AES-SDM tutorial, version May 2015

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The aim of this tutorial is to show, in a *step by step* basis, how to conduct a meta-analysis using SDM software. To this end, you will perform some of the analyses conducted in: *Radua J and Mataix-Cols D. Br J Psychiatry 2009; http://dx.doi.org/10.1192/bjp.bp.108.055046.* Note however that these analyses will be conducted with the updated, anisotropic effect-size-based algorithms (AES-SDM) described in: *Radua J et al. Eur Psychiatry 2012; http://dx.doi.org/10.1016/j.eurpsy.2011.04.001*, and *Radua J et al. Front Psychiatry 2014, http://dx.doi.org/10.3389/fpsyt.2014.00013*. Note also that this tutorial is distributed in the hope that it will be useful, but without any warranty on the accuracy of the text or the data.

Before executing the software

We have invested a lot of time and effort to improve the accuracy of the SDM methods and software. However, calculations might be biased if the following inclusion / exclusion criterion for peak coordinates is not considered when conducting the searches and contacts with the authors:

> *"While different studies may employ different thresholds, you should ensure that within one study the same threshold was used throughout the whole brain*"

This is of utmost importance because it is not uncommon in neuroimaging studies that some regions (e.g. a priori regions of interest) are more liberally thresholded than the rest of the brain.

Preparation of the files

Effect-size SDM allows the combination of statistical maps (in NIfTI format, obtained from e.g. SPM or FSL software) and peak coordinates (e.g. reported in the papers). For this tutorial we will only use peak coordinates, and for your convenience, the text files with this peak information have been already prepared in the folder containing this PDF. Take a look at the names and contents of these text files: coordinates are written in a separate text file for each study, and the filename is just a very short identification of the study (e.g. the name of the first author), plus a dot, plus the software and stereotactic space of the coordinates ("spm_mni", "fsl_mni", "other_mni", "spm_brett", "fsl_brett", "other_tal" or "no_peaks"), plus a dot, plus "txt". These are some of the sample text files:

Carmona.spm_mni.txt
40,39,21,-5.17

Gilbert.spm_mni.txt

```
-26,40,36,-5.73
6,4,72,-4.28
-48,2,36,-3.64
50,34,20,-5.17
20,26,48,-3.65
```

Note that each line specifies a coordinate and its *t* statistic. The coordinate is defined by the first three values (e.g. “40,39,21”), and the t statistic by the forth value (e.g. “-5.17”). Note also that the extension of these two sample files is *.spm_mni.txt, for what these coordinates are understood to be in SPM’s MNI space. The *t* statistic should be:

	A positive number for:	A negative number for:
One-sample fMRI studies:	task > baseline (activations)	task < baseline (deactivations)
Two-sample fMRI studies:	patients > controls in task > baseline (hyper-activations)	patients < controls in task > baseline (hypo-activations)
	patients < controls in task < baseline (failures of deactivation)	patients > controls in task < baseline (hyper-deactivations)
Two-sample VBM / FA studies:	patients > controls (increases of volume / FA)	patients < controls (decreases of volume / FA)

In a real meta-analysis you would have to carefully read the original papers of the studies, and sometimes noted that authors report z scores instead of t statistics. Fortunately, z scores may be straightforwardly converted to t statistics using the online converter that may be found at *http://www.sdmproject.com/utilities/?show=Statistics* (this website may be easily accessed by pressing the [Convert to t values] button within the SDM software).

In case of studies not reporting any measure related to effect size (*t* statistic, *z* score, *p* value, etcetera), you should write a “p” for positive peaks and an “n” for negative peaks. The SDM software conducts a pre-analysis to provide an effect size for these peaks.

IMPORTANT: Statistical maps in a standard stereotactic are preferred to any coordinate text file. If such images are obtained, use the [Convert images] button within the SDM software to prepare them for the analysis. Please contact us in case of questions (a user form may be found at http://www.sdmproject.com/).

Preparation of the SDM software

In this step you should first specify a working folder for the meta-analysis, and afterwards create an SDM table specifying at least the names of the studies and their sample sizes. The latter has been already prepared for you in this tutorial.

