Functional Neuroimaging and the ALE Method: A 2D Analysis

Senior Project

Math 4394

Richard Castillo

Abstract

Over the past decade the functional imaging community has produced a wealth of experimental data in an ongoing attempt to understand the complex relationship between function and anatomy in the human brain. While methods for doing so were only beginning to emerge in the early 90s, they have been under constant refinement and improvement since then, such that today functional imaging studies and their results are widely accepted. With the acquisition of so much data, however, the need has arisen to be able to legitimately compare results across numerous studies. Inherent dissimilarities between any two experimental designs as well as the qualitative nature of most of today's comparison schemes have made this a difficult task. Here we discuss the two most widely employed imaging modalities, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), as well as a new approach for conducting comparison studies, or meta-analyses, know as the activation likelihood estimate (ALE) meta-analysis. A two-dimensional analogue to the ALE analysis is constructed to illustrate certain flaws inherent in the model, as well as to propose a possible means for correcting them.

1 Functional Magnetic Resonance Imaging (fMRI)

Magnetic resonance techniques that allow for the creation of anatomical, or morphological, images have been under development since 1973. MRI is a non-invasive procedure that can produce images with a spatial resolution of less than one millimeter with exquisite soft-tissue discrimination. It is for these reasons that MRI has become the modality of choice for radiologists in the investigations of nearly all brain abnormalities and injuries. However, at one point MR physicists realized that if the technology could be made sensitive to changes in blood flow, it might be possible to utilize magnetic resonance principles when mapping human brain function (1). Ogawa (2) and Turner (3) independently showed in the early 1990's that MR images could be made sensitive to the level of oxygenation in cerebral blood. Sensitivity to cerebral blood oxygenation level is an indirect measure of localized brain activity. This finding led to the development of the field of functional magnetic resonance imaging (fMRI) research.

Although the relationships between neural activity, cellular metabolism, and changes in blood flow are still not fully understood, there is a basic chain of events that is known to take place during neuronal activation (1):

1. A need arises for the brain to perform a task.
2. Neuronal activity increases in certain areas of brain gray matter.
3. Metabolic activity is increased in these areas.
4. The rates of oxygen usage in these areas are increased.
5. Blood flow increases in the arterioles and capillaries of the electrically active tissue.
6. Capillaries experiencing increased blood flow dilate by 5-10%.
7. Oxygen supply to active tissue begins to exceed demand.
8. Oxygen in the venous pool decreases.
9. If neuronal activity persists, vascular and metabolic changes reach equilibrium in 1-3 minutes.
10. When neuronal activity returns to baseline, blood flow returns to baseline.

MR images are affected by these vascular changes. Hemoglobin, the pigment responsible for transporting oxygen from the lungs to the tissues, has magnetic properties that depend on its state of oxygenation, which is regulated by the partial pressure of oxygen in the blood. Oxygenated hemoglobin is a diamagnetic molecule like water and cellular tissue, but deoxyhemoglobin is more paramagnetic than tissue and produces a stronger MR effect. A susceptibility difference is caused between the blood vessel wall and its surrounding tissue due to the presence of deoxyhemoglobin. If an appropriate imaging sequence is selected that takes advantage of these differences in magnetic properties, then the changes in oxygen levels may be large enough to affect MR image intensity, and deoxyhemoglobin functions as an endogenous contrast agent (1).

The goal of fMRI is to detect the MR signal change that occurs during neuronal activity. This is referred to as the blood oxygen level-dependent (BOLD) contrast. In an fMRI experiment, the brain is repeatedly imaged while the subject is presented with some stimulus or required to perform some task. This experiment is characterized by the scanning sequence, the design paradigm of the stimulus, and the method of analysis of the data.

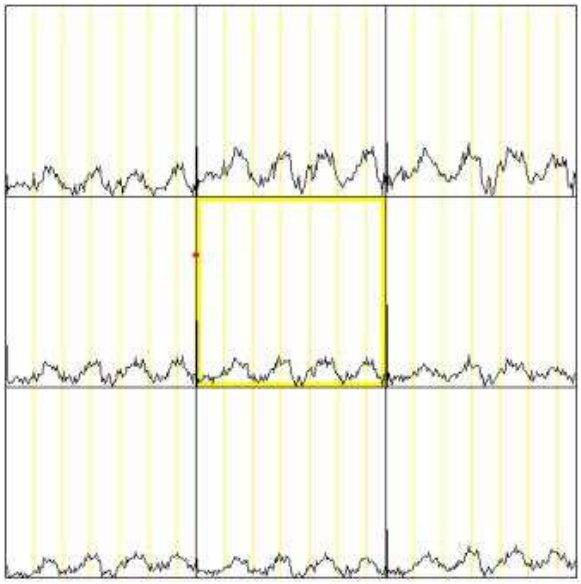

Figure 1: A sample of nine voxels time courses collected during an fMRI scan.

To study changes in oxygen levels in the blood due to some task activation, typically 150 whole brain images are acquired in one scan. For a repetition time of two seconds, this would require a scan length of five minutes. According to the scan protocol, 64 by 64 voxels are imaged in one slice. Each voxel measures 3.75 millimeters by 3.75 millimeters by 7 millimeters. Thus if 150 whole brain images are collected, then each voxel will possess a time series of 150 points that consists of the information of the changes that occurred at that particular voxel during the scan time. After masking out the voxels that are outside the brain, there are approximately 15,000 voxels that compose an fMRI data set, each with a time series of 150 points.

The next stage in an fMRI experiment is to analyze the data to determine the areas that were active during the task performed. In the sample voxel time courses in Figure 1, a simple finger tapping task was performed. This is the most common paradigm design seen in fMRI, called the block design, in which regular epochs of stimulus and rest are produced. It is important to choose the correct stimulus to obtain activation in the areas desired. Some areas are more easily activated than others. For example, the motor cortex is easily activated, but areas involved in memory are a little more difficult to elicit. In the task in this example, self-paced finger-to-thumb tapping is executed with alternating hands by the patient in a block format as shown in Figure 2. Verbal cues are given at the start of each block consisting of the words "Left", "Right" or "Rest". Each block lasts twenty seconds, and 134 whole brain images are acquired during the scan. A good experiment requires complete

patient understanding, no movement, and concentration; however, compliance with task instructions is often difficult to ascertain.

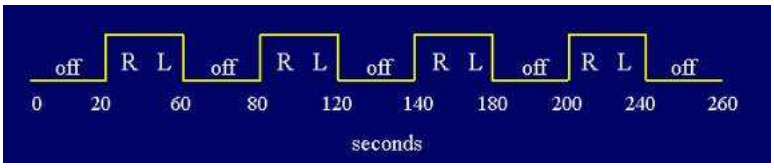

Figure 2: Timing diagram of the finger tapping task.

