VAMCA Tutorial

Timothy J. Herron

Human Cognitive Neurophysiology Laboratory, David L. Woods, Director
Neurology, Research Service, United States Veterans Affairs
Martinez, California, USA

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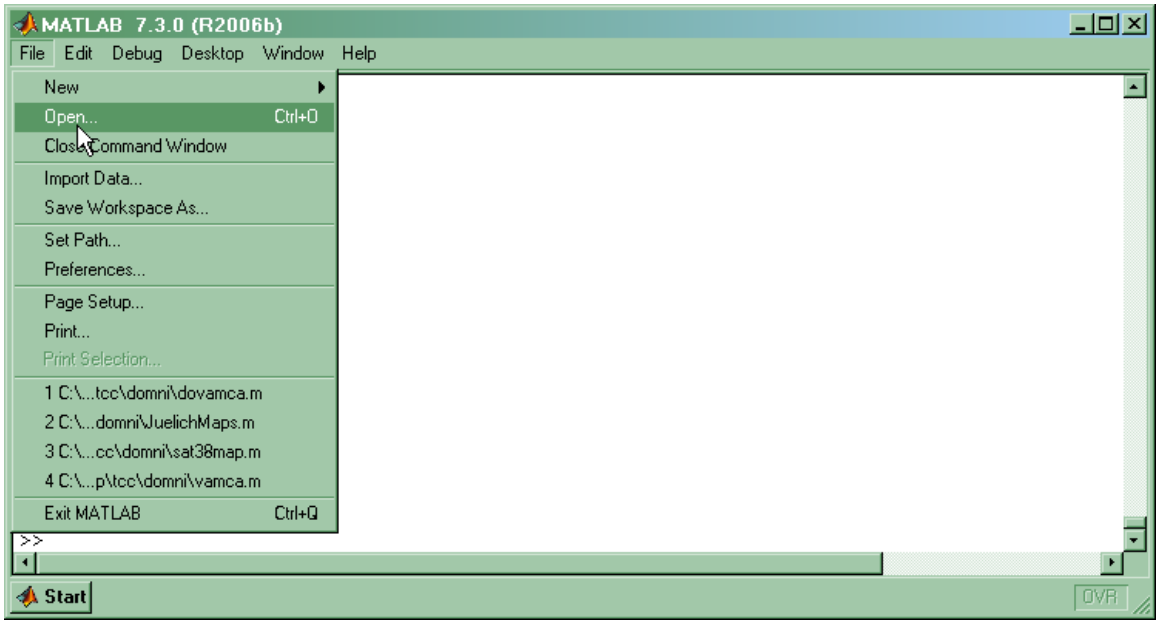
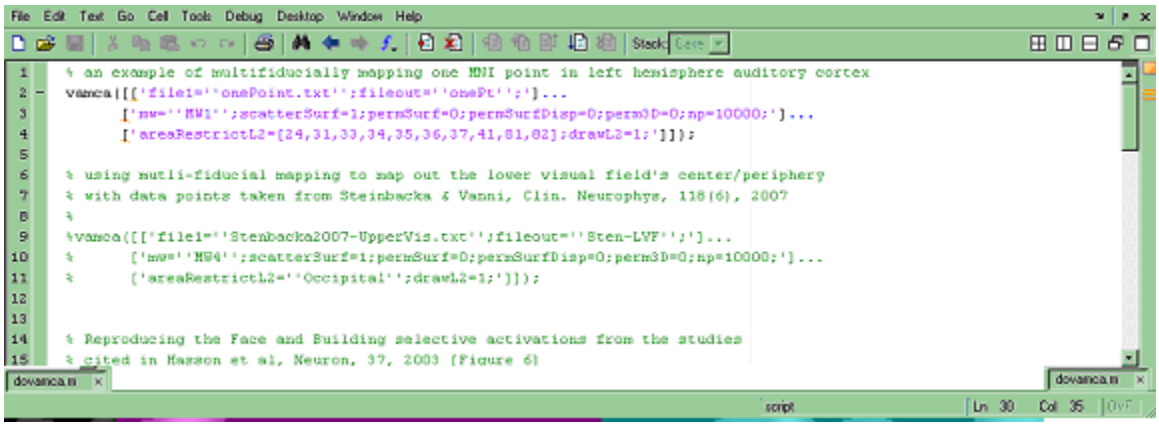
Simple Multi-fiducial Mapping

To start to work with VAMCA, unzip the vamca.zip folder, start up MatLab (version 5.3-7.x), and "cd" to the "vamca" directory that was created during the unzipping process. For users of operating systems other than Windows XP (or if you use Matlab 5.3), you will need to perform one preliminary compile command in MatLab before you start below (see "vamca.readme" for details – it mainly consists of typing "mex Es2.c" at the MatLab command line).

To see a set of sample VAMCA processes, open the file "dovamca.m" within matlab:

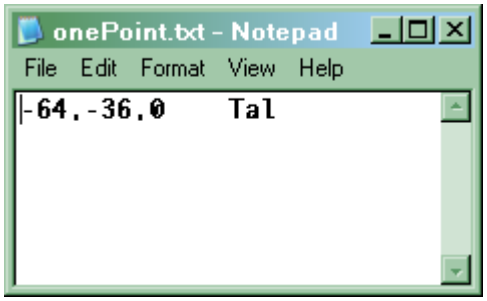




The file "dovamca.m" is a script file that contains several sample VAMCA process commands, only the first of which will run when "dovamca" is typed at the MatLab command line. The vamca command that will run is:

```
% an example of multifiducially mapping one MNI point in left hemisphere auditory cortex
vamca([['file1=''onePoint.txt'';fileout=''onePt'';']...
      ['mw=''MW1'';scatterSurf=1;permSurf=0;permSurfDisp=0;perm3D=0;np=10000;']...
      ['areaRestrictL2=[24,31,33,34,35,36,37,41,81,82];drawL2=1;']]);
```

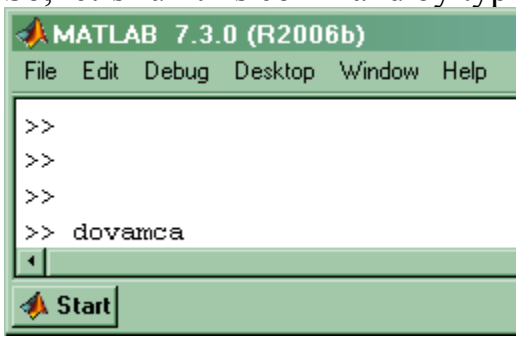
For those who know MatLab, you can see that the "vamca" command accepts one string as its input, and that string specifies parameters (separated by semicolons) for VAMCA to use in processing stereotaxic coordinates. In this case the "vamca" command processes the file "one point.txt":



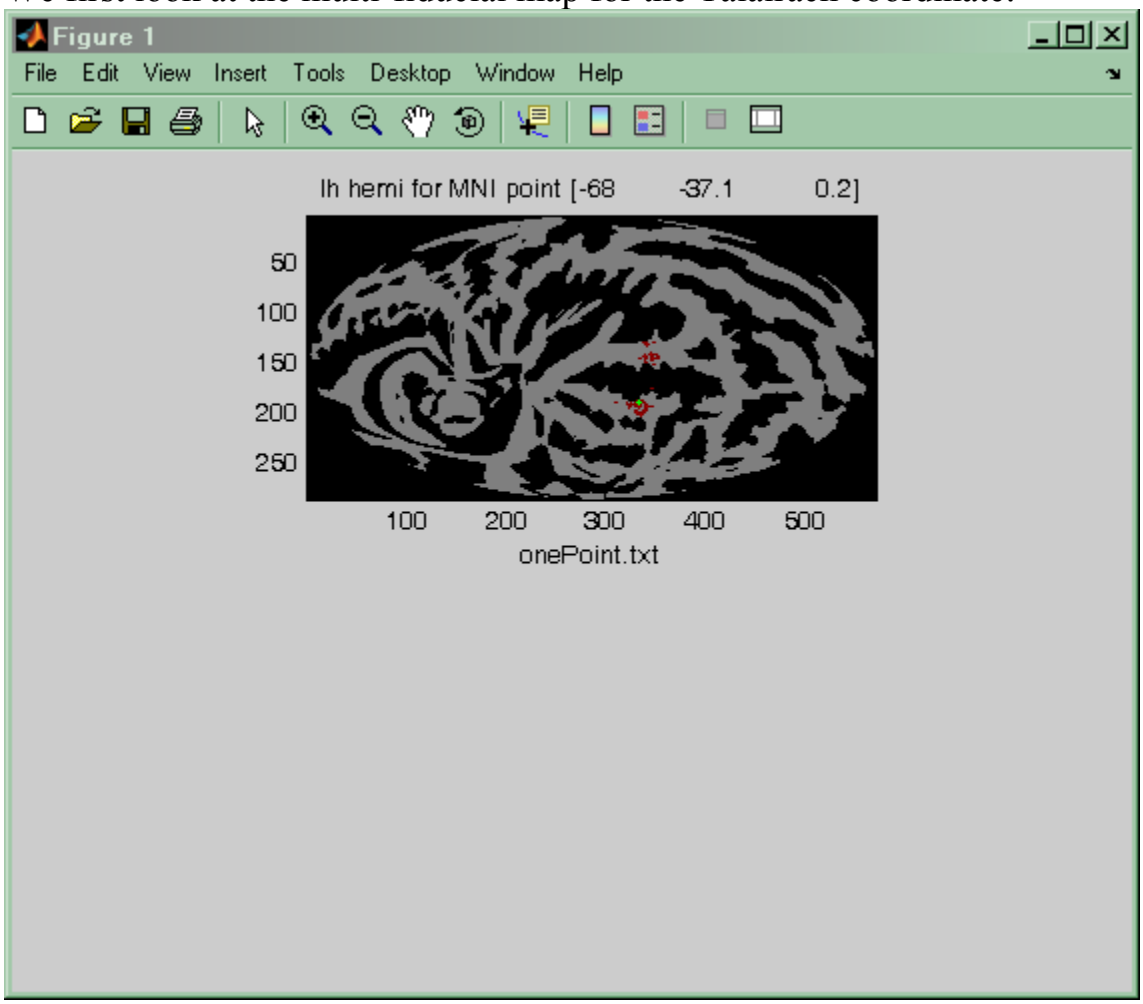
that contains one Talairach space coordinate in a plain text file. Stereotaxic coordinates are specified one per line, are separated by commas or spaces or tabs, and can be contained within brackets (or not) just as long as they are the first three numbers in a given line. One can also specify whether the point is in MNI or Talairach space before or after the coordinates appear on each line (see "vamca.txt" for possible options).

The other relevant *vamca* command parameters shown above are that the output files have name is specified by `fileout=''onePt'';`, that the surface maps will be viewed centered on auditory cortex via the parameter `'mw=''MW1'';`. (see vamca.html for the other three surface map views), and that we want to see explicitly multi-fiducial map results: `scatterSurf=1;`.

