SDM-PSI tutorial, version Jan 2019

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The aim of this tutorial is to show how to conduct a meta-analysis using SDM-PSI software. To this end, you will perform some of the analyses conducted in https://doi.org/10.1192/bjp.bp.108.055046.

Note however that these analyses will be conducted with the updated, SDM-PSI algorithms described in https://doi.org/10.1016/j.neuroimage.2018.10.077, based on the previous works in http://dx.doi.org/10.1016/j.eurpsy.2011.04.001, https://doi.org/10.3389/fpsyt.2014.00013 and https://10.42.0.1/10.1016/j.neuroimage.2018.04.065.

We distribute this tutorial 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, it may yield biased estimations if you not consider the following inclusion / exclusion criterion for peaks 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 rare 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

SDM allows the combination of statistical maps (in NIfTI format, obtained from e.g., SPM or FSL software) and peak information (e.g., reported in the papers). For this tutorial, we will only use peak information, and for your convenience, the text files with this peak information have been already prepared in the folder containing this PDF.

Look at the names and contents of these text files. Coordinates and t-values of the peaks 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 an identification of the software used in the study and stereotactic space of the peak coordinates, plus a dot, plus "txt".

Possible identifications of the software and stereotactic space are:

- *.spm_mni: for SPM studies, reported in MNI space. Very common!
- *.fsl_mni: for FSL studies, reported MNI space. Very common!
- *.other_mni: for studies that used other software, reported MNI space.
- *.spm_brett: for SPM studies, with Brett conversions. Old studies!
- *.fsl_brett: for FSL studies, with Brett conversions.
- *.other_brett: for studies that used other software, with Brett conversions
- *.spm_tal: for SPM studies, reported in Talairach space.
- *.fsl_tal: for FSL studies, reported in Talairach space.
- *.other_tal: for studies that used other software, reported in Talairach space.
- *.no_peaks: whenever there are no peaks, independently of the software and stereotactic space.

These are some of the sample text files:

Carmona.spm_mni.txt

```
40,39,21,-5.14
53,27,21,-3.77
56,23,20,-3.63
...
```

Christian.no_peaks.txt

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., "-5.14"). The extension of the first file is *.spm_mni.txt, for what these coordinates are understood to be in SPM's MNI space. The extension of the second file is *.no_peaks.txt because that study reported no peaks.

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 read carefully the original papers of the studies, and sometimes you might notice that authors report z scores instead of t statistics. You may straightforwardly convert z scores into t statistics using the online converter at https://www.sdmproject.com/utilities/?show=Statistics (you may access this website pressing the [Convert peaks] 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 peak information file. If you are able to obtain these images, use the [Convert images] button within the SDM software to prepare them for the analysis.