In the early days of fMRI, MR scientists created maps of brain activity by subtracting baseline (resting) images from active (tapping) images. However, small signal variations in either the baseline or active images introduced a great amount of noise in the resultant difference image. In addition, there was no way to separate background noise from the true activation signal in this technique. Later, statistical methods were introduced to determine which voxels are significantly active and subsequently create a functional map that displays the results of these analyses (4, 5). Much of the current research in fMRI involves developing and improving these statistical methods to most accurately detect the areas of activation in an fMRI data set.

When determining which voxels are active in an fMRI data set, the first step is to determine the stimulus function of the task performed. In the finger tapping task, there is a stimulus function for the right hand and another function for the left hand. This function is shown in Figure 3 for the right hand in the finger tapping task.

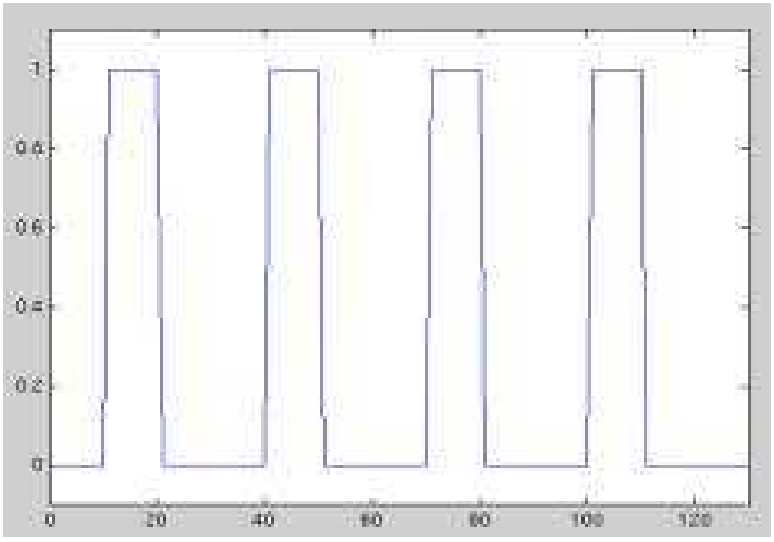

Figure 3: Stimulus function for the right hand in the finger tapping task.

This function is composed of zeros for resting data points and ones for active data points. The hemodynamic response to neural activity is somewhat slower than electrical signaling, and has been modeled by physiological experiments on the brain (4). The hemodynamic response function (HRF) is shown in Figure 4.

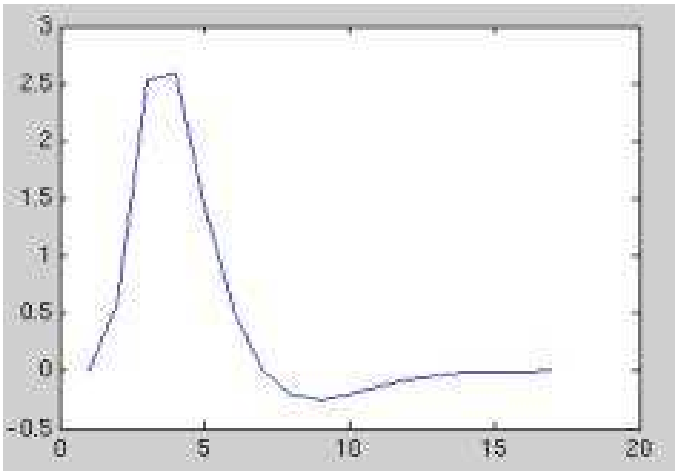

Figure 4: The hemodynamic response function (HRF).

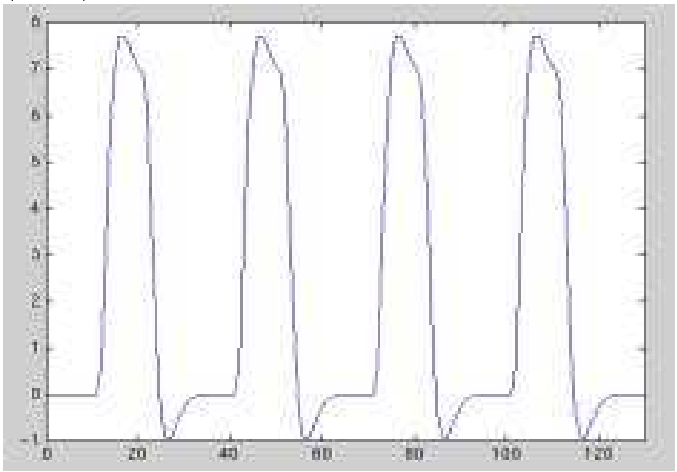

Figure 5: Reference function for the right hand in the finger tapping task.

To obtain a model of the idealized hemodynamic response of the brain to a specific task performed, the stimulus function of the task is convolved with the hemodynamic

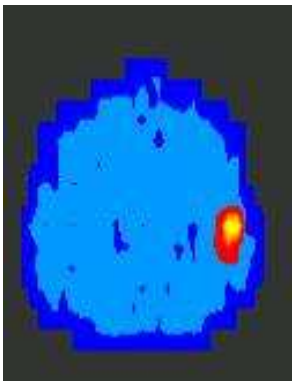

Figure 6: Axial

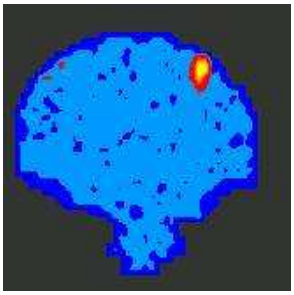

Figure 7: Coronal

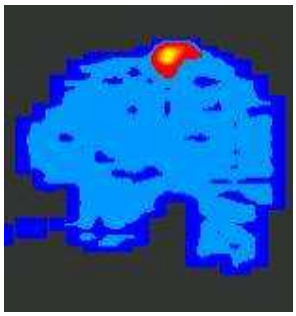

Figure 8: Sagittal

response function. The resulting function is referred to as the reference function of the task performed (Figure 5).

It is then necessary to quantitatively compare the reference function with all other voxel time series in the brain. To achieve this, a test statistic, such as the t-statistic or the correlation coefficient, is computed at each voxel that represents how closely the particular voxel time course agrees with the idealized response of the reference function (4, 5). This statistic is assigned a color intensity value according to the strength of the statistic, to create a functional map, as shown in Figures 6 through 9.

