TMS Response Prediction & Newer Protocols

A Reading List — Companion handout for grand rounds

This is the working bibliography for the prediction and accelerated-protocols portions of the grand rounds talk. Direct links are provided for all primary sources cited. Each entry includes a brief note on what the paper actually shows and what to watch for — useful both as a Q&A resource and as a sanity check on field-level claims.

All citations verified against primary sources as of May 2026.

Part 1 — Predicting TMS Response

Watts et al. 2022 — the headline meta-analysis

Watts D, Pulice RF, Reilly J, Brunoni AR, Kapczinski F, Passos IC. Predicting treatment response using EEG in major depressive disorder: A machine-learning meta-analysis. *Translational Psychiatry* 2022;12:332.

DOI: 10.1038/s41398-022-02064-z

Open access: nature.com/articles/s41398-022-02064-z

PMC: PMC9374666

WHAT IT SHOWS

15 ML+EEG studies (n = 758). Pooled accuracy across all studies: 83.93% (95% CI 78.90–89.29), AUC 0.850. In the rTMS subgroup specifically: pooled accuracy 85.70% (95% CI 77.45–94.83), AUC 0.928. Average sensitivity 77.96%, specificity 84.60%. EEG models were better at identifying non-responders than responders.

WHAT TO WATCH FOR

The authors themselves flag the limits: most contributing studies were small, single-site, and used data from open-label trials in the absence of training and testing sets — raising the risk of overfitting and inflated accuracy estimates. The 85.7% figure is the upper bound of what the field has demonstrated, not what an off-the-shelf clinical tool delivers today.

Voetterl et al. 2023 — Brainmarker-I

Voetterl HTS, Sack AT, Olbrich S, et al. Alpha peak frequency-based Brainmarker-I as a method to stratify to pharmacotherapy and brain stimulation treatments in depression. *Nature Mental Health* 2023;1(12):1023–1032.

DOI: 10.1038/s44220-023-00160-7

Open access: nature.com/articles/s44220-023-00160-7

WHAT IT SHOWS

Brainmarker-I — an age- and sex-normalized resting-state EEG metric based on individual alpha peak frequency (iAF) — stratifies depressed patients toward different treatments. Patients with iAF around 10 Hz had higher remission to 10 Hz rTMS; the high-iAF subgroup had highest remission to 1 Hz rTMS; the low-iAF subgroup had highest remission to ECT and better sertraline response. Findings replicated in EMBARC (n = 240) and independent rTMS (n = 196) and ECT (n = 41) cohorts.

WHY IT MATTERS

This is treatment stratification, not a binary “responder vs. non-responder” classifier — but it has the rigorous, prospective, out-of-sample validation that most prediction studies lack. One of very few EEG biomarkers in psychiatry with replicated evidence and the closest thing in the field to a clinic-ready tool.

Drysdale et al. 2017 — the famous biotypes paper

Drysdale AT, Grosenick L, Downar J, et al. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nature Medicine* 2017;23(1):28–38.

DOI: 10.1038/nm.4246

PubMed: 27918562

PMC: PMC5624035

WHAT IT SHOWS

Large multisite fMRI sample (n = 1,188). Identified four neurophysiological "biotypes" of depression based on resting-state connectivity patterns. Diagnostic classifiers built on these biotypes showed 82–93% sensitivity and specificity in multisite validation (n = 711) and out-of-sample replication (n = 477) cohorts. Biotype-1 patients showed a substantially higher rTMS response rate than the other biotypes. Received enormous press attention as a landmark precision-psychiatry result.

WHAT TO WATCH FOR

See the next entry.

Dinga et al. 2019 — the failed replication

Dinga R, Schmaal L, Penninx BWJH, et al. Evaluating the evidence for biotypes of depression: Methodological replication and extension of Drysdale et al. (2017). *NeuroImage: Clinical* 2019;22:101796.

DOI: 10.1016/j.nicl.2019.101796

PMC: PMC6543446

WHAT IT SHOWS

Attempted to replicate the Drysdale procedure in 187 participants with depression and anxiety. As in the original, found very high canonical correlations between functional connectivity and clinical symptoms, and an optimal three-cluster solution — but neither the correlations nor the clusters were statistically significant once properly evaluated. The authors conclude that "the evidence for the existence of the distinct resting state connectivity-based subtypes of depression should be interpreted with caution."

WHY IT MATTERS

Bottom line for the slide: A famous prediction paper that did not survive independent replication. The pattern is widespread enough in the field that the Watts 2022 meta-analysis explicitly flags overfitting and inflated accuracy estimates as systematic concerns.