So, let's run this command by typing "dovamca" at the prompt:

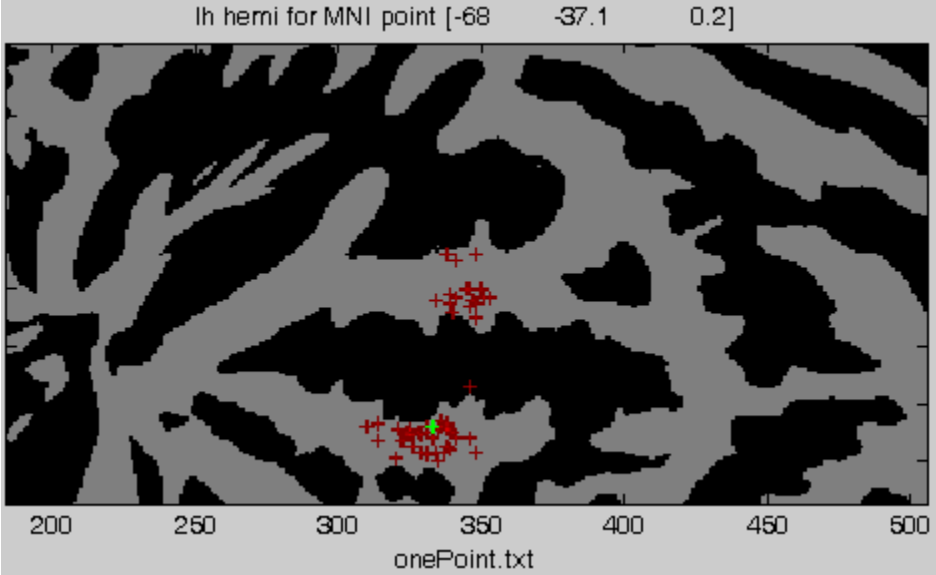


In a few seconds you will see the cortical surface maps output by VAMCA. We first look at the multi-fiducial map for the Talairach coordinate:

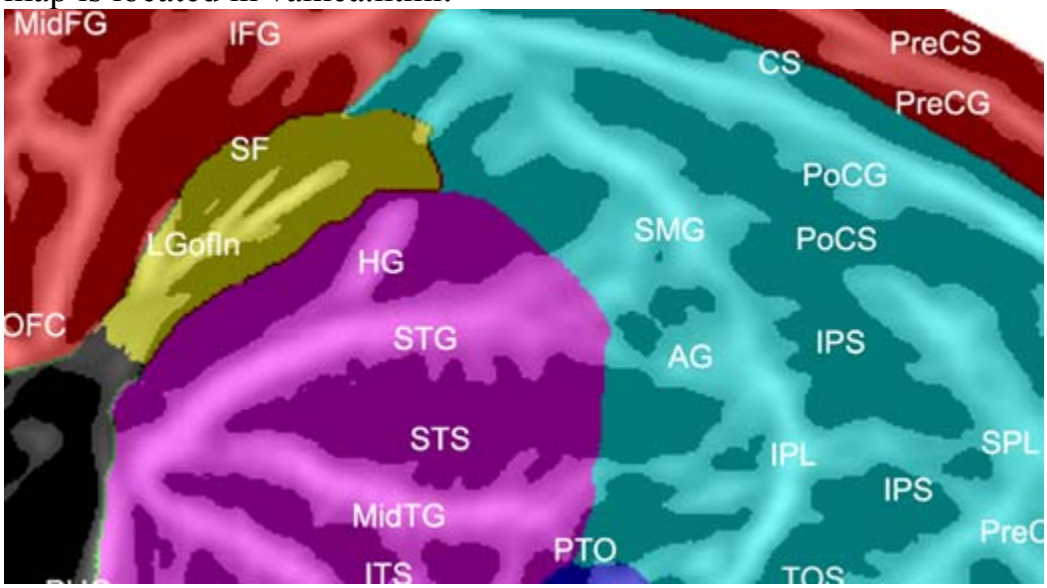


The output is a standard MatLab graphics window that can be manipulated in the usual ways (e.g. using the magnification buttons and print button). The output is a grayscale image showing a mean cortical surface curvature for the left hemisphere that was produced by processing 72 normal controls in the VAMCA database using FreeSurfer; thereby identifying, inflating, and coregistering their cortical surfaces onto a sphere (see "vamca.html" for more details). Then the surfaces are averaged together, projected onto a Mollweide equal-area flat map, and gyri are shaded gray and sulci as black. The database controls also were normalized (using SPM5) into MNI-152 space, so that we know where each cortical surface point is located in stereotaxic space.

Let us magnify the interior of the map so that we can better see the results of the multi-fiducial mapping:



Note first that the Talairach coordinate was converted to MNI-152 space as specified above the image. On the image itself, red crosses represent the cortical locations for the 60 right-handed database controls that correspond to the input Talairach coordinate in "onePoint.txt". The key for the cortical map is located in vamca.html:

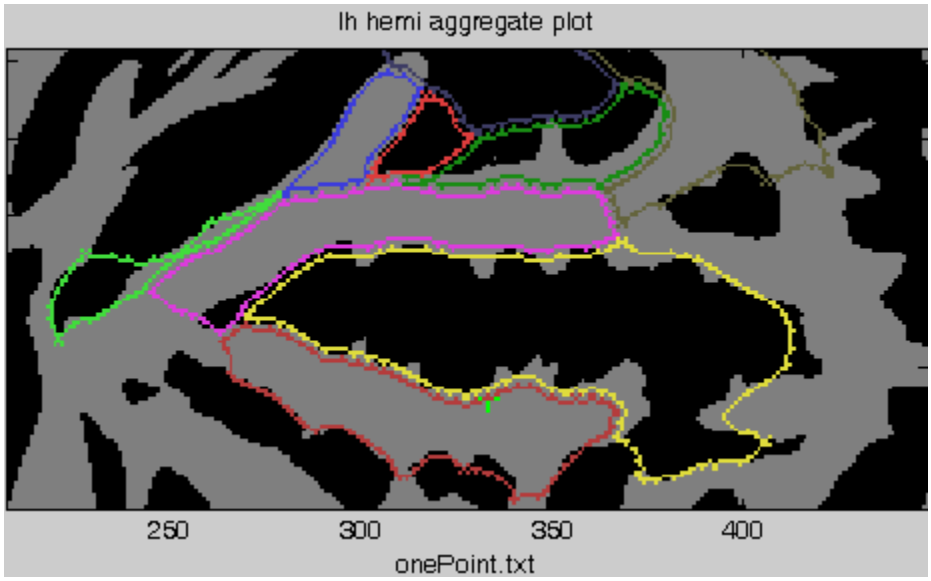


We can see that the stereotaxic coordinate is located either on the middle temporal gyrus (MidTG) or the superior temporal gyrus (STG) for all 60 controls. However, the majority of the controls specify that the MidTG is the location of the Talairach coordinate (-64,-36,0). This fact is indicated by the green cross that represents the location of the 2D (spherical) surface median point for all 60 crosses (the location which minimizes the sum of distances to the 60 crosses). The median is a more useful average locator

then the (spherical) 2D mean because it tends to be located *in* the largest cluster (on the MidTG) rather than *inbetween* two or more clusters (this would place it in the superior temporal sulcus [STS] in this case – and that is definitely incorrect).

The multi-fiducial mapping of stereotaxic coordinates provides a graphical way of showing the anatomical variability of individuals even beyond what can be eliminated using standard, affine 3D normalization.

The only other graph that was produced by the "vamca" command in the script file "dovamca" that we will comment on is an ROI map that shows where the Talairach coordinate's 2D median location is at:



The green cross again shows where the 2D median is located: right at the edge of the MidTG, an ROI that is indicated with a red boundary.

Further information about the Talairach coordinate inside "onePoint.txt" is contained in the two output files: "onePt.img" (and "onePt.hdr") – an Analyze format 3D image file, and "onePt.txt", a plain text format output file.

Let us view the text output file "onePt.txt" first:

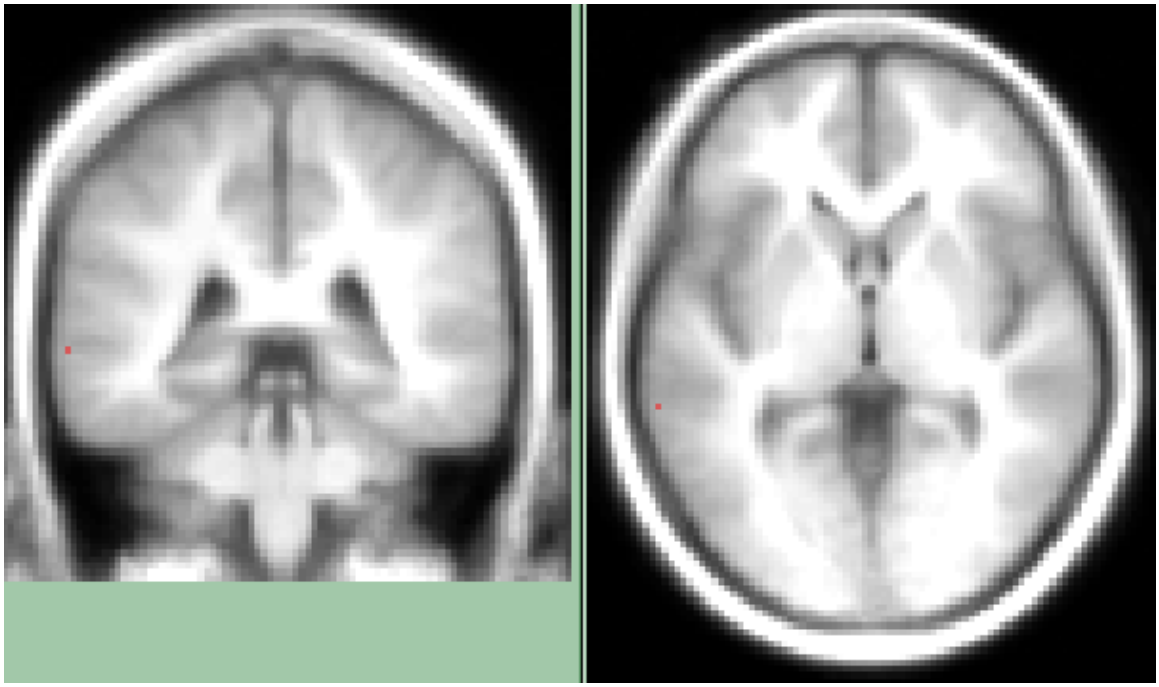
```
VAMCA output file.   Run at 04-Nov-2008  11:04:47 on onePoint.txt
HCNLAB, Veterans Affairs, Martinez, CA, USA. www.ebire.org/hcnlab

 Left Hemisphere.

Points from Group 1: onePoint.txt
(-68.0,-37.1,  0.2)      weighted 3D median.     G_temporal_middle
(-68.0,-37.1,  0.2)      weighted 3D mean.

Original MNI point   Med Dist  Mean Dist  Mn to Surf  Surf Frac  Surface Coord  Frac in ROI   Surface ROI Name
(-68.0,-37.1,  0.2)     0.0       0.0        1.6         0.98    MW1(-23,  32)     0.68       G_temporal_middle

Mean center dist.:           0.0         0.0
Std. center dist.:           0.0         0.0


Right Hemisphere.

Input String:
'file1=''onePoint.txt'';fileout=''onePt'';mw=''MW1'';scatterSurf=1;permSurf=0;permSurfDisp=0;perm3D=0;np=10000;areal

--------------------------------------------------------------------------------
```

The first few and last lines of the output file give information on what processing was done on which input file, and when. The center of the text file indicates various aspects of the whole group of input stereotaxic coordinates. As we only had one coordinate in the input file, the only interesting line in the file was:

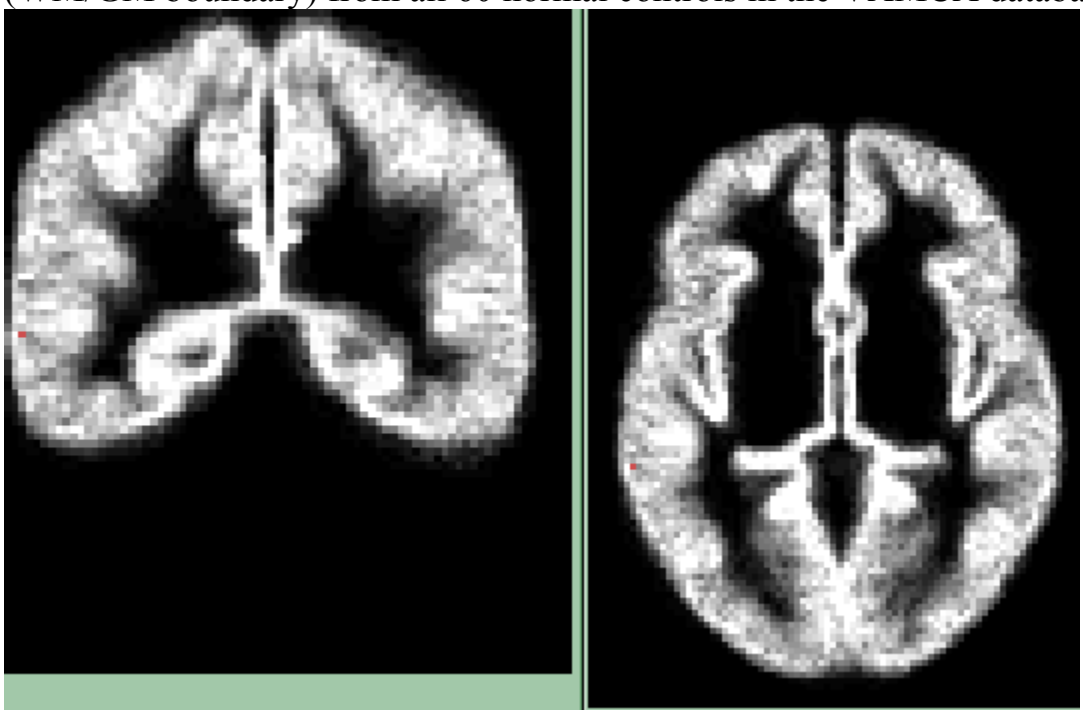
```
Original MNI point   Med Dist  Mean Dist  Mn to Surf  Surf Frac  Surface Coord  Frac in
ROI   Surface ROI Name
(-68.0,-37.1,  0.2)     0.0       0.0        1.6         0.98    MW1(-23,  32)     0.68
G_temporal_middle
```

This line indicates the MNI location of our single input point `(-68.0,-37.1, 0.2)` as well as statistics about it processing. E.g. this point was, on average, 1.2 mm away from the mid gray matter cortical surface of each of the 60 database controls [`Mn to Surf 1.2`], was within 5mm (the default) of that surface for 98% of the controls (i.e. all but 1) [`Surf Frac 0.98`], and 68% of the controls had that 3D location within the middle temporal gyrus ROI [`Frac in ROI 0.68  Surface ROI Name G_temporal_middle`].

