Users' Manual for BrainMap GingerALE 2.0

http://brainmap.org

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1. About GingerALE

GingerALE is used for performing activation likelihood estimation (ALE) meta-analyses. The ALE meta-analysis method was initially developed by Peter Turkeltaub (see Turkeltaub et al., Neuroimage, 16, 765-780, 2002 for details). This method of meta-analysis was adopted by BrainMap in 2003. Several modifications have been made to the ALE algorithm since then, and the current version of our software is reported in Eickhoff et al., Hum Brain Mapp 2009 (full text available on www.brainmap.org/pubs). Users now have a choice of running their meta-analyses in MNI or Talairach space.

2. Performing ALE Meta-Analyses

All output files are written in NIfTI (`.nii`) format. The input for a meta-analysis in GingerALE is a text file of your foci, generated by hand, from an excel worksheet, or as an export of your workspace in BrainMap Sleuth. To load these coordinates into GingerALE, go to File → Open Foci. The main window of GingerALE will then confirm for you the name of your foci file and the number of coordinates and experiments contained therein Fig. 1.

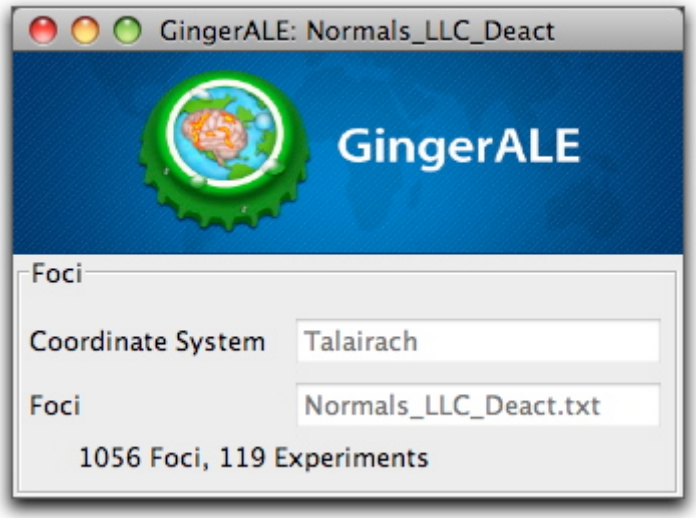

Figure 1. GingerALE: Open Foci.

If you used Sleuth to create a foci file from your workspace, then there is no need to spatially renormalize your MNI coordinates to Talairach

space (or vice versa). This conversion is done automatically when the papers are inserted into the database using a transform called icbm2tal developed by Jack Lancaster (see Lancaster et al., Hum Brain Mapp, In Press, 2007 for details). This new transform provides improved fit over the Brett transform (mni2tal). **Please note that we no longer use the Brett transform for conversion of coordinates from MNI space to Talairach space**.

The ALE meta-analysis procedure follows 3 steps:

2.1. ALE and Testing Significance Fig.2: This step computes the ALE values for each voxel in the brain and performs a test to determine the null distribution of the ALE statistic at each voxel. We no longer require manually entering the FWHM value, as this parameter has been empirically determined (see Eickhoff et al., 2009 for details). A default file prefix is given for the name of the output files, based on the name of your foci file; you may edit this if you like. Then click on "Compute" and the program writes out an image containing the ALE values corresponding to your foci file, and another image of *P* values at each voxel.

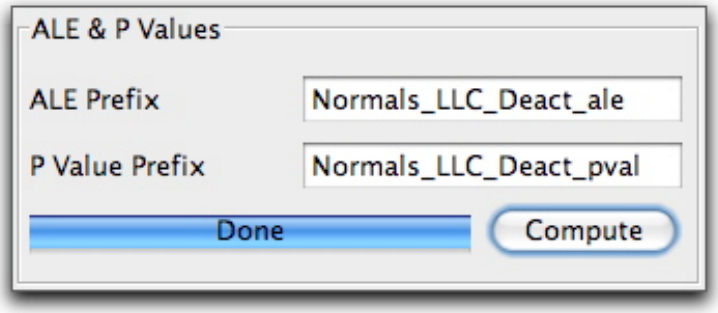

Figure 2. GingerALE: ALE and Testing Significance.

