Functional Disconnectivity in Schizophrenia: a (Macro-)Systems Biological Approach

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Abstract

Systems biology in the sense of Robert Rosen connects microscopic and macroscopic systems, and our studies is in accordance with his spirit.

Schizophrenia is often regarded as a set of symptoms caused by impairments in the connectivity of the information processing macro-networks of the brain. To investigate this hypothesis, an fMRI study involving an associative learning task was conducted with schizophrenia patients and controls. A set of generative models of the BOLD signal generation were defined to describe the interaction of five brain regions and the experimental conditions. The models were fitted to the data using Bayesian model inversion. The comparison of different model connectivity structures lead to the finding that in schizophrenia there is an overall complexity reduction of the information processing structure. Parameter-level analysis also pointed out that there are significant impairments in the top-down control flow in patients. Disconnectivity, observed between brain regions in schizophrenic patients could result from abnormal modulation of (NMDA-dependent plasticity implicated in schizophrenia.

New pharmacological strategies should be suggested by using multi-scale mathematical modeling technique by integrating macro network level description with detailed kinetic models of drug effects on NMDA receptors.
Systems biological framework

Applied to the study of cognitive control deficit and possible repair in schizophrenia
Experiment – The task

- 11 subjects with schizophrenia and 11 healthy controls
- visual associative learning task: objects in the cells of a 3-by-3 grid
- Encoding phase: the objects were shown on their places one by one
- Retrieval phase: only cues were given, patients had to tell what was the object in the cell
- phases were separated by resting periods.
- 8 learning epochs in a row.
Experiment - Results

**Behavioral differences**
- Schizophrenia patients were able to learn the task
- their learning curve converges slower compared to healthy controls

**Data preparation**
- fMRI data were preprocessed and analyzed using a standard processing sequence
- Time series were extracted using a thresholded effects of interest contrast
- stereotactastic region-of-interest maps
Dynamic Causal Modeling

Neural activity dynamics considering the effects of experimental conditions

\[ \dot{x} = \left( A + \sum_{i=1}^{N} u_j B^j \right) x + Cu \]
\[ y = \lambda(x, \theta_h) \]

Mapping from neural activity to BOLD signal (nonlinear)
Bayesian parameter estimation

\[ p(\theta|y,M) = \frac{p(y|\theta,M)p(\theta|M)}{p(y|M)} \]

\( \theta = \{A, B, C, \theta_h\} \)

Assumption: all distributions are Gaussian
Approximation method: Expectation Maximization

Model comparison
Goodness measure: model evidence

\[ p(y|M) = \int p(y|\theta,M)p(\theta|M) d\theta \]

Approximation method: variational Bayesian
Models to compare

Input conditions: presence of a visual stimulus (Visual), encoding phase (Encoding), retrieval phase (Retrieval) and the epoch number (Time)

Two streams of connections:
data stream lower level -> higher level, black on above figure, fixed in the models
control stream higher level -> lower level, black on above figure, varied in the models

First model set: different intrinsic connectivity combinations (A matrix in DCM)
Second model set: different modulatory effects of input conditions (B matrix in DCM)
Results – model structure level

- Model evidences -> Posterior probability densities over the model sets
- Subjects within group are not assumed to have the same structure

Control group
- Clear winner
- The model containing most connections

Patient group
- No clear winner
- Most probable models lack connections in the control stream.
Results – parameter level

- comparing effective connectivity parameters
- reference model was selected (above).

The significance values come from two-sided t-tests on the samples of the two groups.

Significant differences:
- prefronto-hippocampal pathway
- hippocampo-inferior temporal pathway
- the context-dependent modulation of those by the learning procedure.
Correlation with behaviour

How are the DCM model parameters correlated with learning performance of the subjects?

Fitted to performance data \( k \) - the learning rate:

\[
l(t) = 1 - e^{-kx}
\]

- Spearman rank correlation
- averaged over subjects.

most correlated:
- hippocampo-parietal pathway
- hippocampo-inferior temporal connectivity during encoding.
Illness or slow learning?

Common problem in learning experiments: are the differences there due to the disorder, or some subjects are naturally slow learners?

- subjects in control group with no better performance than patients (3 people).
- model comparison for these subjects separately

Posterior probability distribution of models:
- same as for control group
- different from patient group

The method is capable of:
- capturing the underlying structure of the illness
- separate it from slow learning despite of the similar performance
Conclusions

- An associative learning task was performed by schizophrenia patients and healthy controls, patients performed worse.

- Several connectivity models of the BOLD signal generation were defined by DCM and fitted to measurement.

- The information processing networks implemented by patients proved to be fundamentally different than the controls'.

- Impairment in the prefronto-hippocampal and hippocampo-inferior-temporal pathways, which play an important role in the cognitive control of associative memory formation.

- The connection strengths are positively correlated with learning performance.

- The method is able to differentiate natural slow learning and illness.