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State of the Science on Biomarkers: Major Depression

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CDRC
CENTER FOR DEPRESSION RESEARCH & CLINICAL CARE
Better Research. Better Care. Better Outcomes.

Objectives

- Review state of research on biomarkers for diagnosis and severity for depression.

- Review recent findings on the use of biomarkers to guide treatment selection.

Depression Is A Chronic Mental Illness

MDD and other chronic diseases have similar

- Functional outcomes
- Rates of treatment adherence
- Rates of healthcare service utilization

Effective treatment of depressive disorders is chronic disease management.

- Long-term follow-up with treatment guided by measurement based protocols

Biomarkers for Diagnosis and Severity

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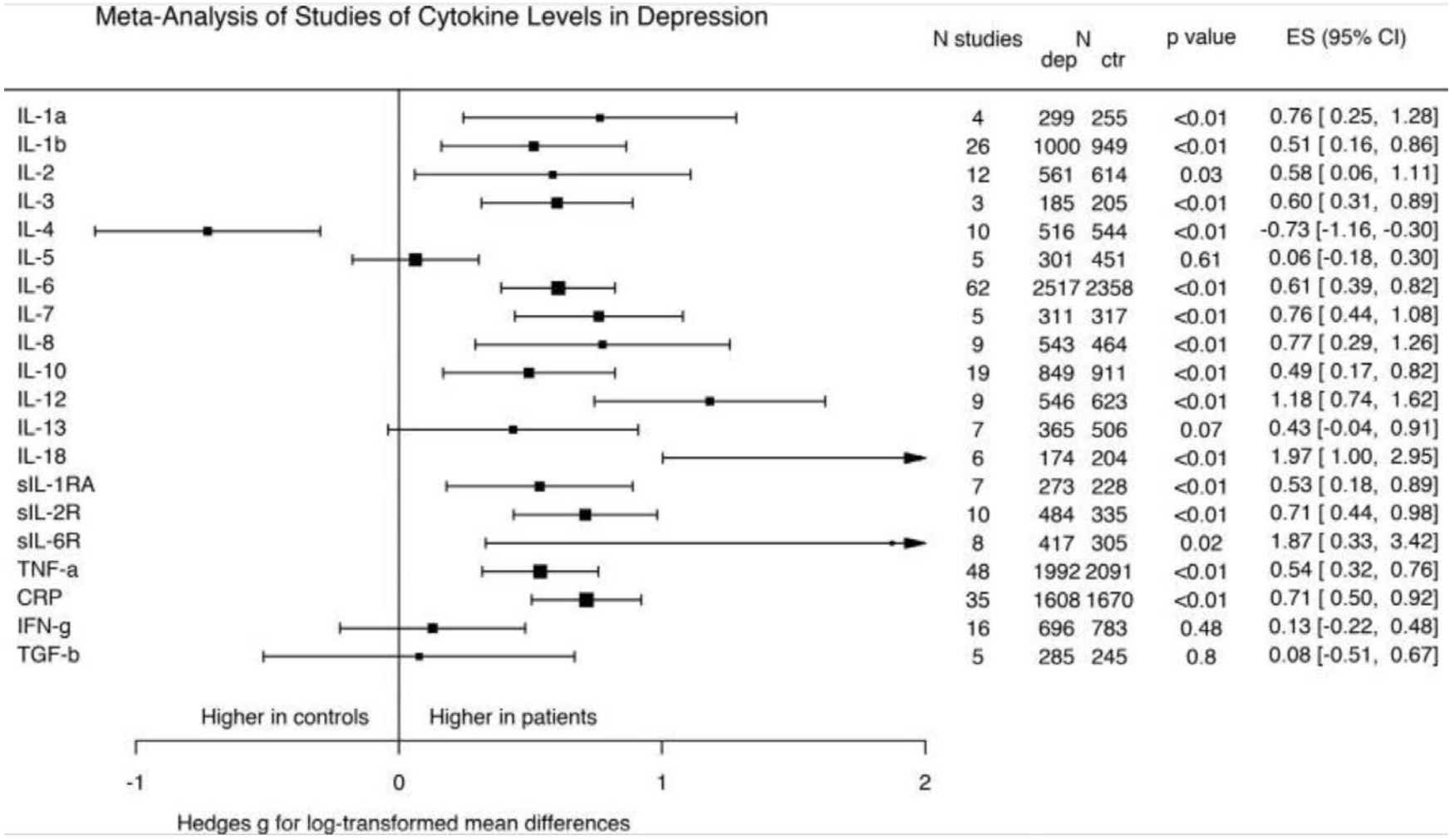
Most Promising Biomarkers in Depression

- Inflammatory Markers
  - CRP, IL1-beta, gene expression
- Neuroimaging (fMRI, EEG)
  - Reward Circuit Deficits Task -- Probabilistic Reward Task
  - Emotion Processing and Regulation Circuit
    - Emotional Conflict Regulation
- Metabolic Markers
- Gut Microbiome

Meta-Analysis of Inflammatory Markers



Osimo et al., 2020

Inflammatory Markers - Severity

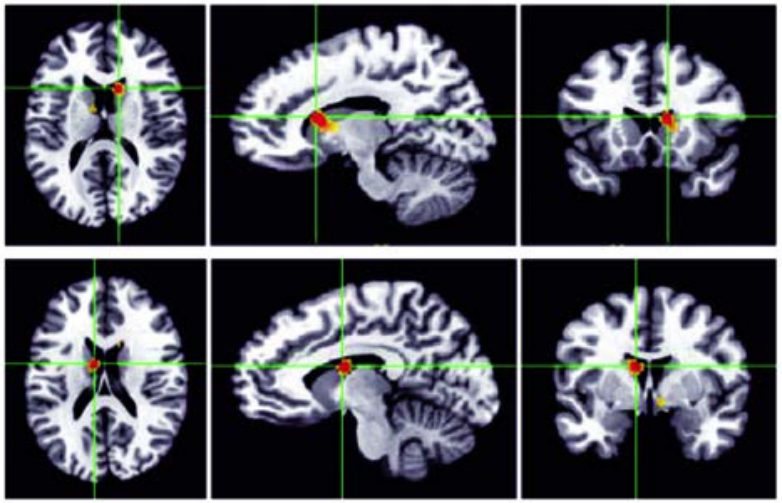
Inflammatory markers	Suicidal versus non-suicidal depressed patients		Suicidal depressed patients versus controls		Postmortem suicidal patients vs. controls
	In vivo	In vitro	In vivo	In vitro	
IL-4	No significant differences	Decreased	No significant differences	Decreased	Increased
IL-1β	–	–	No significant differences	–	Increased
IL-6	Increased	Decreased	No significant differences	Increased	Increased
	No significant differences		Increased		
TNF-α	Increased	–	Increased	–	Increased
	Decreased		No significant differences		No significant differences
			No significant differences		
CRP	Increased	–	No significant differences	–	–