2.2. Thresholding Fig.3: This step takes the *P* values from the previous step and computes the threshold for the ALE map using the algorithm from Tom Nichols's website (http://www.sph.umich.edu/~nichols/FDR/). Choose a False Discovery Rate (q) for the desired level of significance (e.g., 0.05 or 0.01). Also choose a minimum cluster size in mm^3. This step creates the final thresholded ALE map (final output). Only voxels that were found to be statistically significant are assigned a value. The

value that is written out is the computed ALE value. The thresholded map is output in .nii format and can be read by a number of functional neuroimaging software packages.

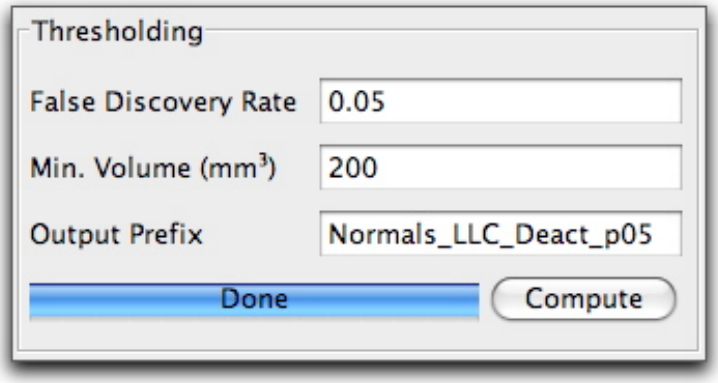

Figure 3. GingerALE: Thresholding.

2.3. Cluster Analysis Fig.4: This step performs cluster analysis on the thresholded map, based on the minimum volume that is specified in the previous step. Anatomical labels of final cluster locations are provided by the Talairach Daemon: http://ric.uthscsa.edu/TDinfo.

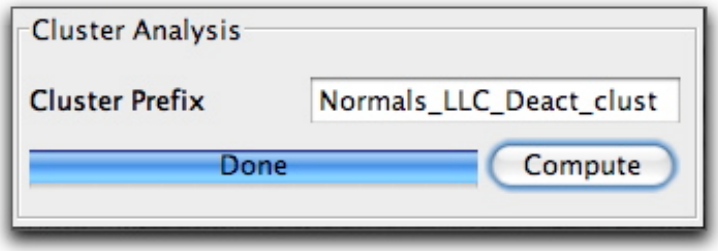

Figure 4. GingerALE: Cluster Analysis.

2.4 Viewing Your Results: Once the thresholded map has been created, you'll need an anatomical underlay in order to view the meta-analysis results. We distribute two templates in Talairach space (one general file and one to be used in AFNI) and one MNI template on GingerALE's website (www.brainmap.org/ale/index.html). Although our .nii files are compatible with most image viewing software, we suggest using Mango to view your meta-analysis results (www.ric.uthscsa.edu/mango/). For meta-analyses performed in Talairach space:

a) Download and open Mango.

b) Open → Open Image → select the Colin1.1.nii file that's available on www.brainmap.org/ale (or you may choose the MNI template).

c) In the brain image that pops up, click on File → Add Overlay → and select the ***_p05.nii image that you created in the penultimate step of GingerALE. This overlays your functional meta-analysis results on top of the anatomical template.

d) Click on Edit → Update Image Range (very important!)

e) To change the color map, go to the smaller rectangular window and click on the red box on the left side, move your cursor down to the next red box, move to the side text box that pops up, move to "Color Table", then click on your preferred color option (Red-to-Yellow and Spectrum are good for ALE results).

f) Moving your cursor throughout the brain will move you through space. Pressing the spacebar will change the orientation of the biggest image (axial, coronal, sagittal).

g) Options → Select Atlas → Talairach Daemon Labels (hit OK in window that pops up) will then give you the anatomical labels of your current location in brain space, as well as the coordinates.

