Computational Psychiatry and Computational Neurology: New Disciplines

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1. Psychiatry and Neurology

2. Computational Psychiatry and Neurology Do We Need It?

3. Functional Disconectivities

4. Pathophysiological Activities

5. Pathological Brain Rhythms and Dynamical Neuropharmacology
   (a) Epilepsy
   (b) Anxiety
   (c) Alzheimer’s Disease

6. Aberrant Decision Making

7. Final remarks
Psychiatry and Neurology

PSYCHIATRY: study, diagnosis, treatment, and prevention of

• mental disorders
• behavioural
• cognitive
• perceptual

abnormalities

NEUROLOGY: diagnosis and treatment of all categories of conditions and disease involving the Central and Peripheral Nervous System
Psychiatry and Neurology

Figure 1

Additive (simple) merger:
Content from each discipline simply combined into larger curriculum

Psychiatry + Neurology → “Neuropsychiatry,” “Behavioral medicine,” etc
Figure 2

 Conjunctive merger: Only content and principles compatible with both disciplines retained in new discipline

Common and compatible material and principles

Psychiatry  Neurology  “Psychiatric neurology”
Figure 3

Reductive merger: The language and principles of one discipline (e.g., psychiatry) are reduced to (subsumed in) language and principles of the other.

Psychiatry + Neurology → “Neurology prime”
Integrative merger: Principles and content of each discipline integrated with one another, bridged by “transformative language”
Computational Psychiatry and Computational Neurology: Do We Need It?

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

- to understand the underlying **mechanisms** of data obtained by brain imaging methods

- to interpret neurological and psychiatric disorders as **dynamical diseases**

- to offer new **therapeutic strategies**
Multiple Levels
understanding of interactions among levels needs "system’s approach"
example: schizophrenia

macronetwork

PFC - hippocampal interaction
gamma rhythms

glutamate- DOPA- GABA
pyramidal cells

calcium current

calcium binding proteins
Computational Psychiatry: Do We Need It?

Multiple Levels

Macro-networks, neural networks and synaptic protein networks

Multiscale networks in the brain
Components of Computational Psychiatry
(Montague - Dolan - Friston - Dayan: Trends in Cognitive Sciences, 2012 January)
Three types of "deviations":

• Disconnectivities

• Arrhythmia

• ”Miscalculations”
Functional Disconnectivities

- 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)
Functional networks

1. Extraction of the time course (C) from R-fMRI data (B) within each anatomical unit (i.e., network node). (B) Anatomical units are obtained according to a prior brain atlas (A) or voxels; 2. Calculation of a functional connectivity (i.e., network edge) correlation matrix (D) between any pairs of nodes; 3. Thresholding the correlation matrix into a binary connectivity matrix (i.e., association matrix, E); 4. Visualization of the association matrix as a graph (F).
Functional Disconnectivities

- 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
Schizophrenia fMRI study: experiment and methods

Task: learning of object-location associations over repeated encoding and retrieval periods

Subjects: 11 diagnosed with schizophrenia and 11 healthy controls

DCM: generative model of the BOLD signal, parameters estimated by Bayesian statistics

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

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

Model space: five areas involved, two sets defined by varying connections and the effects of conditions

Model selection: by the estimation of the Bayesian evidence

Functional Disconnectivities
Functional Disconnectivities

Schizophrenia fMRI study: results

Parameter level comparison: connections between PFC and HPC and HPC and IT are impaired

Model comparison: top-down information flow and the modulatory effects of conditions are less likely to be present in schizophrenia

Slow learning: differentiated from the illness by model probability distribution

Paradigm shift in interpreting dysfunctions!

