Data Supplement for Mackey et al., Mega-Analysis of Gray Matter Volume in Substance Dependence: General and Substance-Specific Regional Effects. Am J Psychiatry (doi: 10.1176/appi.ajp.2018.17040415)

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 data sets 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 <u>not</u> 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 $2^{\wedge 54}$); (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

TABLE S1. 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 1x1mm³	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 1x1mm³	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 = 1x1x1mm³	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]
	Wiers	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=1x1x1mm³	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 0.97x1mm³	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=1x1x1mm³	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=0.9x0.9x0.9mm³	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=0.9x0.9x0.9mm³	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, voxelsize =1x1x1.2mm³	Cousijn et al., 2012[99] Cousijn et al., 2013[100] Cousijn et al., 2014[101]
	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 mm³	
	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 1.2mm³	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=1x1x1mm³	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=1x1x1mm³	Zalesky et al., 2012[109] Harding et al., 2012[110] Jakabek et al., 2016[111] Yücel et al., 2016[112]

TABLE S2. 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 'O' 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	<u>O</u>	X		X X
Temporal Pole				X
Transverse Temporal				

TABLE S3. 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	5. Right Posterior Cingulate	Right Hippocampus
6. Right Nucleus Accumbens	6. Right Nucleus Accumbens	Right Nucleus Accumbens
7. Left Superior Frontal	7. Left Insula	Left Putamen
8. Left Hippocampus	8. Left Posterior Cingulate	
9. Left Paracentral	9. Left Fusiform	_Cortical_
10. Left Inferior Temporal	10. Right Fusiform	Right Fusiform
11. Left Caudal Middle Frontal	11. Right Insula	Left Superior Frontal
12. Right Superior Frontal	12. Right Lateral Orbitofrontal	Right Paracentral
13. Left Amygdala	13. Right Globus Pallidus	Left Posterior Cingulate
14. Left Isthmus Cingulate	14. Left Thalamus	Right Precentral
15. Right Precentral	15. Right Precentral	
16. Right Lateral Occipital	16. Right Paracentral	
17. Left Posterior Cingulate	17. Left Precentral	
18. Left Precuneus	18. Left Superior Frontal	
19. Right Globus Pallidus	19 Left Nucleus Accumbens	
20. Right Paracentral	20. Right Amygdala	

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

Supplemental References

47   Stein, J. L. *et al.* Identification of common variants associated with human hippocampal and intracranial volumes. *Nature genetics* **44**, 552-561, doi:10.1038/ng.2250 (2012).

48   Boedhoe, P. S. *et al.* Distinct Subcortical Volume Alterations in Pediatric and Adult OCD: A Worldwide Meta- and Mega-Analysis. *Am J Psychiatry*, appiajp201616020201, doi:10.1176/appi.ajp.2016.16020201 (2016).

49   van Erp, T. G. *et al.* Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Mol Psychiatry* **21**, 585, doi:10.1038/mp.2015.118 (2016).

50   Hibar, D. P. *et al.* Common genetic variants influence human subcortical brain structures. *Nature* **520**, 224-229, doi:10.1038/nature14101 (2015).

51   Dale, A. M., Fischl, B. & Sereno, M. I. Cortical surface-based analysis - I. Segmentation and surface reconstruction. *NeuroImage* **9**, 179-194, doi:DOI 10.1006/nimg.1998.0395 (1999).

52   Desikan, R. S. *et al.* An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* **31**, 968-980, doi:10.1016/j.neuroimage.2006.01.021 (2006).

53   Sanchez, V. D. Advanced support for support vector machines and kernel methods. *Neurocomputing* **55**, 5-20 (2003).

54   Blaine, S. K., Milivojevic, V., Fox, H. & Sinha, R. Alcohol Effects on Stress Pathways: Impact on Craving and Relapse Risk. *Can J Psychiatry* **61**, 145-153, doi:10.1177/0706743716632512 (2016).

55   Cacciola, J. S., Alterman, A. I., McLellan, A. T., Lin, Y. T. & Lynch, K. G. Initial evidence for the reliability and validity of a "Lite" version of the Addiction Severity Index. *Drug Alcohol Depend* **87**, 297-302, doi:10.1016/j.drugalcdep.2006.09.002 (2007).

56   Saunders, J. B., Aasland, O. G., Babor, T. F., de la Fuente, J. R. & Grant, M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction* **88**, 791-804 (1993).

