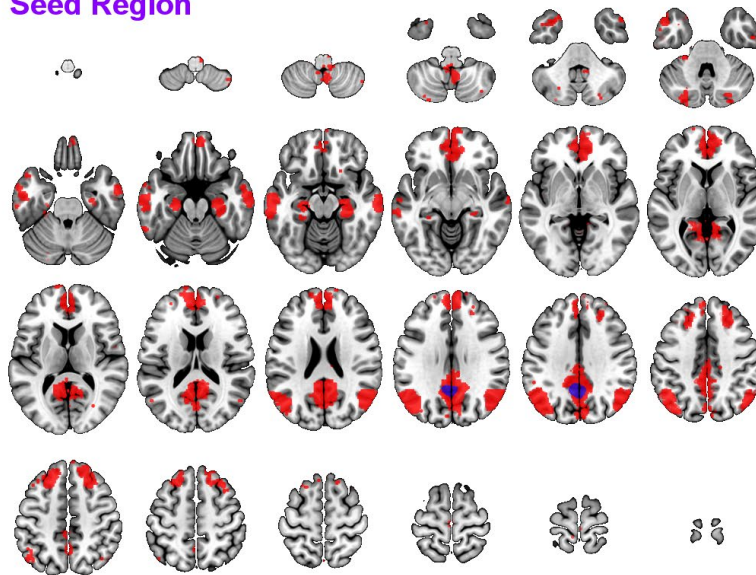


Supplementary Material

Methods

Default Mode Seed Region



Salience Seed Region

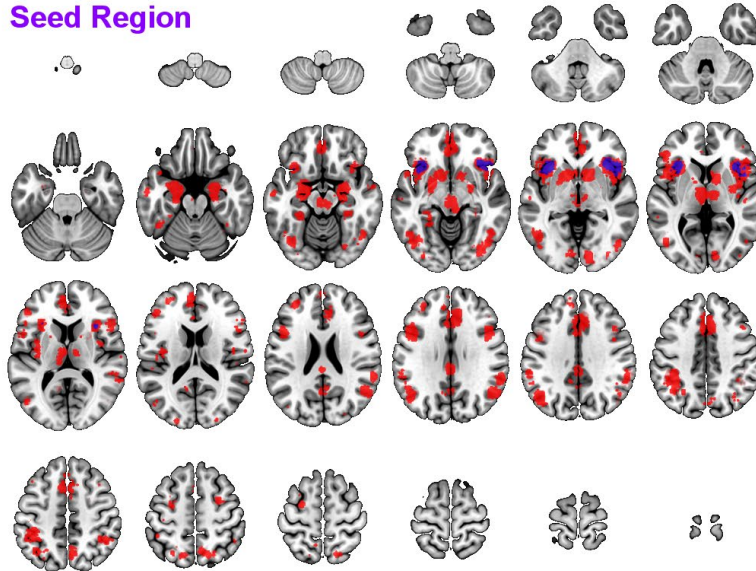


Figure S1. Masks and derived seed-regions used for the seed-based analyses. Masks were derived from automated meta-analytic data provided by Neurosynth (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011) using the ‘default mode’

(<http://www.neurosynth.org/analyses/terms/default%20mode/>) and ‘salience’

(<http://www.neurosynth.org/analyses/terms/salience/>) terms. Posterior cingulate cortex and anterior insula ROIs were derived from these maps for use in the seed-based analyses.

