Supplemental Information

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

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Supplemental Methods

Summary of ENIGMA protocols for multi-site studies

The ENIGMA protocols for multi-site analyses have been described and validated in many previous publications.[47-50] Although neuroimaging data was collected at different sites using a variety of acquisition protocols (see Supplemental Table 1), all datasets were prepared in Freesurfer (version 5.3), a fully automated MRI processing pipeline that identifies 7 bilateral subcortical and 34 bilateral cortical

regions-of-interest.[51,52] Quality control procedures were performed at each site according to standardized protocols. Step-by-step instructions for the ENIGMA imaging quality control protocols are publicly available online: http://enigma.ini.usc.edu/protocols/imaging-protocols/. Downloadable Matlab scripts produce images from individual brains in a series of standard planes that are inspected visually. Although the standard set of images generated from every participant's brain scan is visually reviewed, the protocol scripts also create a separate log of outliers, which are flagged for greater scrutiny during visual inspection. Subjects are excluded from the analysis if structures are poorly segmented or mislabeled. The protocols include specific illustrations of good and bad segmentation. Histograms are also generated to confirm the normal distribution of volume/thickness of each region-of-interest at each site. An additional level of visual inspection was performed centrally at the University of Vermont on a randomly selected sub-sample of participants from each study to ensure uniformity of quality control across sites.

*Investigation of Site*dependence diagnosis interactions*

To investigate the possibility of site by dependence diagnosis interactions, Models 1 and 2 were recalculated with an additional 'site x diagnosis' term included as a random factor. There was no significant site by diagnosis interaction for any region-of-interest in either Model 1 or 2. As a consequence, the interaction term was dropped from the model reported in the main Results section.

Past 30 Day Use

Linear mixed effects models were used to determine whether past 30 day nicotine or past 30 day alcohol use was related to the volume/thickness of regions-of-interest identified by Model 1 or 2 (i.e. those brain regions listed in Table 2). Past 30 day use of nicotine and alcohol is based on self-reported number of cigarettes and alcoholic drinks consumed in the past 30 days. Only dependent individuals were included in this analysis. Age, sex and intracranial volume were included as covariates while site was entered as a random factor. Past 30 day nicotine and alcohol use was measured only in a subset of the studies, i.e. this information was available on 37.7% and 42.2% of dependent participants, respectively. Due to the reduced sample size, an optimized split half strategy was not used in the analysis of past 30 day use. Since a model was constructed for each region-of-interest, a false discovery rate method (i.e. the Benjamini-Hochberg procedure) was used to control for multiple comparisons.

Support Vector Machine classification

Support vector machine classification was implemented in MATLAB with a radial basis function kernel, tuned by parameter sweep in a 10-fold inner loop, nested within an optimized split-half cross validation.[53] The radial basis function kernel has two parameters: the box constraint C, and kernel width σ. The box constraint determines the extent of misclassification tolerated within the training set (C=0 corresponds to a hard-margin classifier that disallows training error), and the kernel width determines the spread of the Gaussian filter on training sample similarity (as measured by Euclidean distance in feature space) imposed by the RBF kernel. The parameters C and σ were tuned to maximize independent test classification area-under-the-curve within a 10-fold validation. For each half of the optimized split-half: (1) The data were divided into 10 stratified groups (same case-to-control ratio in each); (2) one group was selected to be the independent test; (3) four hundred support vector machine classifiers were trained on the remaining 90% of the data, one for each pair of C and σ, each selected from a range of 20 values in log space (C, σ in 2^[54]); (4) each support vector machine was used to classify

the test group (the left-out 10%), area-under-the-curve was computed, and thus each pair of parameter values had an associated area-under-the-curve for this test; (5) steps (2)-(4) were repeated nine more times, allowing each group to be the test set once; and finally (6) the pair of parameter values with the highest mean area-under-the-curve across the 10 tests was selected to train the final support vector machine classifier for this half, which was then tested against the other half.

