CHAPTER III

THEORY

3.1 Statistical Parametric Mapping

Functional mapping studies are usually analyzed with some form of statistical parametric mapping (SPM). Statistical parametric mapping entails the construction of spatially extended statistical processes to test hypotheses about regionally specific effects. Statistical parametric maps are image processes with voxel values that are under the null hypothesis, distributed T or F distributions. These are known colloquially as T- or F-maps. The success of statistical parametric mapping is due largely to the simplicity of the idea. Namely, one analysis each and every voxel using any standard statistical test. The resulting statistical parameters are assembled into an image – the SPM. SPM are interpreted as spatially extended statistical processes by referring to the probabilistic behavior of Gaussian fields. Gaussian random fields model both the univariate probabilistic characteristics of a SPM and any non-stationary spatial covariance structure. Unlikely excursions of the SPM are interpreted as regionally specific effects, attributable to the sensorimotor or cognitive process that has been manipulated experimentally.

Over the years statistical parametric mapping has come to refer to the conjoint use of the *general linear model* (GLM) and *Gaussian random field* (GRF) theory to analyze and make classical inferences about spatially extended data through statistical parametric mapping (SPM). The GLM is used to estimate some parameters that could explain the spatially continuous data in exactly the same way as in conventional analysis of discrete data. GRF theory is used to resolve the multiple comparison problem that ensues when making inferences over a volume of the brain. GRF theory provides a method for correcting p value for the search volume of a SPM and plays the same role for continuous data (i.e.images) as the Bonferonni correction for the number of discontinuous or discrete statistical tests.

The approach was called SPM for three reasons;

- To acknowledge Significance Probability Mapping, the use of interpolated pseudo-maps of p value used to summarize the analysis of multi-channel ERP studies

- For consistency with the nomenclature of parametric maps of physiological or physical parameters (e.g. regional cerebral blood flow rCBF or volume rCBV parametric maps).

- In reference to the parametric statistics that comprise the maps. Despite its simplicity there are some fairly subtle motivations for the approach that deserve mention. Usually, given a response or dependent

variable comprising many thousands of voxels one would use multivariate analyses as opposed to the mass-univariate approach that SPM represents. The problems with multivariate approaches are that, they do not support inferences about regionally specific effects, they require more observations than the dimension of the response variable (i.e. number of voxels), and even in the context of dimension reduction, they are less sensitive to focal effects than mass-univariate approaches.

A heuristic argument, for their relative lack of power is that multivariate approaches estimate the model's error covariance using lots of parameters (e.g. the covariance between the errors at all pairs of voxels). In general, the more parameters (and hyper-parameters) an estimation procedure has to deal with, the more variable the estimate of any one parameter becomes. This renders inferences about any single estimate less efficient.

Multivariate approaches consider voxels different levels of an experimental or treatment factor and use classical analysis of variance, not at each voxel, but by considering the data sequences from all voxels together, as replications over voxel. The problem here is that regional changes in error variance, and spatial correlations in the data, induce profound non-sphericity in the error terms. This non-sphericity would again require large numbers of [hyper] parameters to be estimated for each voxel using conventional technique. In SPM the non-sphericity is

parameterized in a very parsimonious way with just two [hyper] parameters for each voxel. These are the error variance and smoothness estimators. This minimal parameterization lends SPM a sensitivity that surpasses multivariate approaches. SPM can do this because GRF theory implicitly imposes constraints on the non-sphericity implied by continuous and spatially extended nature of the data. This is something that conventional multivariate and equivalent univariate approaches do not accommodate to their cost.

Some analyses use statistical maps based on non-parametric test that eschew distributional assumptions about the data. These approaches are generally less powerful than parametric approaches. However, they have an important role in evaluating the assumptions behind parametric approaches and may supercede in terms of sensitivity when these assumptions are violated

The Bayesian alternative to classical inference with SPM rests on conditional inferences about an effect, given the data, as opposed to classical inferences about the data, given the effect is zero. Bayesian inferences about spatially extended effects use Posterior Probability Maps (PPMs). Although less commonly used than SPM, PPMs are potentially very useful, not least because they do not have to contend with the multiple comparisons problem induced by classical inference. In contradistinction to SPM, this means that inferences about a given

regional response do not depend on inferences about responses elsewhere.

