiverMend Health, Opiant/Lakelight Therapeutics and Jazz Pharmaceuticals; has received research support from the NIH, Veteran's Administration, Mohegan Sun Casino, the National Center for Responsible Gaming, and Pfizer, Forest Laboratories, Ortho-McNeil, Psyadon, Oy-Control/Biotie and Glaxo-SmithKline pharmaceuticals; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse control disorders or other health topics; has consulted for law offices and the federal public defender's office in issues related to impulse control disorders; provides clinical care in the Connecticut Department of Mental Health and Addiction Services Problem Gambling Services Program; has performed grant reviews for the NIH and other agencies; has edited journals and journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. The other authors reported no biomedical financial interests or other conflicts of interest.

weighted data were analyzed using modulated voxel-based morphometry (VBM). Statistical analyses were conducted using whole-brain general-linear models, corrected for family-wise error ($p_{FWE} < .05$). Categorical analyses indicated a main effect of diagnostic group on prefrontal (dorsal anterior cingulate, ventromedial prefrontal cortex) gray matter volumes (GMVs), involving decreased GMVs among cocaine-use disorder participants only. Dimensional analyses indicated a negative association between trait impulsivity and cortical (insula) and subcortical (amygdala, hippocampus) GMVs across all participants. Conjunction analysis indicated little anatomical overlap between regions identified as differentiating diagnostic groups and regions co-varying with impulsivity. These data provide first evidence of neural structural differences between gambling disorder and an illicit substance-use disorder. They further indicate dissociable effects of diagnostic groupings and trait impulsivity on neural structure among individuals with behavioral and drug addictions. Study findings highlight the importance of considering both categorical and dimensional (e.g., Research Domain Criteria; RDoC) analysis approaches within the context of addictions research.

Keywords

cocaine; pathological gambling; voxel-based morphometry

Introduction

Reduced prefrontal cortical (PFC) grey-matter volumes (GMVs) have been relatively consistently reported among individuals with cocaine-use disorder (CUD) (Mackey and Paulus, 2013). These and other alterations (e.g., less consistent reports of altered subcortical volumes) have often been interpreted as resultant from prolonged exposure to an exogenous drug; *reviews in* (Garavan, Brennan, Hester, Whelan, 2013; Mackey and Paulus, 2013; Yip, Carroll, Potenza, 2015). However, in recent years, similar grey-matter alterations have also been reported among individuals with gambling disorder (GD) (Rahman, Xu, Potenza, 2014; Zois, Kiefer, Lemenager, Vollstadt-Klein, Mann, Fauth-Buhler, 2016) - albeit not consistently (Joutsa, Saunavaara, Parkkola, Niemelä, Kaasinen, 2011; van Holst, de Ruiter, van den Brink, Veltman, Goudriaan, 2012; Koehler, Hasselmann, Wustenberg, Heinz, Romanczuk-Seiferth, 2015) - raising the possibility of neural structural similarities across behavioral and drug addictions not solely attributable to substance-use *per se*.

Individual variation in neural structure has been linked to core behavioral features of addictions, such as self-reported or 'trait' impulsivity (Fineberg, Potenza, Chamberlain, Berlin, Menzies, Bechara, Sahakian, Robbins, Bullmore, Hollander, 2010; Moreno-Lopez, Catena, Fernandez-Serrano, Delgado-Rico, Stamatakis, Perez-Garcia, Verdejo-Garcia, 2012; Rahman, Xu, Potenza, 2014). Thus, a competing hypothesis is that possible similarities in neural structure across individuals with behavioral and substance addictions might reflect the elevated rates of impulsivity observed in both groups. However, the extent to which neural structural alterations among individuals with addictions track most closely with diagnosis (e.g., differ between behavioral versus substance addiction diagnoses; categorical, Diagnostic and Statistical Manual (DSM) approach), or with individual differences in

impulsivity (e.g., co-vary with trait impulsivity; dimensional, Research Domain Criteria (RDoC) approach), has not been previously established.

