Developing biomarkers to assess the response to TMS

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Stanford University

Mood Disorders Education Day
08.20.22

@KellerStanfordU

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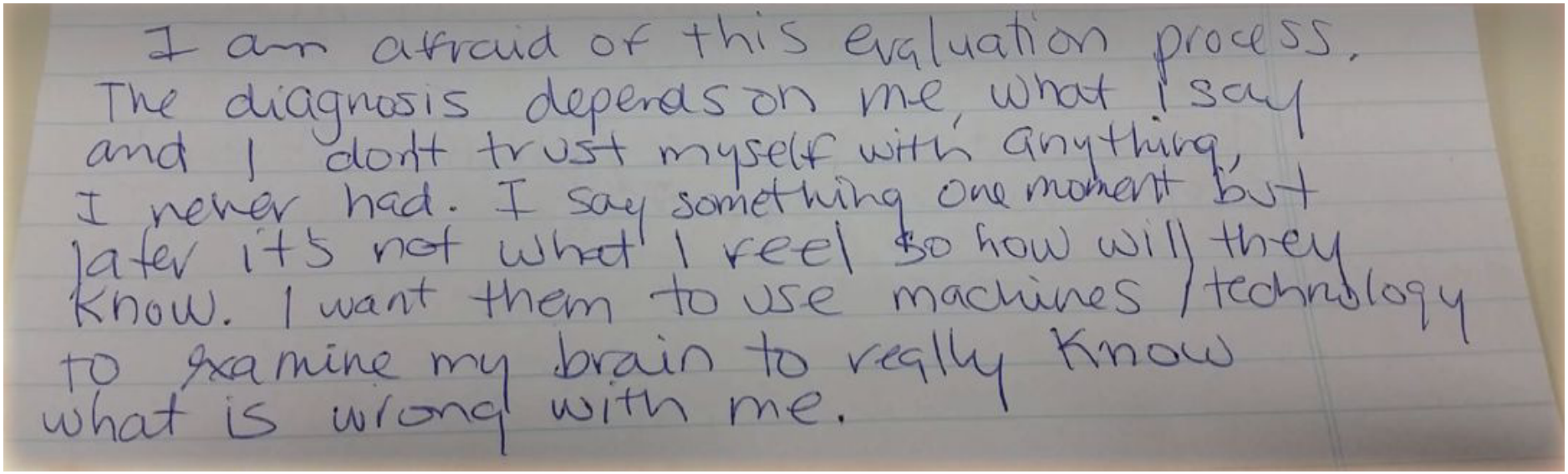
Disclosures

- Funding: NIH, Burroughs Wellcome Fund
- Equity: Alto Neuroscience

Motivation



Patient during residency

Take Home Points

- Interventional psychiatry is an emerging field with much potential

- To personalize and increase efficacy, we need to fill large gaps:
  - Objective brain biomarkers to monitor during treatment
  - Map brain biomarkers to multidimensional stimulation space
  - Optimize real-time monitoring for adaptive or closed-loop stimulation

- Personalized treatment with minimal side effects that can be applied to any brain circuit for any neuropsychiatric disorder

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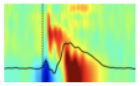
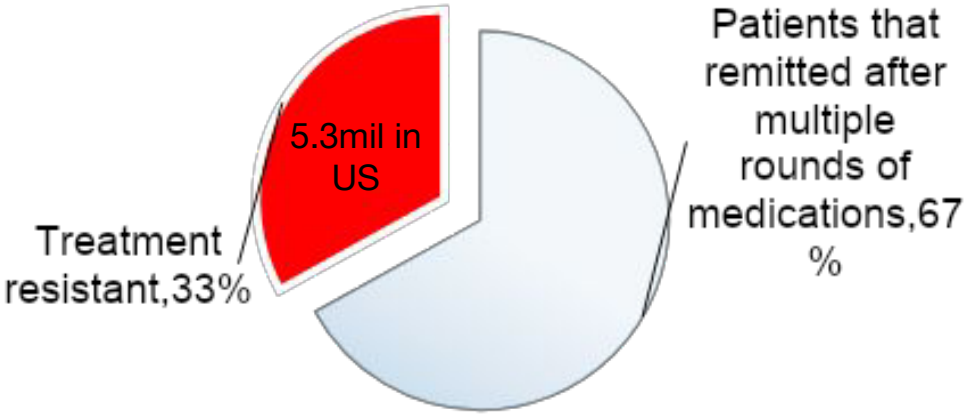


