



Universiteit
Leiden
The Netherlands

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

Mackey, S.; Allgaier, N.; Chaarani, B.; Spechler, P.; Orr, C.; Bunn, J.; ... ; ENIGMA Addiction Working Group

Citation

Mackey, S., Allgaier, N., Chaarani, B., Spechler, P., Orr, C., Bunn, J., ... Garavan, H. (2018). Mega-Analysis of Gray Matter Volume in Substance Dependence: General and Substance-Specific Regional Effects. *American Journal Of Psychiatry*, 176(2), 119-128.
doi:10.1176/appi.ajp.2018.17040415

Version: Accepted Manuscript
License: [Leiden University Non-exclusive license](#)
Downloaded from: <https://hdl.handle.net/1887/81980>

Note: To cite this publication please use the final published version (if applicable).



HHS Public Access

Author manuscript

Am J Psychiatry. Author manuscript; available in PMC 2019 March 21.

Published in final edited form as:

Am J Psychiatry. 2019 February 01; 176(2): 119–128. doi:10.1176/appi.ajp.2018.17040415.

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

A full list of authors and affiliations appears at the end of the article.

Abstract

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

Address correspondence to Dr. Mackey (msmackey@uvm.edu).

AUTHOR AND ARTICLE INFORMATION

From the Department of Psychiatry and the Department of Mathematics and Statistics, University of Vermont, Burlington; Orygen, the National Centre of Excellence in Youth Mental Health, Parkville, Australia; the Department of Psychology, University of Oregon, Eugene; the Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia; the Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York; the Department of Psychiatry and Psychology, University of Barcelona, Barcelona, Spain; the Department of Psychiatry, Donders Institute for Brain, Cognition, and Behavior, Radboud University Medical Center, Nijmegen, the Netherlands; the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn; the Department of Psychiatry and the MRC Unit on Anxiety and Stress Disorders, University of Cape Town, Cape Town, South Africa; the Neuroimaging Research Branch, Intramural Research Program, National Institute on Drug Abuse, Baltimore; the Monash Institute of Cognitive and Clinical Neurosciences and the School of Psychological Sciences, Monash University, Melbourne, Australia; the Departments of Developmental and Experimental Psychology, Utrecht University, Utrecht, the Netherlands; the Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal; the Centre for Population Neuroscience and Precision Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London; the Department of Psychiatry, Oregon Health and Science University, Portland; the Department of Neuroscience and the Ernest J. Del Monte Institute for Neuroscience, University of Rochester School of Medicine and Dentistry, Rochester, N.Y.; the Department of Psychiatry, University of Amsterdam, Amsterdam; the Amsterdam Institute for Addiction Research and Arkin Mental Health Care, Amsterdam; the Department of Psychiatry, University of Michigan, Ann Arbor; the Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia; the Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder; the Department of Psychiatry, Washington University School of Medicine, St. Louis; the David Geffen School of Medicine, University of California at Los Angeles, Los Angeles; the School of Psychology, Faculty of Health Sciences, Australian Catholic University, Melbourne, Australia; the Department of Psychological Sciences, University of Liverpool, Liverpool, U.K.; the Behavioral Science Institute, Radboud University, Nijmegen, the Netherlands; the Joint Doctoral Program in Clinical Psychology, San Diego State University/ University of California, San Diego; the Clinical Neuroimaging Research Core, Division of Intramural Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism, Bethesda, Md.; the VA San Diego Healthcare System and the Department of Psychiatry, University of California San Diego, La Jolla; the Laureate Institute for Brain Research, Tulsa, Okla.; the Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia; the Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany; the Institute of Psychology, Cognitive Psychology Unit, and the Leiden Institute for Brain and Cognition, Leiden University, Leiden, the Netherlands; the School of Psychology and the Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, Australia; the Department of Psychiatry, University of California San Diego, La Jolla; the Department of Psychiatry, VU University Medical Center, Amsterdam; the Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, Australia; the QIMR Berghofer Medical Research Institute, Brisbane, Australia; the Department of Psychiatry, University of Utah School of Medicine, Salt Lake City; the Imaging Genetics Center, Department of Neurology, Keck School of Medicine, University of Southern California, Marina del Rey; and the Department of Psychiatry, University of Montreal, CHU Sainte-Justine Hospital, Montreal.