Here, we combine categorical and dimensional approaches to further understanding of gray-matter structural variation in relation to diagnosis and impulsivity, respectively, among individuals with CUD, individuals with GD and healthy comparison (HC) individuals. We hypothesized dissociable anatomical effects of categorical versus dimensional analysis approaches, as follows.

Prior work has relatively consistently demonstrated decreased GMVs within regions of the PFC among individuals with CUD, *reviewed in* (Mackey, Stewart, Connolly, Tapert, Paulus, 2014), but not among individuals with GD (Joutsa, Saunavaara, Parkkola, Niemelä, Kaasinen, 2011; van Holst, de Ruiter, van den Brink, Veltman, Goudriaan, 2012; Koehler, Hasselmann, Wustenberg, Heinz, Romanczuk-Seiferth, 2015). As prior work therefore most consistently indicates reduced PFC GMVs in CUD – and in light of the neurotoxic effects of cocaine (Pereira, Andrade, Valentao, 2015; Zhang, You, Volkow, Choi, Yin, Wang, Pan, Du, 2016) – we hypothesized that categorical comparisons would identify primarily PFC regions as differentiating diagnostic groups, and that this would involve decreased GMVs among CUD individuals with respect to both GD and HC participants.

Associations between impulsivity-related features and subcortical volumes have been reported among both individuals with addictions and HC participants (Ersche, Barnes, Jones, Morein-Zamir, Robbins, Bullmore, 2011; Rahman, Xu, Potenza, 2014; Tschernegg, Pletzer, Schwartenbeck, Ludersdorfer, Hoffmann, Kronbichler, 2015). We therefore further hypothesized that dimensional analyses would identify primarily subcortical limbic regions (e.g., striatum, amygdala) as negatively co-varying with impulsivity across diagnoses. Finally, we hypothesized no areas of anatomical overlap (as determined using a conjunction analysis) between regions distinguishing diagnoses versus those co-varying with impulsivity.

Materials and methods

Participants

Individuals who met formal diagnostic criteria for CUD or GD with high-resolution T1-weighted structural MRI data (acquired as part of ongoing functional neuroimaging protocols in conjunction with the Center for Excellence in Gambling Research, the Psychotherapy Development Center and the Clinical Neuroscience Research Unit) were considered for inclusion in this study. Primary inclusionary criteria included a DSM-IV diagnosis of pathological gambling for GD participants, and of cocaine dependence for CUD participants, based on structured clinical interview (SCID; (First, Gibbon, Spitzer, Williams, 1995). Primary exclusionary criteria included head trauma or other contraindication to MRI scanning and a history of psychosis (as determined using the SCID). HC participants were excluded for any current or previous psychotropic medication or DSM-IV Axis-I disorder other than nicotine dependence.

Based on the above inclusion criteria, 35 individuals with GD were selected for study inclusion. CUD (n=37) and HC (n=37) participants were then selected based on

demographic and clinical similarities to GD participants, for a final sample of 109 individuals. Primary matching variables for all participants were age, gender and years of education. Group-matching was successful for age and gender but not for years-of-education, which was significantly higher among HC participants in comparison to both GD and CUD participants. GD and CUD participants did not differ in years-of-education. This variable was included as a regressor-of-no-interest in all subsequent analyses. CUD participants were also group-matched to GD participants for rates alcohol-use disorders (AUDs), cannabis-use disorders, major depression and anxiety disorders. Rates of lifetime AUDs among both CUD and GD participants were relatively high (approximately 50%), but were remitted with the exception of two GD and three CUD participants who met criteria for a current AUD. Demographic and clinical information for all participants is shown in Table 1.