	Participants
Age	26.18 (7.13)
Gender (m/f)	8/9
BDI	3.38 (3.12)
TEPS consummatory	43.50 (5.61)
TEPS anticipatory	42.06 (4.85)
TEPS total	86.56 (9.30)
Cannabis SDS	1.13 (1.26)
Alcohol ever used (y/n)	16/0
Alcohol use now (y/n)	16/0
Alcohol days per month	10.81 (4.86)
Alcohol units/session	5.93 (2.08)
Amphetamine ever used (y/n)	8/8
Amphetamine use now (y/n)	0/16
Amphetamine days per month	NA
Amphetamine grams/session	NA
Cannabis ever used (y/n)	16/0
Cannabis use now (y/n)	16/0
Cannabis days per month	8.06 (5.48)
Cannabis days to smoke an 8th	25.88 (33.73)
Cocaine ever used (y/n)	11/5
Cocaine use now (y/n)	3/13
Cocaine days per month	1.0 (0.0)
Cocaine grams/session	0.5 (0.0)
Heroin ever used (y/n)	0/16
Heroin use now (y/n)	0/16
Heroin days per month	NA
Heroin grams/session	NA
Ketamine ever used (y/n)	10/6
Ketamine use now (y/n)	2/14
Ketamine days per month	1.50 (0.71)
Ketamine grams/session	0.75 (0.35)
Mephedrone ever used (y/n)	7/9
Mephedrone use now (y/n)	0/16
Mephedrone days per month	NA
Mephedrone grams/session	NA
MDMA ever used (y/n)	14/2
MDMA use now (y/n)	6/10
MDMA days per month	1.50 (0.84)
MDMA grams/session	0.31 (0.19)
Tobacco ever used (y/n)	15/1
Tobacco use now (y/n)	15/1
Tobacco days per month	11.30 (10.27)
Tobacco cigs/day	3.63 (3.62)
Tobacco average cigs/day	2.16 (3.48)

Table S1. Means (S.D.) and frequencies for demographic data and drug use for participants. Data was missing for one participant for BDI, TEPS and drugs history. TEPS = Temporal Experience of Pleasure scale. BDI = Beck Depression Inventory. SDS = Severity of Dependence Scale.