- Start the graphical user interface (GUI) SDM software:

  Linux users: to start the software click a file called "sdm" in the SDM software folder. If the program does not execute follow the instructions to change file permissions at http://www.sdmproject.com/software/?show=Linux

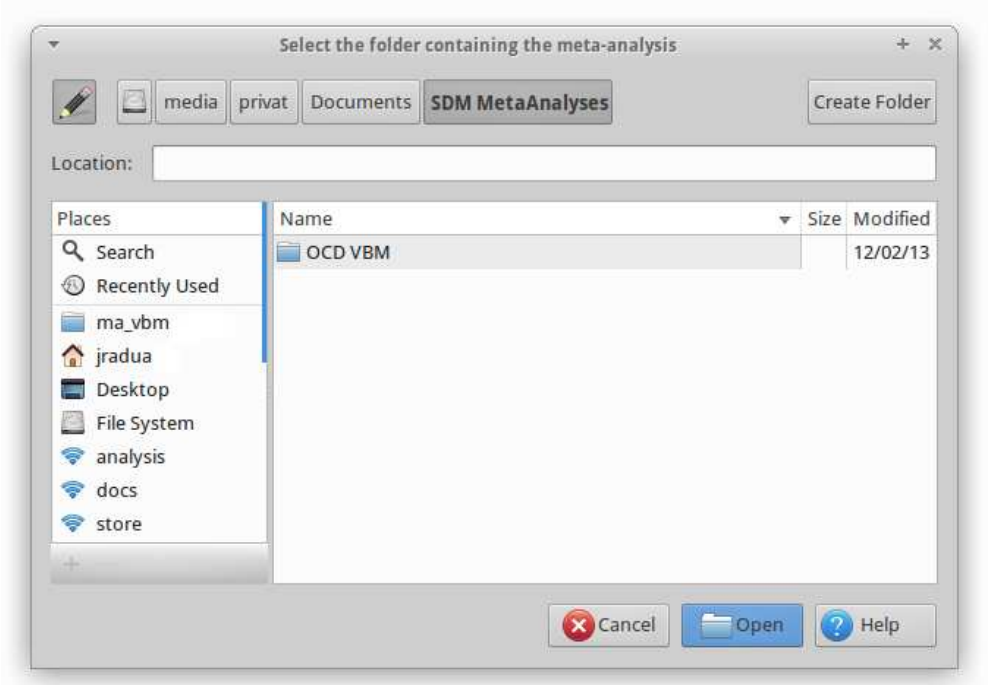
  Mac OSX users: unfortunately, SDM for Mac does not currently include a GUI. However, the analyses may still be conducted typing rather straightforward commands in the terminal. Please see the "How to do it using the terminal" boxes throughout the tutorial.

  Windows users: to start the software click a file called "sdm.bat" in the SDM software folder.

One or two red warnings might be printed in the GUI screen if you haven't used this software before: one complaining about the working folder, and another complaining about the MRIcron program.

- To specify the working folder for the meta-analysis, click the [Change folder / meta-analysis] button, look for the "home/tutorial" folder containing this PDF (within the SDM software folder), and click [Open].

  A dialog similar to the following one should appear:

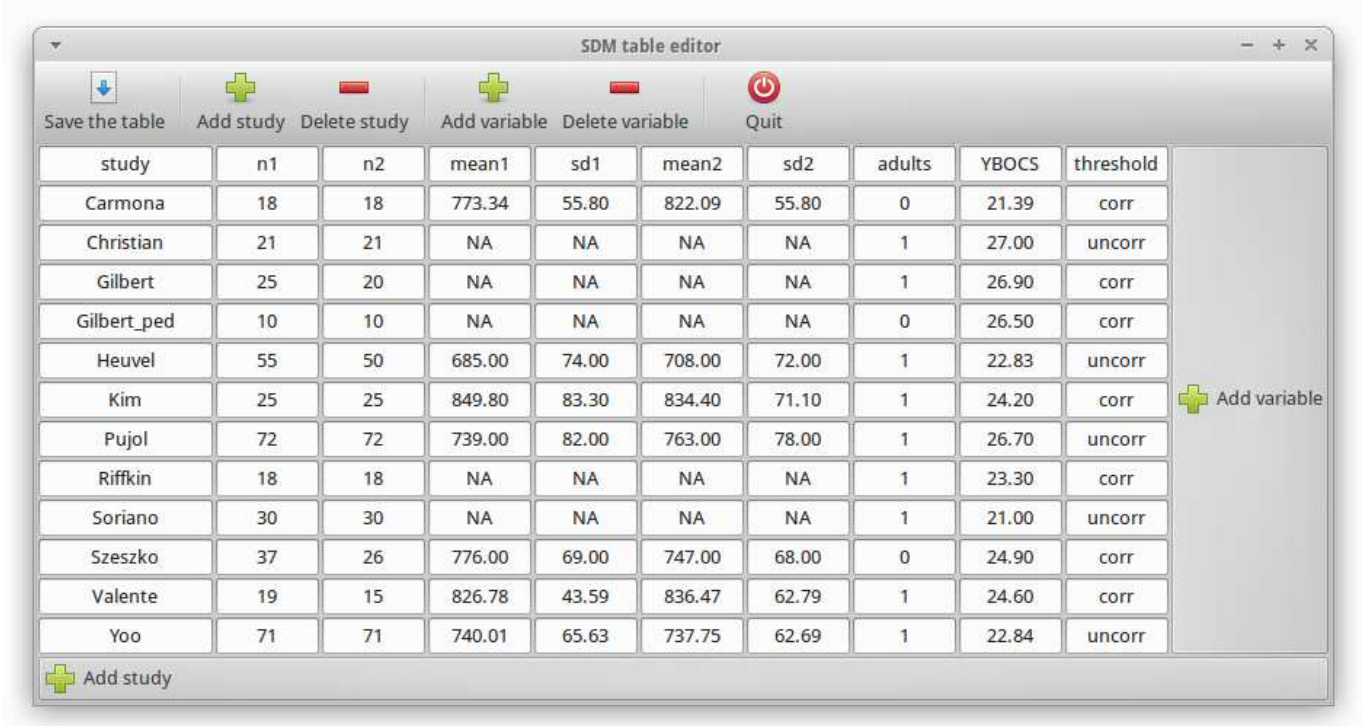


- If SDM software did not found MRIcron or FSLView, you can manually specify its location with the following steps: open the [Tools] menu, select [Settings], click the selection box at the right of [Brain viewer executable], look for the folder which contains the MRIcron or FSLView program (typically something like "C:\Program Files\MRIcroN" in Windows), click [Open] and click [OK].

  A dialog similar to the following one should appear:

- To create or edit the SDM table, click the button [SDM table editor] button.

  A window similar to the following one should appear:



study	n1	n2	mean1	sd1	mean2	sd2	adults	YBOCS	threshold
Carmona	18	18	773.34	55.80	822.09	55.80	0	21.39	corr
Christian	21	21	NA	NA	NA	NA	1	27.00	uncorr
Gilbert	25	20	NA	NA	NA	NA	1	26.90	corr
Gilbert_ped	10	10	NA	NA	NA	NA	0	26.50	corr
Heuvel	55	50	685.00	74.00	708.00	72.00	1	22.83	uncorr
Kim	25	25	849.80	83.30	834.40	71.10	1	24.20	corr
Pujol	72	72	739.00	82.00	763.00	78.00	1	26.70	uncorr
Riffkin	18	18	NA	NA	NA	NA	1	23.30	corr
Soriano	30	30	NA	NA	NA	NA	1	21.00	uncorr
Szeszko	37	26	776.00	69.00	747.00	68.00	0	24.90	corr
Valente	19	15	826.78	43.59	836.47	62.79	1	24.60	corr
Yoo	71	71	740.01	65.63	737.75	62.69	1	22.84	uncorr

Each row in the SDM table specifies one study. In this example, the first column sets the identification of the study (exactly the same than in the text files), the second column specifies the size of the patients' sample ("n1"), the third column the size of the controls' sample ("n2"), the 4th-7th columns optional global

gray matter values, the 8th-9th columns optional variables, and the 10th column a special optional variable called “threshold”, which may be used to specify the threshold type (e.g. “uncorrected” vs “corrected”) used in each study. In case of meta-analyses that only involve healthy controls, the second column (“n1”) should be the size of the samples, and no column should be called “n2”.

How to do it using the terminal (REQUIRED FOR MAC OSX USERS)

To change the directory use the command “cd” e.g. to follow this tutorial and assuming that your SDM software folder is within your Documents folder, you should type something similar to:

`cd Documents/sdm/home/tutorial`	(Linux or Mac OSX)
`cd Documents\sdm\home\tutorial`	(Windows)

Afterwards you should create or modify a text file called “sdm_table.txt” with the information of the SDM table using any text or spreadsheet editor (the file has been already created for this tutorial, but please open and inspect it). To open a text editor from the terminal you may type something similar to:

`gedit sdm_table.txt`	(Linux) Note: you may use any other text editor included in your distribution, e.g. “kwrite”, “mousepad” and etcetera.
`open –a TextEdit sdm_table.txt`	(Mac OsX) Note: if the file “sdm_table.txt” doesn’t exist, you can create it typing: **`echo "" > sdm_table.txt`**
`notepad.exe sdm_table.txt`	(Windows)