To get the ALE values for all voxels (even ones not found to be significant), you'll need to open the file created in the first step, Fig. 2, of the ALE meta-analysis process.

2.5 Citing GingerALE: If you use the above software, procedure, and/or template in your research, please acknowledge our previous work in any resultant publication:

Laird AR, Fox M, Price CJ, Glahn DC, Uecker AM, Lancaster JL, Turkeltaub PE, Kochunov P, Fox PT. ALE meta-analysis: Controlling the false discovery rate and performing statistical contrasts. Hum Brain Mapp 25, 155-164, 2005.

3. Main Menu Items

Figure 5. The Main Application Menu.

3.1 GingerALE

3.1a About GingerALE: This menu item contains basic information about **GingerALE**, such as the homepage, version number, and copyright date.

3.1b Preferences: The menu item addresses certain settings that are relevant to performing ALE meta-analyses. This information is divided into three sections: Mask Options, Default Values, and Output Files.

Coordinate Space ❶,Fig.6:

A radio button is available to select which standard space the meta-analysis should be performed in: Talairach or MNI.

Mask Options ❶,Fig.6:

When a foci file is opened, the coordinates are compared against a mask defining the outer limits of Talairach (or MNI) space. A pop-up window will appear if any of your coordinates are located outside of this mask. The ALE analysis will proceed after this step without any intervention on your part. However, any coordinates located outside of this mask will not be omitted from subsequent analysis and might possibly yield strange activations on the border of your mask that do not appear to have a center of mass.

Normally, finding coordinates outside of the mask will occur for less than 3% of your total foci (we have found this number to be even lower since implementing the Lancaster transform instead of the Brett transform). Finding coordinates located outside of the mask is sometimes due to author error (e.g., missing negative sign, inverted coordinates, etc.). You can often spot this type of error and correct for it manually. For example, if a coordinate is listed as being located in the occipital cortex, but the

given y value is positive and extends outside of the Talairach mask, then we recommend that you change the y value from positive to negative before proceeding with the ALE analysis.

Two options are available for your mask size, a smaller mask or a larger mask. Typically, we use the smaller mask for meta-analyses of functional imaging studies. The larger mask is available for VBM meta-analyses because many reported coordinates in these studies are located on the outside of the brain. We slightly enlarged the mask for these meta-analyses so as to include more foci located at the boundaries of Talairach or MNI space.

