Objective measurement from subjective clinical interviews: Application to drug development

Seth C. Hopkins, PhD

DISCLOSURES

employee of Sumitomo Pharma America, Inc.

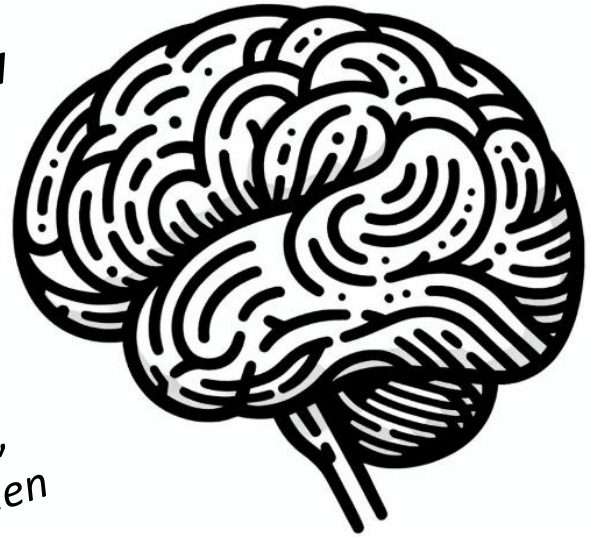
Two ways to measure the brain

Subjective

Psychiatric interview

"In the past week, how have you been feeling..."

- Primary endpoints
- Interviews by a clinician
- Rating scales
- Sum symptom severity
- One "total score" per session
- FDA approval drug-placebo separation



Objective

"How the brain is functioning... "

Cognitive/behavior testing

- Secondary endpoints
- More-objective
- Performance during testing
- Burdensome to acquire
- Exploratory in nature
- Measure of "phenotype"?

  -or-
- Measure of "pharmacodynamics"?

Depression is measured in psychiatry trials with a sum of 10 symptoms

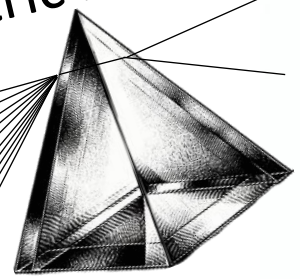
MADRS

Montgomery–Åsberg Depression Rating Scale

1. Apparent Sadness
2. Reported Sadness
3. Inner Tension
4. Reduced Sleep
5. Reduced Appetite
6. Concentration Difficulties
7. Lassitude
8. Inability to Feel
9. Pessimistic Thoughts
10. Suicidal Thoughts

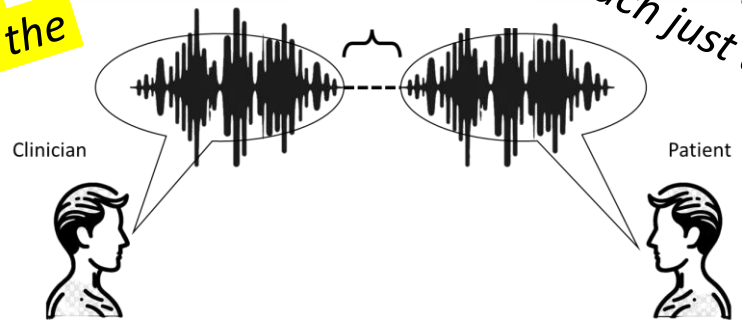
Subjective

Psychiatric interview



"Have you been feeling tense in the past week..."

"uh not really that much just a bit sad"



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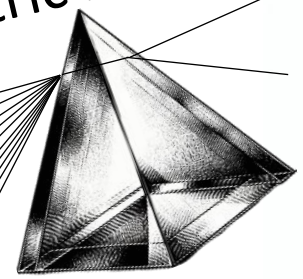
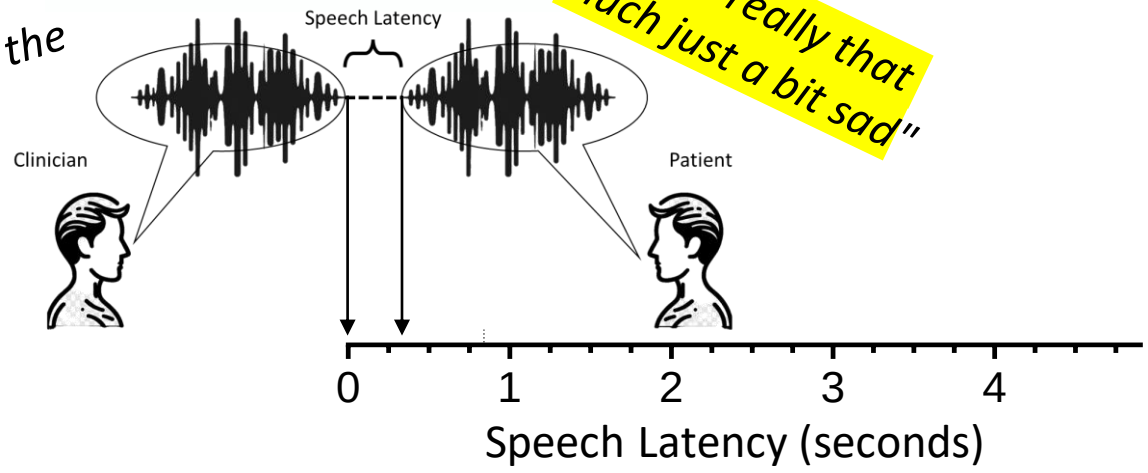


"Have you been feeling tense in the past week..."

Objective

this patient has a fast response time

"uh not really that much just a bit sad"



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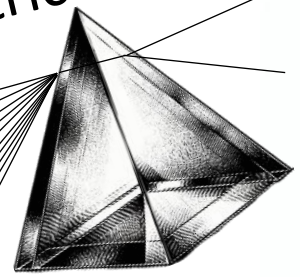
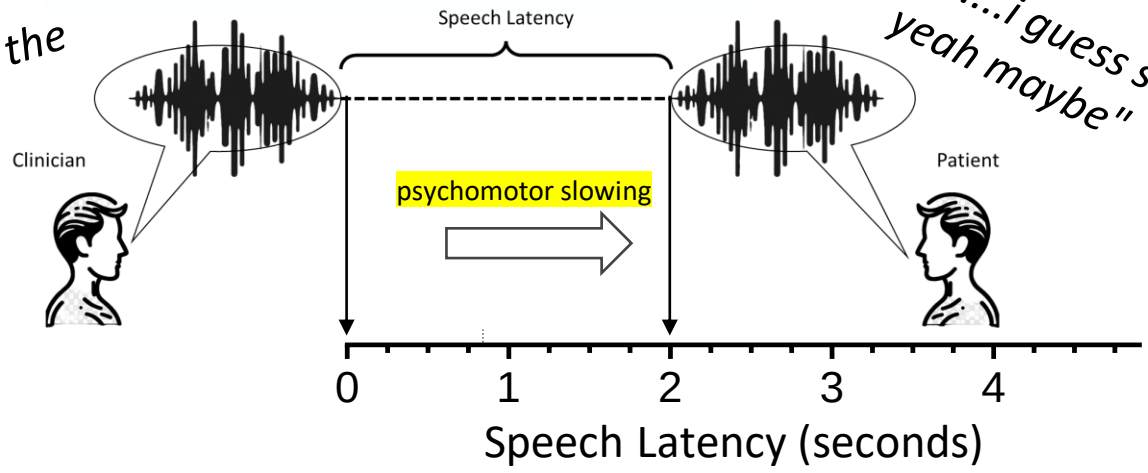


"Have you been feeling tense in the past week..."

Objective

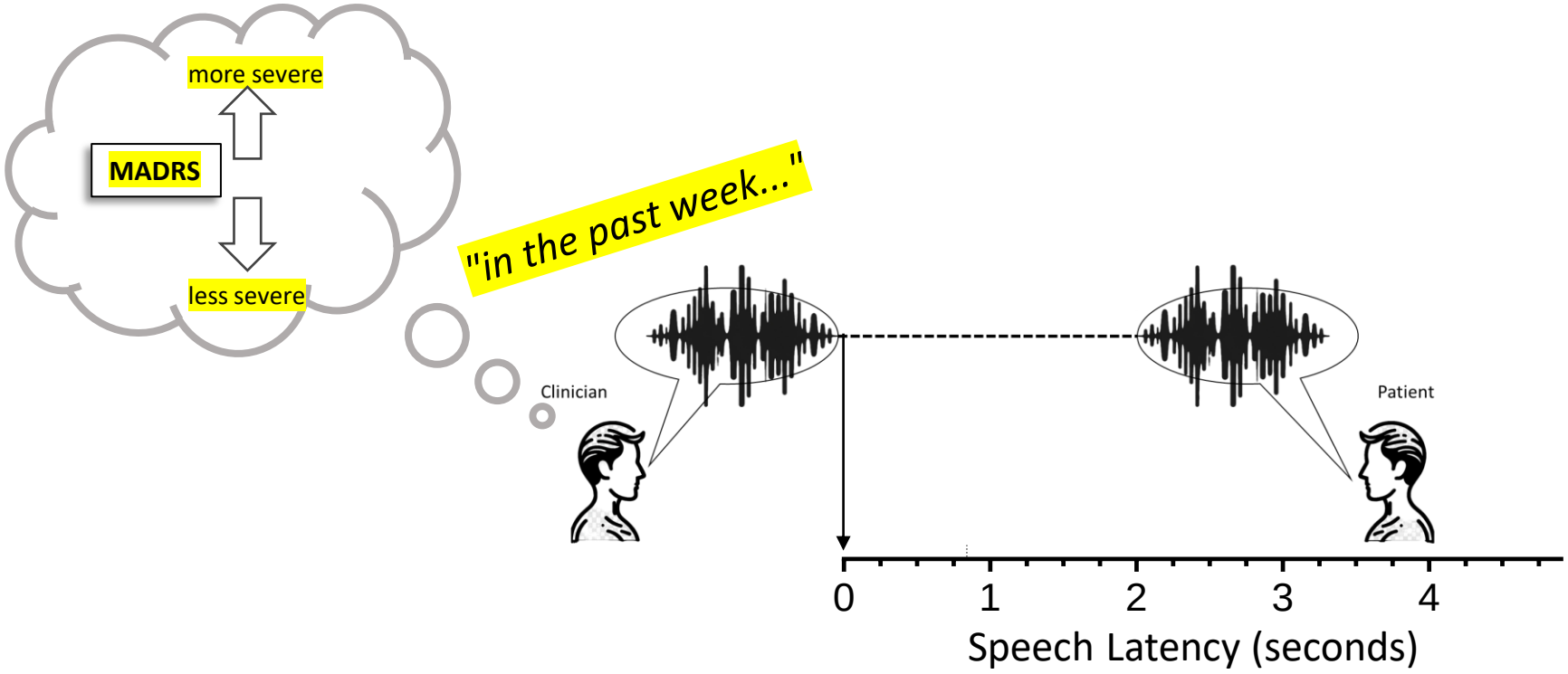
this patient is exhibiting psychomotor slowing