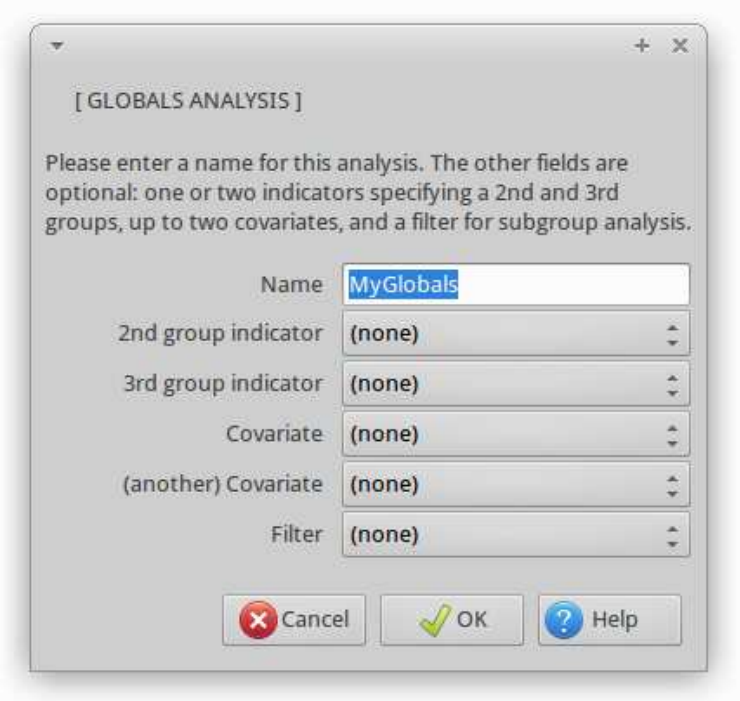
To minimize the risk of errors when SDM reads the file “sdm_table.txt”, I would suggest that when filling it you don’t use any character other than numbers and simple letters (apart from the tabs to separate the columns).

“Globals” analysis

Prior to the voxel-based meta-analysis, you may want to conduct an analysis of the global gray matter volumes. To this end, the following variables must be defined in the SDM table: “mean1” and “mean2” (global gray matter means), and “sd1” and “sd2” (global gray matter standard deviations).

- To conduct the “globals” analysis, click the button [Globals], and click [OK] twice.

A dialog similar to the following one should appear:



This will create and automatically open a web-like file called “globals_MyGlobals.htm” with standard meta-analytic measures for global gray matter. The most important measures are the mean (Hedge’s δ along with its corresponding *Z* and *P* values and the confidence interval) and the analysis of heterogeneity (τ and its corresponding Q and *P* values).

How to do it using the terminal (REQUIRED FOR MAC OSX USERS)

To calculate the global mean and name it “MyGlobals”, just type the following:

```
[SDM] MyGlobals = globals
```

Important: here and in any subsequent call to SDM software you have to replace `[SDM]` by the path of the SDM software, e.g.

```
~/Documents/sdm/sdm MyGlobals = globals
```
(Linux)

```
~/Documents/sdm/sdm_mac MyGlobals = globals
```
(Mac OSX)

```
C:\Users\john\Documents\sdm\sdm.exe MyGlobals = globals
```
(Windows)

If you wish to conduct a more complex analysis or to include covariates, just add the name of the corresponding variables (as it appears in the “sdm_table.txt” file) separated by pluses, e.g.