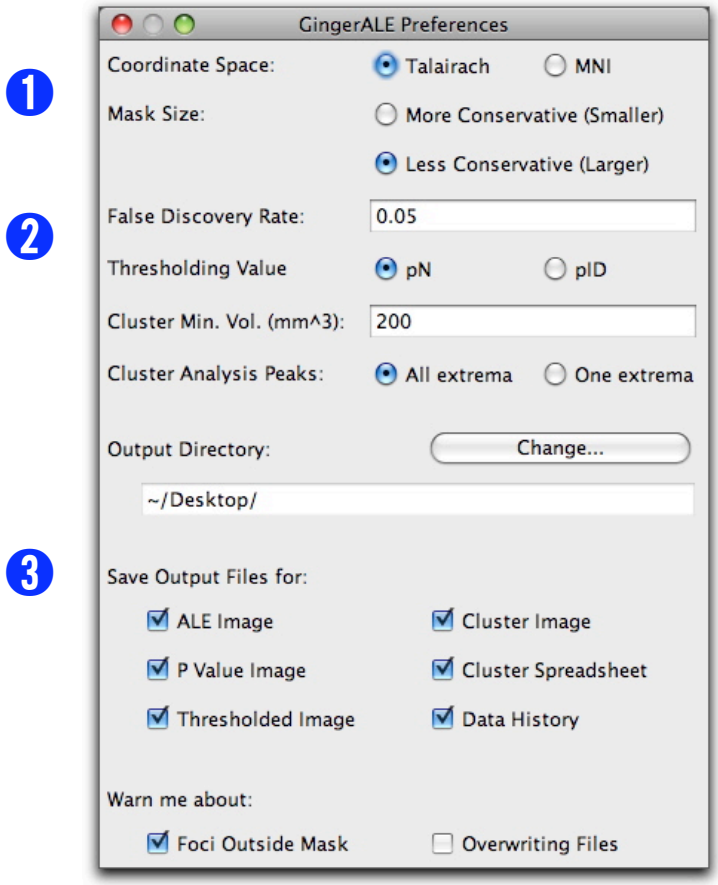

Figure 6. ALE Preferences.

If you have a large number of outlying foci that you do not want omitted from your meta-analysis, then you can select the option of "Less Conservative (Larger)". This option will slightly increase the default mask size, thus including a wider range of coordinates. An image of the

difference between the two mask files for the Talairach template can be seen in Fig. 7. In this difference image, the white areas denote the extra voxels included when using the larger (less conservative) mask file. Please note that if you use this larger mask, some of your resultant ALE clusters may appear to be located outside of the brain when viewed on the `colin.nii` anatomical template.

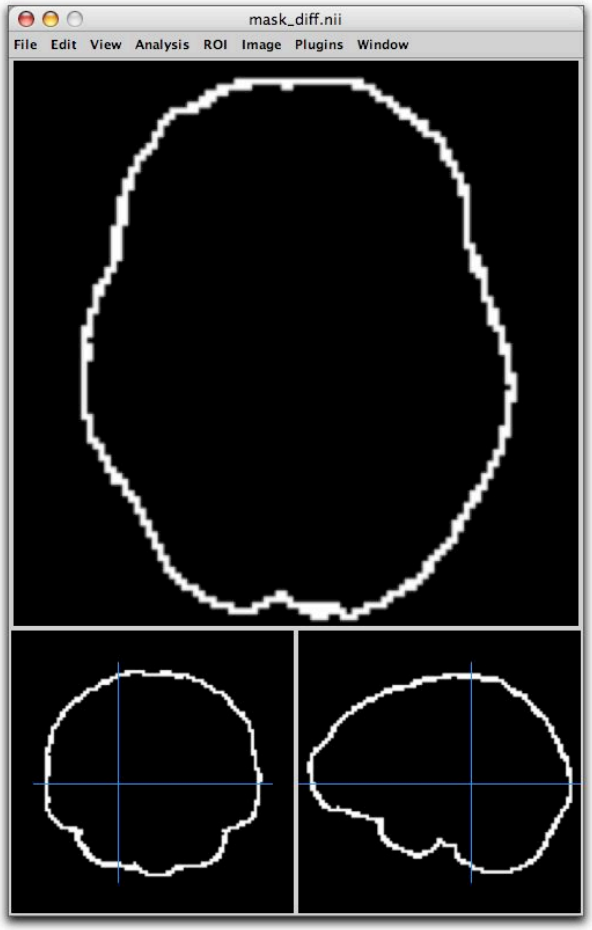

Figure 7. Difference Between Mask Size Options.

Default Values ❷,Fig. 6:

You may set default values for the False Discovery Rate, pN or pID, and minimum cluster volume (mm^3). These values may be changed at any time in the main window of GingerALE for a specific meta-analysis; however, you may set your most commonly used default values here for convenience.

The computation for the false discovery rate will yield two *P* value thresholds. The RIC generally uses thresholds returned by pN. If you prefer pID, you can set it as the default thresholding value in the Preferences. See Genovese et al., Neuroimage, 15, 870-878, 2002 for more details.