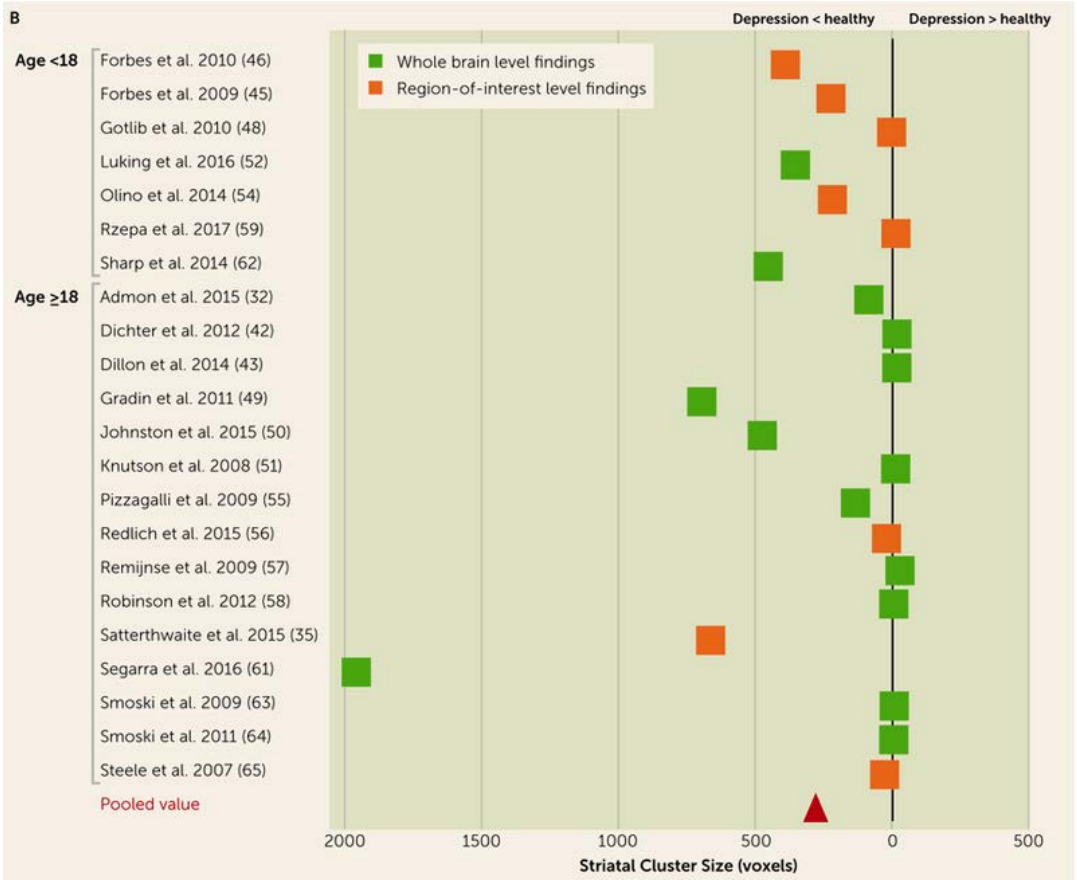
* Sample of inflammatory markers reviewed

Adapted from Marini et al., 2016

fMRI – Reward Processing

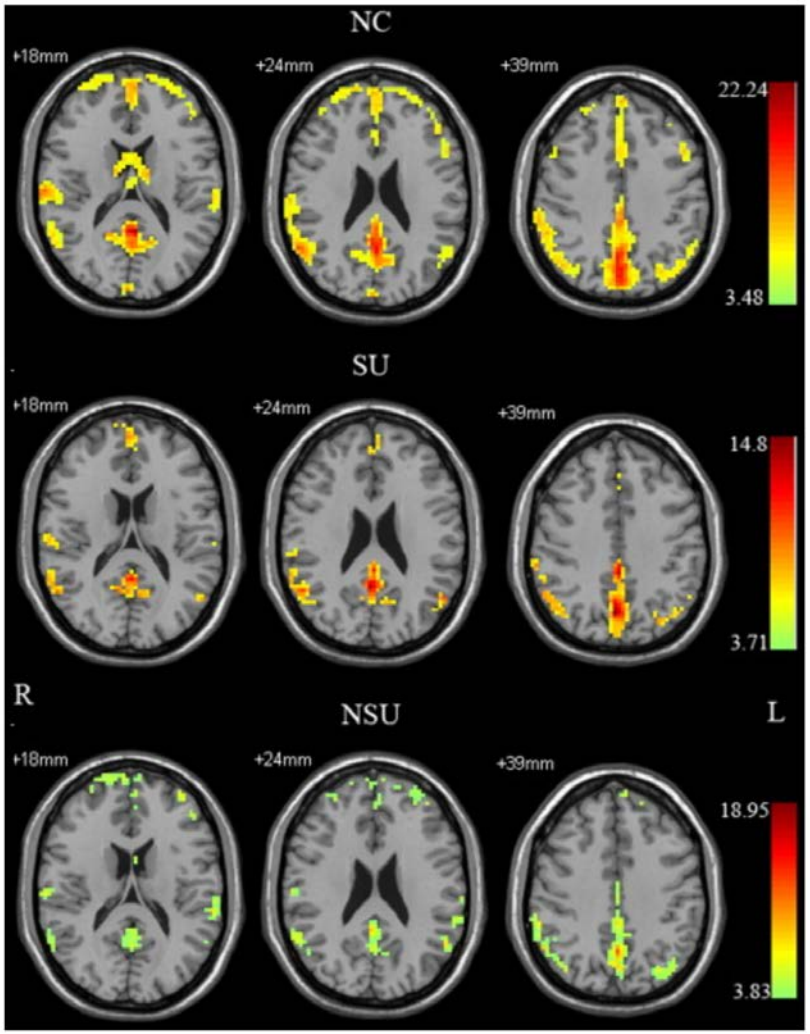
Depressed Versus Healthy Controls





Keren et al., 2018

Neuroimaging - Severity



Normal Controls
N=57

Suicide Attempters
N=27

Non-Suicidal MDD
N=10

Amplitude of Low-Frequency Fluctuation (ALFF)

- Suicide attempters (SU) had increased ALFF in the r-STG compared to non-suicidal MDD patients (NSU) and normal controls (NC).
- Non-suicidal patients had increased ALFF in the r-vMRFG compared to suicide attempters and normal controls.
- Suicide attempters and non-suicidal patients had increased ALFF in the l-ACC and r-PG, and decreased ALFF in the l-MOG and l-AG compared to normal controls.

Fan et al., 2013

Biomarkers for Treatment Selection

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Psychoneuroendocrinology. Author manuscript; available in PMC 2018 Aug 7.

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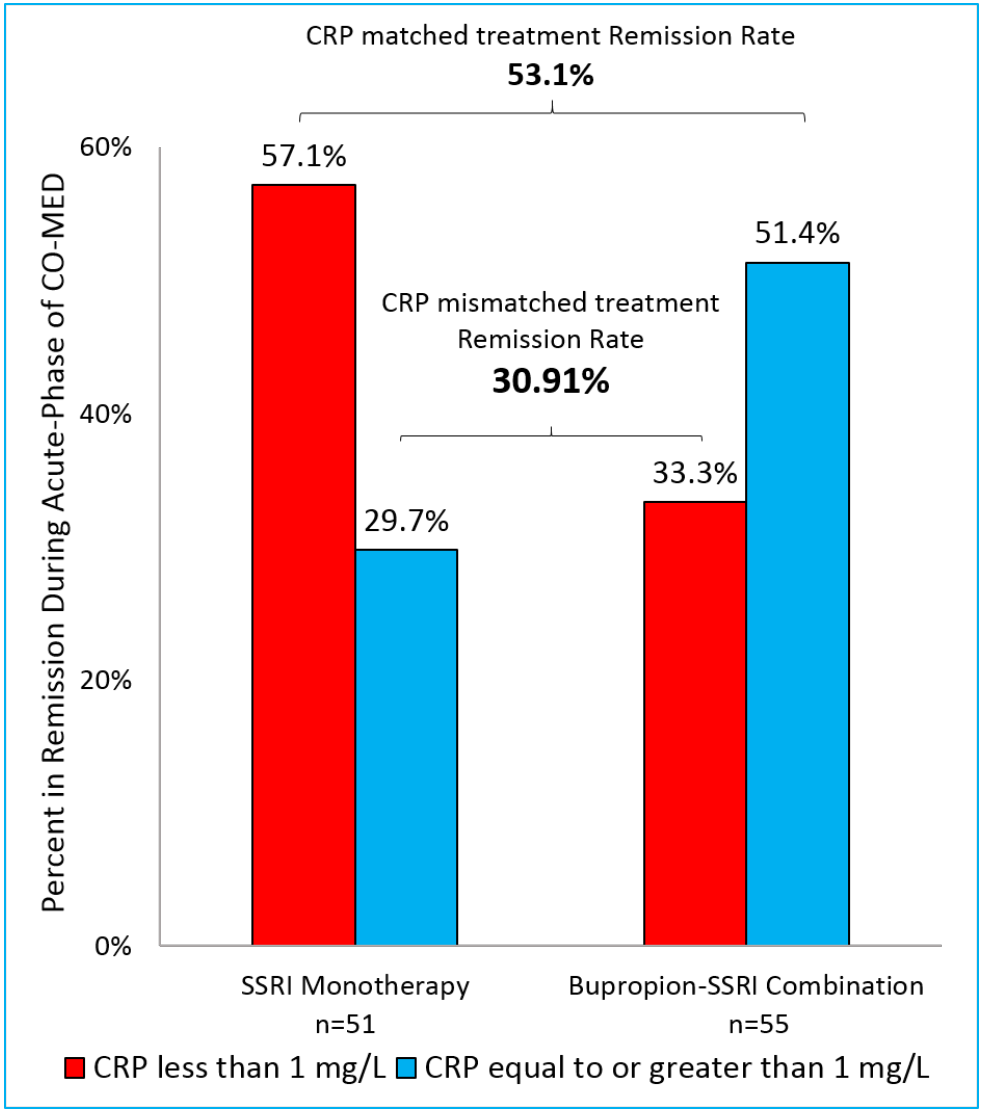
Psychoneuroendocrinology. 2017 Apr; 78: 105–113.