Impulsivity

Trait impulsivity was measured using the Barratt Impulsiveness Scale (BIS-11), a widely used 30-item self-report index of impulsiveness with demonstrated reliability (Patton, Stanford, Barratt, 1995). Consistent with prior work (Moeller, 2002; Lai, Ip, Lee, 2011), BIS-11 scores were significantly higher among GD and CUD participants, in comparison to HC participants (Table 1), but did not differ between GD and CUD groups.

Data acquisition

T1-weighted images were acquired at Yale University's Magnetic Resonance Research Center (MRRC) between 2006 and 2014. Due to an equipment upgrade in 2009, data acquisition was performed using two 3T Siemens Trio scanners. Fifty-seven individuals (19 GD, 21 CUD, 17 HC) were scanned on one system and 52 individuals (16 GD, 16 CUD, 20 HC) were scanned on the other, and these rates did not differ between participant groups ($\chi^2=0.95$, $df=2$, $p=0.62$). Identical acquisition parameters were used for all participants. High-resolution structural data were acquired using a sagittal T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR/TE=2530/3.34ms, flip angle=7°, FOV= 256mm x 256mm, matrix=256 x 256, 176 slices, 1mm³ isotropic voxels). T1-weighted data from 16 GD subjects (Rahman, Xu, Potenza, 2014) and from 12 CUD subjects (Mei, Xu, Carroll, Potenza, 2015) were included in two separate previous publications. None of the prior publications included comparisons between GD and CUD individuals and both used ROI (rather than whole-brain) analysis approaches.

Modulated VBM analysis

T1-weighted images were analyzed using FSL's optimized VBM protocol (FSL-VBM; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM>) (Good, Johnsrude, Ashburner, Henson, Friston, Frackowiak, 2001; Douaud, Smith, Jenkinson, Behrens, Johansen-Berg, Vickers, James, Voets, Watkins, Matthews, James, 2007) using the following recommended steps: Images were brain-extracted and segmented prior to non-linear registration to standard space (GM ICBM-152 template). Registered images were concatenated and averaged to create a study-specific gray-matter template. Native gray-matter images were nonlinearly registered to the template and divided by the Jacobian of the warp field in order to modulate for any expansion/contraction caused by the non-linear registration. This modulation is equivalent to

correcting for total intracranial volume (TIV) via division (Douaud, Smith, Jenkinson, Behrens, Johansen-Berg, Vickers, James, Voets, Watkins, Matthews, James, 2007; Malone, Leung, Clegg, Barnes, Whitwell, Ashburner, Fox, Ridgway, 2015) and therefore makes it unnecessary to include TIV in subsequent statistical models as a covariate. Modulated images were smoothed using an isotropic Gaussian kernel with a sigma of 4mm.

Voxelwise statistics

All voxelwise statistics were conducted using permutation-based non-parametric testing (FSL's 'randomise') with 5000 permutations and cluster-based correction for multiple comparisons across space (Nichols and Holmes, 2002; Winkler, Ridgway, Webster, Smith, Nichols, 2014). These analyses proceeded in several steps, as described below.

Comparison of diagnoses

The main effect of diagnostic groups on modulated GMVs was assessed using a single whole-brain general-linear model (GLM) including years-of-education and scanner as variables of no interest and diagnosis (GD/CUD/HC) as the between-subjects factor ($F > 3.5$, $p_{FWE} < .05$). Follow-up groupwise comparisons were conducted using t-tests with cluster-based correction ($t > 3.0$, $p_{FWE} < .05$) and the same covariates.

Effects of impulsivity

The main effect of impulsivity scores (BIS-11) on modulated GMVs was assessed using a single whole-brain GLM including years-of-education and scanner as variables of no interest and BIS-11 scores as a continuous between-subjects variable ($t > 3.0$, $p_{FWE} < .05$). Impulsivity scores were missing for one GD participant, one HC participant and three CUD participants. Missing data for these five individuals were imputed using mean BIS-11 scores for each diagnostic group separately (means $\pm$ standard deviations shown in Table 1).