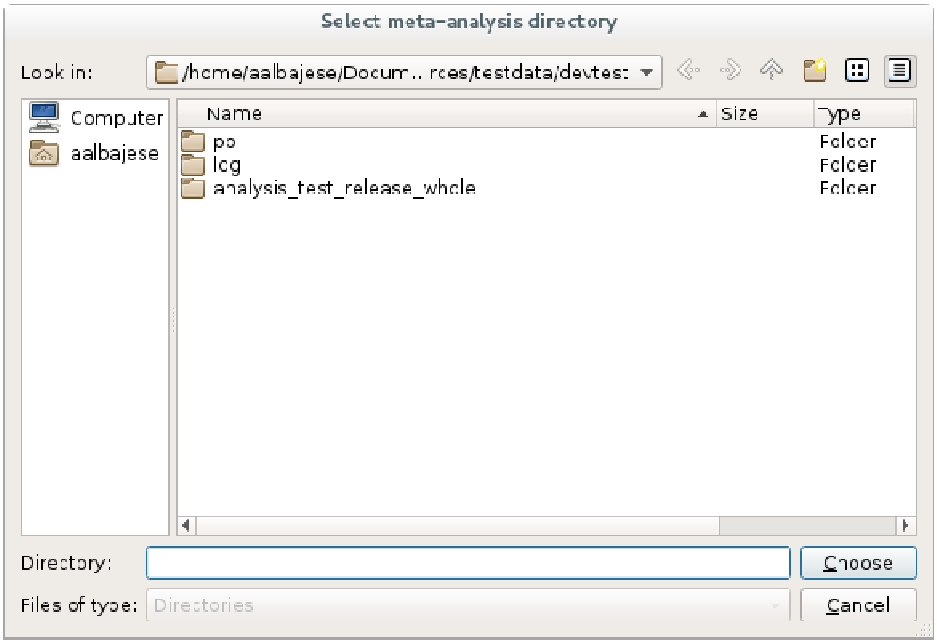
Preparation of the SDM software

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. We prepared the latter for you in this tutorial.

IMPORTANT: To prevent errors, run SDM software from a local disk (rather than from a network drive).

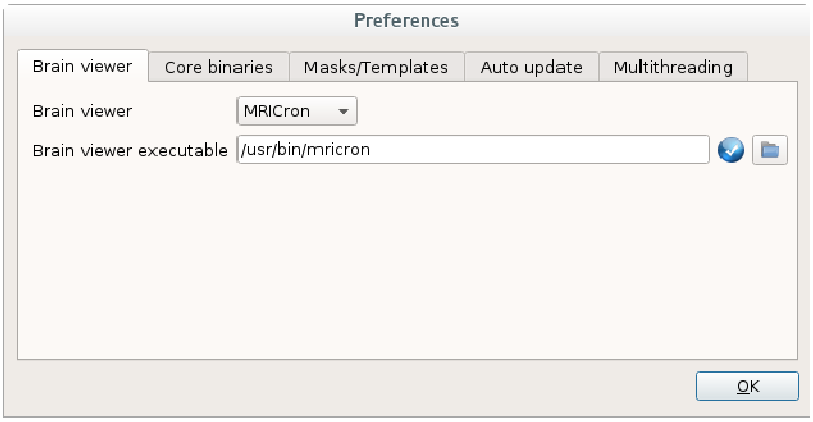
- Start the graphical user interface (GUI) SDM software:
  - *Linux users:* to start the software click a file named “SdmPsiGui” / “SdmPsiGui.desktop” in the SDM software folder. If the program does not execute follow, the instructions to change file permissions at https://www.sdmproject.com/software/?show=Linux
  - *Mac OSX users:* to start the software click a file named "SdmPsiGui" / “SdmPsiGui.app”. If the program does not execute follow, the instructions to change file permissions at https://www.sdmproject.com/software/?show=Mac
  - *Windows users:* to start the software click a file named “SdmPsiGui” / “SdmPsiGui.exe” in the SDM software folder. If the program does not execute follow, the instructions to change file permissions at https://www.sdmproject.com/software/?show=Windows
- To specify the working folder for the meta-analysis, click the [Change meta-analysis] button, look for the “home/tutorial” folder containing this PDF (within the SDM software folder), and click [Choose].

  A dialog similar to the following one should appear:



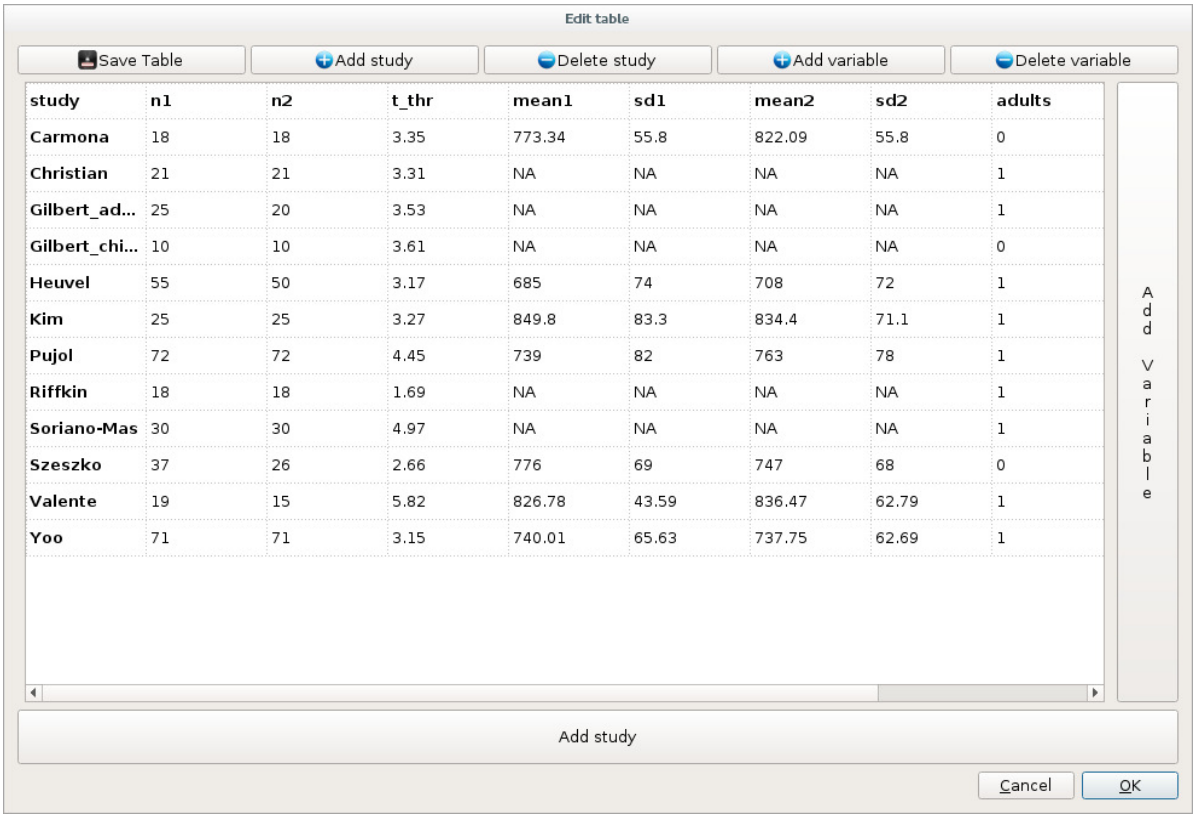
- If SDM software did not found MRIcron, you can manually specify its location with the following steps: open the [Tools] menu, select [Preferences], select the [Brain viewer] tab, and change the [Brain viewer executable] (look for the MRIcron program, typically something like "C:\Program Files\MRIcron\mricron.exe" in Windows). Then click [Open] and [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	t_thr	mean1	sd1	mean2	sd2	adults
Carmona	18	18	3.35	773.34	55.8	822.09	55.8	0
Christian	21	21	3.31	NA	NA	NA	NA	1
Gilbert_ad...	25	20	3.53	NA	NA	NA	NA	1
Gilbert_chi...	10	10	3.61	NA	NA	NA	NA	0
Heuvel	55	50	3.17	685	74	708	72	1
Kim	25	25	3.27	849.8	83.3	834.4	71.1	1
Pujol	72	72	4.45	739	82	763	78	1
Riffkin	18	18	1.69	NA	NA	NA	NA	1
Soriano-Mas	30	30	4.97	NA	NA	NA	NA	1
Szeszko	37	26	2.66	776	69	747	68	0
Valente	19	15	5.82	826.78	43.59	836.47	62.79	1
Yoo	71	71	3.15	740.01	65.63	737.75	62.69	1

Each row in the SDM table specifies one study. In this example, the first column ("study") sets the identification of the study (the same than in the text files). The second and third columns specify the size of the patients' sample ("n1") and of the controls' sample ("n2"). The fourth column ("t_thr") specifies the t-value threshold of statistical significance used in each study, which you might sometimes find in the manuscript or its figures (e.g. something such as "t > 4.3"). If you are unsure, a conservative option might be typing the t-value corresponding to p=0.001 uncorrected (about 3.1, larger in smaller studies). However, if authors applied cluster-based statistics, we suggest using the t-value threshold used to create clusters, which may be <3.1.

