NETRAMARK

NIH National Institute of Mental Health

Explainable AI-Derived Patient Personas Reveal Neurobiological Predictors of Ketamine Response in Treatment Resistant Depression

Joseph Geraci[1,2,3,4], Bessi Qorri PhD[1], Jan Sedway[1], Christian Cumbaa[1], Mike Tsay[1], Paul Leonczyk[1], Adam Gogacz[1], Matt Carland[1], Luca Pani MD[5,6], **Larry Alphs[1]**, Elizabeth Ballard[7], Carlos Zarate Jr.[7]

[1] NetraMark Corp, Toronto ON, Canada; [2] Department of Pathology and Molecular Medicine, Queen's University, Kingston ON, Canada; [3] Arthur C. Clarke Centre for Human Imagination, School of Physical Sciences, University of California, San Diego, La Jolla, CA, USA; [4] Tanenbaum Centre for Pharmacogenetics, Molecular Brain Science Department, Centre for Addiction and Mental Health, Toronto ON, Canada; [5] Department of Psychiatry and Behavioral Sciences, Leonard M. Miller School of Medicine, University of Miami, Coral Gables, FL, USA; [6] Department of Biomedical, Metabolic, and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy; Experimental Therapeutics and Pathophysiology Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA

Key Findings

- Several Personas were identified that defined distinct ketamine responder subgroups based on MADRS improvement from baseline to 7 days post infusion using clinical scales and MRI variables.
- Two reproducible neurobiological profiles of ketamine responders in TRD:
  1. Posterior cingulate–parietal white matter alterations linked to emotional regulation and
  2. Cingulate–lingual grey matter changes linked to interoceptive/autonomic processing.
- These circuit-based phenotypes suggest distinct biological pathways of ketamine's antidepressant effects and provide a framework for precision psychiatry.

SCAN ME

BACKGROUND

Ketamine is a promising rapid-acting therapy for treatment-resistant depression (TRD), yet its strong psychoactive effects complicate blinding and increase expectancy-driven improvement. Identifying reproducible neurobiological signatures of ketamine responders may clarify its treatment effects and support precise use in TRD.

CHALLENGES

- Difficult to distinguish true pharmacologic response from expectancy effects
- Highly heterogeneous TRD populations mask meaningful subgroups
- Lack of reliable, generalizable biomarkers limits trial interpretability

OBJECTIVE

Use advanced AI-based subgroup discovery to isolate stable, biologically meaningful responder signatures to ketamine – separating genuine response from expectance – to improve trial clarity and enable precision treatment strategies.