"....i guess so yeah maybe"



We found that Speech Latency can be derived from MADRS interviews

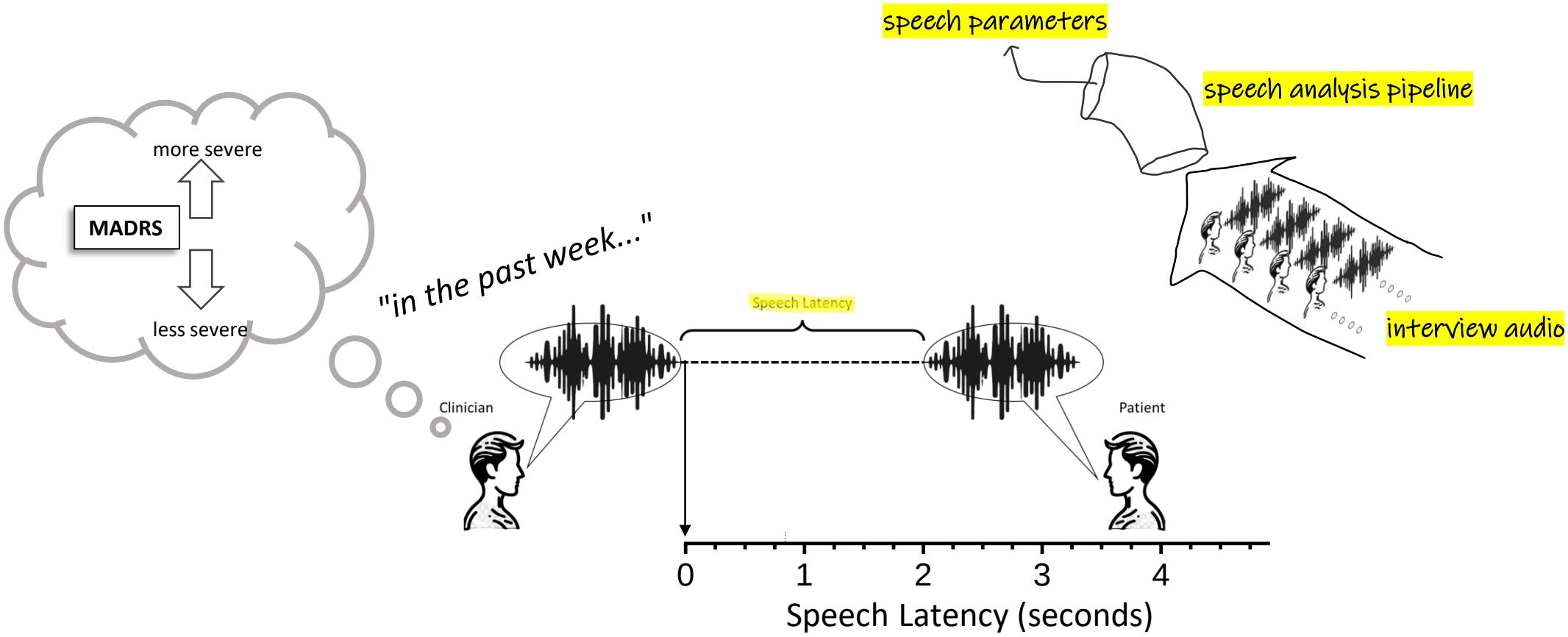
Subjective



We built a speech analysis pipeline to extract Speech Latency from MADRS interviews

Subjective

Objective



We tested the speech pipeline using a prior study

Research paper
Journal of Affective Disorders 296 (2022) 549–558

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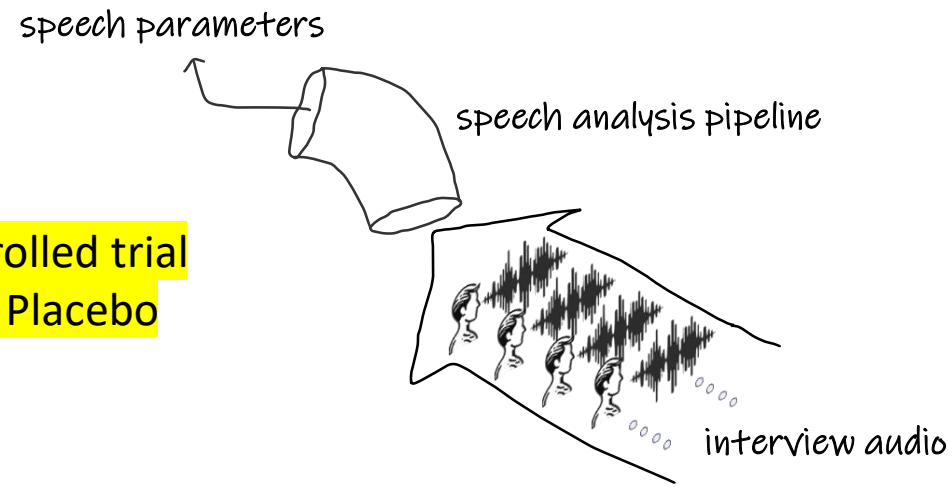
6-week study
3-arm
randomized controlled trial
POC with Drug vs Placebo



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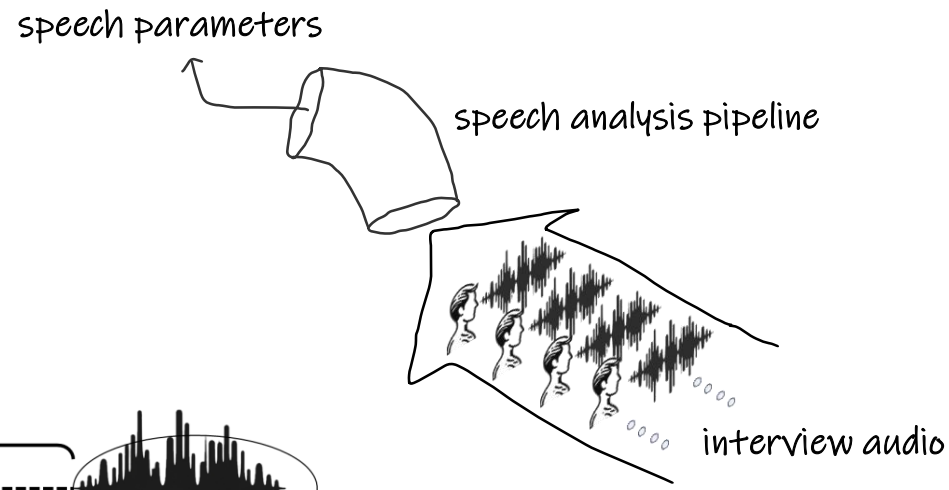
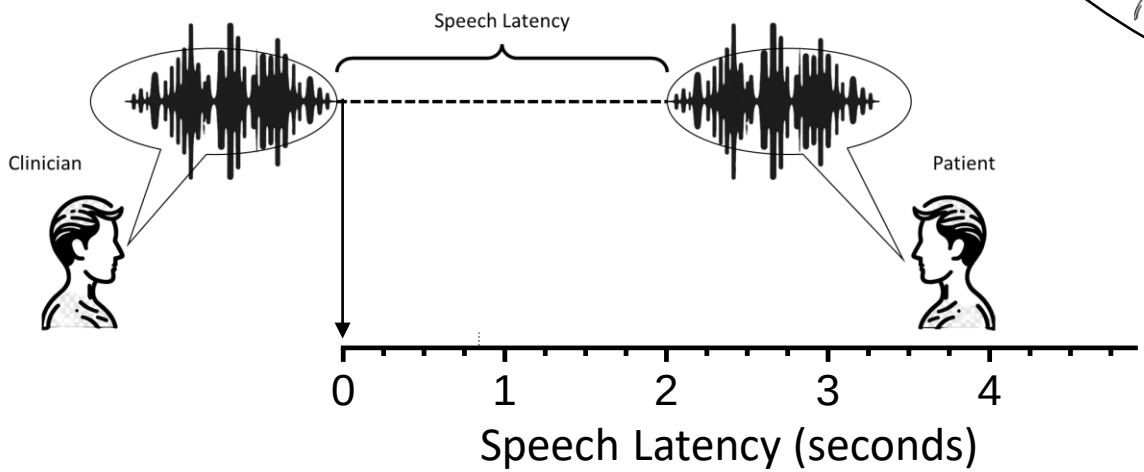
274 subjects
1,369 interviews





