

LEARNING OBJECTIVES

- Demonstrate how integrating multimodal clinical trial data can reveal biologically distinct responder subtypes in TRD treated.
- Describe how multimodal neurobiological signatures inform mechanistic understanding of ketamine's antidepressant effects and support precision psychiatry approaches.

KEY FINDING

Multimodal data integration can link symptom dimensions to brain circuitry, support biomarker-informed patient stratification, and improve interpretability of ketamine trials.

Multimodal Identification of Neurobiological Subtypes Associated with Ketamine Response in Treatment-Resistant Depression Using NetraAI

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BACKGROUND

Ketamine has demonstrated rapid antidepressant effects in treatment-resistant depression (TRD), yet its strong psychoactive properties complicate blinding, increase expectancy-driven improvement, and obscure identification of true biological response. Integrating multimodal clinical and neurobiological data may help resolve response heterogeneity and clarify ketamine's mechanism(s) of action.

CHALLENGES

- Difficult to identify true pharmacologic response
- Heterogeneous TRD populations mask meaningful subgroups

OBJECTIVE

Use advanced AI-based subgroup discovery to isolate stable, biologically meaningful responder signatures to ketamine from multimodal clinical and neurobiological data to improve trial clarity and enable precision treatment strategies.

METHODS

DATASET

Completed small (n=33), randomized, double-blind, placebo-controlled crossover Phase II trial of intravenous racemic ketamine (0.5 mg/kg) versus saline placebo in TRD (NCT0088699) to identify true pharmacologic response.

- **Data Types:** 175 clinical symptom scale (MADRS, HAM-A, HAMD-17, BDI) and lab values/physiological measures, 185 volumetric structural MRI features, and resting-state MEG recordings.
- **Primary Outcome:** 40% or greater improvement in MADRS total score at Day 7.

NETRA^{AI} APPROACH

NetraAI is an explainable AI/ML framework designed to identify low-dimensional human-interpretable feature sets used to analyze and integrate baseline variables. The platform incorporates all available baseline multimodal variables to identify biologically coherent Model-Derived Subgroups (MDS).

MDS are explainable subgroups defined by 2-4 variables and ranges, associated with differential ketamine versus placebo response on the primary endpoint.

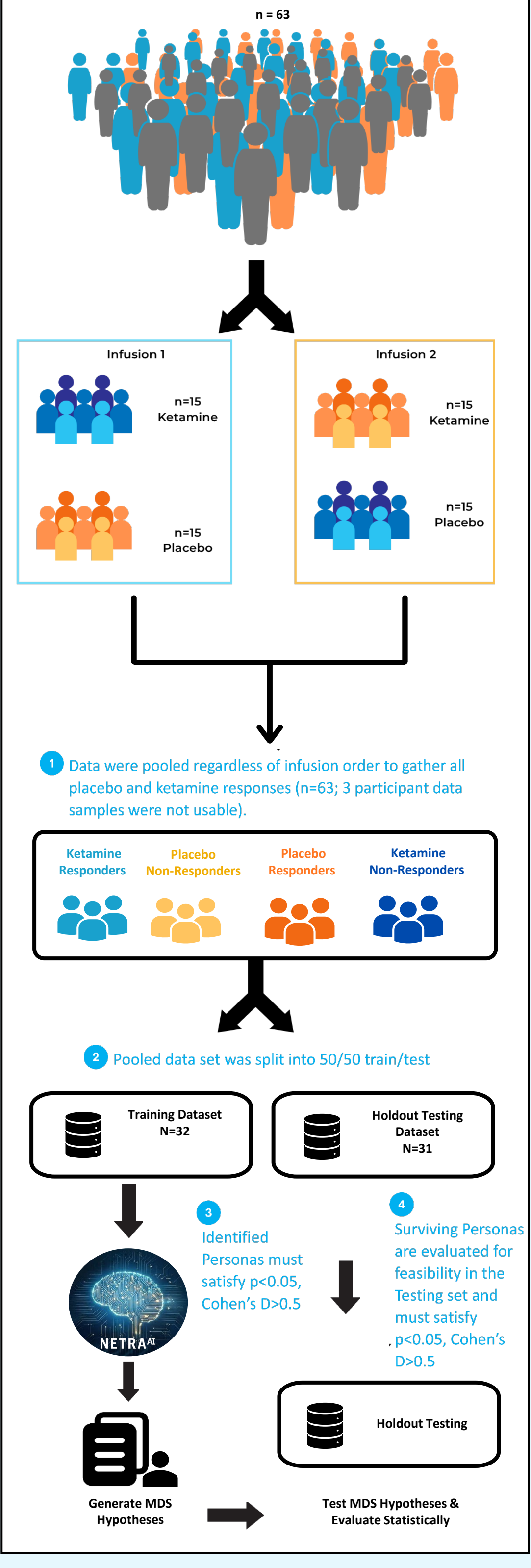


RESULTS

Due to the crossover design, participant data from both infusion sessions were pooled, yielding 63 analyzable cases (3 incomplete subject datasets were excluded).

