The Quantitative Systems Pharmacological Approach: Altered Hippocampal Theta Rhythms, Anxiety, Alzheimer Disease

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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
Computational neuropharmacology

Clinical proteomics in oncology

Genetic diseases and heterotrimeric G proteins

Hypothalamic histamine H1 receptor
Neurological and Psychiatric Disorders as Dynamical Diseases

**Alzheimer-disease**
- Storage and recall of memory traces
- Normal and pathological changes in attractor structure

**Migraine**
- Fixed point attractor
- Periodic attractor

**Schizophrenia**
- Storage and recall of memory traces
- Fixed point attractor → Periodic attractor
- Changes in attractor structure

**Parkinson-disease**
- Fixed point attractor
- Periodic attractor

**Epilepsy**
- Different patterns of electrical activity
- Right temporal lobe seizure shown in box

**ADHD**
- Power (μV/Hz)
- Frequency (Hz)

**Anxiety**
- Power (μV/Hz)
- Frequency (Hz)

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Dynamical diseases
Hippocampal Theta Rhythm

Slow, global rhythmic electrical activity of the hippocampus (4-10 Hz)

- associated with gamma frequency
- studied in anesthetized and non-anesthetized rats
- also found in human hippocampal formation

Functional Roles

- Linked to mnemonic processes
- Used for landmark navigation, path integration
- Correlates to anxiety levels
Hippocampal formation generates (top), controls (right), and uses (left, bottom) theta rhythm
Septohippocampal Rhythm Generation and Pharmacological Control

SEPTOHIPPOCAMPAL SYSTEM

THETA RHYTHM

SKELETON NETWORK

KNOCK−IN, KNOCK−OUT TECHNIQUES

DESENSITIZATION KINETICS

GABA SYNAPSE

RECEPTOR SUBUNITS
Skeleton network of the septo-hippocampal system used to model rhythm generation and control by pharmacological means. The model consists of four cell populations: pyramidal cells of the hippocampal CA1 region (CA1p), stratum oriens interneurons (IO-LM), basket interneurons (IB) and septal GABAergic cells (Isept).

\[
I_{syn} = \bar{g}_{syn}(V - E_{syn}), \quad \frac{ds}{dt} = \alpha F(V_{pre})(1 - s) - \beta s,
\]

\[
F(V_{pre}) = \frac{1}{1 + \exp \left( \frac{V_{pre} - \Theta_{syn}}{K} \right)}
\]

\[
\leftarrow g_{syn} \text{ modified to simulate anxiolytics}
\]
Septohippocampal Rhythm Generation and Pharmacological Control

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

Septohippocampal system

Desired temporal pattern
  Nontrivial
  e.g. theta:
  enhanced cognition
  anxiogenics

Temporal pattern

Computational & pharmaceutical modulation

Comp.

Interface to further testing

INTEGRATING SYSTEM and MOLECULAR LEVELS
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
Septohippocampal Rhythm Generation and Pharmacological Control

- Remarkable analogy between Type I (mobile) and Type II (immobile) theta frequency changes in animals
  - linear relationship between frequency and running speed/reticular stimulation
  - linear relationship affected similarly by anxiolytics

- Anxiolytics reduce stimulus-frequency intercept for Type I theta (also atropine resistant), but intercept and/or slope for Type II (also atropine sensitive)

- Reduction of theta frequency in animals has no false positives or negatives in predicting efficacy of human GAD treatment to date
The effects of anxiolytic drugs on reticular-elicited (100 Hz stimulation) theta activity. Increasing strength of reticular stimulation produces a linear increase in theta frequency. Compared to pre-drug, anxiolytic drugs (CDP5=chlordiazepoxide; DZP5=diazepam; ALP5=alprazolam; AMY5=amylobarbitone) reduced the frequency of theta. Drugs which act to block acetylcholine (ACh), serotonin (5HT), dopamine (DA) or noradrenaline (NA) do not have this effect.
A) Broadly linear relationship between reticular formation stimulation intensity and theta frequency in the anaesthetised rat. B) Anxiolytic drugs reduce theta frequency. Open circles indicate baseline, closed circles effect of drug. C) Buspirone, later discovered anxiolytic drug acting on 5HT-1A receptors. 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 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).

