Computational Psychiatry: A New Discipline

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1. Computational Neuroscience

2. Computational Psychiatry: Do We (You) Need It?

3. Neurological and Psychiatric Disorders as Dynamical Diseases

4. The Schizophrenic Brain: Multiple Levels

5. Nonlinear dynamics approach to schizophrenia I: pathological attractors

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8. Pathological Brain Rhythms and Dynamical Neuropharmacology

9. Towards a Computational Psychiatry
Computational Neuroscience

Neural mechanisms → computational algorithms
To understand the operation of neural structures by using mathematical models

Top down
- starts from behavioral data
- information processing circuit
- implementation of neural mechanisms

Bottom up
- starts from anatomical and physiological reality
- rhythms
- behavior

Figure 1: Brain as a multi-level system
Computational Psychiatry: Do We (You) Need It?

• ”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 brain imaging methods

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

Alzheimer’s disease
- Normal
- Pathological

Migraine
- Dahlem and Chronicle, Neurobiology, 2004

Schizophrenia
- Storage and recall of memory traces
- Changes in attractor structure
- Pathological attractors

Parkinson’s disease
- Fixed point attractor
- Periodic attractor

ADHD
- Power (μV²/Hz)

Anxiety
- Control
- Relaxation (0.3 mg/kg, IV)

Dynamical diseases
Components of Computational Psychiatry
(Montague et al, Trends in Cognitive Sciences, 2012)
Neurological and Psychiatric Disorders as Dynamical Diseases

The theory of dynamical diseases emerged from chaos theory.

Dynamical disease occurs due to the impairment of the control system: associated to 'abnormal' dynamics.

- Develop realistic mathematical models and study effects of parameter changes.
- Neurobiological interpretation.
- Integration of molecular, cellular and system neuroscience.
- Therapeutic strategies.
Neurological and Psychiatric Disorders as Dynamical Diseases

GENETIC versus DYNAMICAL DISEASES

genetic disease:
caused by abnormalities in an individual's genetic material (genome)

There are four different types of genetic disorders:

- single-gene
- multifactorial
- chromosomal
- mitochondrial

even genetic disorders have dynamic aspects
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
Nonlinear dynamics approach to schizophrenia I: pathological attractors

pathological attractors - pruning of cortical connections: Hoffman; NMDA receptor delayed maturation: Ruppin

"delusion","hallucination"
Nonlinear dynamics approach to schizophrenia I: pathological attractors

Reduction in synaptic conductances connected to glutamatergic NMDA receptors implied flatter attractor basins, and consequently less stable memory storage. Combined reduction of NMDA and GABA receptors -> changes in the attractor structure -> implement such positive symptoms (hallucinations and delusion):

Nonlinear dynamics approach to schizophrenia II: about the functional roles of gamma rhythms

- phenomenology: gamma rhythms are disrupted in schizophrenic patients (related to Working Memory)

- mechanism: modulation of the interaction between the glutamate and the NMDA receptors

- mechanism (artificial): ketamine - reduced amplitude and frequency

- possible pharmacological therapeutic procedure: drugs acting on GABA receptors to reconstruct the rhythms

Fig. 9. Robustness of the oscillation in network synchrony. The frequency of the network oscillation \(f_\Theta\) was less sensitive to phase heterogeneity \(\sigma_{ph}\) than to frequency \(f_{input}\) of the input. As the input frequency approached the eigen-frequency of the network (48 Hz at \(I_{AC}/I_{DC} = 0.3\) and \(I_{DC} = 1.4 \, \mu\text{A/cm}^2\), \(f_\Theta\) decreased.
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

• Task related functional connectivity: during object - location associative learning

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

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

\[ \dot{x}_2 = a_{21} x_1 + a_{22} x_2 + b_{21}^{(2)} u_2 x_1 \]
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

Mathematical equations:
\[
\begin{align*}
\frac{dx_1}{dt} &= c_{11} u_1 \\
\frac{dx_2}{dt} &= a_{12} x_1 + a_{22} x_2 + a_{52} x_5 + u_2 a_{42} x_4 \\
\frac{dx_3}{dt} &= a_{13} x_1 + a_{33} x_2 + a_{53} x_5 + u_2 a_{43} x_4 \\
\frac{dx_4}{dt} &= u_2 a_{24} x_2 + a_{44} x_4 + u_2 a_{34} x_3 \\
\frac{dx_5}{dt} &= a_{25} x_2 + a_{55} x_5 + a_{35} x_5
\end{align*}
\]
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)

\[ \dot{x} = (A + \sum_{i=1}^{N} u_j B^j)x + Cu \] (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
Model Selection: Bayesian Estimation

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)
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)
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:

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

(3)