Depression – a leading cause of disease burden

Vohringer PA,Ghaemi SN (2011)
healthline.com; salusworld.com; bbrfoundationorg

Effect of COVID on mental health

'the percentage of adults with recent symptoms of an anxiety or a depressive disorder increased from 36.4% to 41.5%'



*Data extrapolated from STAR*D report*

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The age of interventional psychiatry for TRD

Transcranial Magnetic Stimulation (TMS)

Other Brain Stimulation Methods

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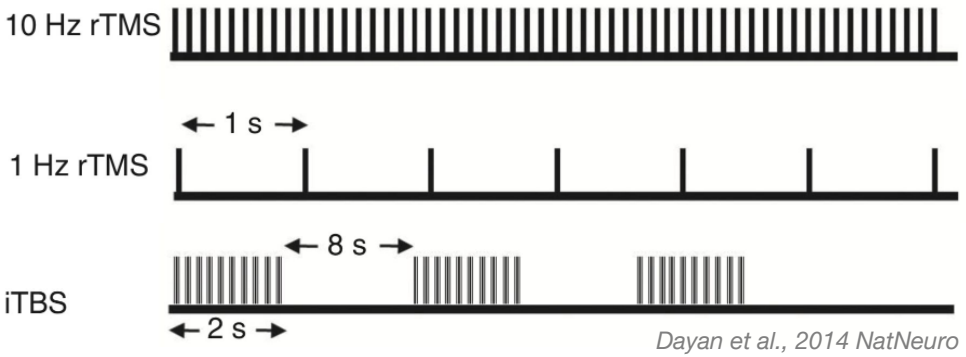
Current state of TMS for depression



Dayan et al., 2014 NatNeuro

- [x] Clinical efficacy for depression (25-50%)

O'Reardon et al 2007 Biol Psych
George et al 2010 Arch Gen Psych
Fitzgerald et al., 2016 Depression and Anxiety (Metaanalysis)
Kedzior et al., 2015 Depression and Anxiety (Metaanalysis)

- [x] Interesting novel treatment patterns
- [ ] Mechanistic understanding
- [ ] Brain markers to stratify, predict, and track
- [ ] Selectively modulate brain marker

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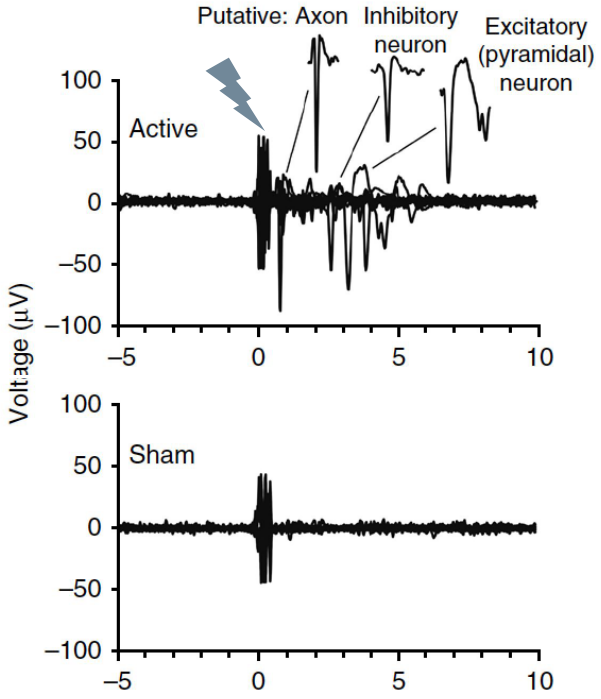
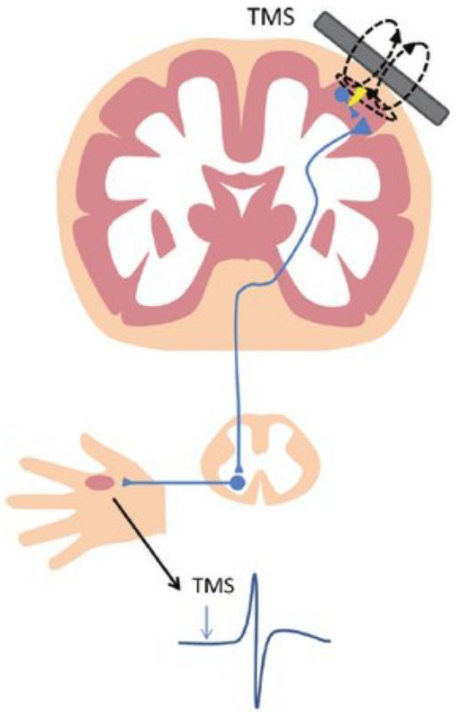
Single pulse TMS generates action potentials and MEPs