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.

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 \$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, metham-phetamine, 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 T₁-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 .

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, 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).

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 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. 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Scott Mackey, PhD¹, Nicholas Algaier, PhD¹, Bader Chaarani, PhD¹, Philip Spechler, BA¹, Catherine Orr, PhD¹, Janice Bunn, PhD², Nicholas B. Allen, PhD^{3,4,5}, Nelly Alia-Klein, PhD⁶, Albert Batalla, MD PhD^{7,8}, Sara Blaine, PhD⁹, Samantha Brooks, PhD¹⁰, Elisabeth Caparelli, PhD¹¹, Yann Ying Chye, PhD¹², Janna Cousijn, PhD¹³, Alain Dagher, MD¹⁴, Sylvane Desrivieres, PhD¹⁵, Sarah Feldstein-Ewing, PhD¹⁶, John J. Foxe, PhD¹⁷, Rita Z. Goldstein, PhD⁶, Anna E. Goudriaan, PhD^{18,19}, Mary M. Heitzeg, PhD²⁰, Robert Hester, PhD²¹, Kent Hutchison, PhD²², Ozlem Korucuoglu, PhD²³, Chiang-Shan R. Li, MD PhD⁹, Edythe London, PhD²⁴, Valentina Lorenzetti, PhD^{12,25,26}, Maartje Luijten, PhD²⁷, Rocio Martin-Santos, MD⁷, April May, MA²⁸, Reza Momenan, MD²⁹, Angelica Morales, PhD²⁴, Martin P. Paulus, MD^{30,31}, Godfrey Pearlson, MA MBBS⁹, Marc-Etienne Rousseau, MSc¹⁴, Betty Jo Salmeron, MD¹¹, Renée Schluter, PhD¹⁸, Lianne Schmaal, PhD^{3,32}, Gunter Schumann, MD PhD¹⁵, Zsuzsika Sjoerds, PhD^{33,34}, Dan J. Stein, PhD¹⁰, Elliot A. Stein, PhD¹¹, Rajita Sinha, PhD⁹, Nadia Solowij, PhD³⁵, Susan Tapert, PhD³⁶, Anne Uhlmann, PhD¹⁰, Dick Veltman, MD PhD³⁷, Ruth van Holst, PhD¹⁸, Sarah Wittle, PhD^{5,38}, Margaret J. Wright, PhD³⁹, Murat Yucel, PhD^{38,12}, Sheng Zhang, PhD⁹, Deborah Yurgelun-Todd, PhD⁴⁰, Derrek P. Hibar, PhD⁴¹, Neda Jahanshad, PhD⁴¹, Alan Evans, PhD¹⁴, Paul M. Thompson, PhD⁴¹, David C. Glahn, PhD⁹, Patricia Conrod, PhD⁴², Hugh Garavan, PhD¹, and ENIGMA Addiction Working Group