Results

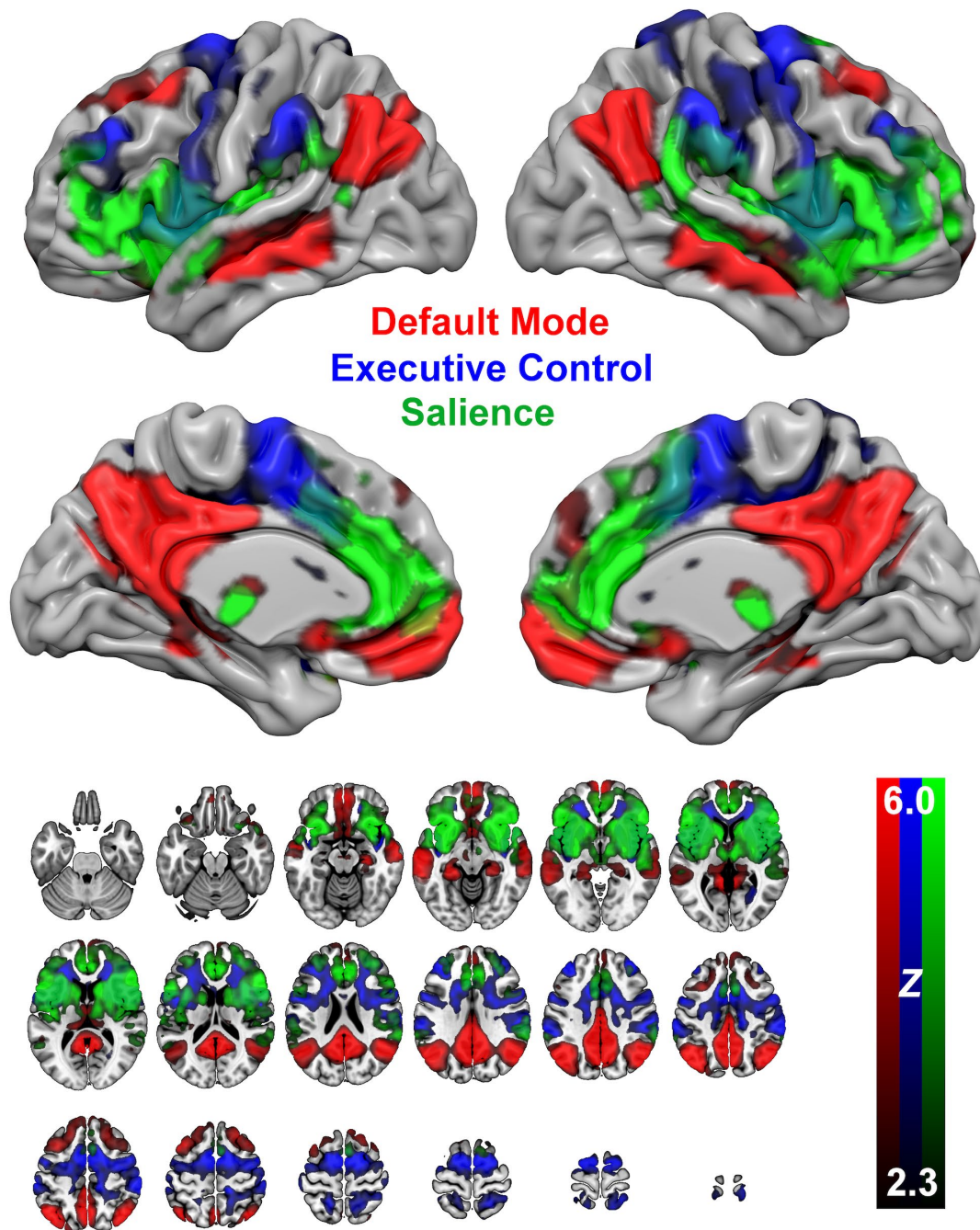


Figure S3. Mean (all subjects, all scans) functional connectivity maps from the seed-region analyses showing the Default Mode Network (DMN; defined by positive connectivity with the PCC seed region; red), the Executive Control Network (ECN; defined by negative connectivity with the PCC seed region; blue), and the Salience network (defined by positive connectivity with the anterior insula seed region; green).

Treatment	Analysis	Anatomical Location	Number of Voxels	Z-Max	P(corr.)	COG-X	COG-Y	COG-Z
Placebo vs. Cann+CBD:	DMN (PCC+)	Hippocampus (RH)	1420	-3.63	6.79E-06	20	-37	-1
		Parietal Lobe (RH)	1365	-4.21	1.04E-05	42	62	38
	ECN (PCC-)	Inferior frontal gyrus (LH)	2189	-3.92	5.96E-08	44	13	23
	SAL (AI+)	Precentral gyrus (LH)	724	-3.75	0.000955	-55	-11	48
		Frontal Pole	438	-3.97	0.0239	-18	53	40
Placebo vs. Cann-CBD:	DMN (PCC+)	Precuneous/PCC	1539	-3.64	2.80E-06	11	-55	15
		Parietal Lobe (RH)	457	-3.51	0.035	49	-47	31
	ECN (PCC-)	Superior frontal gyrus (RH)	564	-3.56	0.0113	-16	-4	68
		Inferior frontal gyrus (LH)	543	-3.42	0.0141	-36	40	-1
	SAL (AI+)	Inferior frontal lobe (LH)	3630	-4.52	2.96E-13	-39	12	-1
		Frontal pole (LH)	399	-4.4	0.0386	-6	49	28

Table S2. Coordinates of the major activation clusters shown in Figures 2, 3, and 4 of the main text. Z-Max = Maximum Z-score in cluster. LH = left Hemisphere, RH = Right Hemisphere. COG = Centre Of Gravity. Coordinates are in MNI space. Z values are negative as only reductions in connectivity (relative to placebo) were found.

VAS Item	Brainstem			Hippocampus			Lateral Parietal		
	<i>r</i>	<i>p</i>	<i>p</i> (FDR)	<i>r</i>	<i>p</i>	<i>p</i> (FDR)	<i>r</i>	<i>p</i>	<i>p</i> (FDR)
Alert	-0.148	0.57	0.820	-0.381	0.131	0.977	0.383	0.129	0.619
Happy	0.099	0.706	0.820	-0.018	0.945	0.977	-0.236	0.362	0.659
Anxious	0.077	0.769	0.820	-0.072	0.782	0.977	-0.063	0.811	0.927
Paranoid	0.213	0.412	0.820	-0.102	0.696	0.977	0.001	0.997	0.997
Mentally impaired	0.505	0.039	0.624	0.408	0.104	0.977	-0.04	0.88	0.939
Stoned	0.249	0.335	0.820	0.013	0.961	0.977	-0.207	0.425	0.659
High	0.335	0.188	0.820	0.151	0.562	0.977	-0.306	0.232	0.619
Feel drug effect	0.27	0.294	0.820	0.14	0.591	0.977	-0.409	0.103	0.619
Like drug effect	0.087	0.739	0.820	0.018	0.944	0.977	-0.195	0.453	0.659
Dry mouth	-0.226	0.384	0.820	-0.155	0.553	0.977	-0.207	0.426	0.659
Enhanced colour perception	0.126	0.631	0.820	0.067	0.799	0.977	-0.447	0.072	0.619
Enhanced sound perception	0.127	0.627	0.820	-0.018	0.946	0.977	-0.328	0.198	0.619
Want to listen to music	0.125	0.634	0.820	-0.038	0.885	0.977	-0.359	0.157	0.619
Want food	-0.104	0.692	0.820	0.008	0.977	0.977	-0.09	0.73	0.898
Want more cannabis balloon	-0.146	0.575	0.820	-0.107	0.683	0.977	-0.107	0.683	0.898
Want to smoke cannabis	0.022	0.933	0.933	-0.113	0.665	0.977	0.197	0.448	0.659