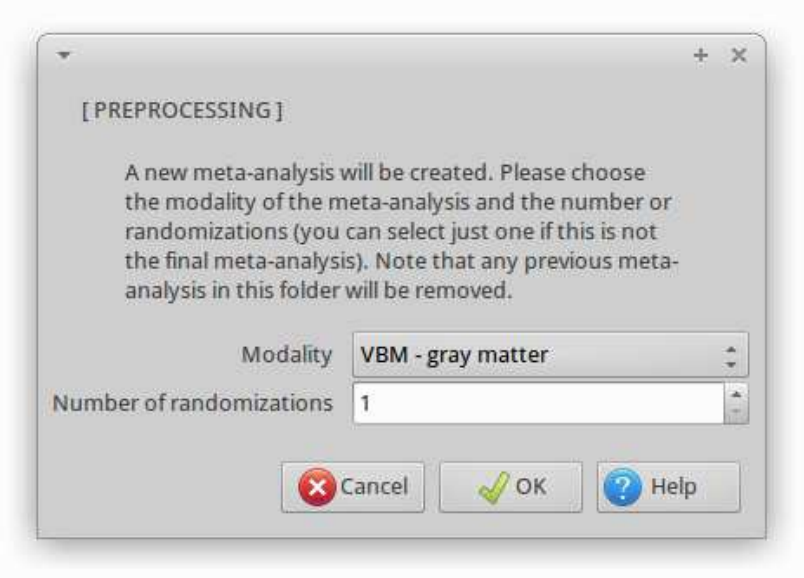
```
sdm ybocs = globals YBOCS + age
```

Pre-processing

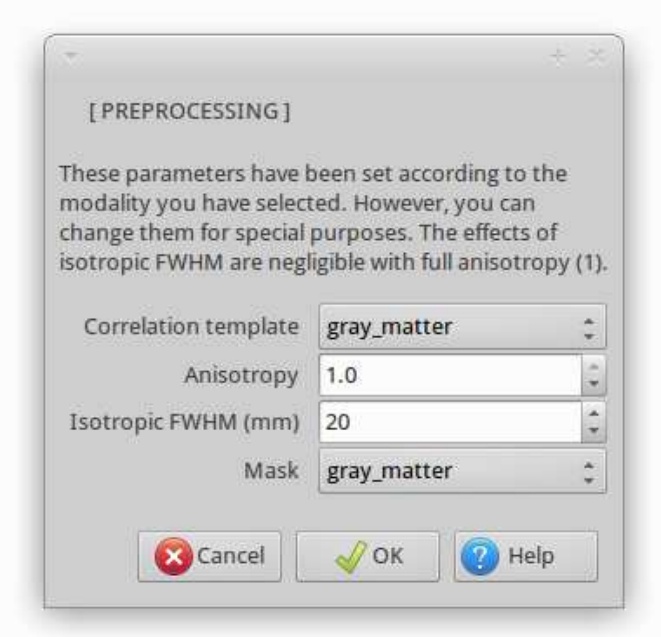
In this step SDM will use the coordinates' text files to recreate the effect-size brain maps of the original studies. Voxels from these brain maps will be then randomly permuted to create Monte Carlo brain maps, useful for estimating the null distributions of the subsequent analyses.

- To pre-process the studies, click the button [Preprocessing], select the [VBM - gray matter] modality, and click [OK].

  A dialog similar to the following one should appear:



  Click [OK] and the following technical dialog will appear. Simply click [OK] again.



This will create:

- A web-like file called “pp.htm” which will be automatically opened. You should check that the absolute maximum and minimum peaks reported in the summary of “pp.htm” roughly correspond to those reported in the original manuscripts. Pay special attention to check the side (left vs. right).
- Two “pp_*.nii.gz” brain image files for each study: one for effect sizes and the other for their variances.

… as well as the following system files:

- An image with the meta-analytic mask (“sdm_mask.nii.gz”).
- A text file with the names of the maps (“sdm_maps.txt”). The subsequent analyses will add the names of the resulting maps to this file.
- A set of “sdm_r*.bin” binary files which contain the Monte Carlo randomizations. Notice that you specified only 1 randomization, but in a real meta-analysis several randomizations are recommended.
- A text file that will contain the null distributions of the subsequent analyses (“sdm_nd.txt”).

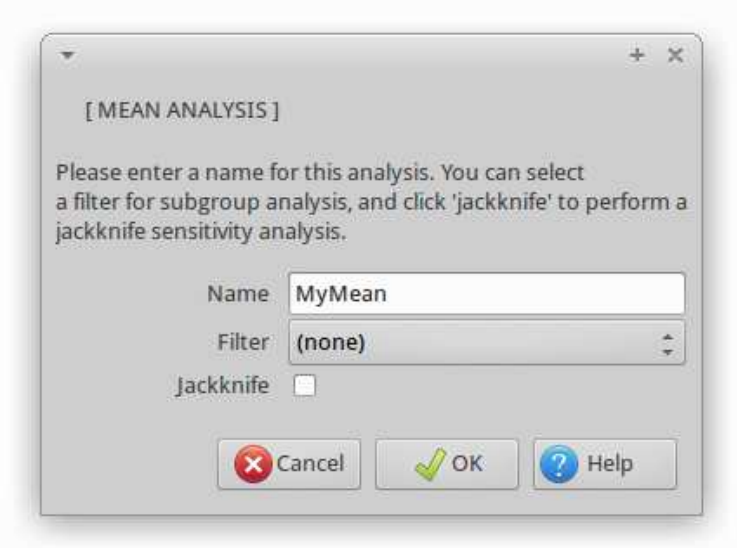
How to do it using the terminal (REQUIRED FOR MAC OSX USERS)
To pre-process using the gray matter correlation template, with full anisotropy (1.0) and 20mm FWHM, within the gray matter mask and conducting 1 randomization, type the following: **`sdm pp gray_matter, 1.0, 20, gray_matter, 1`**

Mean analysis

Now it's time to conduct the mean analysis, which is usually the main (but not the only!) outcome of a meta-analysis. In this tutorial, the mean analysis represents the weighted mean difference in regional grey matter between patients with OCD and healthy controls.