Affiliations

¹Department of Psychiatry, University of Vermont, Burlington VT, USA ²Department of Mathematics and Statistics, University of Vermont, Burlington VT, USA ³Orygen, The National Centre of Excellence in Youth Mental Health, Parkville, Australia ⁴Department of Psychology, University of Oregon, Eugene OR, USA ⁵Melbourne School of Psychological Sciences, The University of Melbourne, Melbourne, Australia ⁶Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York City NY, USA ⁷Department of Psychiatry and Psychology, University of Barcelona, Barcelona, Spain ⁸Department of Psychiatry, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands ⁹Department of Psychiatry, Yale University School of Medicine, New Haven CT, USA ¹⁰Department of Psychiatry and MRC Unit on Anxiety & Stress Disorders, University of Cape Town, Cape Town, South Africa ¹¹Neuroimaging Research Branch, Intramural Research Program, National Institute on Drug Abuse, Baltimore, USA ¹²Monash Institute of Cognitive and Clinical Neurosciences & School of Psychological Sciences, Monash University, Melbourne, Australia ¹³Departments of Developmental and Experimental Psychology, Utrecht University, Utrecht, the Netherlands ¹⁴Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal QC, Canada ¹⁵Centre for Population Neuroscience and Precision Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK ¹⁶Department of Psychiatry, Oregon Health & Science University, Portland OR, USA ¹⁷Department of Neuroscience & The Ernest J. Del Monte Institute for Neuroscience, University of Rochester School of Medicine and Dentistry, Rochester NY, USA ¹⁸Department of Psychiatry, University of Amsterdam, Amsterdam, the Netherlands ¹⁹Amsterdam Institute for Addiction Research & Arkin Mental Health Care, Amsterdam, The Netherlands ²⁰Department of Psychiatry, University of Michigan, Ann Arbor MI, USA ²¹Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia ²²Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, USA ²³Department of Psychiatry, Washington University School of Medicine, St. Louis MO, USA ²⁴David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, USA ²⁵School of Psychology, Faculty of Health Sciences, Australian Catholic University, Melbourne, Australia ²⁶Department of Psychological Sciences, the University of Liverpool, Liverpool, UK ²⁷Behavioural Science Institute, Radboud University, Nijmegen, the Netherlands ²⁸Joint Doctoral Program in Clinical Psychology, San Diego State University/University of California, San Diego, USA ²⁹Clinical Neuroimaging Research Core, Division of Intramural Clinical and Biological Research, National Institute on Alcohol Abuse and Alcoholism, Bethesda MD, USA ³⁰VA San Diego Healthcare System and Department of Psychiatry, University of California San Diego, La Jolla, USA ³¹Laureate Institute for Brain Research, Tulsa OK, USA ³²Centre for Youth Mental Health, The University of Melbourne, Melbourne, Australia ³³Department of Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany ³⁴Institute of Psychology, Cognitive Psychology Unit & Leiden Institute for Brain and Cognition,