Supplemental Results

Supplemental Table 1. Additional information about the samples collected at individual sites. ASI-Lite, Addiction Severity Index-Lite;[55] AUDIT, Alcohol Use Disorders Identification Test;[56] CIDI, Composite International Diagnostic Interview;[57] FTND, Fagerstrom Test for Nicotine Dependence;[58] K-SADS, Schedule for Affective Disorders and Schizophrenia for School-Aged Children;[59] MINI Plus, Mini-International Neuropsychiatric Interview-Plus;[60] PRISM, Psychiatric Research Interview for Substance and Mental Disorders;[61] **SCID,** Structured Clinical Interview for the DSM-IV Disorders.[62]

Substance	PI	Study Name	Total Sample (Female)	Mean Age ± SD	SUD	Diagnostic Instrument	Scan Parameters	References
Alcohol	Hutchison	ETOH	378 (138)	28.7 ± 8.1	378	SCID	3T, 5-echo multi-echo MPRAGE, TR=2530ms, TE= 1.64, 3.5, 5.36, 7.22 & 9.08 ms, flip angle=7˚, matrix= 256x256x176, voxel size=1x 1x1mm^3	Thayer *et al.,* 2016[63]
	Hutchison	Olanzapine	157 (58)	39.5 ± 8.8	157	SCID	3T, 5-echo multi-echo MPRAGE, TR=2530ms, TE= 1.64, 3.5, 5.36, 7.22 & 9.08 ms, flip angle=7˚, matrix= 256x256x176, voxel size=1x 1x1mm^3	Claus *et al.,* 2011[64]
	Sinha	IRC	127 (32)	31.2 ± 8.5	43	SCID	3T, MPRAGE, TR =2530ms, TE=3.34ms, 1 flip angle=7˚, matrix/FOV = 256x256x176, voxel size = 1x1x1mm^3	Sinha & Li, 2007[65] Li *et al.,* 2009[66] Seo *et al.,* 2011[67]
	Momenan	NIAAA	342 (120)	35.5 ± 10.0	203	SCID	3T, MPRAGE **,** TR=4.5-7.8 ms, TE=2.2-3.1ms, flip angle =6˚**,** voxelsize=0.9x0.9 x1-1.5mm^3	Senatorov *et al.,* 2015[68] Grodin *et al.,* 2013[69] Momenan *et al.,* 2012[70]
	Korucuoglu	Neuro-ADAPT	41 (17)	19.1 ± 1.7	18	AUDIT	3T, Gradient Echo, TR=8.17ms, TE=3.8ms, flip angle=8˚, matrix=240x240 x220, voxelsize=1x1x1mm^3	Korucuoglu *et al*., 2016[71]
	Schmaal/ Veltman	TrIP study	48 (0)	40.5 ± 9.0	Alc 16 Coc 16	MINI Plus	3T, Gradient Echo, TR=9ms, TE=3.5ms, flip angle=8˚, matrix=256x256x170, voxel size=1x1x1mm^3	Schmaal *et al.,* 2014[72]
	Sjoerds/ Veltman	NESDA-AD	61 (25)	48.2 ± 9.1	42	CIDI	3T, Gradient Echo, TR=9ms, TE 3.6 ms, flip angle=8˚, matrix= 256x231x170, voxel size=1x1x1mm^3	Sjoerds *et al.,* 2014[73]
	Goudriaan/ Van Holst	ADPG study	52 (0)	40.5 ± 10.4	28	CIDI	3T, Gradient Echo, TR=9ms TE=4.20ms, flip angle 8°, matrix=256×256x170, voxel size=1×1x1mm^3	Jansen *et al.,* 2015[74] van Holst *et al*., 2014[75] van Holst *et al.,* 2012[76]
Nicotine	Dagher	CYP	31 (9)	24.9 ± 4.3	31	FTND	3T, MPRAGE, TR=2300ms, TE=2.98ms, flip angle=9°, matrix=256×256x172, voxel size=1x1x1 mm^3	Tang *et al.,* 2012[77]