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

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

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

(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 2: (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><strong>.145</strong></td>
<td>.106</td>
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<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><strong>.172</strong></td>
<td>.101</td>
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<tr>
<td>5</td>
<td>HPC→SP</td>
<td><strong>.158</strong></td>
<td>.081</td>
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<tr>
<td>6</td>
<td>HPC→SP, PFC→HPC</td>
<td>.095</td>
<td>.116</td>
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<tr>
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<td>HPC→SP, HPC→IT</td>
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<td>.081</td>
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<td>8</td>
<td>HPC→SP, HPC→IT, PFC→HPC</td>
<td>.095</td>
<td><strong>.357</strong></td>
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</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.
## Results

### Table 2: Model probabilities for varying modulatory connections

<table>
<thead>
<tr>
<th>No.</th>
<th>Additional connections</th>
<th>Encoding</th>
<th>Retrieval</th>
<th>SCZ</th>
<th>HC</th>
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<tr>
<td></td>
<td></td>
<td><strong>Encoding</strong></td>
<td><strong>Retrieval</strong></td>
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<td>PF→HC</td>
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<td>.060</td>
<td>.068</td>
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<tr>
<td>13</td>
<td>none</td>
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<td>none</td>
<td>.061</td>
<td>.055</td>
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<tr>
<td>14</td>
<td>none</td>
<td>HC→(SP,IT), PF→HC</td>
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<td>.068</td>
<td>.053</td>
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<tr>
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<td>PF→HC</td>
<td>HC→(SP,IT)</td>
<td>none</td>
<td>.060</td>
<td>.054</td>
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<tr>
<td>16</td>
<td>PF→HC</td>
<td>HC→(SP,IT), PF→HC</td>
<td>none</td>
<td>.059</td>
<td>.054</td>
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<td>17</td>
<td>HC→(SP,IT)</td>
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<td>HC→(SP,IT)</td>
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<td>.054</td>
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<td>.064</td>
<td>.054</td>
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<td>PF→HC</td>
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<td>.059</td>
<td>.053</td>
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<tr>
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<td>.064</td>
<td>.061</td>
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<td>22</td>
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<td>HC→(SP,IT), PF→HC</td>
<td>none</td>
<td>.065</td>
<td>.061</td>
</tr>
<tr>
<td>23</td>
<td>HC→(SP,IT), PF→HC</td>
<td>HC→(SP,IT)</td>
<td>none</td>
<td>.060</td>
<td>.059</td>
</tr>
<tr>
<td>24</td>
<td>HC→(SP,IT), PF→HC</td>
<td>HC→(SP,IT), PF→HC</td>
<td>none</td>
<td>.059</td>
<td>.120</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 probility 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

\[ l(t) = 1 - e^{-kt} \] (5)

Figure 3: 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).
Results

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 4: 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.
Anxiety and computational drug discovery
Pathological Brain Rhythms and Dynamical Neuropharmacology

Specific message: Search for selective anxiolytics

Septo-hippocampal theta activity: enhanced by anxiogenics

**BUT**

shows positive correlation with cognitive performance !!

paradoxical (?) activity

Characteristic frequency bands of EEG signals

<table>
<thead>
<tr>
<th>Frequency Range</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 – 3 Hz</td>
<td>delta  (δ)</td>
</tr>
<tr>
<td>4 – 10 Hz</td>
<td>theta  (Θ)</td>
</tr>
<tr>
<td>8 – 13 Hz</td>
<td>alpha  (α)</td>
</tr>
<tr>
<td>14 – 30 Hz</td>
<td>beta   (β)</td>
</tr>
<tr>
<td>&gt; 30 Hz</td>
<td>gamma  (γ)</td>
</tr>
</tbody>
</table>
Modulation of septo-hippocampal theta activity by GABA receptors: preliminary results

The skeleton network
Pathological Brain Rhythms and Dynamical Neuropharmacology

Modulation of septo-hippocampal theta activity by GABA receptors: preliminary results

Theta modulation in the MS-CA1 system

A control

B negative allosteric modulator

n = 30

n = 100

n = 50

MS–GABA n = 10

pyr n = 10

i (o/a) n = 100

i (o/a) n = 30

Number of cells

Time [s]
Modulation of septo-hippocampal theta activity by GABA receptors: preliminary results

Effect of negative allosteric modulator was taken into account by lowering the synaptic conductance at all pathways.

In all neuron populations clustering of spikes occurs at lower synaptic conductance values.

Timing of action potentials tends to have a well defined value.

Theta power in EEG computed from the activity of pyramidal neurons shows a significant increase during simulated administration of the negative allosteric modulator.
Specific message: Search for selective anxiolytics

Towards a computational/physiological molecular screening and drug discovery

Desired temporal pattern

Nontrivial
e.g. theta:

enhanced cognition

anxiogenics

Septohippocampal system

Temporal pattern

Computational & pharmaceutical modulation

interface to further testing

INTEGRATING SYSTEM and MOLECULAR LEVELS
Towards a computational psychiatry

- Functional Disconnectivities
- Pathophysiological Activities
- Aberrant Decision Making
Collaborators

Vaibhav Diwadkar
Psychiatry & Behavioral Neurosciences, Wayne State University

Hungarian research group
(Former: Mihály Hajos: Pharmacia Upjohn, Pfizer)