Spatio-Temporal Models for Volume of Interest Analyses of Neuroimaging Data

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In vivo functional neuroimaging technology enables the evaluation of behavior-related changes in measured brain activity within specific cortical volumes of interest (VOIs). When sufficient neurophysiological evidence exists to restrict attention to a defined cortical volume, a VOI analysis can provide powerful insights regarding neural representations of cognition, emotions, behaviors, and the neuropathology of psychiatric disorders. Given the complexity and abundance of data from neuroimaging experiments, anatomically focused research questions allow statisticians to explore models that more accurately reflect neurophysiological characteristics of the data than global activation studies. Neural processing characteristics of particular interest, in this article, are spatial correlations stemming from the interplay between spatially distinct regions and temporal correlations between serial measures of brain activity. Despite the simplified data structure of VOI studies, challenges remain in modeling spatial correlations, e.g. due to the fact that the correlations do not necessarily decrease as a function of increasing separation between the measurement locations. This article presents a spatio-temporal model that incorporates a functionally defined distance metric into a parametric structure for spatial correlations and includes temporal correlations between repeated scans. We demonstrate the use of the spatio-temporal model using data simulated from a study evaluating neural processing alterations in the right prefrontal cortex associated with mental arithmetic and using experimental data from a study of the effects of ethanol use on measured brain activity in the cerebellum, which largely controls balance and posture.
1. INTRODUCTION

The neurobiology linked to particular behaviors, emotions, and psychiatric disorders frequently focuses research questions to a specific cortical region or volume of interest (VOI) within the human brain. In addition, secondary analyses may concentrate on a VOI defined by activations from the primary analysis, and also confirmation studies may select a VOI based on results from a pilot experiment. Using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to measure hemodynamic correlates of regional cerebral blood flow (rCBF), \textit{in vivo} functional neuroimaging addresses anatomically focused research objectives by allowing the examination of volume-specific behavior-related alterations in brain activity.

PET and fMRI studies usually obtain a series of scans for each individual, often under different experimental conditions. Each scan contains data at various spatial locations, heuristically defined by a finely partitioned cubic grid of voxels, e.g. $256 \times 256 \times 182$. Spatial correlations exist between localized measures of rCBF throughout the VOI, and more generally throughout the entire cerebral cortex. The multiple measurements of brain activity at a given spatial location exhibit temporal correlations. These characteristics of neuroimaging data prompt the use of a statistical model that incorporates both sources of correlations.

One approach to analyzing VOI data averages measured brain activity over the entire VOI and evaluates behavior-related changes as if the data reflect one anatomical location. Alternatively, a VOI analysis conducts a large number of univariate analyses, one at each voxel. fMRI analyses generally account for temporal correlations using variants of autoregressive models, with some methods inducing a known serial correlation structure (pre-coloring) using temporal smoothing (Friston et al. 1995; Worsley and Friston 1995; Bullmore et al. 1996; Purdon et al. 2001). Bowman and Kilts (2003) employ repeated measures covariance structures within a linear model framework to incorporate temporal correlations in an analysis of PET data. There has been little discussion of spatial correlations in linear models for brain imaging experiments. Lange (2000) outlines a linear model with patterned covariance matrices, potentially accounting for temporal or spatial correlation, but does not apply the methodology to
neuro-fMRI or PET data. In a specific neuroimaging application, Worsley et al. (1991) present a quadratic decay spatial correlation model for PET. They model spatial correlation between defined anatomical regions, rather than voxels, significantly reducing the data and the dimension of the correlation matrix.

Average VOI analyses substantially simplify computations and capture a summary effect of the region. However, this approach results in a loss of information, possibly causing limitations in inferences. Depending on the precision with which the VOI maps to the targeted anatomical region, on the extent of spatial variability in distributed activity within the VOI, and on possible interactions between voxels, the average VOI approach may fail to uncover important localized characteristics for a partially activated VOI.

