Mega-Analysis of Gray Matter Volume in Substance Dependence: General and Substance-Specific Regional Effects

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Objective: Although lower brain volume has been routinely observed in individuals with substance dependence compared with nondependent control subjects, the brain regions exhibiting lower volume have not been consistent across studies. In addition, it is not clear whether a common set of regions are involved in substance dependence regardless of the substance used or whether some brain volume effects are substance specific. Resolution of these issues may contribute to the identification of clinically relevant imaging biomarkers. Using pooled data from 14 countries, the authors sought to identify general and substance-specific associations between dependence and regional brain volumes.

Method: Brain structure was examined in a mega-analysis of previously published data pooled from 23 laboratories, including 3,240 individuals, 2,140 of whom had substance dependence on one of five substances: alcohol, nicotine, cocaine, methamphetamine, or cannabis. Subcortical volume and cortical thickness in regions defined by FreeSurfer were compared with nondependent control subjects when all sampled substance categories were combined, as well as separately, while controlling for age, sex, imaging site, and total intracranial volume. Because of extensive associations with alcohol dependence, a secondary contrast was also performed for dependence on all substances except alcohol. An optimized split-half strategy was used to assess the reliability of the findings.

Results: Lower volume or thickness was observed in many brain regions in individuals with substance dependence. The greatest effects were associated with alcohol use disorder. A set of affected regions related to dependence in general, regardless of the substance, included the insula and the medial orbitofrontal cortex. Furthermore, a support vector machine multivariate classification of regional brain volumes successfully classified individuals with substance dependence on alcohol or nicotine relative to nondependent control subjects.

Conclusions: The results indicate that dependence on a range of different substances shares a common neural substrate and that differential patterns of regional volume could serve as useful biomarkers of dependence on alcohol and nicotine.

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The social and economic costs associated with problematic use of drugs and alcohol place an enormous burden on the individual and society (1–5). In the United States alone, the National Institute on Drug Abuse estimates that the costs associated with problematic substance use—including medical care, law enforcement, and lost productivity—exceed

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$700 billion per year (6). Substance dependence is characterized by a loss of control over drug and alcohol taking behavior, which contributes to high relapse rates (7–10). The therapeutic landscape would be radically altered by the identification of a set of biomarkers that could be used to estimate risk at various stages of the disorder—for example, the risk of transition from occasional to problematic patterns of use or risk of relapse after treatment—and to prescribe the most appropriate treatments on the basis of the individual patient's specific functional vulnerabilities (11, 12).

It remains to be determined whether regional differences in brain volume measured by MRI can provide clinically useful biomarkers of substance dependence. Although brain volumetric studies have routinely observed lower gray matter volume in individuals with substance dependence compared with healthy control subjects who do not have a substance dependence, the brain regions associated with dependence on a specific substance have not been consistent across studies (13–15). Since volumetric studies have tended to focus on one substance at a time, it is also not clear from this literature whether a shared set of brain areas will exhibit altered volume in all individuals with substance dependence regardless of the substance used. Human twin studies suggest that genetic vulnerability to substance dependence is accounted for principally by a shared set of variations regardless of the substance used, with proportionately smaller substance-specific effects (16). On the basis of preclinical research and data from other imaging modalities, several candidate brain regions have been proposed as playing a central role in substance dependence, including the striatum, the insula, and parts of the frontal cortex (reviewed in references 17–19).

The authors of the present study joined to form an international working group within the framework of the Enhancing Neuro-Imaging Genetics Through Meta-Analysis (ENIGMA) project (20, 21) to overcome issues related to low statistical power in individual neuroimaging studies. This first project of the Addiction Working Group has pooled data from 23 laboratories in 14 countries and represents the largest study of brain volumetric data in substance dependence research to date. The objective was to identify general and substance-specific associations between dependence and regional brain volumes. The large sample size facilitated the adoption of a rigorous cross-validation method to address the widespread failure to replicate neuroimaging results, which has been noted in several recent influential reports (22, 23). In addition, a support vector machine classifier was used to explore patterns of regional brain volume that could potentially serve as disease biomarkers.

METHOD

Behavioral Phenotyping

All procedures were performed in accordance with the Declaration of Helsinki. Data sets from the working group were selected that assessed individuals for dependence on one of five substances: alcohol, nicotine, cocaine, methamphetamine, and cannabis. A variety of diagnostic instruments were used to assess substance dependence (see Table S1 in the online supplement). Case and control data were gathered from 23 laboratories on 3,240 individuals, of whom 2,140 were diagnosed with current dependence on at least one of the five substances of interest. Individuals were excluded if they had a lifetime history of neurological disease, a current DSM-IV axis I diagnosis other than depressive and anxiety disorders, or any contraindication for MRI. Control subjects may have used addictive substances recreationally but were not diagnosed as dependent. Summary demographic statistics (sex distribution and mean age) on participants whose data passed the quality control steps described below are provided in Table 1. Site-specific summaries are provided in Table S1 in the online supplement.