Mueller et al., 2013 NatNeuro



Motor evoked potential (MEP)

Fitzgerald et al., 2013, Schiz Bulletin

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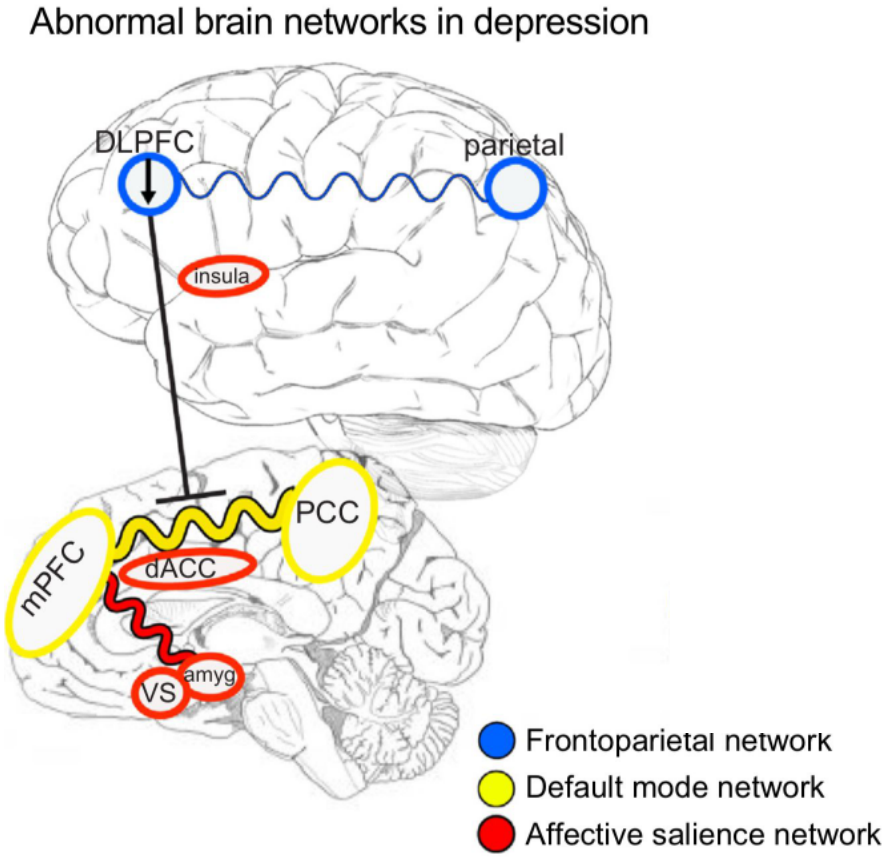
Repetitive TMS (rTMS) – modulating brain networks?