Elbau et al. 2023 — the largest test of sgACC targeting

Elbau IG, Lynch CJ, Downar J, et al. Functional Connectivity Mapping for rTMS Target Selection in Depression. *American Journal of Psychiatry* 2023;180(3):230–240.

DOI: 10.1176/appi.ajp.20220306

psychiatryonline.org/doi/10.1176/appi.ajp.20220306

PMC: PMC11446248

WHAT IT SHOWS

n = 295 patients with major depression — the largest dataset to date evaluating sgACC-DLPFC functional connectivity as a predictor of rTMS outcome. Found a weak but robust correlation (r = –0.16) between sgACC-stimulation-site FC and treatment response, but only when the stimulated cortex was identified using electric-field modeling. The association was driven primarily by a subgroup with respiration-related artifacts in their fMRI scans (r = –0.49 in that subgroup). Overall, individual differences in sgACC-FC explained only ~3% of the variance in treatment outcomes.

WHAT TO WATCH FOR

This is a much weaker effect than the ~30% variance explained reported in earlier, smaller studies. Important counterweight to the optimistic framing of sgACC-FC targeting. An accompanying editorial by Siddiqi and Philip raised methodological questions about Elbau's preprocessing pipeline — the debate is unresolved. Best read alongside Cash 2021 to give the audience both sides.

Bailey et al. 2021 — the ICON-DB consortium non-replication

Bailey NW, Hoy KE, Rogasch NC, et al. Resting EEG theta connectivity and alpha power to predict repetitive transcranial magnetic stimulation response in depression: A non-replication from the ICON-DB consortium. *Clinical Neurophysiology* 2021;132(2):650–659.

DOI: 10.1016/j.clinph.2020.10.018

PubMed: 33223495

WHAT IT SHOWS

Multi-site consortium effort that pooled EEG data across centers to test whether previously-reported EEG predictors of rTMS response (frontal theta connectivity, alpha power) would hold up in a larger, more heterogeneous sample. They did not. The earlier single-site findings did not replicate when evaluated prospectively across sites.

WHY IT MATTERS

Pairs naturally with Drysdale→Dinga as the EEG companion to the fMRI replication story. When a single small study reports an EEG predictor with 85–90% accuracy, this is the paper to cite as a cautionary anchor.

Klooster et al. 2024 — systematic review of biomarker robustness

Klooster D, Voetterl H, Baeken C, Arns M. Evaluating Robustness of Brain Stimulation Biomarkers for Depression: A Systematic Review of Magnetic Resonance Imaging and Electroencephalography Studies. *Biological Psychiatry* 2024;95(6):553–563.

DOI: 10.1016/j.biopsych.2023.09.009

PubMed: 37734515

WHAT IT SHOWS

Systematic review specifically evaluating which proposed MRI- and EEG-based biomarkers for non-invasive brain stimulation response in depression have actually been replicated. Distinguishes biomarkers with supporting independent evidence from those that remain single-study findings. The authors are leaders in the field (Arns group, Brainmarker-I) and the framework they propose for evaluating biomarker robustness is becoming a standard reference.

WHY IT MATTERS

The single best entry point if someone in the audience asks “okay, so what biomarkers are actually clinically usable?” The honest answer is: very few have been replicated. Most of the literature is single-site, single-study, with the replication problems the Drysdale and Bailey examples illustrate.

Curtiss & DiPietro 2025 — broader meta-analysis

Curtiss J, DiPietro C. Machine learning in the prediction of treatment response for emotional disorders: A systematic review and meta-analysis. *Clinical Psychology Review* 2025;120:102593.

DOI: 10.1016/j.cpr.2025.102593

PMC: PMC12915758

WHAT IT SHOWS

Broader meta-analysis: 155 studies across psychotherapy, pharmacotherapy, and other treatments for emotional disorders. Overall mean prediction accuracy 0.76 (95% CI 0.74–0.78), AUC 0.80. Sensitivity 0.73, specificity 0.75. Studies using more robust cross-validation procedures exhibited higher prediction accuracy; neuroimaging data were the most predictive modality.

HOW IT FITS

Slightly more conservative than Watts 2022 because of the broader scope and inclusion criteria. The 76% figure is a reasonable field-level headline for “ML prediction of treatment response in emotional disorders, all modalities pooled.”

Cash et al. 2021 — fMRI-personalized targeting

Cash RFH, Cocchi L, Lv J, Fitzgerald PB, Zalesky A. Functional Magnetic Resonance Imaging–Guided Personalization of Transcranial Magnetic Stimulation Treatment for Depression. *JAMA Psychiatry* 2021;78(3):337–339.