57   Kessler, R. C. *et al.* Clinical calibration of DSM-IV diagnoses in the World Mental Health (WMH) version of the World Health Organization (WHO) Composite International Diagnostic Interview (WMHCIDI). *Int J Methods Psychiatr Res* **13**, 122-139 (2004).

58   Heatherton, T. F., Kozlowski, L. T., Frecker, R. C. & Fagerstrom, K. O. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* **86**, 1119-1127 (1991).

59   Kaufman, J. *et al.* Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* **36**, 980-988, doi:10.1097/00004583-199707000-00021 (1997).

60   Sheehan, D. V. *et al.* The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* **59 Suppl 20**, 22-33;quiz 34-57 (1998).

61   Torrens, M., Serrano, D., Astals, M., Perez-Dominguez, G. & Martin-Santos, R. Diagnosing comorbid psychiatric disorders in substance abusers: validity of the Spanish versions of the Psychiatric Research Interview for Substance and Mental Disorders and the Structured Clinical Interview for DSM-IV. *Am J Psychiatry* **161**, 1231-1237, doi:10.1176/appi.ajp.161.7.1231 (2004).

62   First, M., Spitzer, R., Gibbon, M. & Williams, J. B. W. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition*. (Biometrics Research, New York State Psychiatric Institute, 2002).

63   Thayer, R. E. *et al.* Negative and interactive effects of sex, aging, and alcohol abuse on gray matter morphometry. *Hum Brain Mapp* **37**, 2276-2292, doi:10.1002/hbm.23172 (2016).

64   Claus, E. D., Ewing, S. W., Filbey, F. M., Sabbineni, A. & Hutchison, K. E. Identifying neurobiological phenotypes associated with alcohol use disorder severity. *Neuropsychopharmacology* **36**, 2086-2096, doi:10.1038/npp.2011.99 (2011).

65   Sinha, R. & Li, C. S. Imaging stress- and cue-induced drug and alcohol craving: association with relapse and clinical implications. *Drug Alcohol Rev* **26**, 25-31, doi:10.1080/09595230601036960 (2007).

66   Li, C. S., Luo, X., Yan, P., Bergquist, K. & Sinha, R. Altered impulse control in alcohol dependence: neural measures of stop signal performance. *Alcohol Clin Exp Res* **33**, 740-750, doi:10.1111/j.1530-0277.2008.00891.x (2009).

67   Seo, D. *et al.* Sex differences in neural responses to stress and alcohol context cues. *Hum Brain Mapp* **32**, 1998-2013, doi:10.1002/hbm.21165 (2011).

68   Senatorov, V. V. *et al.* Reduced anterior insula, enlarged amygdala in alcoholism and associated depleted von Economo neurons. *Brain* **138**, 69-79, doi:10.1093/brain/awu305 (2015).

69   Grodin, E. N., Lin, H., Durkee, C. A., Hommer, D. W. & Momenan, R. Deficits in cortical, diencephalic and midbrain gray matter in alcoholism measured by VBM: Effects of co-morbid substance abuse. *Neuroimage Clin* **2**, 469-476, doi:10.1016/j.nicl.2013.03.013 (2013).

70   Momenan, R. *et al.* Effects of alcohol dependence on cortical thickness as determined by magnetic resonance imaging. *Psychiatry Res* **204**, 101-111, doi:10.1016/j.pscychresns.2012.05.003 (2012).

71   Korucuoglu, O. *et al.* Neural response to alcohol taste cues in youth: effects of the OPRM1 gene. *Addict Biol*, doi:10.1111/adb.12440 (2016).

72   Schmaal, L. *et al.* Neural substrates of impulsive decision making modulated by modafinil in alcohol-dependent patients. *Psychol Med* **44**, 2787-2798, doi:10.1017/S0033291714000312 (2014).

73   Sjoerds, Z., van den Brink, W., Beekman, A. T., Penninx, B. W. & Veltman, D. J. Response inhibition in alcohol-dependent patients and patients with depression/anxiety: a functional magnetic resonance imaging study. *Psychol Med* **44**, 1713-1725, doi:10.1017/S0033291713002274 (2014).

74   Jansen, J. M. *et al.* Brain function during cognitive flexibility and white matter integrity in alcohol-dependent patients, problematic drinkers and healthy controls. *Addict Biol* **20**, 979-989, doi:10.1111/adb.12199 (2015).

75   van Holst, R. J., Clark, L., Veltman, D. J., van den Brink, W. & Goudriaan, A. E. Enhanced striatal responses during expectancy coding in alcohol dependence. *Drug Alcohol Depend* **142**, 204-208, doi:10.1016/j.drugalcdep.2014.06.019 (2014).