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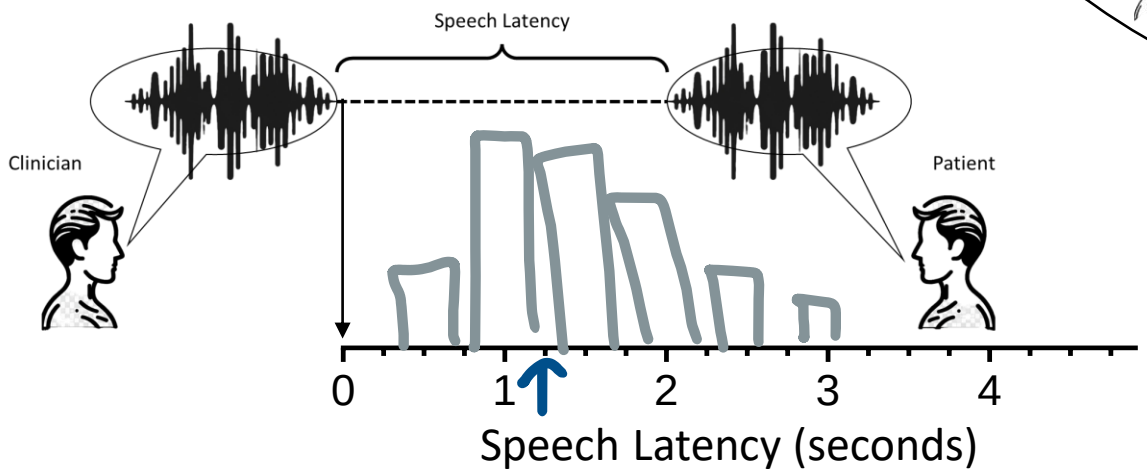
speech parameters

speech analysis pipeline

274 subjects
1,369 interviews
median 71 pauses each interview

interview audio



mean Speech Latency during MADRS interview = 1.2 s

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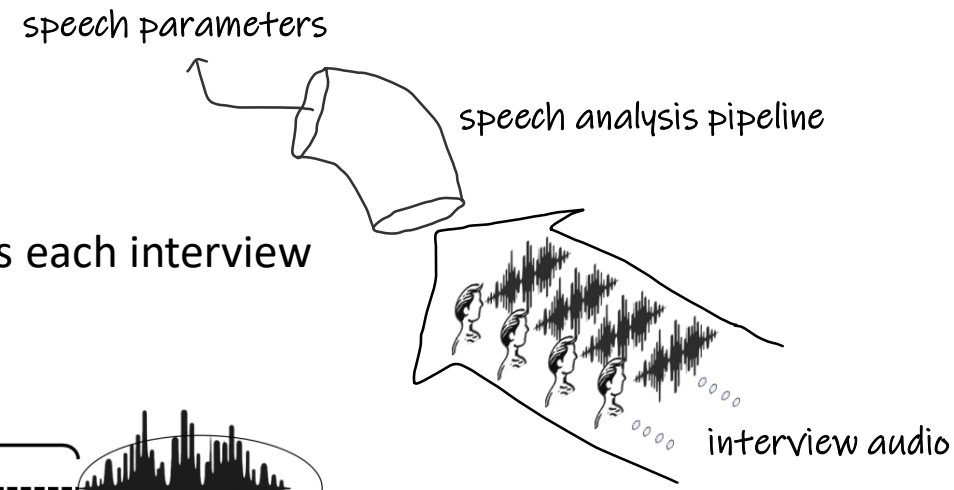

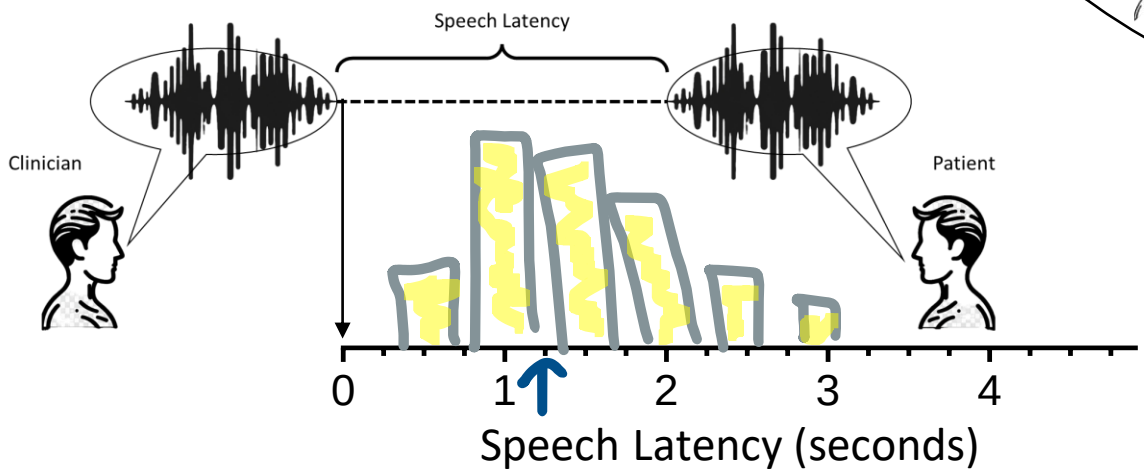

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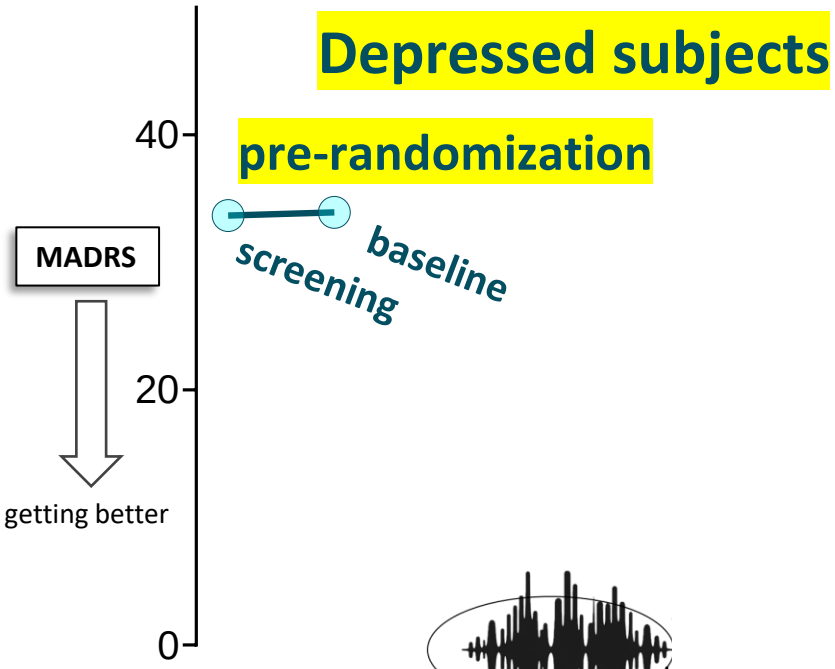

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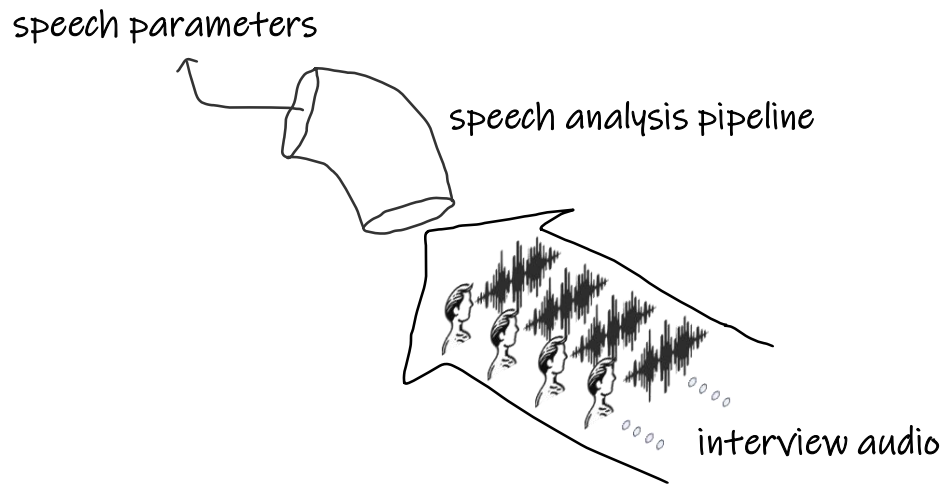

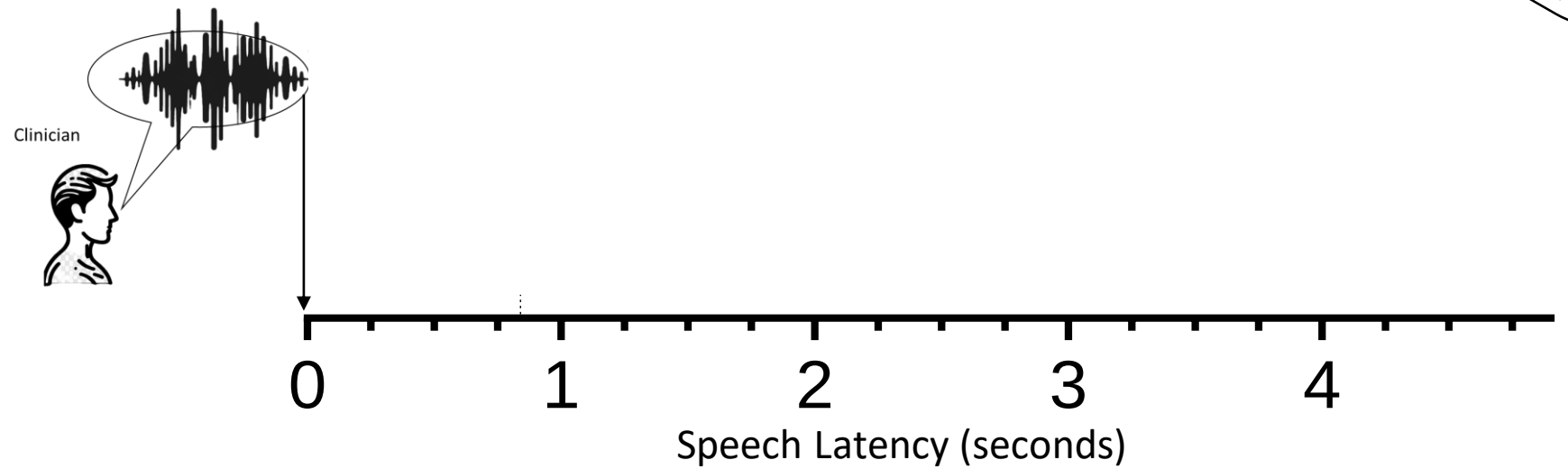

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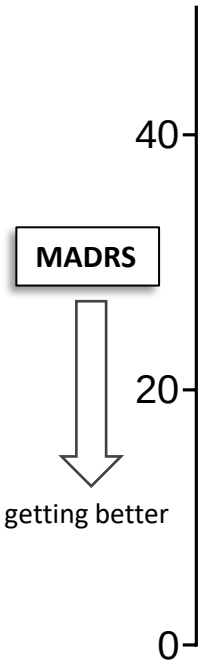
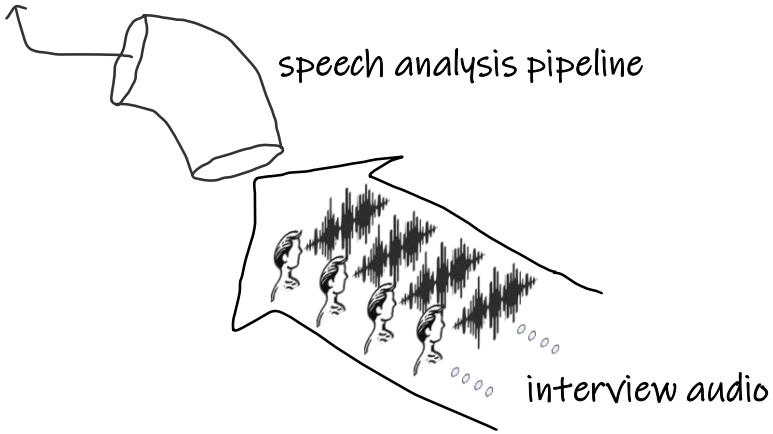


