Functional Disconnectivity in Schizophrenia

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BUDAPEST CNS GROUP
Content

1. Computational psychiatry

2. Disconnection hypotheses of schizophrenia

3. Reduced learning ability: some behavioral and fMRI data

4. Dynamical causal modelling (DCM)

5. Model Selection: Bayesian Estimation

6. Results

7. Schizophrenia - a broken hermeneutic circle

8. Take home messages
Computational Psychiatry

- "All models are wrong, but some are useful."

- to set testable hypotheses about the relationship between brain structure and psychiatric problems

- to understand the underlying mechanisms of data obtained by neuro-physiological and brain imaging methods

- to interpret neurological and psychiatric disorders as dynamical diseases
Neurological and Psychiatric Disorders as Dynamical Diseases

Alzheimer–disease
Normal Pathological
PFIZER Pharma GmbH 2005

Migraine
Dahlem and Chronicle, Neurobiology, 2004

Schizophrenia
storage and recall of memory traces
changes in attractor structure pathological attractors

Dynamical diseases

Parkinson–disease
fixed point attractor periodic attractor

Anxiety
Reboxetine (0.3 mg/kg, IV)

ADHD
Power (\mu V^2/Hz^2)
The Schizophrenic Brain: Multiple Levels

macronetwork

PFC - hippocampal interaction
gamma rhythms

glutamate- DOPA- GABA
pyramidal cells

calcium current

calcium binding proteins
The Schizophrenic Brain: Multiple Levels

Macro-networks, neural networks and synaptic protein networks

Multiscale networks in the brain
Disconnection hypotheses of schizophrenia

Geschwind’s (general) disconnection syndromes (1965)

The pathways implicated in the principle syndromes described by Geschwind, classified into three types: sensory-limbic disconnection syndromes (dotted lines), sensory-motor disconnection syndromes (dashed lines); sensory-Wernicke’s area disconnection syndromes (solid lines).
Disconnection hypotheses of schizophrenia

- Impairments in functional macro-networks in schizophrenia was suggested.
- Abnormal prefronto-hippocampal connectivity?
- Changes in effective connectivity: (i) intrinsic connectivity of the network, (ii) input-dependent changes.

Which connections are significantly impaired during schizophrenia? Quantitative estimation for the degree of impairment.
Reduced learning ability: some behavioral and fMRI data

Associative Learning
Reduced learning ability: some behavioral and fMRI data

Associative Learning
Reduced learning ability: some behavioral and fMRI data

Learning dynamics in the associative memory task in controls and schizophrenia patients over time
Some fMRI data

Encoding

Visual cortex

Inferior temporal cortex

Right hippocampus

Figure legend

black: HC
red: patients
Dynamical Causal Modeling (DCM)

Karl Friston and Klaas Stephan

A

General bilinear state equation

\[ \dot{x} = (A + \sum_{j=1}^{m} u_j B^j)x + Cu \]

B

\[ \dot{x}_1 = a_{11}x_1 + a_{12}x_2 + c_{11}u_1 \]

\[ \dot{x}_2 = a_{21}x_1 + a_{22}x_2 + b_{21}^{(2)}u_2x_1 \]
Dynamical Causal Modeling

black arrows: (functional) connections
grey arrows: external inputs
dotted arrows: transformation of neural activities to hemodynamic responses
specific example: the propagation of visual stimuli

\[
\begin{align*}
\frac{dx_1}{dt} &= c_{11}u_1 \\
\frac{dx_2}{dt} &= a_{12}x_1 + a_{22}x_2 + a_{52}x_5 + u_2a_{42}x_4 \\
\frac{dx_3}{dt} &= a_{13}x_1 + a_{33}x_2 + a_{53}x_5 + u_2a_{43}x_4 \\
\frac{dx_4}{dt} &= u_2a_{24}x_2 + a_{44}x_4 + u_2a_{34}x_3 \\
\frac{dx_5}{dt} &= a_{25}x_2 + a_{55}x_5 + a_{35}x_5
\end{align*}
\]
Neuronal activity induces a vasodilatory and activity-dependent signal \( s \) that increases blood flow \( f \). Blood flow causes changes in volume and deoxyhemoglobin (\( v \) and \( q \)). These two hemodynamic states enter an output nonlinearity, which results in a predicted BOLD response \( y \). In recent versions, this model has six hemodynamic parameters.
Dynamical causal modelling (DCM)

\[ \dot{x} = (A + \sum_{i=1}^{N} u_j B^j) x + C u \]  

(1)

\[ y = \lambda(x, \theta_h) \]  

(2)