76   van Holst, R. J., de Ruiter, M. B., van den Brink, W., Veltman, D. J. & Goudriaan, A. E. A voxel-based morphometry study comparing problem gamblers, alcohol abusers, and healthy controls. *Drug Alcohol Depend* **124**, 142-148, doi:10.1016/j.drugalcdep.2011.12.025 (2012).

77   Tang, D. W. *et al.* Genetic variation in CYP2A6 predicts neural reactivity to smoking cues as measured using fMRI. *Neuroimage* **60**, 2136-2143, doi:10.1016/j.neuroimage.2012.01.119 (2012).

78   Claus, E. D., Blaine, S. K., Filbey, F. M., Mayer, A. R. & Hutchison, K. E. Association between nicotine dependence severity, BOLD response to smoking cues, and functional connectivity. *Neuropsychopharmacology* **38**, 2363-2372, doi:10.1038/npp.2013.134 (2013).

79   Morales, A. M., Ghahremani, D., Kohno, M., Hellemann, G. S. & London, E. D. Cigarette exposure, dependence, and craving are related to insula thickness in young adult smokers. *Neuropsychopharmacology* **39**, 1816-1822, doi:10.1038/npp.2014.48 (2014).

80   Zhang, X. *et al.* Anatomical differences and network characteristics underlying smoking cue reactivity. *Neuroimage* **54**, 131-141, doi:10.1016/j.neuroimage.2010.07.063 (2011).

81   Rose, E. J. *et al.* Chronic exposure to nicotine is associated with reduced reward-related activity in the striatum but not the midbrain. *Biol Psychiatry* **71**, 206-213, doi:10.1016/j.biopsych.2011.09.013 (2012).

82   Sutherland, M. T. *et al.* Down-regulation of amygdala and insula functional circuits by varenicline and nicotine in abstinent cigarette smokers. *Biol Psychiatry* **74**, 538-546, doi:10.1016/j.biopsych.2013.01.035 (2013).

83   Ding, X., Yang, Y., Stein, E. A. & Ross, T. J. Multivariate classification of smokers and nonsmokers using SVM-RFE on structural MRI images. *Hum Brain Mapp* **36**, 4869-4879, doi:10.1002/hbm.22956 (2015).

84   Luijten, M. *et al.* Brain activation associated with attentional bias in smokers is modulated by a dopamine antagonist. *Neuropsychopharmacology* **37**, 2772-2779, doi:10.1038/npp.2012.143 (2012).

85   Bell, R. P., Foxe, J. J., Ross, L. A. & Garavan, H. Intact inhibitory control processes in abstinent drug abusers (I): a functional neuroimaging study in former cocaine addicts. *Neuropharmacology* **82**, 143-150, doi:10.1016/j.neuropharm.2013.02.018 (2014).

86   Luo, X. *et al.* Error processing and gender-shared and -specific neural predictors of relapse in cocaine dependence. *Brain* **136**, 1231-1244, doi:10.1093/brain/awt040 (2013).

87   Li, C. S., Kemp, K., Milivojevic, V. & Sinha, R. Neuroimaging study of sex differences in the neuropathology of cocaine abuse. *Gend Med* **2**, 174-182 (2005).

88   Li, C. S. *et al.* Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. *Neuropsychopharmacology* **33**, 1798-1806, doi:10.1038/sj.npp.1301568 (2008).

89   Seo, D., Ahluwalia, A., Potenza, M. N. & Sinha, R. Gender differences in neural correlates of stress-induced anxiety. *J Neurosci Res* **95**, 115-125, doi:10.1002/jnr.23926 (2017).

90   Gu, H. *et al.* Mesocorticolimbic circuits are impaired in chronic cocaine users as demonstrated by resting-state functional connectivity. *Neuroimage* **53**, 593-601, doi:10.1016/j.neuroimage.2010.06.066 (2010).

91   Hu, Y., Salmeron, B. J., Gu, H., Stein, E. A. & Yang, Y. Impaired functional connectivity within and between frontostriatal circuits and its association with compulsive drug use and trait impulsivity in cocaine addiction. *JAMA Psychiatry* **72**, 584-592, doi:10.1001/jamapsychiatry.2015.1 (2015).

92   Liang, X. *et al.* Interactions between the salience and default-mode networks are disrupted in cocaine addiction. *J Neurosci* **35**, 8081-8090, doi:10.1523/JNEUROSCI.3188-14.2015 (2015).