The 5th-8th columns specify optional global gray matter values, and the 9th-10th columns optional variables. You could also add a special optional column, called "threshold", 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 you should not call any column "n2".

How to do it using the terminal

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 named "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)

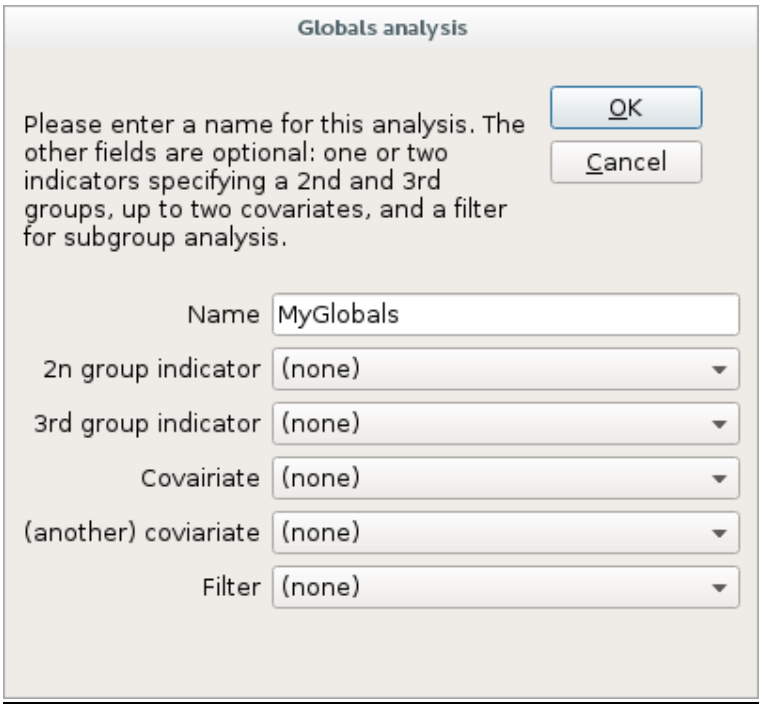
To minimize the risk of errors when SDM reads the file "sdm_table.txt", do not type any character other than numbers and simple letters (apart from the tabs to separate the columns).

"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].

  A dialog similar to the following one should appear:



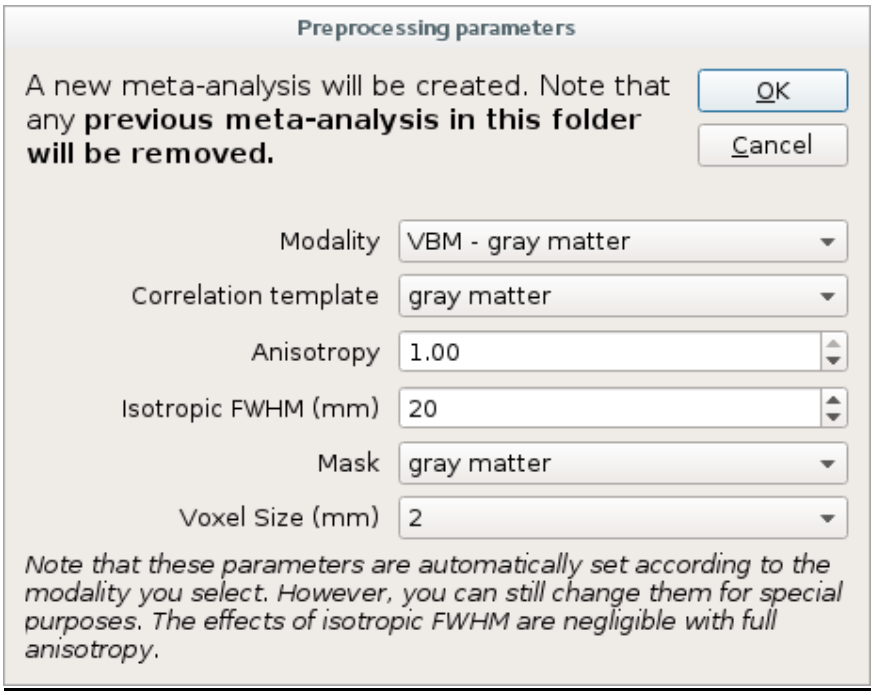
This will create and automatically open a web-like file named "globals_MyGlobals.htm" with standard meta-analytic measures for global gray matter. The most important measures are the mean (Hedge's *g* along with its corresponding Z and *P* values and the confidence interval) and the analysis of heterogeneity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