Preparation of Structural MRI Data

Structural T_1-weighted MRI brain scans were acquired from all participants. Scanner and acquisition details at each site are provided in Table S1 in the online supplement. Data were prepared in FreeSurfer (version 5.3), a fully automated MRI processing pipeline that identifies seven bilateral subcortical and 34 bilateral cortical regions of interest (24, 25). A majority of the data sets were prepared using CBRAIN, a network of high-performance computing facilities in Canada (26). The volume of subcortical regions of interest and mean thickness of cortical regions of interest served as the dependent measure in all analyses. The use of FreeSurfer in multisite analyses has been validated in previous ENIGMA studies (27–30) that established a standardized protocol of quality control procedures performed at each site (http://enigma.ini.usc.edu/protocols/imaging-protocols/). This includes detection of outliers and visual inspection of all data in a series of standard planes (for more details, see the Supplemental Methods section in the online supplement). An additional level of visual inspection was performed centrally at the University of Vermont on a randomly selected subsample of participants to ensure uniformity of quality control across sites.

Linear Mixed-Effects Models With Cross-Validation

Differences in region-of-interest thickness or volume between substance-dependent participants and nondependent control subjects were assessed in each region of interest with two linear mixed-effects models, using SPSS Statistics for Windows, version 21.0 (IBM, Armonk, N.Y.). The linear mixed-effects model effectively accounts for site effects, including sites that did not collect data on nondependent control subjects (31). In model 1, substance-dependent individuals were treated as one group regardless of the substance used; individuals dependent on any of the five substances of interest were coded as "dependent" and control subjects as "nondependent." Model 1 permitted inclusion of individuals who were dependent on more than one substance. In model 2, dependence on the five substances was coded as individual categories in a single fixed factor: individuals were coded as belonging to one and only one of six categories: "nondependent" or dependent on "alcohol," "nicotine,"

"cocaine," "methamphetamine," or "cannabis." Model 2 did not permit inclusion of individuals who were dependent on more than one substance. In both models, MRI site was entered as a random factor, and sex, age, and total intracranial volume were included as covariates. Further analyses were performed to disconfirm the existence of a site-by-diagnosis interaction (see the Supplemental Methods section in the online supplement).

The replicability of neuroimaging results has recently been brought into question (22, 23). The large sample size of the present study facilitated the adoption of an optimized split-half strategy to verify the reliability of effects. The data were split into two halves (a discovery data set and a replication data set) with statistically matched stratification for age, sex, and intracranial volume within each site and dependence status. Since each region of interest was analyzed separately, a false discovery rate method (the Benjamini-Hochberg procedure) was used to control for multiple comparisons on the first half of the data (the discovery data set). Associations discovered in the first half of the data are reported here as significant only if they were replicated in the second half of the data (the replication data set), that is, if the sign of the difference in means was the same and the null hypothesis had a probability <0.05.

TABLE 1. Sex Distribution and Mean Age of Case and Control Subjects, by Dependence Subgroup, in a Mega-Analysis of Gray Matter Volume in Substance Dependence

Group or Dependence Subgroup	Total N	Female		Age (years)	
		N	%	Mean	SD
All Groups					
Control	1,100	449*	40.8	28.5*	9.9
Case	2,140	731	34.2	33.3	10.6
Alcohol					
Control	292	99	33.9	31.3*	10.2
Case	898	291	32.4	34.7	10.7
Nicotine					
Control	290	155*	53.4	26.1*	8.0
Case	602	250	41.5	30.8	9.8
Cocaine					
Control	99	39*	39.4	36.0*	10.3
Case	227	54	23.8	40.2	7.7
Methamphetamine					
Control	173	71	41.0	31.7	9.3
Case	228	78	34.2	32.9	10.0
Cannabis					
Control	246	85	34.6	22.7*	7.5
Case	185	58	31.4	26.5	10.0

*$p<0.05$.

General Versus Substance-Specific Dependence Effects

Model 2 permitted a comparison of the estimated marginal mean region-of-interest volume or thickness between nondependent control subjects and participants dependent on each substance. Significance was defined as in model 1. The large impact of alcohol dependence on the data (see the Results section) influenced the decision to examine whether dependence on any of the substances other than alcohol was related to differences in region-of-interest volume or thickness compared with nondependent control subjects. This was assessed with a secondary linear contrast within model 2 that grouped dependence on nicotine, cocaine, methamphetamine, and cannabis (but not alcohol) in a comparison with nondependent control subjects.

