Users' Manual for BrainMap GingerALE 1.0

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 the Research Imaging Center in San Antonio for use with the BrainMap database in 2003. To this end, several modifications were made to the initial ALE algorithm, including a correction for multiple comparisons during the permutation test and a technique for comparing two ALE meta-analyses (see Laird et al., Hum Brain Mapp, 25, 155-164, 2005 for details). In addition, all GingerALE meta-analyses are performed in Talairach space, not MNI space (as originally developed by Turkeltaub et al.).

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. 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 5 steps:

2.1. ALE Fig.2: This step computes the ALE values for each voxel in the brain in Talairach space. Enter the FWHM value (we generally use 10-12 mm). A default ALE prefix is given for the name of the output file, 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, one value to each voxel.

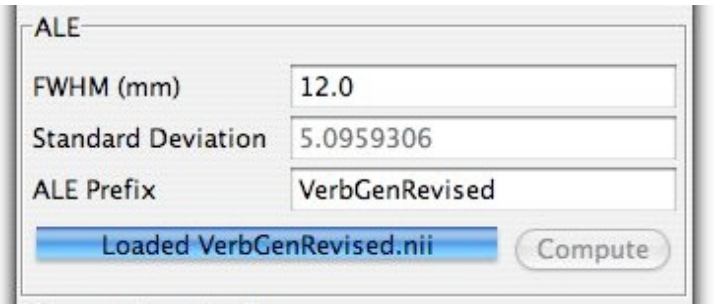

Figure 2. GingerALE: ALE.

2.2. Permutation Testing Fig.3: This step performs a permutation test to determine the null distribution of the ALE statistic at each voxel. We suggest using 5000 permutations. The output is an image of *P* values for each voxel. Note: this test is extremely computationally intensive. We have implemented this step on a network of Apple computers using the Xgrid software: http://www.apple.com/server/macosx/features/xgrid.html. If you are not able to set up a grid for parallel computing, then just be aware that this step takes a very long time.

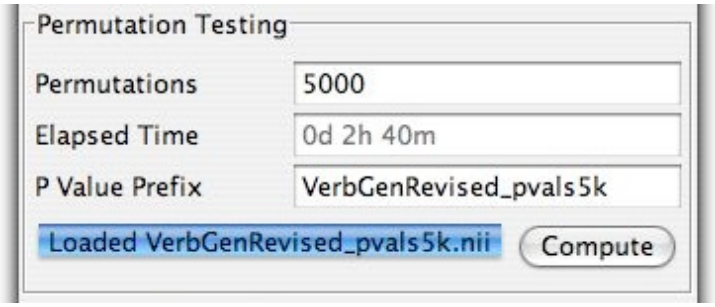

Figure 3. GingerALE: Permutation Testing.

2.3. False Discovery Rate Fig.4: This step takes the *P* values from above and computes the threshold for the ALE map using the algorithm from Tom Nichols's website (http://www.sph.umich.edu/~nichols/FDR/). Please also see Laird et al., Hum Brain Mapp, 25, 155-164, 2005 for more details. Choose a q for the desired level of significance (e.g., 0.05 or 0.01). The computation 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.

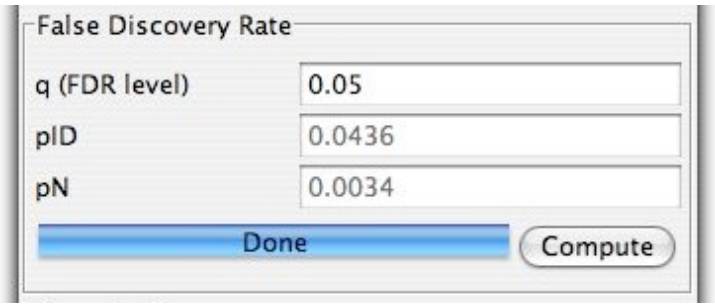

Figure 4. GingerALE: False Discovery Rate.

2.4. Thresholding Fig.5: This step creates the final thresholded ALE map (final output). Select the image-wise *P* value (q according to FDR theory), usually 0.05 or 0.01, and threshold the map that was output in step 1. 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.

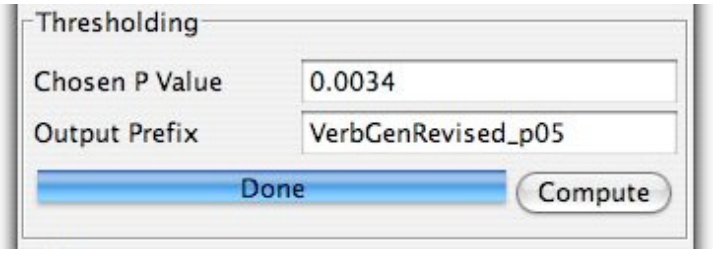

Figure 5. GingerALE: Thresholding.

2.5. Clusters Fig.6: This step performs cluster analysis on the thresholded map. You must input the minimum volume that defines a cluster. Anatomical labels of final cluster locations are provided by the Talairach Daemon: http://ric.uthscsa.edu/TDinfo.

