PERSONALIZED CLOSED-LOOP DBS FOR SEVERE TREATMENT-RESISTANT MAJOR DEPRESSION: PRELIMINARY FINDINGS

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- Consulting
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- Stock Options
  - Big Health, Neurawell

NEUROPSYCHIATRIC DISORDERS ARE CHALLENGING

- Poorly understood
- Heterogenous
- No diagnostic tests

MAJOR DEPRESSIVE DISORDER (MDD)

- Leading cause of disability worldwide ~300 million
- Current treatments have significant limitations;
  - 33% with MDD do not respond to 4 med trials
  - Development of new treatments is stagnant
  - **Provides Motivation for Development of Cortical and Subcortical Brain Stimulation (generally called DBS) for MDD**

Krystal et al., Nature Rev Drug Discov. 2020. Denys and de Geus F, 2005; Trivedi et al., Am J Psych. 2006; Insel, Am J Psych. 2006

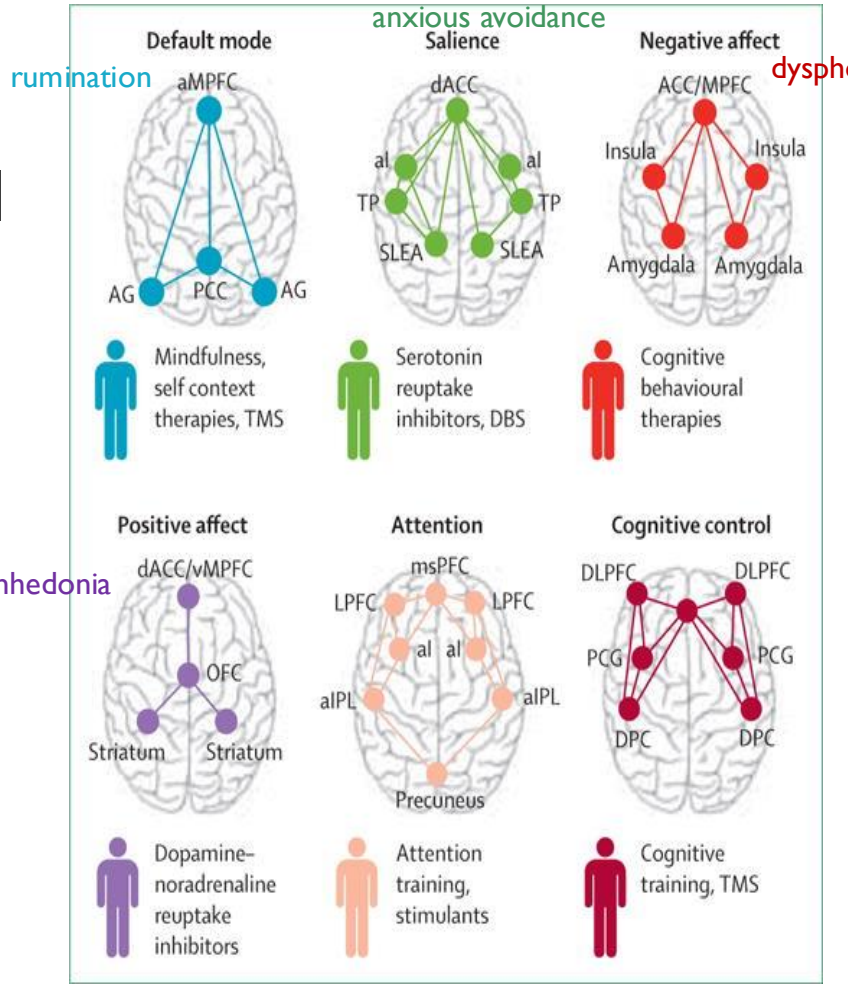
CHALLENGES TO OPTIMIZING DEEP BRAIN STIMULATION FOR MDD

- Where should one stimulate?
  - Definitive understanding of circuitry underlying MDD is lacking
  - No consensus as to optimal target; Multiple different sites have been targeted;
  - Best target may vary among individuals: MDD is a heterogenous condition (diagnosis - 5/9 symptoms)
- Depression treatments are generally continuous which might not be optimal
  - Symptoms may vary significantly over time so stim may often not be needed: What is stimulation doing when symptoms are absent?
  - Totally unknown if helpful or counter-productive to stimulate during sleep
- MDD therapies generally take 4-8 weeks to be effective.
  - This precludes effective optimization of stimulation site and parameters in practical time-frame.
  - Also makes it impossible to effectively dose treatment in an effective way