Past-30-Day Use

Linear mixed-effects models were used to determine whether past-30-day nicotine or alcohol use was related to the volume or thickness of regions of interest identified by model 1 or 2 (i.e., those brain regions listed in Tables 2 and 3). (See the online supplement for more details.)

Support Vector Machine Classification

Support vector machine classification was implemented in MATLAB (MathWorks, Natick, Mass.) with a radial basis function kernel, tuned by parameter sweep in a 10-fold inner loop nested within an optimized split-half cross-validation (32) (for details, see the Supplemental Methods section in the online supplement). The radial basis function kernel facilitates the inclusion of nonlinear relationships in the classifier. In other words, the support vector machine can detect informative patterns in the data that may not be identified by traditional linear analyses such as models 1 and 2. To mitigate site, sex, age, and intracranial volume effects, region-of-interest data were residualized prior to classification. Five studies without control participants were excluded. Area under the receiver operating characteristic curve and corresponding p values based on equivalence with the Mann-Whitney U test were calculated to estimate generalizable classifier performance on the independent half of the data for each of two train–test scenarios (i.e., train on the first half, test on the second, and vice versa). A greater area under the receiver operating characteristic curve, which plots true positive rate against false positive rate, indicates a better separation of the substance-dependent and nondependent groups. The significance threshold for area under the curve was defined as a p value of 0.05 in both classification scenarios. The top 20 features of each classification were determined by the greatest change in cost function resulting from their individual removal from the classification (33).

RESULTS

Basic demographic information (sex distribution and mean age) is provided in Table 1 and by site in Table S1 in the online supplement.

Model 1: Dependent Versus Nondependent Subjects

Subcortical volume in dependent individuals was significantly lower in the left and right hippocampus, the left and right amygdala, and the right nucleus accumbens (Table 2). Lower cortical thickness was observed in several areas,

TABLE 2. Model 1, Individuals With Substance Dependence Compared With Nondependent Control Subjects: Left and Right Hemisphere Regions of Interest That Exhibited Lower Subcortical Volume or Cortical Thickness in a Mega-Analysis of Gray Matter Volume in Substance Dependence[a]

	Left			Right		
	p		Cohen's d	p		Cohen's d
Region and Comparison	1st Half of Data	2nd Half of Data	Both Halves of Data	1st Half of Data	2nd Half of Data	Both Halves of Data
Subcortical volume						
Substance-dependent versus nondependent controls						
Amygdala	0.0002	0.0039	−0.055	0.0011	0.0037	−0.041
Hippocampus	<0.0001	<0.0001	−0.087	<0.0001	<0.0001	−0.081
Nucleus accumbens				0.0068	0.0214	−0.025
Cortical thickness						
Substance-dependent versus nondependent controls						
Caudal middle frontal gyrus	<0.0001	0.0370	−0.038			
Fusiform gyrus	<0.0001	0.0231	−0.036			
Inferior parietal cortex	<0.0001	0.0298	−0.026			
Insula	<0.0001	0.0002	−0.056	0.0007	0.0003	−0.042
Isthmus of cingulate gyrus				<0.0001	0.0447	-0.035
Medial orbitofrontal cortex				0.0095	0.0491	−0.029
Middle temporal gyrus	0.0910	0.0065	−0.030	0.0040	0.0474	−0.026
Paracentral lobule	0.0019	0.0015	−0.031	0.0421	0.0056	−0.024
Precentral gyrus	<0.0001	0.0025	−0.039	<0.0001	0.0042	−0.042
Precuneus	<0.0016	0.0425	−0.023			
Superior parietal cortex	0.0082	0.0472	−0.022			
Supramarginal gyrus	0.0049	0.0131	−0.027	0.0046	0.0319	−0.026

[a] In model 1, all individuals were classified as either substance dependent or nondependent. Only significant associations are shown.

including the left and right insula, precentral gyrus, and supramarginal gyrus and the right medial orbitofrontal cortex. See Table 2 for a complete list and Supplemental Table S2 in the online supplement for an at-a-glance summary.

Model 2: Substance Dependence Groups Compared Separately to Nondependent Control Subjects

All subcortical regions of interest identified in model 1 plus the right thalamus, the left and right putamen, the right globus pallidus, and the left nucleus accumbens had significantly lower volume in model 2 when alcohol-dependent participants were compared with nondependent control subjects. In addition, alcohol-dependent participants exhibited lower average thickness in 27 cortical regions of interest (Table 3, Figure 1). Cocaine dependence was associated with lower cortical thickness in only one brain region (see Table 3, Figure 1). No cross-validated differences in regional volume or thickness were significant for dependence on nicotine, methamphetamine, or cannabis on their own. Since most effects were related to alcohol dependence, a secondary linear contrast was performed to explore the effect of removing alcohol from the analysis. The contrast compared participants dependent on any substance except alcohol against nondependent control subjects. It revealed that the left inferior parietal cortex and the insula bilaterally were significantly thinner in dependent individuals (see Table 3).