Conjunction analysis

A conjunction analysis was conducted to identify anatomical areas of overlap between regions identified as differentiating diagnostic groups versus those identified as co-varying with impulsivity. Group-level statistical maps were converted to binary masks representing voxels surviving cluster-based correction (as described above). To create conjunction maps, masks from diagnosis-based comparisons were each separately combined with the mask image for the impulsivity-based analysis using *fslmaths*. Areas of overlap were defined as any voxel shared between masks (i.e., as indicated by any voxel-value of two or greater in a conjunction map).

Post-hoc tests related to AUD histories and years of cocaine use

Given the relatively high rates of AUD histories in this sample (approximately 50% for both CUD and GD groups) individual participant data values for clusters (i.e., mean value of voxels within each cluster) identified as differentiating diagnostic groups (categorical analysis) or as co-varying with impulsivity (dimensional analysis) were extracted using *fslmaths* and entered into SPSS for follow-up analyses relating to this variable. Extracted

cluster values were further used for exploratory correlational analyses relating to years of cocaine use.

Results

Comparison of DSM-IV diagnoses

There was a significant main effect of DSM-IV diagnostic groupings on modulated GMVs within regions including the dorsal anterior cingulate (ACC), ventromedial PFC (vmPFC), dorsolateral PFC (dlPFC) and medial orbitofrontal cortex (OFC), involving decreased GMVs among CUD individuals in comparison to both GD and HC participants (Table 2, Figure 1A). Follow-up analyses indicated a significant negative association between GMVs within this cluster and years of cocaine use among CUD participants ($r_{(34)} = -0.37$, $p = 0.03$).

In order to further understand the nature of the identified main effect, planned whole-brain groupwise comparisons were conducted (Table 2). These analyses indicated decreased GMVs among CUD versus GD participants within a single cluster encompassing regions of the ACC, OFC and medial frontal cortex and decreased GMVs among CUD versus HC individuals within a single cluster encompassing regions of the left inferior frontal gyrus (IFG), insula and dlPFC. No significant differences in GMVs were found between GD and HC participants.

Follow-up, within-group comparisons indicated no significant effects of AUD histories on modulated GMVs within identified clusters among GD ($F_{(1,31)} = 0.02$, $p = 0.88$) or CUD ($F_{(1,33)} = 2.29$, $p = 0.14$) participants (Figure S1).

Between-group differences in GMVs within the identified clusters (3-group ANOVA) remained significant following exclusion of participants with a history of AUDs ($n = 38$; $F_{(2,66)} = 4.0$, $p = 0.02$).

Effects of impulsivity

Whole-brain regression indicated a significant negative association between impulsivity scores and modulated GMVs within regions including the left and right insula, amygdala, parahippocampal gyrus, hippocampus and temporo-parietal regions including the superior temporal gyrus, precuneus and superior parietal lobule (Figure 1B).

Hierarchical linear regression with diagnosis (step one) and impulsivity scores (step two) confirmed that associations between impulsivity and GMVs were not related to diagnostic groupings ($\beta = -0.02$, $p = 0.87$) and remained significant after controlling for this variable ($\beta = -0.58$, $p < .001$).

Linear regressions with AUD histories indicated that associations between impulsivity and GMVs remained significant after controlling for AUDs ($\beta = -0.53$, $p < .001$; Figure S2), as well as after exclusion of all participants with a history of AUDs ($\beta = -0.53$, $p < .001$).

Anatomical overlap of diagnostic and dimensional findings

There was no overlap between regions identified as co-varying with impulsivity and those differentiating all three diagnostic groups (3-group ANOVA), nor was there overlap between impulsivity-associated regions and regions identified as differentiating GD from CUD individuals (groupwise comparison). A single cluster was identified as overlapping between impulsivity-associated regions and regions identified as differentiating CUD from HC individuals ($k=111$). This cluster included regions of the left anterior insula and IFG.