Okun M. N Engl J Med 2012

NEED FOR PERSONALIZATION: TARGET SELECTION

- Individuals with depression differ in predominant symptoms and underlying alterations in neural circuitry on resting state fMRI
- Consistent With Growing Number of Stimulation Targets
  - Subgenual Cingulate (Mayberg, H 1997)
  - Reward Pathway: ALIC, VC/VS, NAc, MFB
  - BNST (Fitzgerald, P, et al 2018)
  - Lateral Habenula (LHb) (Sartorius A, 2007)
  - Inferior thalamic peduncle (Jimenez, F 2012)
  - Orbitofrontal Cortex (OFC) (Rao V 2018)



Williams, L. Lancet Psychiatry. 2016

DBS CLINICAL TRIALS IN MDD COMPLETED TO DATE

Study	Location	N	Blinded Crossover
Bergfeld et al. 2016	vALIC	16	Yes
Coenen et al. 2019	MFB	16	No
Dougherty et al. 2015	VC/VS	29	No
Fenoy et al. 2018	MFB	6	Yes
Holtzheimer et al. 2012	SCC	10	Yes
Holtzheimer et al. 2017	SCC	85	No
Merkl et al. 2013	SCC	6	Yes
Merkl et al. 2018	SCC	4	Yes *
Puigdemont et al. 2015	SCC	5	Yes
Ramasubbu et al. 2013	SCC	4	Yes
Raymaekers et al. 2017	IC/BST	5	Yes
Raymaekers et al. 2017	ITP	5	Yes

* Only half of the patients crossed over. IC/BST: internal capsule/bed nucleus of the stria terminalis; ITP: inferior thalamic peduncle; MFB: medial forebrain bundle; SCC: subcallosal cingulate; vALIC: ventral anterior limb of the internal capsule; VC/VS: ventral capsule/ventral striatum.