Worsley et al. (1991) define spatial correlations as functions of Euclidean distances between pairs of regions. This approach is common in many areas of statistical application, but it has limitations in context of neuroimaging studies. Many processes that exhibit spatial correlations follow the so-called "First Law of Geography" stating that "everything is related to everything else, but near things are more related than distant things (Tobler 1970)." In contrast, spatial correlations in the brain generally violate this assumption since they are typically not expressible as functions of distances between anatomical locations, e.g. high correlations may exist between distant locations. As a specific example, Broca's area and Wernicke's area, two noncontiguous anatomical regions located in the left-hemisphere for most right-handed individuals, often exhibit similar levels of activity because they jointly control many language related tasks including fluency and comprehension.

This article presents a VOI statistical analysis that incorporates both temporal and spatial correlations in measured brain activity and allows estimation of localized behavior-related changes. Defining spatial separation based on functionality, rather than geometric proximity, leads to the development of a spatial parametric covariance structure that combines with temporal correlation models appropriate for either PET or fMRI. The approach permits estimation of an average volume effect, without sacrificing an examination of localized
activations. To help motivate the proposed methods, the spatio-temporal model is presented in context of data simulated based on a PET study evaluating neural processing associated with mental arithmetic. The spatio-temporal model is further illustrated using experimental data from a study of the effects of ethanol use on measured brain activity in the cerebellum, which largely controls balance and posture.

2. SIMULATED DATA EXAMPLE

The simulated data stem from a volume within the right prefrontal cortex of a PET study involving four experimental conditions. This paper focuses on two of the four experimental conditions (the first and fourth in presentation sequence), namely a resting state and a challenging mental arithmetic task. The data include two replicates of each of the four conditions, totaling eight scans for each of 10 subjects. We examine whether complex probing mental calculations recruit cortical areas in a VOI within the right prefrontal cortex, which neuroscience links to high level processing such as abstract thinking. For the illustrative mental arithmetic example, we select a small volume, consisting of 171 voxels, that exhibited elevated activity during the math task, relative to rest, in the experimental data. The simulated data are drawn from a multivariate normal probability density function with parameters based on the estimates from the experimental data.

3. METHODS

3.1 Defining Anatomical Locations and Volumes

Detailed labeling and coordinate systems exist for identifying anatomical regions of the brain. Popular systems are the Talairach atlas (Talairach and Tournoux 1988), the Montreal Neurological Institute (MNI) template, and Brodmann’s map (Brodmann 1909). The Talairach atlas is a three dimensional stereotactic coordinate system based on a single postmortem brain with the anterior commissure defined as the origin. The MNI template builds on the Talairach system and defines coordinates for averages of MRI scans. Brodmann’s map assigns numerical labels to 52 anatomically and functionally distinct cortical regions.
Analyses that match data to either Talairach or MNI coordinates often link resulting activations to defined Brodmann's areas. Several alternatives exist for defining a VOI, including methods proposed by Hammers et al. (2002). The focus here is on the statistical analysis after selection of a VOI. VOIs for the data applications in this article are selected from scans normalized to Talairach stereotactic coordinates and the volumes are based on either a defined anatomical structure (ethanol data) or on activation maps from a previous experiment (simulated mental arithmetic data).

3.2 Spatial Relationships in Neural Functioning

Localized measurements of brain activity for a given scan are arranged on a regularized cubic grid, and correlations exists between spatial locations. There are numerous challenges to modeling the associations in localized neural processing including the characteristic that spatial correlations do not necessarily decrease with increased separation between measurement locations. Furthermore, the intercommunicating networks of neurons throughout the brain are quite complex and are not completely understood. A compounding challenge stems from the enormous number (e.g. millions) of data locations, but this number is substantially reduced for VOI analyses.