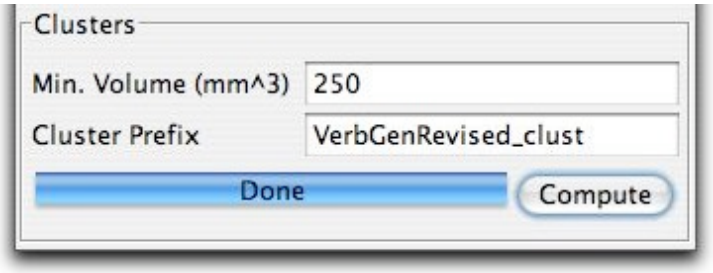

Figure 6. GingerALE: Cluster Analysis.

2.6 Viewing Your Results: Once the thresholded map has been created, you'll need an anatomical underlay in order to view the meta-analysis results. Below is a description of this procedure using AFNI (http://afni.nimh.nih.gov/afni/).

First, download our anatomical template, `colin.nii`, from our website at http://brainmap.org/ale. Open afni and use the `colin.nii` template as the anatomical underlay and the thresholded ALE results as the overlay. As you move through the brain, the afni coordinates that display your location are Talairach coordinates in Talairach space. Again, remember that the ALE maps are thresholded, so you won't get a value at every voxel. 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.

2.7 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 7. The Main Application Menu.

3.1 GingerALE

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

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.

Mask Options ❶,Fig.8:

When a foci file is opened, the coordinates are compared against a mask defining the outer limits of Talairach space. If you checked "Show Outlying Foci Warning", a pop-up window will appear if any of your coordinates are located outside of this mask. This warning should be noted in your records. 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.

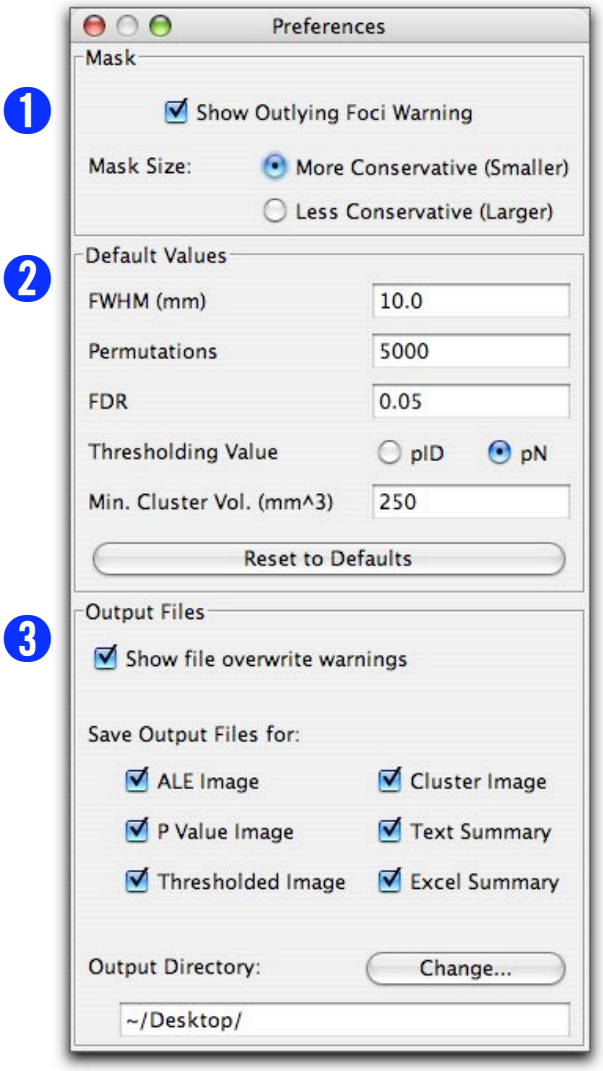

Figure 8. ALE Preferences.

Below the warning option is the setting for the Talairach mask size. By default, this field is set to "More Conservative (Smaller)". This is the mask that we recommend and is the one that matches the `colin.nii`

template that is distributed on our website. However, 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 Talairach coordinates. An image of the difference between the two mask files can be seen in Fig.9. 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.