- In freely moving rats, there is a broadly linear relationship between hippocampal theta frequency and running speed over the normal range of speeds.
- Environmental novelty decreases slope, whereas ANXIOLYTIC DRUGS REDUCE INTERCEPT.
- Variation in slope predicted changes in spatial representation by CA1 place cells and novelty-responsive behavior.
- Variation in intercept predicted anxiety-like behavior.
The Quantitative Systems Approach: Goals

- simulate the effect of stimulating current to nPO on theta frequency
- extend previous model with more realistic septal innervation
- study how chemically diverse anxiolytics modify synaptic parameters and reduce theta frequency (septal GABAergic and glutamatergic synapse modulation → slope reduction?, cholinergic synapse modulation → intercept reduction?)
The Quantitative Systems Approach: Methods

- Simulate effects of varying reticular stimulation on original model
- Implement additional septal innervation to conductance based model of hippocampal CA1 region
- Selectively modify cholinergic, glutamatergic, and GABAergic synaptic conductances and/or dynamics to simulate anxiolytic effects on stimulus-frequency graph

Septohippocampal system modeled as five distinct neuron populations interacting to generate emergent theta rhythm
Power spectra of synthetic EEGs calculated from simulations of varying levels of depolarizing current stimulus to pyramidal cells; shown here are 600 pA (solid line), 625 pA (dashed line), 675 pA (dotted line), and 700 pA (double-dashed line).
Mean frequency of theta band oscillation (3-8 Hz) increases linearly with stimulus (number of simulations run per stimulus, n = 16). Error bars represent standard deviation. Linear regression yields a slope of 0.0193 Hz/pA and intercept -6.91. $R^2 = 0.93$. 

The Quantitative Systems Pharmacological Approach: Some Results
Increase of time constants for synaptically activated GABAergic ion channels by 2 to 3 orders of magnitude in model appears to consistently lower theta frequency for large stimulating currents (compared to line with original constants), but increases variability of frequency for smaller stimulating currents (number of simulations run per stimulus, n = 10, 750τ). Error bars represent standard deviation. Linear regression yields a slope of 0.0051 Hz/pA and intercept 1.69. $R^2 = 0.17$. 

**The Quantitative Systems Pharmacological Approach: Some Results**
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. 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.
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.
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. 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.
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
Early Detection of Alzheimer’s Disease by Connecting Biochemical Events to Oscillatory Electric Signals

Horizon2020: big European consortium

- The biochemical effects of amyloid − β on neurons are most commonly seen after significant progression of the disease its effect on an electrical oscillation has recently been suggested as an early biomarker of AD, while the relevant mechanism is not known.

- A biophysically realistic model of the electrical activity of the hippocampus, an early AD target, is manipulated on a synaptic and cellular level to simulate biochemical effects of amyloid − β accumulation. This can help elucidate a mechanism of age-dependent theta oscillation changes, which reflects changes in synchronous synaptic activity.
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

(Bower & Beeman, 2003)

Slowed Pyr \( I_h \) current (red)

Decreased GABA\(_A\)R Activation

Synaptic Loss due to Amyloid-β Plaques

(Scott et al, 2011)
Biochemical cellular and synaptic mechanisms mediating Alzheimer’s disease onset and progression could be detected using oscillatory network activity data collected noninvasively through an EEG.

The present study suggests that the recently studied effect of human amyloid precursor protein on voltage-gated sodium channel expression specifically in parvalbumin expressing interneurons known to be responsible for oscillatory activity could have a consistent effect on the amplitude of theta rhythm.

Implementing this effect in a computational model of the septo-hippocampal network by reducing the density of fast sodium current channels in basket cells and oriens-lacunosum-moleculare interneurons resulted in an increase in theta rhythm amplitude.