Published online 2017 Jan 24. doi: 10.1016/j.psyneuen.2017.01.023

Can C-Reactive Protein Inform Antidepressant Medication Selection in Depressed Outpatients? Findings from the CO-MED Trial

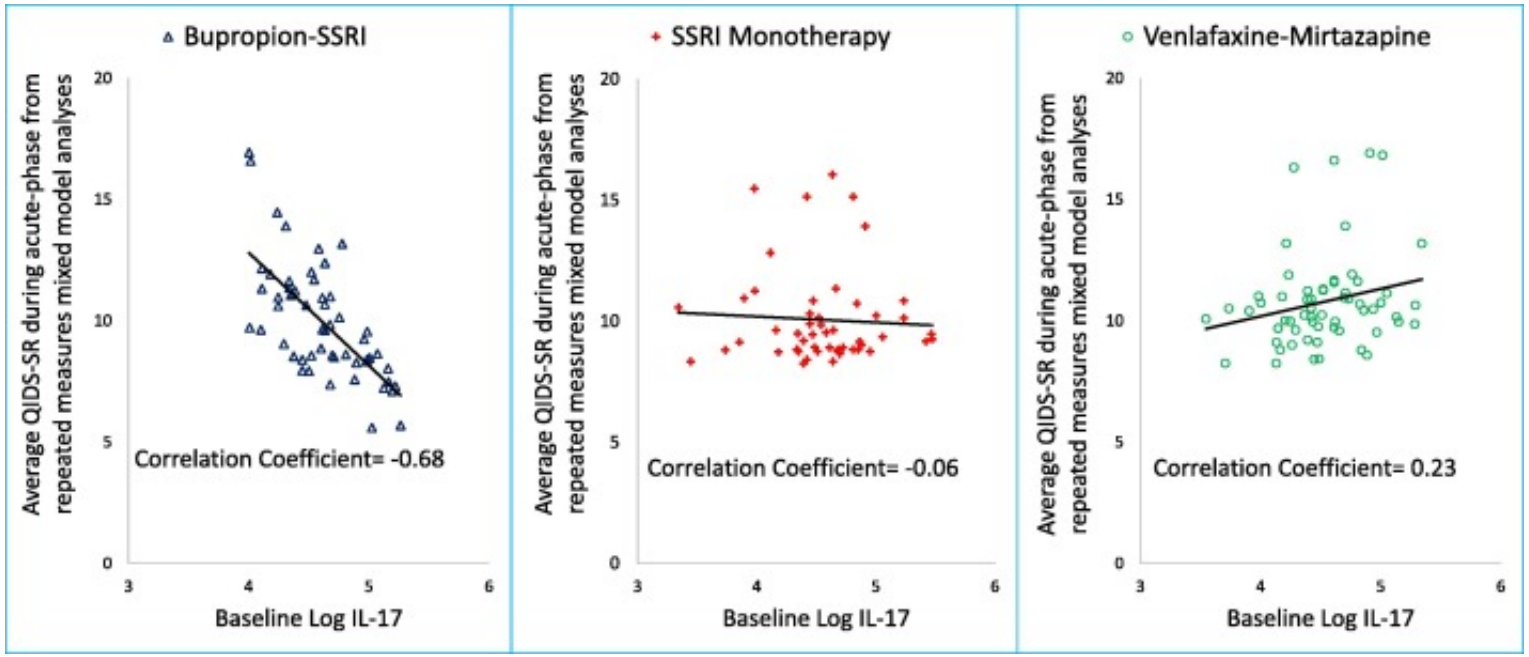
Manish K. Jha, M.B.B.S.,[1] Abu Minhajuddin, Ph.D.,[2] Bharathi Gadad, Ph.D.,[1] Tracy Greer, Ph.D.,[1] Bruce Grannemann, M.A.,[1] Abigail Soyombo, Ph.D.,[1] Taryn L. Mayes, M.A.,[1] A. John Rush, M.D.,[3] and Madhukar H. Trivedi, M.D.[1]

Baseline CRP levels relate differentially to antidepressant treatment outcomes in persons with major depressive disorder.



Jha et al. Psychoneuroendocrinology. 2017 Apr;78:105-113.

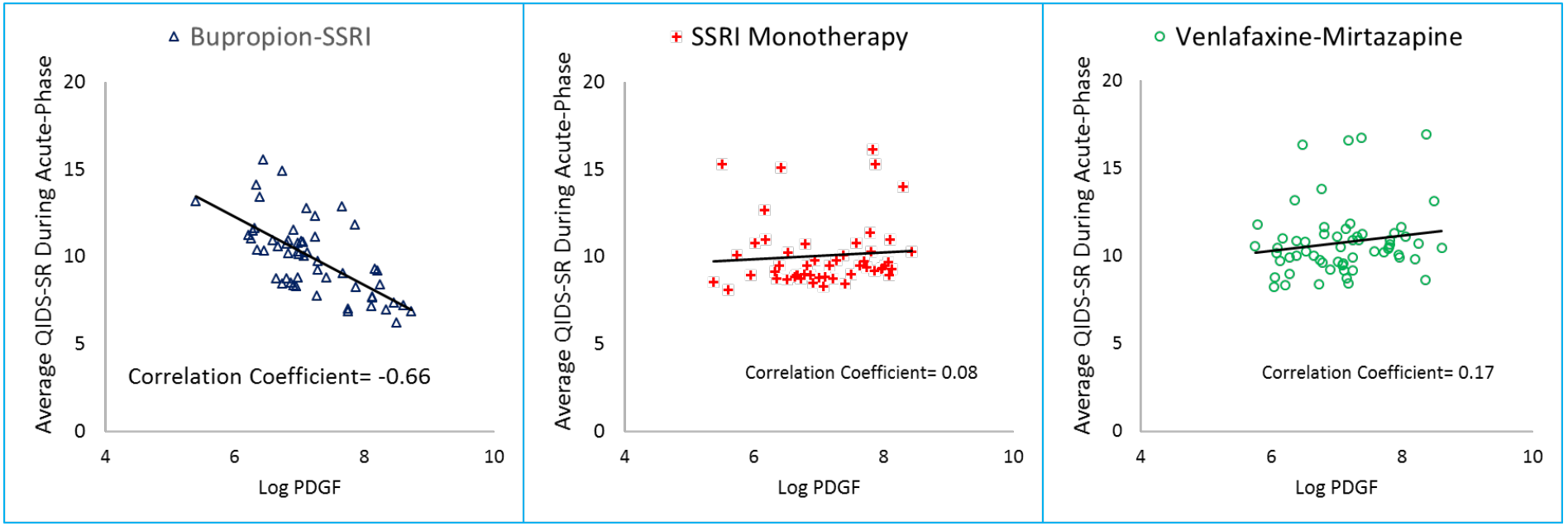
Bupropion-SSRI combination prediction



(Jha et al., 2017, Brain, Behavior, and Immunity)

