

# Voxel-based mapping of lesion-behavior relationships

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## Preliminaries

### Introduction

The purpose of this document is to provide an overview for how to go about voxel-based analysis of the relationship between brain lesion data and behavior, an approach which Bates et al. (2003) have labelled “VLSM” for voxel-based lesion-symptom mapping. Although we don't always think of the behavioral measures as symptoms *per se*, the name “VLSM” is catchy and established, so we'll use it here.

VLSM is conceptually very simple. You have behavioral data and lesion maps from a group of subjects. On a voxel-by-voxel basis, you can assess the relationship between damage in that voxel and the behavioral measure. That's about it. The difficulty comes in doing the statistics and image processing well.

This document is a conceptual overview – it's intended to give you a good idea of how to go about things, but will not help you with the specific details of your study, and will not (for the most part) tell you what software to use or what buttons to push. If you aren't already comfortable with image analysis, we hope you will still learn something from this document, but you won't necessarily be ready to get started.

### VLSM contrasted with non-voxel-based lesion analysis methods

What are the alternatives to voxel-based methods? The main (perhaps the only?) alternatives are data reduction approaches that treat patients categorically, using categories defined behaviorally, by lesion location, or both. For example, we might divide otherwise similar patients into those with and without frontal lesions, and ask whether or not the two groups differ on some behavioral measure. Or we might look for the area of maximum overlap among the lesions of patients who do or don't demonstrate some pattern of behavior.

### VLSM contrasted with fMRI

VLSM seems a lot like fMRI in that we're looking at the association between behavior and data in brain images. Here are some key differences:

	<i>VLSM</i>	<i>fMRI</i>
nature of image data	one image (lesion map) per subject, or perhaps a small set of clinical images	an autocorrelated time series of images from each subject
role of behavior	behavior is the dependent variable	behavior is an independent variable, manipulated by varying task demands (even though you may also collect behavioral data in fMRI studies, those data rarely if ever figure into fMRI analyses as dependent variables)
role of spatial data	the lesion map is the independent variable you expect to predict behavior; so a	the fMRI data are the dependent variables you expect to be predicted by task

	<i>VLSM</i>	<i>fMRI</i>
	different model is fit to the same behavioral data for each voxel	conditions; so the same model is fit to different data for each voxel

## Preparing your data

In a typical VLSM analysis you will have a scalar behavioral score and a 3-dimensional lesion map for each subject. You may have more than one behavioral score, but we can consider each to be subject to an independent analysis, unless you want to do something more complicated, like MANOVA (not discussed here).

The tricky first step in VLSM is to get all of the lesions segmented (delineated in some way) and registered to a common reference. That reference is often but not always a standard template, such as the MNI colin27 template often used with SPM and other imaging packages. The advantages of having your images in this space include compatibility with the large number of studies that report coordinates in MNI space (or other closely related spaces, see Brett et al., 2002 for some helpful discussion) and compatibility with electronic atlases for structure/region labelling that are provided in MNI space (e.g., see MRICron and AAL in the software references below).

Two difficult problems lie at the heart of the segmentation/registration process. First, it's not always easy to decide where a lesion starts and ends. Second, even if you know where a patient's lesion is on that patient's MRI, it's not always easy to decide how that location maps onto a standard template.

There are many other tricky issues in deciding how to segment lesions. For present purposes, I assume you are aware of these issues and have decided how to handle them. In the future, I hope to expand this section with a more detailed discussion of how to address uncertainty in lesion location and status.

### Manual Registration and Segmentation in One Step

This commonly used procedure, in various forms, solves the registration and segmentation problems in one step, at the cost of expert human labor. Basically, a human rater with knowledge of neuroanatomy sits down with a template on the computer (typically in some program like MRICro(n)) and the patient scan(s) in some form. Then, working slice by slice, the rater uses his/her best judgment to draw the lesion onto the corresponding slice on the template. Of course, there isn't always a corresponding slice, but by rotating the template around the LR axis (i.e., changing the pitch), it's usually possible to find a reasonable match. The volume, including the segmented lesion, can be rotated back into its original orientation later.

The major drawback of this procedure is that it's almost entirely manual – labor-intensive and subject to human error and biases. For this reason, when using manual registration/segmentation, it can be a good idea to have at least two raters draw the same lesions. Some useful metrics of inter-rater agreement are described in Fiez et al. (2000), and are implemented in the VoxBo command *vbmaskcompare*. We have also noted that spatial smoothness of lesion maps is invariably greater in the plane in which the lesions are drawn, suggesting that the process would benefit from even more labor, specifically to examine the lesions for continuity in other slice planes.

### Automated Registration

Automated registration algorithms typically work by searching a space of possible

transformations for the one that minimizes a “cost function,” an index of mismatch between two volumes. Fully automated registration can be problematic for brains with large structural lesions, because the lesion does not map readily onto structures in the template brain volume. A typical mode of failure would be mapping the lesion onto a ventricle. Brett et al. (2001) describe a semi-automated solution to this problem, described as “cost function masking.” Briefly, this approach involves excluding the lesion from consideration when calculating the cost function. The algorithm is then free to find the transformation that provides the best match for the surrounding tissue, which should map well onto the template.

Tyler et al. (2005) have also used an approach that minimizes the deleterious effects of large lesions on automatic registration by penalizing “unlikely” transformations, an approach available in SPM. This effectively restricts the space of transformations searched, and can eliminate some degenerate mappings.