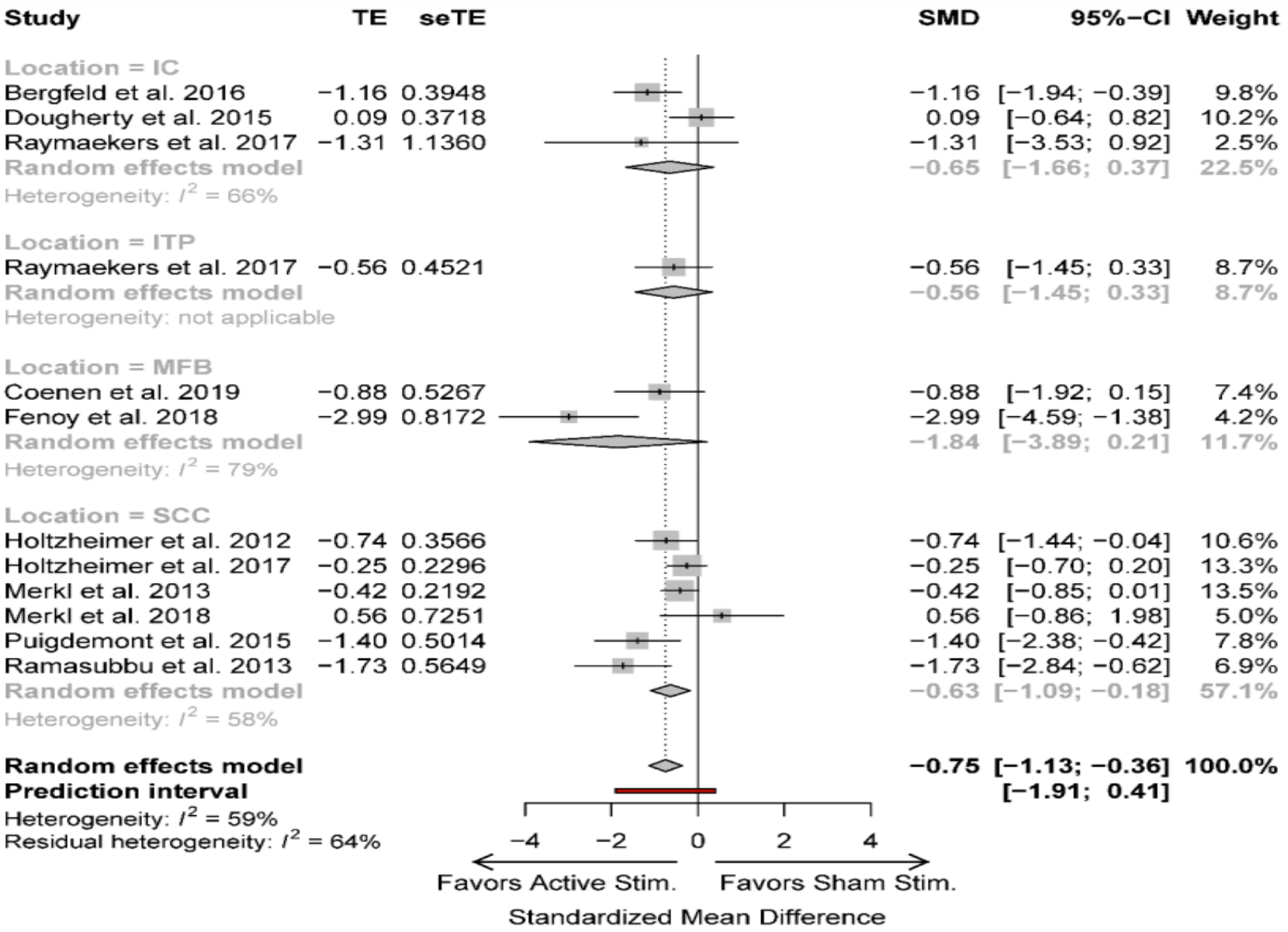


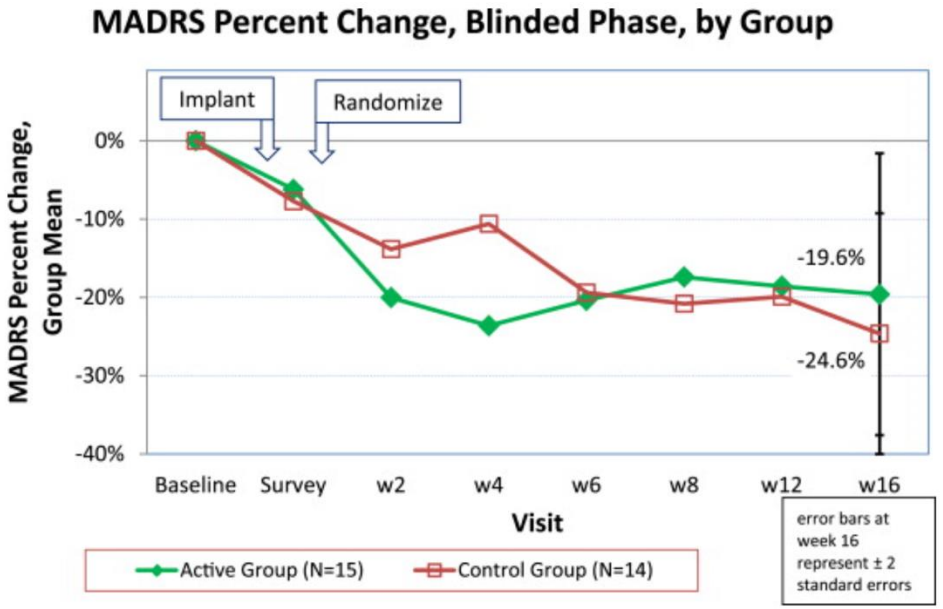
Figure 3. Meta-regression forest plot comparing various stimulation targets. CI: confidence interval; IC: internal capsule; ITP: inferior thalamic peduncle; MFB: medial forebrain bundle; SCC: subcallosal cingulate; SMD: standardized mean difference; TE: treatment effect; seTE: standard error of treatment effect.