Substance-Specific Versus Shared Substance-General Effects

Three distinct patterns of results emerged, which are illustrated in Figure 2.

Pattern 1 (substance specific). In most regions of interest where a significant difference was observed, the effect was demonstrated in model 2 to be related specifically to dependence on alcohol alone (27 regions of interest)—for example, the right nucleus accumbens (Figure 2)—or to both alcohol and cocaine—the right supramarginal gyrus (one region of interest) (see Figure 1, Tables 2 and 3).

Pattern 2 (substance general). Six cortical regions of interest (e.g., the left supramarginal gyrus and the right medial orbitofrontal cortex) were associated with dependence in model 1 but were not significantly thinner in any one particular substance group relative to nondependent control subjects in model 2 (see Tables 2 and 3, Figures 1 and 2).

Pattern 3 (substance general). Three cortical regions of interest (the left inferior parietal cortex and the right and left insula) were significantly thinner when all dependent groups were compared with control subjects (model 1) and when all dependent groups except alcohol were contrasted against control subjects (model 2). In addition, the left insula was significantly thinner in the alcohol-dependent group alone relative to control subjects (Tables 2 and 3, Figures 1 and 2).

TABLE 3. Model 2, Individuals With Specific Substance Dependences Compared With Nondependent Control Subjects: Left and Right Hemisphere Regions of Interest That Exhibited Lower Subcortical Volume or Cortical Thickness in a Mega-Analysis of Gray Matter Volume in Substance Dependence[a]

	Left			Right		
	p		Cohen's d	p		Cohen's d
Region and Comparison	1st Half of Data	2nd Half of Data	Both Halves of Data	1st Half of Data	2nd Half of Data	Both Halves of Data
Subcortical volume						
Alcohol-dependent versus nondependent controls						
Amygdala	<0.0001	0.0021	−0.107	<0.0001	0.0003	−0.111
Globus pallidus				0.0274	0.0005	−0.075
Hippocampus	<0.0001	<0.0001	−0.196	<0.0001	<0.0001	−0.180
Nucleus accumbens	0.0159	0.0013	−0.048	<0.0001	<0.0001	−0.088
Putamen	0.0006	<0.0001	−0.098	0.0001	0.0014	−0.080
Thalamus				0.0149	0.0002	−0.098
Cortical thickness						
Alcohol-dependent versus nondependent controls						
Caudal middle frontal gyrus	0.0006	0.0219	−0.062	0.0264	0.0298	−0.054
Fusiform gyrus	0.0017	0.0002	−0.072	<0.0001	<0.0001	−0.094
Inferior temporal gyrus	0.0021	0.0146	−0.056	0.0148	0.0214	−0.047
Insula	0.0023	<0.0001	−0.087			
Isthmus of cingulate gyrus				0.0009	0.0005	−0.078
Lateral occipital cortex				0.0013	0.0211	−0.042
Lateral orbitofrontal cortex				0.0322	0.0021	−0.061
Medial orbitofrontal cortex	0.0432	0.0197	−0.060			
Parahippocampal gyrus	0.0281	0.0265	−0.076			
Paracentral lobule	0.0002	0.0001	−0.074	0.0053	0.0003	−0.062
Posterior cingulate gyrus	<0.0001	<0.0001	−0.091	0.0004	<0.0001	−0.085
Precentral gyrus	0.0091	0.0007	−0.063	0.0008	0.0003	−0.079
Precuneus	0.0008	0.0003	−0.062	0.0039	0.0002	−0.061
Rostral anterior cingulate cortex	0.0381	0.0090	−0.082			
Superior frontal gyrus	<0.0001	0.0030	−0.071	0.0003	0.0060	−0.071
Superior parietal cortex	0.0198	0.0272	−0.040			
Superior temporal gyrus	0.0239	0.0353	−0.062			
Supramarginal gyrus				0.0493	0.0168	−0.044
Temporal pole				0.0518	0.0464	−0.063
Cocaine-dependent versus nondependent controls						
Supramarginal gyrus				0.0177	0.0491	−0.047
Nicotine-, cocaine-, methamphetamine-, and cannabis-dependent versus nondependent controls						
Inferior parietal cortex	0.0011	0.4630	−0.029			
Insula	0.0057	0.0300	−0.041	0.0303	0.0274	−0.033

[a] In model 2, individuals were sorted by dependence on one and only one substance, and individuals dependent on more than one substance were excluded from the model. Comparisons of estimated marginal means for dependence on alcohol and cocaine relative to nondependent control subjects are presented for model 2. The additional contrast in model 2 included individuals dependent on nicotine, cocaine, methamphetamine, or cannabis (but not alcohol). Only significant associations are shown. There were no significant associations with nicotine, methamphetamine, or cannabis dependence on their own.