In this section you may also choose if you which coordinates to be reported for all submaxima in a single ALE cluster ("All extrema") or only one coordinate for the maximum ALE statistic in that cluster ("One extrema"). Choosing the former option is very useful for large ALE clusters that extend over many different areas of the brain.

Output Files ❸,Fig.6:

Lastly, you may specify the output directory for all of your processed ALE files, which files you want to output, and what your preference is for pop-up windows about boundary foci and overwriting files.

A number of files may be written to output during the ALE procedure. We recommend that all of these options be checked.

1. ALE Image = contains the unthresholded ALE values, one computed at every voxel in the brain
2. *P* Value Image = contains each voxel's *P* value, corrected for multiple comparisons using FDR
3. Thresholded Image = ALE maps thresholded at a given α value; **this is the final image output by GingerALE.**
4. Cluster Image = thresholded ALE map, each cluster given an integer value; this image is required for subsequent FSNA/RDNA analyses.
5. Data History = reports the analysis parameters and the output of the cluster analysis on the thresholded ALE map in text format
6. Cluster Spreadsheet = excel doc of cluster analysis on thresholded ALE map

In the data history and cluster spreadsheet files, the cluster analysis reports a variety of information. In the cluster spreadsheet, you will see 10 columns of information. From left to right these are:

(1) cluster number

(2) volume of cluster in mm^3
(3-5) x,y,z values of the weighted center of mass of the cluster
(6) maximum ALE value observed in the ALE cluster
(7-9) x,y,z values of the location of the maximum ALE value
(10) Talairach Daemon anatomical label associated with the location of the maximum ALE value.

All of this information can be found in both the data history and cluster spreadsheet files. The data history file also includes information on the x,y,z values for the extent of each cluster and reported parameters for different stages of the analysis, such as computing the ALE statistic, performing the permutation test, running FDR and thresholding the ALE map.

3.2 File

Open Foci: This menu item loads in a text file of coordinates into GingerALE. Hotkey: `⌘-O` (Mac) or `ctrl-O` (PC). The format for this file should be three columns of numbers (x,y,z coordinates), separated with tabs or spaces. If you created your foci file in Sleuth, the experiments will be separated by a line break and delineated by first author name, year, and experiment name ("//" comments these descriptors out so that they will not be read by the ALE algorithm). Between the commented experiment name and the list of coordinates, you should also include a line that details the number of subjects for that group of foci. For example, your foci text file should look like:

```
// Sadato, 1998: Rest-Discrimination
//Subjects=18
-18     16      56
-12     52      4
-22     56      12
30      -84     -12
44      -70     0
-24     -94     0
-8      -98     -12
18      -70     -8
-6      -44     56
16      -46     52
0       16      -8
-46     32      4
```

```
// Rosen, 1999: Rest > Endogenous
//Subjects=13
4       -70     31
8       -35     69
-2      -87     2
3       -85     6
-6      -56     19
-55     -10     10
```

Clear Foci: This menu item clears your foci from GingerALE.

Save Data History: This menu item allows you to save a text output that summarizes your ALE meta-analysis at any point in the procedure.

Please Note: With the advent of the new Eickhoff algorithm, GingerALE no longer supports comparison or subtraction meta-analyses, such as those published in Laird et al., Hum Brain Mapp, 25, 155-164, 2005. We are working hard to update our software to include these comparisons. In the meantime, users will need to revert to an older version of GingerALE if they need to perform a comparison or subtraction meta-analysis. Also, due to the new analytic solution to computing *P* values, GingerALE no longer allows you to reopen saved files of ALE scores or *P* values.

3.3 Tools

Export Foci Image: This menu item creates an `.nii` image of your foci file. In this image, each coordinate point is assigned a value. **No blurring** of the coordinate points is performed in this export – this step is simply intended as a way to view your coordinates in standard space. The value assigned to each coordinate point matches the experiment number of your foci file. Remember, different experiments are defined in a foci file simply by including a line break between the groups of foci. By assigning values in this way, it is easy to set each experiment number to a different color in your image viewer so that you can identify the paper and experiment for each coordinate point as you scroll through the brain. If 2 identical coordinate locations are included in different experiments, then the value assigned to that voxel will be n+1, where n equals the

number of total experiments. This is done so that these duplicate coordinates can be seen on the resultant output image.