VC/VS STIMULATION STUDY N=29

Randomized Sham Control Trial

Ventral Capsule

Dose titrated based on immediate effects;
Improvement expected only weeks later.



No significant difference in response rates between the active (20%) and control (14%) arms and no significant difference between change in Montgomery-Åsberg Depression Rating Scale scores.

Dougherty DD et al. Biol Psych 2015

SUBCALLOSAL CINGULATE STUDY N=90

Randomized Sham Control Trial

Dose titrated based on immediate effects; Improvement expected only weeks later.

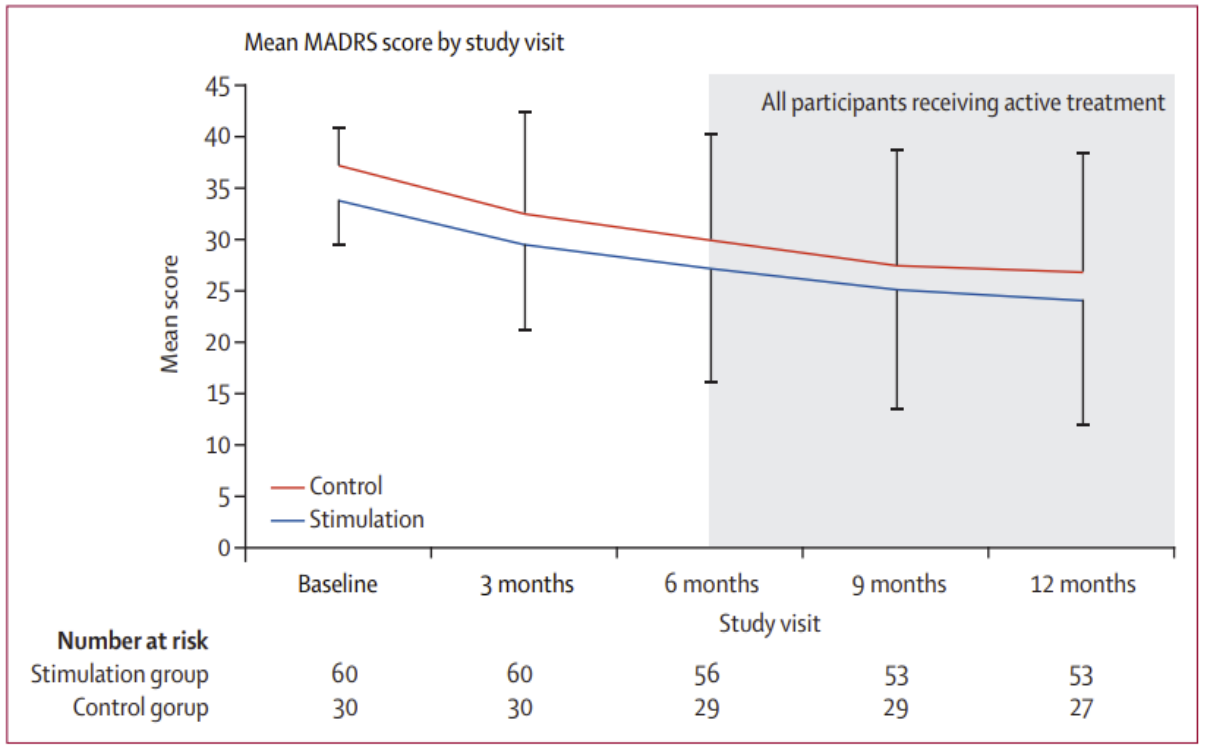


Figure 2: **Depression severity over time in each treatment group**
At months 9 and 12, the control group was receiving active stimulation; therefore, for the control group, 9 months refers to 3 months of active stimulation, and 12 months refers to 6 months of active stimulation. Error bars indicate standard deviations. MADRS=Montgomery-Åsberg Depression Rating Scale.