	Hutchison	BISCUE	123 (54)	31.0 ± 10.1	123	FTND	3T, 5-echo multi-echo MPRAGE, TR=2530ms, TE= 1.64, 3.5, 5.36, 7.22 & 9.08 ms, flip angle=7˚, matrix= 256x256x176, voxel size=1x 1x1mm^3	Claus et al., 2013[78]
	Hutchison	Varenicline	183 (72)	34.3 ± 9.9	183	FTND	3T, MPRAGE, TR=2300ms, TE=2.74ms, flip angle = 8°, matrix = 256x256x176, voxel size =1x1x1mm^3	
	London	Young Smokers	98 (61)	19.4 ± 1.3	37	SCID	3T, MPRAGE, TR=1900-2530 ms, TE=2.26-3.31ms, flip angle=7-9˚, matrix=256x256 x160 voxel size=1x1x1mm^3	Morales *et al.,* 2014[79]
	E Stein	Smokers	371 (181)	30.8 ± 9.0	184	FTND	3T, MPRAGE, TR=2500ms, TE=4.38ms, flip angle=8˚, matrix=256x192x160 voxel size=1x1x1mm^3	Zhang *et al.,* 2011[80] Rose *et al.,* 2012[81] Sutherland *et al.,* 2013[82] Ding *et al.,* 2015[83]
	Luijten/ Veltman	DABIS	86 (28)	22.6 ± 2.8	43	FTND	3T, Inversion Recovery Fast Spoiled Gradient Recalled Echo (FSPGR), TR=10.6ms, TE=2.2ms, matrix=416x256x 192, voxel size = 1x1x1mm^3	Luijten *et al*., 2012[84]
Cocaine	Garavan/ Foxe		43 (6)	38.0 ± 10.4	27	SCID	3T, MPRAGE, TR=11.6ms, TE=4.9ms, flip angle = 8°, matrix=256×256x172, voxel size = 1.2×1.2x1.2 mm^3	Bell *et al.,* 2014[85]
	Li		98 (26)	42.5 ± 7.4	98	SCID	3T, sagittal 3D MPRAGE, TR=2530ms, TE=3.66ms, flip angle=7˚, matrix=256 x256, voxel size=1x1x1mm^3	Luo *et al.,* 2013[86]
	Sinha	SCOR	79 (41)	33.9 ± 8.4	33	SCID	3T, MPRAGE, TR =2530ms, TE=3.34ms, 1 flip angle=7˚, matrix=256x256x176, voxel size = 1x1x1mm^3	Li *et al.,* 2005[87] Li *et al.,* 2008[88] Seo *et al.,* 2017[89]
	E Stein		90 (20)	40.2 ± 7.5	47	SCID	3T, MPRAGE, TR=1900ms, TE=3.51ms, flip angle= 9˚, matrix=256x192x208, voxel size =1x1x1mm^3	Gu *et al.,* 2010[90] Rose *et al.,* 2014[81] Hu *et al.,* 2015[91] Liang *et al.,* 2015[92]
Meth	London		181 (94)	33.5 ± 9.0	80	SCID	1.5T, MPRAGE, TR=1900ms, TE=4.38ms, flip angle=15˚, matrix=256x256x160, voxel size=1x1x1mm^3	Tabibnia *et al.,* 2011[93] Morales *et al.,* 2012[94]
	Paulus	Relapse	91 (29)	37.6 ± 11.4	60	SCID	3T, Spoiled gradient recalled (SPGR), TR=8 ms, TE=3ms**,** flip angle=12°, matrix=192× 256x172, voxel size=0.97x 0.97x1mm^3	Stewart *et al.,* 2014[95]
	D Stein	Meth-CT	129 (26)	27.1 ± 6.4	68	SCID	3T, Mutliecho MPRAGE TR=2530ms;graded TE=1.53, 3.21, 4.89, 6.57ms; flip angle=7˚; slices=160; voxel size=1x1x1mm^3	Uhlmann *et al.,* 2016[96]
Cannabis	Garavan/ Hester	Trinity-THC	30 (6)	22.8 ± 3.9	15	ASI Lite-CF	3T,MPRAGE, TR=2000ms, TE=3ms, flip angle=12˚, matrix=256x256x176, voxel size=0.9x0.9x0.9mm^3	Hester *et al.,* 2009[97]
	Garavan	Orr	27 (2)	16.4 ± 1.5	13	CIDI-SF	3T, MPRAGE, TR=2300ms, TE=3ms, flip angle=12˚, matrix=256x256x180, voxelsize=0.9x0.9x0.9mm^3	Orr *et al.,* 2013[98]
	Cousijn/ Goudriaan	Cannabis Prospective	78 (27)	21.6 ± 2.4	38	MINI	3T, Turbo Field Echo, TR=9.6 ms, TE=4.6ms, flip angle 8°, matrix=256×256x182,	Cousijn *et al.,* 2012[99] Cousijn *et al.,* 2013[100] Cousijn *et al.,* 2014[101]