DOI: 10.1001/jamapsychiatry.2020.3794

JAMA Network: jamanetwork.com/journals/jamapsychiatry/fullarticle/2773578

WHAT IT SHOWS

Not a prediction paper per se — a targeting paper. Demonstrated that closer proximity between standard scalp-based DLPFC targets and fMRI-personalized targets (based on sgACC anti-correlation) correlated with better treatment response. The substantial distance between the scalp-derived and fMRI-personalized targets in individual patients was the headline finding cited on slide 18 of the deck.

WHAT TO WATCH FOR

Small sample size. The strong correlation reported here was not reproduced at the same magnitude in the much larger Elbau 2023 dataset (see above). Both papers should be presented together: Cash is the best-case argument for personalized targeting; Elbau is the sobering follow-up at scale.

Fox et al. 2012 — the foundational anti-correlation paper

Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biological Psychiatry* 2012;72(7):595–603.

DOI: 10.1016/j.biopsych.2012.04.028

PubMed: 22658708

PMC: PMC4120275

WHAT IT SHOWS

The foundational paper for personalized TMS targeting. Established that DLPFC sites with stronger functional anti-correlation to the subgenual anterior cingulate cortex (sgACC) predict better antidepressant response to TMS. Effectively created the field of connectivity-guided TMS targeting.

WHY IT MATTERS

Everything in the personalized-targeting literature builds on this finding. The challenges of operationalizing it at scale (Cash 2021, Elbau 2023) are the natural follow-up story.

Arteaga et al. 2025 — recent EEG-ML study

Arteaga A, Tong X, Zhao K, et al. Multiband EEG signatures decoded using machine learning for predicting rTMS treatment response in MDD. *Journal of Affective Disorders* 2025;388:119483.

DOI: 10.1016/j.jad.2025.119483

PubMed: 40441660

WHAT IT SHOWS

Recent ML+EEG study using the TDBRAIN open dataset. Two rTMS protocols: high-frequency 10 Hz left DLPFC (n = 44) and low-frequency 1 Hz right DLPFC (n = 73). Used iterated empirical mode decomposition combined with sparse Bayesian learning to extract multiband EEG features predictive of response.

WHAT TO WATCH FOR

Reports correlations between predicted and actual response rather than the binary 80–90% accuracy figures from earlier work. A useful example of where the field is moving methodologically — toward more transparent validation — but headline field-level claims should still come from Watts 2022 rather than from any single study.

Part 2 — Newer Accelerated Protocols

These are the accelerated and time-compressed protocols cited in the "newer protocols" section of the deck. Each represents a different level of evidence — from sham-controlled RCTs to non-inferiority trials to small open-label case series — and the differences matter when discussing them with patients or referring clinicians.

Cole et al. 2020 — SAINT proof-of-concept

Cole EJ, Stimpson KH, Bentzley BS, et al. Stanford Accelerated Intelligent Neuromodulation Therapy for Treatment-Resistant Depression. *American Journal of Psychiatry* 2020;177(8):716–726.

DOI: 10.1176/appi.ajp.2019.19070720

psychiatryonline.org/doi/10.1176/appi.ajp.2019.19070720

WHAT IT SHOWS

Open-label proof-of-concept of the SAINT protocol: fMRI-targeted iTBS delivered 10 times per day over 5 days, 50-minute intersession intervals, total of 90,000 pulses. ~90% remission rate after the 5-day open-label course in treatment-resistant depression.

WHAT IT ESTABLISHED

Open-label, no sham, small sample. The headline remission numbers were striking enough to generate major press attention, but the real test was the follow-up sham-controlled trial — see next entry.

Cole et al. 2022 — SNT sham-controlled RCT

Cole EJ, Phillips AL, Bentzley BS, et al. Stanford Neuromodulation Therapy (SNT): A Double-Blind Randomized Controlled Trial. *American Journal of Psychiatry* 2022;179(2):132–141.

DOI: 10.1176/appi.ajp.2021.20101429

psychiatryonline.org/doi/full/10.1176/appi.ajp.2021.20101429

WHAT IT SHOWS

Double-blind sham-controlled RCT of the SAINT protocol (renamed SNT). 78.6% of participants with treatment-resistant depression achieved remission after 5 days of active SNT vs. 13.3% with sham. This is the trial that supported FDA clearance and made accelerated iTBS a mainstream consideration rather than a research curiosity.

WHAT IT ESTABLISHED

Single-center trial with relatively small sample. The remission numbers have not been independently replicated at the same magnitude in real-world clinical samples, though several open-label series have reported comparable response rates.