Fischer, Keller*, Etkin, 2016 Biol Psych CNNI*
Liston et al., 2014 BiolPsych

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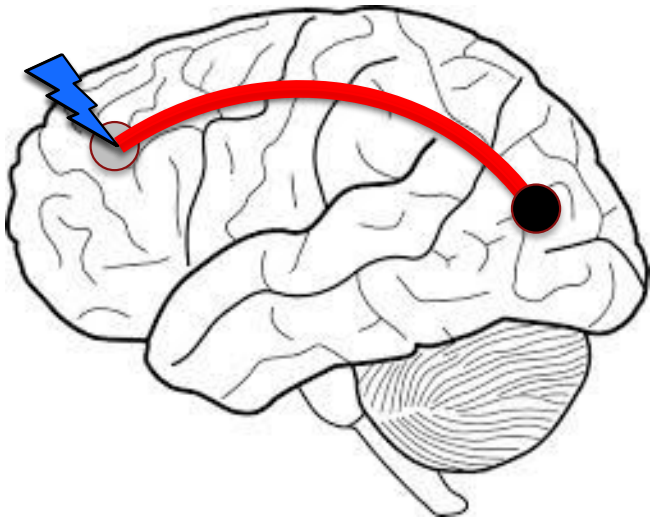
TMS: Selective manipulation of specific brain circuits

Unlimited applications with minimal side effects



Psychiatric disorders

- **MDD (2008)**
- **OCD (2018)**
- **Smoking cessation (2021)**
- PTSD
- Substance use disorder
- Bipolar disorder
- Schizophrenia

Neurologic disorders

- **Migraines (2013)**
- Alzheimer's
- Epilepsy
- Parkinson disorder
- Stroke

Basic neuroscience

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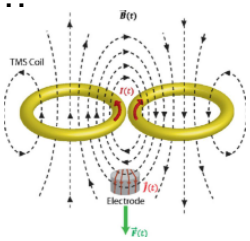
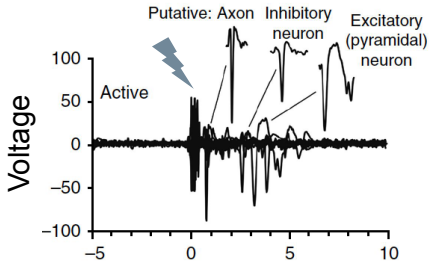
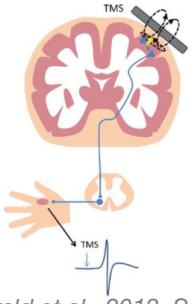
We need to learn the language of TMS

We know the sound of TMS…





Mueller et al., 2013 NatNeuro

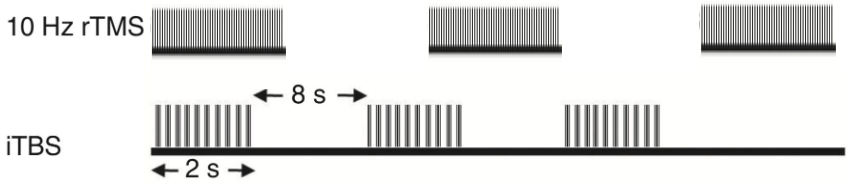


Fitzgerald et al., 2013, Schiz Bulletin

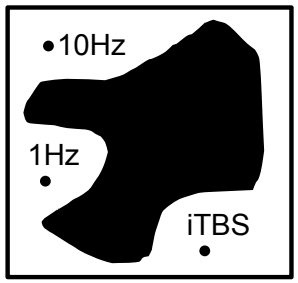
We have a few words…

mein mein mein mein mein mein mein mein

bablos bablos bablos bablos bablos bablos



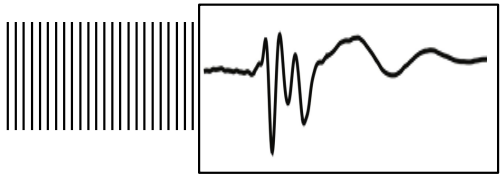
We are missing **everything** else (words, form, content, use)

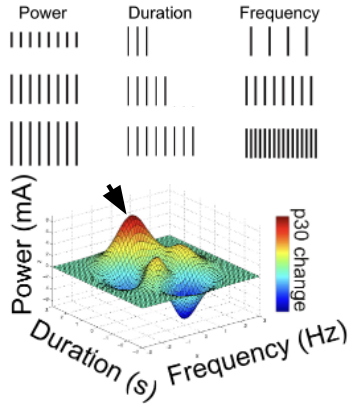


frequency
amplitude
duration
pattern
state

location

Brain biomarker





Personalized
Adaptive

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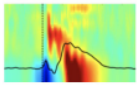

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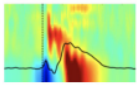

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- Jeffrey Wang
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- Chris Minasi
- Benyamin Meschede-Krada
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- Rachel Manber, PhD

BURROUGHS WELLCOME FUND

NIH National Institute of Mental Health

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Participants

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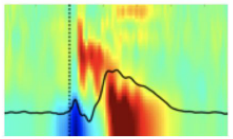

We are hiring!

