



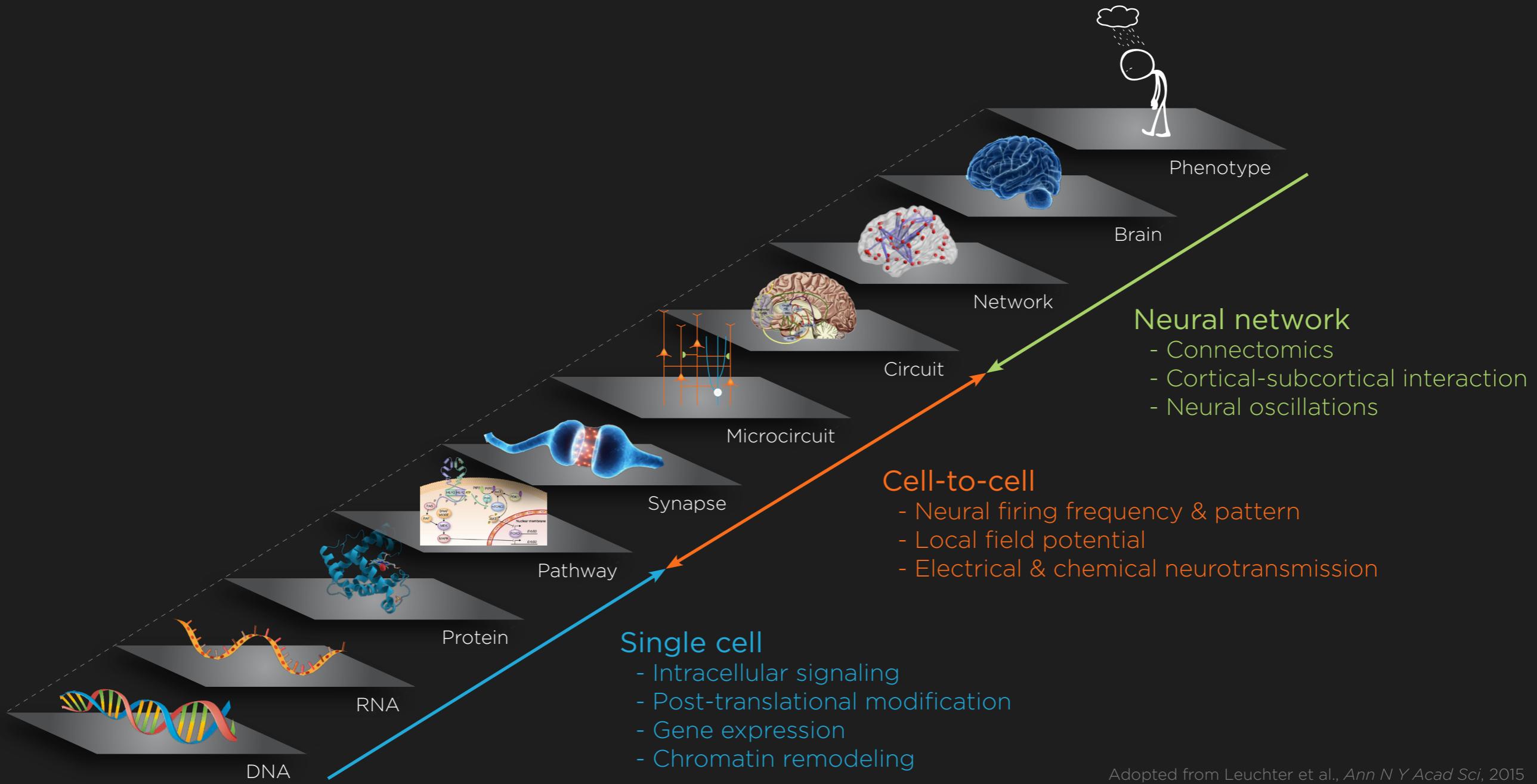
Resolved: Targeted Intermittent Device Delivered Interventions will Ultimately Prove Superior to Maintenance Treatment with Drugs for Brain Disorders

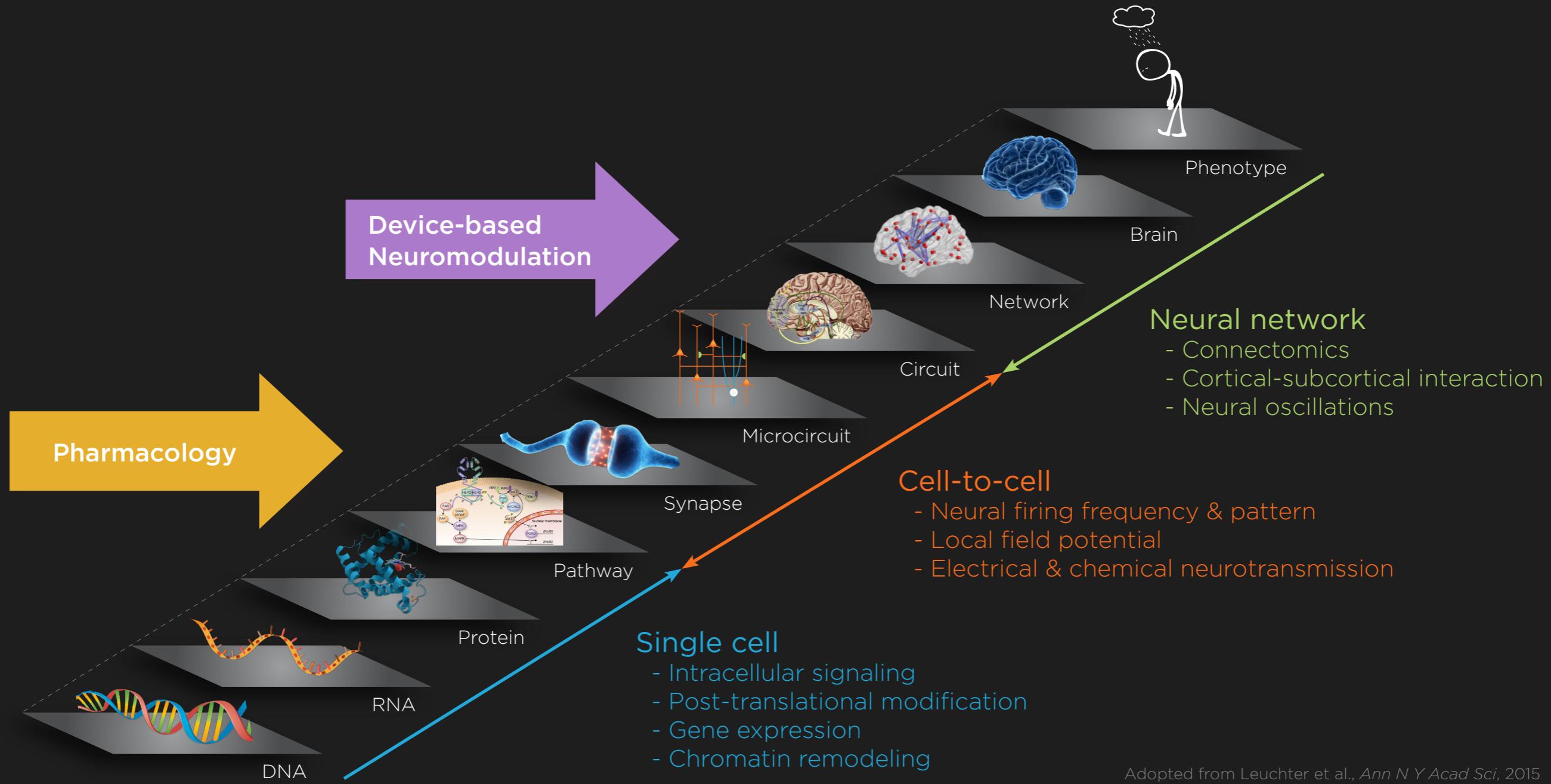
Zhi-De Deng, PhD; Research Fellow, NIMH
Bill Potter, MD, PhD; Sr Advisor, NIMH