METHODS

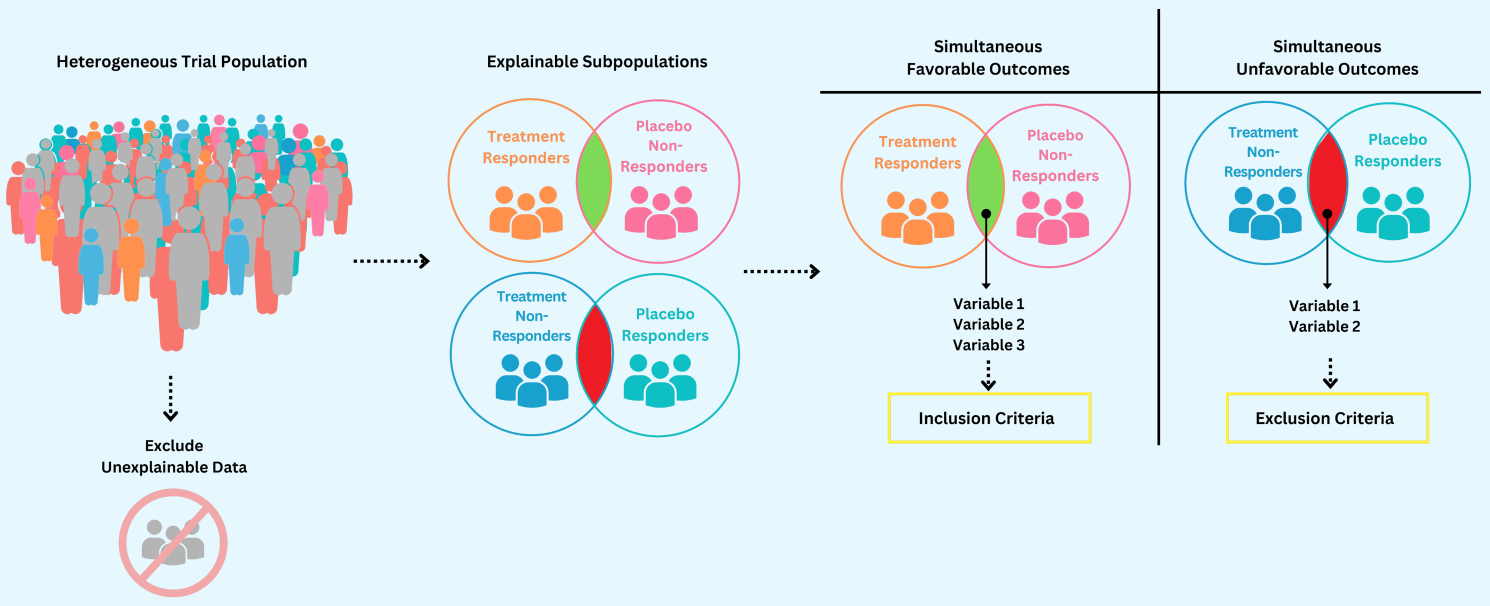
DATASET

Completed randomized, double-blind crossover Phase II study (NCT00088699) of intravenous racemic ketamine (0.5 mg/kg) versus saline placebo for TRD (n=33) sponsored by the NIMH.

- **Data Types:** 175 baseline features, including psychiatric scales and symptom ratings (e.g., MADRS, HAMA, HAMD-17, BDI), lab values/physiological metrics (e.g., BMI), 185 volumetric MRI features, and resting-state MEG recordings.
- **Primary Outcome:** ≥40% reduction in MADRS total score from baseline to Day 7.

ML/AI APPROACH

NetraAI is an explainable, mathematically augmented, iterative machine learning (ML) framework designed to capture complex, high-dimensional interactions between patient features in small, heterogeneous clinical trial data sets.

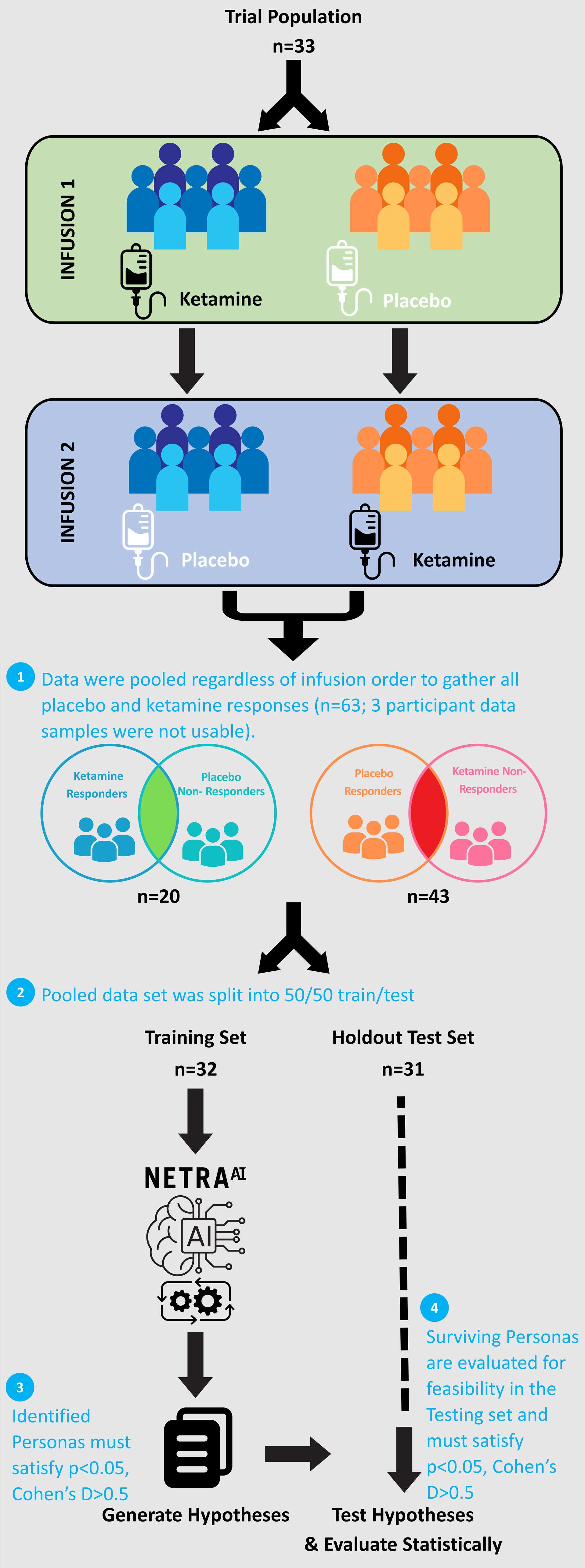


NetraAI segments the patient population into explainable and unexplainable subgroups with explainable subpopulations partitioned into:

- Favorable: ketamine response and placebo non-response
- Unfavorable: ketamine non-response and placebo response

Goal: Identify high-effect-size subpopulations (Personas) characterized by 2-4 baseline or screening variables that simultaneously characterize response.