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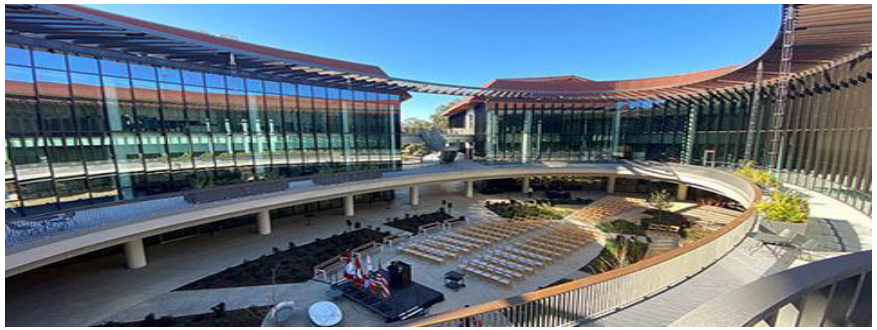

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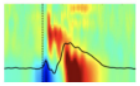
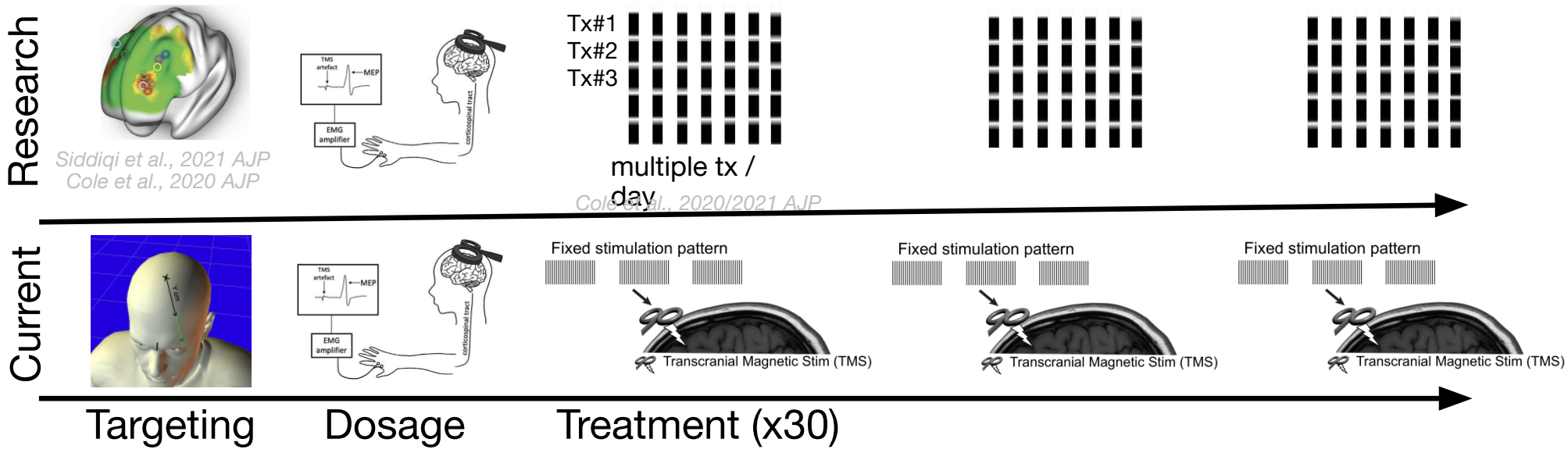