https://www.sciencedirect.com/science/article/pii/S088915911730212X?via%3Dihub

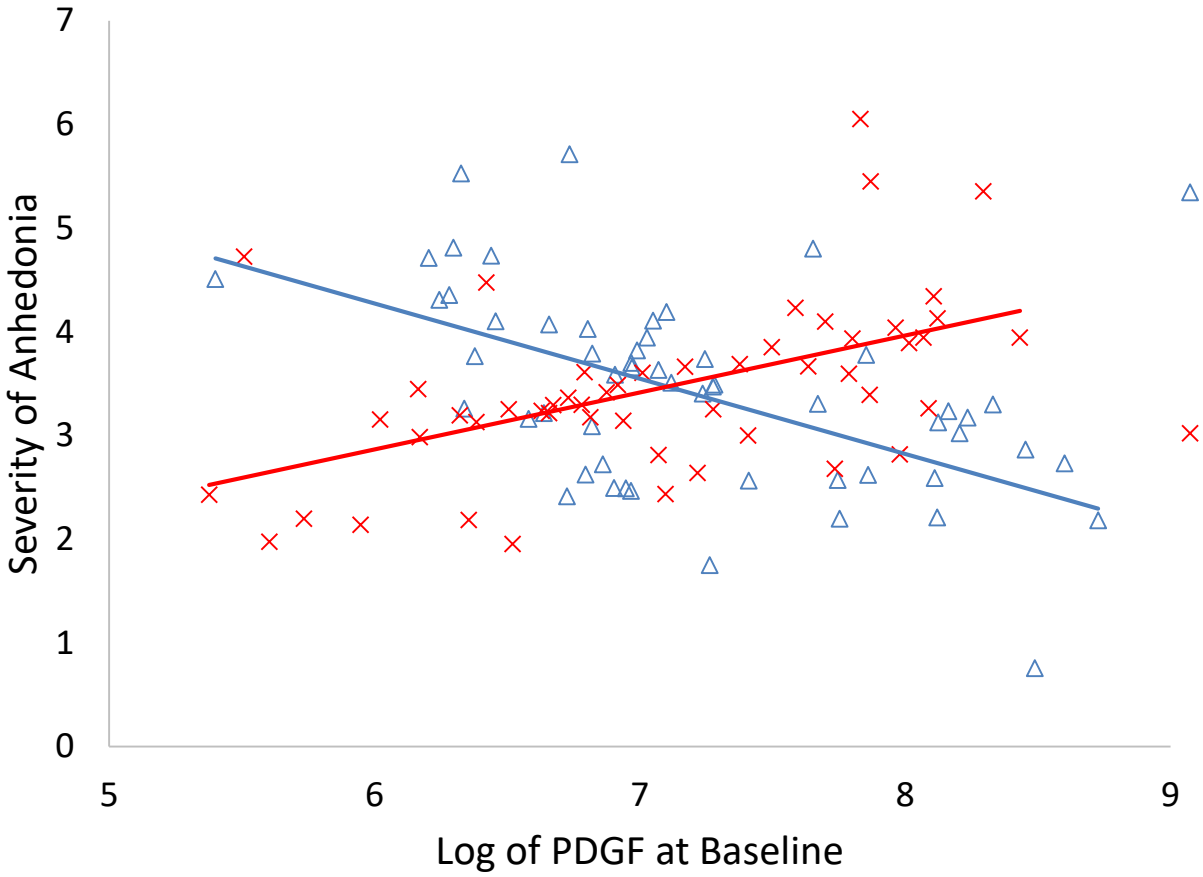
Association of Baseline PDGF and Changes in Depression Severity During Acute-Phase of CO-MED Trial



Depression severity averaged over all visits (baseline and weeks 1-12) plotted against log of PDGF level at baseline.

Jha et al. Psychoneuroendocrinology. 2017 Apr;78:105-113.

Association of Baseline PDGF and Changes in Anhedonia During Acute-Phase of CO-MED Trial



△ Bupropion-SSRI Correlation Coefficient= -0.57

× SSRI Monotherapy Correlation Coefficient = 0.52

Anhedonia severity (obtained from IDS-C averaged over all visits (baseline and weeks 1-12) plotted against log of PDGF level at baseline.

Jha et al. Psychoneuroendocrinology. 2017 Apr;78:105-113.

TrEAD

Exercise as an Augmentation Treatment for Nonremitted Major Depressive Disorder: A Randomized, Parallel Dose Comparison

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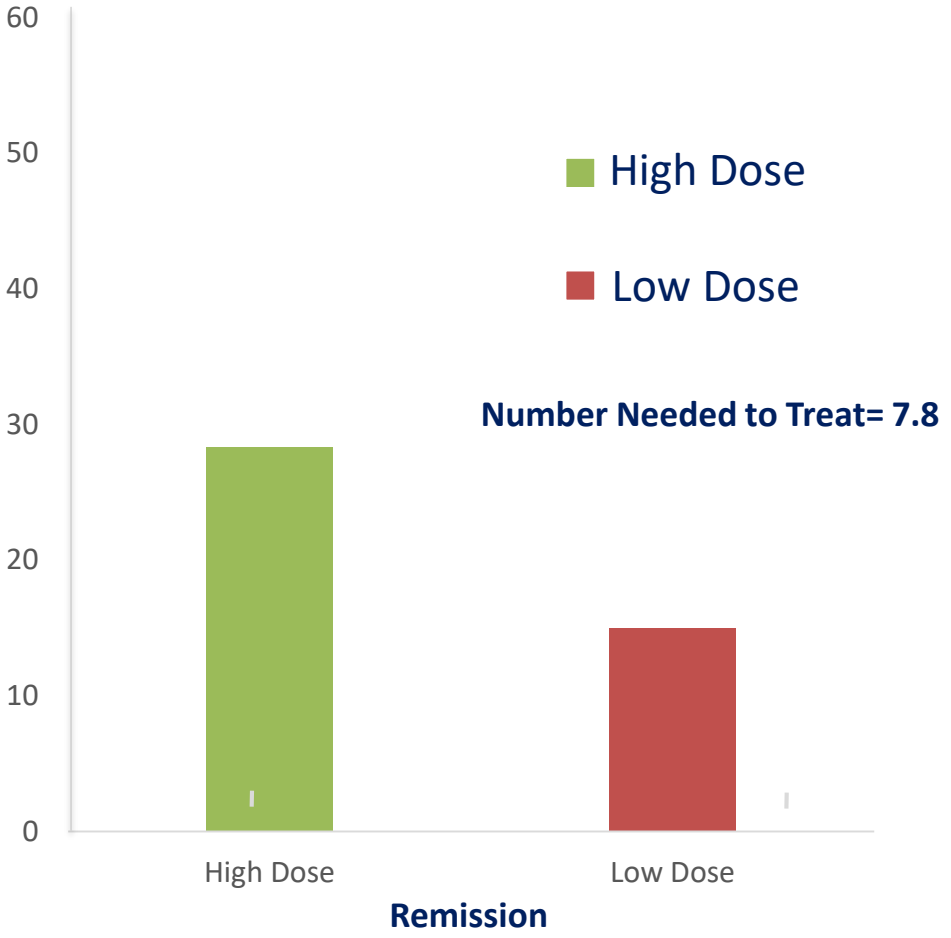
Objective: Most patients with major depressive disorder (MDD) require second-step treatments to achieve remission. The TReatment with Exercise Augmentation for Depression (TREAD) study was designed to test the efficacy of aerobic exercise as an augmentation treatment for MDD patients who had not remitted with antidepressant treatment.