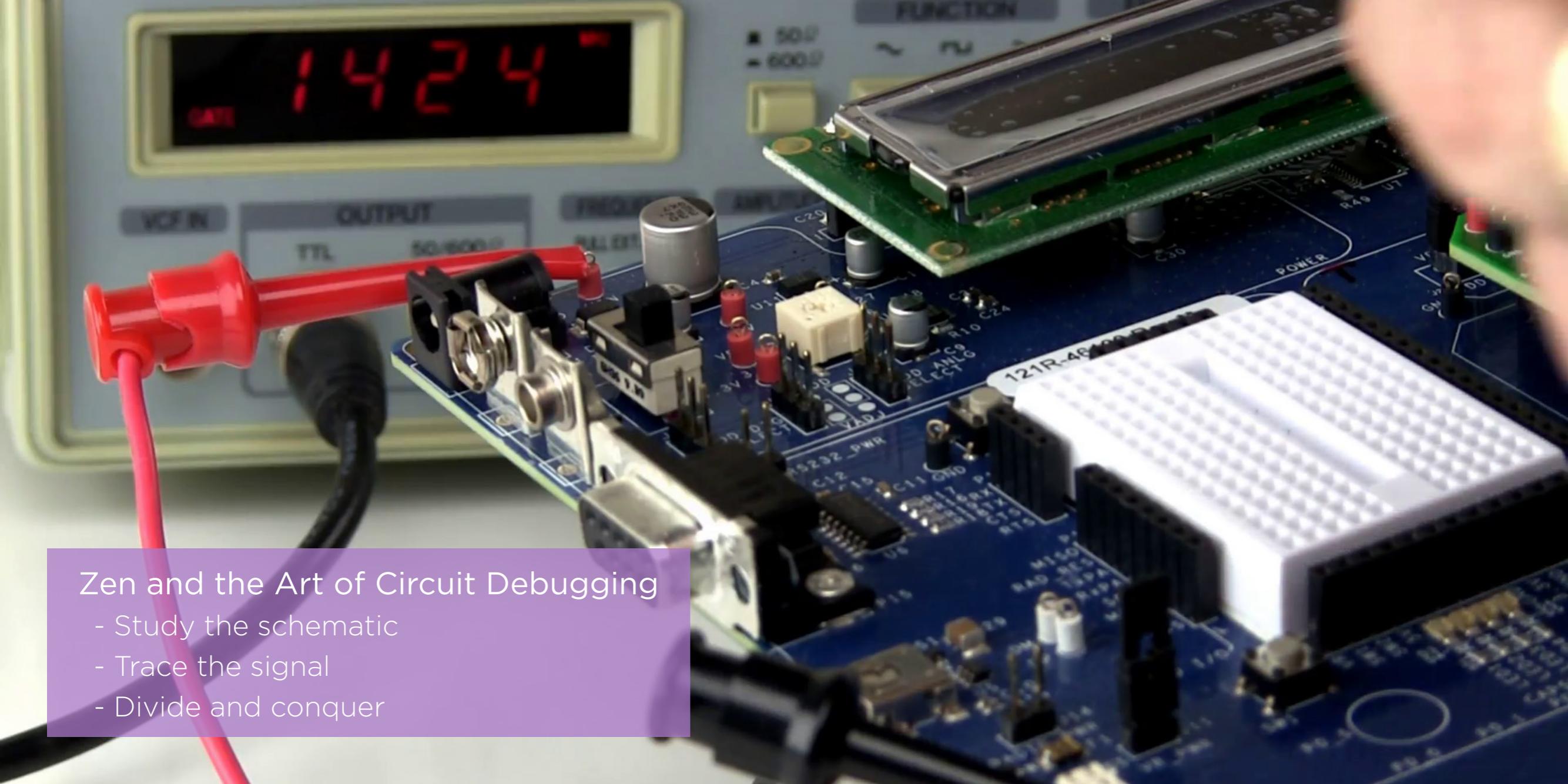
Neuropsychiatric Drug Development Summit, Boston
August 1, 2018

Debate Format

- Zhi outlines general case For
- Bill outlines general case Against
- Zhi provides examples of potential superiority
- Bill champions evolution of pharmacologic target approach
- Zhi provides future vision
- Bill poses question to audience

