

Variance Components Analysis of a Multi-Site fMRI Study

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Function BIRN

What is Function BIRN?

- BIRN = Biomedical Informatics Research Network (NIH funded program)
- Several BIRN projects
- FIRST BIRN or Function BIRN is the “Functional Imaging Research of Schizophrenia Test Bed BIRN”
- Collaboration of 10 sites across U.S.

FBIRN Goals

- Develop tools to facilitate collaboration among sites in imaging studies
 - Calibration (create comparable images despite differences in magnet manufacturer and size)
 - Statistics (data analysis methods)
- Schizophrenia as “test” case – i.e., there are some clinical aims regarding understanding schizophrenia

Multi-Site Preliminary Study

- 5 typical subjects
- 10 sites (11 machines) ... here use 8 machines with data ready first
- 2 visits (consecutive days) per site
- 10 runs (or tasks) per visit (4 repetitions of a sensorimotor task, 2 reps of a breath holding task, 2 reps of a cognitive task, 2 rest periods)
- Ultimate interest is in cognitive task; tools development largely done on others at first

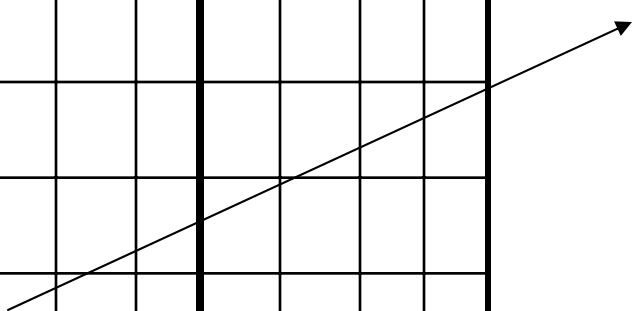
Data collection and processing

- Each run (task) yields 80-100 three-dim brain images (approx 1 per each 3 secs over 4 min run)
- Images may be (and usually are)
 - Corrected for head motion
 - Registered to match high-resolution anatomical scan
 - Normalized to a common brain shape
 - Smoothed

What does the data look like? (sensorimotor task)

Subj	Site	Day 1				Day 2			
		1	2	3	4	1	2	3	4
101	Duk1.5								
	Duk4								
	MGH								
	Minn								
	NMex								
	Stanf								
	UCI								
	UCSD								
102	Duk1.5								
								

Value here is response (??) for subj 101 at Minnesota for the 2nd SM task on during visit 1