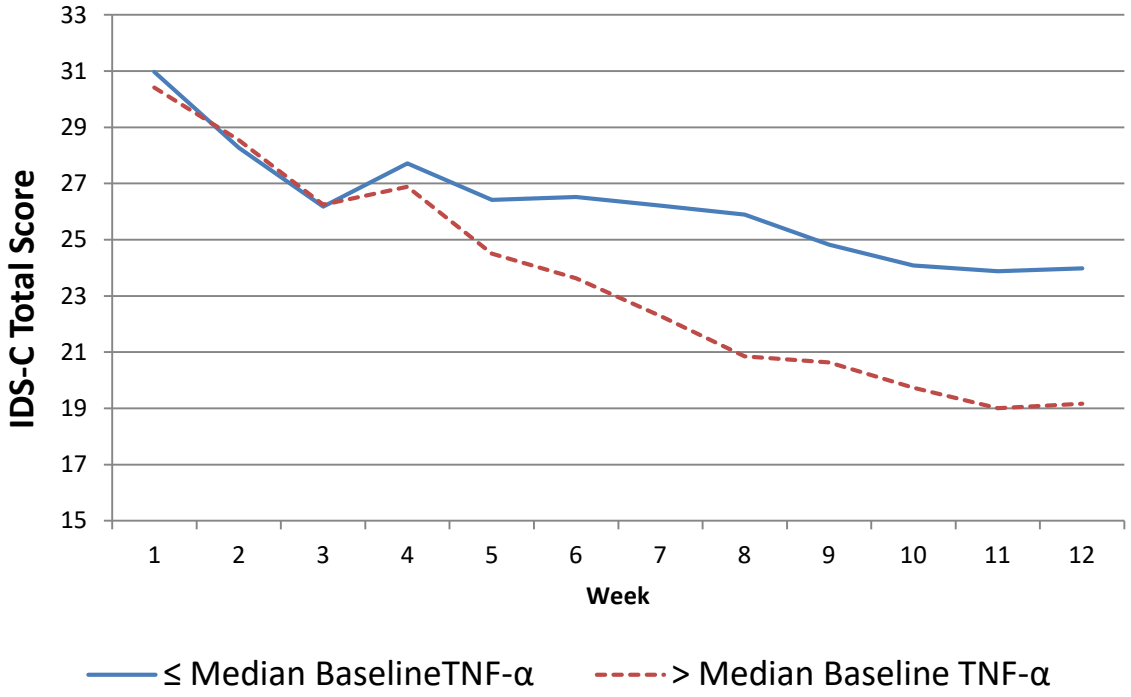
Method: Eligible participants in this randomized controlled trial were sedentary individuals (men and women aged 18–70 years) diagnosed with *DSM-IV* nonpsychotic MDD who had not remitted with selective serotonin reuptake inhibitor (SSRI) treatment. Participants were recruited through physician referrals and advertisements. A total of 126 participants were randomized to augmentation treatment with either 16 kcal per kg per week (KKW) or 4 KKW of exercise expenditure for 12 weeks while SSRI treatment was held constant. Supervised sessions were conducted at The Cooper Institute, Dallas, Texas, with additional home-based sessions as needed to fulfill the weekly exercise prescription. The primary outcome was remission (as determined by a score ≤ 12 on the Inventory of Depressive Symptomatology, Clinician-Rated). The study took place between August 2003 and August 2007.

Results: There were significant improvements over time for both groups combined ($F_{1,121}$ = 39.9, P < .0001), without differential group effect (group effect: $F_{1,134}$ = 3.2, P = .07; group-by-time effect: $F_{1,119}$ = 3.8, P = .06). Adjusted remission rates at week 12 were 28.3% versus 15.5% for the 16-KKW and 4-KKW groups, respectively, leading to a number needed to treat (NNT) of 7.8 for 16 KKW versus 4 KKW. Men, regardless of family history of mental illness, and women without a family history of mental illness had higher remission rates by week 12 with higher-dose (women, 39.0%; men, 85.4%) than with lower-dose exercise (women, 5.6%; men, 0.1%) (women: t_{95} = 2.1, P = .04; men: t_{88} = 5.4, P < .0001) (NNT: women, 3.0; men, 1.2).



Trivedi et al J Clin Psychiatry. 2011 May;72(5):677-84.

Moderator of Treatment Outcome
TNF-α and Exercise as Second Step



Plot of adjusted Least Squares Means for IDS-C Total by Week for those above (>) and below (≤) the median baseline TNF-α value of 5.493 pg/mL

Rethorst et al Molecular Psychiatry (2012), 1–6

Problems with Other Past Approaches

- Post-hoc studies
- Single treatment
- Not used to identify differential outcomes across treatments
- Few agreed upon clinical or biological markers

Pretreatment rACC Theta Activity

Article

Pretreatment Rostral Anterior Cingulate Cortex Theta Activity in Relation to Symptom Improvement in Depression A Randomized Clinical Trial

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Christian A. Webb
Daniel G. Dillon
Craig E. Tenke
Jürgen Kayser
Franziska Goer
Maurizio Fava
Patrick McGrath
Myrna Weissman
Ramin Parsey
Phil Adams
Joseph Trombello
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Patricia Deldin
Maria A. Oquendo
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Thomas Carmody
Gerard Bruder
Madhukar H. Trivedi

Abstract:

IMPORTANCE: Major depressive disorder (MDD) remains challenging to treat. Although several clinical and demographic variables have been found to predict poor antidepressant response, these markers have not been robustly replicated to warrant implementation in clinical care. Increased pretreatment rostral anterior cingulate cortex (rACC) theta activity has been linked to better antidepressant outcomes. However, no prior study has evaluated whether this marker has incremental predictive validity over clinical and demographic measures.

OBJECTIVE: To determine whether increased pretreatment rACC theta activity would predict symptom improvement regardless of randomization arm.

DESIGN, SETTING, AND PARTICIPANTS: A multicenter randomized clinical trial enrolled outpatients without psychosis and with chronic or recurrent MDD between July 29, 2011, and December 15, 2015 (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care [EMBARC]). Patients were consecutively recruited from 4 university hospitals: 634 patients were screened, 296 were randomized to receive sertraline hydrochloride or placebo, 266 had electroencephalographic (EEG) recordings, and 248 had usable EEG data. Resting EEG data were recorded at baseline and 1 week after trial onset, and rACC theta activity was extracted using source localization. Intent-to-treat analysis was conducted. Data analysis was performed from October 7, 2016, to January 19, 2018.

INTERVENTIONS: An 8-week course of sertraline or placebo.