Current state of the field



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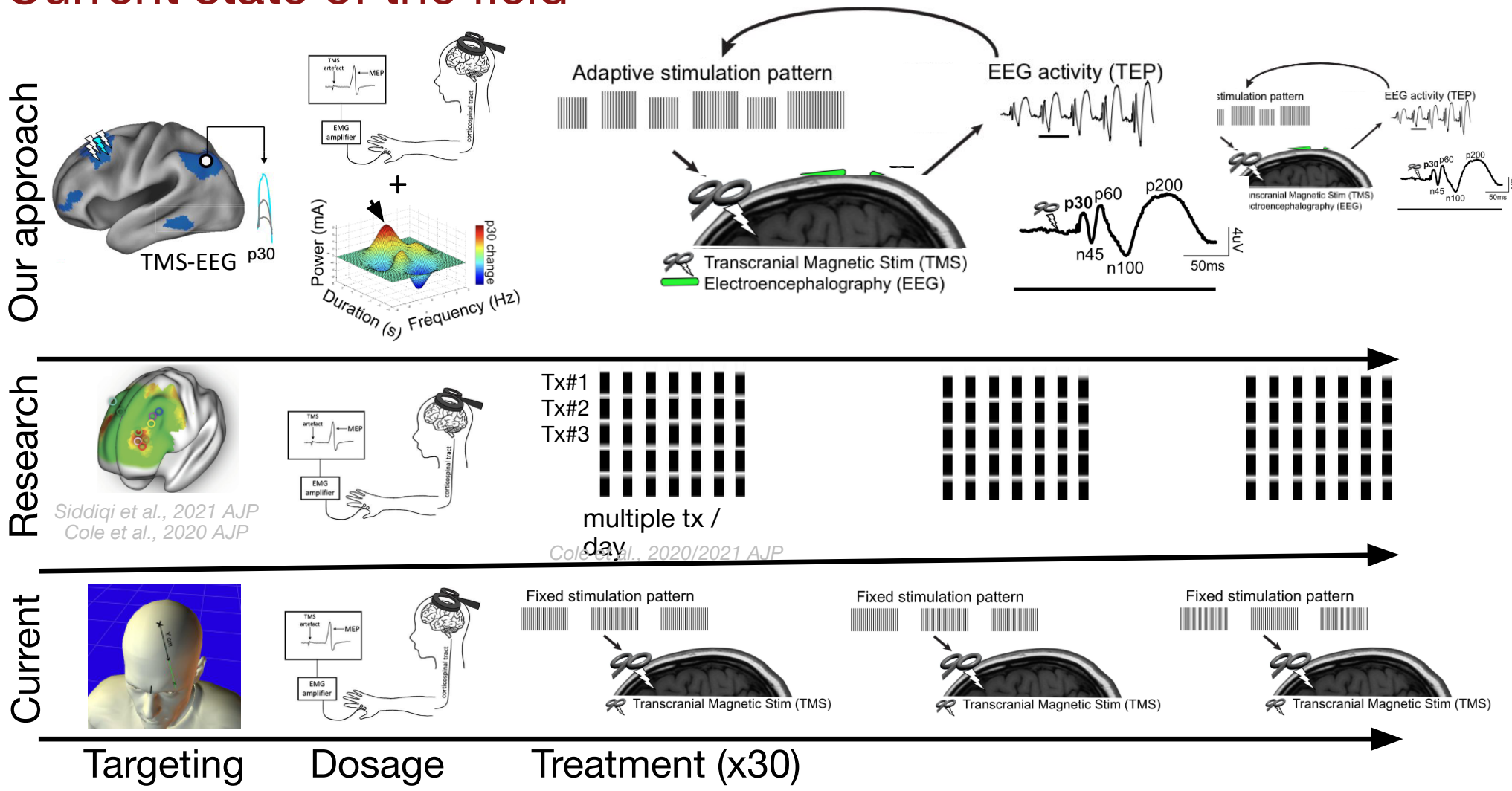
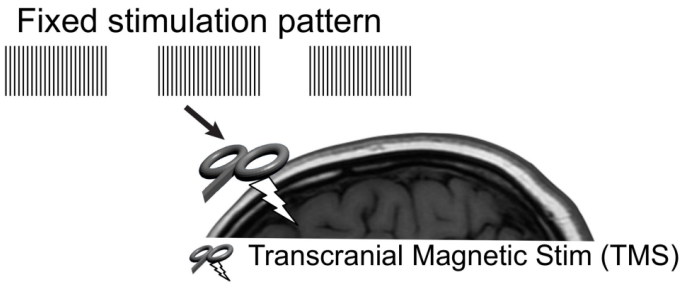


