Procedure

This code is developed to allow researchers to verify the possible influence of the file drawer problem when they are conducting a meta-analysis using ALE. By computing the Fail-Safe N (FSN; Rosenthal, 1979) a researcher knows the amount of null studies (studies with no statistically significant activation) that is needed before a cluster resulting from a meta-analysis is no longer statistically significant.

This code is written in R. Instructions on how to install and use R can be found here: <http://www.r-tutor.com/r-introduction>.

Only two things are needed to run the code:

1. the .txt-file used for the meta-analysis in ALE and
2. the number of null studies you would like to generate.

In the R-code you fill out the working directory, the name of your input file and the number of null studies you would like to generate. Coordinates are listed in MNI space. If you wish to change the coordinates from Talairach space you can use the software that comes with GingerALE. The R-file reads in the text-file and saves the number of peaks and participants per study, and uses these to construct null studies. All null studies will have a number of peaks and sample size equal to one of the studies in the original meta-analysis. The coordinates of these peaks are randomly drawn from the mask used by the ALE-algorithm.

For specifying the number of null studies that need to be generated in total, it is necessary to determine a minimum and maximum FSN to test beforehand. The algorithm below details how you can save time in that way to determine the FSN for a cluster of interest. There are no formal guidelines for the minimum and maximum FSN to be tested, you should determine what seems practically relevant for your meta-analysis. However, looking for a FSN between 2k (with k being the number of studies in your meta-analysis) and 10k seems reasonable. For reference, Rosenthal (1979) used 5k + 10 as a minimum for the FSN.

The output consists of a text-file, constructed in the same way as the original meta-analysis, that is saved in the working directory. To compute the FSN, simply construct a new text-file by combining the original meta-analysis and (some of) the null studies, and perform an ALE meta-analysis with this text file. To minimize the amount of meta-analyses performed, first add the predefined minimum amount of null studies, then add the predefined maximum amount of null studies. Then always add the (rounded) average of the minimum and maximum number of which you are sure that the FSN lies between these values. This algorithm is outlined below and illustrated with a hypothetical example of a meta-analysis that includes results of 15 studies and with the minimum pre-specified FSN set to 15 and the maximum to 150. The procedure for this example is displayed in Figure 1.

1. Run an ALE meta-analysis of interest containing k studies (in the example k=15) and choose a specific statistically significant cluster for which the FSN will be determined.
2. Re-run the meta-analysis with the original studies with m null studies added where m is the pre-specified minimum for the FSN (in the example m=30).  
   Possible results:
   1. The cluster is no longer statistically significant: STOP. Adding m studies alters the significance of your results. This indicates that results may not be robust to bias due to missing (null) studies in the meta-analysis.
   2. The cluster remains statistically significant: proceed to step 3.
3. Add M null studies with M the pre-specified maximum for the FSN (in the example M=150).

Possible results:

* 1. The cluster is no longer statistically significant. The FSN lies between the pre-specified minimum m and maximum M. Set M\*=M and m\*=m and calculate N as the average of M\* and m\*. Proceed to step 4.
  2. The cluster remains statistically significant: the FSN is higher than the pre-specified maximum M. This indicates that results for the cluster may be driven by a small amount of studies. STOP or choose a higher maximum for the Fail-Safe N. Set the minimum to your currently specified maximum. Start again from step 2.

1. Perform a meta-analysis with k real studies and an addition of N null studies.  
   Possible results:
2. The cluster is no longer statistically significant: remove N- N0 null studies with N0 the average of N and m\*.   
   This replaces N by N0, M\* by N and m\* remains unaltered.
3. The cluster remains statistically significant: add N1–N null studies studies with N1 the average of N and M\*.  
   This replaces N by N1, m\* by N and M\* remains unaltered.
4. Repeat step 4 and continue to add and/or remove null studies until the FSN is determined.

See the illustration below for the flow of the algorithm in the hypothetical example.

It is important to keep in mind that the study characteristics have a large influence on the result of your meta-analysis. Even though they should not differ a lot, obtaining the exact same FSN with a different set of null studies is unlikely. Sensitivity analyses for the obtained FSN are possible by altering the set of null studies that are added or removed.