We take a novel approach to modeling spatial correlations in neuroimaging data that builds on functional relationships between measurement sites. To motivate the approach, we begin by considering conceptually different measures of distance in the brain. One immediate measure is a *geometric* or Euclidean distance between two voxel locations (Worsley et al. 1991), but this function does not suitably describe spatial associations in brain activity. A second measure is an *anatomical* distance, conceptually representing anatomical links or the lengths of neuronal pathways connecting different locations. White matter bundles (axons) directly link some brain structures resulting in anatomically close locations, while geometrically more proximal locations may lack such connections making them anatomically more distant. These white-matter connections are quite extensive, with association bundles joining cortical areas within the same hemisphere, commissural bundles linking cortical areas in separate
hemispheres, and projection fibers uniting areas in the cerebral cortex to various subcortical
structures. Due to the impracticality of identifying all such axonal pathways (millions) and the
inaptness of a geometric distance for neuroimaging applications, we propose the use of a
functional distance measure. This measure regards two brain locations as close if they exhibit
similar functionality and distant if they show dissimilar functional patterns.

Based on the length of the difference vector between two mean activity profiles, the
functional distance between voxels $i$ and $j$ is given by

$$d_{ij} = \left[ (\mu_i - \mu_j)^\prime M (\mu_i - \mu_j) \right]^{1/2},$$

(1)

where $M$ is a positive definite matrix. Typical selections of $M$ are the identity matrix or the
covariance matrix associated with estimates of the difference vectors. By incorporating
localized measures of activity profiles, as opposed to location coordinates, $d_{ij}$ represents a
functional distance metric that better characterizes neurophysiological spatial associations. In
practice, one may obtain distances $d_{ij}$ using data from previous studies, run-in periods of a
given study, or a reference group. The mental arithmetic example uses scans from a reference
group of control subjects to determine the $d_{ij}$. Figure 1 displays within-voxel profiles, revealing
the functional similarity between specific spatial locations in the VOI.

3.3 Model and Notation

Corresponding to the data applications presented in this paper, the exposition of the model
reflects a PET context. The general spatio-temporal model for the $k$th subject's rCBF within
the VOI is

$$Y_k = \gamma_k + Z_k \alpha_k + e_k,$$

(2)

decomposing measured brain activity into localized mean components (across subjects)
$\gamma_k = X_k \beta$, individualized mean-zero random deviations that induce temporal correlations
between scans, and random errors that exhibit functionally based spatial correlations.
Specifically, $Y_k = \left[ Y'_{k1} \cdots Y'_{kV} \right]'$ represents measured brain activity with voxel-specific measurements $Y_{kV} = \left[ Y_{kV1} \cdots Y_{kVT} \right]'$. The vector $\beta$ is a fixed parameter, and the corresponding design matrix for the VOI is $X_k = \left( I_V \otimes W_k \right) \times \left( U_k \right)$ resulting in a common matrix $W_k$ for each voxel. The rows of $W_k$ reflect different scans, the columns represent study conditions (experimental stimuli), and $U_k$ contains covariates. Columns of the random effects design matrix $Z_k = (I_V \otimes I_T)$ correspond to voxels, and $\alpha_k$ is the associated random effects parameter vector of individualized mean-zero random rCBF increments. For the mental arithmetic data, where $K = 10$ (subjects), $V = 171$ (voxels), and $T = 8$ (scans), the columns in $W_k$ reflect the four study conditions and $U_k$ is a covariate vector adjusting for the global cerebral blood flow (gCBF) in each scan. The random components from model (2) have the following joint distribution

$$\begin{bmatrix} \alpha_k \\ e_k \end{bmatrix} \sim N\left( \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_t I_V & 0 \\ 0 & (\Phi_k \otimes I_T) \end{bmatrix} \right).$$

(3)

Maitra (1997) provides support for assuming a multivariate normal distribution for PET data, and this framework facilitates estimation and hypothesis testing of parameters in model (2).