The Analyze format output file can be viewed in conjunction with some of the provided mean MNI space image files found in the "…/vamca/Images" directory. E.g. we will overlay "onePt.img" file onto the T1 mean image file "VAMCA_60Subject_T1mean.hdr" using the MRIcroN software:



The red dot is the location in MNI space of the coordinate. One can also locate the 3D coordinate with respect to the probabilistic cortical surface (WM/GM boundary) from all 60 normal controls in the VAMCA database:



Thus, the coordinate is likely a legitimate cortical surface point.

Mapping a single group of stereotaxic coordinates

Now we can move on to mapping several points from a single group. For that we will comment out (via "%") the first "vamca" command in the script "dovamca.m" and uncomment out the second command:

```
% an example of multifiducially mapping one MNI point in left hemisphere auditory cortex
%vamca([['file1=''onePoint.txt'';fileout=''onePt'';']...
%      ['mw=''MW1'';scatterSurf=1;permSurf=0;permSurfDisp=0;perm3D=0;np=10000;']...
%      ['areaRestrictL2=[24,31,33,34,35,36,37,41,81,82];drawL2=1;']]);

% using mutli-fiducial mapping to map out the lower visual field's center/periphery
% with data points taken from Steinbacka & Vanni, Clin. Neurophys, 118(6), 2007
%
vamca([['file1=''Stenbacka2007-UpperVis.txt'';fileout=''Sten-LVF'';']...
      ['mw=''MW4'';scatterSurf=1;permSurf=0;permSurfDisp=0;perm3D=0;np=10000;']...
      ['areaRestrictL2=''Occipital'';drawL2=1;']]);
```

Here we are using points taken from the manuscript by Stenbacka and Vanni where they attempt to map out where the visual field's far periphery is located in the visual cortex. In particular they find the following mean locations as computed from upper visual field fMRI data:

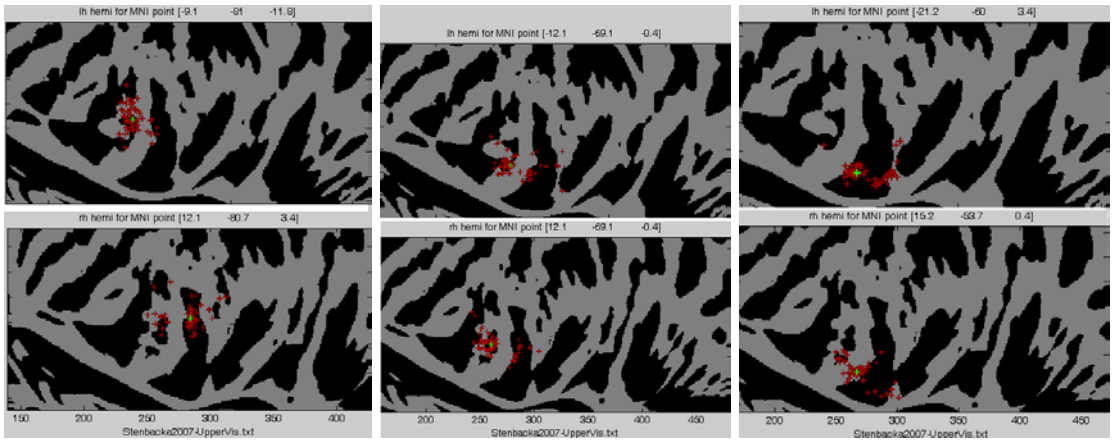
Stenbacka2007-UpperVis.txt - WordPad

File Edit View Insert Format Help

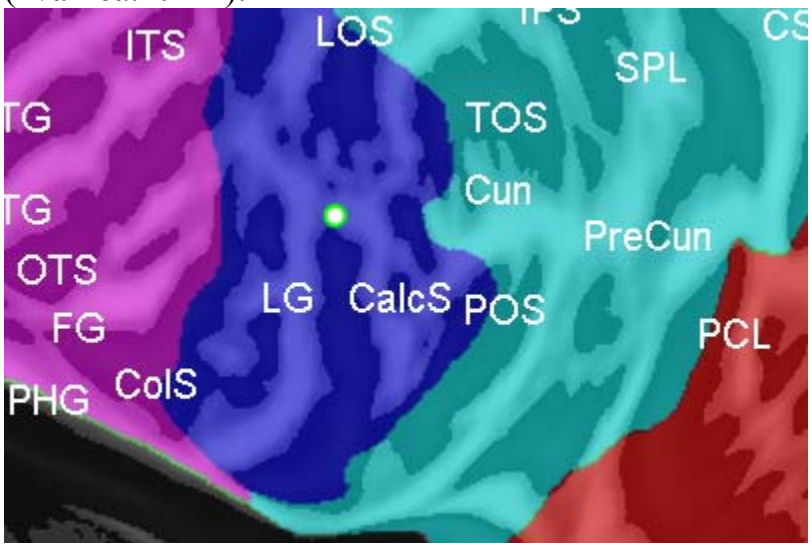
```
+12 -78 +07 TALSPM % 1-12 degrees
-09 -79 -06 TALSPM % 1-12 degrees
+12 -67 +03 TALSPM % 12-30 degrees
-12 -67 +03 TALSPM % 12-30 degrees
+15 -52 +03 TALSPM % 30-49 degrees
-21 -58 +06 TALSPM % 30-49 degrees
```

For Help, press F1

They provide Talairach coordinates (converted from MNI space using the well-known Brett transform – indicated by "TALSPM") for both the left and right hemispheres for 3 visual field ranges (in degrees from the center), as indicated by the comments in the text file (anything after the "%" character is ignored by the "vamca' command). In this VAMCA script, we will view the results with the occipital pole at the center of the world `'mw=''MW4'`. Running the command by typing "dovamca" produces three multi-fiducial figure (#'s 1,2, and 3), one for each of the three stereotaxic coordinates in each hemisphere:



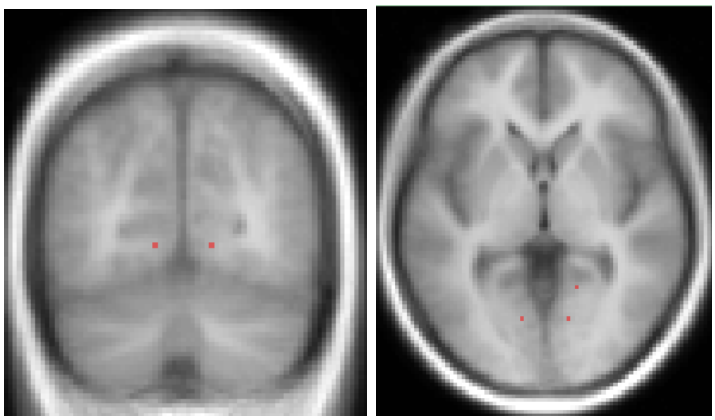
for the visual field degree ranges from left to right of 1-12, 12-30, and 30-45 degrees and where the key for this cortical surface map view is ("vamca.html"):



The left hemisphere is the cortical map in the top of each figure while the right hemisphere data is in the bottom subplot.

The fMRI data indicates that the activation locations moves away from the occipital pole (green and white dot) as the visual stimuli moves out further in the visual filed periphery. The upper visual filed multi-fiducial activations appear to be mainly in the calcarine sulcus (CalcS) and in the sulci associated with the lingual gyrus (LG).

In 3D (Sten-LVF.img) the 12-30 degree coordinates are located at a fairly symmetric location in both hemispheres:



The text file output by VAMCA in this case has the same kind of individual stereotaxic coordinates as before, but also computes the 3D median and mean of all three multi-fiducial medians in each hemisphere.

```
HCNLAB, Veterans Affairs, Martinez, CA, USA. www.ebire.org/hcnlab

 Left Hemisphere.

Points from Group 1: Stenbacka2007-UpperVis.txt
(-12.1,-69.1, -0.4)      weighted 3D median.     G_occipit-temp_med-Lingual_part
(-14.1,-70.1, -3.0)      weighted 3D mean.

Original MNI point   Med Dist  Mean Dist  Mn to Surf  Surf Frac  Surface Coord  Frac in ROI   Surface ROI Name
( -9.1,-81.0,-11.8)    16.8       15.0        1.4         1.00    MW4(-16, -11)     0.88       G_occipit-temp_med-Lingual_part
(-12.1,-69.1, -0.4)     0.0        3.4        1.8         1.00    MW4(-27, -14)     0.60       G_occipit-temp_med-Lingual_part
(-21.2,-60.0,  3.4)    13.4       13.8        1.2         1.00    MW4(-38,  -4)     0.95       S_calcarine

Mean center dist.:          10.1        10.7
Std. center dist.:           8.9         6.4


Right Hemisphere.

Points from Group 1: Stenbacka2007-UpperVis.txt
( 12.1,-69.1, -0.4)      weighted 3D median.     G_occipit-temp_med-Lingual_part
( 13.1,-67.8,  1.1)      weighted 3D mean.

Original MNI point   Med Dist  Mean Dist  Mn to Surf  Surf Frac  Surface Coord  Frac in ROI   Surface ROI Name
( 12.1,-80.7,  3.4)    12.1       13.1        1.5         1.00    MW4(-18,  -1)     0.68       S_calcarine
( 12.1,-69.1, -0.4)     0.0        2.3        1.9         1.00    MW4(-24, -18)     0.58       G_occipit-temp_med-Lingual_part
( 15.2,-53.7,  0.4)    15.8       14.3        1.4         1.00    MW4(-38, -14)     0.67       S_calcarine

Mean center dist.:           9.3         9.9
Std. center dist.:           8.3         6.6
```

In particular, the 3D median of each three points in each hemisphere is in fact the 12-30 degree activation location, and this makes sense given that it is between the other two along the anterior-posterior axis.