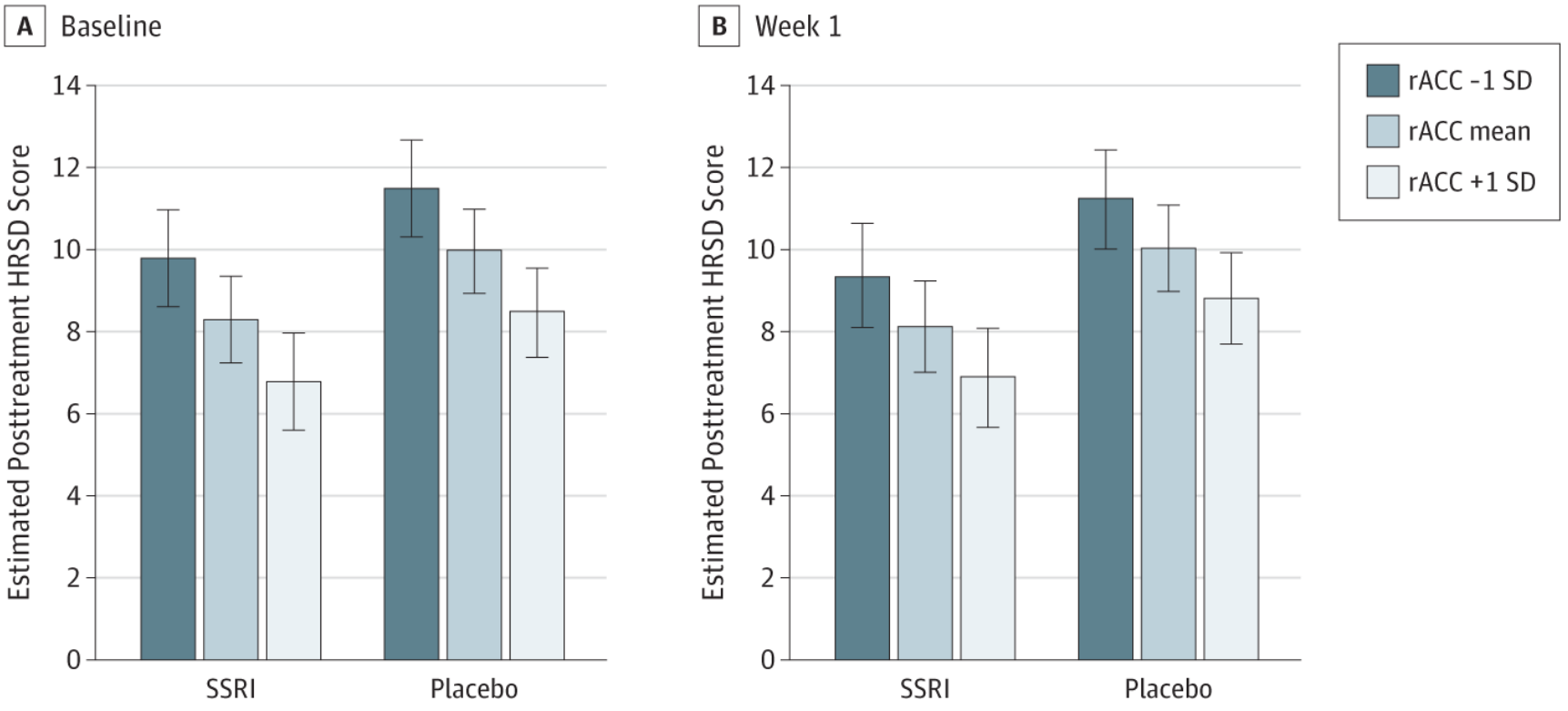
MAIN OUTCOMES AND MEASURES: The 17-item Hamilton Rating Scale for Depression score (assessed at baseline and weeks 1, 2, 3, 4, 6, and 8).

RESULTS: The 248 participants (160 [64.5%] women, 88 [35.5%] men) with usable EEG data had a mean (SD) age of 36.75 (13.15) years. Higher rACC theta activity at both baseline ($b = -1.05$; 95% CI, -1.77 to -0.34; $P = .004$) and week 1 ($b = -0.83$; 95% CI, -1.60 to -0.06; $P < .04$) predicted greater depressive symptom improvement, even when controlling for clinical and demographic variables previously linked with treatment outcome. These effects were not moderated by treatment arm. The rACC theta marker, in combination with clinical and demographic variables, accounted for an estimated 39.6% of the variance in symptom change (with 8.5% of the variance uniquely attributable to the rACC theta marker).

CONCLUSIONS AND RELEVANCE: Increased pretreatment rACC theta activity represents a nonspecific prognostic marker of treatment outcome. This is the first study to date to demonstrate that rACC theta activity has incremental predictive validity.

Pizzagalli et al, 2018, *JAMA Psychiatry*

Figure 2. Estimated Week 8 Hamilton Rating Scale for Depression (HRSD) Scores for the Sertraline and Placebo Groups



Pizzagalli et al, 2018, *JAMA Psychiatry*

rACC Connectivity Predicts Depression Recovery

Article

Pretreatment Rostral Anterior Cingulate Cortex Connectivity With Salience Network Predicts Depression Recovery: Findings From the EMBARC Randomized Clinical Trial.

Alexis E. Whitton
Christian A. Webb
Daniel G. Dillon
Jürgen Kayser
Ashleigh Rutherford
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Melvin G. McInnis
Thomas Carmody
Gerard Bruder
Madhukar H. Trivedi
Diego A. Pizzagalli

Abstract:

BACKGROUND: Baseline rostral anterior cingulate cortex (rACC) activity is a well-replicated nonspecific predictor of depression improvement. The rACC is a key hub of the default mode network, which prior studies indicate is hyperactive in major depressive disorder. Because default mode network downregulation is reliant on input from the salience network and frontoparietal network, an important question is whether rACC connectivity with these systems contributes to depression improvement.

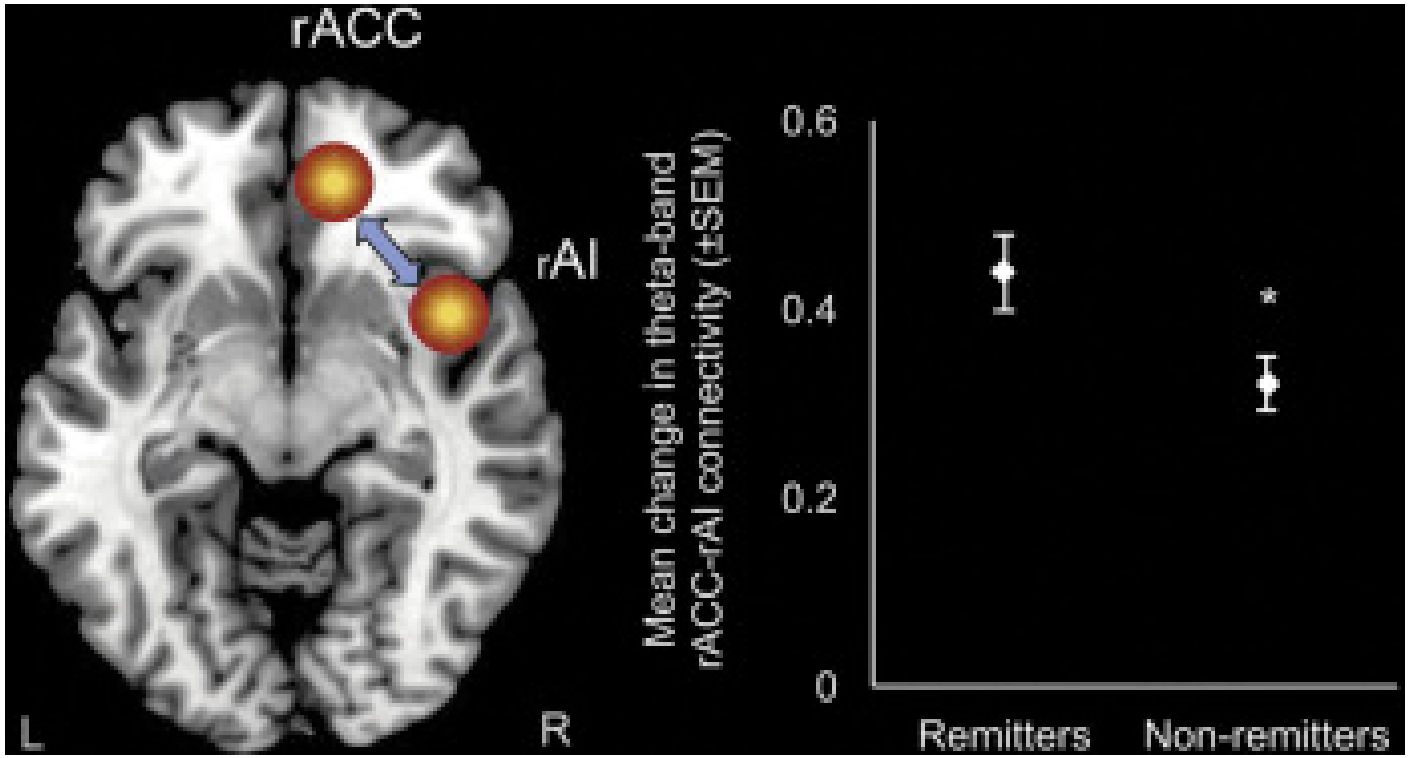
METHODS: Our study evaluated this hypothesis in outpatients (N = 238; 151 female) enrolled in the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) 8-week randomized clinical trial of sertraline versus placebo for major depressive disorder. Depression severity was measured using the Hamilton Rating Scale for Depression, and electroencephalography was recorded at baseline and week 1. Exact low-resolution electromagnetic tomography was used to compute activity from the rACC, and key regions within the default mode network (posterior cingulate cortex), frontoparietal network (left dorsolateral prefrontal cortex), and salience network (right anterior insula [rAI]). Connectivity in the theta band (4.5-7 Hz) and beta band (12.5-21 Hz) was computed using lagged phase synchronization.