Pre-processing

In this step, SDM will use the peaks' text files to voxelwise recreate the lower and upper bounds of the possible effect-size values of the studies.

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

  A dialog similar to the following one should appear:



This will create a folder named "pp" that will contain:

- A web-like file named "pp.htm", which the software will open automatically. 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).

- Four "*.nii.gz" brain image files for each study: two for the lower and upper bounds of the possible effect size and two for the lower and upper bound of the possible t-values.

It will also create the following system files:

- An image with the meta-analytic mask ("sdm_mask.nii.gz").

- A file for study settings named "sdmpsi_params.xml", which may be useful for modifying some parameters when working from the console. Please be aware that the integrity of this xml file is

required to SDM-PSI to be able to execute normally. Therefore, we strongly suggest the user to manipulate this file with the utmost care.

- A file stamping the preprocessing step as done ("sdm_maps.txt"). In absence of this file, the GUI will require the user to perform the preprocessing step before running Mean or Linear Model steps.

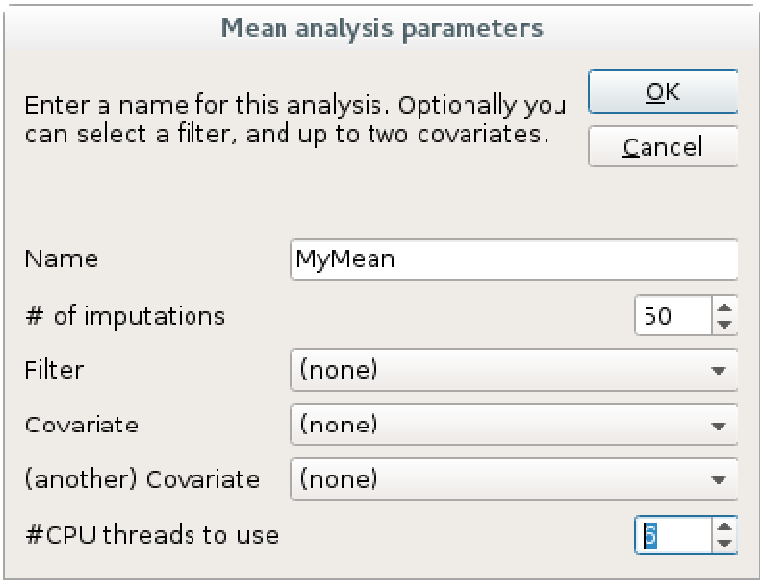
How to do it using the terminal
To pre-process using the gray matter correlation template, with full anisotropy (1.0) and 20mm FWHM, within the gray matter mask and using a voxel size of 2mm, type the following: `sdm pp gray_matter,1.0,20,gray_matter,2` **Important:** here and in any subsequent call to SDM software you have to replace `sdm` by the path of the SDM software, e.g. `~/Documents/sdm/sdm pp gray_matter,1.0,20,gray_matter,2` (Linux) `~/Documents/sdm/sdm_mac pp gray_matter,1.0,20,gray_matter,2` (OSX) `C:\Users\john\Documents\sdm\sdm.bat pp gray_matter,1.0,20,gray_matter,2` (Windows)

Mean analysis

Now it is 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 a folder named "analysis_MyMean" with a folder for the multiple imputations ("mi"), a folder for the beta coefficients ("betaMaps"), the mean map ("_g") with its variance ("_var") and z-value ("_z"), and the between-study heterogeneity maps (τ^2, H^2, I^2 and Q test). It will also create a folder named "log" with internal files describing which kernel has been applied to each of the voxels in the imputations process.