Effects of tobacco and other drug-use

Exclusion of participants with tobacco-use and of GD participants with illicit substance-use histories did not change the primary study findings. Further details are provided in the Supplementary Materials.

Discussion

This study tested the hypothesis of shared GM structural variation between substance and behavioral addictions, via VBM analysis of high-resolution T1-weighted data from 35 individuals with GD, 37 individuals with CUD, and 37 HC participants. Given ongoing debate regarding appropriate classification of psychiatric disorders (Insel, Cuthbert, Garvey, Heinssen, Pine, Quinn, Sanislow, Wang, 2010; Casey, Oliveri, Insel, 2014), data were analyzed using both categorical (DSM-style) and dimensional (RDoC-style) analysis approaches. This was selected over a more standard multivariate approach in order to allow for wholly independent assessments of categorical and dimensional approaches, respectively. Categorical versus dimensional analysis approaches indicated dissociable effects of DSM-diagnostic groupings and self-reported (“trait”) impulsivity. Specifically, categorical analyses revealed between-group differences in primarily prefrontal cortical regions involving relatively decreased GM among CUD participants, in comparison to both GD and HC participants. By contrast, transdiagnostic, RDoC-based analyses identified primarily subcortical and parietal regions as inversely related to impulsivity (BIS-11 scores).

Categorical findings

Findings from functional and diffusion-weighted imaging studies directly comparing behavioral and substance addiction diagnoses suggest both similarities and differences between GD and CUD (Worhunsky, Malison, Rogers, Potenza, 2014; Contreras-Rodriguez, Albein-Urios, Vilar-Lopez, Perales, Martinez-Gonzalez, Fernandez-Serrano, Lozano-Rojas, Clark, Verdejo-Garcia, 2015; Kober, Lacadie, Wexler, Malison, Sinha, Potenza, 2016; Yip, Morie, Xu, Constable, Malison, Carroll, Potenza, 2016). For example, while CUD and GD groups both exhibit increased anticipatory responding relative to controls within mesolimbic and ventrocortical circuits, these effects were observed during different phases of simulated slot-machine play (Worhunsky, Malison, Rogers, Potenza, 2014). Similarities in diffusion indices within subcortical white-matter microstructures have also been noted between CUD and GD individuals (Yip, Morie, Xu, Constable, Malison, Carroll, Potenza, 2016). Existing data therefore indicate some overlap in neural function and structure between GD and CUD individuals. However, we found no evidence of shared GM structural features between GD and CUD individuals.

No significant differences in GM were found between GD and HC participants. These findings contrast with prior reports of both increased (Koehler, Hasselmann, Wustenberg, Heinz, Romanczuk-Seiferth, 2015) and decreased (Rahman, Xu, Potenza, 2014; Zois, Kiefer, Lemenager, Vollstadt-Klein, Mann, Fauth-Buhler, 2016) prefrontal and subcortical GMVs, but are consistent with findings from several other prior GD studies (Joutsa, Saunavaara, Parkkola, Niemelä, Kaasinen, 2011; van Holst, de Ruiter, van den Brink, Veltman, Goudriaan, 2012; Fuentes, Rzezak, Pereira, Malloy-Diniz, Santos, Duran, Barreiros, Castro, Busatto, Tavares, Gorenstein, 2015). Seemingly discrepant findings across studies may relate to sample size variation, e.g., $n=12$ (Joutsa, Saunavaara, Parkkola, Niemelä, Kaasinen, 2011) versus $n=107$ (Zois, Kiefer, Lemenager, Vollstadt-Klein, Mann, Fauth-Buhler, 2016), analytic approaches (region-of-interest versus whole-brain approaches) or heterogeneity between study samples, or uncontrolled within-study heterogeneity. With respect to the last possibility, uncontrolled effects of alcohol or other substance-use may contribute (Weinberger and Radulescu, 2016), although these have been examined in some studies; e.g., (Rahman *et al*, 2014). In the current study, exclusion of participants with AUD or other substance-use histories left our primary study findings unchanged. Nevertheless, as AUDs in this study were almost entirely remitted, the possibility of an effect of current AUDs on neural structure in GD cannot be excluded, particularly given recent data from a large sample suggesting dissociable effects of substance- and alcohol-use on GMVs in GD (Zois, Kiefer, Lemenager, Vollstadt-Klein, Mann, Fauth-Buhler, 2016). Thus, further work assessing the effects of current versus former AUDs (and of alcohol-use severities) on neural structure across substance and behavioral addictions is warranted.