							voxelsize =1x1x1.2mm^3	
	Allen	ADS	100 (50)	19.0 ± 0.5	7	K-SADS	3T, gradient echo volumetric acquisition, TR=36ms, TE=9ms, flip angle=35˚, matrix=410x410, voxel size=1.5x0.49x0.49 mm^3	
	Martin-Santos	Chronic cannabis users (Barcelona)	59 (0)	21.7 ± 2.9	30	PRISM	1.5T, Fast Spoiled Gradient Inversion-Recovery, TR=11.8 ms, TE=4.2ms, flip angle= 15˚, matrix=256x256x124, voxel size=1.17x1.17x 1.2mm^3	Blanco-Hinojo *et al.,* 2016[102] Pujol *et al.,* 2014[103] Batalla *et al.,* 2014[104]
	Solowij	Chronic Cannabis	34 (3)	36.9 ± 9.8	16	SCID	3T, Spoiled Gradient-Recalled Echo, TR=6.4ms, TE=2.9ms, flip angle=8˚, matrix= 256x256x180, voxel size=1x1x1mm^3	Yucel *et al.,* 2008[105] Solowij *et al.,* 2011[106] Solowij *et al.,* 2013[107] Lorenzetti *et al.,* 2015[108]
	Yucel	Chronic Cannabis-Memory	103 (55)	31.5 ± 11.0	66	SCID	3T, MPRAGE, TR=1900ms, TE=2.15ms, flip angle=, matrix=256x256x176, voxelsize=1x1x1mm^3	Zalesky *et al.,* 2012[109] Harding *et al.,* 2012[110] Jakabek *et al.,* 2016[111] Yücel *et al.,* 2016[112]

Supplemental Table 2. At-a-glance summary of left and right hemisphere regions-of-interest that exhibited lower subcortical volume/cortical thickness. Names of the cortical regions-of-interest are as they appear in the Freesurfer atlas. In Model 1, all individuals were classified as either dependent or non-dependent. In Model 2, individuals were sorted by dependence on one and only one substance, i.e. individuals dependent on more than one substance were excluded from Model 2. Comparison of estimated marginal means for dependence on alcohol and cocaine relative to non-dependent controls are presented for Model 2. There were no significant associations with nicotine, methamphetamine or cannabis dependence on their own. The additional contrast in Model 2 included individuals dependent on nicotine, cocaine, methamphetamine and cannabis (i.e. but not alcohol). An 'X' indicates detection of association using false discovery rate procedure in the first half of the data and confirmation at $p < 0.05$ in the second half of the data. An '<u>O</u>' indicates region-of-interest was significantly associated with dependence in Model 1 but not with dependence on any particular substance in Model 2.

	Model 1		Model 2					
	Left	Right	Left			Right		
	Dep vs. Ctrl	Dep vs. Ctrl	Alcohol vs. Ctrl	Cocaine vs. Ctrl	Contrast vs. Ctrl	Alcohol vs. Ctrl	Cocaine vs. Ctrl	Contrast vs. Ctrl
Subcortical Volume								
Thalamus						X		
Caudate Nucleus								
Putamen			X			X		
Globus Pallidus						X		
Hippocampus	X	X	X			X		
Amygdala	X	X	X			X		
Nucleus Accumbens		X	X			X		

Cortical Thickness						
Banks Sup. Temporal Sulcus						
Caudal Anterior Cingulate						
Caudal Middle Frontal	X		X		X	
Cuneus						
Entorhinal						
Frontal Pole						
Fusiform	X		X		X	
Inferior Parietal	O			X		
Inferior Temporal			X		X	
Insula	X	O	X	X		X
Isthmus Cingulate		X			X	
Lateral Occipital					X	
Lateral Orbitofrontal					X	
Lingual						
Medial Orbitofrontal		O	X			
Middle Temporal	O	O				
Parahippocampal			X			
Paracentral Lobule	X	X	X		X	
Pars Opercularis						
Pars Orbitalis						
Pars Triangularis						
Pericalcarine						
Postcentral						
Posterior Cingulate			X		X	
Precentral	X	X	X		X	
Precuneus	X		X		X	
Rostral Anterior Cingulate			X			
Rostral Middle Frontal						
Superior Frontal			X		X	
Superior Parietal	X		X			
Superior Temporal			X			
Supramarginal	O	X			X	X
Temporal Pole					X	
Transverse Temporal						

Supplemental Table 3. Two classifications per drug were generated using a machine learning approach i.e. a support vector machine was trained on the first half of the data, tested on the second half, and vice versa. The classification of alcohol and nicotine dependence was significant in both while the classification for cocaine came exceptionally close to being significant. The top twenty features in each decision function were determined as described in the Methods Section. The Table lists the top twenty features in each classification**.** The third column lists ROIs which appeared in both lists. Names of the cortical ROIs are as they appear in the Freesurfer atlas.