### Automated Segmentation

We have little to say about automated segmentation at this time. But you may want to read Stamatakis et al. (1999) and Stamatakis et al. (2005) for an approach that involves identifying lesions by comparison to a reference group of intact brain volumes.

## **Analysis**

VLSM analyses proceed by calculating a test statistic for the test to be carried out in each voxel and choosing a standard for significance.

### Choosing a test statistic

It's important to choose a test statistic that measures what you really want. By default, we assume you'll be using the t statistic, whether to contrast two groups (lesioned vs. intact in a given voxel) or to assess the correlation between continuous-valued lesion scores (probability of a lesion in a given voxel ranging from 0 to 1) and behavior. Many others could be appropriate, depending on your study, and if you use permutation testing (see below), your options are not restricted to measures that can be readily transformed to have a known parametric distribution. We hope to have more to say about this in the future.

### Choosing a standard for significance

Although the t statistic is usually used with the t-test, it doesn't have to be. Here we treat the statistic as a metric of the relationship between lesion and behavior, but we recommend testing that relationship non-parametrically, with a permutation test.

Software for fMRI analysis usually assumes the image is your dependent measure and behavior is an independent measure. Although lesion analysis reverses this relationship logically, we can carry out the test backwards as long as there are no other covariates in the model (except an intercept term). That is, pretend the lesion score is your dependent measure and behavior is the independent measure. Doing so may be helpful if you want to use fMRI packages that have not been retrofit for lesion analysis.

In the event you do have other covariates in the model, they can be first removed by regressing the behavioral data on them and then by using the residual behavioral score as your dependent measure. In the event you have image data covariates, the situation is even more complicated, as you would then have image data for both the dependent and the independent variable. As yet, we don't know of any software that makes this kind of analysis practical, let alone with permutation testing (although the recently released BPM toolkit seems

promising). We are currently retrofitting VoxBo to handle it, and it will be an option as of release 1.8.5.

## Power Analysis

Power analysis is critical in lesion analysis for many reasons, including the scarcity of patients, variability in performance, and sparse spatial distribution of lesions. VLSM complicates power analysis in several ways. First, there is a correction for multiple comparisons. VLSM datasets are in general highly spatially coherent – the lesion status of a given voxel is very well predicted by the lesion status of adjacent voxels. The problem is even larger when lesions are drawn at arbitrarily high resolution, which increases the number of voxels without necessarily increasing the amount of information (i.e., the number of *independent voxels*).

The permutation test described above can be used to bootstrap a rough estimate of the number of independent voxels in a dataset. In our article (Kimberg et al., in preparation), we carried out a permutation test using fabricated dummy behavioral data. An effective number of independent comparisons was derived by finding the number of comparisons for which Bonferroni correction would yield the same threshold as the permutation test. This at least gives us a more palatable correction for multiple comparisons. Having this correction, we can carry out power analysis on a voxel-by-voxel basis for the statistic of interest, in the same way we would do so for a univariate test.

A second complication with power analysis in VLSM is the spatial variability in power. At some level, fMRI shares this problem. However, it is likely worse in VLSM because the non-random spatial distribution of lesions (depending on the patient group) can lead to regions in which very few lesions are present. For example, in the sample dataset described in Kimberg et al. (in preparation), regions of critical interest varied in estimated power from well over 0.8 to well below 0.4, based solely on the distribution of lesion locations in a group of 55 left hemisphere patients.

This general approach to mapping power for VLSM studies would of course need to be tailored to the demands of a given study in terms of the test statistic used and the distribution of lesions.

## **References**

### Articles

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## Software

The following software packages were discussed in this article:

### **VoxBo**

[www.voxbo.org](http://www.voxbo.org)

free (GPL), runs on Linux, OSX, and Windows (via cygwin)

VoxBo is a complete package for fMRI analysis that is currently being extended to address lesion analysis.

### **SPM**

<http://www.fil.ion.ucl.ac.uk/spm/>

free (GPL), requires MATLAB

SPM is the most widely used package for fMRI data analysis. Numerous add-on toolkits are available, including two listed below.

### **SnPM**

<http://www.sph.umich.edu/ni-stat/SnPM/>

freely distributed, requires SPM

SnPM is an extension to SPM to provide non-parametric permutation testing.

### **BPM**

<http://www.fmri.wfubmc.edu/>

free (unknown), requires SPM/MATLAB

BPM stands for biological parametric mapping. It is an SPM extension that provides for image independent variables.

### **VLSM**

<http://crl.ucsd.edu/vlsm/>

free (GPL), requires MATLAB

VLSM is an independent lesion analysis package, written in MATLAB.

### **MRicro**

<http://www.sph.sc.edu/comd/rorden/mricro.html>

free (binary only), runs on Windows, Linux, and Solaris x86

MRicro is widely used for lesion tracing and image viewing. It also has some lesion

analysis tools built in.

### ***MRlcron***

<http://www.sph.sc.edu/comd/rorden/mricron/>

open source, runs on Linux, OSX, and Windows

MRlcron is a new program that we assume will supplant MRlcro. It's in the early stages of development, but provides exciting new analysis functionality.

### ***Anatomical Automatic Labeling (AAL)***

<http://www.cyceron.fr/freeware/>

freely available, requires SPM99 or SPM2

AAL is an atlas in MNI space.