Leiden University, Leiden, Netherlands ³⁵School of Psychology and Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, Australia ³⁶Department of Psychiatry, University of California San Diego, La Jolla, USA ³⁷Department of Psychiatry, VU University Medical Center, Amsterdam, the Netherlands ³⁸Melbourne Neuropsychiatry Centre, Department of Psychiatry, The University of Melbourne and Melbourne Health, Melbourne, Australia ³⁹QIMR Berghofer Medical Research Institute, Brisbane, Australia ⁴⁰Department of Psychiatry, University of Utah School of Medicine, Salt Lake City UT, USA ⁴¹Imaging Genetics Center, Department of Neurology Keck School of Medicine, University of Southern California, Marina del Rey, USA. ⁴²Department of Psychiatry, Université de Montreal, CHU Ste Justine Hospital, Montreal QC, Canada

Acknowledgments

Supported by NIDA grant 1R21DA038381 to Dr. Garavan and by NIH grant U54 EB 020403 with funds provided for the trans-NIH Big Data to Knowledge (BD2K) initiative. Data collection: Dr. Korucuoglu received support for the Neuro-ADAPT study from VICI grant 453.08.01 from the Netherlands Organization for Scientific Research (NWO), awarded to Reinout W. Wiers. Drs. Schmaal and Veltman received funding from Netherlands Organization for Health Research and Development (ZonMW) grant 31160003 from NWO. Drs. Sjoerds and Veltman received funding from ZonMW grant 31160004 from NWO. Drs. Goudriaan and van Holst received funding from ZonMW grant 91676084 from NWO. Drs. Luijten and Veltman received funding from VIDI grant 016.08.322 from NWO, awarded to Ingmar H.A. Franken. Drs. Cousijn and Goudriaan received funding for the Cannabis Prospective study from ZonMW grant 31180002 from NWO. Drs. Garavan and Foxe received funds from NIDA grant R01-DA014100. Dr. Li received funding from NIDA grants R01AA021449, R01DA023248, and K25DA040032. Dr. London was supported by NIDA grant R01 DA020726, the Thomas P. and Katherine K. Pike Chair in Addiction Studies, the Endowment From the Marjorie Greene Family Trust, and UCLA contract 20063287 with Philip Morris USA. Data collection by Dr. Momenan was supported by the Intramural Clinical and Biological Research Program of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Dr. Morales was supported by NIDA grant T32 DA024635. Dr. Paulus received funding from NIMH grant R01 DA018307. Dr. Stein was supported by the Intramural Research Program of NIDA and NIH. Dr. Sinha received funds from NIDA (PL30-1DA024859-01), the NIH National Center for Research Resources (UL1-RR24925-01), and NIAAA (R01-AA013892). Dr. Solowij received funding from the Clive and Vera Ramaciotti Foundation for Biomedical Research National and Health and Medical Research Council Project grant 459111 and was supported by Australian Research Council Future Fellowship FT110100752. Prof. Yücel was supported by National Health and Medical Research Council Fellowship 1117188 and the David Winston Turner Endowment Fund.