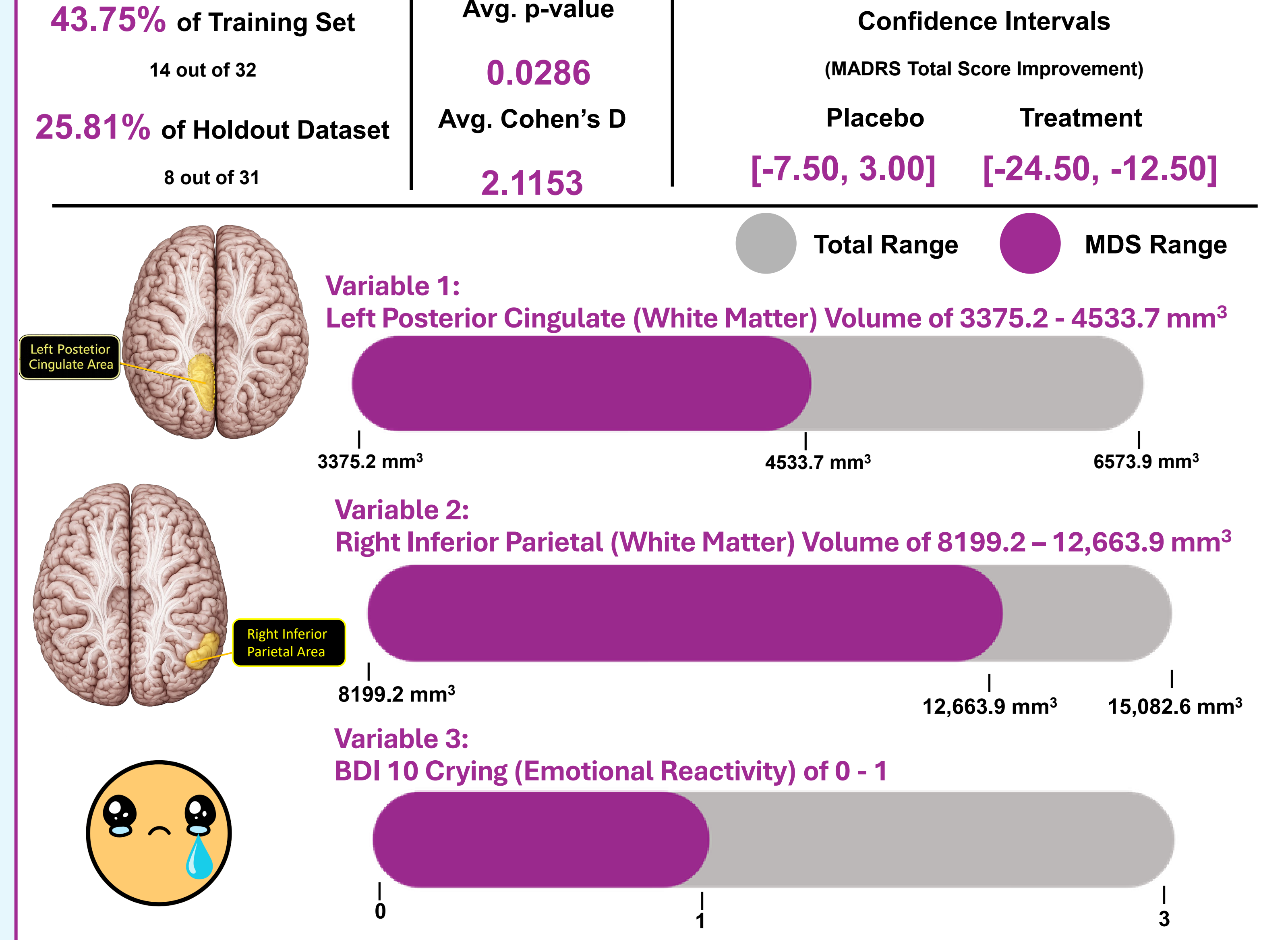
Pooling was performed to increase statistical power while preserving within-subject treatment labels.

NetraAI analysis focused on identifying stable subgroup structure rather than independent observations.