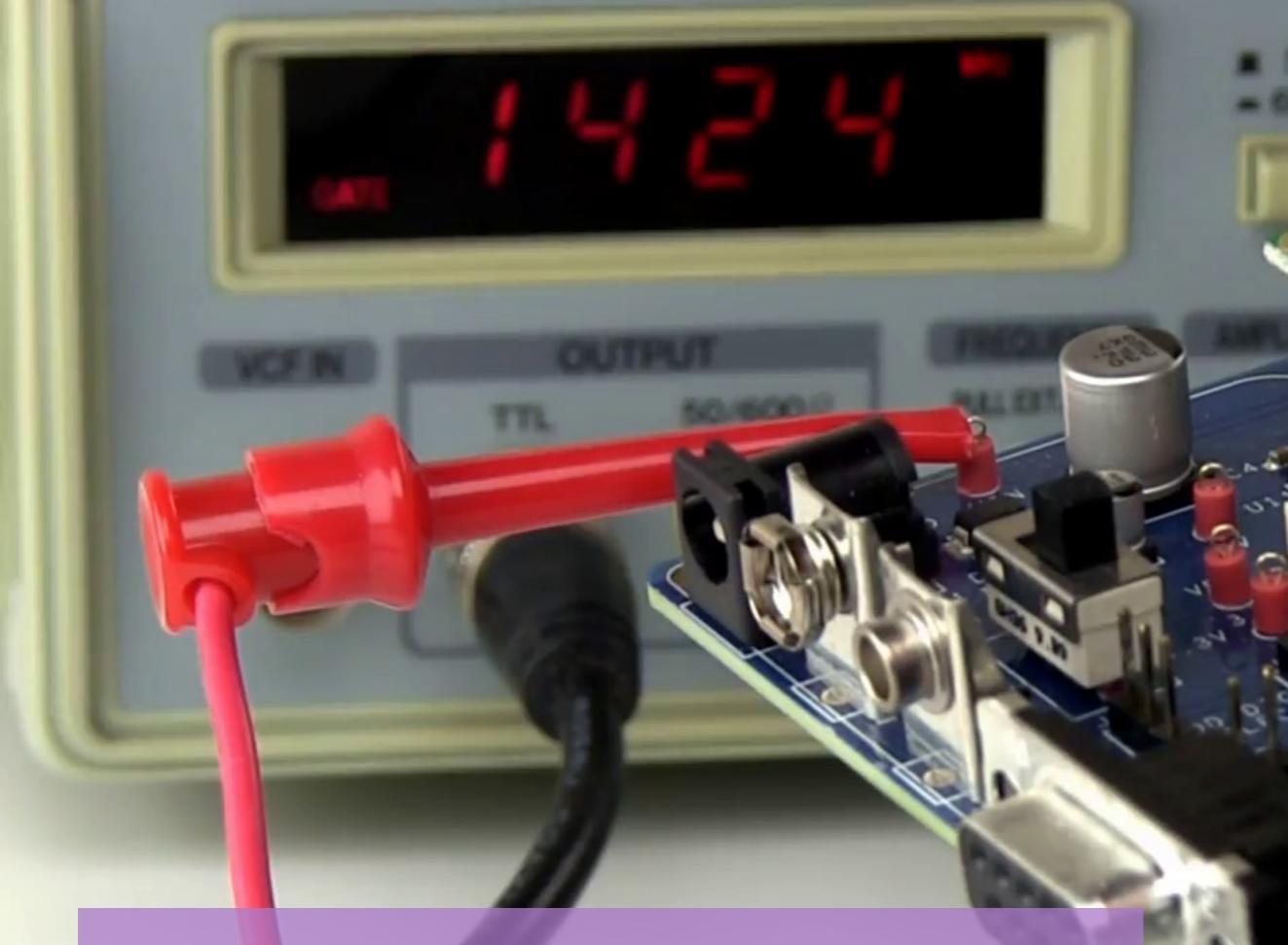






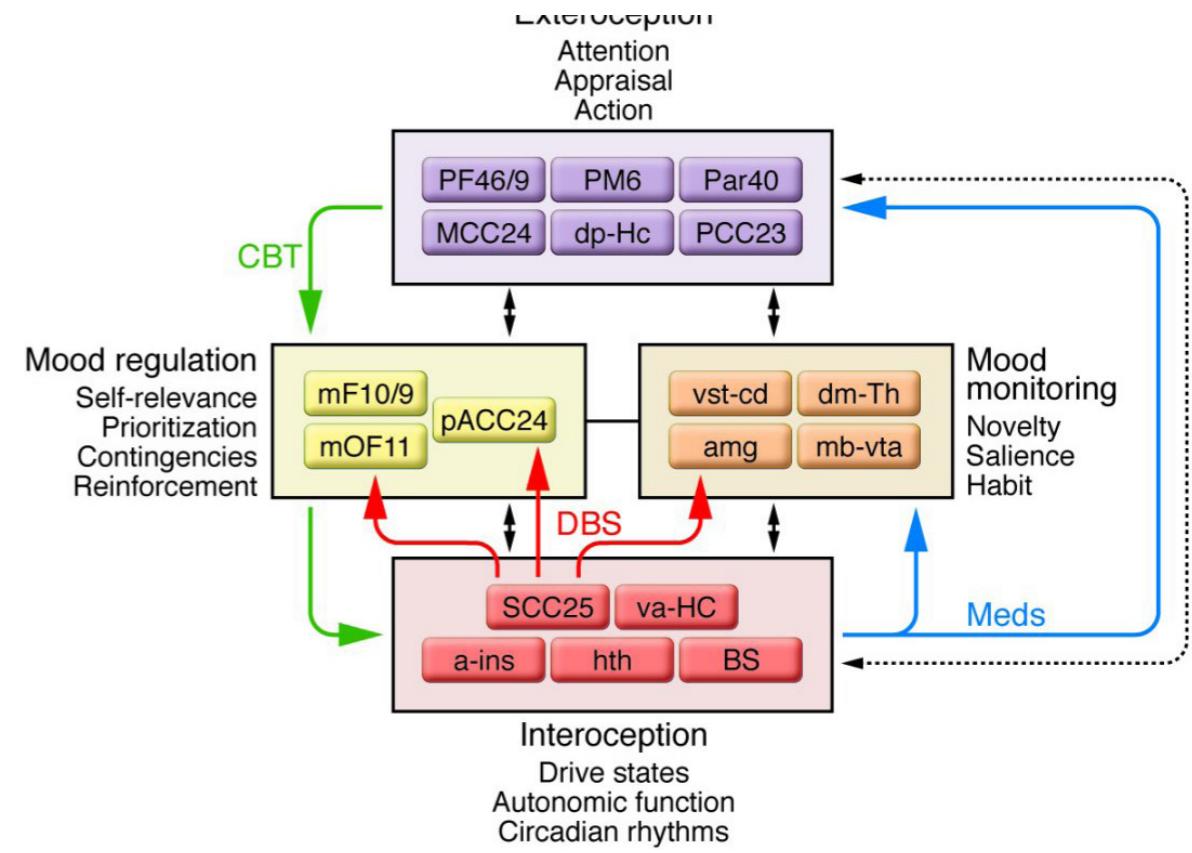
Zen and the Art of Circuit Debugging

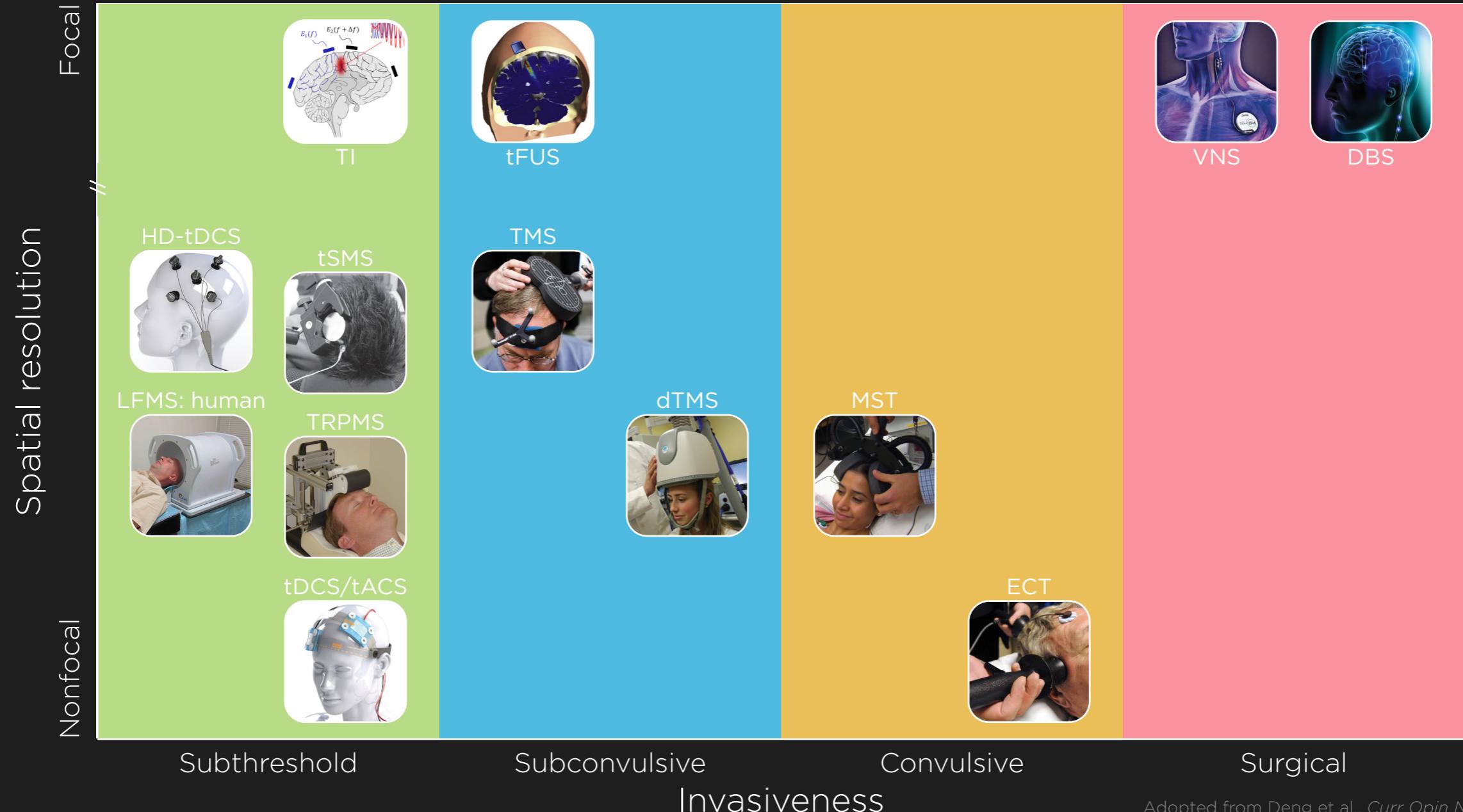
- Study the schematic
- Trace the signal
- Divide and conquer



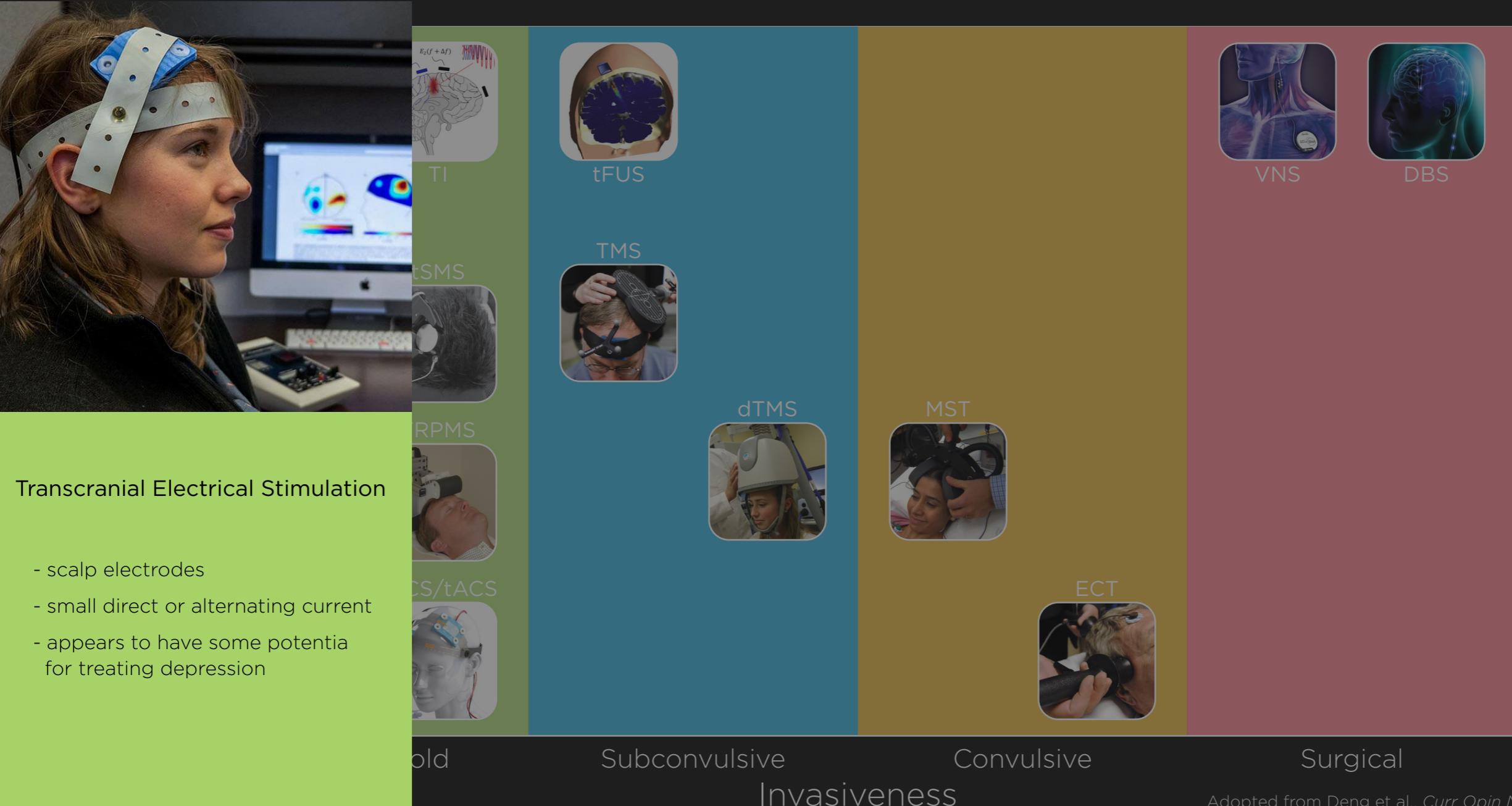
Zen and the Art of Circuit Debugging

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Adopted from Deng et al., *Curr Opin Neurobiol*, 2015





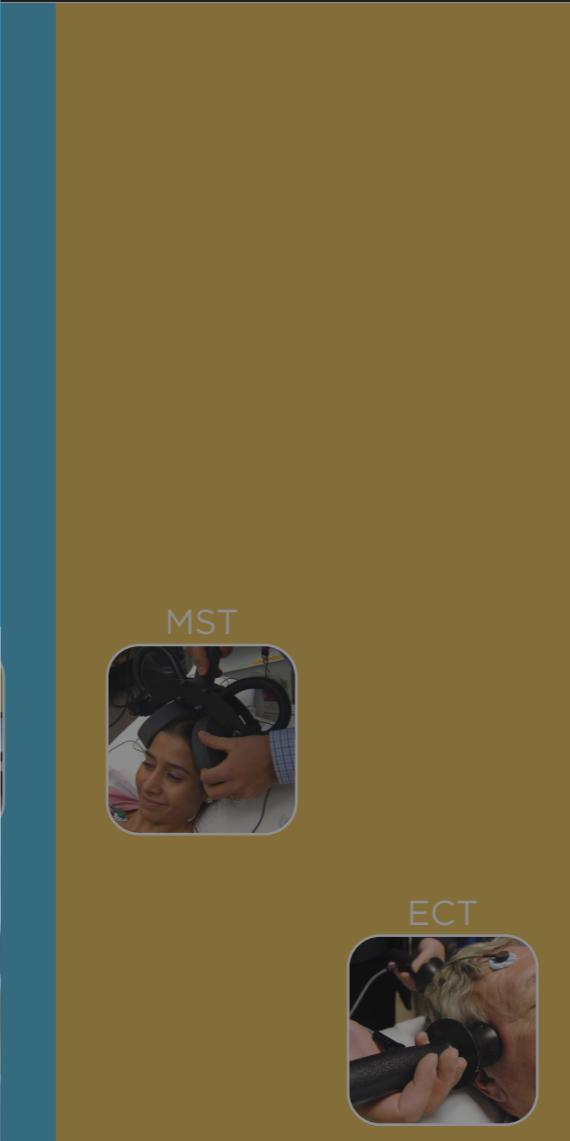
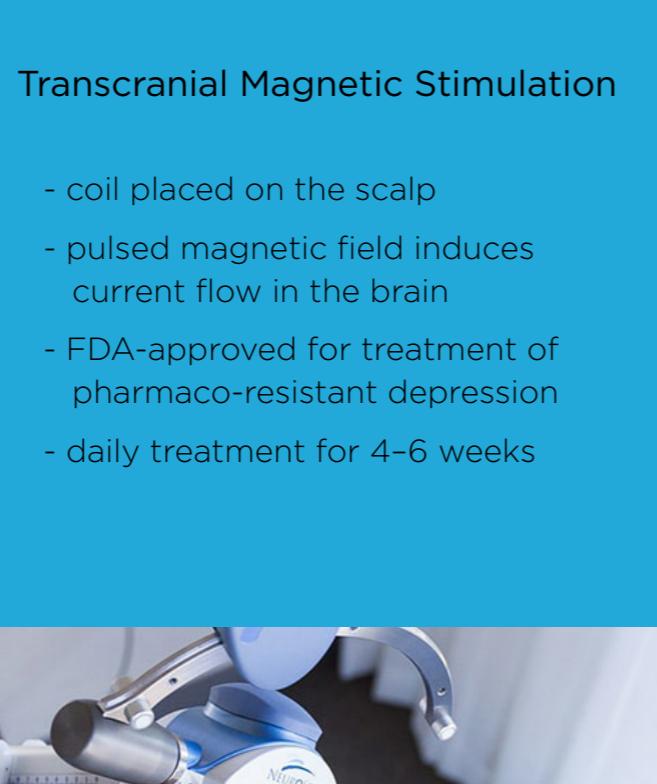
Transcranial Electrical Stimulation