- ADHD as a brain network dysfunction
- Functional network dysfunction in anxiety and anxiety disorders
- A network dysfunction perspective on neurodegenerative diseases (e.g. Alzheimer)
- Brain network dysfunction in bipolar disorder
Neurodegenerative disorders can disrupt molecular pathways, synapses, neuronal subpopulations and local circuits in specific brain regions, as well as higher-order neural networks. Abnormal network activities may result in a vicious cycle, further impairing the integrity and functions of neurons and synapses, for example, through aberrant excitation or inhibition. Palop, Chin and Mucke Nature 443, 768-773 (19 October 2006)
Pathophysiologic Activities

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

Dynamical Diseases

Migraine
- Normal
- Pathological

Alzheimer’s Disease
- Normal
- Pathological

Epilepsy
- Right temporal lobe seizure shown in box

Parkinson’s Disease
- Fixed point attractor
- Periodic attractor

ADHD
- \( \chi^2 = 11.9 \)
- \( \chi^2 = 10.6 \)

Anxiety
- Control
- Reboxetine (0.3 mg/kg, IV)
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
Pathological Brain Rhythms and Dynamical Neuropharmacology

- Epilepsy
- Anxiety
- Parkinson Disease
- Alzheimer’s Disease
Pathological Brain Rhythms and Dynamical Neuropharmacology

THETA RHYTHM

SEPTOHIPPOCAMPAL SYSTEM

KNOCK-IN, KNOCK-OUT TECHNIQUES

THETA RHYTHM

SKELETON NETWORK

GABA SYNAPSE

RECEPTOR SUBUNITS

DESENSITIZATION KINETICS
Pathological Brain Rhythms and Dynamical Neuropharmacology

- ANXIETY vs Theta rhythm
- there are CHEMICALLY VERY DIFFERENT anxyolitics
- with surprisingly common electrophysiological effect:
- reduction of the frequency of THETA rhythm
- Anxiolytic drugs and altered hippocampal theta rhythms: The quantitative systems pharmacological approach. Tibin John, Tamás Kiss, Colin Lever, Péter Érdi
RUNNING SPEED (cm/s)

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<th>8.4</th>
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| 0 10 20 30 |
| 9.0 8.6 8.2 7.8 |

FREELY MOVING RAT: theta during locomotion

**D** Anxiolytic Drug

**E** Anxiolytic Drug

**F** Putative Anxiolytic Drug

**G** New spatial context

**A** ANAESTHETISED RAT: theta during RPO stimulation

**B**

- CDP
- DZP
- ALP
- AMY
- HAL
- CPZ

**C**

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**FREELY MOVING RAT: theta during locomotion**

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<tr>
<th>D</th>
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<tr>
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Figure 1: Anxiolytic drugs reduce hippocampal theta frequency. In the anaesthetised rat, anxiolytic drugs reduce frequency of reticular-stimulated hippocampal theta. A) Broadly linear relationship between reticular formation stimulation intensity and theta frequency in the anaesthetised rat. Adapted from Siok et al, 2009. B) Anxiolytic drugs reduce theta frequency. Open circles indicate baseline, closed circles effect of drug. Adapted from Gray and McNaughton, 2000. C) Buspirone, later discovered anxiolytic drug acting on 5HT-1A receptors. Adapted from McNaughton and Coop, 1991. In the freely moving rat, anxiolytic drugs reduce the offset/intercept of the theta frequency to running speed relationship (D, E, F), while spatial novelty reduces its slope (D). Three neurochemically-different anxiolytic drugs (all i.p. injections: D, CDP, benzodiazepine agonist, 5mg/kg; E, Buspirone, 5HT-1A agonist, 1mg/kg; F, O-2545, putative anxiolytic, CB1 agonist, 100 µg/ml, 0.5ml/kg) have the common effect of reducing the zero cm/s intercept of the theta frequency to running speed relationship. In contrast, exploration of a novel spatial context reduces the slope of this relationship (G), which then recovers as the novel spatial context itself becomes familiar (not shown). Parts F and G present data from the same rats (i.e. a within-subjects double dissociation of intercept and slope effects is observed). Open squares indicate y-intercept of regression lines. All recording sites are from CA1. Adapted from Wells et al (2013).
Figure 2: A) Structure of septo-hippocampal network model. Three hippocampal neuron populations and one medial septal population are modeled explicitly. Two medial septal populations are modeled indirectly by their rhythmic or tonic effects on the system (squares). Red symbols and black circles indicate inhibitory populations and synapses, respectively; yellow symbols and open triangles indicate excitatory populations and synapses.
Figure 3: Modulation of synaptic dynamics within septo-hippocampal system affects theta rhythm frequency. Top, Voltage clamp analysis of A) GABA and B) AMPA mediated post-synaptic currents at -70 mV for different synaptic decay time constants, where a synaptic event is triggered after 10 msec. Middle, Effect of varying synaptic decay time constants for AMPA and GABA mediated synapses on mean network frequency for C) 600 nA of depolarizing current to pyramidal somata and D) 800 nA, with corresponding current to other populations. Arrows point to minimal frequency point that is tested further in Figure ???. Bottom, Standard error of the mean (E, F) for the N=18 runs of the simulation for each of the 16 evenly spaced points in each search.
Figure 4: Modulation of synaptic dynamics affects frequency of nPO stimulation elicited theta rhythm. Mean frequency and standard error are shown with default parameter settings (black) and with GABA decay time constant doubled (blue; arrows in Figure ??) for N=12 runs of the simulation per point.
Figure 5: Slowing down pyramidal hyperpolarization-activated (Ih) current dynamics slightly lowers intercept of nPO elicited theta frequency relationship. Mean theta frequency and standard error are shown for a range of nPO stimulation levels with default parameter settings (black) and with Ih conductance rise and fall rates cut in half (red) for 12 runs of the simulation per point. Models effect of potentially selective anxiolytic drug.
Figure 6: Modulation of maximal synaptic conductance associated with GABA receptors within septo-hippocampal system has negligible effect on theta frequency. Error bars indicate standard error of the mean of N=12 runs of the simulation. Depolarizing currents of 600 nA, 1.4 µA, and 2.2 µA to pyramidal somata, basket cells, and MS-GABA cells was used, respectively, with a MS-Glu population firing rate modulation of 6 Hz.
Early detection of Alzheimer’s disease (a big European project)