Preliminary Data Analysis

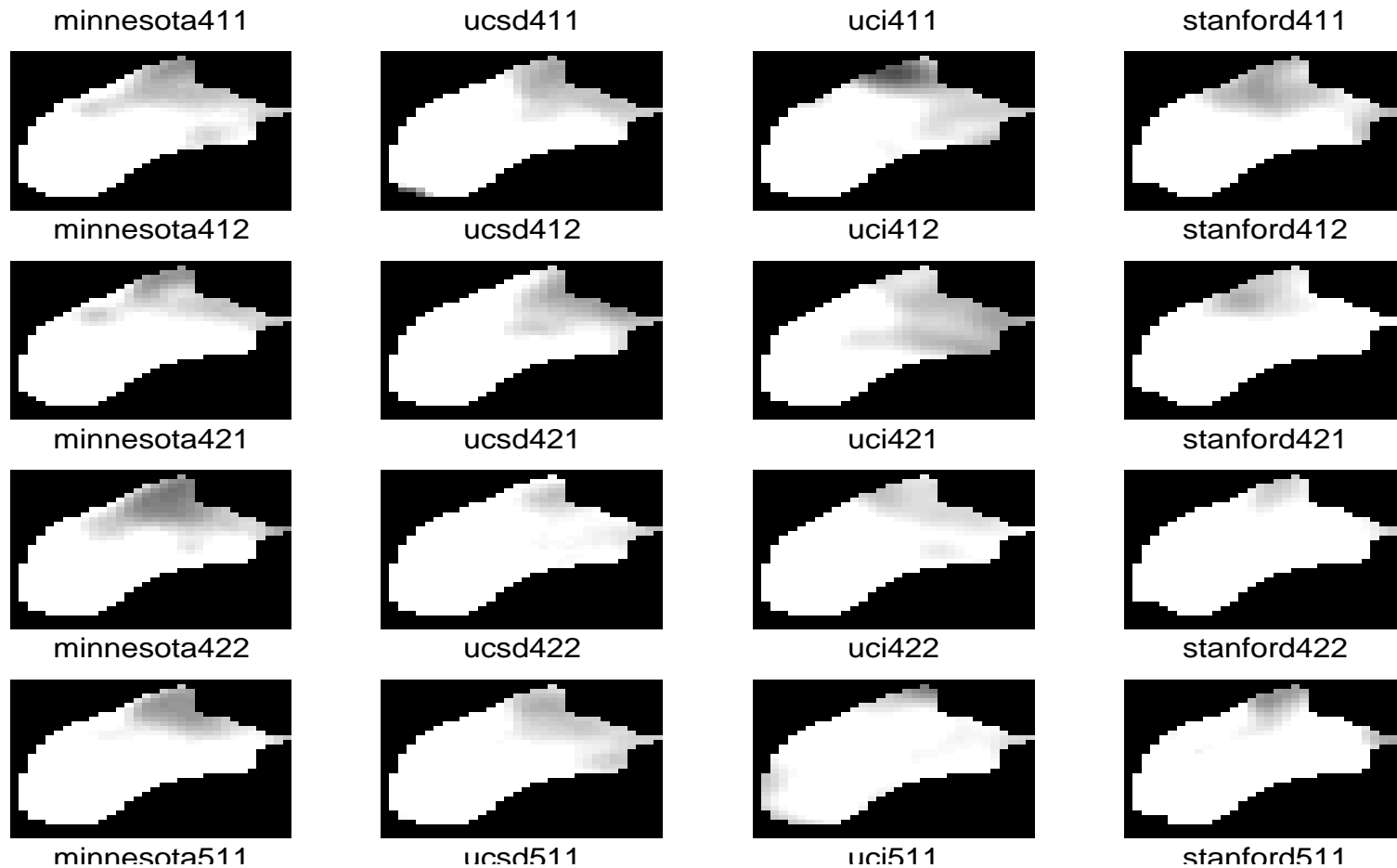
or

What goes inside one of the data matrix boxes?

- Analysis is voxel-by-voxel
(over 100k voxels in 3-dim brain image)
- Fit a generalized linear model using SPM software
(model relates response to protocol/other predictors)
- Response = effect size measure
(e.g., regression coefficient corresponding to within run comparison of times performing sensorimotor task and times not performing task)
- Can also use t-statistics or other summaries

Examining the images – SM task

- Slice of left occipital lobe (associated with vision)
- Labels give site/subj/visit/run



Variance components analysis

- Examine variation in measured effect attributable to different sources (between runs within a single visit, between visits, etc.)
- Check for consistency of variance components
 - data from different brain locations
 - data averaged over different size regions
 - estimated from different number of runs

A variance components model

- Simple starting model
- Response is average β for a particular region (single voxel, small area, brain region)
- Model response as sum of
 - Overall mean (across subject, site, etc.)
 - Subject effect
 - Site effect
 - Subj x site interaction
 - Day/Visit (within a subject, site pair)
 - Run (within a day)

Variance component estimation

- Tables that follow give posterior medians for variance components
- Results are provided for two different definitions of the response
 - mean β over entire region being considered
 - mean of top 10% of β values (proxy for activated voxels)
- Results are given as variance component estimates and as proportions of the total variance

Variance component results (entire brain regions)

- Results: variance proportions are similar across regions

	Left PCG (motor)		Left STG (auditory)	
	variance	proportion	variance	proportion
Region avg.	mean β value is .049		mean β value is .172	
subj	.0124	.46	.0125	.42
site	.0056	.21	.0056	.19
subj.site	.0043	.16	.0030	.10
visit	.0017	.06	.0033	.11
run	.0027	.10	.0054	.18
Top 10% avg.	mean β value is .553		mean β value is .835	
subj	.0112	.12	.0332	.15
site	.0309	.32	.0562	.26
subj.site	.0297	.31	.0934	.43
visit	.0197	.20	.0173	.08
run	.0056	.06	.0172	.08

Variance component results

(varying the size of region – in left PCG)

Results- Variance proportions are consistent between single voxel and 5x5x5 cube but whole region proportions are different

Region (with mean β)	Variance estimate			Proportion of total variance		
	1 voxel (.266)	5x5x5 cube (.248)	Whole region (.049)	1 voxel	5x5x5 cube	Whole region
subj	.0264	.0243	.0124	.29	.34	.46
site	.0289	.0217	.0056	.32	.30	.21
subj.site	.0196	.0149	.0043	.22	.21	.16
visit	.0041	.0036	.0017	.05	.05	.06
run	.0105	.0075	.0027	.12	.10	.10

Variance component results

(varying the size of region – in left STG)