Mapping two groups of coordinates

Now we can move on to mapping several points from a two groups. For that we will comment out (via "%") the second "vamca" command in the script "dovamca.m" and uncomment out the third command:

```
% Reproducing the Face and Building selective activations from the studies
% cited in Hasson et al, Neuron, 37, 2003 [Figure 6]
%
vamca([['file1=''ffa.txt'';file2=''ppa.txt'';fileout=''FacePlace'';']...
      ['mw=''MW2'';scatterSurf=0;permSurf=0;permSurfDisp=0;perm3D=1;np=10000;']...
      ['permL2=0;areaRestrictL2=0;drawL2=0;cext=4;']]);
```

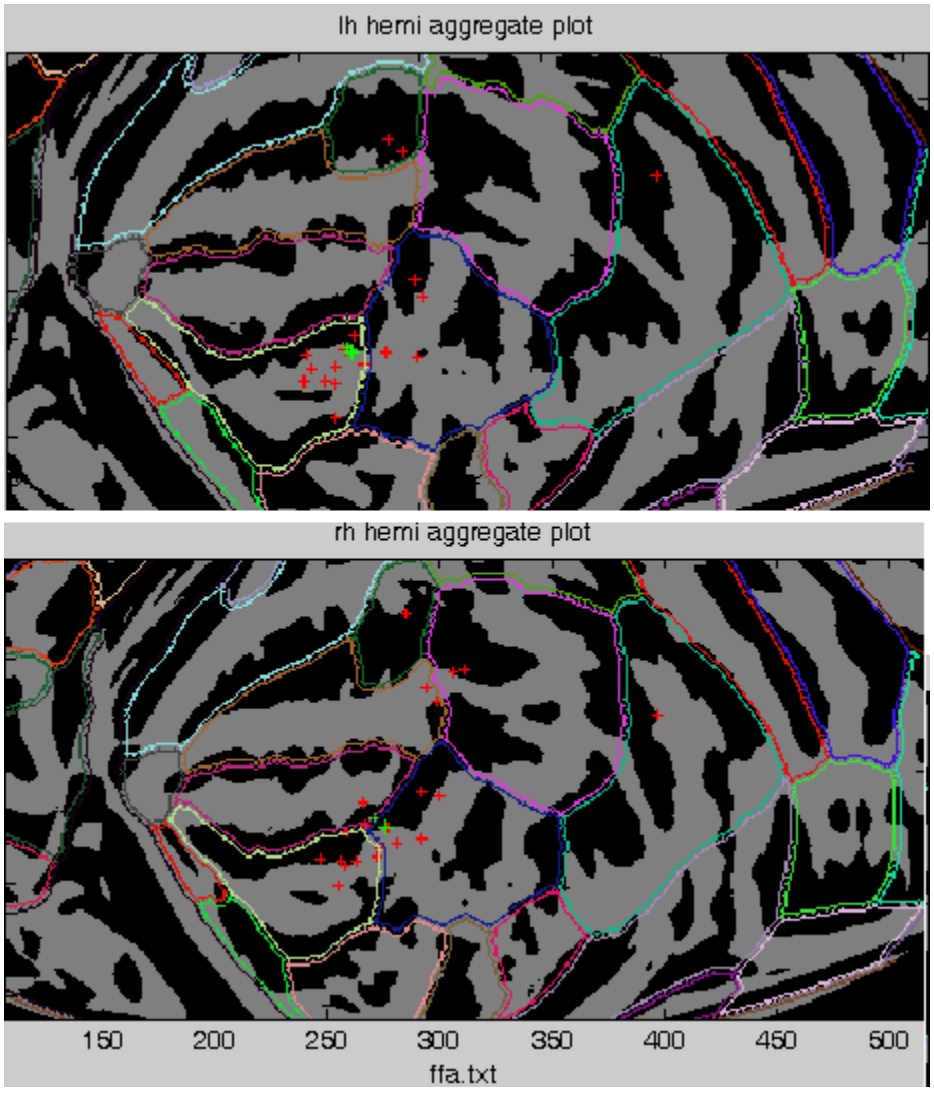
This data is taken from articles appearing in a small meta-analysis in the Hasson et al paper comparing (among other things) face-selective activation locations vs. building selective activation locations.

```
(-32,-65,-12)     % data fr
(38,-65,-14)
(-46,-60,-16)
(42,-50,-18)
(48,-56,-20)
(-44,-46,-20)
(44,-54,16)
(-37,-60,-22) Tal
(39,-55,-22) Tal
(-31,-82,-15) Tal
(41,-79,-14) Tal
(-33,-52,45) Tal
(29,-58,50) Tal
(52,-60,-24) Tal
(-42,-68,-22) Tal
(39.8,-55.4,-10.2) Tal
(-35.2,-63.2,-8.4) Tal
(54.6,-54.0,9.0) Tal
```

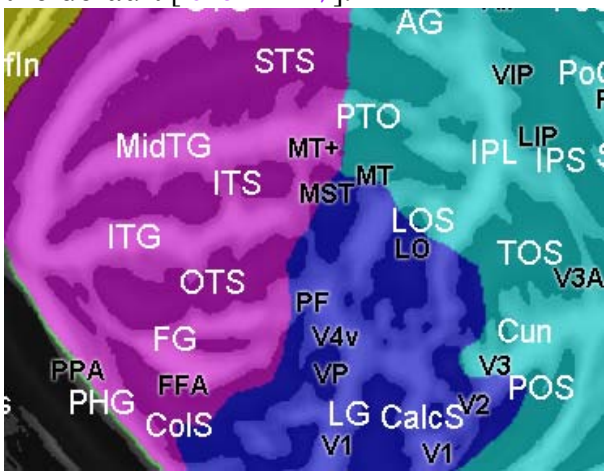
```
(18,-39,-6) Tal          % da
(-6,-34,30) Tal
(-20,-65,-10)
(32,-65,-12)
(-34,-50,-16)
(34,-60,-10)
(16,-36,-6)
(-22,-38,-12)
(-36,-82,24)
(-21,-82,-14) Tal
(24,-83,-11) Tal
(-27,-52,-14) Tal
(24,-55,-12) Tal
(-23,-87,7) Tal
(31,-86,14) Tal
(28,-42,-13) Tal
(-26,-46,-10) Tal
(-22,-43,-9) Tal
```

Face-selective data ("ffa.txt") is on the left, and building selective data ("ppa.txt") is on the right [file1="ffa.txt";file2="ppa.txt";]. Note that the default normalization is MNI-152 data.

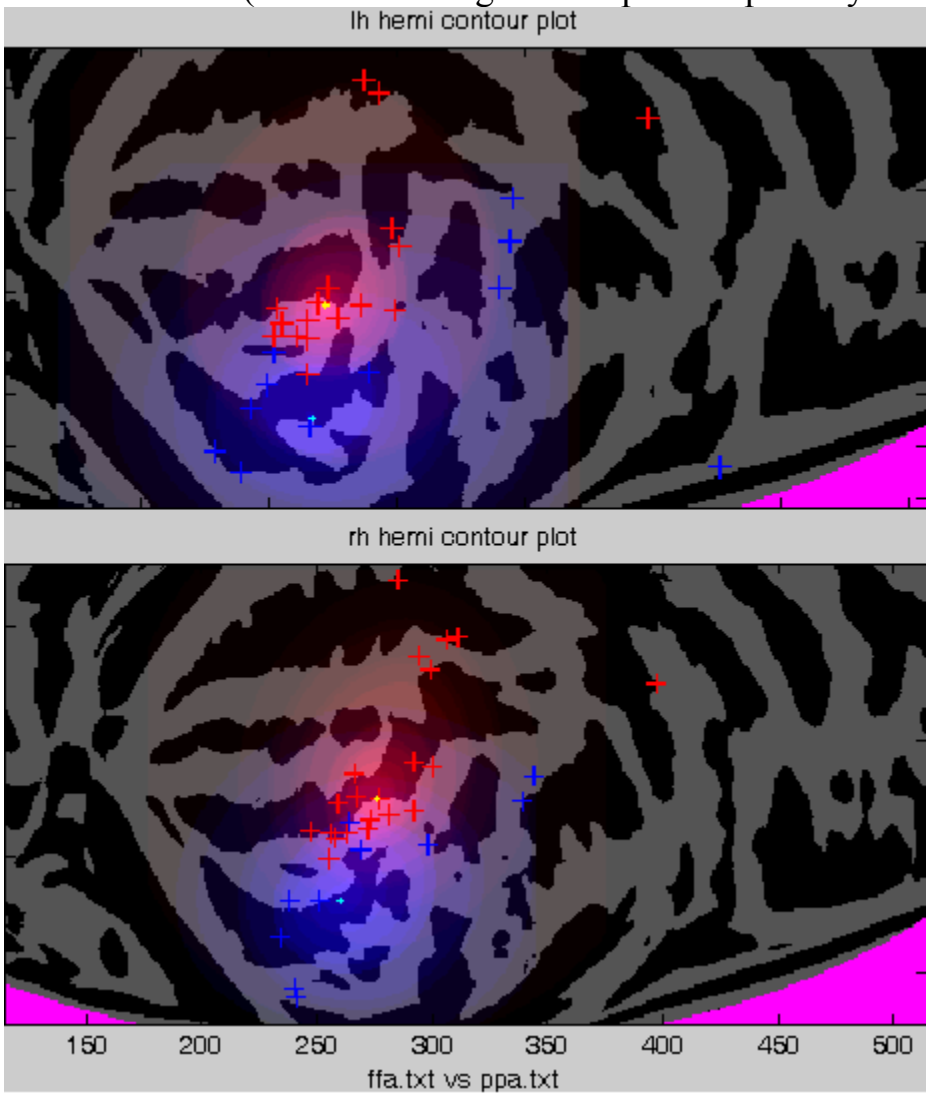
In this VAMCA analysis we no longer look at the multi-fiducial scatter maps, but instead focus on the median surface location data for all points in both group files. The first plot to look at (#1005) is the one that shows the locations (red crosses) of the 2D medians for each point in group 1 (ffa.txt), along with the 2D mean (small green cross) and 2D median (larger green cross):



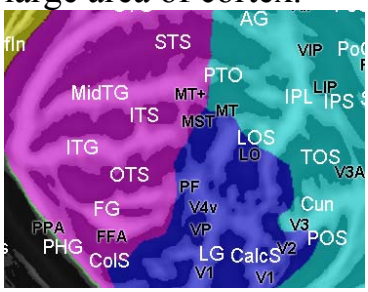
The data is plotted on the mean anatomy (grayscale) and with the coarse mean FreeSurfer ROI location boundaries in different colors [this option is the default [`drawL1=1;`].



The second plot to look at is the plot containing both groups on the same cortical surface (both left and right hemisphere separately – top and bottom).



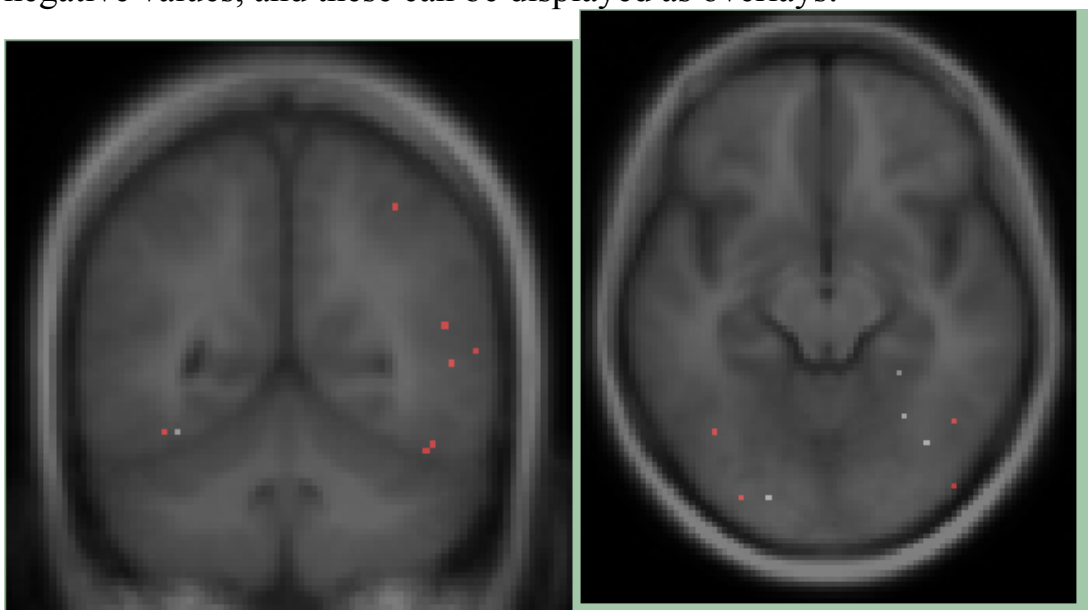
In this pair of surface maps, ffa.txt (red) vs. ppa.txt (blue) 3D coordinates mapped to the surface are shown. The yellow cross is the group 2D median for the red crosses (ffa.txt) while the cyan cross is the group 2D median for the blue crosses (ppa.txt). There appears to be not much overlap between the main clusters for each group, though each group is spread out over a large area of cortex.