93   Tabibnia, G. *et al.* Different forms of self-control share a neurocognitive substrate. *J Neurosci* **31**, 4805-4810, doi:10.1523/JNEUROSCI.2859-10.2011 (2011).

94   Morales, A. M., Lee, B., Hellemann, G., O'Neill, J. & London, E. D. Gray-matter volume in methamphetamine dependence: cigarette smoking and changes with abstinence from methamphetamine. *Drug Alcohol Depend* **125**, 230-238, doi:10.1016/j.drugalcdep.2012.02.017 (2012).

95   Stewart, J. L. *et al.* Striatum and insula dysfunction during reinforcement learning differentiates abstinent and relapsed methamphetamine-dependent individuals. *Addiction* **109**, 460-471, doi:10.1111/add.12403 (2014).

96   Uhlmann, A. *et al.* Fronto-temporal alterations and affect regulation in methamphetamine dependence with and without a history of psychosis. *Psychiatry Res* **248**, 30-38, doi:10.1016/j.pscychresns.2016.01.010 (2016).

97   Hester, R., Nestor, L. & Garavan, H. Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology* **34**, 2450-2458, doi:10.1038/npp.2009.67 (2009).

98   Orr, C. *et al.* Altered resting-state connectivity in adolescent cannabis users. *Am J Drug Alcohol Abuse* **39**, 372-381, doi:10.3109/00952990.2013.848213 (2013).

99   Cousijn, J. *et al.* Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. *Neuroimage* **59**, 3845-3851, doi:10.1016/j.neuroimage.2011.09.046 (2012).

100   Cousijn, J. *et al.* Neural responses associated with cue-reactivity in frequent cannabis users. *Addict Biol* **18**, 570-580, doi:10.1111/j.1369-1600.2011.00417.x (2013).

101   Cousijn, J. *et al.* Effect of baseline cannabis use and working-memory network function on changes in cannabis use in heavy cannabis users: a prospective fMRI study. *Hum Brain Mapp* **35**, 2470-2482, doi:10.1002/hbm.22342 (2014).

102   Blanco-Hinojo, L. *et al.* Attenuated frontal and sensory inputs to the basal ganglia in cannabis users. *Addict Biol*, doi:10.1111/adb.12370 (2016).

103   Pujol, J. *et al.* Functional connectivity alterations in brain networks relevant to self-awareness in chronic cannabis users. *J Psychiatr Res* **51**, 68-78, doi:10.1016/j.jpsychires.2013.12.008 (2014).

104   Batalla, A. *et al.* Modulation of brain structure by catechol-O-methyltransferase Val(158) Met polymorphism in chronic cannabis users. *Addict Biol* **19**, 722-732, doi:10.1111/adb.12027 (2014).

105   Yucel, M. *et al.* Regional brain abnormalities associated with long-term heavy cannabis use. *Arch Gen Psychiatry* **65**, 694-701, doi:10.1001/archpsyc.65.6.694 (2008).

106   Solowij, N. *et al.* Cerebellar white-matter changes in cannabis users with and without schizophrenia. *Psychol Med* **41**, 2349-2359, doi:10.1017/S003329171100050X (2011).

107   Solowij, N. *et al.* Alteration to hippocampal shape in cannabis users with and without schizophrenia. *Schizophr Res* **143**, 179-184, doi:10.1016/j.schres.2012.10.040 (2013).

108   Lorenzetti, V. *et al.* Gross morphological brain changes with chronic, heavy cannabis use. *Br J Psychiatry* **206**, 77-78, doi:10.1192/bjp.bp.114.151407 (2015).

109   Zalesky, A. *et al.* Effect of long-term cannabis use on axonal fibre connectivity. *Brain* **135**, 2245-2255, doi:10.1093/brain/aws136 (2012).

110   Harding, I. H. *et al.* Functional connectivity in brain networks underlying cognitive control in chronic cannabis users. *Neuropsychopharmacology* **37**, 1923-1933, doi:10.1038/npp.2012.39 (2012).

111   Jakabek, D., Yucel, M., Lorenzetti, V. & Solowij, N. An MRI study of white matter tract integrity in regular cannabis users: effects of cannabis use and age. *Psychopharmacology (Berl)* **233**, 3627-3637, doi:10.1007/s00213-016-4398-3 (2016).

112   Yucel, M. *et al.* Hippocampal harms, protection and recovery following regular cannabis use. *Transl Psychiatry* **6**, e710, doi:10.1038/tp.2015.201 (2016).