Holzheimer et al. Lancet Psych 2017

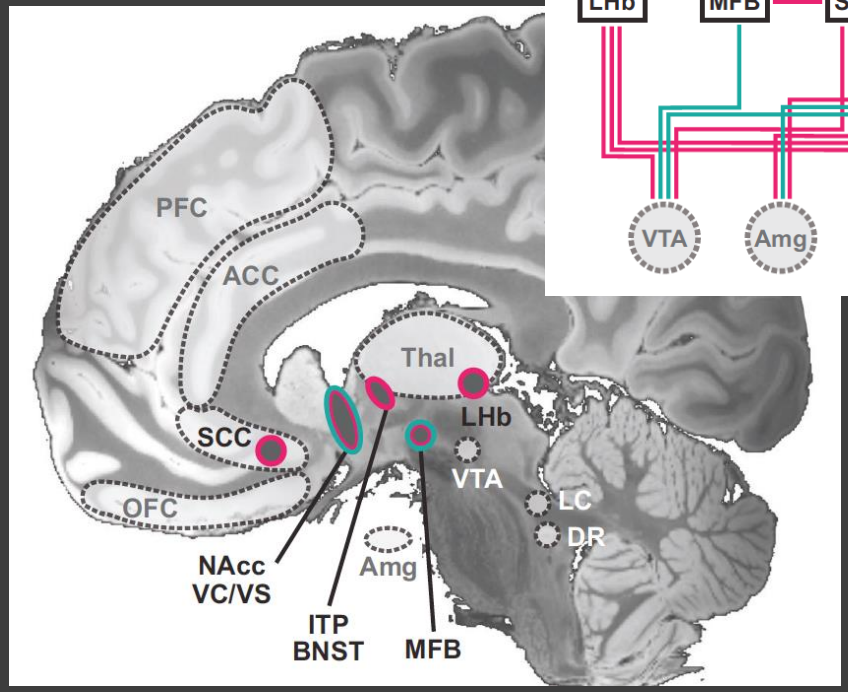
Subcallosal Cingulate

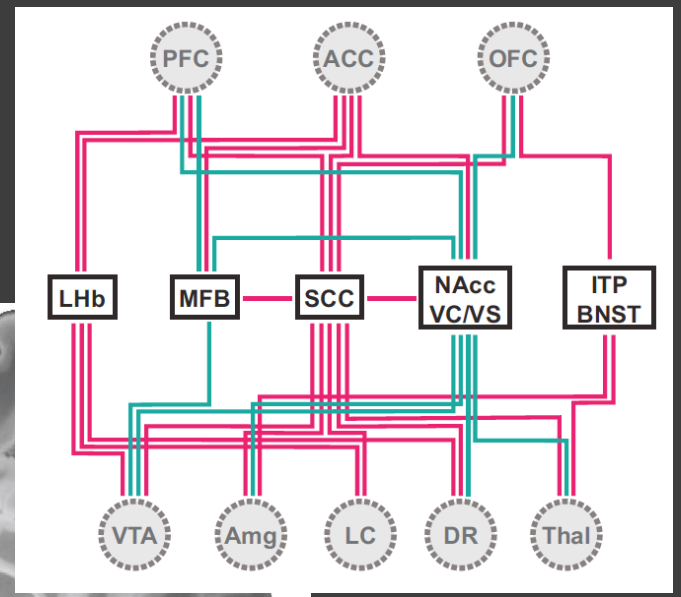
No statistically significant difference in response during the double-blind, sham-controlled phase (Active 20%; Sham 17%.

