Date

LEICA: Lab Journal

# 27.01.2020

# Daily Goals

We have established that LEICA analysis can extract significant differences in activation magnitude between patient and control groups. However, it remains unclear whether LEICA is better suited to this task than less intensive analyses. Therefore, we will run comparisons on alternatively processed timeseries.

## Comparison of dFC leading eigenvector in ROI space

### Concatenated

### Subject-level

## Comparison of dFC leading eigenvectors in IC space

### Concatenated

### Subject-level

## Comparison of activations of ICs on full upper/lower triangle

### Concatenated

### Subject-level

## Permutation testing

Simultaneous with expanding fit range:

## ~~Fit entire structural connectivity matrix~~

## ~~Fit node-level bifurcation parameters~~ *~~a~~*

## Group-level comparison of ECs

## Compare nodewise *a* across groups

# Methods

## Comparison of dFC leading eigenvector in ROI space

### Concatenated: concatenated patient time series vs. concatenated control time series

### Subject-level: can only compare summary statistics, not entire time series

#### Mean:

#### Median:

#### Standard deviation:

#### Entropy:

#### Metastability:

#### Cohesion:

## Comparison of dFC leading eigenvectors in IC space

### Subject-level: need summary statistics

#### Mean:

#### Median:

#### Standard deviation:

#### Entropy:

#### Metastability:

#### Cohesion:

## Comparison of IC activations on full dFC upper/lower triangle

### Run full triangle through assembly script (will require overnight run)

### Compare

## Permutation testing

### Scramble label of patient vs. control BOLD signals

### Run scrambled BOLD signals through LEIDA pipeline

### Test whether labeled distributions (patients, controls) display significant differences vs. scrambled distributions.

Simultaneous with expanding fit range:

## ~~Fit entire effective connectivity matrix~~

### ~~Set template SC as prior~~

### ~~Set~~ *~~N~~~~2~~* ~~as number of variables~~

### ~~Fit all~~ *~~N~~~~2~~* ~~connectivity weights for each subject~~

## ~~Fit node-level bifurcation parameters~~ *~~a~~*

### ~~Set prior at 0~~

### ~~Set~~ *~~N~~* ~~as number of parameters~~

### ~~Fit all~~ *~~N~~* ~~bifurcation parameters for each subject~~

## Compare ECs at group level

### NBS

### Number of nonzero connections

### Degree weights

## Compare nodewise *a* at group level

### Compare each node

### Search for significance at each node

# Findings

## Comparison of dFC leading eigenvector in ROI space

### Concatenated:

#### 83 ROIs display significant group-level differences after FDR correction

#### 67 ROIs display significant group-level differences after Bonferroni or Sidak correction

### Subject-level:

#### Mean:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

#### Median:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

#### Standard deviation:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

#### Entropy:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

#### Metastability:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

#### Cohesion:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

## Comparison of dFC leading eigenvectors in IC space

### Subject-level:

#### Mean:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

#### Median:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

#### Standard deviation:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

#### Entropy:

##### FDR correction: no significant difference

##### Sidak correction: no significant difference

##### Bonferroni correction: no significant difference

#### Metastability:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

#### Cohesion:

##### FDR correction:

##### Sidak correction:

##### Bonferroni correction:

## Comparison of activations of ICs on full upper/lower triangle

## Permutation testing

# Questions

## Why use the kNN entropy calculation method of HShannon\_kNN\_k\_estimation, as opposed to the standard definition of entropy?

## Should we normalize the IC vectors to unit magnitude, as in physics?

## If we begin to search for a temporal cost function, which should we use?

### Frequency spectrum?

### Cannot use as a cost function if there is not significant difference in the data

#### Must show that cost function is significantly different in data

## Check dimensionality of each group, each subject

### Similar dimensionalities

#### across groups?

#### across subjects?

### Project patients onto control ICs:

#### Check if patients match control dimensionality

#### Metrics of interest:

##### See if patient activations(?) match control activations?

## Permutation group-level comparisons:

### Metastability:

### Entropy

### IC time series magnitudes:

### ROI time series magnitudes:

## Frequency spectra: how to determine whether spectra are significantly different? Cannot use standard statistical tests; this defeats the purpose of using spectra.

## Fitting strategies:

### Serial or parallel fitting of *alpha*, connectivity?

### If serial, which order?

### How to measure features of interest?

# 03.02.2020

# Questions

## ~~How to determine whether spectra are significantly different? Cannot use standard statistical tests; this defeats the purpose of using spectra.~~