The authors thank Alex Wonnell, Alexandra Ivanciu, Noah Markowitz, Michael Lawler, Styles Crawford, and Mitchell Snowe at the University of Vermont for excellent technical assistance in tabulating the behavioral data and performing final quality control checks on the neuroimaging data.

Dr. Sinha has served on the scientific advisory board of Embera Neuro-therapeutics. Prof. Yücel has received funding from several law firms in relation to expert witness reports. Dr. Hibar is an employee at Janssen Research and Development. The other authors report no financial relationships with commercial interests.

REFERENCES

1. Whiteford HA, Degenhardt L, Rehm J, et al.: Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; 382: 1575–1586 [PubMed: 23993280]
2. US Department of Health and Human Services: *The Health Consequences of Smoking: 50 Years of Progress: A Report of the Surgeon General*. Atlanta, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014
3. World Health Organization (WHO): *WHO Report on the Global Tobacco Epidemic 2011*. Geneva, WHO, 2011

4. Sacks JJ, Gonzales KR, Bouchery EE, et al.: 2010 national and state costs of excessive alcohol consumption. *Am J Prev Med* 2015; 49: e73–e79 [PubMed: 26477807]
5. National Drug Intelligence Center: National Drug Threat Assessment. Washington, DC, US Department of Justice, 2011
6. National Institute on Drug Abuse: Trends and Statistics. 2016 <https://www.drugabuse.gov/related-topics/trends-statistics>
7. Bauld L, Bell K, McCullough L, et al.: The effectiveness of NHS smoking cessation services: a systematic review. *J Public Health (Oxf)* 2010; 32:71–82 [PubMed: 19638397]
8. Ray R, Schnoll RA, Lerman C: Nicotine dependence: biology, behavior, and treatment. *Annu Rev Med* 2009; 60:247–260 [PubMed: 19630572]
9. McLellan AT, Lewis DC, O'Brien CP, et al.: Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. *JAMA* 2000; 284:1689–1695 [PubMed: 11015800]
10. Moos RH, Moos BS: Rates and predictors of relapse after natural and treated remission from alcohol use disorders. *Addiction* 2006; 101:212–222 [PubMed: 16445550]
11. Garrison KA, Potenza MN: Neuroimaging and biomarkers in addiction treatment. *Curr Psychiatry Rep* 2014; 16:513 [PubMed: 25308385]
12. Paulus MP: Pragmatism instead of mechanism: a call for impactful biological psychiatry. *JAMA Psychiatry* 2015; 72:631–632 [PubMed: 25992540]
13. Mackey S, Paulus M: Are there volumetric brain differences associated with the use of cocaine and amphetamine-type stimulants? *Neurosci Biobehav Rev* 2013; 37:300–316 [PubMed: 23253945]
14. Bühler M, Mann K: Alcohol and the human brain: a systematic review of different neuroimaging methods. *Alcohol Clin Exp Res* 2011; 35:1771–1793 [PubMed: 21777260]
15. Martin-Santos R, Fagundo AB, Crippa JA, et al.: Neuroimaging in cannabis use: a systematic review of the literature. *Psychol Med* 2010; 40:383–398 [PubMed: 19627647]
16. Tsuang MT, Lyons MJ, Meyer JM, et al.: Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch Gen Psychiatry* 1998; 55:967–972 [PubMed: 9819064]
17. Koob GF, Volkow ND: Neurocircuitry of addiction. *Neuro-psychopharmacology* 2010; 35:217–238
18. Goldstein RZ, Craig AD, Bechara A, et al.: The neurocircuitry of impaired insight in drug addiction. *Trends Cogn Sci* 2009; 13:372–380 [PubMed: 19716751]
19. Everitt BJ, Robbins TW: Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 2005; 8:1481–1489 [PubMed: 16251991]
20. Thompson PM, Stein JL, Medland SE, et al.: The ENIGMA Consortium: large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging Behav* 2014; 8:153–182 [PubMed: 24399358]
21. Mackey S, Kan KJ, Chaarani B, et al.: Genetic imaging consortium for addiction medicine: from neuroimaging to genes. *Prog Brain Res* 2016; 224:203–223 [PubMed: 26822360]
22. Ioannidis JP: Excess significance bias in the literature on brain volume abnormalities. *Arch Gen Psychiatry* 2011; 68:773–780 [PubMed: 21464342]
23. Button KS, Ioannidis JP, Mokrysz C, et al.: Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci* 2013; 14:365–376 [PubMed: 23571845]
24. Dale AM, Fischl B, Sereno MI: Cortical surface-based analysis, I: segmentation and surface reconstruction. *Neuroimage* 1999; 9: 179–194 [PubMed: 9931268]
25. Desikan RS, Ségonne F, Fischl B, et al.: An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 2006; 31:968–980 [PubMed: 16530430]
26. Sherif T, Rioux P, Rousseau ME, et al.: CBRAIN: a web-based distributed computing platform for collaborative neuroimaging research. *Front Neuroinform* 2014; 8:54 [PubMed: 24904400]
27. Stein JL, Medland SE, Vasquez AA, et al.: Identification of common variants associated with human hippocampal and intracranial volumes. *Nat Genet* 2012; 44:552–561 [PubMed: 22504417]