RESULTS: Stronger baseline theta-band rACC-rAI (salience network hub) connectivity predicted greater depression improvement across 8 weeks of treatment for both treatment arms (B = -0.57, 95% confidence interval = -1.07, -0.08, p = .03). Early increases in theta-band rACC-rAI connectivity predicted greater likelihood of achieving remission at week 8 (odds ratio = 2.90, p = .03).

CONCLUSIONS: Among patients undergoing treatment, theta-band rACC-rAI connectivity is a prognostic, albeit treatment-nonspecific, indicator of depression improvement, and early connectivity changes may predict clinically meaningful outcomes.

Whitton et al, 2019, *Biological Psychiatry*

Figure 2.



Early changes (baseline to week 1) in theta-band connectivity between the rostral anterior cingulate cortex (rACC) and the right anterior insula (rAI)—a major region in the salience network—as a function of depression remission status. Remission was defined as a Hamilton Rating Scale for Depression score of ≤7 at week 8. *p = .02. L, left; R, right.

Whitton et al, 2019, *Biological Psychiatr*

Whitton, A. E. et al.
Pretreatment Rostral Anterior Cingulate Cortex Connectivity With Salience Network Predicts Depression Recovery: Findings From the EMBARC Randomized Clinical Trial
Biol. Psychiatry 85, 872–880 (2019)

The rostral anterior cingulate cortex (rACC) is a node of the default mode network (DMN) and its pre-treatment activity predicts depression improvement.

The DMN is involved in introspection/rumination and is hyperactive in depression. The DMN is regulated by interactions/connectivity with the salience and executive control networks.

Resting EEG from 238 depressed EMBARC subjects was used to calculate connectivity between nodes of these networks to investigate if node-to-node, frequency-specific connectivity better predicts treatment outcome.

Theta band connectivity between the rACC (DMN) and right insula (salience network) predicted depression improvement in both treatment groups.

nature biotechnology

ARTICLES

https://doi.org/10.1038/s41587-019-0397-3

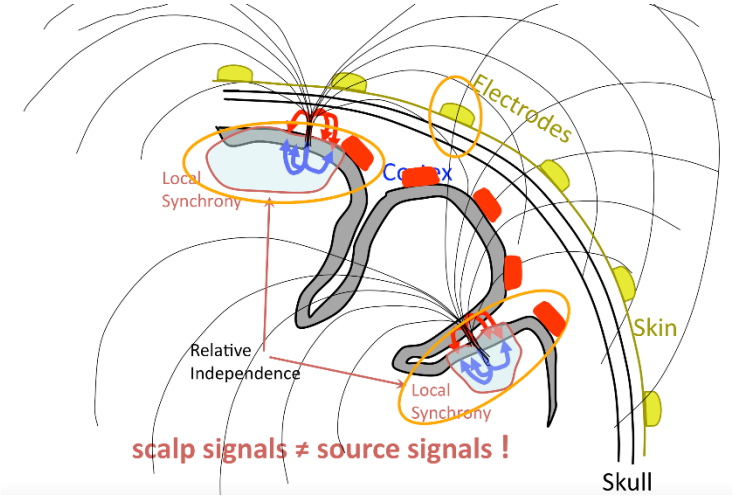
Check for updates

An electroencephalographic signature predicts antidepressant response in major depression

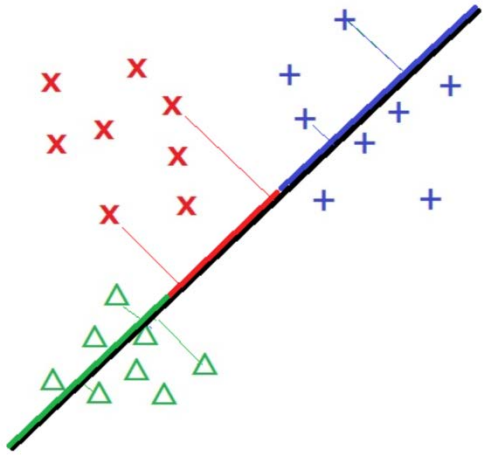
Wei Wu[1,2,3,4], Yu Zhang[2,3,4], Jing Jiang[2,3,4], Molly V. Lucas[2,3,4], Gregory A. Fonzo[2,3,4], Camarin E. Rolle[2,3,4], Crystal Cooper[5,6], Cherise Chin-Fatt[5,6], Noralie Krepel[7,8], Carena A. Cornelssen[2,3,4], Rachael Wright[2,3,4], Russell T. Toll[2,3,4], Hersh M. Trivedi[2,3,4], Karen Monuszko[2,3,4], Trevor L. Caudle[2,3,4], Kamron Sarhadi[2,3,4], Manish K. Jha[5], Joseph M. Trombello[5,6], Thilo Deckersbach[9], Phil Adams[10], Patrick J. McGrath[10], Myrna M. Weissman[10], Maurizio Fava[9], Diego A. Pizzagalli[9], Martijn Arns[7,11,12], Madhukar H. Trivedi[5,6,13] and Amit Etkin[2,3,4,13] ✉