Table S3. Correlation coefficients between ROIs defined based on the results of the Cann+CBD treatment in the DMN (PCC+), and visual analogue scale scores of subjective effects, taken in the same treatment session. Tables show Pearson's *r*, the uncorrected *p* values, and FDR-corrected *p* values for each region.

VAS Item	Dorsolateral Prefrontal Cortex			Inferior Frontal			Medial Frontal Gyrus		
	<i>r</i>	<i>p</i>	<i>p</i> (FDR)	<i>r</i>	<i>p</i>	<i>p</i> (FDR)	<i>r</i>	<i>p</i>	<i>p</i> (FDR)
Alert	-0.050	0.848	0.987	-0.148	0.572	0.785	0.014	0.958	0.976
Happy	0.096	0.715	0.987	0.133	0.611	0.785	0.211	0.416	0.976
Anxious	0.106	0.686	0.987	-0.206	0.427	0.785	-0.191	0.463	0.976
Paranoid	0.086	0.743	0.987	-0.114	0.663	0.785	-0.015	0.955	0.976
Mentally impaired	-0.223	0.389	0.987	-0.106	0.687	0.785	0.100	0.704	0.976
Stoned	0.006	0.983	0.987	0.280	0.276	0.785	-0.008	0.976	0.976
High	-0.018	0.947	0.987	0.279	0.279	0.785	0.071	0.787	0.976
Feel drug effect	0.004	0.987	0.987	0.204	0.431	0.785	-0.116	0.657	0.976
Like drug effect	-0.232	0.371	0.987	0.256	0.321	0.785	-0.037	0.888	0.976
Dry mouth	-0.075	0.776	0.987	0.071	0.788	0.829	-0.255	0.323	0.976
Enhanced colour perception	-0.102	0.697	0.987	0.198	0.446	0.785	-0.072	0.783	0.976

Enhanced sound perception	-0.100	0.704	0.987	0.133	0.611	0.785	-0.151	0.562	0.976
Want to listen to music	-0.058	0.824	0.987	0.488	0.047	0.752	0.231	0.373	0.976
Want food	0.184	0.481	0.987	0.316	0.217	0.785	-0.029	0.911	0.976
Want more cannabis balloon	-0.083	0.752	0.987	0.057	0.829	0.829	-0.215	0.408	0.976
Want to smoke cannabis	0.159	0.542	0.987	0.144	0.583	0.785	-0.022	0.934	0.976

Table S4. Correlation coefficients between ROIs defined based on the results of the Cann+CBD treatment in the ECN (PCC-), and visual analogue scale scores of subjective effects, taken in the same treatment session. Tables show Pearson's r , the uncorrected p values, and FDR-corrected p values for each region.