The random effects incorporate temporal correlations between an individual's localized rCBF measurements from repeated scans through the matrix $\Psi_k = \sigma_t Z_k Z_k'$. The model errors account for spatial correlations between measured brain activity in a single scan, reflected in $\Phi_k$. The full spatio-temporal covariance matrix for the $k$-th individual's rCBF measurements is

$$\Omega_k = (\Phi_k \otimes I_T) + (I_V \otimes \Psi_k).$$

(4)

The general covariance model is flexible, allowing alternative parameterizations, different specifications of temporal or repeated measures covariances, and a range of spatial parametric structures.
3.4 Parametric Covariance Models

The general covariance model in (4) reflects an equicorrelation parametric structure to account for covariances between rCBF measures from repeated scans. This structure may be suitable for PET studies with basic experimental designs, but different experimental paradigm or fMRI data may prompt the use of more complex structures. The spatial component of the covariance model in (4) may involve a large number of parameters, particularly for sizable VOIs. In the illustrative mental arithmetic example, with a relatively small VOI, defining $\Phi_k$ as any positive definite matrix leads to a spatial covariance matrix consisting of 14,707 distinct parameters. To aid estimation and interpretation, the spatial correlation can be succinctly modeled in terms of relatively few parameters using structures that include higher correlations for voxels with profiles that are functionally closer together.

The variograms in Figure 2 assist in exploring the nature of the spatial covariance, depicted here for the mental arithmetic data. Averaging rCBF measures at common functional distances, the variogram in Figure 2(a) reveals correlations that decay toward zero and exhibits an overall pattern that prompts the examination of an exponential or perhaps a Gaussian model. Given the irregularity of functional distances, Figure 2(a) displays a smoothed variogram (Cressie 1993), averaging over the intervals $[c_{i-1}, c_i)$ spanning the range of distances, where $(c_i - c_{i-1}) = 0.2$ and $c_0 = 0$. For comparison, Figure 2(b) shows the variogram at lags representing geometric distances between voxel locations. The geometric variogram increases over the range of distances without leveling off, possibly indicating nonstationarity. The geometric variogram also exhibits slightly larger measurement error than the functional variogram, since the smallest geometric distance is 1 mm, whereas numerous functional distances fall between zero and one.

<Insert Figure 2 about here>
Based on the variogram in Figure 2(a) and empirical model comparisons presented later in the paper, we propose a functionally based exponential spatial covariance model defined by

\[
\Phi_k = \sigma_s^2 \begin{bmatrix}
1 & e(-\phi d_{12}) & e(-\phi d_{13}) & \cdots & e(-\phi d_{1V}) \\
e(-\phi d_{21}) & 1 & e(-\phi d_{23}) & \cdots & e(-\phi d_{2V}) \\
e(-\phi d_{13}) & e(-\phi d_{23}) & 1 & \cdots & e(-\phi d_{3V}) \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
e(-\phi d_{1V}) & e(-\phi d_{2V}) & e(-\phi d_{3V}) & \cdots & 1
\end{bmatrix},
\]

where \( \phi \geq 0 \). This parametric representation is based on functional associations and specifies covariances (correlations) that decay toward zero for voxels with unrelated functionality. A related model is the spatial power structure, which results from setting the spatial correlation parameter in the exponential model to \( \phi = -\log \lambda \), where \( 0 \leq \lambda \leq 1 \). For other neuroimaging applications, one can model \( \Phi_k \) using alternative structures where the \((i,j)\)th element is

\[
(\Phi_k)_{ij} = \sigma_s^2 f(d_{ij}),
\]

for some function \( 0 \leq f(d_{ij}) \leq 1 \).

The full spatio-temporal covariance matrix \( \Omega_k \) expresses the variance of a rCBF measurement at a particular voxel from a given scan as \( \sigma_s^2 + \sigma_t \), including parameters for both components of variation. The temporal equicorrelation structure specifies the correlation between measurements from two scans at the same location as \( \rho_t = \sigma_t / (\sigma_s^2 + \sigma_t) \), reflecting the proportion of total variance accounted for by the scan to scan variability. The correlation between two distinct spatial locations, say voxels \( i \) and \( j \), within a scan is \( \rho_s \exp(-\phi d_{ij}) \), where \( \rho_s = (1 - \rho_t) \) is the proportion of total variability accounted for by spatial variation. The spatial correlation, therefore, encompasses the degree of functional association between voxels, scaled by a factor representing the proportion of total variation due to spatial variability. The parsimony of the full spatio-temporal covariance model is an extremely beneficial feature, given the high computing demand of neuroimaging analyses.