28. Boedhoe PS, Schmaal L, Abe Y, et al.: Distinct subcortical volume alterations in pediatric and adult OCD: a worldwide meta- and mega-analysis. *Am J Psychiatry* 2017; 174:60–69 [PubMed: 27609241]
29. van Erp TG, Hibar DP, Rasmussen JM, et al.: Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Mol Psychiatry* 2016; 21:585 [PubMed: 26283641]
30. Hibar DP, Stein JL, Renteria ME, et al.: Common genetic variants influence human subcortical brain structures. *Nature* 2015; 520: 224–229 [PubMed: 25607358]
31. Galbraith S, Daniel JA, Vissel B: A study of clustered data and approaches to its analysis. *J Neurosci* 2010; 30:10601–10608 [PubMed: 20702692]
32. Sanchez VD: Advanced support vector machines and kernel methods. *Neurocomputing* 2003; 55:5–20
33. Guyon I, Weston J, Barnhill S, et al.: Gene selection for cancer classification using support vector machines. *Mach Learn* 2002; 46: 389–422
34. Craig AD: How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 2002; 3:655–666 [PubMed: 12154366]
35. Paulus MP, Tapert SF, Schulteis G: The role of interoception and alliesthesia in addiction. *Pharmacol Biochem Behav* 2009; 94:1–7 [PubMed: 19698739]
36. Naqvi NH, Rudrauf D, Damasio H, et al.: Damage to the insula disrupts addiction to cigarette smoking. *Science* 2007; 315:531–534 [PubMed: 17255515]
37. Koenigs M, Barbey AK, Postle BR, et al.: Superior parietal cortex is critical for the manipulation of information in working memory. *J Neurosci* 2009; 29:14980–14986 [PubMed: 19940193]
38. Ptak R: The frontoparietal attention network of the human brain: action, saliency, and a priority map of the environment. *Neuroscientist* 2012; 18:502–515 [PubMed: 21636849]
39. Mackey S, Olafsson V, Aupperle RL, et al.: Greater preference consistency during the willingness-to-pay task is related to higher resting state connectivity between the ventromedial prefrontal cortex and the ventral striatum. *Brain Imaging Behav* 2016; 10: 730–738 [PubMed: 26271206]
40. Bechara A, Tranel D, Damasio H: Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain* 2000; 123:2189–2202 [PubMed: 11050020]
41. Seo D, Lacadie CM, Tuit K, et al.: Disrupted ventromedial prefrontal function, alcohol craving, and subsequent relapse risk. *JAMA Psychiatry* 2013; 70:727–739 [PubMed: 23636842]
42. Brewer JA, Worhunsky PD, Carroll KM, et al.: Pretreatment brain activation during Stroop task is associated with outcomes in cocaine-dependent patients. *Biol Psychiatry* 2008; 64:998–1004 [PubMed: 18635157]
43. Krishnan-Sarin S, Balodis IM, Kober H, et al.: An exploratory pilot study of the relationship between neural correlates of cognitive control and reduction in cigarette use among treatment-seeking adolescent smokers. *Psychol Addict Behav* 2013; 27:526–532 [PubMed: 23586458]
44. Sutherland MT, Ray KL, Riedel MC, et al.: Neurobiological impact of nicotinic acetylcholine receptor agonists: an activation likelihood estimation meta-analysis of pharmacologic neuroimaging studies. *Biol Psychiatry* 2015; 78:711–720 [PubMed: 25662104]
45. Rehm J, Lachenmeier DW, Room R: Why does society accept a higher risk for alcohol than for other voluntary or involuntary risks? *BMC Med* 2014; 12:189 [PubMed: 25424648]