Depressed subjects

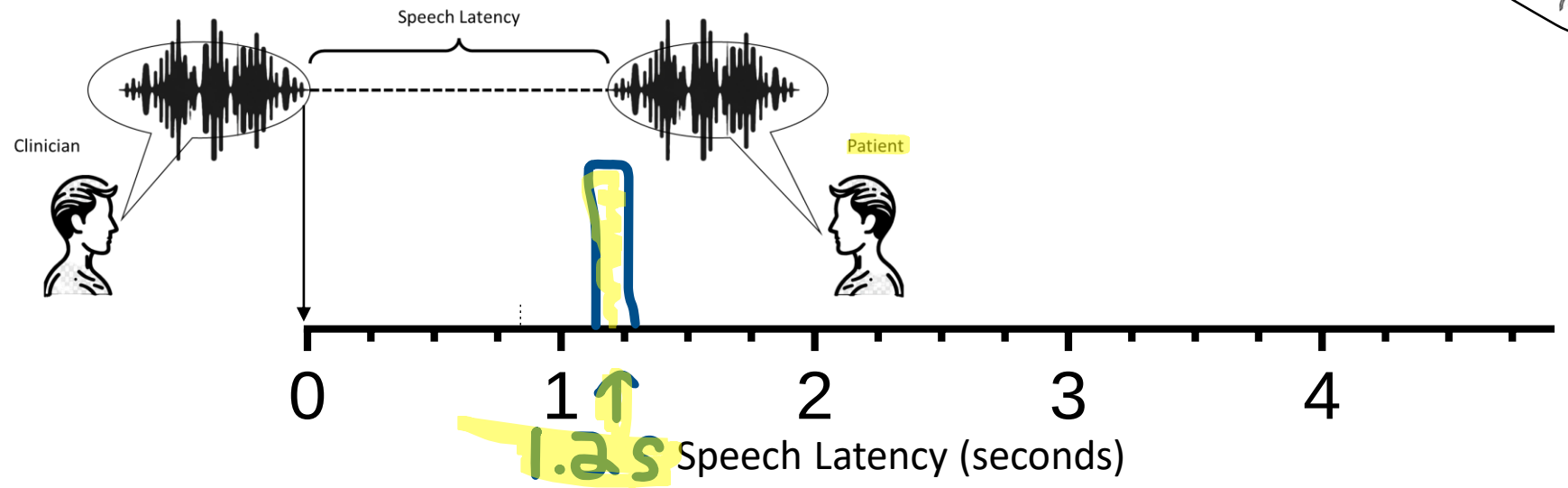
pre-randomization

screening — baseline

speech parameters



mean Speech Latency during MADRS interview



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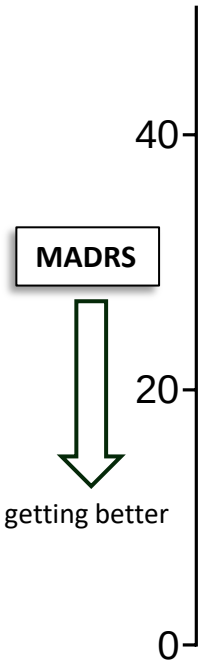

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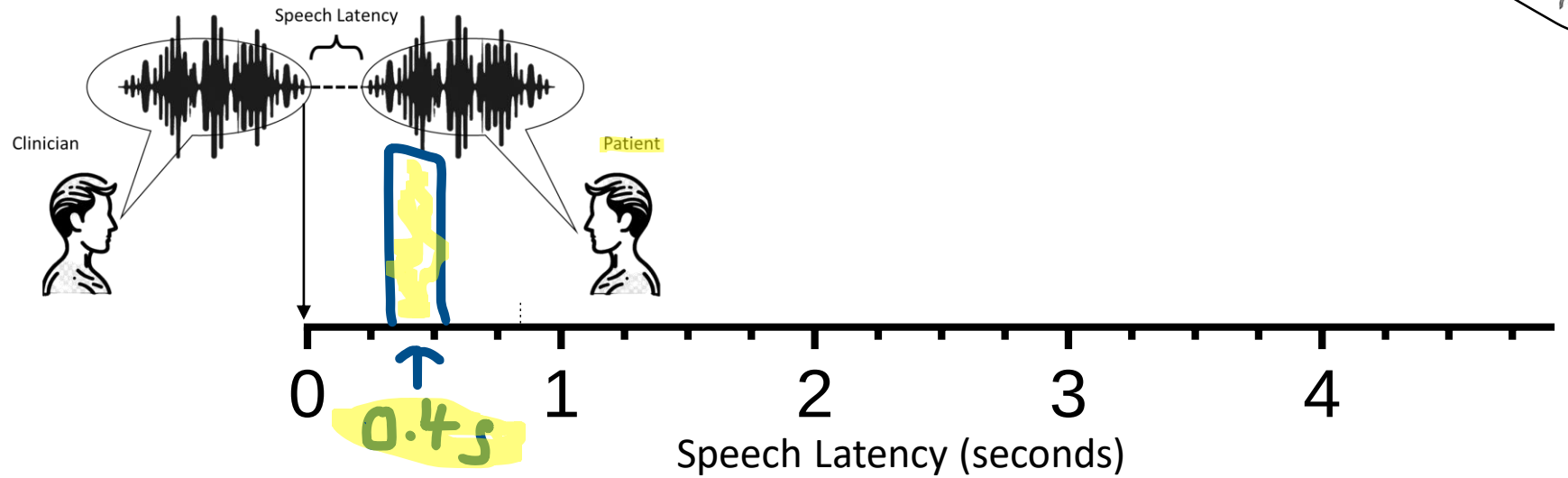

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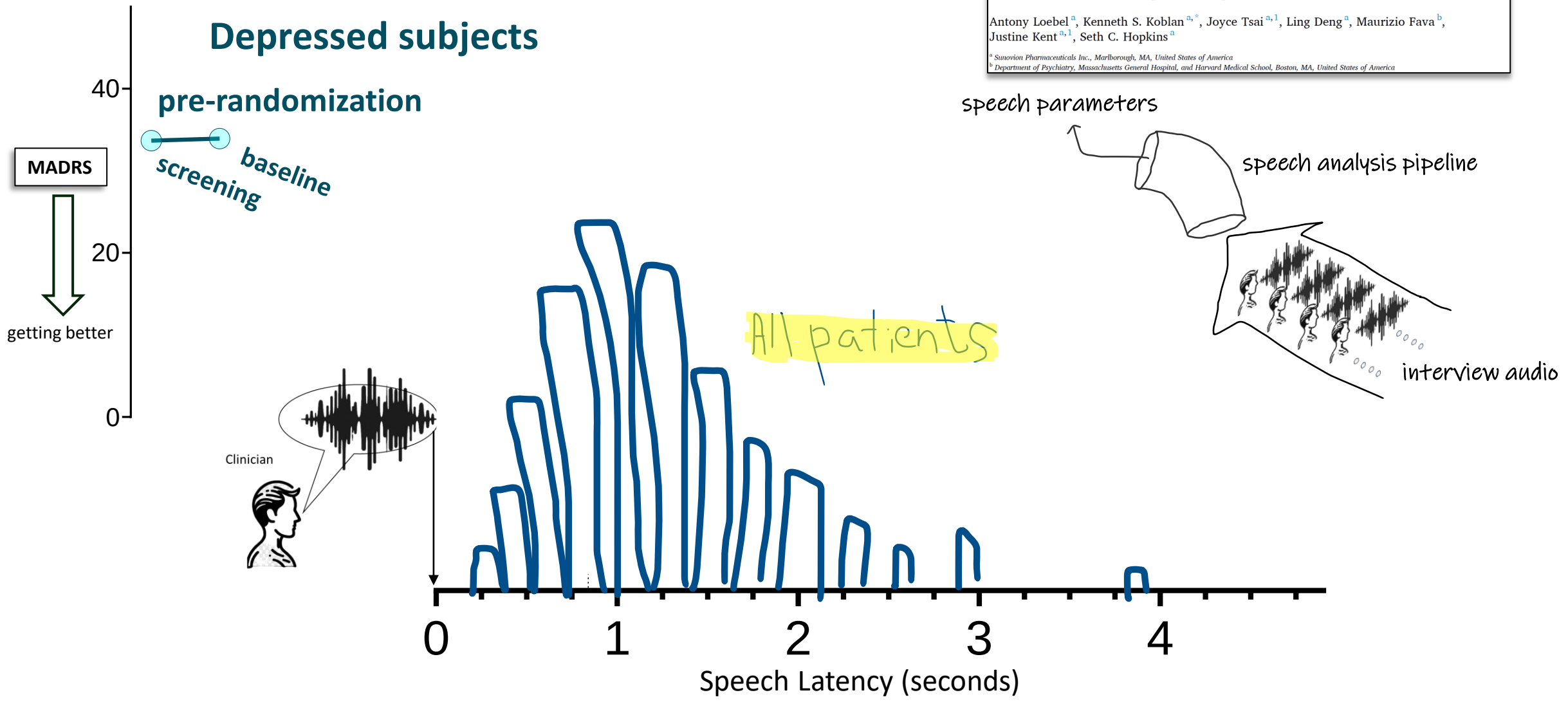