- scalp electrodes
- small direct or alternating current
- appears to have some potential for treating depression



Transcranial Magnetic Stimulation

- coil placed on the scalp
- pulsed magnetic field induces current flow in the brain
- FDA-approved for treatment of pharmaco-resistant depression
- daily treatment for 4-6 weeks



Convulsive
siveness



VNS

DBS

Surgical

Adopted from Deng et al., *Curr Opin Neurobiol*, 2015



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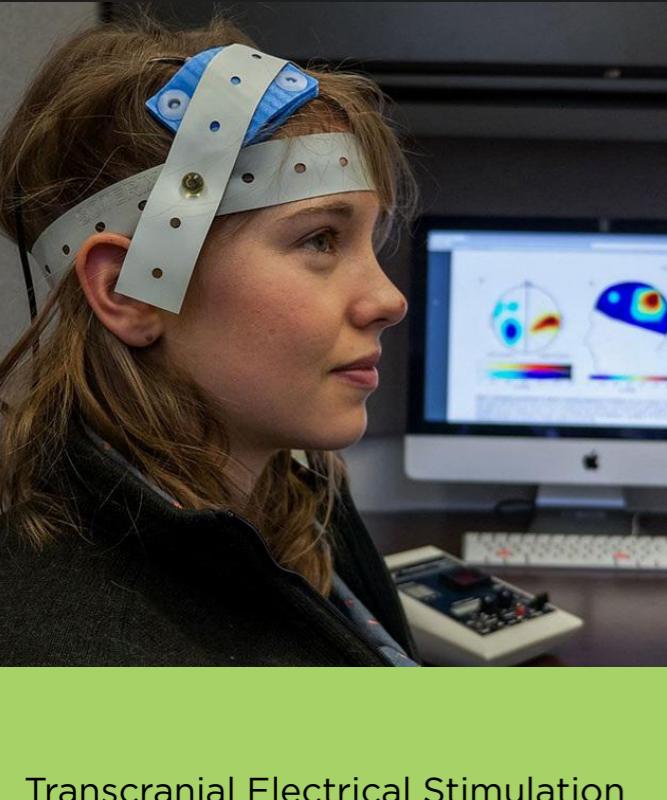


Electroconvulsive Therapy

- current delivered to brain via scalp electrodes
- induces seizure in anesthetized patients
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- 3x-weekly treatment for 4 weeks



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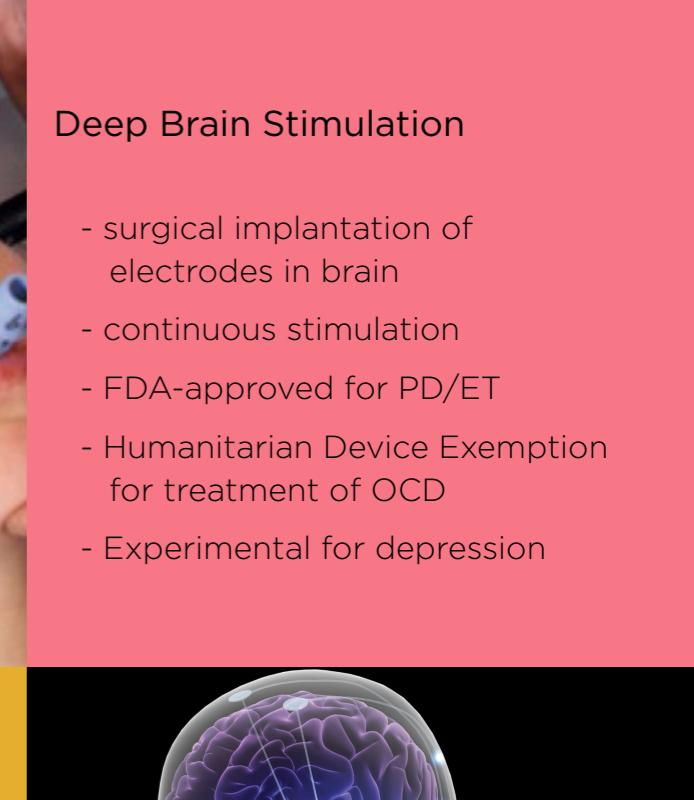
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Deep Brain Stimulation

- surgical implantation of electrodes in brain
- continuous stimulation
- FDA-approved for PD/ET
- Humanitarian Device Exemption for treatment of OCD
- Experimental for depression



Historical Psychiatric Drug Success Antecedent—Mostly Serendipity

- **Psychiatric Disorder Drug “Discovery”**
 - 1950’s period of relative ease of trying out compounds in mainly hospitalized psychiatric patients
 - Non-specific sedative goal—platforms underlying “first generation” antipsychotics and antidepressants
 - Tuberculosis: monoamine oxidase inhibitors (MAOIs)
 - Misguided uric acid theory: lithium
- **Psychiatric Drug “Development”**
 - Understanding what molecular properties were needed for efficacy allowing for selective targeting of various monoamine receptors with improved side effect profiles but no improvement in efficacy
 - Attempts to target other mechanisms without successfully ruling in (or out in most cases) their therapeutic potential using trial design of looking for efficacy under steady-state condition after several weeks
- **Neurologic Disorders: More Mixed History**
 - L-DOPA for PD, animal models informing novel anti-epileptics with “add-on” benefit as point of entry
 - Genetics that allow for identification of primary pathology to which drugs can be targeted—in most cases approach is to alter average state of system with sustained administration of drug

Historical Neurologic Success Antecedent—Mixed Paths

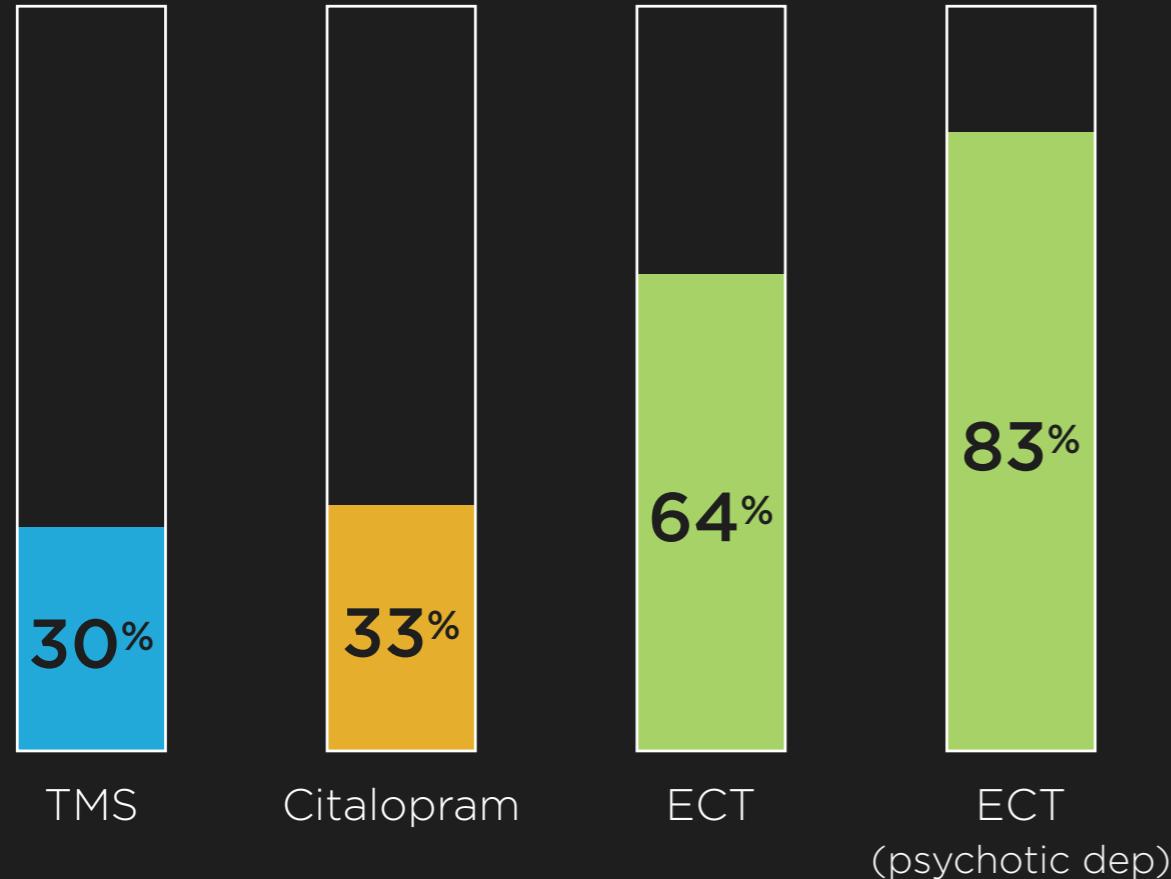
- Neurologic Disorders: More Pathophysiology Based
 - L-DOPA and other ways of manipulating dopamine function for PD with some sustained treatment although one does see immediate effects;
 - PD “on-off” phenomena raises question of intermittent targeting
 - PD focus for gene therapy and brain stimulation as well
 - Epilepsy: acute and chronic prophylactic treatment with animal models informing identification of novel compounds (with poorly understood molecular mechanisms)
 - Genetics that allow for identification of primary pathology to which drugs can be targeted—in most cases approach is to alter average state of system with sustained administration of drug
 - Alzheimer approaches open up concept of long term treatment to change function of system before emergence of clinical symptoms