Convert Foci: This menu item uses a dialog window Fig.8 to guide you through the conversion of your coordinates from MNI space to Talairach space and vice versa. You are given options for selecting your input file of coordinates, the transform you would like to use, and the name and location of your output file.

There are 8 coordinate transforms included in GingerALE:

The first three transforms convert coordinates from MNI space to Talairach space using the Lancaster transform, icbm2tal. This transform is broken into 3 options, based on what software you used for spatial normalization of your data (SPM, FSL, or Other):

(1) MNI (SPM) to Talairach
(2) MNI (FSL) to Talairach
(3) MNI (Other) to Talairach

The second three transforms perform the corresponding transforms from Talairach space to MNI space using the Lancaster transform. Again, this transform is broken into 3 software options:

(4) Talairach to MNI (SPM)
(5) Talairach to MNI (FSL)
(6) Talairach to MNI (Other)

The last 2 transforms are reproductions of the Brett transform, mni2tal. Two options are given for the Brett transform, one for converting from MNI space to Talairach space, and the other for converting from Talairach space to MNI space:

(7) Brett: Talairach to MNI
(8) Brett: MNI to Talairach

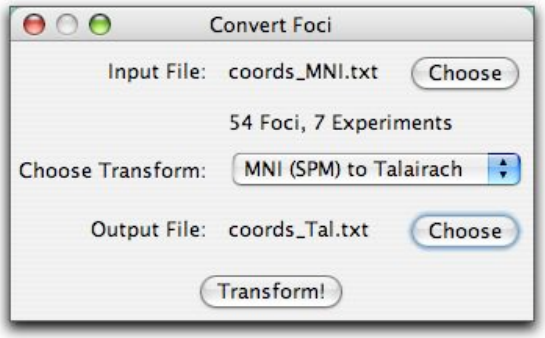

Figure 8. Transforming Coordinates: MNI and Talairach Spaces.

Although the BrainMap database no longer supports use of the Brett transform, we feel it is still important that we include it in our software. If one of the studies included in your meta-analysis generated its coordinates by using SPM for spatial normalization and published those coordinates after conversion using the Brett transform, then we recommend that you "un-Brett" the published coordinates using the above transform "Brett: Talairach to MNI" and then proceed with the Lancaster transform "MNI (SPM) to Talairach". This will correctly move your coordinates into the Talairach space.

3.4 Help

Check for Updates: This menu item will check the BrainMap website to see if you have the latest version of GingerALE.

Show Manual: This menu item will show the current manual for GingerALE (this document). An internet connection is necessary for this menu option.

Show Read Me: This menu item will show the current readme file for GingerALE. The readme file contains information about installation and version changes. An internet connection is necessary for this menu option.

Show License: This menu item will show the current license information for GingerALE. An internet connection is necessary for this menu option.

4. Troubleshooting

4.1 What are the minimum number of papers needed to perform an ALE meta-analysis?

There's no definitive answer to this question. For paradigms that involve simple sensory processing (e.g., passive listening), you only need a handful of coordinates (approximately 20-30) since that type of paradigm tends to only activate a few areas (e.g., primary, secondary auditory cortices, etc). But for a cognitive task like the Stroop task or the n-back task, a wider network of activations is expected. Thus, you'll need a higher number of input coordinates in order to see substantial convergence (at least 100 foci or so). These are VERY loose estimates, but it should give you an idea of what you should be looking for when performing your literature search. Lastly, please keep in mind that it really depends on how varied the results are for your particular paradigm or domain. For example, TMS/PET studies vary widely and their results do not overlap nicely. In contrast, verb generation tasks are highly concordant and produce a very robust ALE meta-analysis map.