- To correct for multiple comparisons, click the button [FWE correction], specify the number of CPU threads to use, and click [OK].

We strongly suggest you to increase the number of CPU threads to use to a value close to the maximum available on your machine (you can see this maximum value at the "preferences" dialog of SdmPsiGui). However, one way or another, it will take a lot of time!

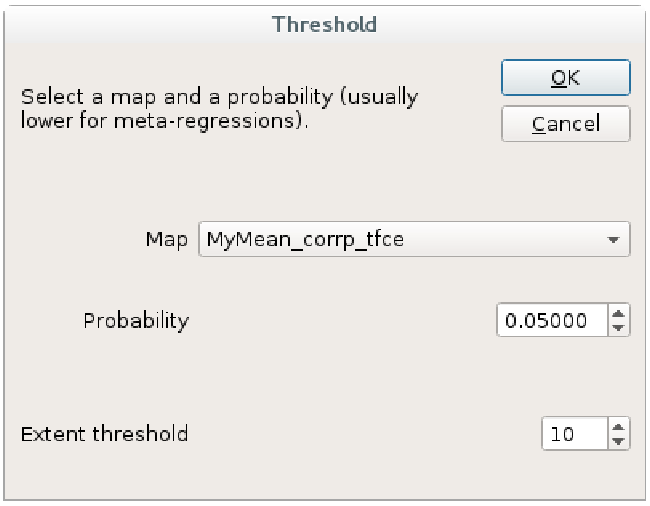
Do anything else while the software works…

Take also a coffee…

After a long, long time, it will finished. It will have created a folder for the distribution of the maximum statistics ("fwe") and the maps of corrected p-values ("corrp_*").

- To threshold and see the results, click the button [Threshold], select the map of TFCE-corrected values and click [OK].

  A dialog similar to the following one should appear:



This will create and automatically open a web-like file named something like "MyMean_z_p0.05000_10.htm" with several statistics, coordinates and brain regional breakdowns, and it will start the MRIcron program to inspect visually them. In addition, it will create the following images:

- MyMean_z_p0.05000_10.nii.gz (positive statistically significant differences)
- MyMean_z_p0.05000_10_p.nii.gz (p-values of the positive differences)
- MyMean_z_p0.05000_10_neg.nii.gz (negative statistically significant differences).
- MyMean_z_p0.05000_10_neg_p.nii.gz (p-values of the negative differences).
- A folder with masks for each blob and peak.

How to do it using the terminal
To calculate the mean and threshold it using a p-value = 0.05, and 10 voxels extent, type the following (at this point you may want to very carefully modify the file sdmpsi_params.xml and raise the number of CPU threads to use, variable): **sdm MyMean=mi 50** **sdm perm 1000,MyMean** **sdm threshold analysis_MyMean/corrp_tfce,analysis_MyMean/MyMean_z,0.05,10**