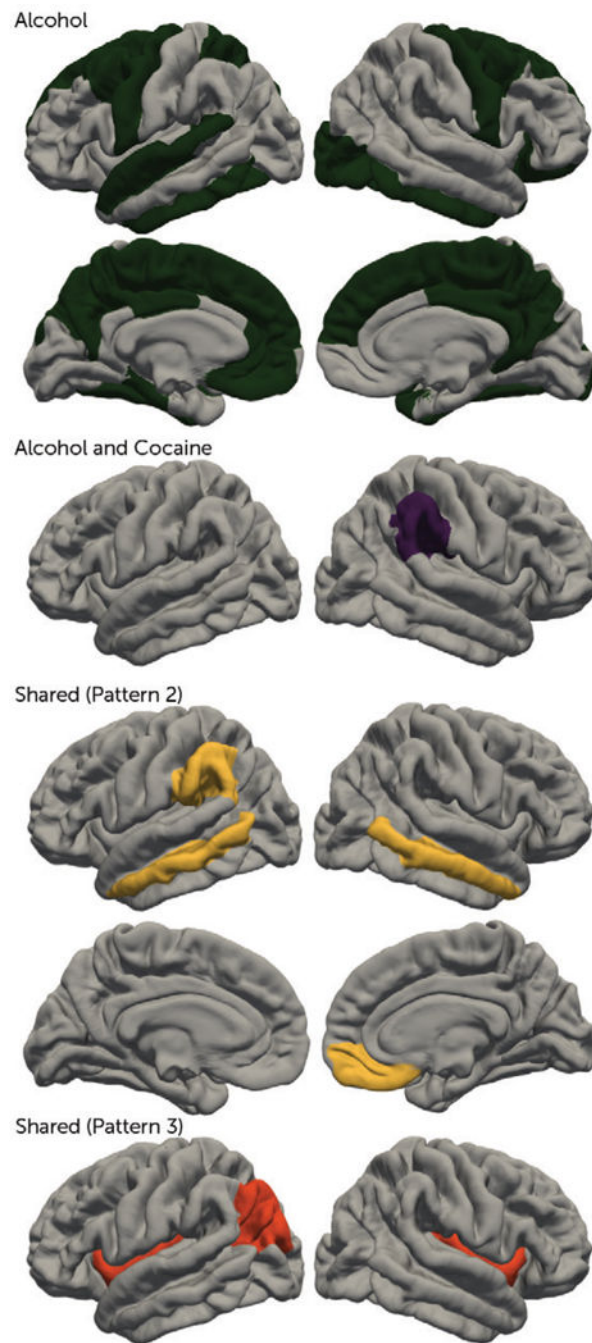


FIGURE 1. Cortical Regions of Interest Exhibiting Substance- Specific or Shared Substance-General Effects Displayed on the Surface of Partially Inflated Average Brains^a

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

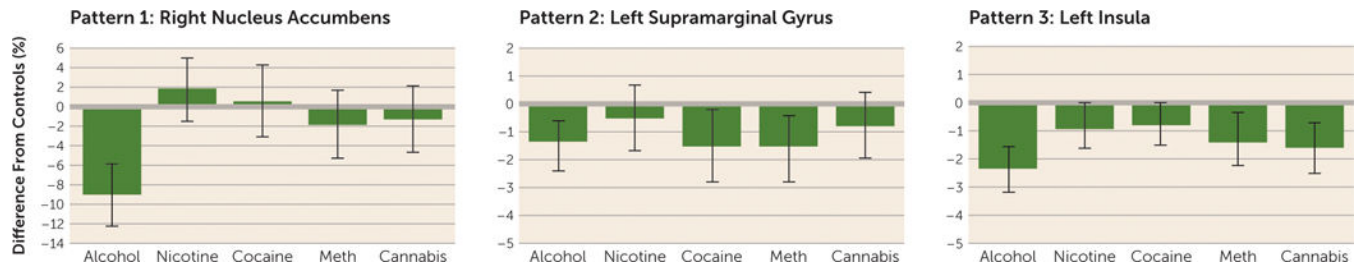


FIGURE 2. Different Contributions of Dependence on the Five Substances Studied to the Association of Lower Volume or Thickness With Substance Dependence^a

^a For illustration purposes, both halves of the data (serving as the discovery and replication datasets) 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.