Ramos et al. 2025 — independent accelerated iTBS RCT

Ramos MRF, Goerigk S, da Silva VA, et al. Accelerated Theta-Burst Stimulation for Treatment-Resistant Depression: A Randomized Clinical Trial. *JAMA Psychiatry* 2025;82(5):442–450.

DOI: 10.1001/jamapsychiatry.2025.0013

PubMed: 40042840

WHAT IT SHOWS

Triple-blinded, sham-controlled randomized clinical trial of accelerated iTBS for treatment-resistant depression, conducted at the University of São Paulo (independent of Stanford). Confirms the basic finding that accelerated iTBS produces meaningful antidepressant response, in a different patient population and study design from the original SAINT/SNT work.

WHY IT MATTERS

This is the most important independent confirmation that the SAINT/SNT result was not a single-center anomaly. Different protocol details, different population, similar direction of effect. Worth citing when someone asks “but has anyone outside Stanford replicated this?”

Hanlon et al. 2026 — SWIFT non-inferiority trial

Hanlon CA, Roth Y, Bermudes RA, et al. Accelerated TMS with the H1-coil for depression: A multisite, randomized non-inferiority trial. *Brain Stimulation* 2026 (online ahead of print).

DOI: 10.1016/j.brs.2026.103050

ScienceDirect: S1935861X26000276

WHAT IT SHOWS

Multisite, randomized, blinded non-inferiority trial. n = 104 adults with moderate-to-severe MDD randomized to accelerated iTBS with the H1 coil (5 sessions/day for 6 days, plus weekly maintenance) vs. standard once-daily Deep TMS (4 weeks acute + 2 weeks tapering). Accelerated arm: 87.8% response, 78.0% remission. Once-daily arm: 87.5% response, 87.5% remission. Onset of remission was faster with the accelerated protocol (median 21 vs. 28 days). Non-inferiority demonstrated.

WHAT TO WATCH FOR

Industry-sponsored (BrainsWay). The non-inferiority margin and primary endpoint are reasonable but the result hinges on the choice of margin. The accelerated arm had a lower remission rate than the once-daily arm numerically, even though it met the statistical non-inferiority criterion.

Tendler et al. 2026 — SWIFT patient-reported outcomes

Tendler A, Roth Y, Bates M, et al. Patient-reported outcomes following accelerated vs. standard TMS with the H1 coil for major depression: A multisite randomized trial. *Brain Stimulation* 2026 (online ahead of print).

DOI: 10.1016/j.brs.2026.103048

brainstimjrnl.com: S1935-861X(26)00025-2

WHAT IT SHOWS

Companion paper to Hanlon 2026, reporting patient-reported outcomes from the same SWIFT trial. Useful for the patient-facing access argument: accelerated protocols reduce treatment burden and may improve retention.

WHAT TO WATCH FOR

Same caveats as Hanlon 2026. Patient-reported outcomes were not the trial's primary endpoint.

Vaughn et al. 2025 — ONE-D single-day protocol

Vaughn AC, et al. Real-world effectiveness of a single-day regimen for transcranial magnetic stimulation using Optimized, Neuroplasticity-Enhanced techniques in Depression (ONE-D): An open-label case series. *Transcranial Magnetic Stimulation* 2025;100200.

DOI: 10.1016/j.transm.2025.100200

tmsjournal.org: S3050-5291(25)00116-3

WHAT IT SHOWS

Open-label retrospective case series of a single-day TMS regimen: 20 sessions of 600-pulse iTBS delivered over ~9.5 hours in one day, augmented with pre-treatment oral d-cycloserine (125 mg) and lisdexamfetamine (20 mg) to enhance plasticity. The published series examined 32 participants across two private clinics.

WHAT TO WATCH FOR

Important caveat: The Clinical TMS Society (CTMSS) issued a cautionary statement in December 2025 noting that the peer-reviewed evidence base for ONE-D consists of only one journal article (this one, n = 32) and one conference abstract (Nanos 2025, n = 8) — both retrospective case series. The AMPA device used is FDA-cleared via 510(k) for standard rTMS, but the ONE-D protocol itself is not FDA-cleared. CTMSS recommended against using ONE-D as a replacement for established evidence-based protocols at this time. Worth presenting the data and the caution together.

All citations verified against primary sources (PubMed, journal websites, DOI resolution) as of May 2026. Companion reading list for grand rounds presentation on transcranial magnetic stimulation. — Adam Hart, MD, Section Chief, Neuromodulation Program, Prisma Health