Temporal dynamics of resting state fMRI functional connectivity

Adi Maron-Katz David Amar 2013

Functional magnetic resonance imaging (fMRI)

- Blood-oxigen levels
- High spatial resolution (2-3mm³)
- Low temporal resolution (2-3 secs)
- ~160,000 voxels
- ~50,000 voxels of gray matter
- High inter-signal dependency





The resting state

- Ongoing spontaneous changes in brain activity (EEG, fMRI)
- Resting state activity a compulsive user of brain energy
- Slow correlated activity within functional networks in the resting state (i.e. RSNs)



Biswal 95\2008,, Raichle 2001, Greicius and Menon 2003, Beckmann 2005, Fox 2007, Vincent 2007, Martuzzi 2010, Buckner 2008

Characterizing RSNs

Altered RS functional connectivity (FC) associated with

- Cognitive impairments and psychiatric disorders Menon 2011, Rabinak et. Al. 2011, Kim et. Al. 2011, Assaf et. Al. 2010, Hawellek et. Al. 2011

- Self reported anxiety levels in healthy subjects Seely et. Al. 2007, Kim et. Al 2011

- Temporal stationary traditionally assumed (seek FC over all time points)
- Recent studies demonstrate time varying properties E.g. Kang et. Al.2011, Smith et. Al 2012, allen et. Al. 2012

The study of Allen et. Al. Cerebral cortex 2012

- •N= 400 subjects (200 females)
- C=100 components->50 ICNs/RSNs
 - A IDENTIFICATION OF INTRINSIC CONNECTIVITY NETWORKS (ICNs)



Figure 1. Illustration of analysis steps. (A) Group ICA decomposes resting-state data from M = 405 subjects into C = 100 components, $C_1 = 50$ of which are identified as intrinsic connectivity networks (ICNs). GICA1 back reconstruction is used to estimate the TCs (\mathbf{R}_i) and SMs (\mathbf{S}_i) for each subject. (B) Stationary FC between components (left, \sum_i) is estimated as the covariance of \mathbf{R}_i . Dynamic FC (right, $\sum_i^{11}(w)$) is estimated as the series of regularized covariance matrices from windowed portions of \mathbf{R}_i .

Allen et. Al. Cerebral cortex 2012



Allen et. Al. Cerebral cortex 2012











Our questions:

- Given a resting state network: which parts are constant and which are transient/dynamic?
- Core connectome stability?
- Transient patterns reproducibility?
- What can we learn from such information?



How to address it?

- Use a predefined parcellation
- Identify stable connections ("Core" network)
- Identify unstable connections ("Dynamic" network)
- Integrate the two into a representation of FC dynamics



Preliminary attempts – core network

- Sliding window of 15 TRs (1 TR shift)
- Node = parcel with at least 5 voxels
- an edge e(i,j) exists iff

 $(\Sigma_{s} \text{perc}(R_{w}(i,j),p))/S \ge t_{R}$

- Evaluation:
 - Network size
 - Stability within subjects (LOOCV): precision, recall, ROC, Wilcoxon ranksum pval

Stability scores

- m = model un-weighted graph
 s = sample un-weighted graph
 precision = |{e_m}∩{e_s} |/|{e_s}|
 Recall = |{e_m} ∩{e_s} |/|{e_m} |
- Given a sample weighted graph s: Wilcoxon ranksum pval is calculated for population of {w_{es}/e_sem} vs. {w_{es}/e_sem}
- ROC score: model edges = positive class and weights = predictions

Preliminary analysis- core

- 5min RS fMRI scan, 57 male subjects
- Craddock 500 parcellation
- 25 subjects used as train set (LOOCV)
- t_R (correlation thresh)= {0.2,0.3,0.4,0.5}
- P (cor percentile) = {5,10,15,20}
- Whole window was also used with t_R ={0.4,0.5,0.6,0.7}

Core – preliminary results

	Perc for								
Ct	thresh	#nodes	#edges	LOO avg(R)	Wilcoxon pval	ROC	precision	Recall	
0.2	5	309	506	0.287	8.74E-233	0.952	0.637	0.136	
0.2	10	411	980	0.307	0.00E+00	0.944	0.663	0.173	
0.2	. 15	442	1519	0.321	0	0.935	0.678	0.191	
0.2	20	453	2213	0.331	0	0.923	0.689	0.203	
0.3	5	215	243	0.363	2.19E-116	0.966	0.630	0.111	
0.3	10	302	486	0.383	1.78E-231	0.959	0.655	0.143	
0.3	15	392	837	0.392	0.00E+00	0.952	0.667	0.174	
0.3	20	432	1267	0.407	0.00E+00	0.945	0.683	0.192	
0.4	5	132	101	0.432	1.66E-53	0.975	0.621	0.081	
0.4							47	0.114	
0.4		69							
0.4		ALANS					74	0.170	
0.5		PAG ANT	1 Actor				25	0.041	
0.5	AL X	CH AS	CALLS!	A A A A			20	0.076	
0.5	0			THE REAL		Where a	52	0.109	
0.5						100	63	0.138	
0.5	Singl			State -			18	0.230	
0.6	Single win	5/5	//0	0.002	U	0.900	v. 0 99	0.209	
0.7	Single win	216	245	0.737	3.03E-128	0.983	0.680	0.158	