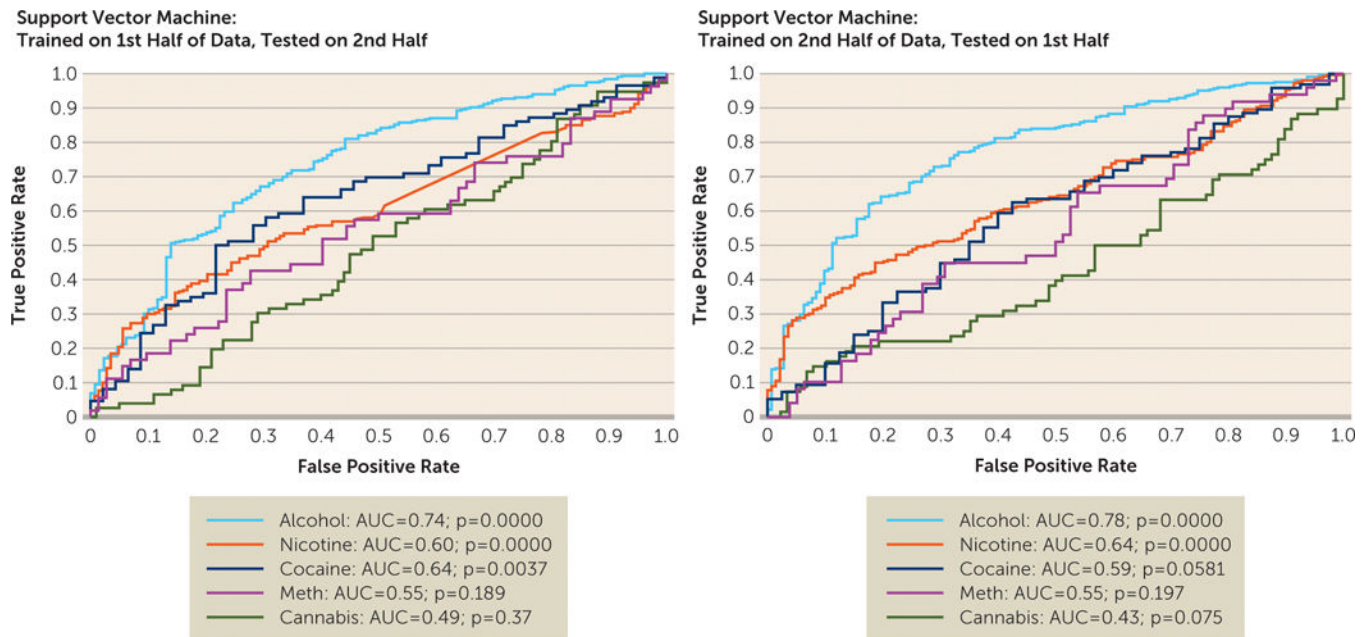


FIGURE 3. Plot of Receiver Operating Characteristic Curves for the Support Vector Machine Classification of Individuals Dependent on One of Five Substances Relative to Nondependent Control Subjects^a

^aThe 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.

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	41.6	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.

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

TABLE 2.

Region and Comparison	Left			Right		
	P		Cohen's d	P		Cohen's d
	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

^aIn model 1, all individuals were classified as either substance dependent or nondependent. Only significant associations are shown.

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

TABLE 3.

Region and Comparison	Left			Right		
	1st Half of Data	p	2nd Half of Data	Cohen's d		Both Halves of Data
				1st Half of Data	2nd Half of Data	
Subcortical volume						
Alcohol-dependent versus nondependent controls						
Amygdala	<0.0001	0.0021	0.0021	-0.107	<0.0001	0.0003
Globus pallidus					0.0274	0.0005
Hippocampus	<0.0001	<0.0001	<0.0001	-0.196	<0.0001	<0.0001
Nucleus accumbens	0.0159	0.0013	0.0013	-0.048	<0.0001	<0.0001
Putamen	0.0006	<0.0001	<0.0001	-0.098	0.0001	0.0014
Thalamus					0.0149	0.0002
						-0.111
						-0.075
						-0.180
						-0.088
						-0.080
						-0.098
Cortical thickness						
Alcohol-dependent versus nondependent controls						
Caudal middle frontal gyrus	0.0006	0.0219	0.0219	-0.062	0.0264	0.0298
Fusiform gyrus	0.0017	0.0002	0.0002	-0.072	<0.0001	<0.0001
Inferior temporal gyrus	0.0021	0.0146	0.0146	-0.056	0.0148	0.0214
Insula	0.0023	<0.0001	<0.0001	-0.087		
Isthmus of cingulate gyrus					0.0009	0.0005
Lateral occipital cortex					0.0013	0.0211
Lateral orbitofrontal cortex					0.0322	0.0021
Medial orbitofrontal cortex	0.0432	0.0197	0.0197	-0.060		
Parahippocampal gyrus	0.0281	0.0265	0.0265	-0.076		
Paracentral lobule	0.0002	0.0001	0.0001	-0.074	0.0053	0.0003
Posterior cingulate gyrus	<0.0001	<0.0001	<0.0001	-0.091	0.0004	<0.0001
Precentral gyrus	0.0091	0.0007	0.0007	-0.063	0.0008	0.0003
Precuneus	0.0008	0.0003	0.0003	-0.062	0.0039	0.0002
						-0.061
						-0.054
						-0.094
						-0.047
						-0.078
						-0.042
						-0.061
						-0.062
						-0.085
						-0.079

Region and Comparison	Left			Right			
	1st Half of Data	2nd Half of Data	Cohen's d Both Halves of Data	p	1st Half of Data	2nd Half of Data	Cohen's d Both Halves of Data
Rostral anterior cingulate cortex	0.0381	0.0090	-0.082				
Superior frontal gyrus	<0.0001	0.0030	-0.071	0.0003	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

⁴In 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.