(1): neural state equation, \( x \): neural state variables, \( u \): input variables (conditions defined by the experiment)

(2): hemodynamic model: nonlinear mapping from the neural activity to the BOLD signal \( y \)

Parameters: \( \theta_n = \{A, B, C\} \), \( \theta_h \): hemodynamic parameters

\( A \): endogenous coupling parameters, the causal effects of the ROIs on each other

\( B \): modulatory parameters, the effects of the inputs on the endogenous connections

\( C \): the direct effects of the inputs on the ROIs.
Dynamical causal modelling (DCM)

- estimating effective connectivity from neuroimaging data
- capture
  - causal interaction between regions within the network: intrinsic connections
  - modulation of intrinsic connections by the experimental context
  - driving inputs to regions
- selection from competitive models from Bayesian technique
Brain regions of a functional macro-network for associative memory

- Superior Parietal Cortex (SP)
- Dorsolateral Prefrontal Cortex (PFC)
- Visual Cortex (VC)
- Inferior Temporal Cortex (IT)
- Hippocampus (HiPP)
Model Selection: Bayesian Estimation

- VC: visual signal processing
- IT: object recognition
- SP: location recognition
- HIPP: associative memory
- PFC: motivation, attention, context, cognitive control

How they are connected? Model selection (model discrimination)
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)
Model Selection: Bayesian Estimation

To estimate the values of the parameter set, $\theta = \{\theta_h, \theta_n\}$ best fitting to measurement data, the "inverse problem" should be solved.

One possible procedure to do so is the Bayesian maximum a posteriori (MAP) estimation technique:

$M$: specific connectivity pattern of the model;

$$p(\theta \ | \ y, M) = \frac{p(y \ | \ \theta, M)p(\theta \ | \ M)}{p(y \ | \ M)}$$ (3)

Both the prior $p(\theta \ | \ M)$ and posterior $p(\theta \ | \ y, M)$ distributions: Gaussian
Model Selection: Bayesian Estimation

Models with different connectivity patterns are compared: by estimating their model evidence:

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

(4)

evidence: the probability of obtaining the actual measurement conditioned on the model form, integrated on the whole parameter space of the model (regardless of the choice of parameters).
Figure 1: (A) Intrinsic connections in most probable fitted DCM models. Solid arrows denote causal connections present in both HC and SCZ groups, dashed arrows denote connections present in the HC group only. (B) Some of the modulatory connections in most probable fitted DCM models.
Results

Model structure level

Table 1: Model probabilities for varying endogenous connections

<table>
<thead>
<tr>
<th>No.</th>
<th>Additional connections</th>
<th>SCZ</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>.099</td>
<td>.079</td>
</tr>
<tr>
<td>2</td>
<td>PFC → HPC</td>
<td>.145</td>
<td>.106</td>
</tr>
<tr>
<td>3</td>
<td>HPC → IT</td>
<td>.099</td>
<td>.079</td>
</tr>
<tr>
<td>4</td>
<td>HPC → IT, PFC → HPC</td>
<td>.172</td>
<td>.101</td>
</tr>
<tr>
<td>5</td>
<td>HPC → SP</td>
<td>.158</td>
<td>.081</td>
</tr>
<tr>
<td>6</td>
<td>HPC → SP, PFC → HPC</td>
<td>.095</td>
<td>.116</td>
</tr>
<tr>
<td>7</td>
<td>HPC → SP, HPC → IT</td>
<td>.136</td>
<td>.081</td>
</tr>
<tr>
<td>8</td>
<td>HPC → SP, HPC → IT, PFC → HPC</td>
<td>.095</td>
<td>.357</td>
</tr>
</tbody>
</table>

Connections present in all models: V1 → (IT, SP), SP → (HPC, PFC), IT → (HPC, PFC)

In the control group there is a clear winner for both the endogenous and modulatory connection patterns, the model that contains the full control stream. In the SCZ group, there is no clear winner, there are several more probable models. While the most probable models in the SCZ group lack more or less connections, information processing network of schizophrenia patients is fundamentally different than the one of controls.
Table 2: Model probabilities for varying modulatory connections