Study stopped at midway point due to positive futility analysis

DEEP BRAIN STIMULATION (DBS) FOR MDD

- Standard DBS is continuous 24/7 and in one brain location in each study
- Two largest RCTs failed to show benefit
- Evidence of some benefit if include results from multiple studies using multiple different DBS stimulus locations
- Personalization of location and dose needed
  - Not possible with standard DBS because, like nearly all antidepressant therapies, it takes months to work

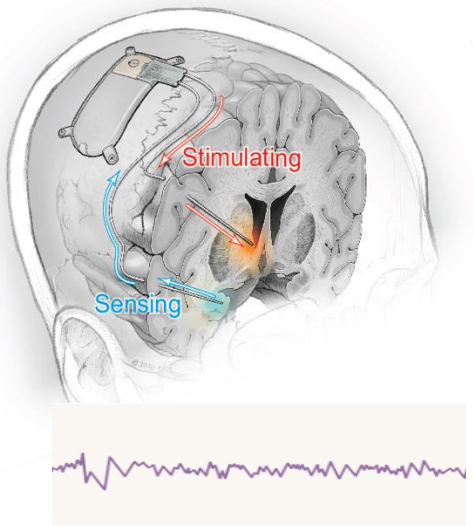




Johnson K, Okun M, Scangos K, et al (2024) Mol Psychiatry

UCSF PRESIDIO STUDY: SINGLE CENTER SAFETY AND FEASIBILITY TRIAL OF PERSONALIZED CLOSED-LOOP DBS FOR RESISTANT MDD

-Design driven by explicit hypotheses: 1) **it is possible to achieve immediate therapeutic effects from stimulation**; 2) **it is possible to stimulate only when needed** using a "closed-loop" approach with stim triggered by iEEG biomarker**.** Based on our DARPA Subnets (PI: E Chang) experience where: Immediate mood-improving effects of lateral OFC were observed, Increased lateral OFC theta activity was a biomarker for mood that decreased with lateral OFC stim



-Adopting these hypotheses enabled critical elements of the study design:

1) Placing 10 SEEG electrodes (16 contacts) for **personalized site/stimulus parameter optimization** via stimulus/response mapping in 10 day inpatient stay; Identification of **personalized biomarker of MDD severity** "normalized" by stim

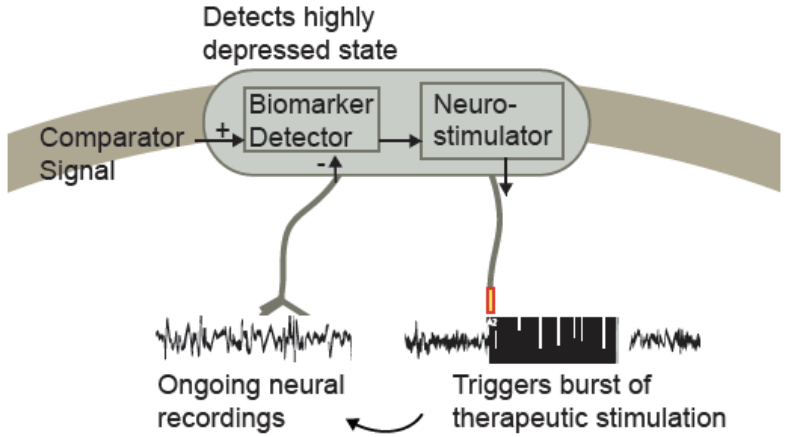
2) Placing Neuropace RNS device with leads in best stim and biomarker recording site and **implementing closed-loop treatment paradigm** where stim is only delivered when biomarker indicated elevated MDD severity

Rao et al., Curr Biol. 2018 Dec 17;28(24):3893-3902; Scangos et al. Nature Medicine 2021; 27(2):229-231. Nature Medicine 2021;27.(10):1696-1700.

