Understanding Brain Neurochemistry: Imaging Neuromodulators with High Spatiotemporal Resolution

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Brain Imaging: Challenge of Space and Time Scales

Sub-Cellular

Multi-Cellular

Functional

nm
μm
mm
cm

Neuronal Synapse
Cell diameter
Neuron length
Brain Functional Regions

<ms
ms
s
day/week
month +

Action Potential
Neurotransmission
Sensory processing
Cell Growth
Tissue regen/Disease

The Brain Structure-Function Relationship

Electrical Activity

Structure & Connectivity

Chemical Activity

~6% probability of dopamine release


“Missing dimension” in neurobiology

Modulatory Neurotransmitters

Norepinephrine

Dopamine

Serotonin

Del Bonis et al., Nano Research (2018)
**Types of Neurochemical Communication**

**Fast Synaptic Transmission:**
- Neurotransmitter binds ligand-gated ion channels - allows positively or negatively charged ions to flow into the cell
- Ion flux rapidly changes membrane potential (ms timescale)

**Neuromodulation:**
- Neuromodulators escape synaptic cleft
- GPCRs are main target of neuromodulators (no current passed)
- GPCRs engage intracellular second messenger pathways to modulate function of downstream substrates (s-min)

Beyene et al., ACS Biochemistry (2018)
Overview of our (Incomplete) Roadmap to the Brain

Stimulus

Behavior

Reward prediction
Motivation
Learning...

Aberrations lead to disease

Behavior

Stimulus

Neural activity & structure

Stimulus

Neurotransmission

Compensatory mechanisms?

Blockers
Antipsychotics
Stimulants/supplements
Parkinson’s, Huntington’s
Re-uptake blockers
Antidepressants

Dopamine

Responsible for

Dopamine

Responsible for

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Responsible for
Why is it so difficult to image neurochemistry?

**Chemistry**

Brain can tell these molecules apart

DA \[\text{HO-}C_7H_4-b-C_7H_5-CH-\text{NH}_2\]  
Tyr \[\text{HO-}C_7H_4-b-C_7H_5-CH-\text{NH}_2\]  
Epi \[\text{HO-}C_7H_4-b-C_7H_5-CH(OH)-\text{NH}_2\]  
5-HT \[\text{HO-}C_7H_4-b-C_7H_5-CH-\text{NH}_2\]

... we cannot

**Physics**

Neuromodulation happens deep inside the awake & living brain

Visible microscopy can only image surface-features

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Tools to Study Neuromodulation

Microdialysis

Fast scan cyclic-voltammetry

CNiFERs

No spatial information
Low temporal information

False-fluorescent neurotransmitters
Tools to Study Neuromodulation

Microdialysis

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No spatial information
High temporal information
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Target molecule

HEK293

Low spatial information
Low temporal information
Tools to Study Neuromodulation

Microdialysis

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CNiFERs

False-fluorescent neurotransmitters


High spatial information
Moderate temporal information
Determining Nanosensor Parameters for Dopamine Imaging

**Modeling dopamine release in the striatum**

**Governing Equation**

\[
\frac{\partial c(r,t)}{\partial t} = D\nabla^2 c(r,t) + Q - U
\]

**Quantal Release:**

probabilistic release into spherical terminal

\[
Q = \sum_{f=1}^{F} \left( \frac{R_o / N_A}{\alpha \cdot [2\pi \cdot (dr)^2]^{3/2}} \cdot \psi(p) \cdot \delta(t - t_f) \right) \cdot \delta(r)
\]

**Uptake:**

Michaelis-Menten kinetics

\[
U = \frac{r_{\text{max}} c(r,t)}{c(r,t) + k_m}
\]

Beyene et al. ACS Chemical Neuroscience 2017
What Nanosensor Kinetics are Optimal for Dopamine Imaging?

Depends where (in the brain) you are

Low $K_d$ aren’t always best!

Beyene et al. ACS Chemical Neuroscience 2017
Human DA receptors are covalently conjugated to a cpGFP
Dopamine binding induces a conformational change \( \rightarrow \) increases fluorescence of cpGFP

Genetically tractable \( \rightarrow \) *In vivo* dopamine imaging

New probes for neuromodulators: Synthetic Nanosensors

Signal Transducer

Amphiphilic Polymer

~200 nm

1 nm

Analyte Produces Selective Change in I or λ

Intensity

Wavelength (nm)

Intensity

Wavelength (nm)


Imaging Stimulated Dopamine Release with Synthetic Nanosensors

With Linda Wilbrecht
UC Berkeley Psychology

Mouse brain → Coronal slices → Sensor incubation

**img:**

- **Single pulse**
- **nIRCat dose-response to varying stimulation amplitudes**

*N=5 animals
Error is std.dev*

Drugs Exhibit Variable Effects on Dopamine Modulation

- **Quinpirole** - psychoactive drug
  - D2 and D3 receptor agonist
  - Decreases synaptic dopamine

**0.25 μM** – drug does not saturate dopamine receptors

**Dopamine re-uptake kinetics?**

*Image of a scatter plot showing the relationship between hotspot (count) and ΔF/F ratio. The image also includes a table with the count of hotspots for different ΔF/F ratios.*
Acknowledgements

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Stanley Fahn
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