Trained on 1st Half, Tested on 2nd Half	Trained on 2nd Half, Tested on 1st Half	Appeared in Both Lists
Alcohol		
1. Right Amygdala	1. Left Hippocampus	*Subcortical*
2. Right Hippocampus	2. Right Hippocampus	Right Amygdala
3. Left Putamen	3. Left Putamen	Right Globus Pallidus
4. Right Putamen	4. Right Thalamus	Left Hippocampus

5. Right Fusiform 6. Right Nucleus Accumbens 7. Left Superior Frontal 8. Left Hippocampus 9. Left Paracentral 10. Left Inferior Temporal 11. Left Caudal Middle Frontal 12. Right Superior Frontal 13. Left Amygdala 14. Left Isthmus Cingulate 15. Right Precentral 16. Right Lateral Occipital 17. Left Posterior Cingulate 18. Left Precuneus 19. Right Globus Pallidus 20. Right Paracentral	5. Right Posterior Cingulate 6. Right Nucleus Accumbens 7. Left Insula 8. Left Posterior Cingulate 9. Left Fusiform 10. Right Fusiform 11. Right Insula 12. Right Lateral Orbitofrontal 13. Right Globus Pallidus 14. Left Thalamus 15. Right Precentral 16. Right Paracentral 17. Left Precentral 18. Left Superior Frontal 19 Left Nucleus Accumbens 20. Right Amygdala	Right Hippocampus Right Nucleus Accumbens Left Putamen *Cortical* Right Fusiform Left Superior Frontal Right Paracentral Left Posterior Cingulate Right Precentral
Nicotine		
1. Right Inferior Temporal 2. Left Temporal Pole 3. Right Pericalcarine 4. Left Rostral Anterior Cingulate 5. Left Medial Orbitofrontal 6. Left Fusiform 7. Right Temporal Pole 8. Right Cuneus 9. Left Insula 10. Right Posterior Cingulate 11. Right Caudal Anterior Cingulate 12. Right Putamen 13. Right Medial Orbitofrontal 14. Right Fusiform 15. Left Posterior Cingulate 16. Right Rostral Anterior Cingulate 17. Right Inferior Parietal 18. Left Superior Temporal 19. Left Amygdala 20. Right Lateral Orbitofrontal	1. Left Nucleus Accumbens 2. Right Caudate 3. Left Inferior Parietal 4. Right Fusiform 5 Left Pericalcarine 6. Left Rostral Anterior Cingulate 7. Right Pars Opercularis 8. Left Caudate 9. Left Cuneus 10. Right Medial Orbitofrontal 11. Left Fusiform 12. Left Lingual 13. Right Frontal Pole 14. Left Parahippocampal 15. Right Entorhinal 16. Right Banks Superior Temporal 17. Right Superior Frontal 18. Right Lateral Occipital 19. Left Lateral Orbitofrontal 20. Left Transverse Temporal	*Cortical* Left Fusiform Right Fusiform Right Medial Orbitofrontal Left Rostral Anterior Cingulate
Cocaine		
1. Left Lingual 2. Left Rostral Middle Frontal 3. Left Entorhinal 4. Right Pars Orbitalis 5. Right Isthmus Cingulate 6. Right Putamen 7. Left Amygdala 8. Left Isthmus Cingulate 9. Right Rostral Middle Frontal	1. Left Supramarginal 2. Right Bank Superior Temporal 3. Right Pars Opercularis 4. Left Middle Temporal 5. Pars Triagularis 6. Right Supramarginal 7. Right Superior Temporal 8. Left Caudate 9. Right Caudal Middle Frontal	*Cortical* Right Supramarginal

10. Right Post Central	10. Left Precentral	
11. Right Lingual	11. Right Thalamus	
12. Left Superior Frontal	12. Left Inferior Temporal	
13. Right Nucleus Accumbens	13. Left Thalamus	
14. Left Putamen	14. Left Pars Opercularis	
15. Right Lateral Occipital	15. Right Precentral	
16. Left Superior Temporal	16. Left Paracentral	
17. Right Supramarginal	17. Right Hippocampus	
18. Right Globus Pallidus	18. Right Inferior Parietal	
19. Right Posterior Cingulate	19. Left Post Central	
20. Left Posterior Cingulate	20. Right Pericalcarine	

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