The new part added to the text file that VAMCA outputs (FacePlace.txt) is the group 2 analysis:

```
Points from Group 2: ppa.txt
(-26.1,-57.9, -7.0)      weighted 3D median.     S_occipito-temporal_medial_and_S_Lingual
(-25.3,-62.4,  0.8)      weighted 3D mean.

Original MNI point   Med Dist  Mean Dist  Mn to Surf  Surf Frac  Surface Coord  Frac in ROI   Surface ROI Name
( -4.9,-31.6, 32.2)    51.8       48.5        1.2         1.00    MW2(-58, 134)     0.85       G_cingulate-Main_part
(-20.4,-68.8, -8.6)    12.4       12.4        1.6         1.00    MW2(-48, -16)     0.60       S_occipito-temporal_medial_and_
(-35.7,-53.5,-16.6)    14.3       22.1        1.8         1.00    MW2(-32, -24)     0.75       G_occipit-temp_lat-Or_fusiform
(-22.7,-40.3,-13.7)    19.1       26.5        1.4         1.00    MW2(-55, -51)     0.45       S_occipito-temporal_medial_and_
(-37.2,-83.4, 31.2)    47.2       38.8        1.6         1.00    MW2(  0,  38)     0.60       G_occipital_middle
(-21.5,-87.3,-11.3)    30.0       28.0        1.8         1.00    MW2(-36,   2)     0.40       G_and_S_occipital_inferior
(-28.1,-55.4,-14.3)     8.0       16.9        1.2         1.00    MW2(-39, -28)     0.50       G_occipit-temp_lat-Or_fusiform
(-23.4,-90.4, 12.6)    38.1       30.5        1.8         1.00    MW2(-18,  35)     0.45       S_occipital_middle_and_Lunatus
(-27.0,-48.6,-10.5)    10.0       17.9        1.3         1.00    MW2(-44, -33)     0.67       S_occipito-temporal_medial_and_
(-22.7,-45.3, -9.8)    13.4       20.3        1.3         1.00    MW2(-59, -46)     0.45       S_occipito-temporal_medial_and_
(-35.2,-81.4, 17.5)    35.2       27.2        1.5         1.00    MW2( -9,  37)     0.50       S_occipital_superior_and_transv

Mean center dist.:          25.4        26.3
Std. center dist.:          15.7        10.4
```

Also, the 3D coordinates from group 2 are added to the output file as negative values, and these can be displayed as overlays:

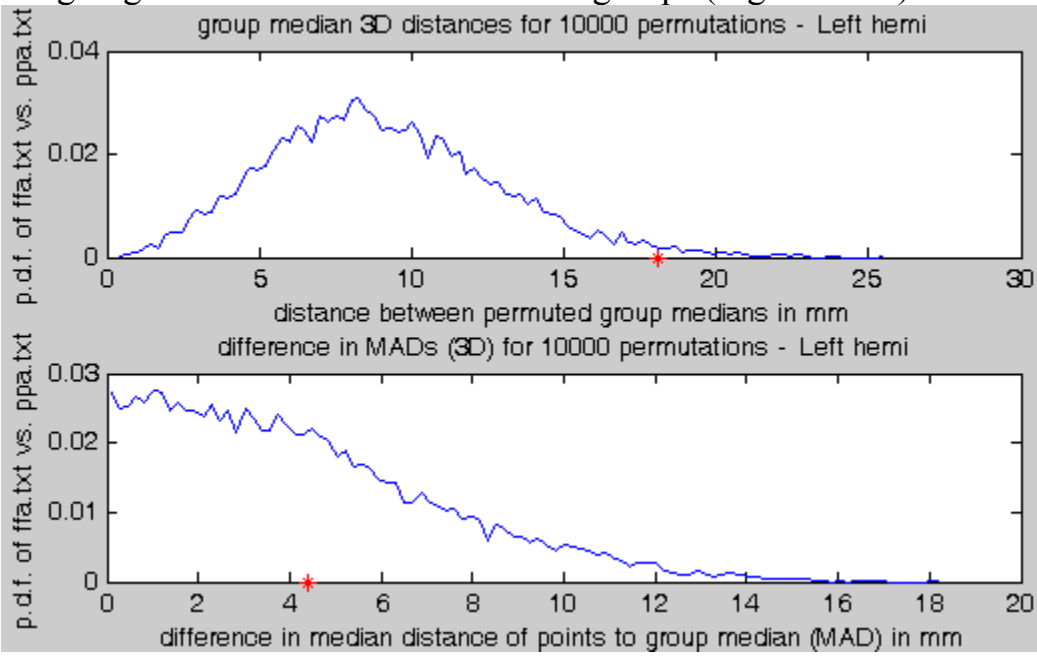


with the red as from group 1 (ffa.txt) and the gray from group 2 (ppa.txt).

When we observe the overlays, we notice that the face activations and building activations are somewhat clustered in different locations (accounting for the separate red and blue glows in the surface maps one page earlier). We now walk through the results of an analysis of the significance of this apparent 3D group separation.

Analysis of the 3D separation of two groups of coordinates

To analyze the separation of the group medians in 3D space from the current example, we chose the VAMCA options [`perm3D=1;np=10000;`] which tells it to perform a two-group permutation test of 10,000 permutations of group membership. The test is a test to see whether or not the two group medians are a significant distance apart compared to what would happen if randomly assigning all 3D coordinates to the two groups (Figure 1000):



So for the left hemisphere, the top blue line shows the distribution of median inter-group distances in 3D (the distance between brightest + and – dots in the overlay) obtained when we repeat the above analysis after first randomly assigning processed points to ffa.txt and ppa.txt. The red asterisk "*" is the actual distance using correct group assignments, and we see that it appears to be unusually large, indicating that the ffa.txt and ppa.txt groups are significantly separated from each other. This can be confirmed by looking at the output file again:

```
3D Distance (mm) between the two group medians:    18.1
p value computed using 10000: permutations of the 2 groups:  0.017
```

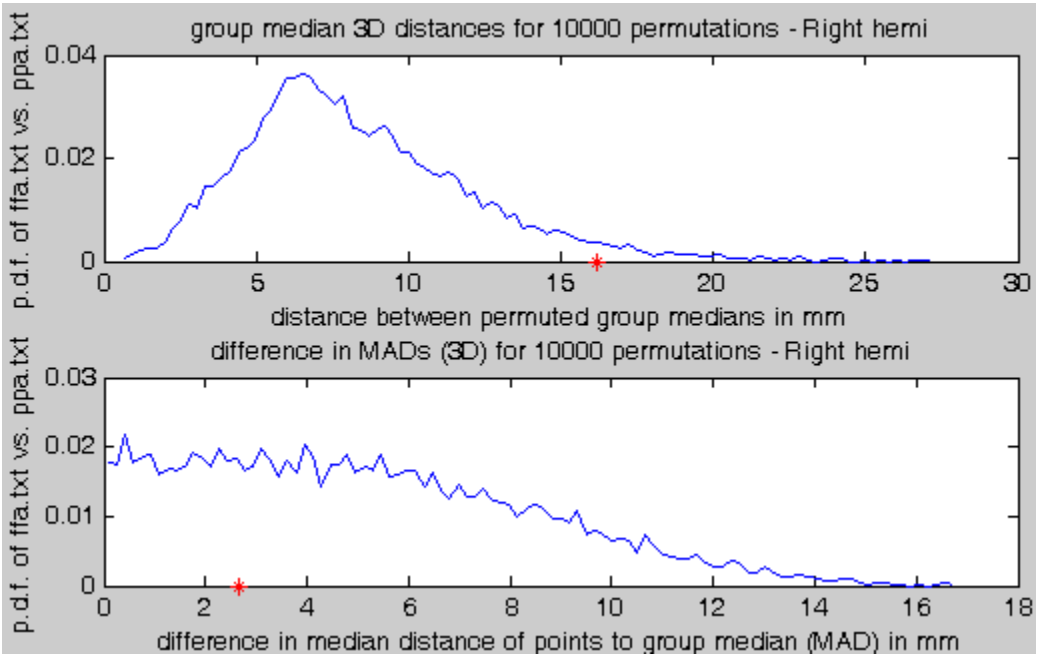
The bottom graph helps us check to see if the two groups have comparable spatial spread in 3D; again a permutation test computes the distribution (blue) of median absolute distances from the group median within each group and subtracts them and compares that to the current such value (red).

It appears that our two group's internal coordinate dispersions are (accounting random scatter) the same.

```
2 groups' median 3D distance to the group median (MAD):    14.7,    19.1
p value computed using 10000: permutations of |MAD(1)-MAD(2)|:  0.416
Robust d: (Medians's Distance)/(MAD/0.6745):    0.82
```

Thus, the primary separation analysis above is probably valid[1], with reasonably strong robust d' separation of ~0.8.

We get similar results when analyzing the MNI space coordinates for group separation (Figure 1001):




```
3D Distance (mm) between the two group medians:    16.2
p value computed using 10000: permutations of the 2 groups:  0.038
```

```
2 groups' median 3D distance to the group median (MAD):   15.8,    18.4
p value computed using 10000: permutations of |MAD(1)-MAD(2)|:  0.712
Robust d: (Medians's Distance)/(MAD/0.6745):    0.68
```

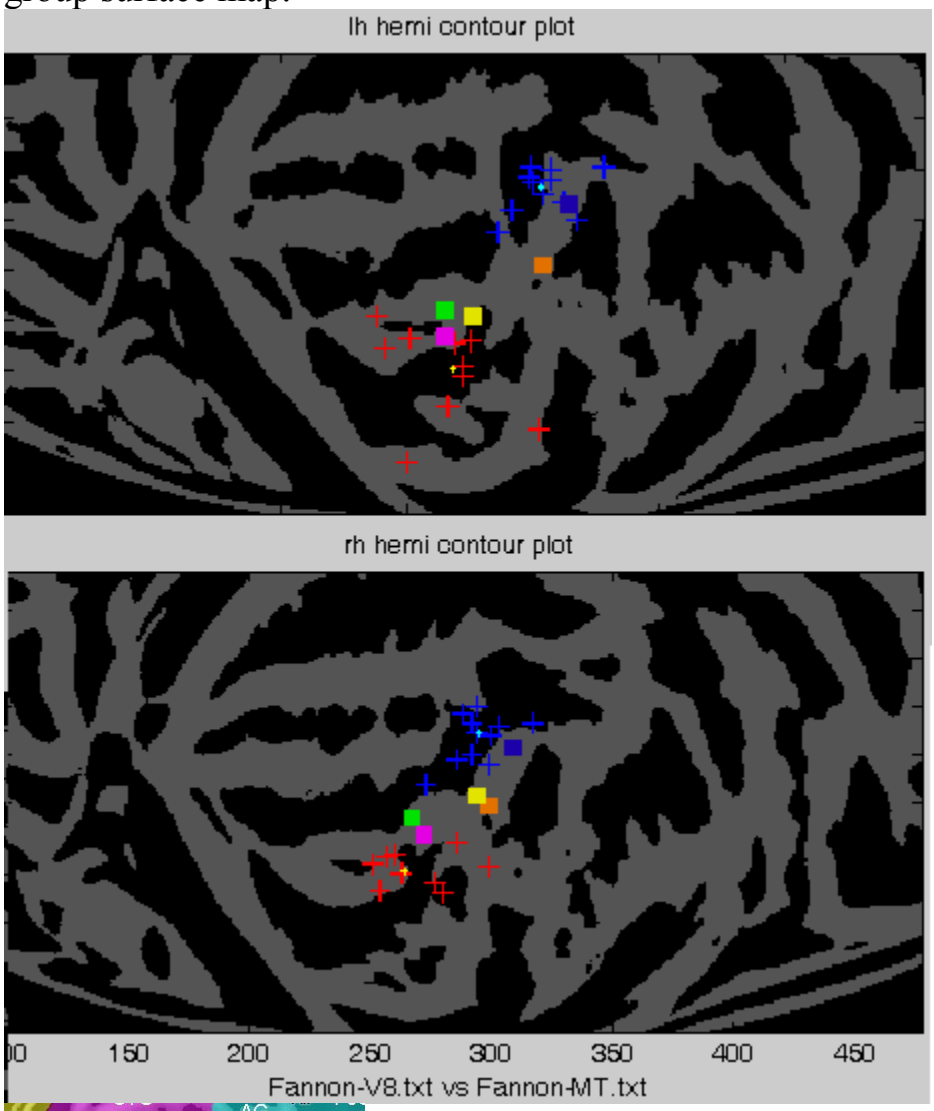
The left hemi 3D separation is perhaps a bit stronger.

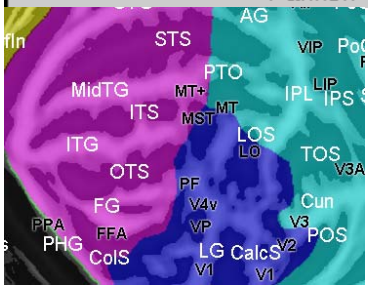
[1] Permutations tests are subject a similar problem affecting more familiar significance tests like basic t-tests: they work best when two groups are homoscedastic, i.e. having roughly the same dispersion. Otherwise a permutation-based separation test can generate a (rather weak) false positive separation p value from two spatially heteroscedastic groups.

Adding additional coordinates to a map

```
% reconstructing Figure 3 in Fannon et al, Frontiers in Neuroscience, 1(7), 2007
vamca([['file1=''Fannon-V8.txt'';file2=''Fannon-MT.txt'';fileout=''Fannon'';']...
      ['mw=''MW2'';scatterSurf=0;permSurf=0;permSurfDisp=0;perm3D=0;np=10000;']...
      ['permL2=0;areaRestrictL2=0;drawL2=0;extraPoints=''Fannon-extra.txt'';cext=4;']]);
```

The parameter [`extraPoints=''Fannon-extra.txt'';`] tells “vamca” to include the points in the specified file as extra plots to be added into the main both-group surface map.