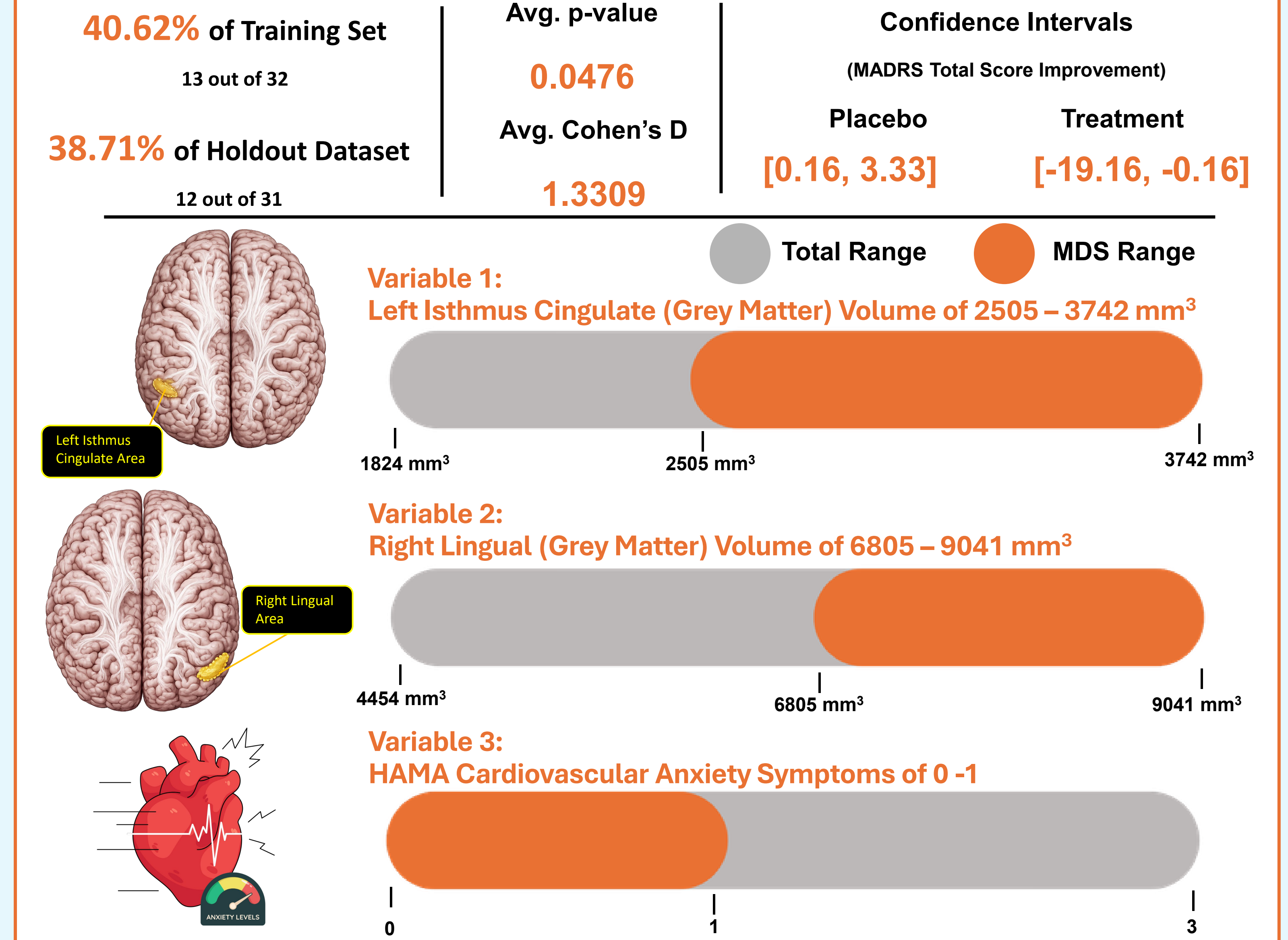
Multimodal integration revealed two internally consistent reproducible ketamine responder MDS characterized by convergent clinical, anatomical, and functional signatures.

Model-Derived Subgroup 1: White matter emotional regulation



Elevated emotional reactivity with reduced posterior cingulate and inferior parietal white matter volumes implicates default mode network and emotional regulation circuitry, consistent with ketamine's glutamatergic modulation of large-scale networks.

Model-Derived Subgroup 2: Grey matter interoceptive/autonomic



Cardiovascular anxiety symptoms with elevated isthmus cingulate and lingual grey matter volumes suggest altered interoceptive and autonomic processing within salience-related networks.

CONCLUSIONS AND SIGNIFICANCE

Integrating clinical symptoms, physiological measures, structural neuroanatomy, and functional network dynamics identifies distinct neurobiological pathways associated with ketamine response in TRD. The large effect sizes of the identified MDS indicate clinically meaningful separation of strong ketamine responders. 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. Findings should be interpreted in the context of modest sample size and crossover design but collectively support the potential of explainable multimodal approaches to advance precision psychopharmacology and trial enrichment strategies in neuropsychiatric drug development.

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).