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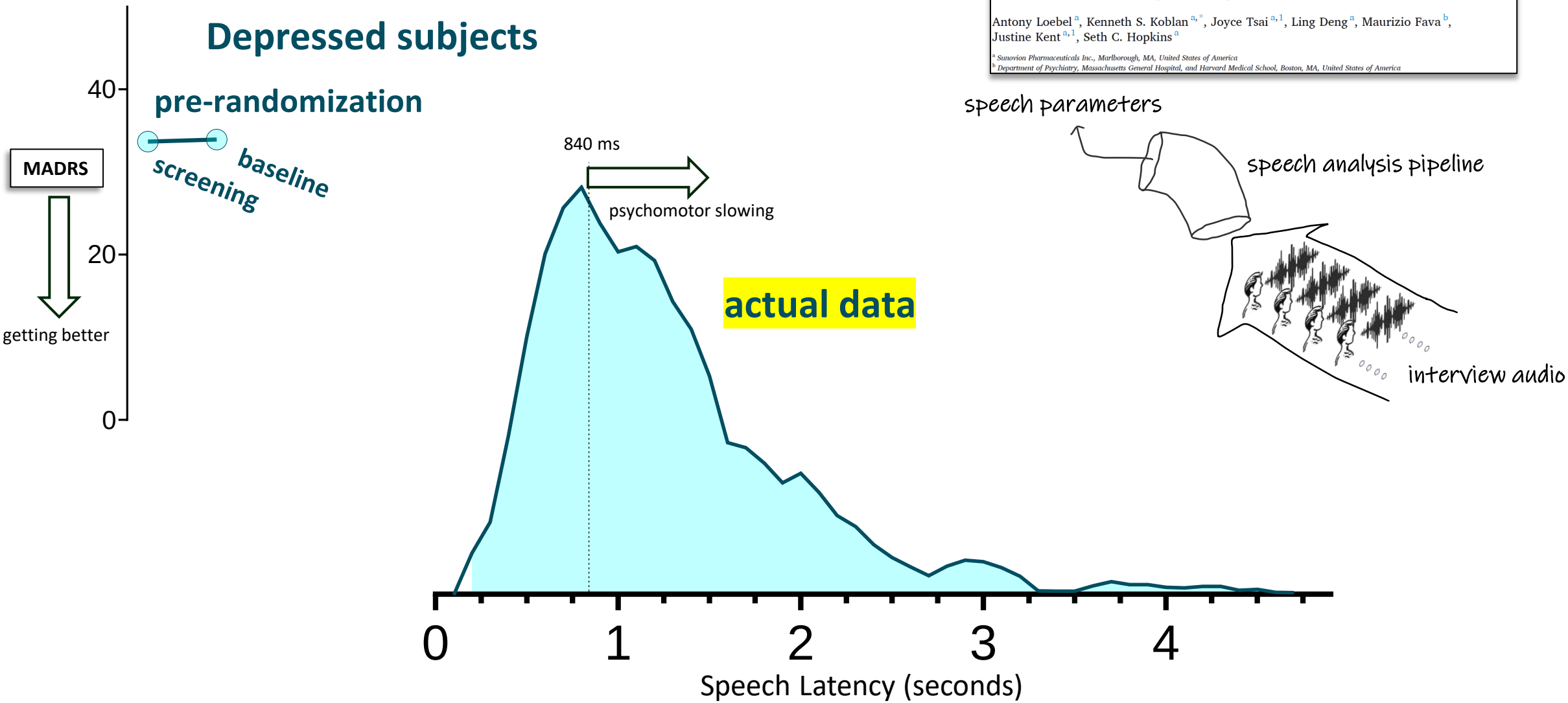

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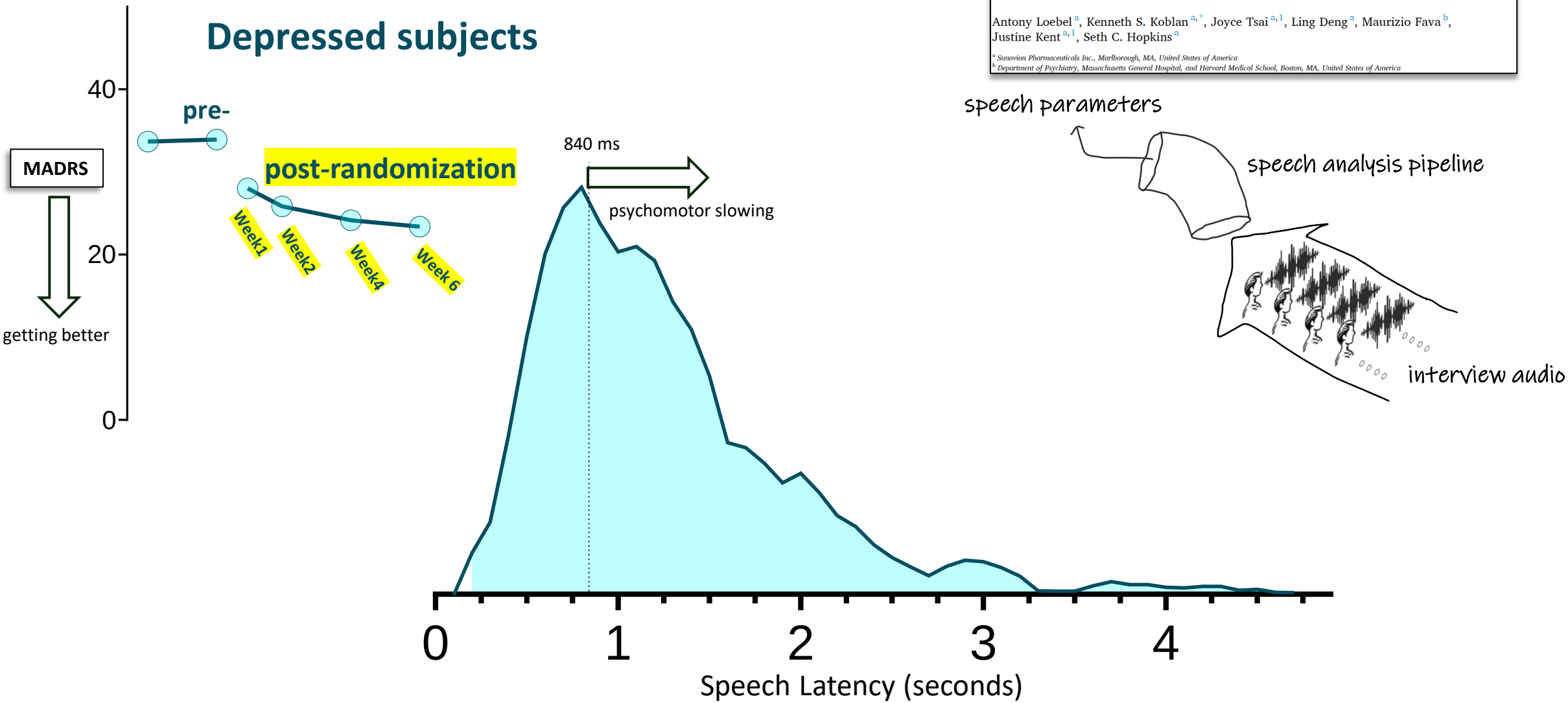

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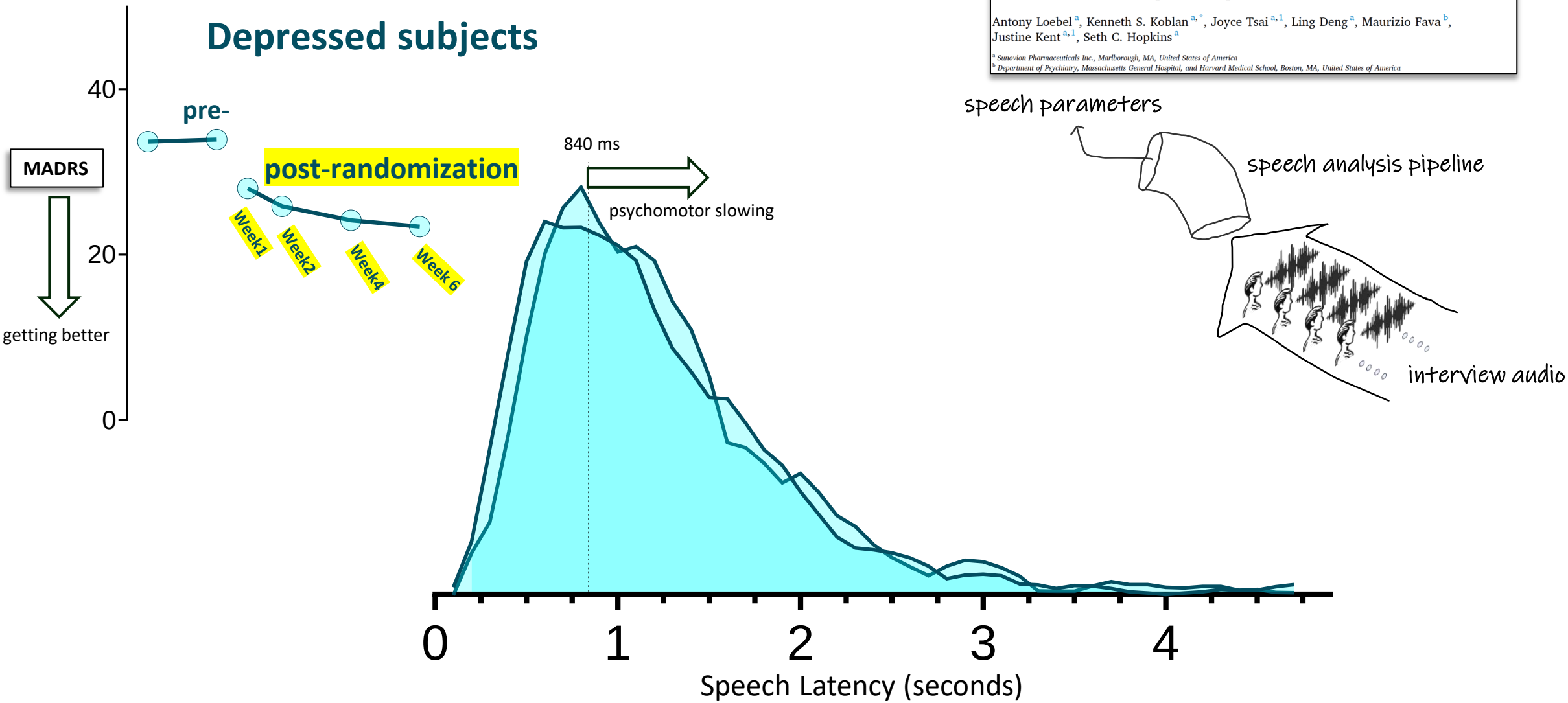