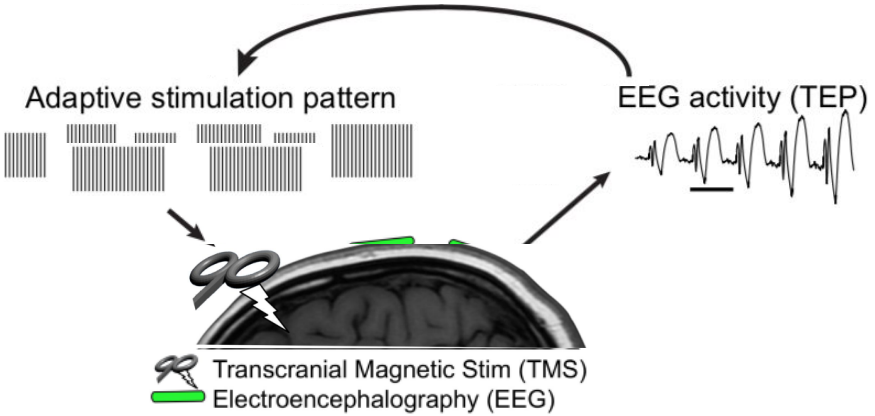
Next generation brain stimulation: *personalized + adaptive*

Current v1.0: open-loop



- Largely same as 2008 approval
- Blind to one's physiology / plasticity
- One size fits all

v2.0: Adaptive, closed-loop



- Adapt tx based on biomarker
- Based on one's physiology / plasticity
- Faster and (much) more effective

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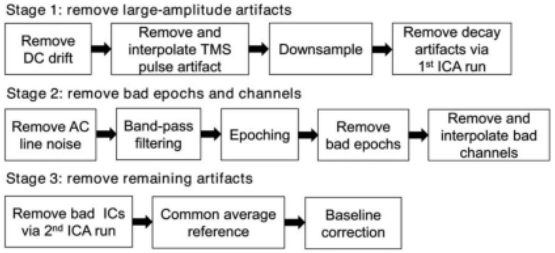
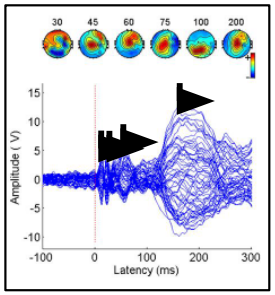
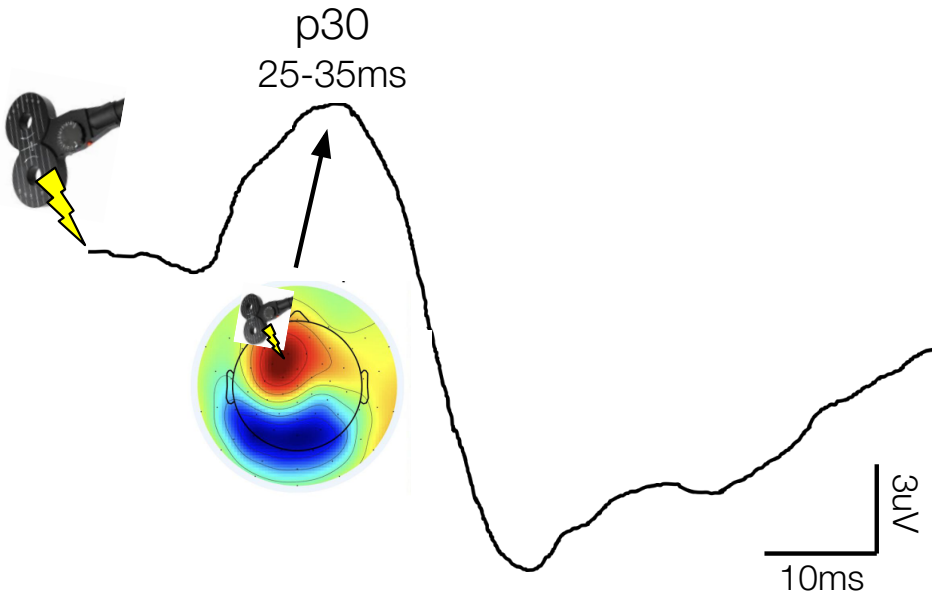
TMS-EEG ‘p30’: a biomarker for TMS

