Computational approach to the schizophrenia: disconnection syndrome and dynamical pharmacology

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1. General framework: dynamical diseases
2. Long-term plan
3. Basic behavioral data
4. Basic fMRI data
5. fMRI data processing
6. A neural model of normal and pathological associative learning
7. Much left to be done
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
General framework: dynamical diseases

Schizophrenia
storage and recall of memory traces

changes in attractor structure
pathological attractors

Dynamical diseases

Alzheimer’s disease

Migraine

Epilepsy

Anxiety

ADHD

Long term plan

- Some schizophrenic phenomena as dysconnection syndrome?
- Combined behavioral and fMRI data
- Neural model of interacting regions for normal and impaired learning
- fMRI data analysis: uncover the normal and pathological information flow
- Computational pharmacology: to shift the system from dynamical pathological state to normal one
Basic Behavioral Data

Associative Learning

ENC RET ENC RET ENC

...
Basic Behavioral Data

Associative Learning
Basic Behavioral Data
Brain areas involved

- Superior Parietal Cortex (SP)
- Dorsolateral Prefrontal Cortex (PFC)
- Visual Cortex (VC)
- Inferior Temporal Cortex (IT)
- Hippocampus (HIPP)
Group random-effects analysis showing regions of greater average activation during the encoding of objects and locations relative to a fixation baseline ($p < .005$, uncorrected). Network consists of regions in the Superior Parietal and ITp, primary visual cortex (V1), and the hippocampus (MTL).
Basic fMRI data

fMRI Data - Schizophrenia

Encoding

Retrieval
Correlation with sensory signal

- Red: recall
- Black: learning
- Filled: schizo
- Open: HC

Brain regions: Occ, SP, IT, Hpc, PFC, Fro, Cing

Correlation values: -0.15, -0.05, 0.00, 0.05, 0.10, 0.15, 0.20

fMRI data processing
A neural model of normal and pathological associative learning
Brain Area Function

- VC: visual signal processing (receptive fields)
- IT: object recognition
- SP: location recognition
- HIPP: associative memory
- PFC: motivation, attention, context
Behavioral Data (once again)
We intended to build a model in order to compare the 1, activities with the fMRI data; 2, the performance with the behavioral data.
The retina: sample images

The retinal images we use are 8x8 pixel sized, random images placed on a 16x16 pixel arena. The 9 different positions are overlapping.
The visual cortex

- Recieves input from retina
- Use receptive fields to process images. \(2^4 - 1\) possible patterns can be detected at each location of the retina.
- Sends processed data to the IT and SP

Preferred stimuli used here (black pixels are active):

The same position

The same preferred stimulus
The visual system
IT: stores representation of the different objects as discrete, stable attractors in an RNN.
Superior Parietal Cortex (SP)

Processed Image

Input

Object Neglected

Encoding Created

Output
The hippocampal model

Learning

Before the experiment, we initialize our network by

- storing different number of objects in the recurrent network of IT;

- random synaptic matrices, modelling associations not relevant for the current context.
DG - competitive network

Competitive network in the Dentate Gyrus, to make unique, orthogonal representation for each object-location pair. Cortical signals (from SP and IT) arrive to the hippocampus through the entorhinal cortex.

\[
a_{dg}^i = \sum_j w_{sp2dg}^{ji} r_{sp}^j + \sum_k w_{it2dg}^{ki} r_{it}^k
\]

\[
r_{dg}^i = F(a_{dg}, sp_{dg})
\]

\[
\Delta w_{sp2dg}^{ij} = \alpha r_{dg}^j (r_{sp}^i - w_{sp2dg}^{ij})
\]

\[
\Delta w_{it2dg}^{ij} = \alpha r_{dg}^i (r_{it}^i - w_{it2dg}^{ij})
\]
CA3 - heteroassociative stage

The strong mossy fiber synapses act as teacher signal for CA3 pyramidal neurons. Perforant path synapses are modified via Hebbian learning.

\[
a^{i}_{ca} = \sum_{j} w^{ji}_{dg2ca} r^{j}_{dg}
\]

\[
r^{i}_{ca} = F(a^{i}_{ca}, s^{ca}_{pca})
\]

\[
\Delta w^{ij}_{sp2ca} = \alpha r^{j}_{ca} (r^{i}_{sp} - w^{ij}_{sp2ca})
\]
The hippocampal representations are associated to the representation of the original object in the IT.
During the recall connections are not modified. The attractor network in the IT help the recall by converging to one of the learned objects.
Results

Number of pre-learned patterns:

- 200
- 400
- 700

Learning Rate:

- 0.005
- 0.01
- 0.015

Performance vs. Trial number
Results

Control subjects

Parameters:
- \( \text{r.dg} = 0.0003 \)
- \( \text{r.ca3, r.it} = 0.017 \)
- \( \text{n.patterns} = 550 \)

Schizophrenic patients

Parameters:
- \( \text{r.dg} = 0.0003 \)
- \( \text{r.ca3, r.it} = 0.02 \)
- \( \text{n.patterns} = 700 \)
**Results**

**Control subjects**

- Parameters:
  - $r_{dg} = 0.0003$
  - $r_{ca3}, r_{it} = 0.017$
  - $n_{patterns} = 550$

**Schizophrenic patients**

- Parameters:
  - $r_{dg} = 0.0003$
  - $r_{ca3}, r_{it} = 0.02$
  - $n_{patterns} = 700$

**Diagrams**

- Recall of learned memory traces
- Recall of never learned items

"delusion", "hallucination"
Much left to be done

• fMRI analysis: estimation of functional connectivities for normal and pathological situations

• the inclusion of prefrontal cortex into the model

• the role of the reduced NMDA-related plasticity. Kinetic model of the drug-altered glutamate-NMDA receptor interaction: test and design of drugs