Once the values of the test statistic have been determined for all voxels according to the chosen statistical test, it is necessary to determine the level of significance of this function map. Thus, after applying a threshold such that only the voxels that are significantly active are visible, the functional maps are overlaid onto high-resolution anatomical images (4). The anatomical images are acquired during the same scan session as the functional scan. Figure 10 displays the results of the activation of the right hand during the finger tapping task ($p<0.05$). In order to implement voxel-based analysis of imaging data, analyzed data from different subjects must originate from identical locations. Spatial transformations are therefore applied that "warp" the images such that they conform to some standard brain. Reporting areas of activation as coordinates in reference to this standard space not only provides a conventional means of reporting results, but also greatly facilitates inter-subject as well as inter-study comparison of results (6).

Development of fMRI as a method of localizing brain activity is important for many reasons. This modality offers the neuroscience community a non-invasive method for understanding the functional organization of the normal brain and allows us to learn more about neuropathology. In addition, fMRI is useful in assessing the effects of brain injury and helps aid in pre-surgical mapping in brain tumor patients.

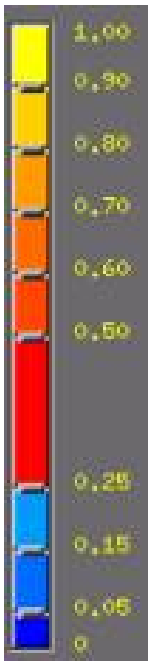

Figure 9: Color intensity scale for statistical maps.

In pre-surgical mapping studies, a tumor might displace the functional tissue. The goal is then to reduce the removal of healthy tissue in order to avoid post-operative disorder, and also to maximize the resection of abnormal growth. Further research is necessary to determine the limits of the power of fMRI as a tool in functional neuroimaging.

2 Positron Emission Tomography (PET)

In a typical PET scanning experiment, a radioactive tracer, usually ^{15}O radiolabeled water is administered intravenously or by $C^{15}O_2$ inhalation. Emitted positrons collide with electrons, resulting in the production of a pair of 511Kev gamma rays traveling in opposite directions. The gamma rays have the same energy and arrive at oppositely placed detectors simultaneously. After recording the simultaneous arrival of gamma rays, and correcting for scattered radiation and attenuation, one is left with an image of a cross section of the distribution of radioactivity in the brain (7). By taking a series of images over time, one acquires a time series of activity in all parts of the brain, which can be compared to models of the tracer kinetics to create functional images of regional cerebral blood flow. As in the case of fMRI, thresholds are applied and the results overlaid onto a high-resolution anatomical scan of the subject. Several

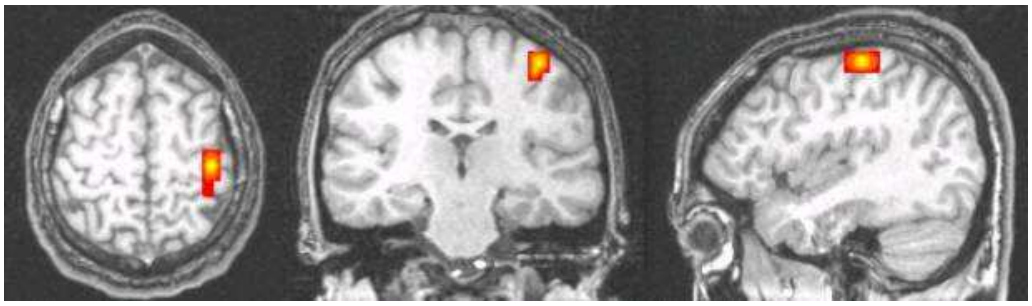

Figure 10: Functional maps overlaid onto anatomical images for the right hand in the finger tapping task for axial **(a)** coronal **(b)**, and sagittal **(c)** slices

examples of these resultant images are shown below in Figure 11. These particular images were acquired from stuttering subjects during a speech production task. As is the case with fMRI, PET studies traditionally report areas of activation in the form of x-y-z coordinates referenced to a standard brain space.

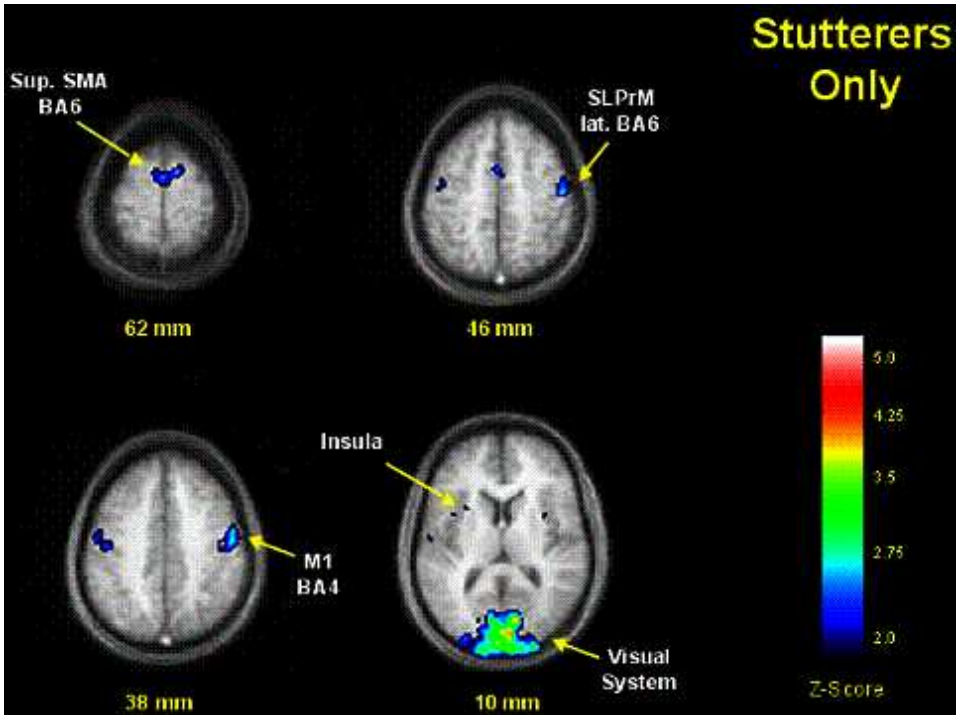

Figure 11: Functional maps overlaid onto anatomical images for a speech production task in stuttering subjects.