- Causal perturbation
- Millisecond time resolution
- Clinic-ready
- Relatively inexpensive

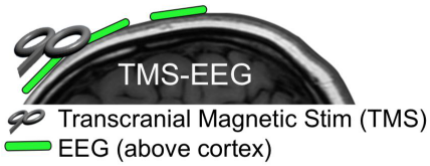






‘p30’

- Earliest discernable peak in TMS-EEG
- Present in invasive and noninvasive EEG recordings (Keller et al., 2018)
- Reflects brain excitability (Tremblay 2015, Lioumis 2009)
- Suppressed after 10Hz TMS in healthy controls (Donati et al., in prep)
- Suppressed after 4 weeks of 10Hz TMS for depression and related to clinical outcome (Eshel et al., 2020)



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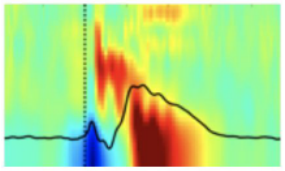
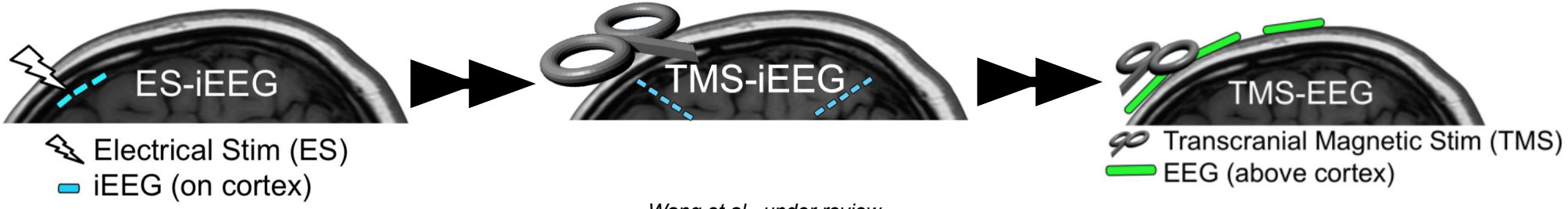


Multidisciplinary lab approach focused on neuromodulation and human electrophysiology

We deconstruct brain stimulation to establish the fundamental mechanisms underlying human neuroplasticity and develop real-time, closed-loop treatments for mental health disorders

1) To develop novel methods to probe the human brain in a causal and directional manner
2) To better understand the mechanisms underlying human brain plasticity
3) To create real-time, closed-loop solutions for mental health disorders

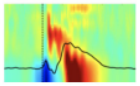


Keller et al., PNAS 2011
Keller et al., Journal of Neuroscience, 2014
Keller et al., PhilTrans, 2014
Keller et al., Human Brain Mapping, 2017
Keller et al., Journal of Neuroscience, 2018
Huang et al., Journal of Neuroscience, 2019

Wang et al., under review

Wu, Keller et al., HBM, 2018
Kerwin, Keller, et al., BrainStim, 2018
Eshel, Keller et al., NPP, 2020
Ross et al., 2022
Gogulski et al., under review
Cline et al., in prep
Donati et al., in prep

Non-invasive Brain Stimulation 2.0: biologically-based, personalized, adaptive

- Develop **brain biomarker** to track brain change → symptoms (Goal 1)
- Understand how **stimulation parameters** affect brain biomarkers (Goal 2)
- Develop **real-time** monitoring and **closed-loop stimulation** (Goal 3)

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