Developing biomarkers to assess the response to TMS

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Motivation

"I am afraid of this evaluation process. The diagnosis depends on me, what I say and I don't trust myself with anything. I never had. I say something one moment but later it's not what I feel so how will they know. I want them to use machines/technology to examine my brain to really know what is wrong with me."
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**
Depression – a leading cause of disease burden

**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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Vohringer PA, Ghaemi SN (2011) healthline.com; salusworld.com; bbrfoundation.org
The age of interventional psychiatry for TRD

Transcranial Magnetic Stimulation (TMS)  Other Brain Stimulation Methods

MagVenture  Brainsway  Magstim

D  BS  VNS  T

TDCS/T  ACS

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Current state of TMS for depression

✔ 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)

✔ 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

Motor evoked potential (MEP)

Mueller et al., 2013 NatNeuro

Fitzgerald et al., 2013, Schiz Bulletin
Repetitive TMS (rTMS) – modulating brain networks?

Abnormal brain networks in depression

Fischer*, Keller*, Etkin, 2016 Biol Psych CNNI
Liston et al., 2014 BiolPsych
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
We need to learn the language of TMS

We know the sound of TMS...

We have a few words...

mein mein mein mein mein mein mein mein

bablos bablos bablos bablos bablos bablos bablos

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

- 10 Hz
- 1 Hz
- iTBS

frequency amplitude duration pattern state

Brain biomarker

location
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We are hiring!
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- **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 parameters**
  - 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**
Current state of the field

Transcranial Magnetic Stim (TMS)

Fixed stimulation pattern

Targeting  Dosage  Treatment (x30)

Siddiqi et al., 2021 AJP
Cole et al., 2020 AJP

Cole et al., 2020/2021 AJP

multiple tx / day
Current state of the field

Our approach

Transcranial Magnetic Stim (TMS)
Electroencephalography (EEG)

Adaptive stimulation pattern
EEG activity (TEP)

Research

Siddiqi et al., 2021 AJP
Cole et al., 2020 AJP

multiple tx / day

Current

Targeting
Dosage
Treatment (x30)
Next generation brain stimulation: *personalized + adaptive*

**Current v1.0: open-loop**
- Fixed stimulation pattern
- Transcranial Magnetic Stim (TMS)
- Largely same as 2008 approval
- Blind to one’s physiology / plasticity
- One size fits all

**v2.0: Adaptive, closed-loop**
- Adaptive stimulation pattern
- EEG activity (TEP)
- 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)
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

Wang et al., under review
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)