3.2 Statistical inference and the theory of Random Fields

Classical inferences using SPM can be of two sorts depending on whether one knows where to look in advance. With an anatomically constrained hypothesis, about effects in a particular brain region, the uncorrected p value associated with the height or extent of that region in the SPM can be used to test hypothesis. With an anatomically open hypothesis (a null hypothesis that there is no effect anywhere in a specified volume of the brain) a correction for multiple dependent comparisons is necessary. The theory of random fields provides a way of adjusting the p-value that takes into account the fact that neighboring voxels are not independent by virtue of continuity in the original data. Provided the data are sufficiently smooth the GRF correction is less severe (i.e. is more sensitive) than a Bonferroni correction for the number of voxels. As noted above GRF theory deals with the multiple comparisons problem in the context of continuous, spatially extended statistical fields, in a way that is analogous to the Bonferroni procedure for families of discrete statistical tests. There are many ways to appreciate the difference between GRF and Bonferroni corrections. Perhaps the most intuitive is to consider the fundamental

difference between a SPM and a collection of discrete T values. When declaring a connected volume or region of the SPM to be significant, we refer collectively to all the voxels that comprise that volume. The false positive rate is expressed in terms of connected sets of voxels above some threshold, under the null hypothesis of no activation. This is not the expected number of false positive voxels. One false positive region may contain hundread of voxels, if the SPM is very smooth. A Bonferroni correction would control the expected number of false positive regions. Because a false positive region can contain many voxels, the corrected threshold under a GRF correction is much lower, rendering it much more sensitive. In fact, the number of voxels in a region is somewhat irrelevant because it is a function of smoothness. The GRF correction discounts voxel size by expressing the search volume in terms of smoothness or resolution elements (Resels). This intuitive perspective is expressed formally in terms of differential topology using the Euler characteristic. At high thresholds the Euler characteristic corresponds to the number of regions exceeding the threshold.

There are only two assumptions underlying the use of GRF correction:

- The error field (but not necessarily the data) are a reasonable lattice approximation to an underlying random field with a multivariate Gaussian distribution

-These fields are continuous, with a differentiable and invertible autocorrelation function.

A common misconception is that the autocorrelation function has to be Gaussian. It does not. The only way in which these assumptions can be violated is if (i) the data are not smoothed, violating the reasonable lattice assumption or (ii) the statistical model is mis-specified so that the errors are not normally distributed. Early formulations of the GRF correction were based on the assumption can now be relaxed due to a revision of the way in which the smoothness estimator enters the correction procedure. In other words, the corrections retain their validity, even if the smoothness varies from voxel to voxel.

3.2.1 Anatomically closed hypotheses

When making inferences about regional effects(e.g. activations) in SPM, one often has some idea about where the activation should be. In this instance a correction for the entire search volume is inappropriate. However, a problem remains in the sense that one would like to consider activations that are near the predicted location, even if they are not exactly coincident. There are two approaches one can adopt pre-specify a small search volume and make the appropriate GRF correction or used

the uncorrected p value based on spatial extent of the nearest cluster. This probability is based on getting the observed number of voxels, or more in given cluster (condition on that cluster existing). Both these procedures are based on distributional approximations from GRF theory.

3.2.2 Anatomically open hypotheses and levels of inference

To make inferences about regionally specific effects, the SPM is threshold, using some height and spatial extent thresholds that are specified by the user. Corrected p-value can then be derived that pertain to

- the number of activated region (number of clusters above the height and volume threshold) set level inferences
- the number of activated voxels (volume) comprising a particular region –cluster level inferences and the p-value for each voxel within that cluster-voxel level inferences.

These p-values are corrected for multiple dependent comparisons and are based on the probability of obtaining c, or more, cluster with k, or more, voxels, above a threshold u in an SPM of known or estimated smoothness. This probability has a reasonably simple form.

Set-level refers to the inference that the number of clusters comprising an observed activation profile is highly unlikely to have occurred by chance and is a statement about the activation profile, as characterized by its constituent regions. Cluster-level inferences are

special case of set-level inferences, that obtain when the number of cluster $c = 1$. Similarly voxel-level inferences are special cases of cluster-level inferences that result when the cluster can be small (i.e. $k=0$). Using a theoretical power analysis of distributed activations, one observes that set-level inferences are generally more powerful than cluster-level inferences and that cluster-level inferences are generally more powerful than voxel –level inferences. The price paid for this increased sensitivity is reduced localizing power. Voxel-level tests permit individual voxels to be identified as significant, whereas cluster and set-level inferences only allow clusters or sets of clusters to be declared significant. It should be remembered that these conclusions about the relative power of different inference levels are based on distributed activations. Focal activation may well be detected with greater sensitivity using voxel-level tests based on peak height. Typically, people use voxel-level inferences and spatial extent threshold of zero. This reflects the fact that characterizations of functional anatomy are generally more useful when specified with a high degree of anatomical precision.