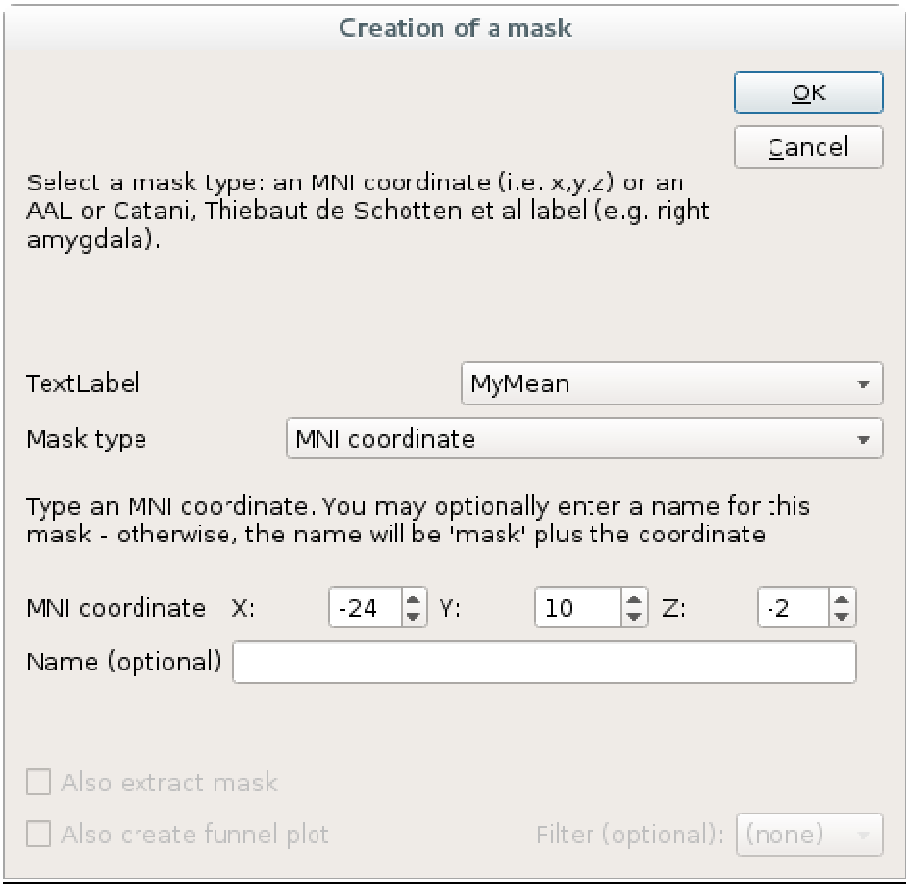
Assessment of heterogeneity and potential publication bias

We strongly recommend extracting values from relevant peaks, inspecting the corresponding I^2 statistics (or other heterogeneity estimates) and check their funnel plots. You may also use extracted values to create meta-regression plots with Microsoft Excel, R or similar software.

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. Fortunately, the "Thresholding" automatically creates the masks for the peaks.

- 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].

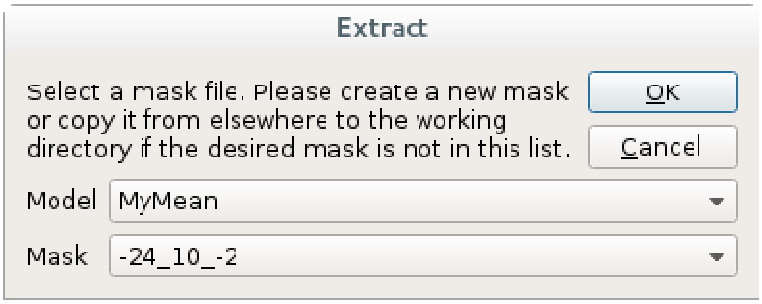
A dialog similar to the following one should appear:



This will create a file named "analysis_MyMean/masks/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 model "MyMean", 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 named "analysis_MyMean/extracts/extract_-24_10_-2.htm" with the gray matter values of each map in this voxel. In addition, it will create a simple text file for programming purposes.

How to do it using the terminal
To create the mask and extract the values, type the following: **sdm -24_10_-2 = mask MyMean, coordinate, -24, 10, -2** **sdm extract MyMean,-24_10_-2** To create a mask of an atlas' structure, please use the codes at the end of this tutorial (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 MyMean, label, 117**

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].

