341.06 / LLL56

Comparison of Univariate and Multivariate Lesion Symptom Mapping Methods for the Analysis of Brain-Behavior Relationships in Stroke

T. Herron[1], M. Ivanova[1,2,3], N. Dronkers[1,2], B. Curran[1,4], C. Ludy[1], A. Zhong[1,5], A. Turken[1], & J. Baldo[1]

[1]VA Northern California Health Care System, [2]Univ of California, Berkeley, [3]National Research University, HSE, Moscow, Russia, [4]Univ of California, San Francisco, [5]New York Medical College

Introduction

Mass-univariate lesion symptom mapping methods (ULSM), such as the original voxel-based lesion symptom mapping (VLSM), provide statistical comparisons of behavioral performance in brain-injured patients with and without a lesion on a voxel by voxel basis[1,2] . New multivariate lesion-symptom mapping (MLSM) methods have been developed that consider the entirety of all lesion patterns (all measurement units) simultaneously in one model[3,4]. Advantages and disadvantages of ULSM and MLSM techniques have been discussed in the literature, but very little work has been done to empirically test these claims.[4] In the current study, we directly compared ULSM and MLSM methods by analyzing their performance on both artificial and real datasets of brain-behavioral relationships (BBRs).

Procedures: Simulated Data & Real Data

Synthetic Data:

1. Single parcel, proportional BBR conditions (% of target lesioned ~ % of behavioral deficit) in the left middle cerebral artery (MCA) territory over a fully crossed design:
   - 16 or 30 GM parcels of Left MCA as BBR targets
   - lesion masks from our site (n=209) and another site[4] (n= 131)
   - 13 lesion symptom mapping methods (8 MLSM)
   - 4mm lesion mask smoothing vs. none
   - 7 different patient sample sizes: n=32,48,64,80,96,112, &128
   - multiple spatial accuracy measures (6 distance & 2 overlap)
   - 3 behavioral noise levels
2. Procedure above was repeated with two-parcel networks, testing redundant, dependent, and extended networks.

Real Data:

Western Aphasia Battery language data from LH stroke patients:
repetition subscore (verbal repetition of words, phrases)
comprehension subscore (auditory comprehension), and
fluency subscore.

Procedures: LSM Methods Tested

Multivariate LSM*

ICA-L1	ICA - Independent
ICA-L2	component analysis
LPCA-L1	LPCA – Logistic principal
LPCA-L2	component analysis
SVD-L1	SVD – Singular value
SVD-L2	decomposition
PLS_5	Partial least squares (dense)
SVR	Support Vector Regression

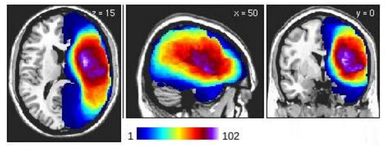
*[L1 – elastic net regression ; 95% L1 penalty]
[L2 – elastic net regression ; 95% L2 penalty]

Univariate LSM**[6]

T-max	Maximum t value
T-nu=125	125th highest t value [Mirman]
T-0.0001	cluster size when p<0.0001
T-0.001	cluster size when p<0.001
T-0.01	cluster size when p<0.01

**All U-VLSM methods used linear regression at every voxel plus permutation testing to set familywise thresholds based on five different criteria listed above.

Lesion Coverage Map



Overlay of stroke patients' lesions from our site, showing voxels included in the real LSM analyses. Color bar shows the degree of lesion overlap.

- 168 single chronic left stroke (36 female)
- mean post-stroke: 51 months (range 12-271)
- mean age: 61 (range 31-86)
- includes both aphasic (n=120) and non-aphasic patients (n=48)

Results: Single Anatomical BBR Target

A	32	48	64	80	96	112	128
ICA-L1	0.74	0.89	0.97	0.99	0.99	1	1
ICA-L2	0.77	0.91	0.98	1	1	1	1
LPCA-L1	0.80	0.93	0.99	0.99	1	1	1
LPCA-L2	0.81	0.95	0.99	1	1	1	1
PLS	0.69	0.88	0.97	0.99	1	1	1
SVD-L1	0.76	0.88	0.96	0.99	1	1	1
SVD-L2	0.75	0.88	0.94	0.98	1	1	1
SVR	0.85	0.96	1	1	1	1	1
T-max	0.91	0.99	1	1	1	1	1
T-0.0001	0.91	0.99	1	1	1	1	1
T-0.001	0.93	0.99	1	1	1	1	1
T-0.01	0.89	0.98	1	1	1	1	1