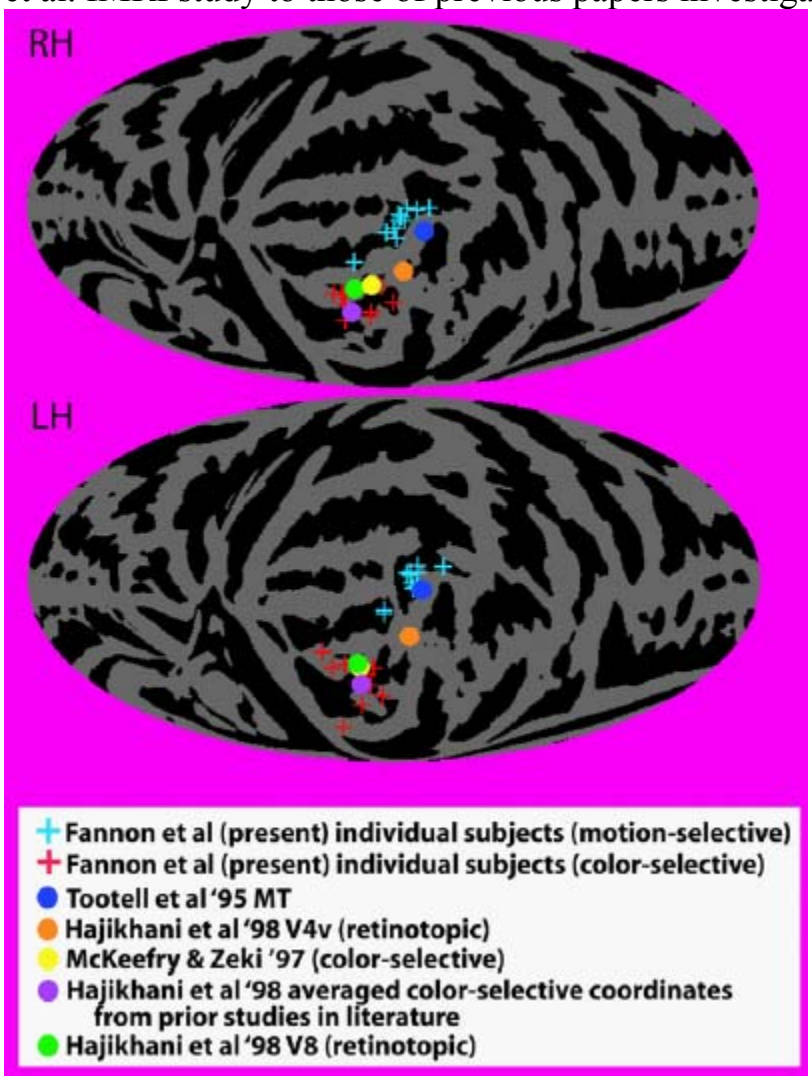




The “extraPoints” file includes additional RGB color values and block size value after the MNI/Talairach coordinates appear that control the look of the added.

```
Tal -32 -87 -16.1  840.3    % data from Fannon et al, Frontiers in Neuroscience, 1(7), 2007
Tal 32 -87 -16.1   840.3    %
Tal -33 -65 -14.1  080.3    % "weights" here are color/size data in RGB.S format
Tal 33 -65 -14.1   080.3    %
Tal 45 -76 3.1     106.3    % R - how much red color 0-9
Tal -45 -76 3.1    106.3    % G - how much green color 0-9
-29.3 -74.4 -10.5  880.3    % B - how much blue color 0-9
34.0  -82.8 -17.9  880.3    % S - how big a square to plot 1-9
Tal -27.5 -67.5 -11.5 808.3
Tal 28 -71 -14        808.3
```

The added points in this case are used to compare the results of the Fannon et al. fMRI study to those of previous papers investigating visual cortex:



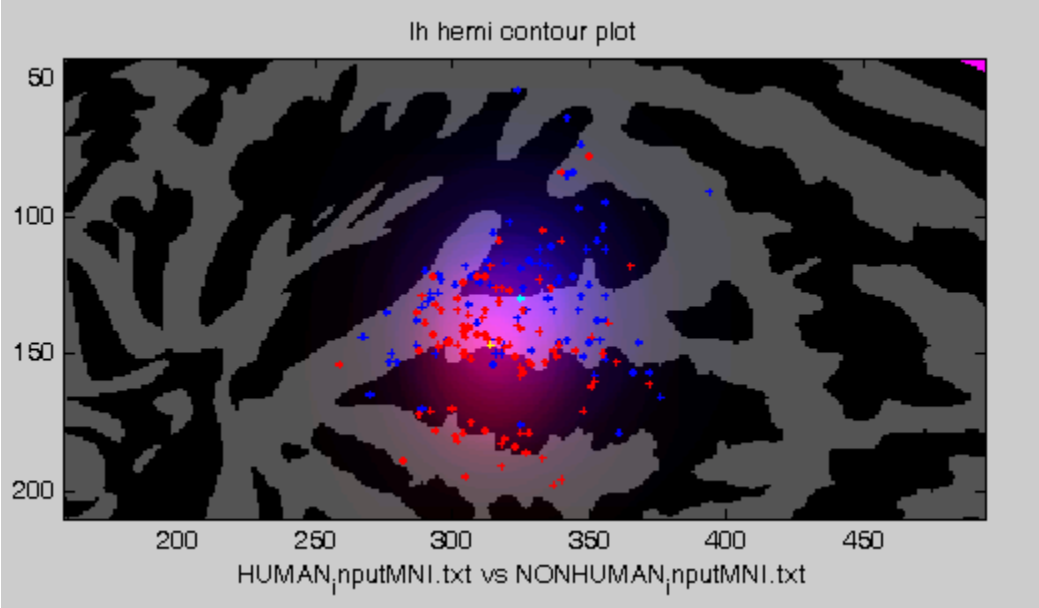
The figure from the paper. Not identical because we have made some small surface corrections in the database in the meantime.

Analysis of surface separation of two groups

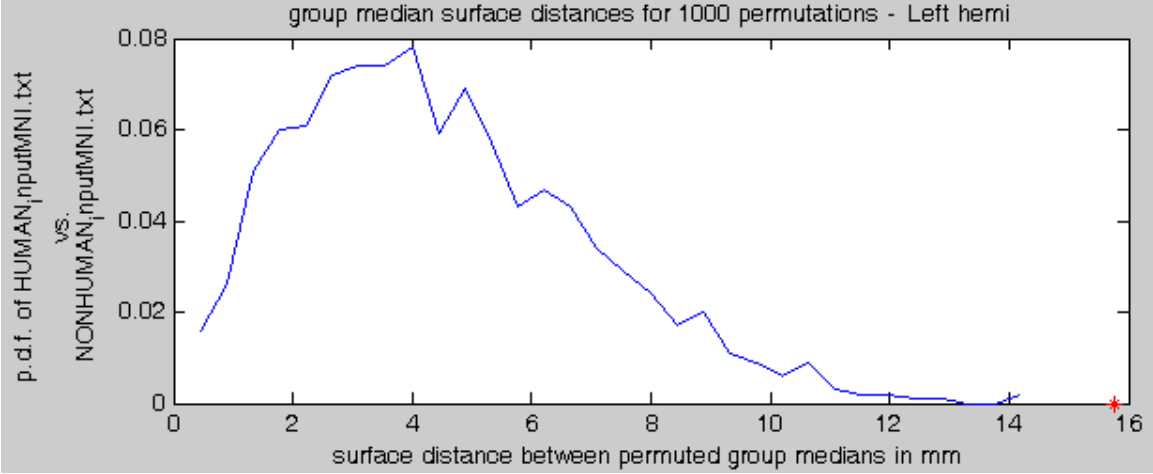
Now we move on to do some statistical analyses of group separation on the 2D cortical surface in the hopes of gaining some separation power because the 2D surface stretches out sulci by unfolding it during inflation (the inflation that was performed during the creation of the database). Thus, we execute the following analysis in "dovamca.m" to analyze the activation locations within auditory cortex of some human-made sounds vs those sounds not generated by humans.

```
% Example 1 in VAMCAmethod.pdf (CNS 2008 poster) [data from VAMCAauditory.pdf]
% showing an example of a meta-analysis significance test
%
vamca([['file1=''HUMAN_inputMNI.txt'';file2=''NONHUMAN_inputMNI.txt'';fileout=''HumanvsNo
nhuman'';'']...
      ['mw=''MW1'';scatterSurf=0;permSurf=1;permSurfDisp=0;perm3D=1;np=5000;']...
      ['permL2=1;areaRestrictL2=[24,31,33,34,35,36,37,41,81,82];drawL2=1;']]);
```

We obtain the usual map of the two groups of median surface coordinates (and two group medians):



In addition to the 3D permutation test of group separation, we also specified that a test of group surface distance separation be done given the apparent distance between the cyan and yellow crosses above: `permSurf=1;`. We then obtain the following graph (Figure 1010):

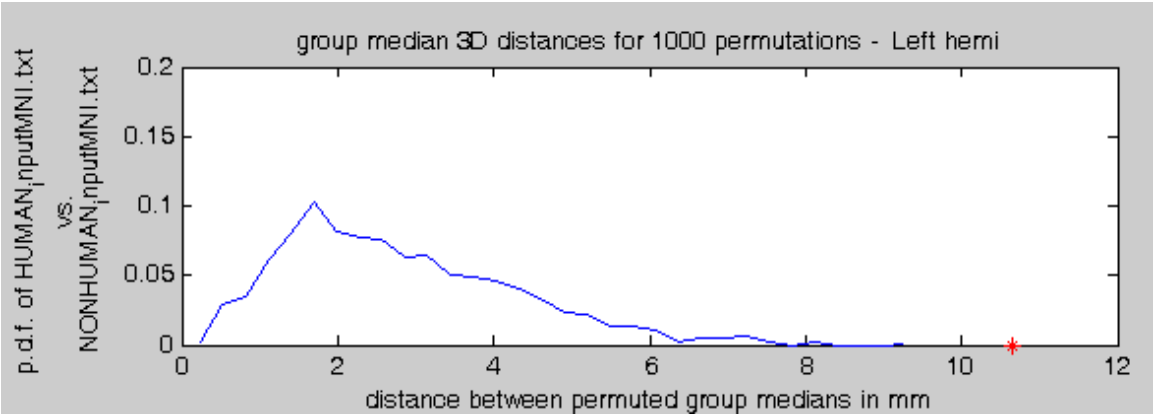


along with the numerical information in the associated text file "HumanvsNonhuman.txt":

```
Surface Distance between the two group medians (mm):    15.8
p value computed using 1000 permutations of the 2 groups:  0.000
```

This confirms that the surface distance between the two group centroids is unusually large (similar to what the 3D analysis concludes). If we had set the vararіable `scatterSurf=0;` to 1 instead of 0, we could have generated a comparison of the two groups' dispersions as we did in the 3D separation analysis – however, such a check of group homoscedasticity takes quite a while to do so (up to a few hours), so we skip it for now.