CUD participants exhibited reductions in primarily prefrontal cortical GMVs, including regions of the dorsal ACC, OFC, dlPFC and vmPFC, when compared to both HC and GD participants. These regions are involved in multiple processes including goal-directed behavior, stimulus-response learning and inhibitory control and, within the specific context of addictions, are hypothesized to contribute to decreased reactivity to non-drug rewards, craving processes and aberrant decision-making (London, 2000; Goldstein and Volkow, 2011). Our findings of reduced GM within these regions is consistent with those from most prior GM studies conducted in CUD; however, to our knowledge, this is the first study to include a matched psychiatric control group (Mackey and Paulus, 2013). GD and CUD groups were well-matched for demographic and clinical factors; thus, reduced prefrontal GMVs in this study may be a consequence of chronic exposure to cocaine. Consistent with this interpretation, there was a negative association between years of cocaine and prefrontal GMVs among CUD individuals. However, given the cross-sectional nature of this study, we cannot exclude the possibility pre-existing GMV reductions prior to cocaine use solely on the basis of these data.

While conclusions about causality cannot be made solely on the basis of these data, the above interpretation relating to cocaine exposure is consistent with preclinical data demonstrating neurotoxic effects of cocaine (Pereira, Andrade, Valentao, 2015; Zhang, You, Volkow, Choi, Yin, Wang, Pan, Du, 2016). Our data are further consistent with a recent report of differential OFC-ACC functional connectivity between CUD and GD individuals (Contreras-Rodriguez, Albein-Urios, Vilar-Lopez, Perales, Martinez-Gonzalez, Fernandez-Serrano, Lozano-Rojas, Clark, Verdejo-Garcia, 2015), but differ somewhat from data

demonstrating no between-group differences in prefrontal white-matter between CUD, GD and HC individuals (Yip, Morie, Xu, Constable, Malison, Carroll, Potenza, 2016). Although associations between gray- and white-matter tissue characteristics are beyond the scope of the present study (which seeks to compare categorical and dimensional approaches within a single modality), further research utilizing multimodal analysis techniques, e.g., fusion ICA (Sui, Pearlson, Caprihan, Adali, Kiehl, Liu, Yamamoto, Calhoun, 2011), appears warranted to clarify relationships between gray- and white-matter features among individuals with addictions.

Dimensional findings

Transdiagnostic research efforts, such as RDoC, challenge traditional categorical, diagnosis-based approaches, instead emphasizing dimensional assessment of neurobiology as it relates to measurable behavioral features (Insel, Cuthbert, Garvey, Heinssen, Pine, Quinn, Sanislow, Wang, 2010). Within this context, dimensional constructs such as impulsivity are hypothesized to underlie core psychiatric symptoms and to map onto neurobiological features independent of diagnosis (Casey, Oliveri, Insel, 2014). Consistent with this framework, we observed a negative association between impulsivity and GM structural variation that was not related to diagnostic groupings.