B	32	48	64	80	96	112	128
0.00	0.95	0.99	1	1	1	1	1
0.38	0.88	0.98	1	1	1	1	1
0.77	0.67	0.84	0.96	0.98	0.99	1	1

LSM Power: Fraction of time that LSM produces a cluster ostensibly identifying the target. **A**: LSM method (rows) vs. # of Patients in LSM (columns). **B:** Behavioral Noise Level (rows; fraction of behavioral std. dev. White noise added) vs. # of Patients (columns). *ICA*, *SVD*, *LPCA* are the lesion mask data reduction methods.

LSM Method	mm	Target Center	mm	# of Patients	mm
ICA-L1	6.4	COM	5.9	32	5.4
ICA-L2	7.1	AnyHit	3.1	48	4.7
LPCA-L1	6.0			64	4.5
LPCA-L2	5.9			80	4.4
PLS	6.4	Mask Smooth	mm	96	4.2
SVD-L1	4.0	4mm	4.3	112	4.2
SVD-L2	3.9	0mm	4.6	128	4.2
SVR	2.8				
T-max	2.8				
T-0.0001	3.0	Cluster Location	mm	Noise Level	Mm
T-0.001	3.3	COM	5.4	0.00	4.5
T-0.01	3.6	Max	3.5	0.38	4.5
T-nu=125	3.3	wCOM	4.6	0.77	4.4

LSM Accuracy: Distance from LSM Cluster center to Anatomical Target center averaging over multiple center definitions. *Target Center*: *COM:* Center of Mass ; *AnyHit:* closest target location. *Mask Smoothing*: Gaussian smoothing (FWHM). *Cluster Location*: *COM*: cluster Center Of Mass. *Max*: maximum LSM voxel location. *wCOM*: Weighted cluster center of mass. *Noise Level*: see LSM Power Table.

Results: Two Parcel BBR Target (Network)

	64	80	96	112	128
Fragile	0.99	0.99	1.00	1.00	1.00
Extended	0.98	0.99	1.00	1.00	1.00
Redundant	0.81	0.88	0.91	0.94	0.96

LSM Power: LSM success fraction: # of Subjects (columns) vs. two anatomical target network type (rows).

LSM Methods	Dice	# of patients	Dice
ICA-L1	0.09	64	0.11
ICA-L2	0.07	80	0.1
LPCA-L1	0.07	96	0.1
LPCA-L2	0.07	112	0.1
PLS	0.06	128	0.09
SVD-L1	0.08		
SVD-L2	0.09		
SVR	0.15		
T-max	0.15		
T-0.0001	0.14	Network Type	Dice
T-0.001	0.12	Fragile	0.09
T-0.01	0.1	Extended	0.1
T-nu=125	0.13	Redundant	0.11

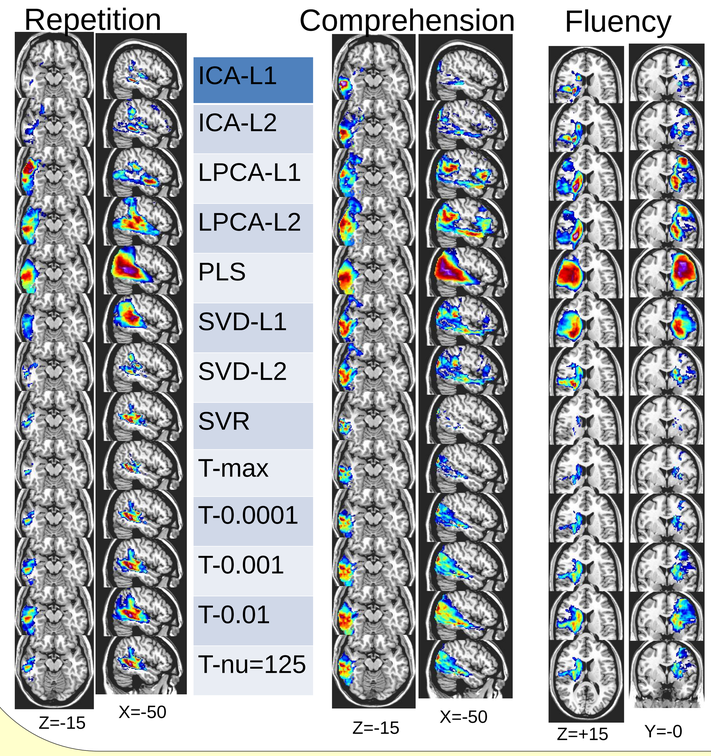
LSM Accuracy: Dice coefficients for above threshold LSM clusters vs. two target network.