It was also suggested that this could be mediated by distinct effects on single cell firing patterns, namely a reduced action potential amplitude in basket cells and somewhat less so in O-LM cells leading to increased synchrony of their firing and thus of synaptic activity afferent to pyramidal cells generating theta rhythm.

The overall effect of amyloid precursor protein in mice, however, was experimentally shown to be a decrease in theta rhythm power over time, so this mechanism may represent an early cause of hypersynchrony that is subsequently overcompensated.
Early Detection of Alzheimer’s Disease by Connecting Biochemical Events to Oscillatory Electric Signals

- Computational methods: compartmental technique
- Single cell effects
- Network effect
Mice overexpressing the amyloid-precursor protein (hAPPJ20 mice) exhibited impaired firing compared to non-transgenic (NTG) mice (expressing only a marker) in parvalbumin (PV) expressing interneurons, which are known to be critical in generating oscillatory electrical signals in the parietal cortex and hippocampus. These interneurons showed decreased action potential amplitude in current clamp experiments. This effect is thought to be primarily mediated by a reduced expression of voltage-gated sodium channel subunits that colocalize with PV resulting from amyloid-beta peptides.
Early Detection of Alzheimer’s Disease by Connecting Biochemical Events to Oscillatory Electric Signals

Primarily basket cells but also O-LM cells are interneurons expressing PV in the present hippocampal CA1 model. The above voltage traces show the response of basket cells to a step current of 10 pA. These cells modeled as single compartments with a fast sodium channel and delayed rectifier potassium current both in this simulation and when in the network. Upper trace (shifted up 100 mV) shows baseline cell response and lower trace shows impaired cell with sodium channel density reduced by 15%, exhibiting approximately 10% decrease in action potential amplitude.
Early Detection of Alzheimer’s Disease by Connecting Biochemical Events to Oscillatory Electric Signals

Effects of lower voltage-gated sodium channel densities of PV-expressing interneurons within septo-hippocampal network. Left, Electrical patterns resulting from 15% reduction in Na channel density in basket cells only. Right, 50% reduction in Na channel density in both basket and O-LM cells, representing a stronger effect. Top, Voltage traces of basket cell soma activity within network. Two effected cells are shifted up 10 and 20 mV, demonstrating differential (left) or synchronous firing (right), and black trace is baseline. Middle, Average local field potential (LFP) measured along pyramidal cells with biochemical effects implemented as specified (n=24,48). Bottom, Average power spectra of local field potentials quantifying the amplitude of oscillations in the LFP as a function of frequency in the theta rhythm band (4-12 Hz, error bars indicate SEM).
Early Detection of Alzheimer’s Disease by Connecting Biochemical Events to Oscillatory Electric Signals

Oriens-lacunosum-moleculare interneurons have channels which regulate interspike dynamics as well as spike generating channels, and their firing patterns in the network differ from that of basket cells because of this. Top, 15% reduction in Na channel density in basket cells only. Bottom, 50% reduction for basket and O-LM cells. Black, voltage traces in baseline network.
Early Detection of Alzheimer’s Disease by Connecting Biochemical Events to Oscillatory Electric Signals

Age-dependent reduction in the amplitude of nPO-stimulation elicited theta rhythm for transgenic mice (APP/PS1) exhibiting increasing $A\beta$ plaque loads from 2 months to 8 months. No theta power reduction in wildtype (WT) mice, which do not exhibit $A\beta$ plaques, was observed: Scott et al. (2012)
Conclusions

• Quantitative systems pharmacology: integrating molecular, cellular, network and system levels

• Computational Neurology and Computational Psychiatry: do we need it?

• Neurochemistry, Electrophysiology and Behavior

• Computational Modeling: we really need it
Collaborators

Tibin T. John: Goldwater scholar (2014) (Kalamazoo College)

Tamás Kiss: Pfizer, Integrative and Circuit Neuroscience (Boston): general expert :-)

Colin Lever (Durham University, UK): motivation, data, interpretation