3 Meta-Analyses and the ALE Method

Meta-analysis is most generally defined as the post hoc combination of results from independently performed studies to better estimate a parameter of interest (8). Within the functional neuroimaging domain, the widely accepted method of reporting results in coordinate form has made functional imaging studies particularly well-suited for this type of analysis. Meta-analyses are being performed in hopes of attaining a better understanding of the spatial distribution of brain activations corresponding to the performance of particular tasks. While various methods exist for achieving this end, the ultimate success of any meta-analytic technique lies in its ability to objectively correlate results from any number of similar, independent studies, to reveal those regions of consistent activation. The ability to meaningfully combine data across numerous studies is essential for the testing and reformulation of new hypotheses regarding the functional anatomy of the brain.

The most common and conceptually straightforward method for combining data across studies has been to compile relevant coordinates reported in similar experiments onto a single table or map. The figure below represents such a compilation.

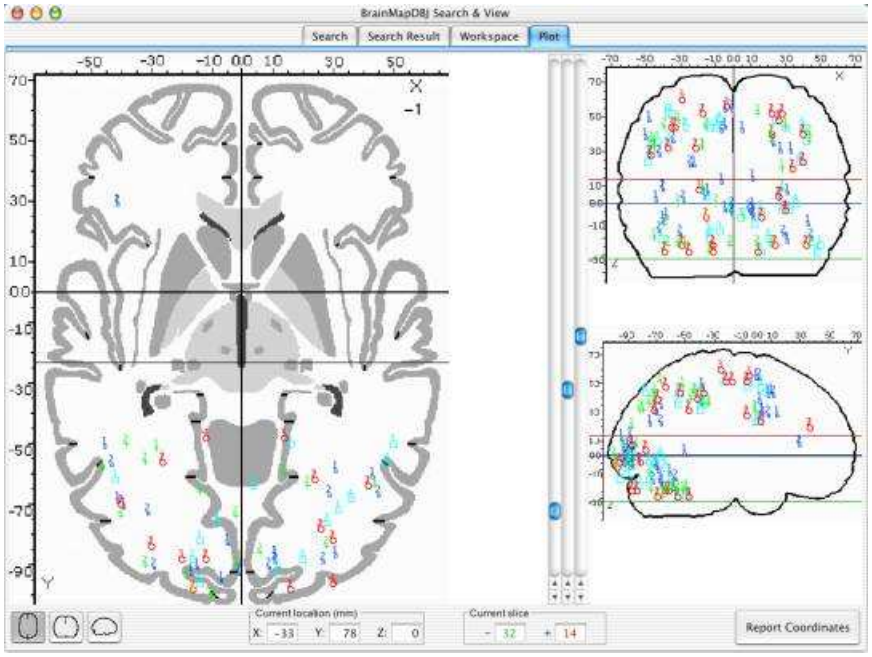

Figure 12: Image displaying a compilation of data reported across 6 independent functional imaging studies. The coordinates plotted are the results of Braille reading > control experiments in blind subjects.

While there does appear to be a certain degree of overlap among the results re-

ported in the six studies used to generate the image, the apparent level of concordance is largely subjective. While it may provide qualitative insight into the neural processes at hand, visual inspection of a graph such as this is in no way an appropriate means for rigorously determining the validity of any hypothesis.

An effective method for quantitatively determining significant consistency among various studies is to represent the location of an activation focus as a probability distribution centered about the reported coordinate, rather than as a strictly defined point (9). Conceptually, this is a logical representation when one considers the variability in the localization of activation foci due to differences in image acquisition parameters, analysis methods, and inter-subject anatomy that are inherent in the comparison of any functional imaging studies. This particular technique for conducting meta-analyses was developed and first performed by Turkeltaub et al. in 2002 and is known as the activation likelihood estimate, or ALE, method (9).

The end result of an ALE meta-analysis is a statistical map in which each voxel is indexed by a value, referred to as the ALE score, equal to the probability that at least one activation focus from the reported data lies within that voxel. The probability that an individual focus will lie within a particular voxel is determined using the 3-dimensional Gaussian distribution function:

$$p = \frac{e^{-d^2/2\sigma^2}}{(2\pi)^{1.5}\,\sigma^3},$$

where d corresponds to the distance between the center of the voxel and the activation focus, and σ is the standard deviation of the distribution. Since the value $p$actually represents the probability that the individual focus lies at the center of a given voxel, it is then multiplied by a constant factor to estimate the probability that the focus lies within a voxel of particular volume. For each individual voxel, the union of these values for every reported focus is the ALE value for that voxel.

To determine a significance threshold for the ALE values, the same analysis is performed on n permutations of x randomly chosen coordinates, where n is typically $\sim$1000 and x is equal to the number of reported foci. The result is a single histogram representing the average number of voxels per permutation corresponding to each ALE value calculated in the n permutations. The probability of obtaining ALE values greater than a given threshold under the random distribution was calculated as the fraction of the total voxels in the noise histogram greater than that threshold. Thus the ALE value corresponding to a given threshold probability α for the random distribution was that particular value with $100 * \alpha\%$ of the area under the noise histogram to its right (9). ALE values in the statistical map lower than the threshold are disregarded as statistically insignificant. The resultant image is a high-resolution statistical map, quantitatively revealing those regions that have been consistently

activated across multiple studies and similar experiments. Below are examples of ALE maps generated for a Stroop task meta-analysis. Nineteen individual studies contributed to a total of 205 foci.

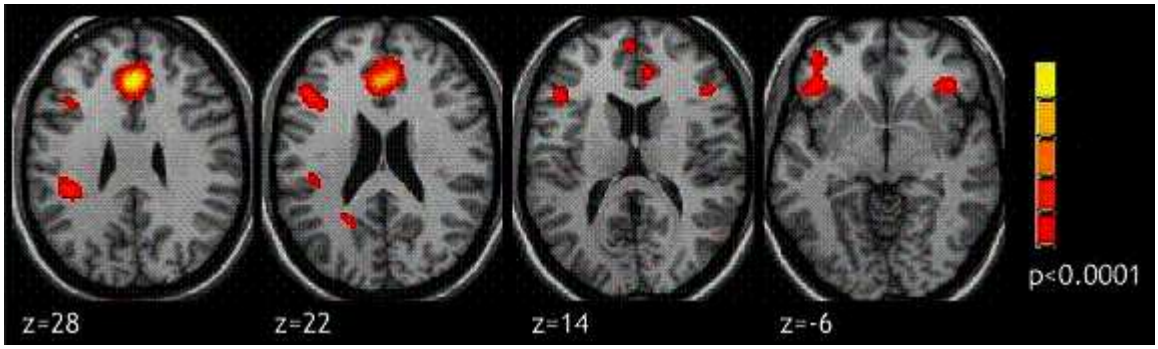

Figure 13: ALE images obtained from a Stroop-task meta-analysis. In this task, subjects view words of color names prsented in vrious ink colors and are instructed to name the ink color in which a color name is presented.