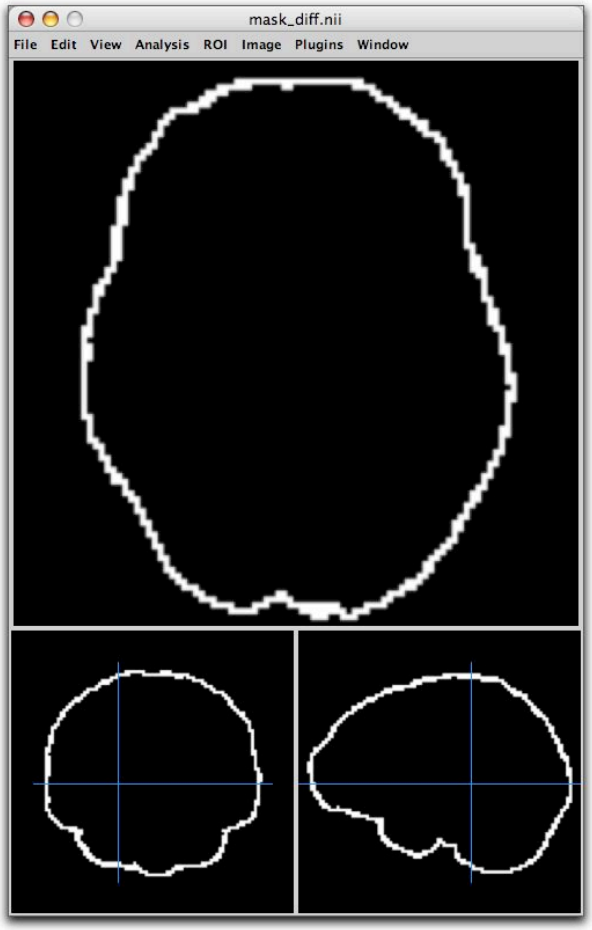

Figure 9. Difference Between Mask Size Options.

Default Values ❷,Fig.8:

You may set default values for the FWHM value, number of permutations, FDR threshold, 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. Typically, we employ FWHM values that range from 10 mm to 12 mm. We recommend using at least 5000 permutations during the permutation test.

Output Files ❸,Fig.8:

At the top of this portion of the preferences window, there is a checkbox labeled "Show file overwrite warnings" that allows for dialog windows to warn you before a file is overwritten.
There is also the option to write out a number of files during the ALE procedure. We recommend that all of these options be checked, especially the ALE images and the *P* Value image. That way, if you want to reload your files later, you won't have to wait for the entire permutation test to run again.

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, computed via permutation test, 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. Text Summary = reports the analysis parameters and the output of the cluster analysis on the thresholded ALE map in text format
6. Excel Summary = excel doc of cluster analysis on thresholded ALE map

At the bottom you have the option of specifying the directory that you would like your files written to by default.

In the summary text and excel files, the cluster analysis reports a variety of information. In the excel file, 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 text summary and excel summary files. The text summary 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. 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). Hotkey: ⌘-O (Mac) or ctrl-O (PC).

Open Subtraction Foci: This menu item refers to the comparison meta-analysis presented in Laird et al., Hum Brain Mapp, 25, 155-164, 2005. If you open a foci file, then choose to open a subtraction foci file, you will notice that both of these files are loaded into the main GingerALE window. This subtraction meta-analysis will yield an ALE map that shows regions in which the two groups of foci are significantly different. This is often helpful when comparing paradigm types (e.g., n-back and Sternberg) or subject groups (e.g., schizophrenics and controls). For a simple ALE meta-analysis of a single group of coordinates, no subtraction foci should be opened.

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

Open ALE Scores: This menu item allows you to open previously computed ALE scores. Hotkey: shift-⌘-O (Mac) or shift-ctrl-O (PC).

Open *P* Values: This menu item allows you to open previously computed *P* values. In order to load in your saved *P* value file, you will need to first load in the corresponding ALE scores (see above). This step is useful if you would like to save a final ALE map at a different threshold than initially computed.

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 Talairach 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. This image should be viewed with the `colin.nii` template as the anatomical underlay.

Convert Foci: This menu item uses a dialog window Fig.10 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

Although the BrainMap database no longer supports use of the Brett transform, 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.

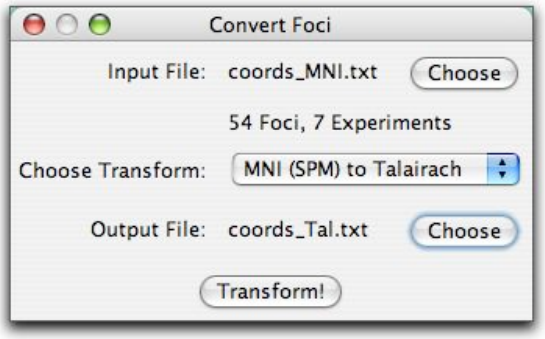

Figure 10. Transforming Coordinates: MNI and Talairach Spaces.

3.4 Help

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.

4.2 I ran the same ALE meta-analysis and obtained different results. What's going on?

Yes, when you run repeated analyses of the same data, you'll get **slightly** different results each time. That's because we're using permutation tests to determine the voxel-wise *P* values. For the large

clusters, the difference between analyses will not be significantly different. Clusters will be a little larger or smaller or more/less intense. But smaller clusters (those speckled ones around 100 mm^3 or less) will vary greatly. But essentially you're looking at the same map. The variation between repeated analyses will be greater for studies including a fewer number of coordinates. One way of avoiding this issue is to increase the number of permutations. Generally, we suggest using 5000 permutations, but if you're concerned about this issue you might want to increase to using 10,000 permutations.