Results- Variance proportions are consistent between single voxel and 5x5x5 cube but whole region proportions are different

Region (with mean β)	Variance estimate			Proportion of total variance		
	1 voxel (.704)	5x5x5 cube (.634)	Whole region (.172)	1 voxel	5x5x5 cube	Whole region
subj	.0213	.0216	.0125	.09	.13	.42
site	.0491	.0422	.0056	.21	.25	.19
subj.site	.1021	.0593	.0030	.44	.36	.10
visit	.0172	.0118	.0033	.07	.07	.11
run	.0400	.0314	.0054	.17	.19	.18

Variance component results

(varying the number of runs used to estimate)

Note: response is entire region mean for left PCG

- Result: Two runs are enough to estimate the variance components

Runs (with mean β)	Variance estimate			Proportion of total variance		
	First 2 runs (.049)	Last 2 runs (.051)	All 4 runs (.049)	First 2 runs	Last 2 runs	All 4 runs
subj	.0119	.0129	.0124	.47	.45	.46
site	.0054	.0061	.0056	.22	.21	.21
subj.site	.0041	.0046	.0043	.16	.16	.16
visit	.0017	.0025	.0017	.07	.09	.06
run	.0022	.0029	.0027	.09	.10	.10

Variance component results

(varying the number of runs used to estimate)

Note: response is mean of top 10% for left PCG

- Result: Two runs are enough to estimate the variance components

Runs (with mean β)	Variance estimate			Proportion of total variance		
	First 2 runs (.566)	Last 2 runs (.546)	All 4 runs (.554)	First 2 runs	Last 2 runs	All 4 runs
subj	.0284	.0313	.0297	.29	.32	.31
site	.0319	.0303	.0309	.33	.31	.32
subj.site	.0199	.0180	.0197	.20	.18	.20
visit	.0070	.0080	.0056	.07	.08	.06
run	.0104	.0097	.0112	.11	.10	.11

Model checking

- The additive variance components model is a very simple one
- Need to assess how well it summarizes the data
- One idea – cross validation
 - Remove data from one subject at one site and fit variance components model
 - Use fitted model to predict what would be seen for removed subject/site combination

Cross-validation study

- Response: β for single voxel or mean β over $5 \times 5 \times 5$ cube in left PCG
- For a given subj/site pair following tables give
 - Mean and std.dev. of the 8 actual measurements
(recall that we have 4 runs on each of 2 days)
 - Posterior predicted response from variance components model fit to other subj/site pairs
 - Prediction based on a “naïve” reference method
(avg over all other measurements for subject and site)

Predictive ability results (one voxel, left PCG)

	Observed mean and s.d.	Posterior predicted mean response	Naive predicted response
Subject 5			
Site 2	.245 (.083)	.282	.304
Site 3	.391 (.180)	.491	.381
Site 4	.396 (.067)	.316	.312
Site 5	.167 (.057)	.284	.308
Site 6	.317 (.187)	.289	.305
Site 7	.858 (.145)	.476	.357
Site 8	.565 (.142)	.573	.408
Mean Abs Err		.107	.138
Site 8			
Subject 1	.486 (.062)	.472	.344
Subject 2	.615 (.087)	.407	.310
Subject 3	.791 (.153)	.462	.348
Subject 4	.040 (.070)	.349	.244
Subject 5	.565 (.142)	.573	.408
Mean Abs Err		.174	.250

Predictive ability results (5x5x5 mean, left PCG)

	Observed mean and s.d.	Posterior predicted mean response	Naïve predicted response
Subject 5			
Site 2	.256 (.062)	.254	.277
Site 3	.330 (.158)	.469	.358
Site 4	.380 (.061)	.301	.290
Site 5	.169 (.048)	.267	.285
Site 6	.307 (.160)	.261	.277
Site 7	.728 (.136)	.441	.333
Site 8	.489 (.113)	.500	.365
Mean Abs Err		.095	.115
Site 8			
Subject 1	.343 (.053)	.390	.295
Subject 2	.562 (.070)	.383	.298
Subject 3	.704 (.120)	.420	.324
Subject 4	.055 (.056)	.274	.212
Subject 5	.489 (.113)	.500	.365
Mean Abs Err		.148	.194

Summary

- Variance components analysis shows 15-30% of variance in β values is run-to-run or visit-to-visit variation
- Results are consistent over brain locations considered
- Size of brain region of interest affects the absolute size of variance components but not the relative size (proportions)
- Using 2 runs instead of 4 does not affect variance components
- Cross validation study suggests that variance components model has some predictive ability
- Much to be done as FBIRN moves towards clinical studies