Use of Computational Tools for AD Biomarker Discovery

- Model neural membrane as equipotential compartment(s) with electrical properties of equivalent RC circuit(s)
- Use experimentally verified channel distribution, dynamics, network connectivity
- Manipulate biophysically realistic model of theta rhythm generation and control

Hodgkin-Huxley formalism

Slowed Pyr $I_h$ current (red)

Decreased $\text{GABA}_A$R Activation

Synaptic Loss due to Amyloid-β Plaques

(Bower & Beeman, 2003)

(ScoT et al., 2011)
maybe next time
Schizophrenia-Related Delta Oscillations in the Thalamo-Cortical System

Nicholas Vogel and Péter Erdő

Introduction

The application of the Fast Fourier Transform (FFT) to the derivation of frequency bands in the brain is a standard method to study normal brain and abnormal brain activity. The main brain frequencies include delta (0.3 to 4 Hz), theta (4 to 7 Hz), alpha (8 to 13 Hz), and beta (14 to 30 Hz). In normal brain activity, these frequencies are found in the brain waves, but in pathological conditions, such as schizophrenia, they are altered. The delta band is particularly important for understanding the brain's activity and its connection to schizophrenia.

Minimalist Model of Delta-Rhythm Generation

A minimalistic model for the delta-rhythm generation has been proposed by a team of researchers at the Institute of Neuroinformatics, ETH Zurich. The model is based on the assumption that the delta rhythm is generated by a network of neurons that are interconnected in a specific way. The network includes both excitatory and inhibitory neurons, and the balance between these two types of neurons is crucial for the generation of the delta rhythm.

Data Analysis Results

The data analysis results show that the delta rhythm is generated by a network of neurons that are interconnected in a specific way. The network includes both excitatory and inhibitory neurons, and the balance between these two types of neurons is crucial for the generation of the delta rhythm.

Conclusions

The delta rhythm is an important indicator of brain activity, and its alterations can be used to diagnose and treat neurological disorders. The model proposed by the researchers at the Institute of Neuroinformatics, ETH Zurich, provides a new perspective on the generation of the delta rhythm and offers a new approach for studying brain activity in neurological disorders.

Future Directions

The next step is to model a detailed delta oscillator with synaptic connections, including an excitatory-to-inhibitory circuitry and a thalamo-cortical loop. The model will be used in a simulation study to test the assumption of a network of neurons that are interconnected in a specific way. The model will be refined to include both excitatory and inhibitory neurons, and the balance between these two types of neurons will be studied.