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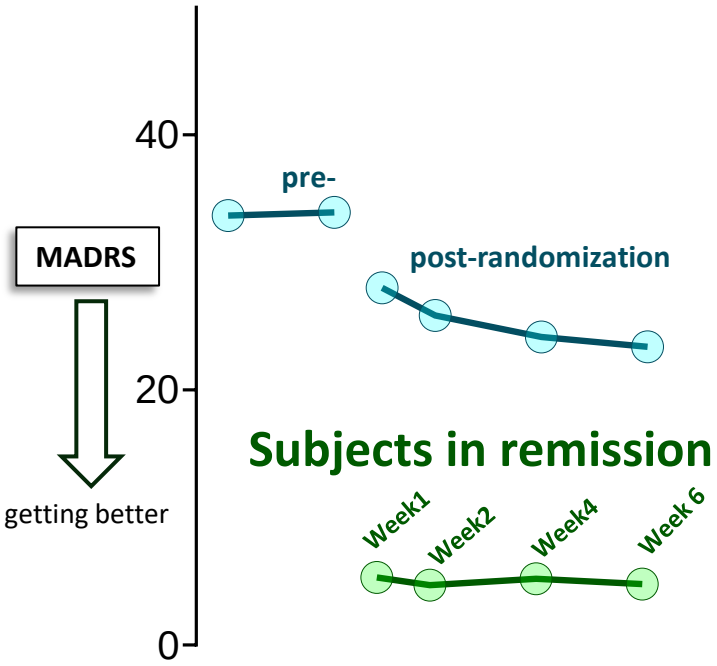

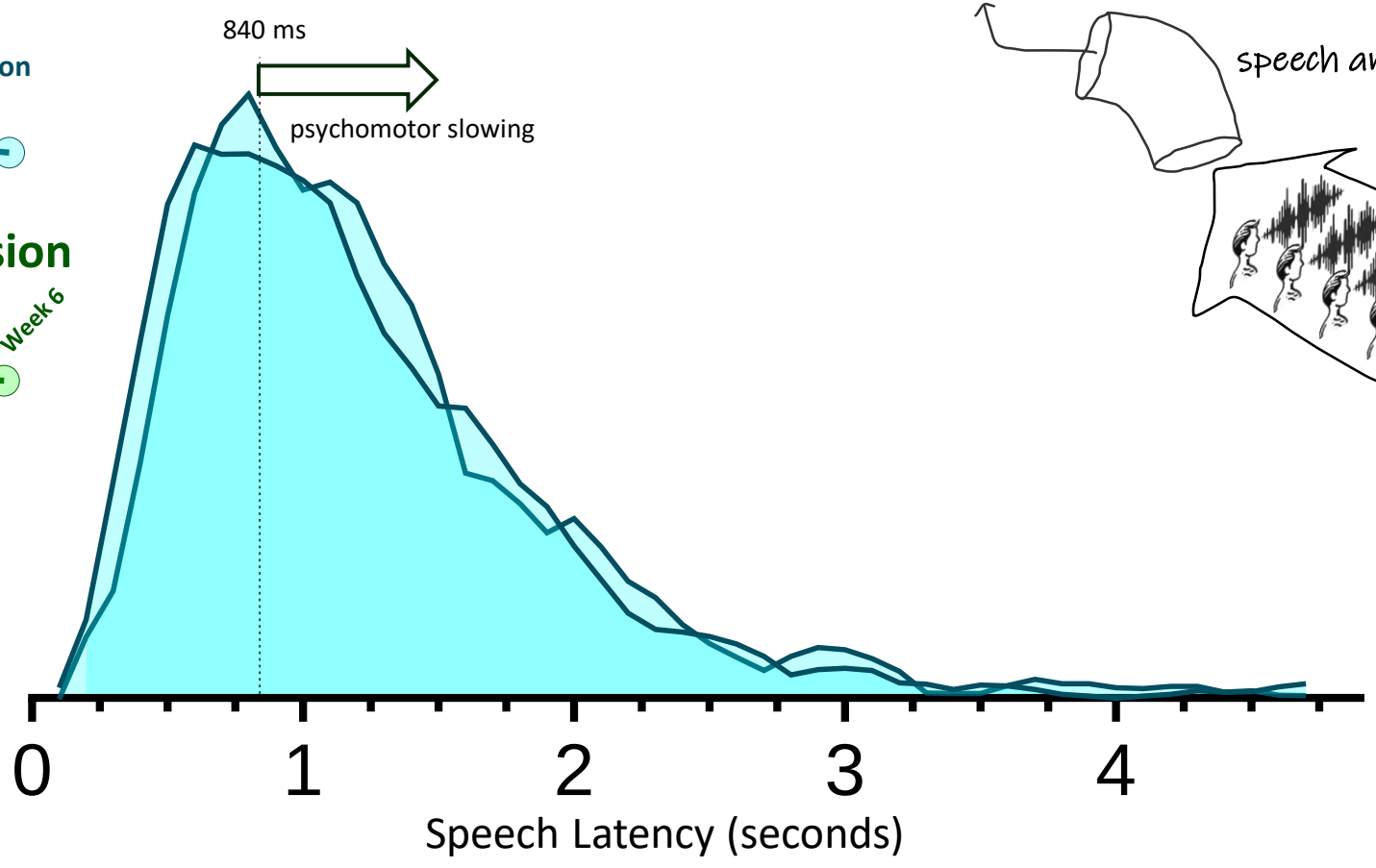

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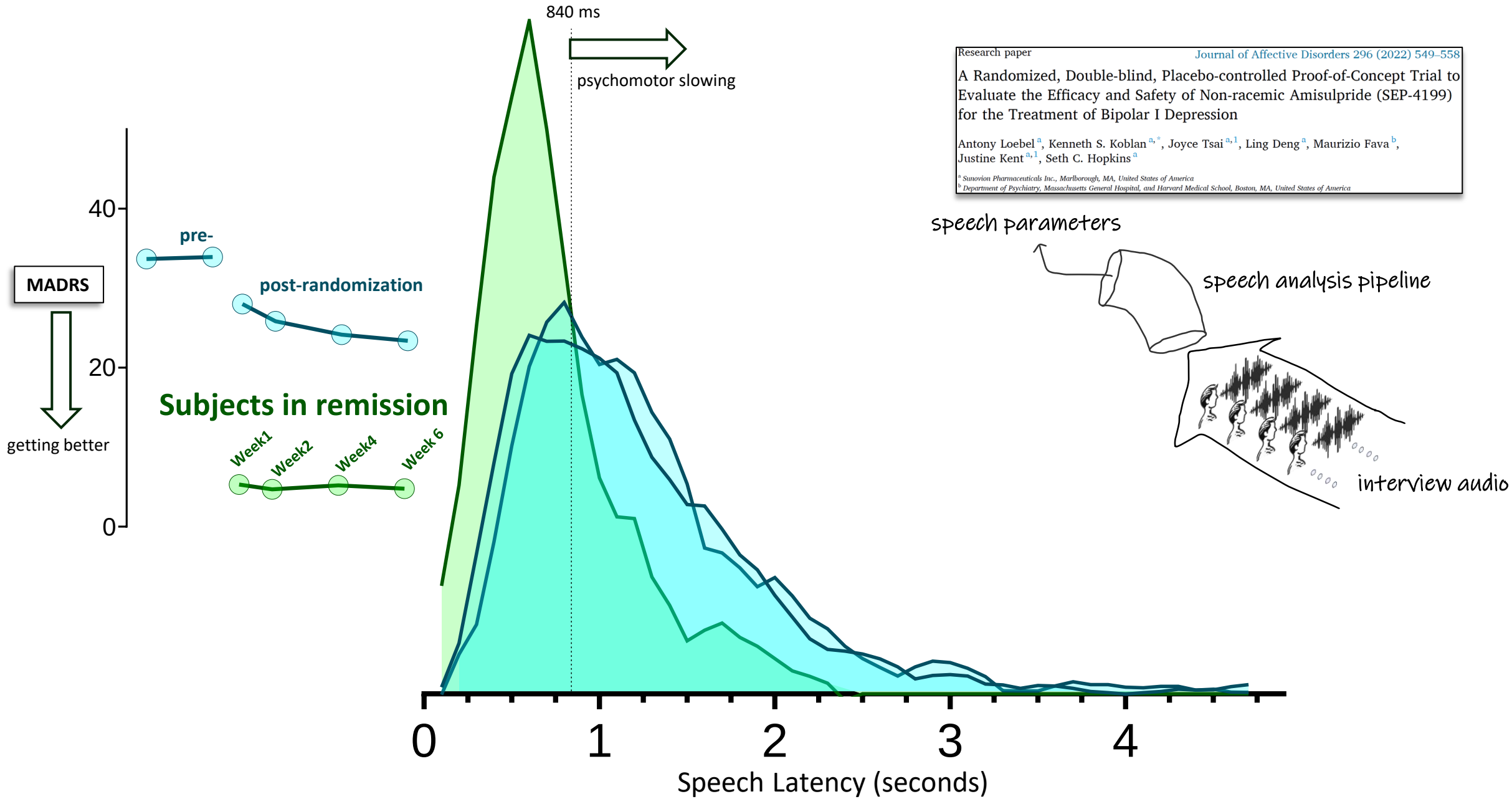