4. ESTIMATION

The spatio-temporal model for VOI rCBF measurements has a general linear mixed effects model structure, so the restricted maximum likelihood (REML) (and maximum likelihood)
method is appropriate for estimation. There is an extensive literature in this area including the seminal paper by Laird and Ware (1982) and other important contributions by Jennrich and Schlucuter (1986), Laird, Lange, and Stram (1987), and Lindstrom and Bates (1988). We provide a brief discussion of the estimation methods in context of the spatio-temporal model for neuroimaging applications, since variations of our covariance model may exceed the range of parametric structures available in standard statistical software packages. Additional details regarding the methods, their properties, and programming facilities are available in the above references.

The REML method proceeds by iteratively estimating $\beta$ using

$$\hat{\beta} = \left( \sum_{k=1}^{K} X_k' \Omega_k^{-1} X_k \right)^{-1} \sum_{k=1}^{K} X_k' \Omega_k^{-1} Y_k$$

and estimating covariance parameters $\tau = (\sigma^2, \sigma^2, \phi)'$ (in $\Omega$) by maximizing the log-likelihood function (ignoring constants) of $N - p$ linearly independent error contrasts from the ordinary least-squares (OLS) residuals

$$L_{\text{REML}}(\tau) = -\frac{1}{2} \left[ \sum_{k=1}^{K} \log|\Omega_k| + \log \left| \sum_{k=1}^{K} X_k' \Omega_k^{-1} X_k \right| + \sum_{k=1}^{K} \hat{r}_k' \Omega_k^{-1} \hat{r}_k \right]$$

where $\hat{r}_k = (Y_k - X_k \hat{\beta})$. REML is more suitable for estimation than ML, given the downward bias of ML (Laird and Ware 1982) and the large number of fixed effects in our model. We use Fisher’s scoring and the Newton-Raphson algorithms to iteratively estimate $\theta = (\tau', \beta')'$ from the log-likelihood function. A third alternative for estimation is the expectation-maximization (EM) algorithm. For the spatio-temporal covariance model defined by (4) and (5), the maximization stage at each iteration of EM employs a scoring step to increase the log-likelihood function (generalized EM), rather than complete maximization.

In context of neuroimaging applications, particularly those consisting of large $V$, calculating and inverting the Hessian matrix of second partial derivatives involves costly
computations. Some computational gains arise by noting that the spatio-temporal covariance matrix is common to each individual. The usual shortcut for inverting a covariance matrix (Lindstrom and Bates 1988) takes the following special form for the spatio-temporal model

$$\Omega^{-1}_{k} = \left( \Phi^{-1}_{k} \otimes I_T \right) - \left( \Phi^{-1}_{k} \otimes 1_T \right) \left[ T \Phi^{-1}_{k} + \sigma_t^{-1} I_V \right]^{-1} \left( \Phi^{-1}_{k} \otimes 1_T \right)$$

reducing the inversion of a TV-dimensional matrix to a V-dimensional matrix inversion. The benefit of this shortcut becomes limited as the number of voxel-specific random effects increases, and it provides no advantage for some alternative model specifications.

5. DATA APPLICATIONS AND RESULTS

5.1 Results of Mental Arithmetic Study

The covariance estimates from the spatio-temporal model are $\sigma_t = 25.09$, $\phi = 0.11$, and $\sigma_s^2 = 15.75$. The decaying correlations depicted in the variogram in Figure 2(a) reach the sill at a functional distance of roughly 13, and this distance corresponds to a model-based correlation estimate of 0.09. The temporal variability accounts for a higher proportion of the total variation (0.61) than the spatial variability (0.39) for these data. The smaller proportion of spatial variability dampens the exponential spatial correlations, yielding overall spatial correlations ranging from 0.024 to 0.389. The exponential spatial model (5) provides a much better fit to the data than a Gaussian spatial model $\sigma_s^2 \exp \left( -d_{ij}^2 / \lambda^2 \right)$, according to both the Akaike Information Criterion (AIC) (Akaike 1974) and the Bayesian Information Criterion (BIC) (Schwarz 1978), e.g. with AIC values of 25259.1 for the exponential model and 41219.3 for the Gaussian model.