➢ To conduct the mean analysis, click the button [Mean], specify a name for this analysis (we will call it “MyMean”) and click [OK].

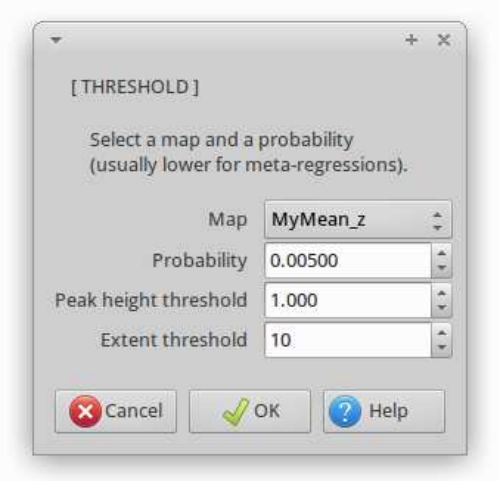
A dialog similar to the following one should appear:



This will create the mean and the between-study heterogeneity estimates, variance or I^2, z and probability maps ("MyMean_z_var/z/p.nii.gz" and "MyMean_z_I2/QH_z/p.nii.gz") and new web-like and text files ("MyMean_z.htm/txt" and "MyMean_z_QH.htm/txt") with the statistical thresholds obtained after calculating the mean and the heterogeneity in each randomization for diagnostic purposes. The name and null distribution for these maps are added to the "sdm_maps.txt" and "sdm_nd.txt" files.

- To threshold and see the results, click the button [Threshold], click [OK], select the "MyMean_z" map, and click [OK].

  A dialog similar to the following one should appear:



This will create and automatically open a web-like file called something like "MyMean_z_p0.00500_1.000_10.htm" with several statistics, coordinates and brain regional breakdowns, and will also start the MRIcron or FSLView program to visually inspect them. The following images will be also created:

- MyMean_z_p0.00500_1.000_10.nii.gz (positive statistically significant differences)

- MyMean_z_p0.00500_1.000_10_p.nii.gz (p-values of the positive differences)
- MyMean_z_p0.00500_1.000_10_neg.nii.gz (negative statistically significant differences).
- MyMean_z_p0.00500_1.000_10_neg_p.nii.gz (p-values of the negative differences).
- Masks for each blob.

Important: Please notice that the *p* values of SDM *z* scores have been found using randomizations, and they are usually much different from the *p* values associated to standard *z* scores!

How to do it using the terminal (REQUIRED FOR MAC OSX USERS)

To calculate the mean and threshold it using a p-value = 0.005, z = 1 and 10 voxels extent, type the following:

```
sdm MyMean = mean
sdm threshold MyMean_z, p, 0.005, 1, 10
```

Visual inspection of heterogeneity

To obtain a map of the inter-study heterogeneity (in which Q_H statistics have been converted into *z* scores), click the button [Threshold], select the "MyMean_z_QH" map, and click [OK].

This map should be only taken for guidance, e.g. to know which brain regions are more heterogeneous. Its exact values, however, should be taken with caution as the recreation of maps from peak coordinates might result in highly inflated statistics.

Important: It is strongly recommended to extract values from relevant peaks (see later), and inspect their funnel plots with Excel, R or any other program that you use for standard meta-analyses. Note however that studies with null *z* scores (i.e. because no peak coordinates were reported in the proximity of the voxel) will all be in a straight line, thus creating "artificially ugly" plots!

Subgroup analysis of adult samples

This is similar to the mean analysis, with the exception that you will specify the "adults" filter in order that only studies with adult samples are included in the analysis.

- To conduct the subgroup analysis, click the button [Mean], specify a name for this analysis (we will call it "myAdults"), select the "adults" filter, and click [OK].
- To threshold and see the results, click the button [Threshold], click [OK], select the "myAdults_z" map, and click [OK].

Tip: Please notice that you will be able to threshold any time any result from previous analyses, you do not have to conduct the calculations again!

How to do it using the terminal (REQUIRED FOR MAC OSX USERS)

To calculate the subgroup mean and threshold it, type the following:

```
sdm myAdults = mean, adults
sdm threshold myAdults_z, p, 0.005, 1, 10
```

Jackknife sensitivity analysis

This is again similar to the mean analysis, with the exception that you will select the "Jackknife" option. Note that this analysis is only to assess the robustness (specifically the sensitivity); you must still conduct the "main" mean analysis described above.