OVERALL STRATEGIC IMPACT: Most novel CNS drug development operates with goal of selecting molecular target(s) that can be chronically modulated and continues to offer best chance of therapeutic advances in near term

Improving Existing Paradigm vs Investing at this Stage in Alternatives

- Advances in ability to study drug action in brain should increase probability of success (POS) and definitely can avoid costly clinical studies of inactive doses of compounds
 - Provides clear data on what doses have full target engagement, which if well tolerated, allows for simple testing paradigm of efficacy after weeks to couple of months at steady-state
 - Rules out advancing compounds that may have target engagement in terms of receptor occupancy but no evidence of downstream functional brain effects
 - Allows for more and more well established (rodents to non-human primates to humans) translational biomarkers of drug effect exploration so that ***molecular mechanistic hypotheses*** can be directly tested—stimulation of circumscribed areas in brain much more elusive and uncertain in terms of translation from animals to humans
 - From business perspective opportunities for modification of existing patent structure

Remission rate

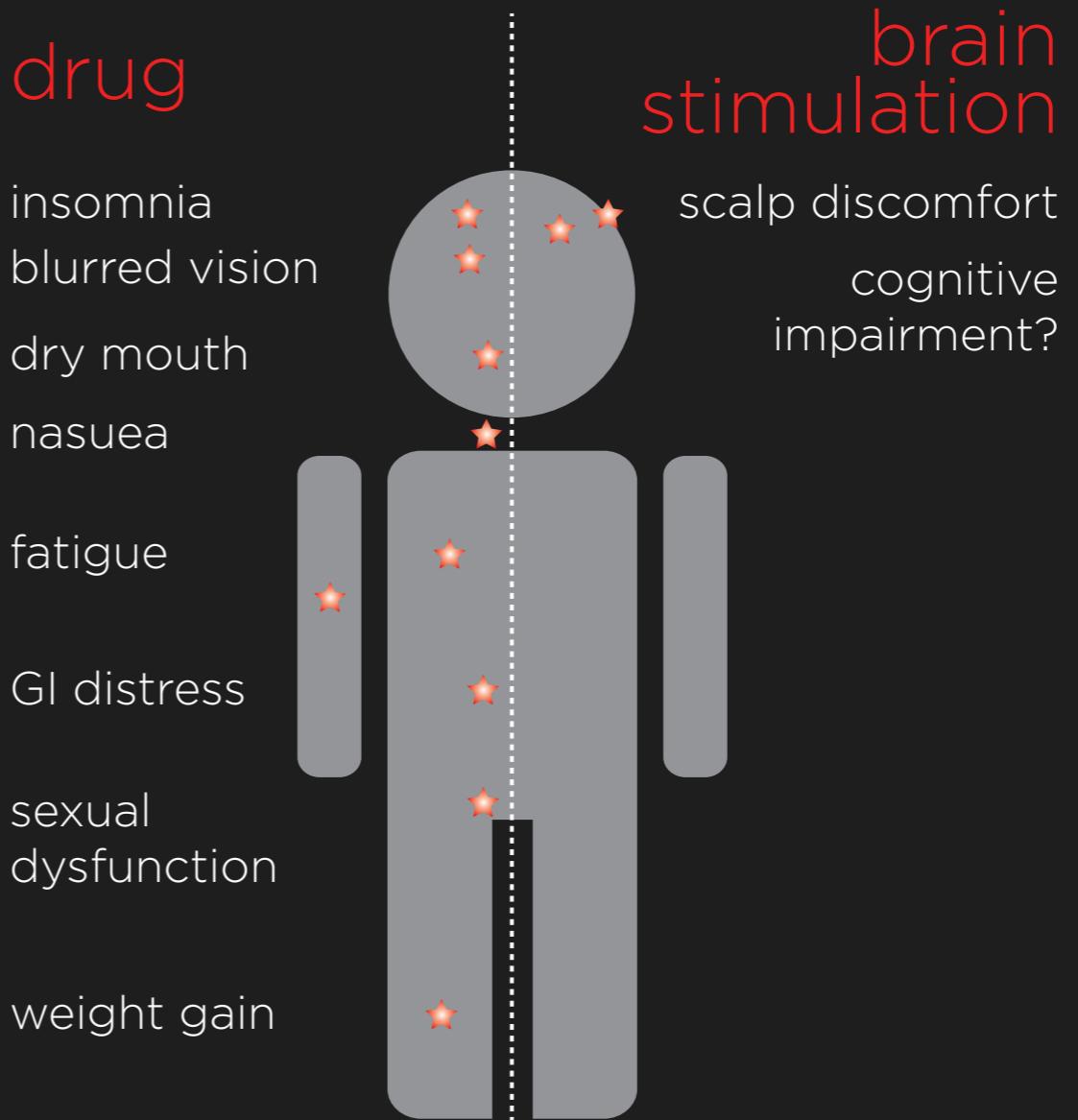


ECT...

the most effective treatment for severe major depressive disorder, catatonia, mania, suicidal ideation...

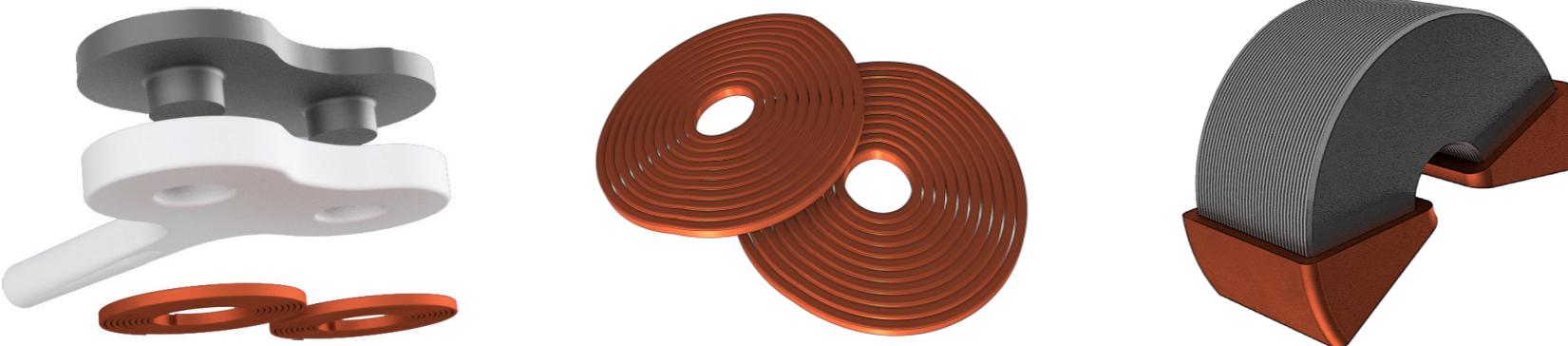
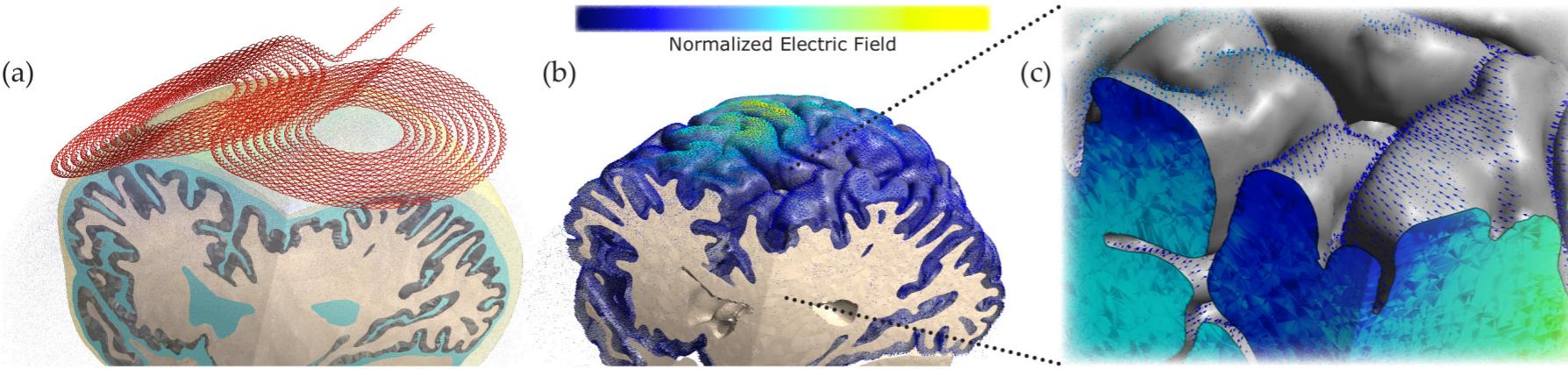
... or any condition where “*there is a need for rapid, definitive response.*” (FDA 2011)