PRESIDIO STUDY: SINGLE CENTER SAFETY AND FEASIBILITY TRIAL OF PERSONALIZED CLOSED-LOOP DBS FOR RESISTANT MDD

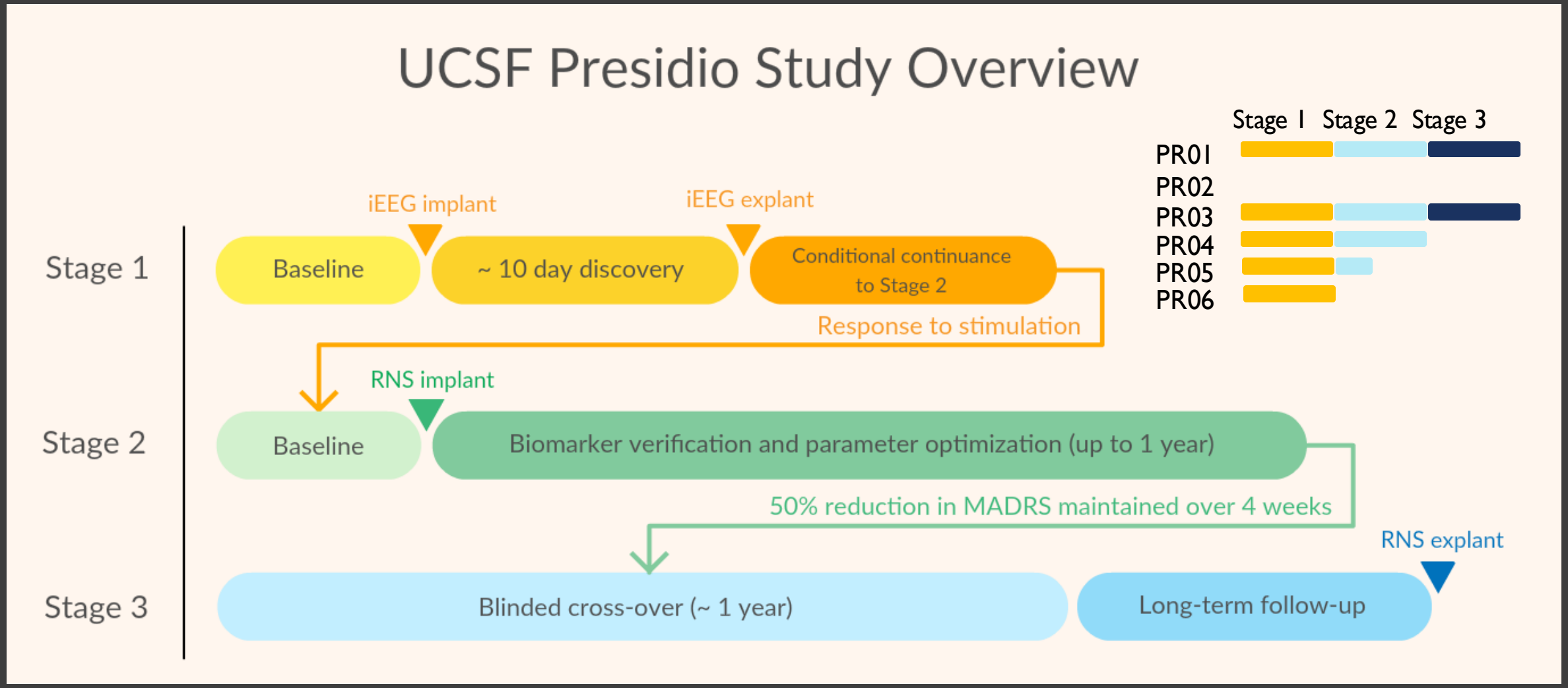
- Place 10 iEEG electrodes for personalized site/stimulus parameter optimization via stimulus/response mapping in 10 day inpatient stay
  - Intracranial EEG monitoring and mapping stage enables personalization
  - Common procedure in epilepsy
  - UCSF was the first to use for MDD
  - Enables discovery of personalized biomarker of MDD severity “normalized” by stim

- Place Neuropace RNS device with leads in best stimulation and biomarker recording sites and implement a closed-loop treatment paradigm where stim is only delivered when biomarker indicates elevated MDD severity