<table>
<thead>
<tr>
<th>No.</th>
<th>Additional connections</th>
<th>SCZ</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Encoding</td>
<td>Retrieval</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>none</td>
<td>none</td>
<td>.063</td>
</tr>
<tr>
<td>10</td>
<td>none</td>
<td>PF→HC</td>
<td>.064</td>
</tr>
<tr>
<td>11</td>
<td>PF→HC</td>
<td>none</td>
<td>.060</td>
</tr>
<tr>
<td>12</td>
<td>PF→HC</td>
<td>PF→HC</td>
<td>.060</td>
</tr>
<tr>
<td>13</td>
<td>none</td>
<td>HC→(SP,IT)</td>
<td>.061</td>
</tr>
<tr>
<td>14</td>
<td>none</td>
<td>HC→(SP,IT), PF→HC</td>
<td>.068</td>
</tr>
<tr>
<td>15</td>
<td>PF→HC</td>
<td>HC→(SP,IT)</td>
<td>.060</td>
</tr>
<tr>
<td>16</td>
<td>PF→HC</td>
<td>HC→(SP,IT), PF→HC</td>
<td>.059</td>
</tr>
<tr>
<td>17</td>
<td>HC→(SP,IT)</td>
<td>none</td>
<td>.073</td>
</tr>
<tr>
<td>18</td>
<td>HC→(SP,IT)</td>
<td>PF→HC</td>
<td>.061</td>
</tr>
<tr>
<td>19</td>
<td>HC→(SP,IT), PF→HC</td>
<td>none</td>
<td>.064</td>
</tr>
<tr>
<td>20</td>
<td>HC→(SP,IT), PF→HC</td>
<td>PF→HC</td>
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<tr>
<td>21</td>
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<td>22</td>
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<td>HC→(SP,IT), PF→HC</td>
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<tr>
<td>23</td>
<td>HC→(SP,IT), PF→HC</td>
<td>HC→(SP,IT)</td>
<td>.060</td>
</tr>
<tr>
<td>24</td>
<td>HC→(SP,IT), PF→HC</td>
<td>HC→(SP,IT), PF→HC</td>
<td>.059</td>
</tr>
</tbody>
</table>

Connections present in all models: Time→All, Visual→(V1→(IT,SP), SP→(HC,PF), IT→(HC,PF)
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.
A new question:

No clear winner in the SCZ population:

can be the basis of the CLASSIFICATION of the illness ??
Parameter level
the model selection does not provide the SPECIFIC pathways being impaired, so the parameter level analysis is also necessary

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.
Correlations

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

Figure 2: Correlations between the learning rate of the subjects and the connectivity parameters of the models fit to their BOLD data. Mostly positive, and high for the hippocampal-superior parietal interaction in the endogenous (A) and also in the modulatory parameter arrays (B).
Illness or slow learning?

Subjects from the control group who did not perform better than the SCZ group (there were 3 such subjects in the HC group). Distribution over the model class is similar to the one obtained for the control group and shares no common features with the one obtained for the SCZ group.

Figure 3: Subjects from the control group who did not perform better than the SCZ group (there were 3 such subjects in the HC group). Distribution over the model class is similar to the one obtained for the control group and shares no common features with the one obtained for the SCZ group.
Executive summary

- Comparative study of schizophrenia patients (SCZ) and healthy controls (HC)

- Model comparison results: solid arrow - connection present in SCZ and HC, dashed arrow - present only in HC

- Impairment of prefrontal-hippocampal causal interaction and of the effects of Retrieval in SCZ (supports the disconnection syndrome hypothesis)

- Estimated parameters of the model containing all indicated connections. Black: HC, red: SCZ
"A physicist friend of mine once said that in facing death, he drew some consolation from the reflection that he would never again have to look up the word "hermeneutic" in the dictionary." (Steve Weinberg)

Understanding situations: needs hermeneutic interpretation

- logic, rule-based algorithms, and similar computational methods are too rigid to interpret ill-defined situations,
- hermeneutics, "the art of interpretation" can do it.
- hermeneutics: emphasize the necessity of self-reflexive interpretation and adopts circular causality

To understand other minds: i.e. to show empathy is to simulate other minds.

The neural basis of theory of mind related to mirror neurons, which is the key structure of imitation, and possibly language evolution (Michael Arbib).

A failure in interpreting self-generated action generated by the patient himself: (lack of ability to close the hermeneutic circle) can be characteristic for schizophrenic patients (Chris Firth). -> Neural basis: disconnection syndrome
Take home messages

- DCM + Bayesian estimation of dynamical system works!

- Reduced fronto-temporal functional connectivity seems to be justified for schizophrenic patients, some quantitative information was obtained

- the role of prefrontal cortex: interpretation of the incoming signals

- if the PFC does not tell to the hippocampus when to learn and when to recall; \(\rightarrow\) poorer performance

- disconnection syndrome hypothesis is supported

- the hermeneutic circle is broken

- therapeutic strategy: loops to be healed: towards a computational psychopharmacology: another story
Collaborators

Mihály Bányai  Vaibhav Diwadkar