	64	80	96	112	128
Fragile	-0.20	-0.07	+0.01	+0.08	+0.13
Extended	-0.13	-0.00	+0.10	+0.16	+0.22
Redundant	-0.35	-0.25	-0.17	-0.09	-0.04

LSM Accuracy: Distribution comparisons of LSM values inside targets vs. outside targets using a one-sided Kuiper test [+1=best, -1=worst] for LSM methods and sample size (below) or Network type and sample size (above)

	64	80	96	112	128
ICA-L1	-0.44	-0.35	-0.26	-0.18	-0.13
ICA-L2	-0.24	-0.15	-0.04	0.04	0.1
LPCA-L1	-0.06	0.08	0.19	0.25	0.32
LPCA-L2	-0.01	0.12	0.23	0.3	0.36
PLS	-0.09	0.03	0.08	0.12	0.16
SVD-L1	0	0.15	0.25	0.29	0.32
SVD-L2	-0.01	0.16	0.22	0.3	0.33
SVR	-0.64	-0.53	-0.43	-0.36	-0.28
T-max	-0.52	-0.41	-0.31	-0.24	-0.17
T-0.0001	-0.37	-0.26	-0.17	-0.09	-0.03
T-0.001	-0.21	-0.11	-0.02	0.04	0.09
T-0.01	-0.03	0.07	0.14	0.19	0.22
T-nu=125	-0.3	-0.19	-0.1	-0.04	0.02

Results: LSM Output with Real Language Data



LSM results on real data for Repetition, Fluency, and Comprehension scores from the WAB, covaried for lesion size, age, education, gender, (log) months post-stroke, two lesion site dummy variables, & overall aphasia severity score (minus the target subscore), The minimum power per voxel was 0.25 at p<0.001.

Summary

Modern ULSM techniques[6] provide a robust solution for detecting single targets, and required a smaller sample size than MLSM to achieve a similar level of power and spatial accuracy.

- With certain metrics, some (but not all) MLSM methods have advantages for detecting two-target networks, but cluster-size based ULSM methods can also provide insight into this case.
- Noise level has a modest impact on ULSM and MLSM results, mostly affecting LSM power.
- ULSM methods do better with noiseless data, but certain distance metrics reduce LSM cluster spatial sensitivity to behavioral noise.
- Smoothing at 4mm improves accuracy of localization across all metrics for both ULSM and MLSM methods, despite there being no anatomical imprecision in the synthetic models.
- Weighted center-of-mass (*wCOM*) and peak statistical value (*Max*) locations of obtained LSM clusters provide the most robust accuracy results across all methods.
- Dice overlap scores were unacceptably low for all methods (for single targets as well), but distributional comparisons (inside vs. outside target(s)) proved useful for method evaluation.

References

1.Bates, E. et al. (2003). *Nature Neuroscience*, *6*(5), 448–50. doi: 10.1038/nn1050
2.Rorden, C. et al. (2007). *J Cognitive Neuroscience*, *19*(7), 1081–1088. doi: 10.1162/jocn.2007.19.7.1081
3.Mah, Y. et al (2014). *Brain*, *137*(9), 2522–2531. doi: 10.1093/brain/awu164
4.Pustina, D. et al. (2018). *Neuropsychologia*, *115*, 154–166. doi:10.1016/j.neuropsychologia.2017.08.027
5.DeMarco, A. & Turkeltaub, P. *Hum Brain Mapp*. **2018** Nov;39(11):4169-4182. doi: 10.1002/hbm.24289
6.Wilson, S. et al, *Brain*, 2010 Jul;133(Pt 7):2069-88. doi: 10.1093/brain/awq129

For information/reprints, email tjherron@ebire.org