Despite the apparent effectiveness of the ALE meta-analysis in extracting significant overlap across similar studies, a number of flaws in the technique appear to be present. Of particular interest is the following: in a validation study performed by Turkeltaub et al. in 2002, the results of the ALE meta-analysis performed for a single word reading task were compared to those obtained from a single fMRI study of the same task. One consistent difference between the ALE and the fMRI statistical maps is the tendency for maxima to be more centrally located in the meta-analysis (9). This phenomenon is illustrated in the figure 14.

A possible explanation for the effect suggests that PET tends to detect activity at the bottom or base of activated regions, thus resulting in a bias towards centrality for reported maxima. This same tendency has not been proven to exist for the fMRI signal. Thus it might seem feasible that the effect should remain, perhaps even become more pronounced, in an ALE analysis including results from multiple PET studies.

A second possibility suggests that the effect is purely mathematical, resulting from the particular nature of the ALE method. Consider, for example, a voxel located deep within the brain volume. Clearly it is surrounded by a large number of candidate voxels that could house published foci, which would in turn contribute large values to its ALE score. A voxel located near the brain surface, on the other hand, is surrounded by relatively fewer candidates and thus seems more likely to end up with the lower ALE score between the two chosen voxels. Thus one might be left to conclude that the probability of achieving high ALE scores increases with movement towards the center of the brain volume (9), resulting in an inward shift of the maxima.

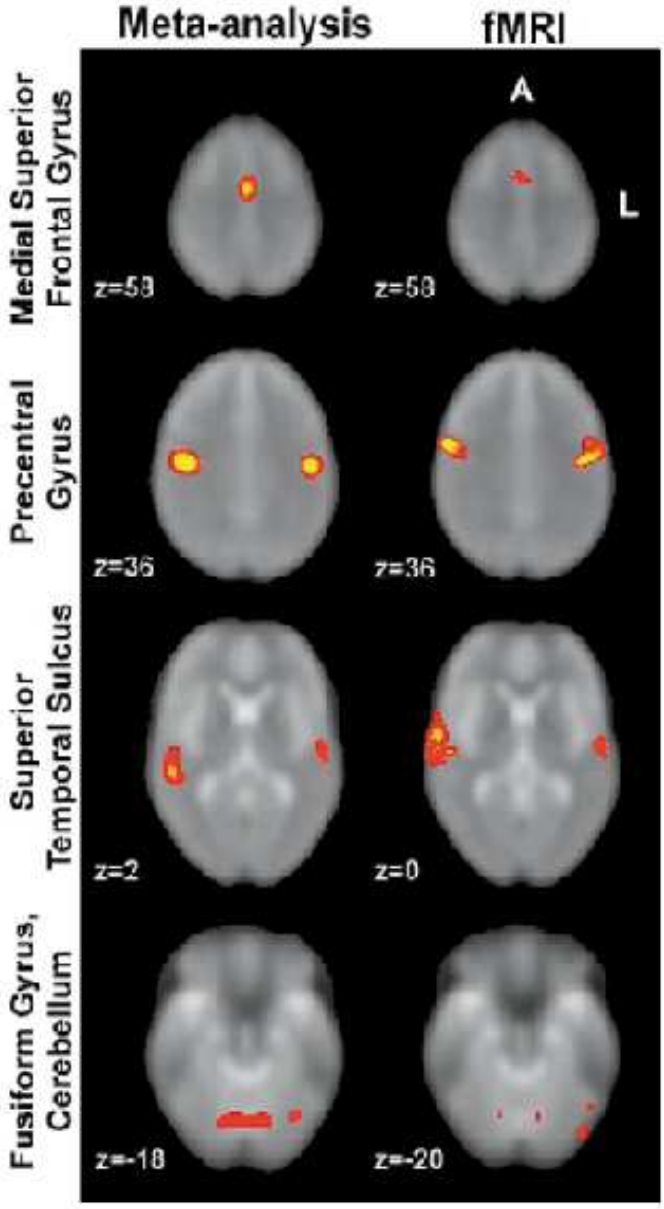

Figure 14: Slices illustrating significant activation in both ALE and fMRI statistical maps. Maxima in the ALE map appear shifted inward relative to those in the fMRI map.

As the ALE meta-analysis is still a fairly recently developed technique, the contributions by each of the above possible explanations to the inward-drift effect have not yet been evaluated. In this study further investigation was conducted employing both

a 2D brain model as well as a 2D ALE analysis analogue in an attempt to identify and perhaps correct the most significant contributing factor.

2-Dimensional Analysis

To begin, a (53x37) matrix was constructed in MATLAB representing the below image, which served as a 2D brain model.

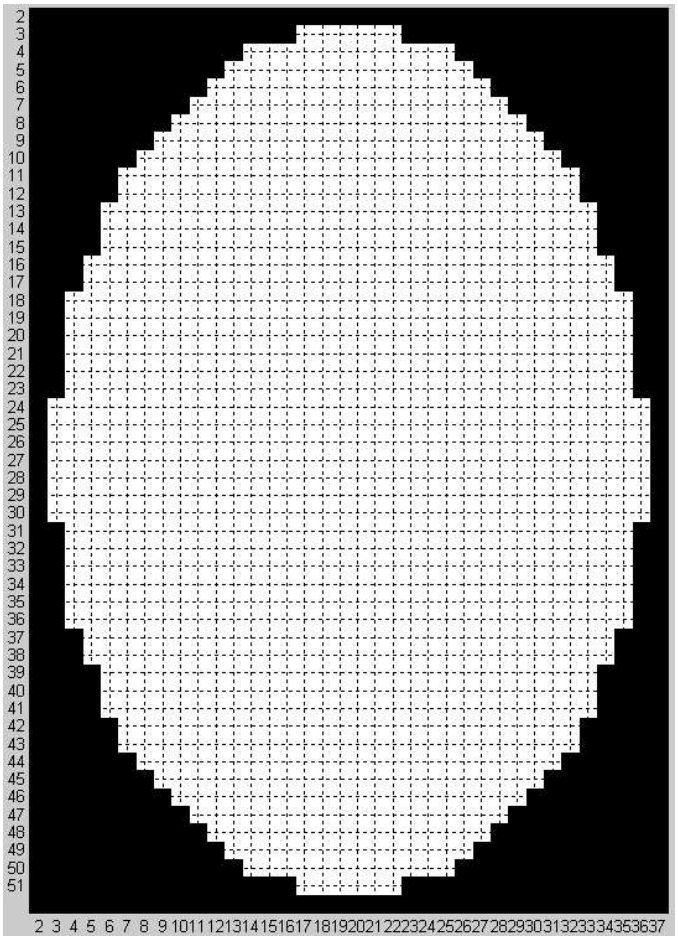

Figure 15: (53x37) zeros and ones matrix constructed in MATLAB to serve as a 2D model of the brain.