The VOI consists of cortical matter in the right superior frontal gyrus or more specifically Brodmann’s areas 9 and 10. Brodmann’s areas 9 and 10 are thought to be instrumental to abstract thinking and decision making. We estimate voxel-specific parameters in the VOI and test both voxel-specific and voxel-averaged contrasts. The results reveal increases in measured neural activity during a challenging mental arithmetic task, relative to a resting state.
Contrast maps of the mental arithmetic task versus rest appear in Figure 3 for (a) the true parameter values, (b) spatio-temporal model estimates, and (c) OLS estimates. The pictured regions are enlarged from axial slices ranging from +28 mm to +34 mm in the Talairach atlas and constitute a subset of slices in the VOI. The maps are smoothed for visualization using a Gaussian filter with 8 mm full width at half maximum. The spatio-temporal contrast estimates are more accurate than the OLS estimates, although analytically OLS provides unbiased estimation.

<Insert Figure 3 (enlarged activations) about here>

Maps of t-statistics from the spatio-temporal model appear in Figure 4(a), and for comparison, t-statistic maps from an OLS analysis appear in Figure 4(b). In addition to estimation differences revealed by Figure 3, the increased precision of the spatio-temporal estimates, relative to OLS, is implicitly apparent in Figure 4, reflected by the more radiant t-maps. The spatio-temporal analysis produces activations that are spatially extensive, extending throughout much of the VOI, but only a limited number of activations result from the OLS analysis. The spatio-temporal analysis yields significant activations in 74% of the voxels in the VOI compared to only 34% for the independence OLS analysis. All activations are significant at the voxel level $\alpha = 0.00029$, corresponding to a VOI (familywise) error rate $\alpha = 0.05$ with a Bonferroni multiplicity correction.

<Insert Figure 4 (enlarged activations) about here>

Conducting a voxel-averaged hypothesis test from the spatio-temporal model estimates provides generalized information regarding increases in rCBF, within the VOI, during mental arithmetic. The voxel-averaged test reveals significant activation of the VOI, with $p \leq 0.0001$, complementing results of the localized tests. Activation maps in Figure 5 display the voxel-averaged results for selected slices from axial, coronal, and sagittal views. The significant activations reveal that the VOI within the prefrontal cortex actively participates in mental calculation and abstract thinking.

<Insert Figure 5 about here>
5.2 Neural Correlates of Ethanol Use

It is well known, from a behavioral perspective, that drinking alcohol impairs balance, motor coordination, and cognition, and there is extensive literature regarding the effects of ethanol on the brain at a cellular level. Yet, the neural representation of the effects of drinking alcohol on the human brain is poorly understood. We use *in vivo* PET imaging to examine the impact of ethanol on distributed neural processing within the cerebellum, an area associated with balance and learned motor movements. The VOI consists of central portions of the left and right cerebellar hemispheres roughly 24 mm below the anterior commissure.

The analysis includes ten male subjects who are infused with a small dose of ethanol just prior to the third of ten scans and with a large dose just prior to the sixth scan. Subjects undergo a series of ten PET scans, each obtained ten minutes apart, and blood alcohol concentrations are drawn every five minutes, beginning with the third scan. The first two scans represent baseline measures with zero mg/ml blood alcohol concentrations. The mean blood alcohol concentration profile (not shown) reveals zero or very low levels of ethanol during the first three scans and exhibits increasing levels thereafter, except for a slight decrease from scan five to scan six.