If we compare the 3D group separation permutation test to the surface group separation permutation test, we see that the separation of the groups medians that are on opposite sides of the superior temporal gyrus is greater on the surface:



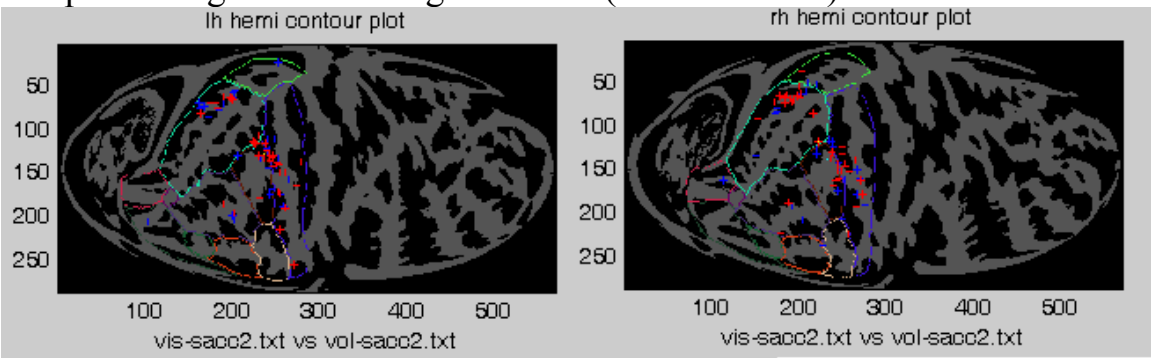
However, the level of significance of the separation tends to be similar for the two analyses**.**

ROI density analysis & coordinate weighting

In the next sample analysis we look at redoing an analysis that tries to detect significant differences in the distribution of activations for two conditions (visually triggered vs voluntarily triggered saccades) when the coordinates are spread over a rather large area – in this case over the frontal lobe. Here we also do the analysis with three different weightings in order to try and insure that various potential problems with the coordinates are not driving the results. Thus, in "dovamca.m" we want to execute the following 3 commands, all of which include the parameter `areaRestrictL1=''Frontal'';` that screens out coordinates determined not to reside in the frontal lobe:

```
% Example 2 in VAMCAmethod.pdf (CNS 2008 poster) [data from www.brainmap.org using
%                               studies from Grosbras et al, Human Brain Mapping, 28, 2005]
%
% First using evenly weighted 3D coordinates
vamca([['file1=''vis-sacc.txt'';file2=''vol-sacc.txt'';fileout=''VisvsVol'';']...
      ['mw=''MW3'';scatterSurf=0;permSurf=0;permSurfDisp=0;perm3D=0;np=10000;']...
      ['permL1=1;areaRestrictL1=''Frontal'';drawL1=1;cext=4;cmext=0;sext=4;smext=8;']]);
%
% Second using experiment-weighted coordinates
vamca([['file1=''vis-sacc2.txt'';file2=''vol-sacc2.txt'';fileout=''VisvsVol2'';']...
      ['mw=''MW3'';scatterSurf=0;permSurf=0;permSurfDisp=0;perm3D=0;np=10000;figureAdd=10000;']...
      ['permL1=1;areaRestrictL1=''Frontal'';drawL1=1;cext=4;cmext=0;sext=4;smext=8;']]);
%
% Third using experiment-and-subject-weighted coordinates
vamca([['file1=''vis-sacc3.txt'';file2=''vol-sacc3.txt'';fileout=''VisvsVol3'';']...
      ['mw=''MW3'';scatterSurf=0;permSurf=0;permSurfDisp=0;perm3D=0;np=10000;figureAdd=20000;']...
      ['permL1=1;areaRestrictL1=''Frontal'';drawL1=1;cext=4;cmext=0;sext=4;smext=8;']]);
```

Note that when we call VAMCA three times, we assign separate figures to each of the analyses via the parameter `figureAdd=20000;`. This parameter adds the quantity assigned (`20000`) to all of the figure numbers generated in that analysis. For example in the experiment-weighted analysis (#2), the group comparison figure will be Figure 11015 (=1015+10000):



where the frontal lobe ROIs are the only ROIs on the cortex that are outlined in color.

In these analyses, the weightings assigned to each coordinate file are specified manually as the 4th number in each row, e.g.:

C:\...\David L. Woods\Desktop\tcc\domni\vis-sacc.txt

```
TAL     -14     -76     28      1.00002
TAL     14      -76     -24     1.00003
TAL     -18     -68     36      1.00004
TAL     -2      -74     36      1.00005
TAL     -24     -6      52      1.00006
TAL     20      -2      52      1.00007
```

C:\...\David L. Woods\Desktop\tcc\domni\vis-sacc2.txt

```
TAL -14.000000 -76.000000 28.000000 0.166667
TAL 14.000000 -76.000000 -24.000000 0.166667
TAL -18.000000 -68.000000 36.000000 0.166667
TAL -2.000000 -74.000000 36.000000 0.166667
TAL -24.000000 -6.000000 52.000000 0.166667
TAL 20.000000 -2.000000 52.000000 0.166667
TAL -33.000000 -63.000000 54.000000 0.100000
TAL 21.000000 -63.000000 46.000000 0.100000
```

In the first file, the weighting is the default weighting where every coordinate has equal weight – a simple analysis that is reasonable when most studies in the analysis have equal power and report roughly the same number of coordinates. The second analysis weights each study's coordinates to sum to 1, which is useful when there are serious imbalances in the number of coordinates reported between studies included.

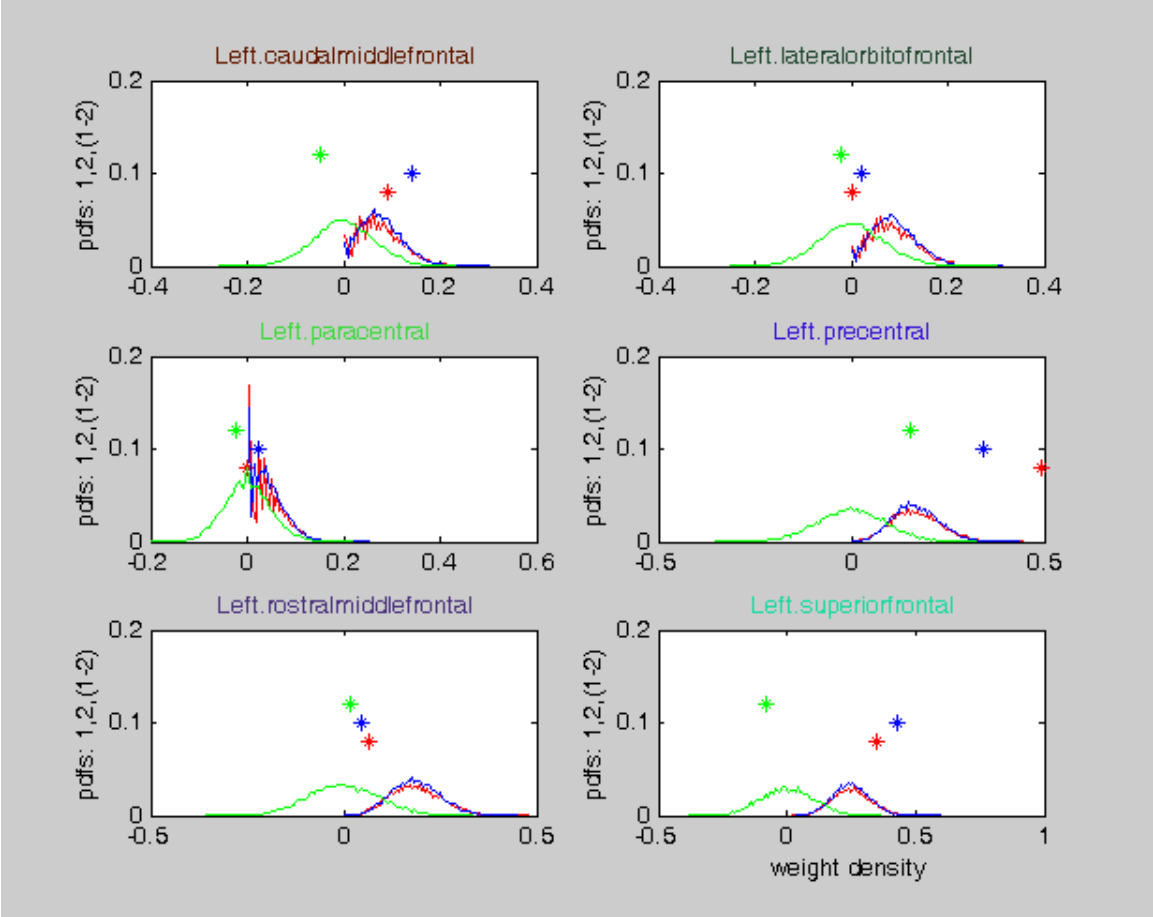
In all of the three analyses above we have asked VAMCA to execute a more familiar ROI-based analysis that is useful when the coordinates input are spread out over the cortex more widely than in the previous examples. Here, we are trying to determine, first, whether or not there are an unusually large number of coordinates from a group in any given cortical ROI. Thus, we again use a permutation test to compare actual densities (from coordinate weightings) of coordinates within ROIs to densities of coordinates when randomly scattered (evenly given a cortical ROI's mean area) over the cortical surface locations under consideration – here the whole frontal lobe (see vamca.txt for more information about specifying location restrictions). Thus, in the left hemisphere for the second (study weighted) analysis, we obtain from the output file "VisvsVol2.txt":

```
p value for ROI point density of group 1, group 2, & (1-2) (10000 permutations
L1 # 4 caudalmiddlefrontal     :  0.351 ,  0.086 , -0.207
L1 #13 lateralorbitofrontal    :  0.989 ,  0.947 , -0.370
L1 #18 paracentral             :  0.916 ,  0.718 , -0.325
L1 #25 precentral              :  0.000 ,  0.005 ,  0.040
L1 #28 rostralmiddlefrontal    :  0.978 ,  0.994 ,  0.411
L1 #29 superiorfrontal         :  0.100 ,  0.009 , -0.223
```

The rows indicate the frontal lobe ROIs that have one or more coordinates located within them. The first column of numbers indicates the p values (from the permutation test) of densities for each ROI given the coordinates in group 1 – significant in the precentral area and maybe a trend in the superior frontal ROI. Column two likewise contains density p values for

group 2, which again shows significant density in the precentral ROI and in the superior frontal ROI and perhaps a trend in the caudal middle frontal ROI.

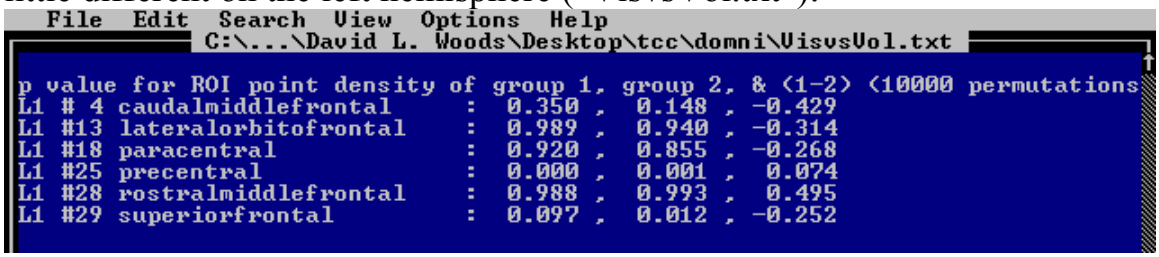
Second, if two groups have been input, we also analyze via a group membership permutation test if there are group density differences within any ROI, thus in this case testing if there is a location difference in the BOLD activations for visual vs voluntary eye movements. This latter analysis is not so dependent upon the questionable assumption (as is the first) that activations would otherwise be spread evenly across the region of cortex in question. In the above analysis the p values for density differences are contained in the third column, where we see in this case that the only significant difference is that group 1 (visual saccades) appears to have more summed weights from coordinates than does group 2 (voluntary saccades) in the precentral area (p=0.04). The numerical results from the output file are also displayed in graphic form in Figure 11020:



The red and blue colored "*"s show actual relative densities within each ROI for each group (ROI label colors match ROI outlines in the Figures) and

correspondingly colored distribution functions show the density results of the group permutation calculation. Green colored distributions and "*" are for the group density differences, which shows the precentral ROI having the only (marginal) density difference unlike, e.g., the superior frontal area.

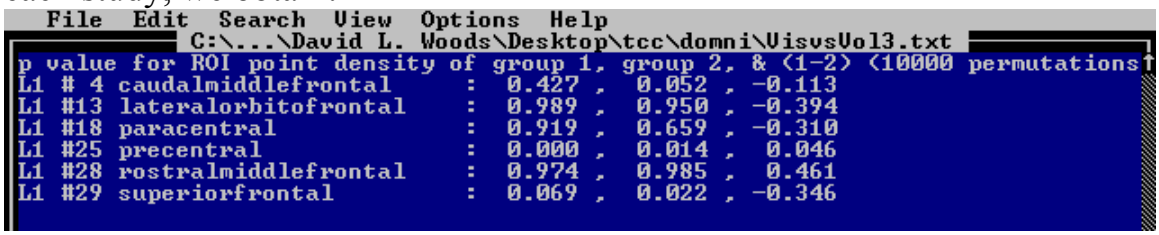
The analysis in the evenly weighted coordinate case (first analysis) looks a little different on the left hemisphere ("VisvsVol.txt"):


File Edit Search View Options Help
C:\...\David L. Woods\Desktop\tcc\domni\VisvsVol.txt

```
p value for ROI point density of group 1, group 2, & (1-2) (10000 permutations
L1 # 4 caudalmiddlefrontal     :  0.350 ,  0.148 , -0.429
L1 #13 lateralorbitofrontal    :  0.989 ,  0.940 , -0.314
L1 #18 paracentral             :  0.920 ,  0.855 , -0.268
L1 #25 precentral              :  0.000 ,  0.001 ,  0.074
L1 #28 rostralmiddlefrontal    :  0.988 ,  0.993 ,  0.495
L1 #29 superiorfrontal         :  0.097 ,  0.012 , -0.252
```

Here, the difference in density between the two groups in the Precentral ROI doesn't quite hit significance, so we should probably treat the result rather cautiously.