- To conduct the jackknife analysis, click the [Mean] button, specify a name for this analysis (we will call it "MyMean" again), select the "Jackknife" option, and click [OK].

The software will repeat the mean analysis several times, including each time all the studies but one. The names of the resulting maps will be "MyMean", plus "JK", plus the name of the discarded study. E.g. the analysis including all the studies but "Carmona" will be called "MyMeanJKCarmona".

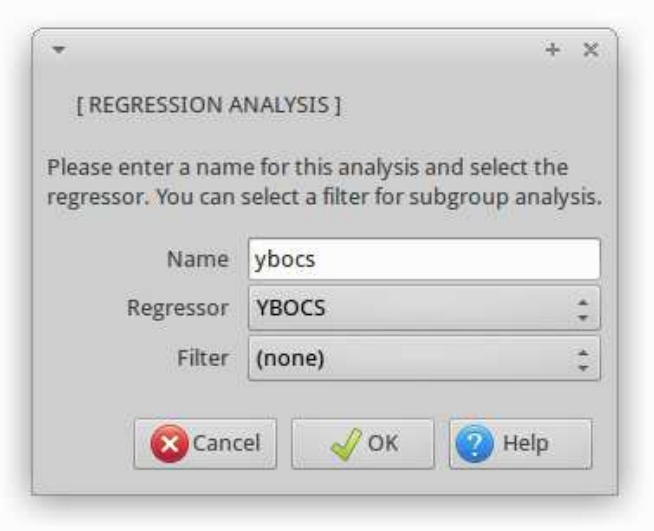
- To threshold and see the results, click the [Threshold] button, click [OK], select one of the maps (e.g. "MyMeanJKCarmona_z"), and click [OK].

Meta-regression by YBOCS

The last analysis of this tutorial will be a meta-regression of voxel values across the studies by the YBOCS of the corresponding patients' samples.

- To conduct the regression analysis, click the button [Linear model], select [Meta-regression] and click [OK], specify a name for this analysis (e.g. "ybocs"), select "YBOCS" as the regressor, and click [OK].

A dialog similar to the following one should appear:



This will create three maps: "ybocs_1" (differences between patients with maximum YBOCS and healthy controls), "ybocs_0" (differences between patients with minimum YBOCS and healthy controls), and "ybocs_1m0" (differences between patients with maximum YBOCS and patients with minimum YBOCS).

- To threshold and see the results, click the button [Threshold] button, click [OK], select one of the analyses (e.g. "ybocs_1_z"), specify a conservative probability if the "_1m0" map, and click [OK].

Please remember that statistical significance of these meta-regressions should be taken with caution.

How to do it using the terminal (REQUIRED FOR MAC OSX USERS)
To calculate the regression and threshold its output maps, type the following: **sdm ybocs = lm YBOCS** **sdm threshold ybocs_0_z, p, 0.005, 1, 10** **sdm threshold ybocs_1m0_z, p, 0.0005, 1, 10** **sdm threshold ybocs_1_z, p, 0.005, 1, 10**

Extraction of values

Extraction of values is needed in order to create graphics such as funnel or meta-regression plots with Microsoft Excel, R or similar software, either for providing figures for a publication or for visually inspecting the heterogeneity or publication bias. You should first create a mask that includes the voxel or region from where you want to extract the values, and then extract these values using the mask. In this tutorial you will extract values from the voxel (MNI: -24,10,-2), located in left putamen nucleus.

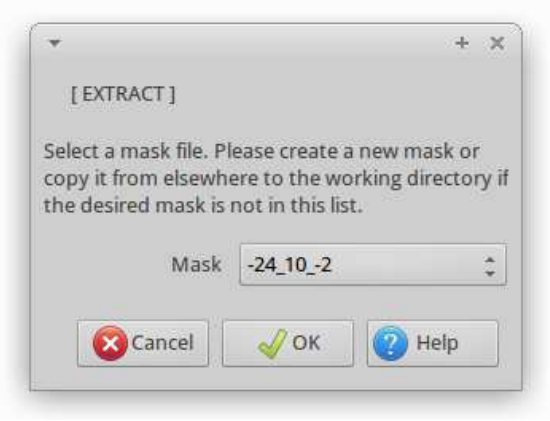
- To create the mask, click the [Create a mask] button, select [MNI coordinate], click [OK], type the coordinate (X = -24, Y = 10, Z = -2), and click [OK].