Past-30-Day Use

The volume of several subcortical regions of interest were negatively associated with past-30-day use of alcohol after a false discovery rate correction for multiple comparisons: the left and right amygdala and nucleus accumbens, the right hippocampus, and the left globus pallidus. No brain regions were related to past-30-day nicotine use.

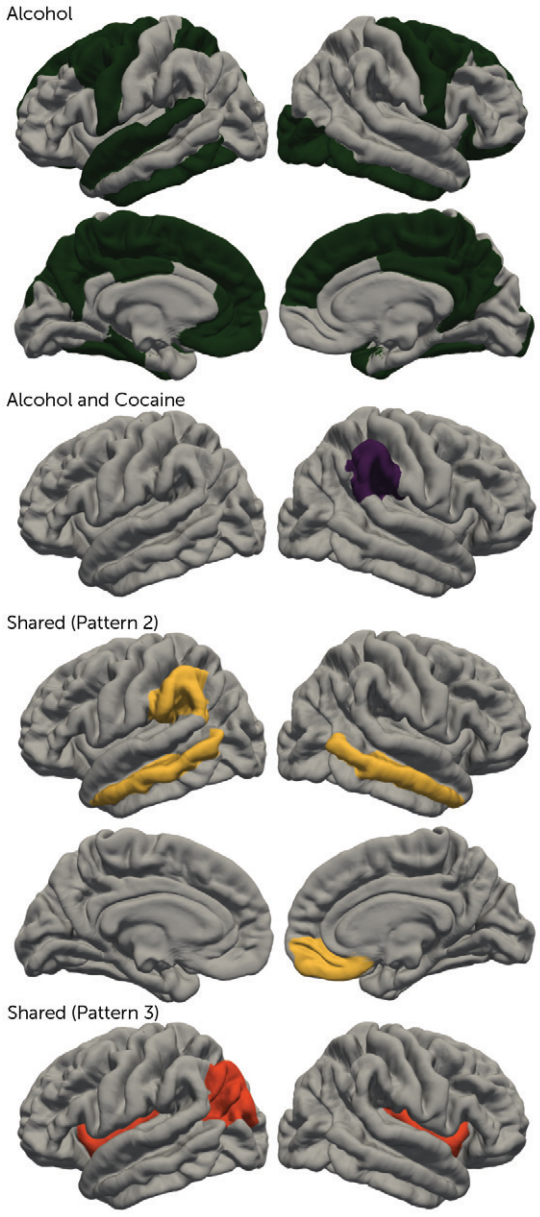
Support Vector Machine

The support vector machine produced a significant classification of alcohol- and nicotine-dependent individuals relative to nondependent control subjects (Figure 3) in both halves of the data ($p<0.05$). The classification of cocaine-dependent individuals approached significance. The top 20 structural predictors distinguishing dependence on each substance from nondependent control subjects in each classification are listed in Table S3 in the online supplement.

DISCUSSION

Subcortical volume or cortical thickness was significantly lower on average in substance-dependent individuals compared with nondependent control subjects across widespread parts of the brain (i.e., 22 distinct regions of interest out of a total of 82) (see Table 2; see also Table S2 in the online supplement). Some of these differences were substance

FIGURE 1. Cortical Regions of Interest Exhibiting Substance-Specific or Shared Substance-General Effects Displayed on the Surface of Partially Inflated Average Brains[a]



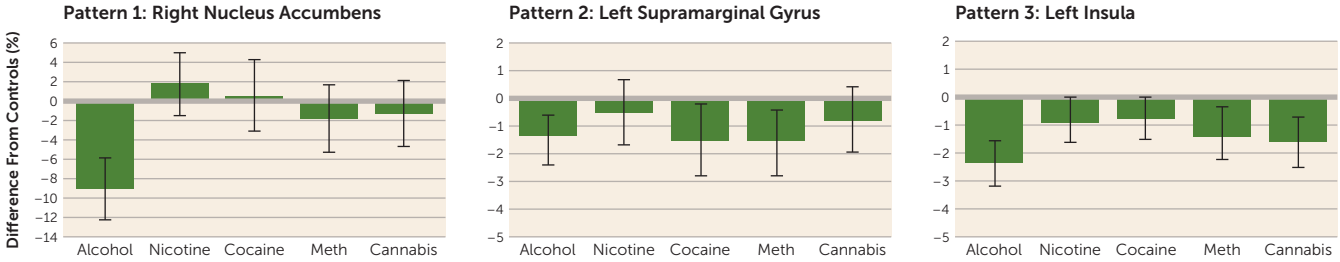
[a] Substance specific: alcohol alone (green), alcohol and cocaine (purple); substance general: pattern 2 (yellow), pattern 3 (orange).