Regions identified as co-varying with impulsivity across diagnoses included bilateral insula, amygdala-hippocampal complex and parahippocampal gyri. In addition to their well-documented roles in emotion regulatory processes (Paulus and Stein, 2006; Hartley and Phelps, 2010), these regions are critically involved in key aspects of reward processing including incentive salience and prediction-error encoding (Gradin, Kumar, Waiter, Ahearn, Stickle, Milders, Reid, Hall, Steele, 2011; Paulus and Stewart, 2014). The amygdala interacts with corticostriatal circuits influencing aspects of inhibitory control and reward-seeking behaviors (Kramer and Gruber, 2015) and insula-amygdala connectivity has been implicated in core features of addiction, including withdrawal from nicotine (Sutherland, Carroll, Salmeron, Ross, Hong, Stein, 2013). Thus, it is possible that reduced GM within these regions might confer vulnerability to heightened impulsivity via alterations in valence processing (e.g., decreased encoding of negative consequences of reward-seeking behaviors). Taken together with recent data demonstrating a prospective association between reduced subcortical limbic volumes and subsequent stimulant use (Becker, Wagner, Koester, Tittgemeyer, Mercer-Chalmers-Bender, Hurlmann, Zhang, Gouzoulis-Mayfrank, Kendrick, Daumann, 2015), these findings raise the possibility that reduced amygdala-hippocampal volumes might confer vulnerability for a range of impulsive behaviors.

Notably, there was almost no anatomical overlap between regions identified as co-varying with impulsivity versus those identified as differentiating diagnostic groups. The one exception was a single small cluster including portions of the anterior insula and IFG, which was reduced among CUD versus HC individuals and also co-varied with impulsivity across diagnoses. The anterior insula and IFG are involved in inhibitory control processes and have been implicated in responses to behavioral treatments (Garrison and Potenza, 2014). Thus, future research should consider possible interaction effects between impulsivity and treatment responses in relation to insula and IFG structural variation.

These data suggest dissociable effects of diagnostic groupings and trait impulsivity on neural structure among individuals with behavioral and drug addictions. They represent a critical first step in understanding interactions between dimensional versus categorical approaches to studying mental illness. As heightened impulsivity is a core feature of multiple psychiatric disorders, including mood and personality disorders (Swann, Lijffijt, Lane, Steinberg, Moeller, 2009; Swann, Lijffijt, Lane, Steinberg, Moeller, 2009), an important next step will be to extend our findings to other diagnoses.

Strengths, limitations and conclusions

Study findings should be viewed within the context of several limitations. T1-weighted data were acquired in conjunction with several different neuroimaging protocols. This approach resulted in a relatively robust sample size (n=109), but limited the number of measures shared across all participants. We were therefore unable to explore effects of other core behavioral and personality-related variables on GMVs, such as compulsivity and mood symptoms, nor were we able to conduct more nuanced analyses related to alcohol-use severity (due to the absence of a common measure of alcohol-use severity). Given ongoing concerns regarding multiple comparisons in neuroimaging, we chose to limit our dimensional analyses solely to the total BIS-11 score. Thus, an important direction for future studies with more robust sample sizes will be the assessment of impulsivity sub-domains. GD and CUD groups were well-matched for most variables, but differed from HCs in years-of-education. While we controlled statistically for this variable in all analyses, we cannot exclude the possibility that this may have influenced our primary findings. Finally, as we did not systematically assess for Axis-II disorders, we also cannot exclude the possibility that co-occurring personality disorders may have influenced our findings.

This study also has several strengths, including the relatively novel combination of both DSM- and RDoC-style analysis approaches. To our knowledge, this is also the first study to directly compare GM neural structure between individuals with a behavioral addiction and those with an illicit-substance addiction. These data represent first evidence of largely separable effects of DSM-diagnostic groupings and trait impulsivity on neural structure. Study findings support both categorical and dimensional approaches and highlight the utility of combining multiple analysis approaches within a single dataset.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Monica Sorlonzano and Stephen Healy for help with data collection and organization and Dr. Zu Wei for helpful conversations regarding statistical analysis.