VAS Item	LH Motor Cortex		
	r	p	p (FDR)
Alert	0.059	0.822	0.877
Happy	-0.416	0.097	0.585
Anxious	-0.213	0.411	0.750
Paranoid	-0.207	0.425	0.750
Mentally impaired	0.020	0.939	0.939
Stoned	-0.471	0.056	0.585
High	-0.362	0.154	0.585
Feel drug effect	-0.292	0.256	0.585
Like drug effect	-0.059	0.822	0.877
Dry mouth	-0.382	0.130	0.585
Enhanced colour perception	-0.318	0.213	0.585
Enhanced sound perception	-0.312	0.223	0.585
Want to listen to music	-0.131	0.617	0.849
Want food	-0.188	0.469	0.750
Want more cannabis balloon	0.124	0.637	0.849
Want to smoke cannabis	-0.092	0.727	0.877

Table S5. Correlation coefficients between ROIs defined based on the results of the Cann+CBD treatment in the SAL (AI+) network, and visual analogue scale scores of subjective effects, taken in the same treatment session. Tables show Pearson's r , the uncorrected p values, and FDR-corrected p values for each region.

VAS Item	Hippocampus			Posterior Cingulate		
	<i>r</i>	<i>p</i>	<i>p</i> (FDR)	<i>r</i>	<i>p</i>	<i>p</i> (FDR)
Alert	-0.035	0.895	0.990	-0.283	0.271	0.394
Happy	-0.157	0.547	0.990	0.059	0.823	0.933
Anxious	0.488	0.047	0.376	0.188	0.469	0.577
Paranoid	0.511	0.036	0.376	0.225	0.386	0.515
Mentally impaired	0.218	0.401	0.917	0.513	0.035	0.078
Stoned	0.300	0.241	0.771	0.573	0.016	0.043
High	0.381	0.131	0.699	0.607	0.010	0.035
Feel drug effect	0.308	0.228	0.771	0.669	0.003	0.021
Like drug effect	0.020	0.938	0.990	0.409	0.103	0.165
Dry mouth	-0.052	0.842	0.990	0.667	0.003	0.021
Enhanced colour perception	0.139	0.594	0.990	0.602	0.011	0.035
Enhanced sound perception	0.242	0.349	0.917	0.657	0.004	0.021
Want to listen to music	-0.075	0.774	0.990	0.022	0.933	0.933
Want food	0.034	0.898	0.990	-0.031	0.905	0.933
Want more cannabis balloon	0.003	0.990	0.990	0.466	0.060	0.107
Want to smoke cannabis	0.032	0.904	0.990	0.504	0.039	0.078

Table S6. Correlation coefficients between ROIs defined based on the results of the Cann-CBD treatment in the DMN (PCC+), and visual analogue scale scores of subjective effects, taken in the same treatment session. Tables show Pearson's *r*, the uncorrected *p* values, and FDR-corrected *p* values for each region. Significant (FDR-corrected) *p* values are highlighted in bold text.

VAS Item	LH Supplementary Motor Area			LH Orbitofrontal Cortex		
	<i>r</i>	<i>p</i>	<i>p</i> (FDR)	<i>r</i>	<i>p</i>	<i>p</i> (FDR)
Alert	0.147	0.573	0.813	-0.269	0.296	0.773
Happy	0.102	0.696	0.813	-0.339	0.183	0.773
Anxious	0.205	0.431	0.791	-0.010	0.971	0.985
Paranoid	0.217	0.403	0.791	-0.056	0.831	0.985
Mentally impaired	0.335	0.189	0.791	0.276	0.283	0.773
Stoned	0.227	0.382	0.791	0.011	0.965	0.985
High	0.103	0.695	0.813	0.190	0.466	0.773
Feel drug effect	0.229	0.378	0.791	0.206	0.427	0.773
Like drug effect	-0.259	0.316	0.791	-0.005	0.985	0.985
Dry mouth	-0.199	0.445	0.791	-0.051	0.847	0.985
Enhanced colour perception	0.162	0.536	0.813	0.283	0.272	0.773
Enhanced sound perception	0.079	0.762	0.813	0.189	0.468	0.773
Want to listen to music	0.080	0.759	0.813	0.183	0.483	0.773
Want food	-0.238	0.358	0.791	-0.324	0.205	0.773
Want more cannabis balloon	-0.045	0.863	0.863	-0.040	0.878	0.985

Want to smoke cannabis 0.291 0.257 0.791 -0.200 0.441 0.773

Table S7. Correlation coefficients between ROIs defined based on the results of the Cann-CBD treatment in the ECN (PCC-), and visual analogue scale scores of subjective effects, taken in the same treatment session. Tables show Pearson's r , the uncorrected p values, and FDR-corrected p values for each region.