Figure 6 displays smoothed rCBF profiles of (a) raw means from the VOI for each subject, with the bold line representing the overall average, as well as (b) sample means within each voxel. The individualized profiles, averaged over the VOI, generally reveal decreases in blood flow to the cerebellum over the duration of the study. One subject exhibits a substantially more rapid decline in rCBF than other subjects. Although the spatio-temporal model defines voxel-specific means, it is worth noting that many individuals show similar rates of decreases in the VOI-averaged rCBF. The voxel-specific profiles display rCBF averages over the ten subjects and suggest a quadratic trend with decreasing activity extending through scan nine, ending in a slight rise in blood flow at scan ten.

<Insert Figure 6 about here>
Guided by descriptive figures, such as those given in the mental arithmetic example, and by empirical comparisons of alternative covariance selections using BIC and AIC, we use model (2) with a functional exponential spatial correlation structure to describe the ethanol data. The mean model, for subject $k$ at time $t$, specifies a quadratic orthogonal polynomial function over time (scans)

$$\gamma_{kt} = \beta_0 + \beta_1 X_{kt} + \beta_1 X_{kt}^2.$$  

The model for rCBF also includes localized random intercepts across scans, within 4 mm voxel neighborhoods. The model formulates localized random regressions that include common curvilinear patterns of change over time and neighborhood-specific random shifts in the rCBF profile for each individual. This accounts for temporal correlations from scan to scan in localized anatomical areas. The parametric structure in (5) accounts for spatial correlations between measurement locations, weighting correlations based on functional similarities between voxels.

The covariance estimates from the model are $\sigma_t = 0.78$, $\phi = 0.20$, and $\sigma^2_e = 10.58$, revealing the relative contribution of the spatial and temporal components. The spatial variability accounts for roughly 93% of the total variation in the data, which suggests the importance of spatial modeling for these neuroimaging data. We calculate functional distances using auxiliary data from six subjects, not included in the main analysis. The functional distances between all pairs of anatomical locations range from 26.42 down to 0.15, corresponding to correlations ranging from 0.01 to 0.90, respectively.

Figure 7 displays voxel-specific deactivations with $p \leq 0.005$ (uncorrected) within the VOI. The deactivation map clearly demonstrates spatially extensive significant reductions in localized blood flow to the cerebellum corresponding to increases in the subjects' blood alcohol levels. Analyzing a contrast that averages across the VOI provides additional evidence of a significant decrease in measured brain activity associated with increases in blood alcohol concentration ($p \leq .0001$). Portions of the cerebellum appear to essentially go off line in
conjunction with increased blood alcohol concentrations. Given the important role of the
cerebellum in the regulation and coordination of movement, posture, and balance, the observed
decrease in blood flow to this area helps explain motor skill deficiencies resulting from alcohol
use.

6. DISCUSSION

We present a novel approach to analyzing in vivo neuroimaging data, within a defined VOI. By
defining a distance metric that reflects relationships between voxels based on functionality, rather
than anatomical proximity, our model incorporates both spatial and temporal correlations
between measurements of brain activity. This approach substantially simplifies the consideration
of detailed anatomical connections and more accurately measures similarity in the brain than
geometric distances between measurement locations. The model also encompasses temporal
correlations, which are not widely included in PET analyses. The relative contributions of spatial
and temporal correlations in the ethanol analysis suggest the importance of modeling spatial
variability in some neuroimaging applications.

An important advantage of the proposed method is that it enables empirical
comparisons to alternative models. This may seem insubstantial, but model comparisons are
often not practical in the typical voxel-by-voxel analysis that applies a large number of models to
the data. The typical analysis yields localized model fits, so the analyst must resort to examining
fit or comparing models within a small subset of the total number of voxels. Selection of the
spatio-temporal model for the ethanol study resulted from empirically comparing several
alternatives using Wald tests for mean model parameters and using AIC and BIC for covariance
model selection. Some examples of alternative models considered include higher order
polynomial terms in the mean model as well as random intercept and linear trends over time, a
first-order autoregressive model, and a model with a spatial Gaussian structure. The random
intercept spatial exponential model presented above provided the best fit to the data among the
alternatives considered.
Unlike typical VOI analyses that proceed after averaging data across the volume, the proposed model provides results that reflect VOI averages, without solely limiting inferences to such summaries. In the absence of a significant voxel-averaged activation for the VOI, the spatio-temporal model analysis allows examination of the voxel specific tests. An advantage of conducting voxel-specific tests about behavior-related alterations in brain activity is that it may reveal partially (de)activated VOIs. This may be important, for example, for small anatomical regions that may not be accurately captured in the selected VOI.