RESULTS



Persona 1: White matter emotional regulation

43.75% of Training Set (14 out of 32)

25.81% of Holdout Dataset (8 out of 31)

Avg. p-value	Avg. Cohen's D
0.0286	2.1153

Confidence Intervals (MADRS Total Score Improvement)

Placebo	Treatment
[-7.50, 3.00]	[-24.50, -12.50]

Data Range / Persona Range

Variable	Data Range min	Persona Range boundary	Data Range max
Variable 1: Left Posterior Cingulate (White Matter) Volume	3375.2 mm³	4533.7 mm³	6573.9 mm³
Variable 2: Right Inferior Parietal (White Matter) Volume	8199.2 mm³	12,663.9 mm³	15,082.6 mm³
Variable 3: BDI 10 Crying (Emotional Reactivity)	0	1	3

Patients with this profile showed preferential benefit from ketamine, consistent with findings regarding ketamine and default mode network emotional regulation circuits and emotional reactivity.

Persona 2: Grey matter interoceptive/autonomic

40.62% of Training Set (13 out of 32)

38.71% of Holdout Dataset (12 out of 31)

Avg. p-value	Avg. Cohen's D
0.0476	1.3309

Confidence Intervals (MADRS Total Score Improvement)

Placebo	Treatment
[0.166, 3.33]	[--19.16, -0.16]

Data Range / Persona Range

Variable	Data Range min	Persona Range boundary	Data Range max
Variable 1: Left Isthmus Cingulate (Grey Matter) Volume	1824 mm³	2505 mm³	3742 mm³
Variable 2: Right Lingual (Grey Matter) Volume	4454 mm³	6805 mm³	9041 mm³
Variable 3: HAMA Cardiovascular Anxiety Symptoms	0	1	3

This phenotype implicates ketamine's modulation of salience and interoceptive networks, supporting a mechanism of autonomic recalibration.

CONCLUSIONS & SIGNIFICANCE

By integrating clinical, physiological, structural, and functional neurobiology, we identified reproducible patient Personas that map onto ketamine's mechanistic effects in TRD. These phenotypes suggest ketamine exerts antidepressant activity through at least two neurobiologically distinct pathways:

1. Restoration of emotional regulation circuits via posterior cingulate-parietal white matter networks and
2. Recalibration of interoceptive/autonomic processing via cingulate-lingual grey matter and salience circuitry.

These findings support precision psychiatry approaches for patient stratification and clinical trial enrichment in TRD.

Disclosures: J.G is the founder of NetraMark and a significant shareholder of NetraMark Holdings. Drs L.P., B.Q., J.S., P.L., and L.A., and M.T., C.C., A.G., and M.C. are employed by NetraMark. L.P. disclosures: AbbVie, USA; Acadia, USA; Alexion, Italy; BCG Switzerland; Boehringer Ingelheim International GmbH, Germany; Compass Pathways, UK; EDRA-LSWR Publishing Company, Italy; Ferrer, Spain; Gedeon-Richter, Hungary; GLG-Institute, USA; Immunogen, USA; Inpeco SA, Switzerland; Ipsen-Abireo, France; Johnson & Johnson USA; NeuroCog Trials, USA; Novartis-Gene Therapies, Switzerland; Sanofi-Aventis-Genzyme, France and USA; NetraMark, Canada*; Otsuka, USA; Pfizer Global, USA; PharmaMar, Spain; Relmada Therapeutics, USA*; Takeda, USA; Vifor, Switzerland; WCG-VeraSci/Clinical Endpoint Solutions, USA (* options / shares). E.D.B and C.A.Z.J are employees of the United States Government, and this work was completed as part of their official duties as Government employees. The views expressed do not necessarily reflect the views of the NIH, the Department of Health and Human Services, or the United States Government. Funding for this work was provided in part by the Intramural Research Program at the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH; ZIAMH002927).