VAS Item	Putamen			Dorsomedial Prefrontal Cortex			Dorsolateral Prefrontal Cortex		
	r	p	p (FDR)	r	p	p (FDR)	r	p	p (FDR)
Alert	-0.423	0.091	0.918	-0.260	0.314	0.625	-0.169	0.518	0.872
Happy	-0.104	0.691	0.918	-0.102	0.698	0.798	-0.160	0.538	0.872
Anxious	-0.304	0.236	0.918	-0.421	0.093	0.380	-0.298	0.246	0.872
Paranoid	-0.216	0.404	0.918	-0.674	0.003	0.048	-0.079	0.763	0.872
Mentally impaired	0.065	0.805	0.918	-0.418	0.095	0.380	0.120	0.646	0.872
Stoned	0.141	0.589	0.918	-0.206	0.427	0.625	-0.036	0.890	0.932
High	0.325	0.204	0.918	-0.182	0.484	0.645	0.022	0.932	0.932
Feel drug effect	0.131	0.616	0.918	-0.205	0.430	0.625	-0.085	0.746	0.872
Like drug effect	0.219	0.398	0.918	0.008	0.974	0.974	0.205	0.430	0.872
Dry mouth	0.201	0.440	0.918	0.160	0.539	0.663	-0.080	0.760	0.872
Enhanced colour perception	-0.030	0.908	0.918	-0.444	0.074	0.380	-0.093	0.722	0.872
Enhanced sound perception	0.083	0.753	0.918	-0.302	0.238	0.625	0.091	0.728	0.872
Want to listen to music	-0.031	0.906	0.918	-0.083	0.751	0.801	0.254	0.325	0.872
Want food	-0.027	0.918	0.918	-0.229	0.378	0.625	0.313	0.221	0.872
Want more cannabis balloon	-0.156	0.551	0.918	-0.291	0.257	0.625	-0.237	0.359	0.872
Want to smoke cannabis	-0.071	0.787	0.918	-0.233	0.368	0.625	-0.257	0.319	0.872

VAS Item	Frontal Operculum			Medial Orbitofrontal cortex		
	r	p	p (FDR)	r	p	p (FDR)
Alert	0.319	0.212	0.436	-0.430	0.085	0.275
Happy	0.362	0.153	0.436	-0.276	0.284	0.499
Anxious	-0.241	0.352	0.481	-0.409	0.103	0.275
Paranoid	0.180	0.490	0.490	-0.510	0.036	0.203
Mentally impaired	0.395	0.117	0.436	-0.342	0.179	0.358
Stoned	0.243	0.347	0.481	-0.257	0.320	0.499
High	0.200	0.442	0.481	-0.139	0.595	0.680
Feel drug effect	0.233	0.369	0.481	-0.245	0.343	0.499
Like drug effect	0.421	0.092	0.436	-0.160	0.541	0.666
Dry mouth	0.221	0.394	0.481	-0.005	0.984	0.984
Enhanced colour perception	0.315	0.218	0.436	-0.615	0.009	0.144
Enhanced sound perception	0.436	0.080	0.436	-0.362	0.153	0.350
Want to listen to music	0.584	0.014	0.224	-0.088	0.736	0.785

Want food	0.329	0.198	0.436	-0.170	0.515	0.666
Want more cannabis balloon	0.200	0.441	0.481	-0.506	0.038	0.203
Want to smoke cannabis	0.291	0.257	0.791	-0.200	0.441	0.773

Table S8 and S9. Correlation coefficients between ROIs defined based on the results of the Cann-CBD treatment in the SAL (AI+) network, and visual analogue scale scores of subjective effects, taken in the same treatment session. Tables show Pearson's r , the uncorrected p values, and FDR-corrected p values for each region. Significant (FDR-corrected) p values are highlighted in bold text.

References

Yarkoni, T., Poldrack, R. A., Nichols, T. E., Van Essen, D. C., & Wager, T. D. (2011). Large-scale automated synthesis of human functional neuroimaging data. *Nature Methods*, 8(8), 665–670. <http://doi.org/10.1038/nmeth.1635>