Pixels within the brain area were represented as ones in the image matrix and those not were represented as 0s. A function*[1] was written to calculate and store ALE

[1]* A separate command was employed for the random and simulated activity cases. They are displayed in Appendices A & B respectively.

scores for each pixel in the brain area using the 2D Gaussian distribution function:

$$p = \frac{e^{-d^2/2\sigma^2}}{(2\pi)\,\sigma^2}.$$

To simulate reported foci representing actual activation, 22 coordinates were selected such that their distribution exhibited two definite clusters as well as scatter coordinates, typically present when data from multiple studies are combined. The number 22 was chosen such that the ratio of reported foci/total pixels (voxels in the 3D case) was approximately the same for the 2D and 3D cases. A 2D ALE statistical map was then generated with $\sigma = 10$. The simulated foci as well as the corresponding ALE map are displayed in Figure 16.

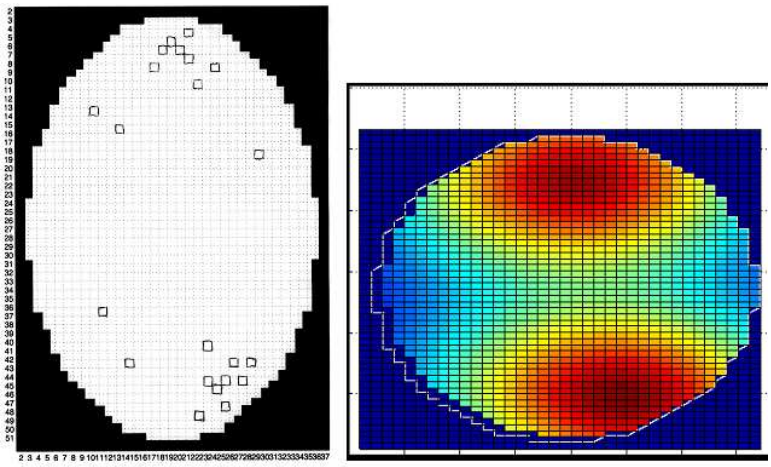

Figure 16: (Left) 2D braind model plotted with 22 simulated activation foci. (Right) ALE statistical map generated for foci shown on the left.

To determine a significance threshold, the process was repeated for 1000 permutations of 22 random coordinates distributed uniformly throughout the brain area. The average ALE score over the 1000 permutations was calculated for each pixel and stored in a new matrix. The corresponding image is shown in Figure 17.

A histogram was then generated displaying the number of pixels achieving a given ALE score for all scores achieved in the random permutations. Based on a chosen $\alpha = .001$, an ALE threshold of .0107 was calculated for the activity-simulated statistical map. It is worthy to note here that the highest score achieved over the 1000 permutations for any pixel within the brain area was .0113, compared to .0151 for the activity map. The thresholded image displays both anterior and posterior peaks and is shown in Figure 18.

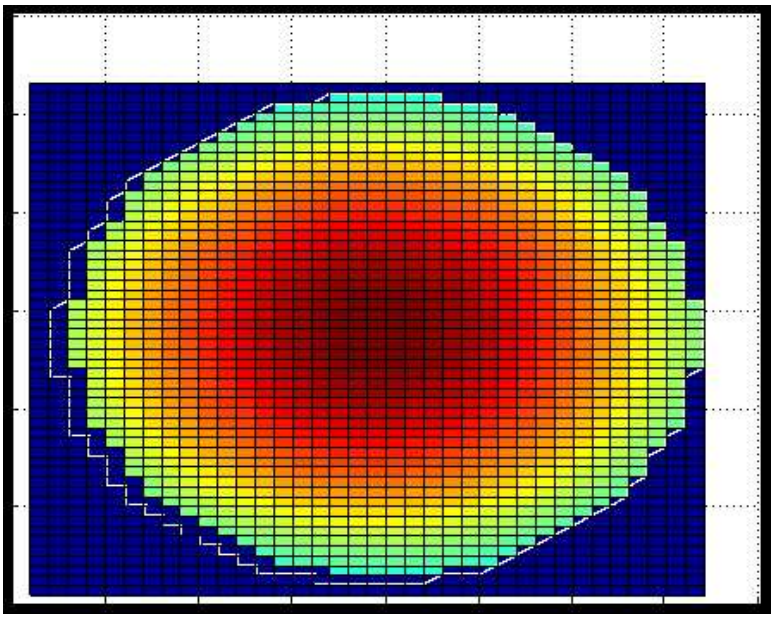

Figure 17: ALE statistical map representing the average ALE score achieved at each pixel over 1000 permutations of 22 random foci each.

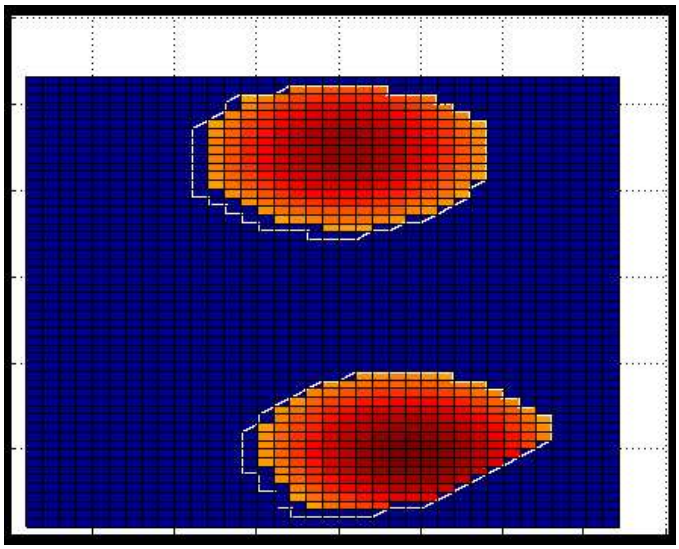

Figure 18: Thresholded counterpart to Figure 15. For a chosen $\alpha = .001$ the calculated threshold was $t = .0107$.