A dialog similar to the following one should appear:

This will create a file called “mask_-24_10_-2.nii.gz” which contains the mask. Note that you can copy this file to the folder of another meta-analysis in order to avoid creating it again.

- To extract the values using this mask, click the [Extract] button, select “-24_10_-2”, and click [OK].

A dialog similar to the following one should appear:



This will create and automatically open a web-like file called “extract_-24_10_-2.htm” with the gray matter values of each map in this voxel. A text file will be also created for programming purposes.

How to do it using the terminal (REQUIRED FOR MAC OSX USERS)

To create the mask and extract the values, type the following:

sdm -24_10_-2 = mask coordinate, -24, 10, -2
sdm extract -24_10_-2

To create a mask of an atlas structure please use the codes below (which could change in future versions of SDM!). E.g. to create a mask of the left anterior commissure and name it “ac”, type the following:

sdm ac = mask label, 117

Atlas codes (subject to change)

Anterior commissure	117
Cerebellum, vermic lobule I / II	109
Cerebellum, vermic lobule III	110
Cerebellum, vermic lobule IV / V	111
Cerebellum, vermic lobule VI	112
Cerebellum, vermic lobule VII	113
Cerebellum, vermic lobule VIII	114
Cerebellum, vermic lobule IX	115
Cerebellum, vermic lobule X	116
Corpus callosum	132
Left amygdala	41
Left angular gyrus	65
Left anterior cingulate / paracingulate gyri	31
Left anterior thalamic projections	118
Left arcuate network, anterior segment	120
Left arcuate network, long segment	122
Left arcuate network, posterior segment	124
Left calcarine fissure / surrounding cortex	43
Left caudate nucleus	71
Left cerebellum, crus I	91
Left cerebellum, crus II	93
Left cerebellum, hemispheric lobule III	95
Left cerebellum, hemispheric lobule IV / V	97
Left cerebellum, hemispheric lobule VI	99
Left cerebellum, hemispheric lobule VIIB	101
Left cerebellum, hemispheric lobule VIII	103
Left cerebellum, hemispheric lobule IX	105
Left cerebellum, hemispheric lobule X	107
Left cortico-spinal projections	133
Left cuneus cortex	45
Left face U tract	135
Left frontal aslant tract	137
Left frontal inferior longitudinal fasciculus	140
Left frontal orbito-polar tract	142
Left frontal superior longitudinal	144
Left fronto-insular tract 1	146
Left fronto-insular tract 2	148
Left fronto-insular tract 3	150
Left fronto-insular tract 4	152
Left fronto-insular tract 5	154
Left fronto-marginal tract	156
Left fusiform gyrus	55
Left gyrus rectus	27
Left hand inferior U tract	158
Left hand middle U tract	160
Left hand superior U tract	162
Left heschl gyrus	79
Left hippocampus	37
Left inferior frontal gyrus, opercular part	11
Left inferior frontal gyrus, orbital part	15
Left inferior frontal gyrus, triangular part	13
Left inferior network, inferior fronto-occipital fasciculus	164
Left inferior network, inferior longitudinal fasciculus	166
Left inferior network, uncinate fasciculus	129

Right inferior network, uncinate fasciculus	131
Right inferior occipital gyrus	54
Right inferior parietal (excluding supramarginal and angular) gyri	62
Right inferior temporal gyrus	90
Right insula	30
Right lenticular nucleus, pallidum	76
Right lenticular nucleus, putamen	74
Right lingual gyrus	48
Right median cingulate / paracingulate gyri	34
Right median network, cingulum	130
Right middle frontal gyrus	8
Right middle frontal gyrus, orbital part	10
Right middle occipital gyrus	52
Right middle temporal gyrus	86
Right olfactory cortex	22
Right optic radiations	169
Right paracentral lobule	70
Right paracentral U tract	171
Right parahippocampal gyrus	40
Right pons	173
Right postcentral gyrus	58
Right posterior cingulate gyrus	36
Right precentral gyrus	2
Right precuneus	68
Right rolandic operculum	18
Right striatum	128
Right superior frontal gyrus, dorsolateral	4
Right superior frontal gyrus, medial	24
Right superior frontal gyrus, medial orbital	26
Right superior frontal gyrus, orbital part	6
Right superior longitudinal fasciculus I	175
Right superior longitudinal fasciculus II	177
Right superior longitudinal fasciculus III	179
Right superior occipital gyrus	50
Right superior parietal gyrus	60
Right superior temporal gyrus	82
Right supplementary motor area	20
Right supramarginal gyrus	64
Right temporal pole, middle temporal gyrus	88
Right temporal pole, superior temporal gyrus	84
Right thalamus	78