In the third analysis that also takes into account the number of subjects in each study, we obtain:


File Edit Search View Options Help
C:\...\David L. Woods\Desktop\tcc\domni\VisvsVol3.txt

```
p value for ROI point density of group 1, group 2, & (1-2) (10000 permutations
L1 # 4 caudalmiddlefrontal     :  0.427 ,  0.052 , -0.113
L1 #13 lateralorbitofrontal    :  0.989 ,  0.950 , -0.394
L1 #18 paracentral             :  0.919 ,  0.659 , -0.310
L1 #25 precentral              :  0.000 ,  0.014 ,  0.046
L1 #28 rostralmiddlefrontal    :  0.974 ,  0.985 ,  0.461
L1 #29 superiorfrontal         :  0.069 ,  0.022 , -0.346
```

The good news is that, for the most part, the three variations on the ROI analysis agree with each other, though it would be best to check the coordinate files just to make sure that one or two studies are not driving the results obtained (one could also do a jackknife analysis just to be sure).

In the next example in this tutorial, we will see what we would consider the best ROI type analysis that takes into account the each study as the unit of analysis and weights it according to the number of subjects it contained.

ROI specification and study-based weighting

In this final tutorial example we extend the ROI density analysis to easily handle more sophisticated situations where we want to try and insure that the significant densities or density differences detected are robust to variations in or complications of the analysis. Here we look at analyzing anatomical and metabolic data associated with traumatic brain injury - in particular recording locations of MR-indicated anatomical damage or hypometabolism associated with TBI groups.

```
% Penultimate example in VAMCA_TBI.pdf (CNS 2009 poster) Cortical Metabolic deficits
%                       due to traumatic brain injury vs. cortical anatomical damage due to
%                       traumatic brain injury
%
vamca([['file1=''tbiMetabolix.txt'';file2=''tbiBadAnat.txt'';fileout=''metaVSanat-out'';']...
      ['mw=''MW3'';scatterSurf=0;permSurf=0;permSurfDisp=0;perm3D=0;np=10000;']...
      ['drawL1=1;permL1=1;cext=4;cmext=0;sext=4;smext=0;figureAdd=70000;sdmax=5;hemax=3;']...
      ['areaRestrictL1=[2:4,6:36];balanceLxWeights=0;numNullStudies1=1;numNullWeights1=sqrt(5)/2;']...
      'pureROIanalysis=0;']);
```

The first interesting extensions under this analysis is found in the coordinate files, e.g. for the hypometabolism data "tbiMetabolix.txt":

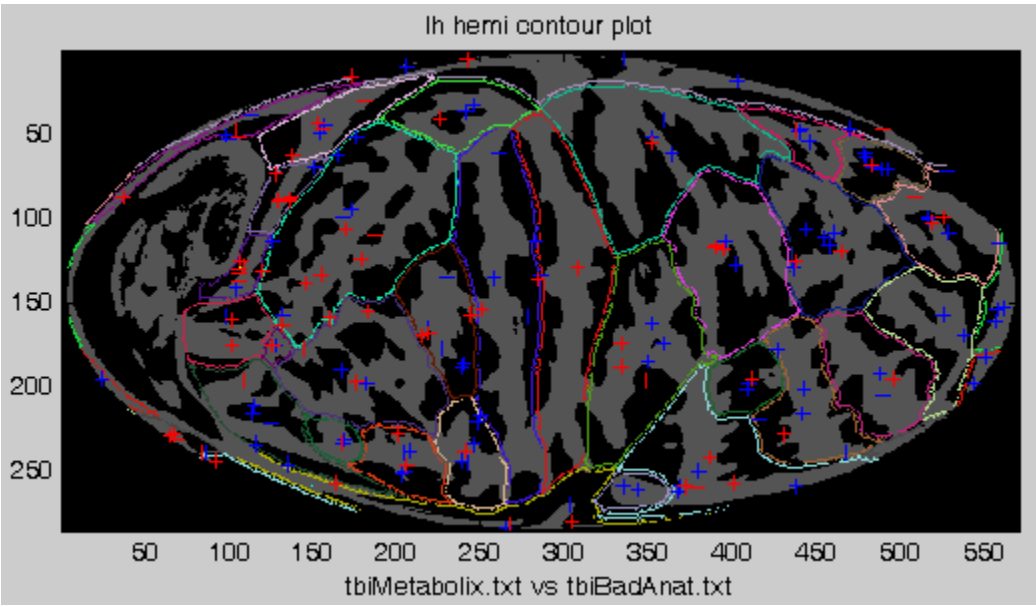
```
talspm 46 21 -16        0.0625  subjects 36      % kato2007 spm2+brett hypometabolic
talspm 44 16 -24        0.0625
talspm 48 13 -19        0.0625
talspm 4 -26 33 0.0625
talspm 2 -43 28 0.0625
talspm 10 -21 12        0.0625
talspm 4 -15 8  0.0625
talspm 14 -35 -5        0.0625
talspm 4 34 -20 0.0625
talspm 2 17 -18 0.0625
talspm 2 47 14  0.0625
talspm 44 19 -16        0.0625
talspm -36 21 -3        0.0625
talspm -34 18 -26       0.0625
talspm  -40 -17 8       0.0625
talspm  40 -48 -30      0.0625
mni rh 1 3 0.1  subjects 52% Nakayama2006 DAI hypometabolism in PET
mni rh 1 27 0.1
mni lh 1 3 0.1
mni lh 1 27 0.1
mni rh 1 15 0.1
mni lh 1 15 0.1
mni rh 2 4 0.1
mni rh 2 5 0.1
mni lh 2 4 0.1
mni lh 2 5 0.1
```

First, note that the coordinates are grouped explicitly by study here, and that the number of subjects per study is indicated by adding "subjects 36", e.g. after the very first coordinate weight. When this is done, the square root of the number of subjects is multiplied by each coordinate weight to get the final weight for each coordinate. In the above two studies, this means that the studies will have weights summing to the square root of the number of subjects.

Second, note that the second study – Nakayama 2006 - does not have coordinates specified. In fact what is being specified are the significant ROIs directly from the paper, which is useful in order to include studies that do not list 3D normalized coordinates (but do look for anatomically-specified damage/activations everywhere in the cortex). See "vamca.txt" for more information on how to specify ROIs directly: e.g. "mni rh 1 27 0.1" is the way to specify an activation in the right hemisphere's rostral anterior cingulate.

One other modification of the input appears in the VAMCA parameter specification line as `numNullStudies1=1;numNullWeights1=sqrt(5)/2;` . This tells VAMCA that we found one 5 subject PET metabolism study not listed in the input coordinate file that showed no significant differences between TBIs and normal controls – the parameters allows to use that fact in the ROI density permutation test. These parameters can also be used to test the robustness of analyses by allowing one to input null studies that might exist but were never published – i.e. as a way of trying to deal with the "file drawer" problem.

The resulting maps of TBI-related deficits are widely distributed throughout the cortex:



The significantly activated ROIs or those showing ROI density differences in the left hemisphere are:

```
p value for ROI point density of group 1, group 2, & (1-2) (10000 permutations):
L1 # 3 caudalanteriorcingulate :  0.001 ,  0.428 ,  0.000
L1 # 7 entorhinal              :  0.646 ,  0.007 , -0.005
L1 #11 isthmuscingulate        :  0.011 ,  0.071 ,  0.069
L1 #13 lateralorbitofrontal    :  0.773 ,  0.081 , -0.046
L1 #17 parahippocampal         :  0.723 ,  0.009 , -0.006
L1 #19 parsopercularis         :  0.739 ,  0.023 , -0.012
L1 #21 parstriangularis        :  0.532 ,  0.019 , -0.020
L1 #24 posteriorcingulate      :  0.010 ,  0.454 ,  0.011
L1 #27 rostralanteriorcingulate:  0.000 ,  0.448 ,  0.000
L1 #31 superiortemporal        :  0.081 ,  0.274 ,  0.181
L1 #34 temporalpole            :  0.002 ,  0.108 ,  0.010
L1 #36 insula                  :  0.091 ,  0.021 , -0.321
```

Many interesting ROIs on the medial and ventral surfaces are involved with TBI. However, the two analysis types (MRI vs PET) seem to highlight disjoint cortical areas as being damaged for the most part.

Two further options could have been selected but were not in the above analysis:

1) `balanceLxWeights=0;` If we set this =1, it allows one to make sure that the total weighting across two groups is the same. This can be useful in the case where there are many more coordinates/experiments in one group than another so that the smaller group density is competitive in the density difference permutation test.
2) If `pureROIanalysis=1;,` then VAMCA would perform an indicator-style ROI density permutation test on the input values (Etkins and Wager, J Am Psychiatry 164: 10 2007). In this, each study assigns the one weight (sqrt(# subjects)) to every ROI if there is one or more coordinates assigned to that ROI – a given study puts no extra weight into an ROI for having more than one point within an ROI. Such a weighting implements a very strict random-effects-style analysis, so the ROI must be activated consistently across studies in order for the density to be significantly above chance.

Additional Executable Functions

One function is available for use as post-processing executables. For example after processing the vamca command:

```
% Reproducing the Face and Building selective activations from the studies
% cited in Hasson et al, Neuron, 37, 2003 [Figure 6]
%
vamca([['file1=''ffa.txt'';file2=''ppa.txt'';fileout=''FacePlace'';']...
      ['mw=''MW2'';scatterSurf=0;permSurf=0;permSurfDisp=0;perm3D=1;np=10000;']...
      ['permL2=0;areaRestrictL2=0;drawL2=0;cext=4;']]);
```

If one later wants to come back and view the basic graphs associated with each input:

```
vamcaPlot('ffa.txt');
```

This uses the saved files ‘lh.ffa.txt.mat’ and ‘rh.ffa.txt.mat’ and redisplays the images from Figure 1005 in the original analysis using VAMCA plus 2 multifiducial maps, 1016 and 1017, showing a “cloud” of individual surface location for each coordinate with respeact to each database subject.

If we call

```
vamcaPlot('ffa.txt','ppa.txt');
```

This also recreates the figure 1006 along with plots on the multifiducial maps.

3D Image Files included in the /Image directory

1) *VAMCA_60Subject_T1mean.img* – ANALYZE format file mean T1 file for 60 subject VAMCA database. Useful for displaying VAMCA output files as overlays on this.
2) *VAMCA_60Subject_WMsurface_L1.img* – ANALYZE format file median 60 subject cortical surface as broken into the 34-parcel L1 cortical partition (see vamca.txt for codes). Can use this for seeing how close a 3D point is to a likely ROI.
3) *VAMCA_60Subject_WMsurface_prob.img* – ANALYZE format file 60 subject probabilistic cortical surface.
4) *VAMCA_60Subject_SubcorticalGrayMatter.img* – ANALYZE format file median subcortical GM parcellation file using FreeSurfer values. Can be used to see if a coordinate is near to the basal ganglia, etc.
5) *VAMCA_60Subject_Ventricles.img* – ANALYZE format file median file showing likely location of ventricles.
6) *VAMCA_DTI_FA.img* – Mean fractional anisotropy diffusion image map of 40 of 60 subjects in the VAMCA (young RH) database.
7) *VAMCA_DTI_MD.img* – Mean diffusivity DTI image map of 40 of 60 subjects in the VAMCA (young RH) database.
8) *VAMCA_DTI_Cl.img* – Linear fiber index DTI image map of 40 of 60 subjects in the VAMCA (young RH) database.
9) *VAMCA_DTI_DirX.img* – Medial/Lateral primary diffusion direction DTI image map of 40 of 60 subjects in the VAMCA (young RH) database.
10) *VAMCA_DTI_DirY.img* – Anterior/Posterior primary diffusion direction DTI image map of 40 of 60 subjects in the VAMCA (young RH) database.
11) *VAMCA_DTI_DirX.img* – Inferior/Superior primary diffusion direction DTI image map of 40 of 60 subjects in the VAMCA (young RH) database.