Side effects profile



Spatial Control

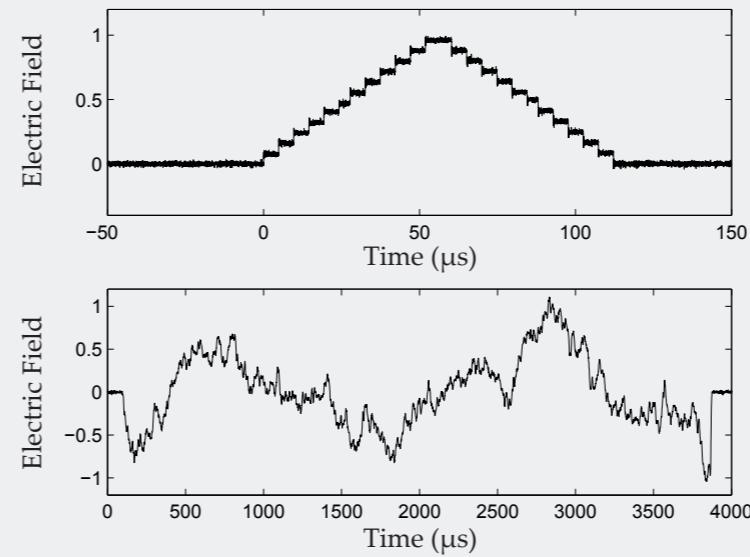
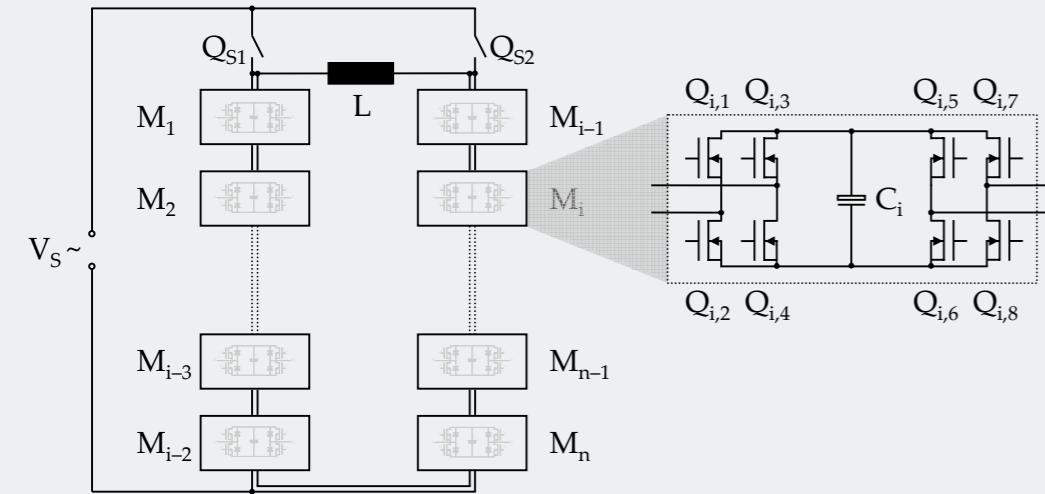
With computational modeling, we can **quantify & predict** dose of electricity delivered to the brain on an individual basis



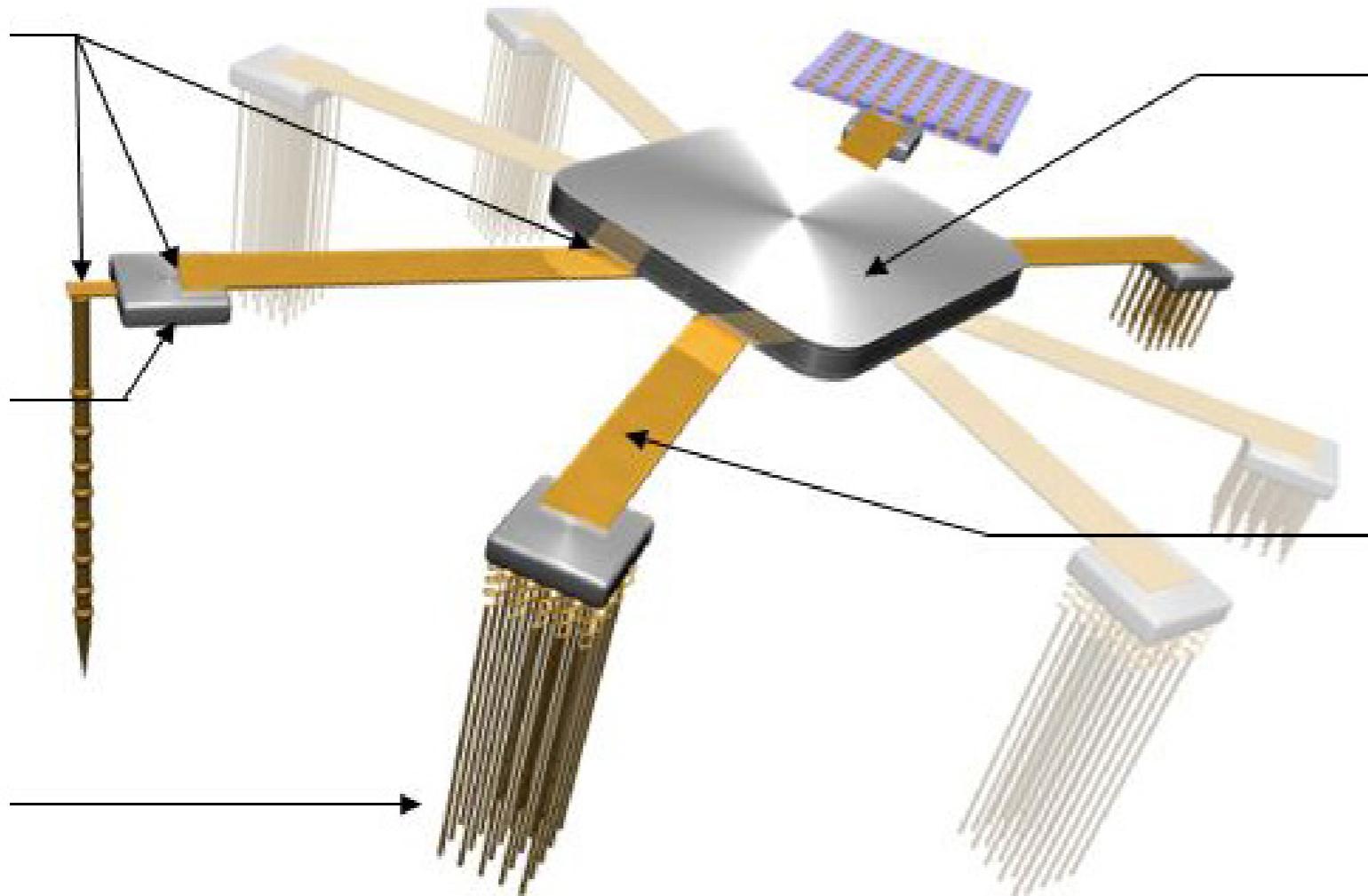
With novel coil designs, we can **control spatial distribution** & focality of induced electric field

Temporal Control

(f)



With novel stimulators, we can generate efficient temporal waveforms to interact with and **entrain brain dynamics**



Closed-loop & multi-focal stim

record, analyze, & stimulate
multiple brain regions

example: DARPA Systems-Based Neurotechnology for Emerging Therapies (SUBNETS) program

Molecular Target Selection Criteria adopted at NIMH

- Specific and testable hypothesis
- PET ligand to evaluate receptor occupancy
- Brain functional target engagement measures (e.g., fMRI, EEG)
- Target-selective and CNS penetrant
- Use RDoC principles to allow for testing of brain functional domain specific effects linked to molecular/circuit hypothesis

Approach Can be Implemented: Kappa Opiate Antagonist Example

- NIMH funded test of a selective kappa opiate antagonist with doses selected based on human PET RO to assure the highest level of binding compatible with selectivity
- Subjects selected on basis of a clinical scale to detect “anhedonia” (Snaith-Hamilton) but studied in terms of whether drug altered the degree of activation of preselected brain regions using BOLD fMRI during a reward task
- A behavioral task (Probabilistic Reward Task[PRT]) was also included hypothesized to be sensitive to any drug effects on reward function

Efficacy Results Based on Mixed Effects Models in ITT Population Means (SD) at End of Double-Blind Treatment Period

Variable	Mean JNJ-67953964 (SD)	Mean Placebo (SD)	p	Effect Size (Hedges' g)
Primary Outcome Measure				
fMRI Ventral Striatal Activation in MID Task in Anticipation of Gain Contrasted with Non-Incentive Trials	0.72 (0.67)	0.33(0.68)	0.0095	0.57
Secondary Outcome Measures				
SHAPS	30.8 (3.7)	32.4 (3.6)	0.0345	0.44
PRT	0.059 (0.15)	0.066 (0.15)	>0.10	N/A