specific, and others appear to constitute a shared neural substrate associated with dependence regardless of the substance used (see Table 3 and Figure 1). A majority of the identified regions of interest were smaller or thinner specifically in the brains of alcohol-dependent individuals (e.g., the left and right posterior cingulate and superior frontal cortex). A more limited set of seven regions with lower cortical thickness across substance dependence groups included the left and right insula, the left inferior parietal cortex, the right medial orbitofrontal cortex, the left and right middle temporal gyrus, and the left supramarginal gyrus. No region of interest was significantly larger or thicker in substance-dependent individuals relative to control subjects. An unexpected finding of the study was the absence of substance-specific linear effects on brain volume related to nicotine, methamphetamine, or cannabis dependence despite the collection of large pooled samples. Also, the successful classification of individuals dependent on nicotine, alcohol, or cocaine using the support vector machine approach suggests that the development of clinically useful neuroimaging biomarkers of substance dependence may be more productive if based on broader patterns of brain function or structure rather than differences in unique brain regions considered alone.

The set of brain regions identified with substance dependence in general is supported by previous evidence. The insula performs a central role in the perception of the internal state of the body (34). Disruption of the insula could alter regulation of the intense positive and negative bodily states associated with drug taking and withdrawal, biasing the individual toward relapse as a maladaptive response to anticipated challenges to physiological homeostasis (35). It has been reported that smokers who have suffered brain damage involving the insula have subsequently lost the urge to smoke (36). The parietal cortex has been associated with attention and working memory (37, 38). Disruption of these processes could interfere with self-awareness about a substance use problem and the management of stressful situations. The medial orbitofrontal region of interest defined by FreeSurfer (also known as the ventromedial prefrontal cortex) encodes the subjective value of future rewards during decision making (39). Lesions of this region produce disadvantageous choices on gambling tasks that model real-life decisions (40). Altered neural activity in the insula and the medial orbital and parietal cortex has frequently been linked to substance dependence and may predict greater craving and risk of relapse (41–44). The present results support the idea that substance dependence is mediated by a shared set of mechanisms across substance groups. Indeed, twin studies suggest that vulnerability to substance dependence is accounted for principally by a shared set of genetic variations regardless of the substance used, with proportionately smaller substance-specific effects (16).

Although subtle in magnitude, the wide spatial distribution of alcohol-specific effects is a striking finding of the study. Alcohol consumption enjoys greater cultural acceptance in the countries from which the data for this study were sampled relative to the other substances examined (45). Alcohol is legal to buy and consume, and widely publicized government-sanctioned guidelines exist for "safe" low-dose use of alcohol. This tolerance of alcohol-related health risks is unlike the cultural views toward any of the other substances investigated here, whose use even in small amounts is discouraged (45). It should be noted that lifetime exposure to each substance could not be uniformly assessed in the data sets used here. As a consequence, the scope of the alcohol dependence effects may in part be related to greater absolute consumption of alcohol relative to the other substances.

FIGURE 2. Different Contributions of Dependence on the Five Substances Studied to the Association of Lower Volume or Thickness With Substance Dependence[a]



[a] For illustration purposes, both halves of the data (serving as the discovery and replication data sets) have been combined in the bar graphs. Three different patterns are illustrated. In pattern 1 (substance-specific effect), lower volume in the right nucleus accumbens was largely accounted for by dependence on alcohol alone. In pattern 2 (substance-general effect), volume in the left supramarginal gyrus was significantly lower in dependent compared with nondependent individuals (model 1) but was not significantly lower in any one particular substance group (model 2) compared with control subjects. In pattern 3 (substance-general effect), volume in the left insula was lower when either the alcohol-dependent group or the linear contrast of all substance groups except alcohol was compared with nondependent control subjects. Bars represent estimated marginal means expressed as percent difference from mean volume or thickness in nondependent control subjects. Error bars represent standard error. Meth=methamphetamine.