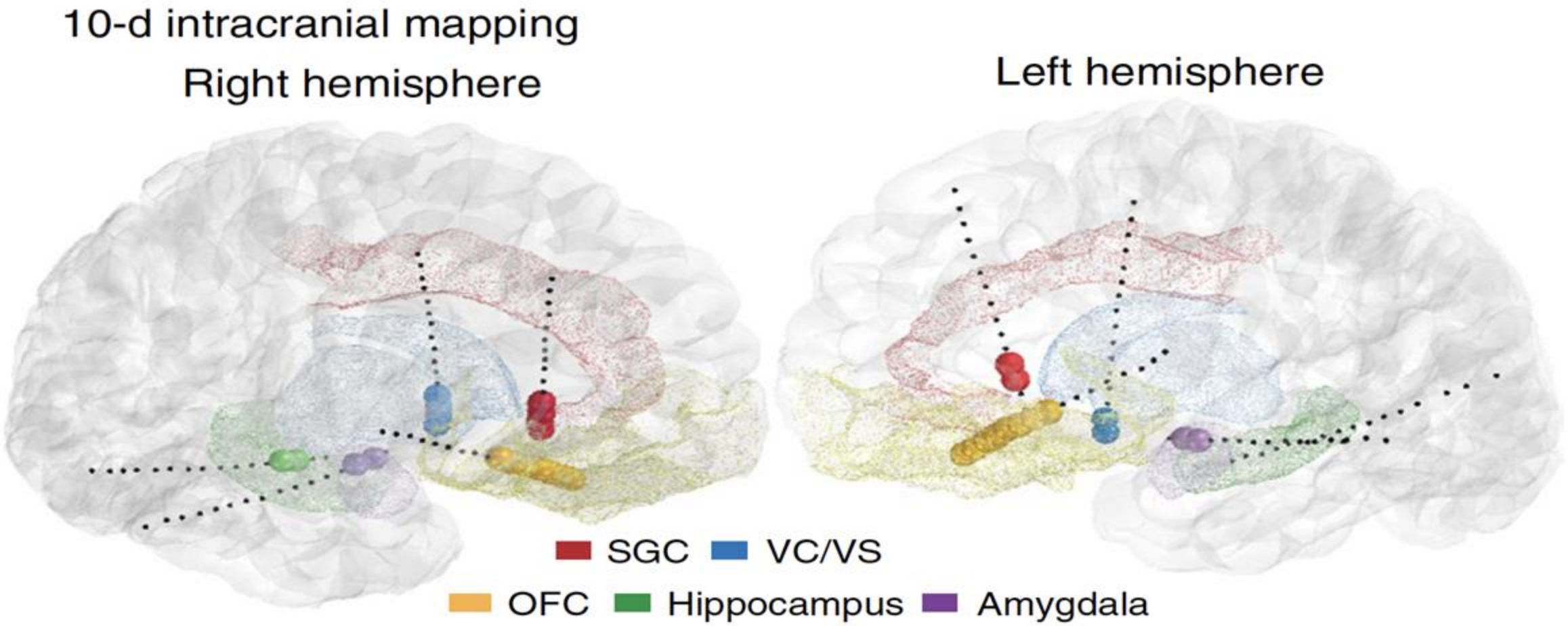


- Neural signals are continually assayed
- Sensed neural signal compared to reference signal
- If difference reaches threshold stimulation is triggered

CLINICAL TRIAL DESIGN



LOCATION OF INTRACRANIAL ELECTRODES



Scangos et al. *Nature medicine* 27.10 (2021): 1696-1700.

SUMMARY

- Study provides unprecedented evidence of the need for personalization
- Establishes that it is possible to find biomarkers of mood state
- Establishes that immediate antidepressant effects can be achieved with brain stimulation
- Preliminary evidence that cIDBS may be viable treatment option for the 2 million Americans who have failed all available treatments

The New York Times

A 'Pacemaker for the Brain': No Treatment Helped Her Depression — Until This

It's the first study of individualized brain stimulation to treat severe depression. Sarah's case raises the possibility the method may help people who don't respond to other therapies.

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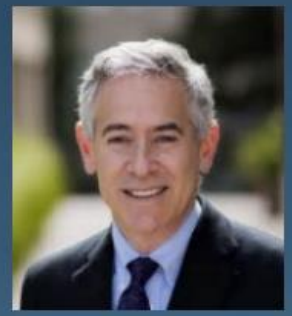



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