Challenges of EEG machine learning

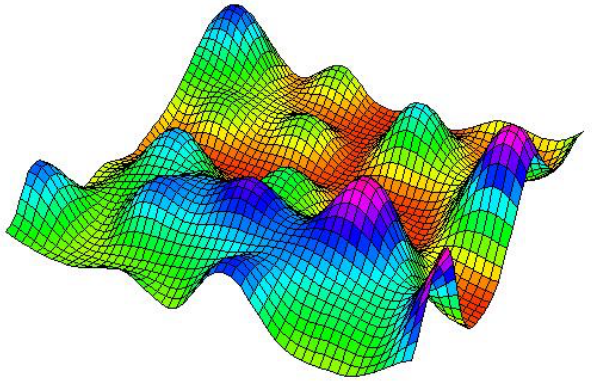
volume conduction



dimensionality reduction

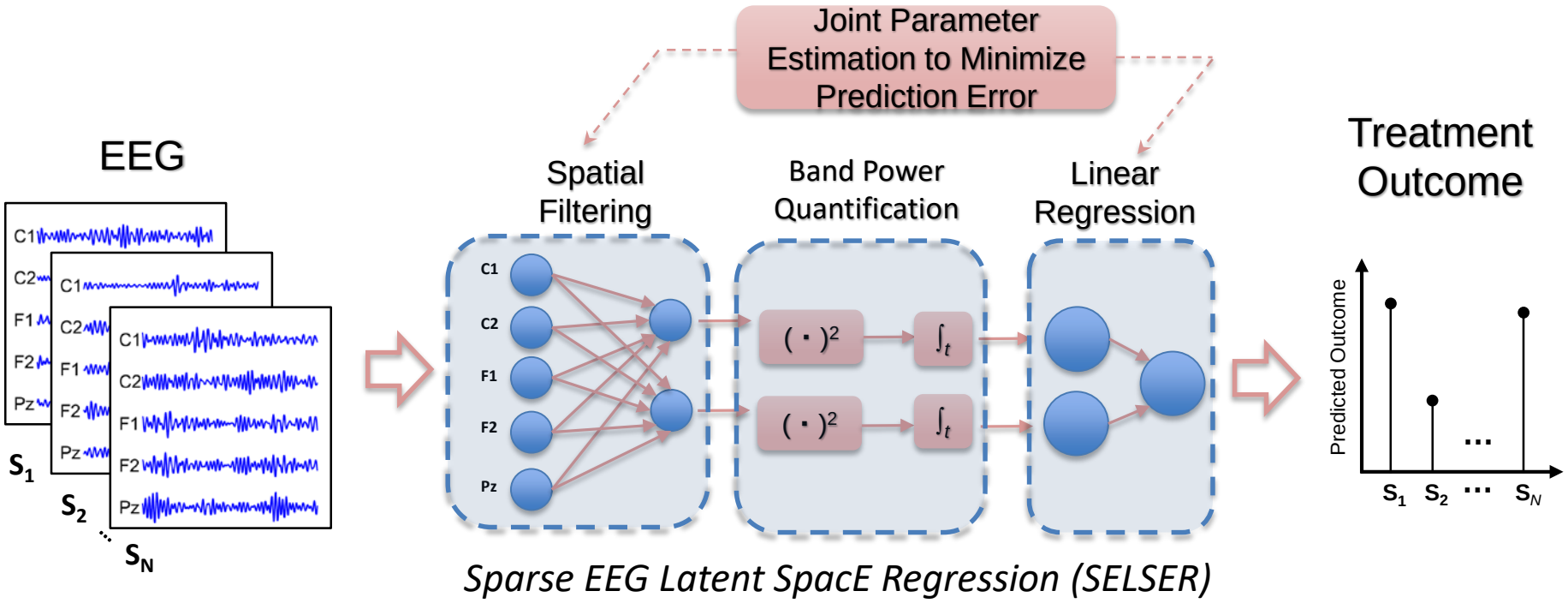


optimization



A novel machine learning approach for outcome prediction

Traditional approach does not leverage spatiotemporal structure of EEG



Sparse EEG Latent SpacE Regression (SELSER)

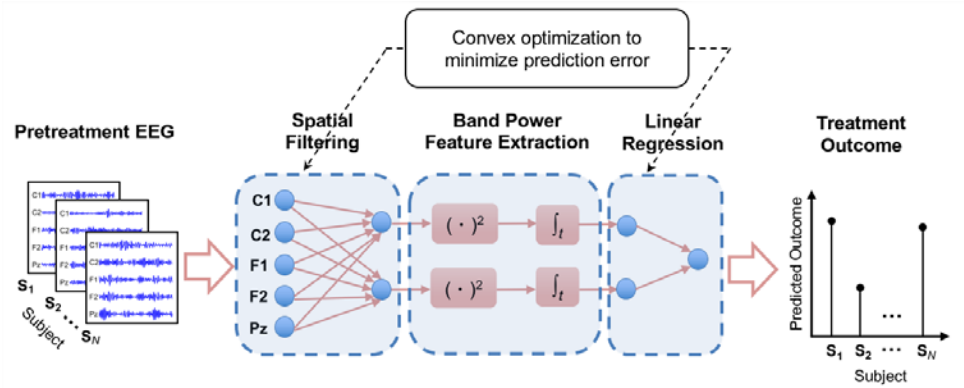
Each of the challenges is addressed:

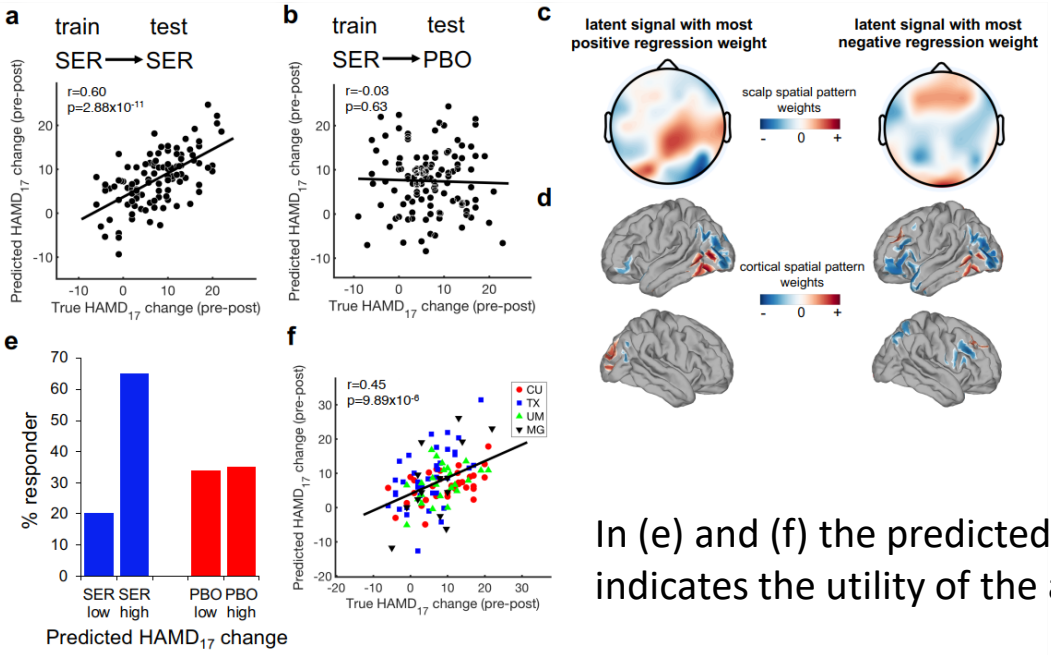
- **Volume conduction:** supervised spatial filtering to ensure optimality w.r.t. treatment prediction
- **Dimensionality reduction:** low-rank regularization to minimize number of latent signals
- **Optimization:** convex optimization to address local minimum issue

Wu et al., Nature Biotechnology, 2020

An electroencephalographic signature predicts antidepressant response

The algorithm reduces dimensionality of EEG data via spatial filters. Features are extracted from the power at different frequency bands to produce predictive variables of treatment outcome.





In (a) and (b), the algorithm predicts treatment response to sertraline and no response to placebo.

In (c) and (d) the topographies of these predictive signals demonstrate overlap with nodes of all 3 canonical cognitive functional networks.

In (e) and (f) the predicted versus actual symptom improvement indicates the utility of the algorithm and machine learning in general.

Wu, W. et al. *Nature Biotechnology*

Summary

- Approximately two-thirds of depressed individuals will not achieve remission with their first antidepressant.
- Treatment selection continues to be by trial and error.
- Increasing Evidence for Biomarkers for MDD
- Identifying “true” moderators of treatment response is becoming a reality
- Subtyping based on combinatorial markers is a more likely fit.
- Personalized Medicine for Depression is on the horizon.

Future Directions

- Identifying biomarkers that can lead to prevention of depression in at-risk populations.
- Prospective studies of biomarkers as moderators treatment outcomes.
- Subtyping based on combinatorial markers rather than single modality biomarkers.

Questions?

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