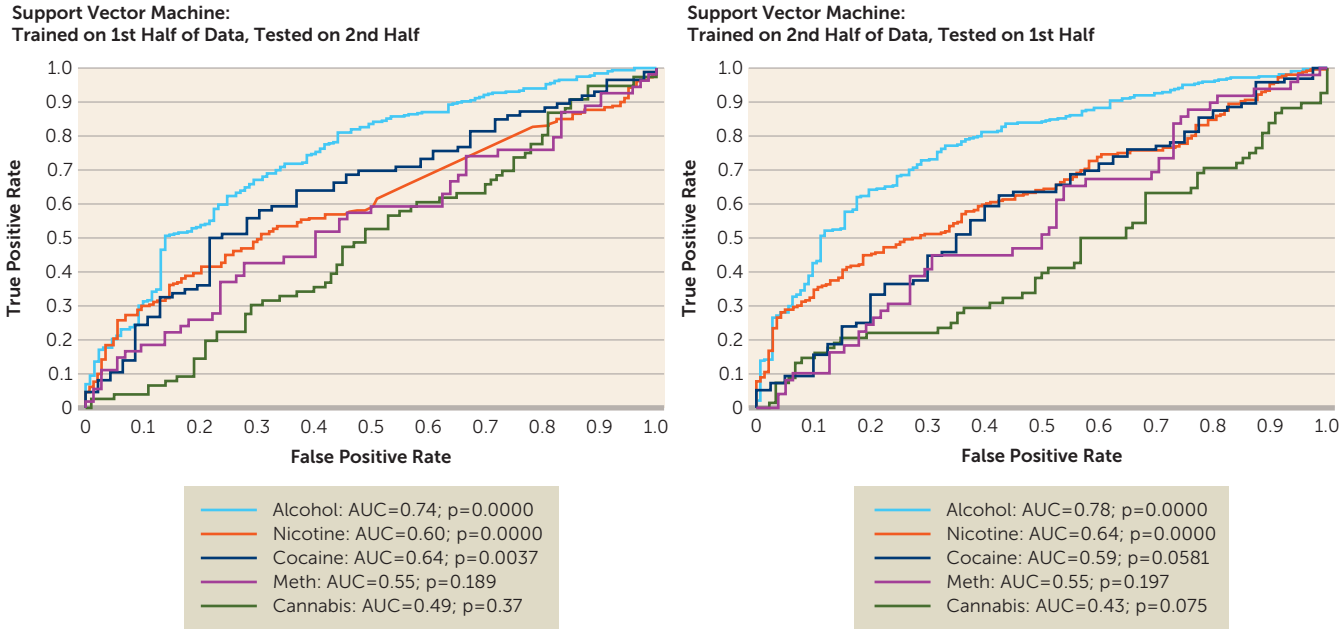
It was possible to assess past-30-day use of nicotine and alcohol, a limited proxy of level of exposure, in a sizable minority of the data sets. Several subcortical regions of interest, such as the amygdala and the nucleus accumbens, were significantly smaller in individuals who reported the highest numbers of alcoholic drinks consumed in the past 30 days, consistent with the notion that greater exposure could be responsible for the magnitude of the observed alcohol effects. Further studies will be required to clarify whether the greater number of observed alcohol-specific effects relative to the other substances is related to differences in toxicity or total exposure.

It is also notable that, besides the seven brain regions associated with dependence in general, there were no drug-specific effects for dependence on nicotine, methamphetamine, and cannabis. Although cross-validation demonstrated that the volumetric differences observed were reliable, the effect sizes were uniformly small (see Tables 2 and 3). This suggests that the lack of consistency in the literature (13–15) may be related to the insufficient power of most studies to detect true effects. Other imaging modalities, such as task-based functional MRI (41–44) and higher-resolution structural imaging, may be required to detect reliable substance-specific nicotine, methamphetamine, or cannabis effects if they exist. It is also possible that substance dependence has multiple, heterogeneous interactions with brain volume that are not well assessed by simple linear analyses. Evidence for this is provided by the support vector machine classification.