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Figure 1.
Findings from whole-brain modulated VBM analyses (pFWE<.05)

Table 1

Demographic and clinical characteristics of participants (n=109)

	Gambling Disorder (n=35)		Cocaine Use Disorder (n=37)		Healthy Controls (n=37)	
	n (%)	n (%)	n (%)	n (%)	χ^2	p
Gender (male)	26 (74.3)	25 (67.6)	28 (75.7)		0.69	0.71
	mean (SD)	mean (SD)	mean (SD)		F	p
Age (years)	38.40 (11.80)	42.43 (6.10)	38.00 (11.03)		2.24	0.11
Education (years)	13.23 (1.57)	12.38 (1.11)	14.38 (1.92)		15.10	<.001 ^a
Impulsivity (BIS-11)	70.06 (11.40)	64.44 (12.14)	51.94 (9.04)		25.44	<.001 ^a
	n (%)	n (%)			χ^2	p
Alcohol-use disorder^{c, d}	20 (57.1)	18 (48.6)	--		0.51	0.47
Cannabis-use disorder^d	10 (28.6)	11 (29.7)	--		0.01	0.91
Major Depression^d	7 (20.0)	9 (24.3)	--		0.20	0.66
Anxiety Disorders^d	4 (11.4)	1 (2.6)	--		2.11	0.15

^a Post-hoc comparisons indicated significantly fewer years of education and higher BIS-11 scores among both patient groups, in comparison to controls. Gambling disorder and cocaine-use disorder groups did not differ in years of education or BIS-11 scores ($p > .05$).

^b BIS-11 scores not available for 1 GD, 1 HC and 3 CUD participants.

^c Two gambling disorder and 3 cocaine-use disorder participants met criteria for a current AUD; all other AUDs were remitted.

^d Healthy control participants were excluded for Axis-I disorders. Statistics shown for comparison of gambling disorder patients versus cocaine-use disorder patients.

Voxel-based morphometry results for between-group comparisons of diagnostic groups (pFWE<.05)

Table 2

Main Effect of Diagnostic Group (ANOVA)		BA	k	F-value	x	y	z
Medial Frontal Gyrus / anterior cingulate / middle frontal gyrus / superior frontal gyrus / vmPFC / premotor cortex		9, 10, 32	4520	8.32	18	48	-10
Between-Group Comparisons (t-tests)							
<i>Gambling Disorder > Cocaine-Use Disorder</i>		BA	k	t-value	x	y	z
Anterior Cingulate / medial frontal gyrus / anterior cingulate gyrus / superior frontal gyrus / medial frontal cortex / vmPFC		10, 11, 32	785	3.93	-4	44	-8
<i>Cocaine-Use Disorder < Healthy Comparison</i>							
Insula / inferior frontal gyrus / frontal operculum / middle frontal gyrus / dlPFC / precentral gyrus		9, 12, 44, 45, 46	847	4.4	-48	18	28

There were no significant differences in grey matter volumes between gambling disorder and healthy control participants.

BA=Brodman area; k=cluster size (2mm³ voxels); dlPFC=dorsolateral prefrontal cortex; OFC=orbitofrontal cortex; vmPFC=ventromedial prefrontal cortex

Table 3

Voxel-based morphometry results for regression analysis with BIS-11 score (pFWE<.05, k>100)

	BA	k	t-value	x	y	z
R superior parietal lobule / precuneus / postcentral gyrus / angular gyrus	7	1167	5.02	16	-56	70
L insula / rolandic operculum / precentral gyrus / central operculum	13	531	3.64	-36	-18	22
R insula / superior temporal gyrus / parietal operculum	13, 41	302	3.67	40	-38	18
L parahippocampal gyrus / amygdala / hippocampus		239	4.11	-34	-4	-20
R parahippocampal gyrus / amygdala / hippocampus		169	5.49	34	-4	-20
R cerebellum (declive)		124	4.46	32	-90	-28

BA=Brodmann area; k=cluster size (2mm³ voxels); DLPFC=dorsolateral prefrontal cortex;

BIS-11=Barratt Impulsiveness Scale