Core Models



Core Models



STD across time windows vs. average correlation



Clustering core with Markov Clustering (MCL) - Background

- MCL = a graph clustering algorithm based on random walks
- Random walk: at each step randomly select an outgoing edge
- Upon visiting a dense cluster, high probability of covering a large fraction of it before leaving
- Markov Chain: a sequence of variables X1, X2, X3 (e.g transition matrix) where, given the present state, the past and future states are independent

MCL

- In MCL, two processes are alternated between repeatedly:
 - Expansion (taking the Markov Chain transition matrix



- Expansion allows flow to connect different regions of the graph
- Inflation strengthens intra cluster connections and weakens inter-cluster connections

MCL Algorithm

- Input: an un-directed graph, power parameter e, and inflation parameter r
- Create associated matrix
- Add self loops (optional)
- Normalize matrix (divide vecs by norm)
- Expand by taking the eth power of the matrix
- Inflate by taking inflation of the resulting matrix with parameter r
- Repeat steps 5 and 6 until a steady state is reached (convergence)
- Interpret resulting matrix to discover clusters

MCL on core 0.6 whole window - results

- # Clusters: 88
- Average size: 4.193
- Maximum size: 23
- Minimum size: 2
- Modularity: 0.697















Core – preliminary results – test set

	Perc for							
Ct	thresh	#nodes	#edges	LOO avg(R)	Wilcoxon pval	ROC	precision	Recall
0.2	2 5	309	503	0.256	0.000	0.946	0.603	0.134
0.2	2 10	410	977	0.274	0.000	0.935	0.623	0.169
0.2	2 15	443	1523	0.291	0.000	0.925	0.641	0.187
0.2	2 20	454	2207	0.304	0.000	0.912	0.655	0.199
0.3	3 5	214	241	0.325	0.000	0.960	0.582	0.106
0.3	3 10	301	480	0.355	0.000	0.953	0.621	0.140
0.3	3 15	391	833	0.367	0.000	0.945	0.631	0.169
0.3	3 20	432	1264	0.381	0.000	0.936	0.649	0.188
0.4	1 5	134	101	0.391	0.000	0.970	0.561	0.077
0.4	l 10	204	217	0.423	0.000	0.966	0.598	0.108
0.4	l 15	277	395	0.446	0.000	0.962	0.628	0.141
0.4	1 20	353	646	0.457	0.000	0.955	0.639	0.165
0.5	5 5	40	26	0.476	0.000	0.979	0.557	0.038
0.5	5 10	105	79	0.493	0.000	0.976	0.580	0.073
0.5	5 15	178	158	0.512	0.000	0.973	0.597	0.101
0.5	5 20	236	282	0.528	0.000	0.969	0.617	0.131
0.5	5 Single win	449	1747	0.568	0.000	0.939	0.676	0.227
0.6	5 Single win	371	776	0.641	0.000	0.962	0.657	0.206
0.7	7 Single win	216	245	0.711	0.000	0.978	0.619	0.154

Preliminary attempts – dymanic network

- Sliding window of 15 TRs (1 TR shift)
- Node = parcel with at least 5 voxels
- an edge e(i,j) exists iff

 $STD(R_w(i,j)) >= STD_p$ in at least f fraction of the subjects p= percentile of STDs (within subject) $R_w(i,j)$ =the correlation between signals i and j in the wth window

• Evaluation: network size, stability within subjects (LOOCV) (?)

Preliminary analysis- dynamic

- 5min RS fMRI scan, 57 male subjects
- Craddock 500 parcellation
- 25 subjects used
 P (min std perc) = {70,80,90}

Dynamic edge distributions



Analysis of network pairs – ModuleMap algorithm



- Interaction types can differ: within ("positive") vs. between ("negative") functional units
- Input: networks P, N with same vertex set
- Goal: summarize both networks in a module map
 - Node module: gene/voxel set highly connected in P
 - Link two modules highly interconnected in N
- ModuleMap algorithm:
 - Initiator (initial modules)
 - Improver (merging/excluding)
 - * Different definitions for the links and the optimization objective function
 - * Problems are NP hard

DICER algorithm, Amar et al. PLoS CB 2013



Preliminary results – ModuleMap

- Results effected mainly by dynamic graph
- Best results obtained with the 80% std dynamic graph



Module 21 to module 29 connections



Where are 21 and 29 in the Brain



Future plans –dynamic FC

- Healthy-Schizophrenic core comparisons
- Task-rest core comparisons
- Evaluate dynamic networks (reproducibility)
- Compare results with previous works (e.g. Allen et. Al)
- Compare subject groups in terms of dynamic patterns
- Can this add information in relation to stationary analysis?