The support vector machine classification found that the pattern of regional volume differences could be used successfully to distinguish between nondependent control subjects and individuals dependent on alcohol and nicotine. The transformation of the data with a radial basis function kernel prior to classification facilitated the detection of nonlinear patterns that cannot be detected by models 1 and 2. Additionally, the support vector machine can identify a multivariate pattern of effects across numerous regions of interest, each of which, in isolation, may not pass statistical threshold. Thus, the support vector machine detected useful information in the pattern of results that was not apparent from the linear analysis. The significant classifications suggest that the overall pattern of volumetric effects may contain useful clinical information that would not be apparent if only traditional univariate linear analyses were performed. While influential features in the classification partly overlapped with the regions of interest identified by the univariate analyses—for example, brain regions associated with alcohol dependence, such as the hippocampus and amygdala—additional regions not identified by the linear mixed effects analyses (i.e., model 1 and model 2) were also involved (see Table S3 in the online supplement). Future efforts of the Addiction Working Group will include the incorporation of other imaging modalities with which it may be possible to distinguish individuals with dependence on additional substances, such as methamphetamine and cannabis, from nondependent control subjects. It would also be clinically useful to examine whether the support vector machine classifications developed in this study offer an index of the strength of substance dependence in individuals who go on to recover or relapse. It is worth noting that current blood and urine tests do not identify dependence, as the machine learning classifier in the present study does, but rather detect, and to an extent quantify, recent substance use. While the present findings are preliminary and the support vector machine classifications should be tested on other independent samples, if brain volume is confirmed as a viable biomarker of dependence, or of biological risk of dependence, it could be used to plan how prevention and treatment resources are allocated to individual patients as well as, potentially, to track intervention success. A structural MRI scan in combination with other factors known to be related to substance use problems (e.g., change in employment or marital status, health issues) could be used to assess risk of transition to problematic patterns of use or to quantify the current degree of dependence, which would influence the intervention strategy.

Several factors limit the interpretation of the study findings. Different diagnostic instruments were used to assess

FIGURE 3. Plot of Receiver Operating Characteristic Curves for the Support Vector Machine Classification of Individuals Dependent on One of Five Substances Relative to Nondependent Control Subjects[a]



[a] The area under the curve (AUC) is significant for alcohol or nicotine dependence when trained on the first half of the data and tested on the second half (left) as well as when trained on the second half and tested on the first half (right). Meth=methamphetamine.

substance dependence (see Table S1 in the online supplement). Although the validity of each of these instruments has been well established, variation between instruments could add noise to the measured behavioral phenotype. This, however, could be an advantage because the extrapolation of significant findings to the general population is also likely to be more robust by virtue of generalizing across different methods of assessment. The absence of nutrition and education information, which are potential confounders, also limits the interpretability of the results. A perennial concern with multisite studies is variation attributable to different scanners and acquisition protocols. This issue was mitigated by using a standard data extraction protocol developed by the ENIGMA project that has been validated in previous multisite reports (20, 28–30) and by the formal consideration of potential site differences in all statistical analyses. As discussed above, the degree of exposure to the various substances was not characterized uniformly across studies, which limits, for instance, the interpretation of the widespread alcohol effects and whether alcohol represents a greater source of toxicity than the other substances examined. It should be emphasized, however, that this study examined brain volumetric associations with dependence and not with total lifetime substance use. A beneficial outcome of this first study of the Addiction Working Group will be to raise awareness of the data needed to estimate the relation between brain volume and total exposure and, more generally, of the utility of uniform phenotypic data for data pooling. Greater consideration of how data may be used in international collaborations may influence the collection of data in future studies, which will increase their impact beyond their primary research focus. The PhenX Toolkit (https://www.phenxtoolkit.org/), for example, provides an extensive catalog of standardized measures expressly intended to facilitate secondary cross-study comparisons. Finally, co-occurring substance use limits the interpretation of the findings. Pervasive recreational substance use is a general issue for all studies of human substance dependence. For example, it is likely epidemiologically that a methamphetamine user will be exposed to alcohol. Methamphetamine users who do not use any other addictive substance would be an unusual group who, in practice, would be difficult to identify but, more importantly, would not be characteristic of the real-world population of methamphetamine users—that is, there would be a selection bias. Unlike studies in animal models, it is not possible to randomly assign humans to groups with restricted exposure to one substance alone. The typical strategy, which was used in the data sets included in this study, is to screen subjects for dependence on other substances but not to exclude for nondependent use of other substances.

The field of neuroimaging faces a crisis of relevance if published studies cannot be replicated, as noted in a series of reviews (22, 23). The authors of the present study joined to form a working group within the preexisting framework of the ENIGMA project to assemble a sufficiently large sample to overcome issues related to low statistical power that affect most individual neuroimaging studies. Using a rigorous cross-validation method, several brain regions were found to have a reliable association with substance dependence, including a shared set of regions across substances, such as the insula and the medial orbitofrontal cortex. Although the

univariate analyses failed to identify linear effects in relation to dependence on nicotine, methamphetamine, and cannabis specifically, a machine learning algorithm, which was also able to detect nonlinear patterns in the data, successfully classified individuals dependent on alcohol or nicotine relative to nondependent control subjects. This suggests that the overall pattern of volumetric effects may contain more useful information with regard to the development of a neuroimaging biomarker of substance dependence than is revealed by the magnitude of single brain regions examined in isolation.

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