3.3 Epilepsy

Epilepsy is a neurological condition which causes repeat seizures in the patient. Epilepsy is caused by such things as head trauma, malformed sections of the brain, tumors and other afflictions of the brain. Epileptogenic seizures can be marked by various different symptoms and may not simply be the uncontrollable shaking and muscle movement that people normally equate with epilepsy. In fact, partial epileptic seizures can occur that allow a person continue to function normal while in the middle of being afflicted.

Epilepsy is normally treated with prescribed medications. Some forms of epilepsy can also be controlled or healed through surgery, neuro-stimulatory implants, or even specific diets.

3.4 Epilepsy Brain SPECT

Partial epilepsy or focal epilepsy is a type of epilepsy in which seizures are thought to arise from a particular part of brain. This part of the brain which causes seizures is called epileptic region or focus. During a seizure, brain cells in this epileptic region become overactive and there is a localized increase in electrical activity and blood flow in that part of the brain.

Video-EEG monitoring helps to localize the epileptic region by recording the brains electrical activity during a seizure. SPECT can help

further localize the epileptic region by showing the abnormal blood flow associated with a seizure.

As SPECT plays a major role in nuclear medicine study, SPECT imaging (as in figure 3.1), can show brain function, as opposed to CT and MRI imaging which show brain structure.
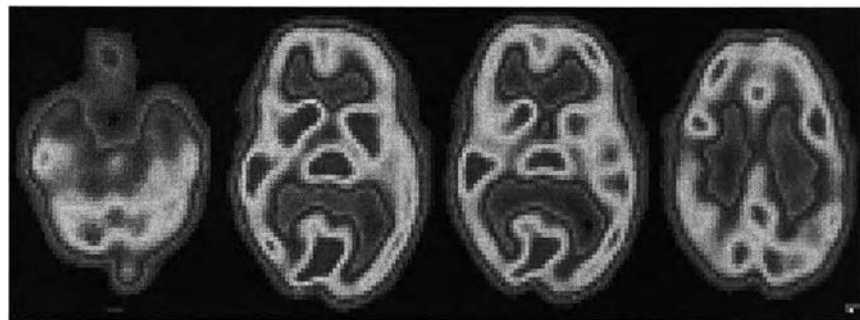

Figure3.1: Brain scan using SPECT at King Chulalongkorn Memorial Hospital

Brain SPECT imaging involves an intravenous injection of two substances, technetium99m and blood flow agent. The injection is given during or immediately following a seizure (ictal SPECT). Technetium99m is a low energy, radioactive substance that is used in nearly all nuclear medicine scans in infants, children and adults. The total body radiation dose from technetium99m injection is very small, being less than that which the chest or brain receives with an x-ray or CT scan.

SPECT imaging usually takes place in conjunction with video-EEG monitoring in the neuroscience unit. The procedure requires the patient to have an intravenous line in the back of the hand or forearm.

When a typical seizure occurs, rapidly mix the technetium99m and blood flow agent is injected at the appropriate dose. A brain scan is then performed in nuclear medicine department, within a few hours of the injection. It takes approximately 45 minutes to obtain the images.

Only one ictal SPECT scan is usually performed (as in figure 3.2 and 3.3). However, some case required a repeat SPECT scan during another seizure, usually when the patient has several types of seizures or the injection was well after seizure finished. In some patient, a SPECT scan is done when they are not having a seizure (interictal SPECT). This scan is used as a baseline for comparison and may be arranged as an outpatient.
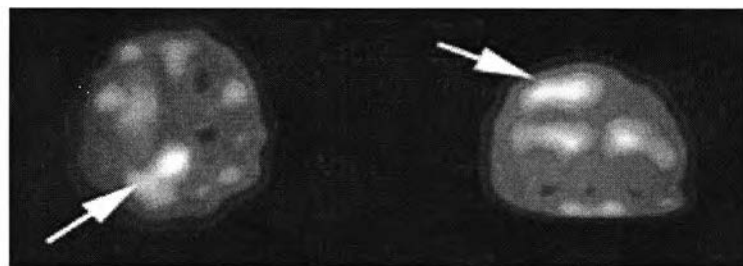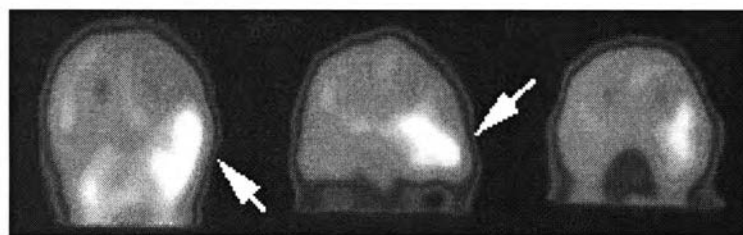

Figure 3.2: Ictal SPECT in frontal lobe epilepsy

Figure 3.3: Ictal SPECT in temporal lobe epilepsy