Given that the spatio-temporal model uses iterative estimation methods for large amounts of data, computational constraints may arise, potentially limiting the size of a VOI. Relatively small changes to the random effects structure may substantially increase computing demands. For example, exploring the inclusion of random linear trends in the model for the ethanol data required an increase of roughly 200 megabytes of memory, relative to the random intercepts spatial exponential model. The analyses included in this article were run on a 3.06 gigahertz Pentium 4 laptop computer with one gigabyte of random access memory, and memory is likely not to be a factor for some computing systems, e.g. large UNIX networks. For applications with large VOIs, modeling random effects within locally expanded voxel neighborhoods accelerates computations and permits more spatially extensive VOIs.

A potential approach to extend our methodology to whole brain analyses is to spatially segment the brain into distinct regions and apply separate spatiotemporal models within each region. For example, one may classify the brain into regions defined by Brodmann's areas, which have corresponding theorized physiological functions. A second approach is to identify distinct functional networks using cluster analysis or other classification procedures (Balslev et al., 2002; Bowman, Patel, and Lu, 2004; Bowman and Patel, 2004; Cordes et al. 2002; Fadili et al., 2000; Filzmoser, Baumgartner, and Moser, 1999; and Goutte et al, 1999). These approaches reduce a massive and complex problem of spatial estimation that is typically infeasible in practice into smaller and simpler components that are better suited for spatial analyses.
This article proposes a model that advances conventional neuroimaging statistical methods for VOI analyses. The novel approach to modeling spatial correlation bridges neurophysiological associations with models employed in more traditional applications of spatial statistics. The proposed spatial correlation model, based on functional distances, is attractive because it captures important characteristics present in neural processing. Theoretically, there is an upper limit on the volume of blood in the brain, making it likely that negative correlations exists, between voxels with extreme differences in functional neural activity. The proposed model essentially treats measured brain activity between such voxels as uncorrelated. A useful extension to our model, for future research, is one that encompasses both positive and negative correlations.

REFERENCES


FIGURE LEGENDS

Figure 1. Smoothed voxel-specific brain activity profiles, within the VOI, characterizing the functional distances between voxels. Values are scaled so that elements within a profile are independent with equal variances.

Figure 2. Empirical variograms of VOI mental arithmetic data, averaged across study conditions, at (a) functional and (b) geometric (mm) lags.

Figure 3. Enlarged maps of (a) true contrasts, (b) spatio-temporal contrast estimates, and (c) ordinary least-squares contrast estimates from axial slices of the VOI.

Figure 4. Enlarged maps of t-statistics for selected axial slices in the VOI from the (a) spatio-temporal model and (b) ordinary least-squares.

Figure 5. Images of the VOI voxel-averaged activation within the right superior frontal gyrus from a coronal (top left), a saggittal (top right), and an axial view (bottom) ($p \leq 0.0001$).

Figure 6. Smoothed rCBF/1000 profiles of (a) VOI means for each subject, with bold line representing the overall average and (b) sample means within each voxel.

Figure 7. Right and left cerebellar hemispheric deactivations, related to infusion of ethanol ($p \leq 0.005$, uncorrected).
FIGURES

Figure 1.

(a) Functional Distance Variogram

(b) Geometric Distance (mm)
Figure 3.

(a) Slice 51  
Slice 52  
Slice 53  
Slice 54

(b) Slice 51  
Slice 52  
Slice 53  
Slice 54

(c) Slice 51  
Slice 52  
Slice 53  
Slice 54

Figure 4.

(a) Slice 51  
Slice 52  
Slice 53  
Slice 54

(b) Slice 51  
Slice 52  
Slice 53  
Slice 54
Figure 5.

Figure 6.

Figure 7.