To understand the purely mathematical contribution to the inward-drift effect, we again turn our attention to the randomly generated statistical map. Over the 1000

permutations, the highest average ALE scores were achieved by pixels in the center of the image. The ALE score distribution is symmetric about the image origin, with scores increasing smoothly with movement toward the center. Based on the random distribution it is not unreasonable to suppose that this bias toward centrality led to an inward-drift effect in the activity map. As a means for investigating this claim, we wish to calculate for every pixel an adjusted ALE score, one that effectively flattens the random distribution, such that the probability for achieving any given score is the same for any pair of pixels within the brain area. Presumably, with the bias toward centrality effectively removed, the distribution of this adjusted score in the activity map will exhibit the same maxima, displaced outwardly from the image center.

The adjusted ALE score[+2] for each (i,j) pixel was calculated using the following formula:

$$adjustedALE(i,j) = \frac{1}{AVG(i,j)} \cdot p(i,j),$$

where p is the 2D Gaussian distribution function and $AVG(i,j)$ is the average ALE score obtained by the particular (i,j) pixel over the initial 1000 random permutations. This time employing the adjusted method, 1000 permutations were again performed for sets of 22 random foci and the average scores for each pixel stored in a new matrix. The resultant distribution is shown in Figure 19.

Clearly, this adjusted distribution displays the desired result, namely the removal of any bias whatsoever based on location within the brain area.

Lastly, the adjusted analysis is performed on the activity data set. The statistical map was thresholded as before, resulting in the image shown in Figure 20.

4 Discussion

Qualitative inspection of Figures 17 & 19 certainly indicates an outward shift in the location of maxima in the adjusted statistical map relative to the unadjusted result. Inspection of the max values of both image matrices verifies that a shift has occurred in either of the two peaks. In (i,j) notation:

- Anterior peak: shift from approximately (46,20) to approximately (51,21)
- Posterior peak: shift from approximately (10,24) to approximately (5,26).

Thus, based on the results of our 2D model we are left to conclude that there is a definite bias toward centrality present in the original ALE analysis, leading to an inward shift of maxima in the ALE statistical map.

[+2] See Appendices A & B for a word about the random and group commands in MATLAB.

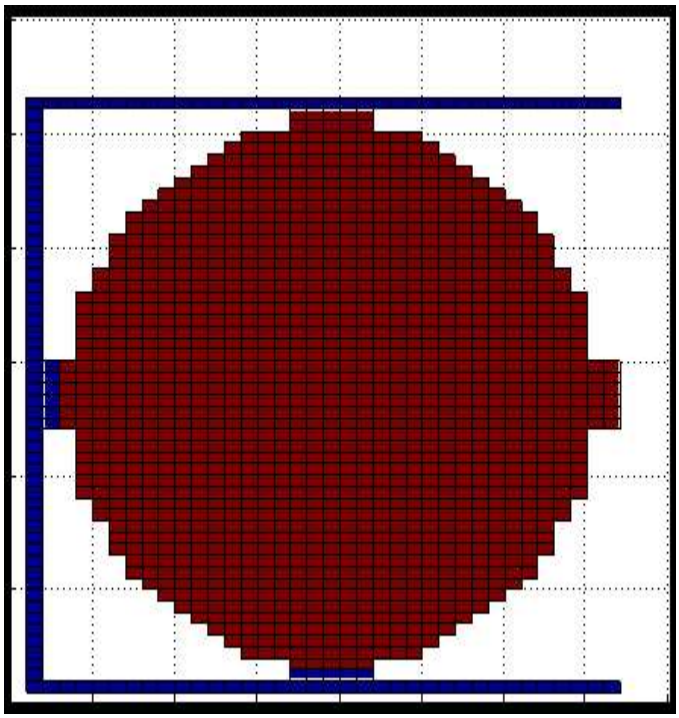

Figure 19: Adjusted ALE statistical map displaying the average score achieved at each pixel over 1000 random permutations of 22 foci each. The adjusted calculations have removed any bias in ALE score based on location within the brain area.

A preliminary model solution is to adjust the ALE calculation such that the adjusted ALE score at any pixel for a given focus is the 2D Gaussian probability divided by the average ALE score obtained at that pixel over 1000 permutations of x random foci; x corresponding to the number of reported coordinates. This is not the whole story, however, as visual inspection of Figure 18 prompts one important question: why does the thresholded adjusted result occupy so much more area than that which was obtained by the original ALE analysis? One might suggest that the threshold value for the adjusted map should be scaled so that it ends up at a higher value, resulting in peaks of approximately the same area for both maps. There is no basis for doing so, however, considering that the process by which the threshold values are calculated ensures that the value is tailored to the analysis method by way of the random permutations. That is to say, if the threshold needed to be higher, the random permutations would have said so. Thus the problem becomes that the adjusted ALE scores are too high. One can only be certain that the coefficient multiplying p in the adjusted analysis is proportional to the reciprocal of the random average at each pixel. A possible suggestion worth investigating is whether or not the coefficient could

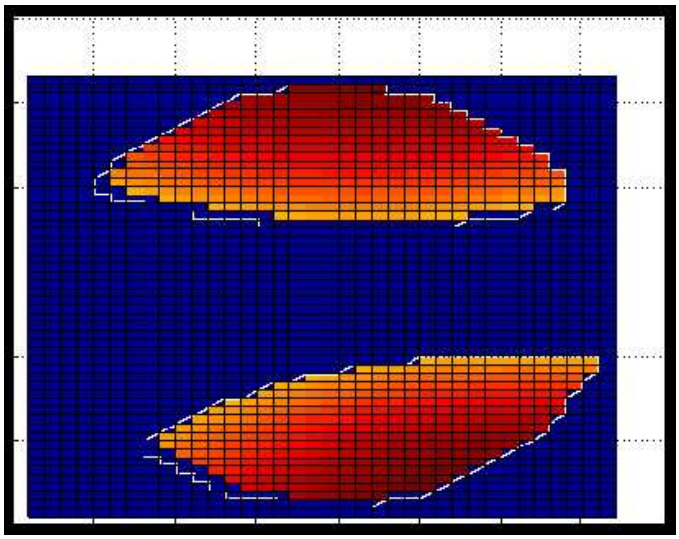

Figure 20: Thresholded statistical map for the adjusted ALE calculations applied to the simulated activity foci. The threshold value was approximately $t \approx 0.67$ for $\alpha = .001$.

also be proportional to some difference between the adjusted and original scores. Of course, if this were the case, the nature of the general shift between the statistical maps would have to be considered. In any case, a positive characteristic of the nature of the solution is that a 3D analogue would be simple to construct; multiplying by some constant in three dimensions is just as straightforward as it is in two.

An additional topic requiring further attention is the value of σ. In this study, $\sigma = 10$ was calculated as a rough approximation to range divided by 4, where the range is the max minus the smallest value the distance d can take on in the p calculation. While integer changes in the value exhibit very pronounced consequences right away, the effects of subtly varying σ in the decimal range should be further investigated.