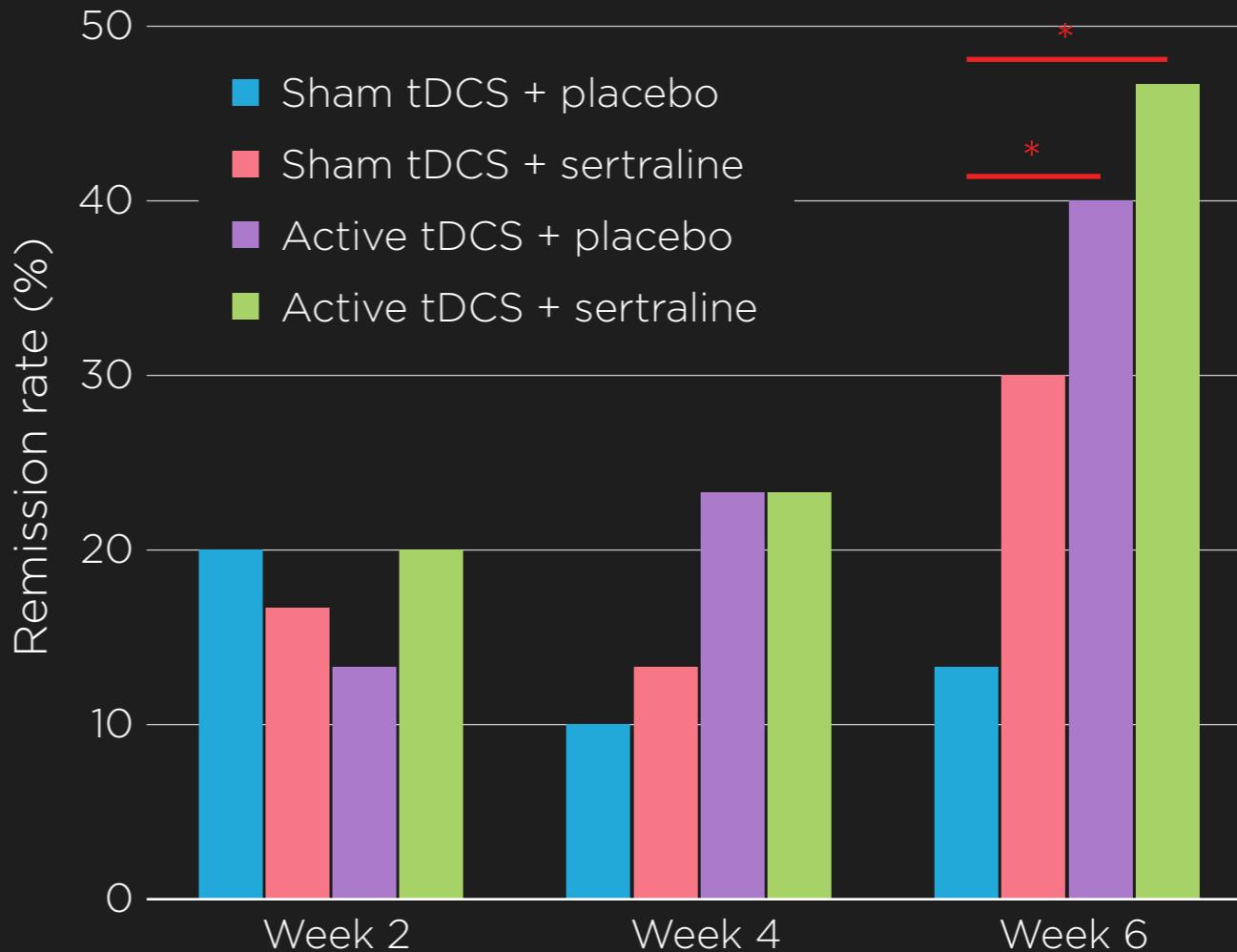
fMRI vs Clinical: Inter-Measure Correlation Matrix

	fMRI MID Gain Mean	fMRI MID Gain Max	fMRI MID Loss Mean	fMRI MID Loss Max	SHAPS	PRT	HAM-D	HAM-A	TEPS-Antic	TEPS-Consum
fMRI MID Gain Mean	X	0.78***	0.63***	0.53***	0.17	-0.05	-0.14	-0.12	0.16	0.01
fMRI MID Gain Max	X	X	0.57***	0.66***	0.11	-0.01	-0.10	-0.07	0.10	-0.05
fMRI MID Loss Mean	X	X	X	0.74***	0.1d4	-0.07	-0.14	-0.10	0.11	-0.04
fMRI MID Loss Max	X	X	X	X	0.21*	-0.03	-0.11	-0.12	0.01	-0.10
SHAPS	X	X	X	X	X	-0.09	0.47***	0.37**	-0.65***	-0.56***
PRT	X	X	X	X	X	X	0.13	0.06	-0.03	-0.07
HAM-D	X	X	X	X	X	X	X	0.79***	-0.44***	-0.35***
HAM-A	X	X	X	X	X	X	X	X	-0.31***	-0.16
TEPS-Antic	X	X	X	X	X	X	X	X	X	
TEPS-Consum	X	X	X	X	X	X	X	X	X	X