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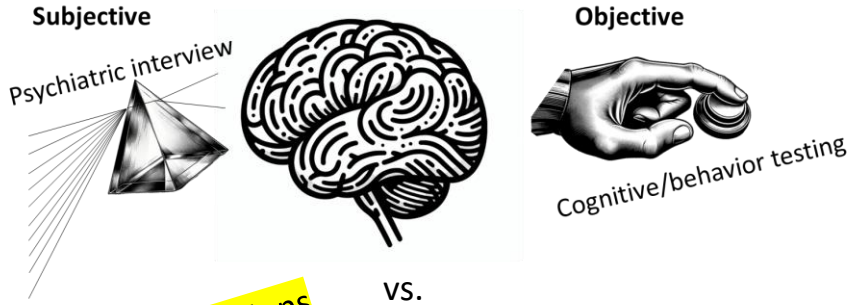
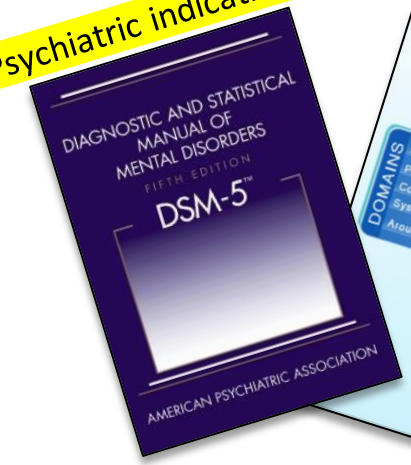
Future directions

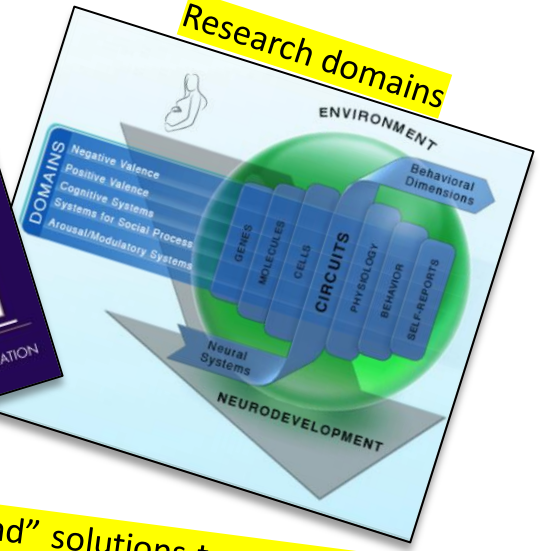


vs.

Psychiatric indications

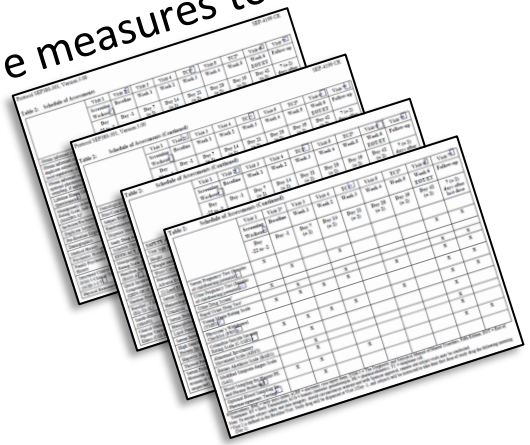


Research domains



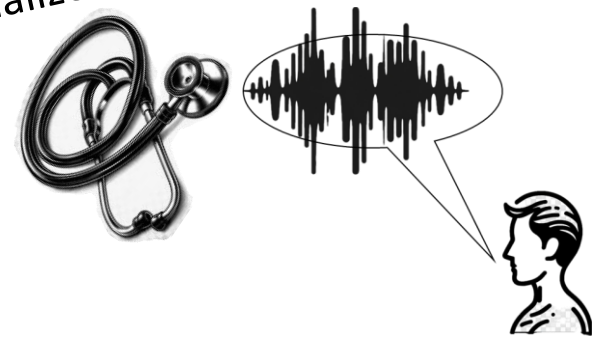
enables "both/and" solutions to measurement

Add objective measures to our trials

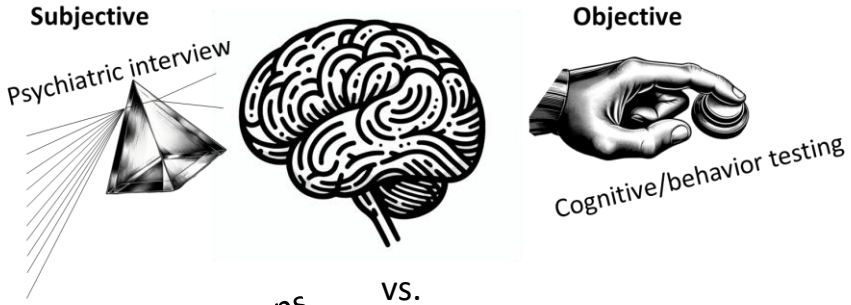


reduce the burden of drug development protocols!

personalized medicine via drug-device

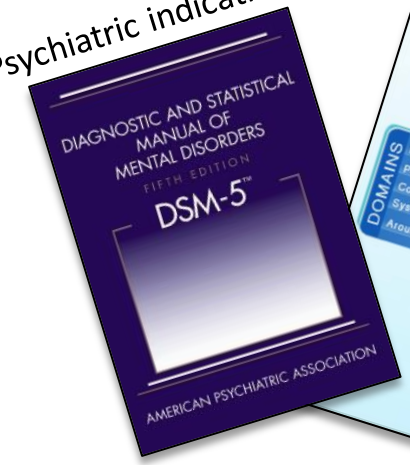


Future directions

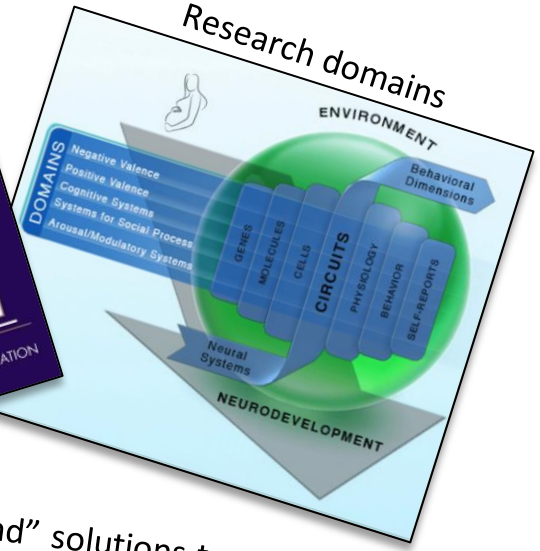


vs.

Psychiatric indications

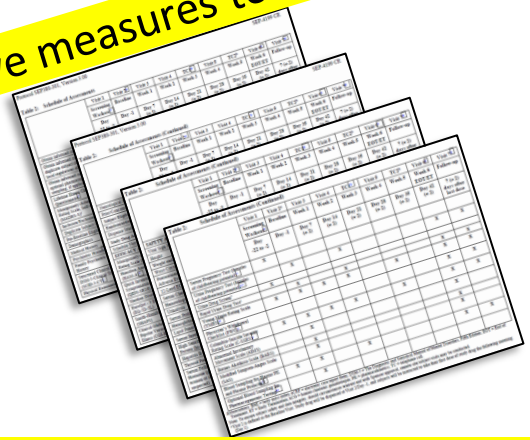


Research domains



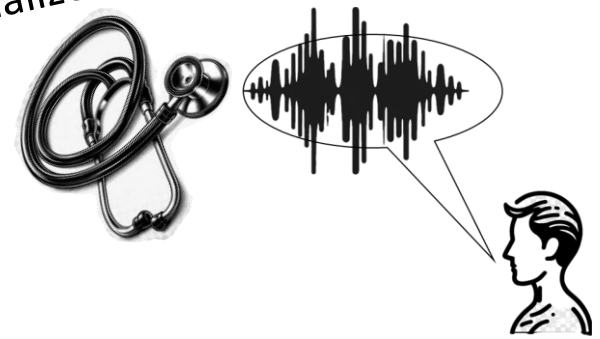
enables "both/and" solutions to measurement

Add objective measures to our trials



reduce the burden of drug development protocols!

personalized medicine via drug-device



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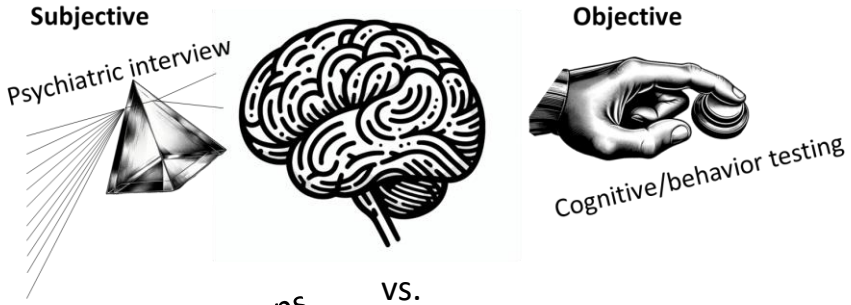

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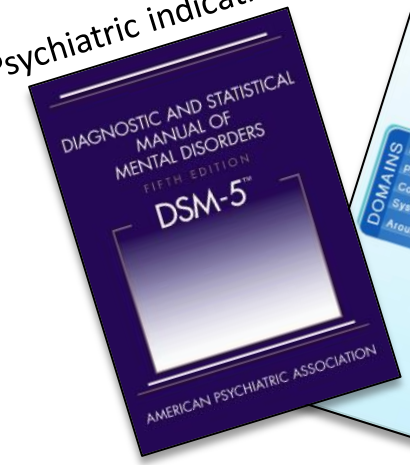

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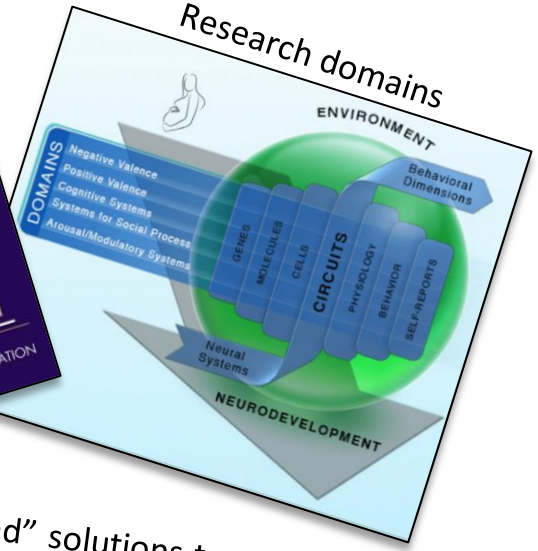