Finally, what of the PET effect? While there is no way, based on this study, to either validate or discount the notion of the modality's contribution to the inward drift effect, we can say with certainty that the ALE model itself contributes a very large bias toward centrality, resulting in a noticeable inward shift of ALE maxima. A possible means for determining at least a qualitative feel for the PET contribution would be to produce an adjusted ALE map for the ALE data represented in Figure 12, where the adjusted calculation multiplies p at each voxel by the reciprocal of the average ALE score obtained at that voxel over the random permutations used to calculate the threshold. A comparison of the statistical maps obtained from the ALE, adjusted ALE, and fMRI analyses could then be inspected to determine what fraction of the shift exhibited in Figure 12 is accounted for by just the ALE procedure.

5 Conclusion

In summary, a 2D model was constructed to illustrate a flaw in the ALE meta-analysis method, namely, a bias towards centrality in the calculation of maxima, resulting in an inward shift of those maxima in the ALE statistical map. Results of this study indicate that there is a definite bias of purely mathematical origin present, resulting in an inward shift. The exact degree to which the actual effect can be attributed to a flaw in the model is yet to be determined. A solution to correcting the problem, once fully realized, will likely lend itself to easy implementation to both the 2D and 3D cases. At this point it seems probable that the solution will involve adjusting the ALE score at each voxel by some factor proportional to the reciprocal of the average ALE value attained at that voxel over some number of random permutations. The role σ plays in effecting the final ALE statistical map, as well as the possible PET contribution to the inward drift are topics requiring further research.

Appendix A

Below is the MATLAB command used to perform the ALE analysis on random sets of foci:

```
% Richard Castillo
function [ALEmap] = ALE3(o3,sigma,n) % (image, stdeviation, # of random coords)
ProbDenominator = (2*pi)*((sigma)^2); % Denominator in probability calculation
ExpDenominator = 2*((sigma)^2); % Denominator in probability exponential
ALEmap = zeros(53,37); % Bin for storing union of probabilities
Rx = -17 + (17 + 17)*rand(n,1); % Random #s from which random x-coord is chosen
Ry = -24 + (24 + 24)*rand(n,1); % Random #s from which random y-coord is chosen
%%%% Begin with random coordinate (a,b), where a=Rx(k,1) and b=Ry(k,1),
%%%% and calculate a p value for each individual pixel (i,j) in the image.
for k = 1:n
rj = round(Rx(k,1));
ri = round(Ry(k,1));
index = o3(ri+27,rj+20);
if (index==1) % if the random coordinate (a,b) lies within the oval image,
% continue with p calculation
for i = 3:51
for j = 3:36
% First calculate distance between current oval element and
% current random coordinate. The geometric image origin is at
% j=19.5, i=26.5
d=sqrt((j-19.5-rj)*(j-19.5-rj)+(i-26.5-ri)*(i-26.5-ri));
% Now compute the probability value and store in ALEmap
p=o3(i,j)*exp((-1)*(d^2)/ExpDenominator)/ProbDenominator;
ALEmap(i,j)=ALEmap(i,j)+p*(1-ALEmap(i,j));
end
end
else % If the current random coordinate lies outside the oval image,
% set the probability equal to 0.
p=0;
end
end
```

The adjusted random code mimics this with the exception that:

```
adjustedp = Rec(i,j)*p;
```

ALEmap(i,j)=ALEmap(i,j)+adjustedp*(1-ALEmap(i,j));
replaces the bold type above.

Appendix B

Below is the MATLAB command used to perform the ALE analysis on activity-simulating sets of foci:

% Richard Castillo

function [ALEmap] = ALE3Group(o3,sigma,n,GroupX,GroupY) % (image, stdeviation, # of coords,x coord,y coord)

ProbDenominator = (2*pi)*((sigma)^2); % Denominator in probability calculation

ExpDenominator = 2*((sigma)^2) % Denominator in probability exponential

ALEmap = zeros(53,37); % Bin for storing union of probabilities

%%%% Begin with coordinate (a,b), where a=Rx(k,1) and b=Ry(k,1),

%%%% and calculate a p value for each individual pixel (i,j) in the image.

for k = 1:n

rj = (GroupX(k,1));

ri = (GroupY(k,1));

index = o3(ri+27,rj+20);

if (index==1) % if the coordinate (a,b) lies within the oval image,

% continue with p calculation

for i = 3:51

for j = 3:36

% First calculate distance between current oval element and

% current coordinate. The geometric image origin is at

% j=19.5, i=26.5

d=sqrt((j-19.5-rj)*(j-19.5-rj)+(i-26.5-ri)*(i-26.5-ri));

% Now compute the probability value and store in ALEmap

p=o3(i,j)*exp((-1)*(d^2)/ExpDenominator)/ProbDenominator;

ALEmap(i,j)=ALEmap(i,j)+p*(1-ALEmap(i,j));

end

end

else % If the current coordinate lies outside the oval image,

% set the probability equal to 0.

p=0;

end

end

The adjusted group code mimics this with the exception that:

adjustedp = Rec(i,j)*p;

ALEmap(i,j)=ALEmap(i,j)+adjustedp*(1-ALEmap(i,j));

replaces the bold type above.

References

1. Turner R, Ordidge RJ. Technical challenges of functional magnetic resonance imaging. IEEE Eng Med Biology 2000;19:42-54.

2. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci USA 1990; 87:9868-9872.

3. Turner R, Le Bihan D, Moonen CT, Despres D, Frank J. Echo-planar time course MRI of cat brain oxygenation changes. Magn Reson Med 1991; 22:159-166.

4. Friston KJ, Jezzard P, Turner R. Analysis of functional MR time-series. Hum Brain Mapp 1994; 1:153-171.

5. Bandettini PA, Jesmanowicz A, Wong EC, Hyde JS. Processing strategies for time-course data sets in functional MRI of the human brain. Magn Reson Med 1993; 30:161-173.

6. Frackowiak RSJ, Friston KJ, Frith CD, Dolan RJ, Mazziotta JC. Human Brain Function. Academic Press 1997; 2:30-36, 12:275-296.

7. Roland PE. Brain Activation. Wiley-Liss, Inc 1993; 1:1-7, 17:425-431.

8. Fox P, Parsons LM, Lancaster JL. Beyond the single study: function/location metanalysis in cognitive neuroimaging. *Current Opinion in Neurobiology.* 8: 178-187.

9. Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-Analysis of the Functional Neuroanatomy of Single-Word Reading: Method and Validation. *NeuroImage.* 16: 765.