## Check dimensionality of each group, each subject

### Dissimilar dimensionalities across groups and subjects; patients have higher dimensionality than controls.

### What conclusions can we extract from this finding?

#### More abnormal ‘networks’ in patients

#### Not main focus of paper;

##### no clear interpretation/connection

##### too few datapoints for reliable ICA

## Project patients onto control ICs:

### Repeat analyses from CIC in GIC

### Seeking differences between patients, controls

#### Treating control ICs as reference distribution

#### See which space is more sensitive

## Repeat analysis on *z*-scored BOLD signal

### Two spaces:

#### Without IC

#### With IC

### Compare size of effect in entropy, timeseries KS distance with phase ICs

## Permutation group-level comparisons:

### Metastability: negative result

### Entropy: positive result

#### Should not use KS tests: want normal test

#### Use Wilcoxon, permutation tests

### ~~IC time series magnitudes: [waiting]~~

#### ~~Use KStests:~~

#### ~~Check~~

### ~~ROI time series magnitudes: [waiting]~~

#### ~~KStests giving remarkably low p-values; why?~~

#### ~~View histograms of sample of significantly different, similar ROI dFC values~~

## Fitting strategies:

### Serial or parallel fitting of *alpha*, connectivity?

### If serial, which order?

### How to measure features of interest?

11.02.2020

Status: LEICA and ZICA

# Findings

Our goal is to find the space which maximizes the difference in subject entropy. We hypothesize that the space defined by the significantly covarying independent components of the dFC’s leading eigenvector will maximize the entropy difference between two groups. To test this hypothesis, we extracted these independent components from a dataset containing both healthy controls and OCD patients and ran group-level comparisons on the subject entropies and phase-locked dFC eigenvector magnitudes in the space defined by these components. As a control, we project the *z*-scored BOLD signal of each subject onto the IC space and ran identical group-level comparisons on these BOLD signals. In addition, we tested the efficacy of using the leading eigenvector by repeating the dFC analysis with alternative compression methods, i.e. an exponentially scaled average and the uncompressed N(N-1)/2 dFC space.

## Entropy: reported *p*-values in IC space

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | LEICA | MICA | ICA | ZICA |
| CIC | 0.00750.0228 | 0.2045 | 0.0167 | 0.0043 |
| GIC, Control | 9.999 \* 10-5 | 0.0172 |  | 9.999 \* 10-5 |
| GIC, Patient | 0.1049 | 9.999 \* 10-5 |  | 0.0118 |

## Entropy: reported effect sizes/tests statistics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | LEICA | MICA | ICA | ZICA |
| CIC | -0.5312 | 0.2918 | -0.5377 |  |
| GIC, Control | -1.8204 | -0.5560 |  | -1.7122 |
| GIC, Patient | 0.3710 | 1.1143 |  | 0.5873 |

## Activations: number of assemblies which survive FDR correction

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | LEICA | MICA | ICA | ZICA |
| BOLD (out of 90) | KStest2: 53permutation: 0 | KStest2: 53permutation: 0 | KStest2: 53permutation: 0 | KStest2: 0permutation: 0 |
| dFC (out of 90) | KStest2: 84/90permutation: 72/90 | KStest2: 89/90permutation: 81/90 | KStest2: 3583/4005permutation: 3011/4005 |  |
| CIC | KStest2: 14/16permutation: 12/16 | KStest2: 7/11permutation: 8/11 | KStest2: 0/386permutation: 0/386 | KStest2: 0/14permutation: 0/14 |
| GIC, Control | KStest2: 15/15permutation: 5/15 | KStest2: 11/11permutation: 8/11 |  | KStest2: 12/12permutation: 0/12 |
| GIC, Patient | KStest2: 17/17permutation: 11/17 | KStest2: 11/11permutation: 7/11 |  | KStest2: 9/14permutation: 0/14 |

# Conclusions

Loss of information on difference in magnitudes (section C) in control space seems to be increasing discrimination in total information transferred.

## The reported *p*-values of LEICA and ZICA suggest that both methods are capable of separating patients from controls in IC space. In stark contrast to the original hypothesis, results suggest that ZICA may be superior to LEICA in terms of separating conditions in this space. However, a comparison in the original AAL space may provide additional information on this topic.

## The reported effect sizes of LEICA and ZICA comparisons confirm that control space provides a superior separation between conditions than patient space. Notably, ZICA produces a control space effect size comparable to LEICA, and a substantially larger effect size in patient space. This further suggests that ZICA is able to compete with LEICA in entropy-based separation in IC space.

## In terms of detecting significantly differing regions/ICs between conditions, phase-based LEICA clearly outperforms ZICA. This suggests that functional connectivity strengths differ substantially between conditions, i.e. that one condition is more closely interconnected than the other. That this holds true for both the two-sample Kolmogorov-Smirnov test and the permutation test only reinforces this conclusion.

# Future Steps

## For AAL comparisons:

### Use the filtered, demeaned, detrended BOLD timeseries (no dFC, no *z*-score)

### Compare histograms

## Questions:

### Is LEICA more informative than ZICA? (activation histograms)

### Which space is most informative (concatenated, control, patient)?

#### why is control space less informative than patient, concatenated space for magnitudes but more so for entropy?

#### Need to normalize entropy values by number of components to compare LEICA-ZICA? Cannot compare entropies with different dimensionalities.

## Pattern for paper:

### Compare LEICA and ZICA for entropy discrimination

### Conclude that control space is most discriminative

### Repeat LEICA vs. ZICA comparison in control space

#### Similar results for entropy

#### LEICA more sensitive for activation magnitudes

## Fitting:

### Avoid fitting C and *a* simultaneously