How to do it using the terminal

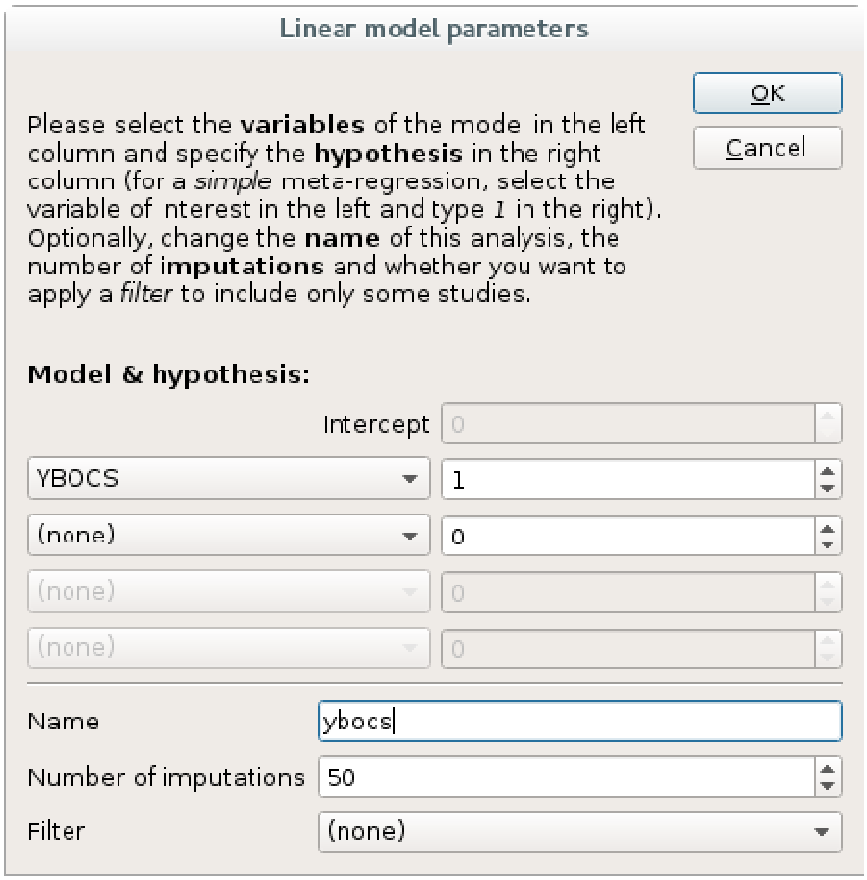
To calculate the subgroup mean and threshold it, type the following:
 	
`sdm myAdults = mi 50,,adults`
`sdm perm 1000,myAdults`
`sdm threshold analysis_myAdults/corrp_tfce,analysis_myAdults/myAdults_z,0.05, 10`

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], specify a name for this analysis (e.g., "ybocs"), select "YBOCS" as the first variable, set its contrast value to "1" and click [OK].

A dialog similar to the following one should appear:



This will create a new folder named "analysis_ybocs/" for the meta-regression by the YBOCS variable. Run then the FWE correction and threshold the resulting maps.

How to do it using the terminal

To calculate the regression and threshold its output maps, type the following:
 	
`sdm ybocs = lm_mi YBOCS,0+1,50`
`sdm perm 1000,ybocs`
`sdm threshold analysis_ybocs/corrp_tfce,analysis_ybocs/ybocs_z,0.05,10`

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
Left inferior occipital gyrus	53
Left inferior parietal (excluding supramarginal and angular) gyri	61
Left inferior temporal gyrus	89
Left insula	29
Left lenticular nucleus, pallidum	75
Left lenticular nucleus, putamen	73
Left lingual gyrus	47
Left median cingulate / paracingulate gyri	33
Left median network, cingulum	127
Left middle frontal gyrus	7
Left middle frontal gyrus, orbital part	9
Left middle occipital gyrus	51
Left middle temporal gyrus	85
Left olfactory cortex	21
Left optic radiations	168
Left paracentral lobule	69
Left paracentral U tract	170
Left parahippocampal gyrus	39
Left pons	172
Left postcentral gyrus	57
Left posterior cingulate gyrus	35
Left precentral gyrus	1
Left precuneus	67
Left rolandic operculum	17
Left striatum	126
Left superior frontal gyrus, dorsolateral	3