Combined Therapy

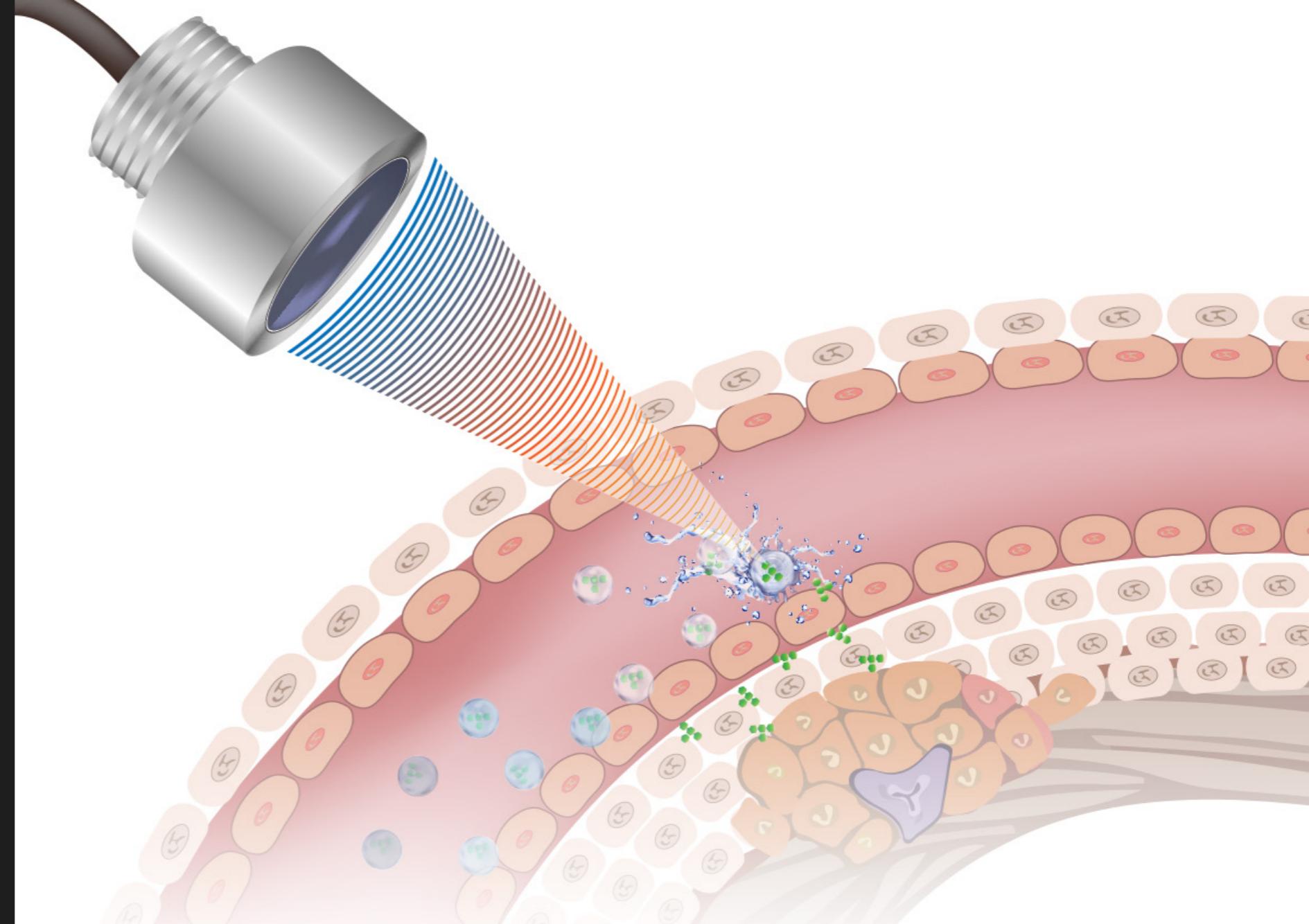


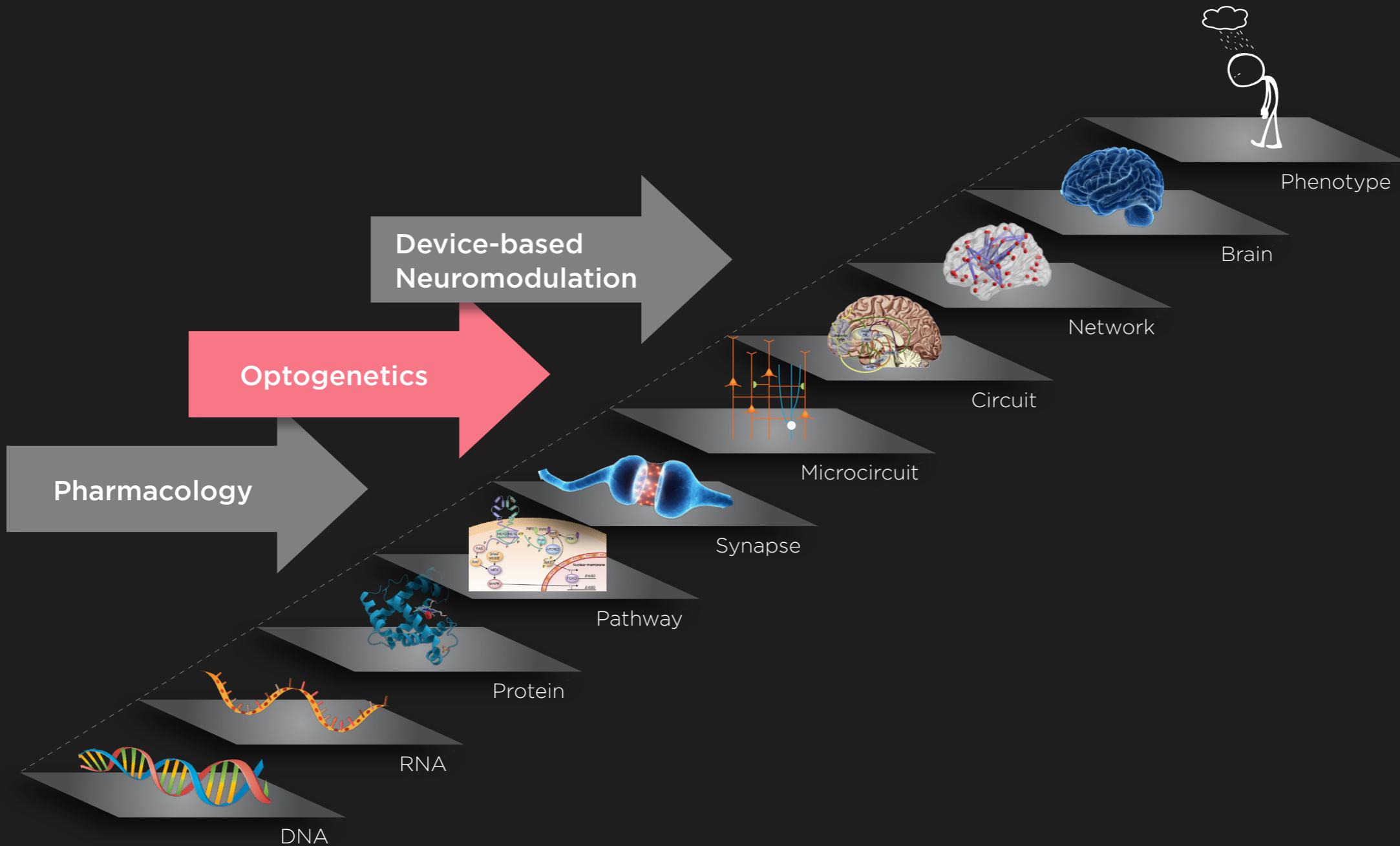
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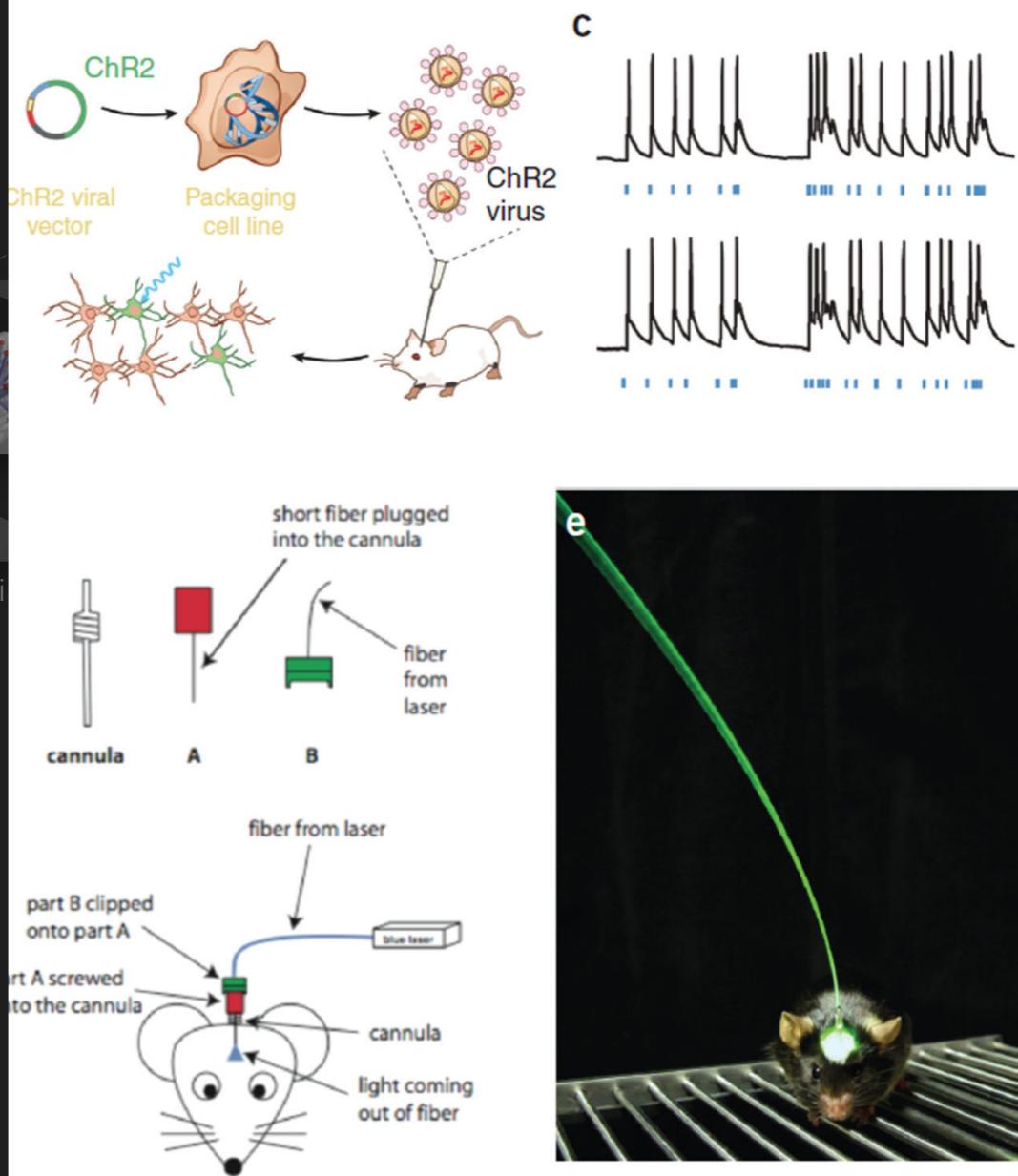
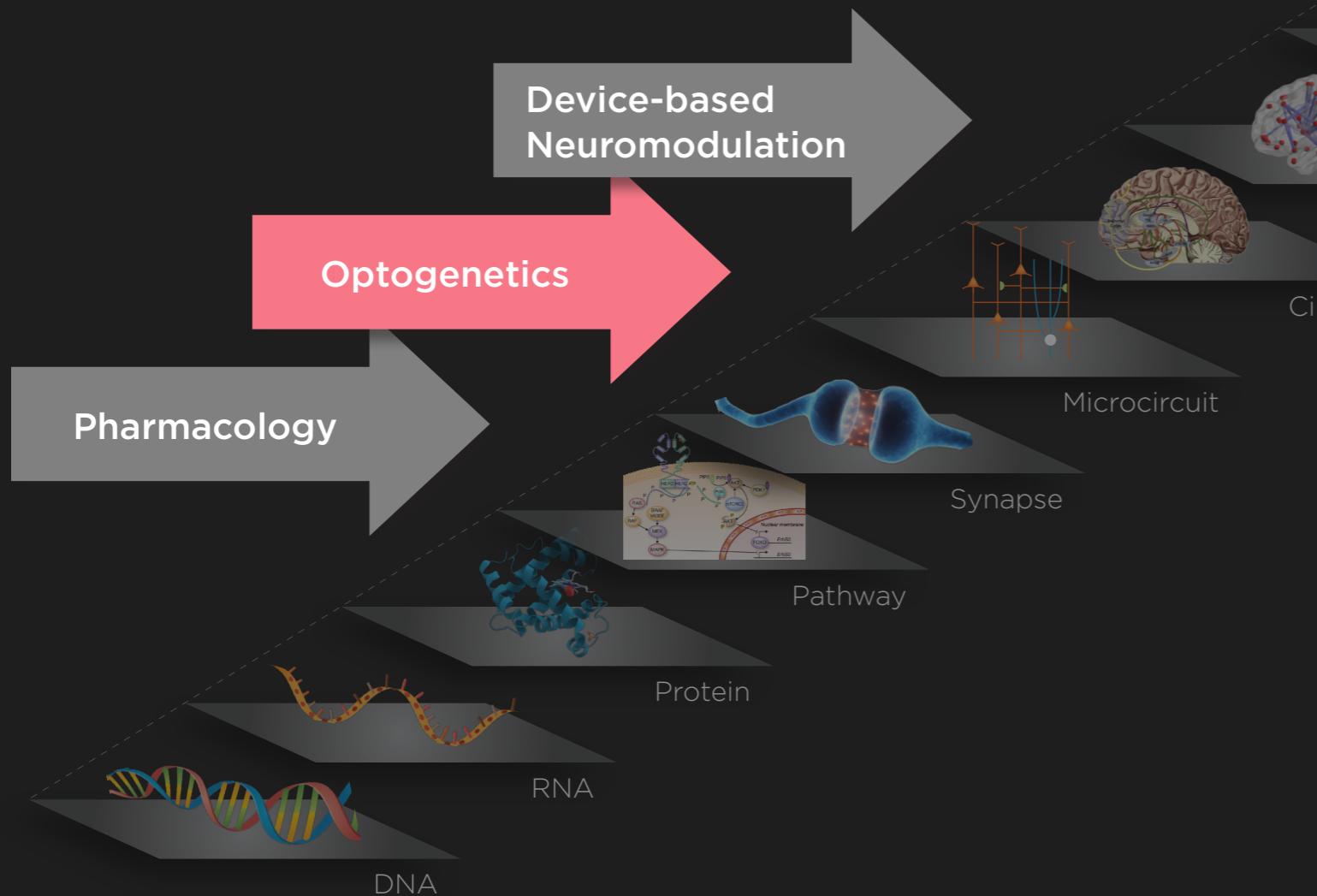


Device-Facilitated Local Drug Delivery

use transcranial focused ultrasound to localize drug release from micro-bubble packet or disrupt blood brain barrier







Deisseroth, *Nat Neurosci*, 2015

WOULD YOU INVEST IN SYNERGY WITH DEVICES?

- Molecular target hypothesis testing has better preclinical to clinical path and utilizes classes of tools which have been constantly improved over decades from chemistry to high throughput screens
- ECT provides POC that altering system in transient manner may deliver changes not yet possible with chronic alteration of chemical state
- Is there a path within an industrial business model to explore whether synergy or even additivity can be achieved by combining these very different types of interventions?



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Call for Application

The NIMH intends to publish a new Funding Opportunity Announcement to support the next generation of brain stimulation devices for treating mental health disorders through the R01 activity code.

The FOA is expected to be published in Fall 2018 with an expected application due date in Winter 2018.

For more info, visit:
<https://grants.nih.gov/grants/guide/notice-files/NOT-MH-18-037.html>