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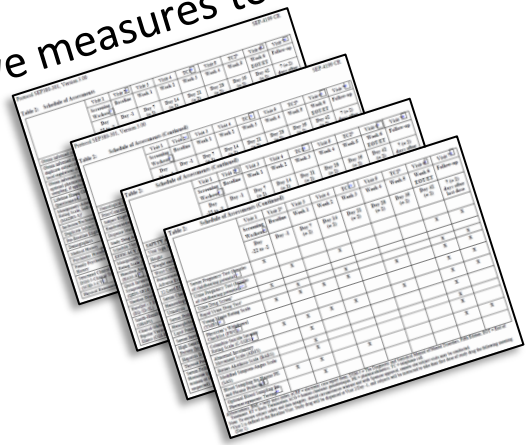

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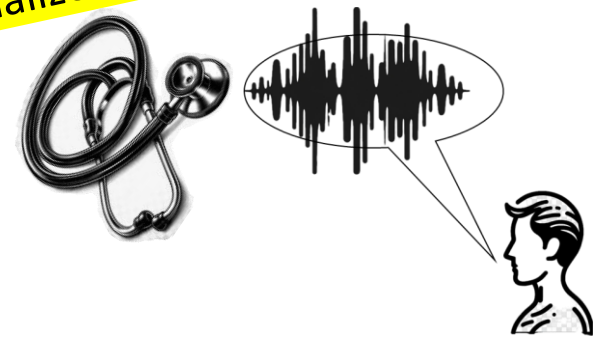

Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs

I. INTRODUCTION

The purpose of this guidance is to assist industry in developing enrichment strategies that can be used in clinical investigations intended to demonstrate the effectiveness of drug and biological products. Enrichment is the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population. Although this guidance focuses on enrichment directed at improving the ability of a study to detect a drug's effectiveness, similar strategies can be used in safety assessments.

The enrichment strategies described in this guidance are intended to increase the efficiency of drug development and support precision medicine, i.e., tailoring treatments to those patients who will benefit based on clinical laboratory, genomic, and proteomic factors. This guidance also discusses design options for enrichment strategies and discusses the interpretation of the results of studies that use enrichment strategies.

Three broad categories of enrichment strategies as listed below are addressed in this guidance:

(1) Strategies to decrease variability — These include choosing patients with baseline measurements of a disease or a biomarker characterizing the disease in a narrow range (decreased interpatient variability) and excluding patients whose disease or symptoms improve spontaneously or whose measurements are highly variable (decreased intrapatient variability). The decreased variability provided by these strategies would increase study power (see section III., Decreasing Variability).

(2) Prognostic enrichment strategies — These include choosing patients with a greater likelihood of having a disease-related endpoint event (for event-driven studies) or a substantial worsening in condition (for continuous measurement endpoints) (see section IV., Prognostic Enrichment Strategies — Identifying High-Risk Patients). These strategies would increase the absolute effect difference between groups but would not be expected to alter relative effect.

(3) Predictive enrichment strategies — These include choosing patients who are more likely to respond to the drug treatment than other patients with the condition being treated. Such selection can lead to a larger effect size (both absolute and relative) and can permit use of a smaller study population. Selection of patients could be based on a specific aspect of a patient's physiology, a biomarker, or a disease characteristic that is related in some manner to the study drug's mechanism. Patient selection could also be empiric (e.g., the patient has previously appeared to respond to a drug in the same class) (see section V., Predictive Enrichment — Identifying More-Responsive Patients).

An example application of Speech Latency for enrichment and patient selection

Research paper
Journal of Affective Disorders 296 (2022) 549–558

A Randomized, Double-blind, Placebo-controlled Proof-of-Concept Trial to Evaluate the Efficacy and Safety of Non-racemic Amisulpride (SEP-4199) for the Treatment of Bipolar I Depression

Antony Loebel [a], Kenneth S. Koblan [a,*], Joyce Tsai [a,1], Ling Deng [a], Maurizio Fava [b], Justine Kent [a,1], Seth C. Hopkins [a]

[a] Sunovion Pharmaceuticals Inc., Marlborough, MA, United States of America
[b] Department of Psychiatry, Massachusetts General Hospital, and Harvard Medical School, Boston, MA, United States of America

Subjects without psychomotor slowing at baseline

MADRS

getting better

40
20
0

?

placebo

active drug

840 ms

psychomotor slowing

0 1 2 3 4

Speech Latency at **baseline** (seconds)

An example application of Speech Latency for enrichment and patient selection

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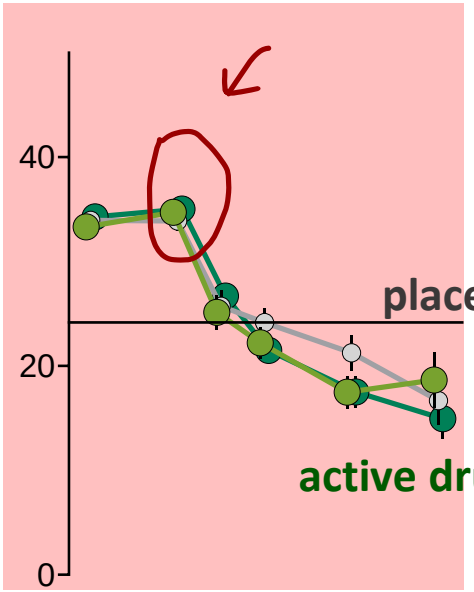
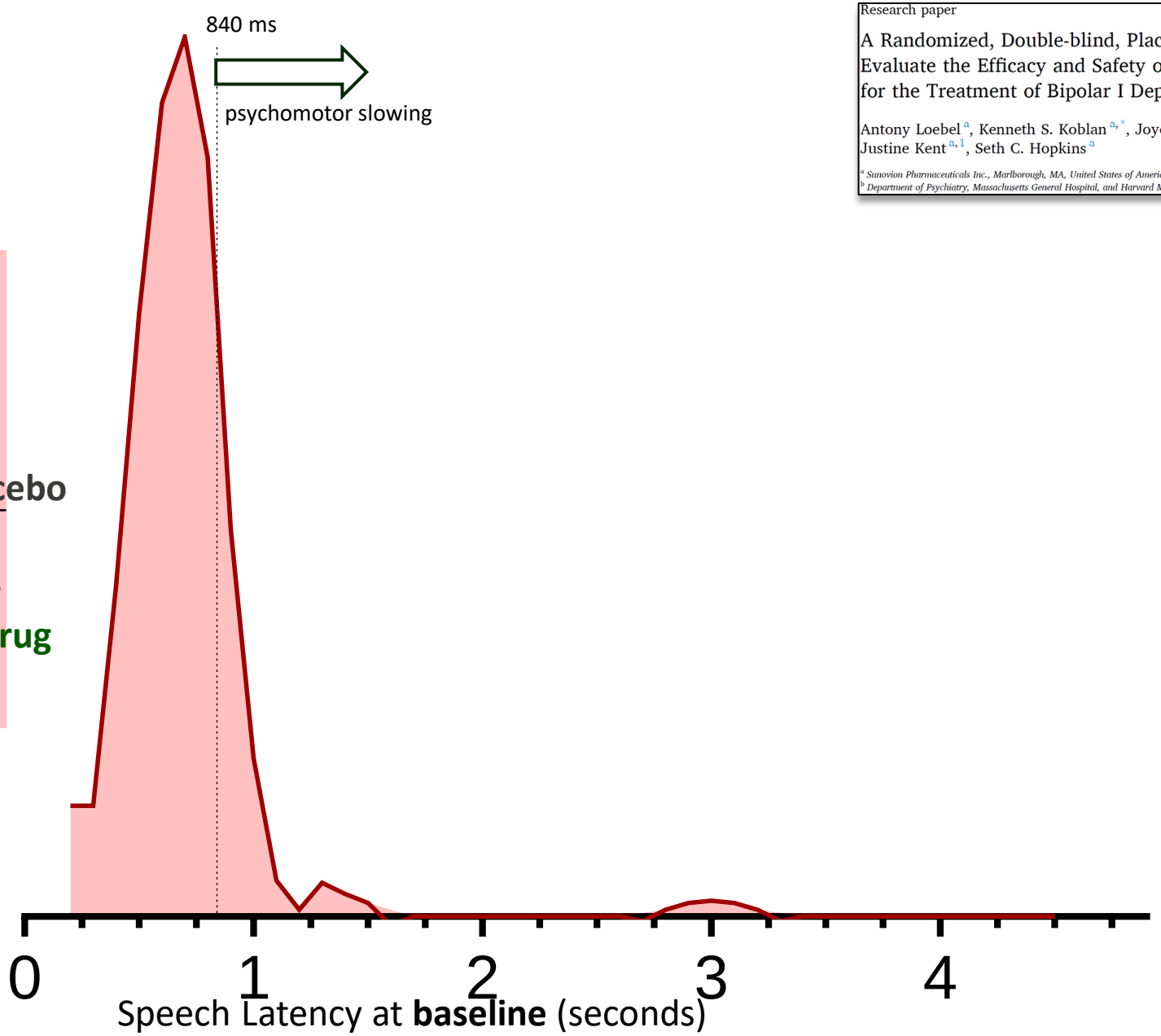


large placebo change, inability to detect drug effect



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840 ms

psychomotor slowing

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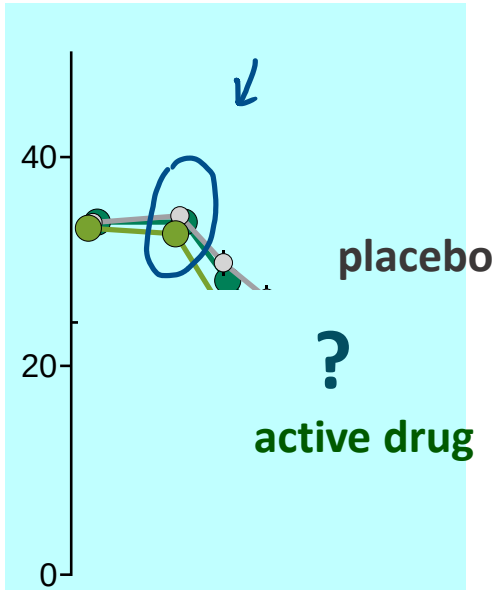
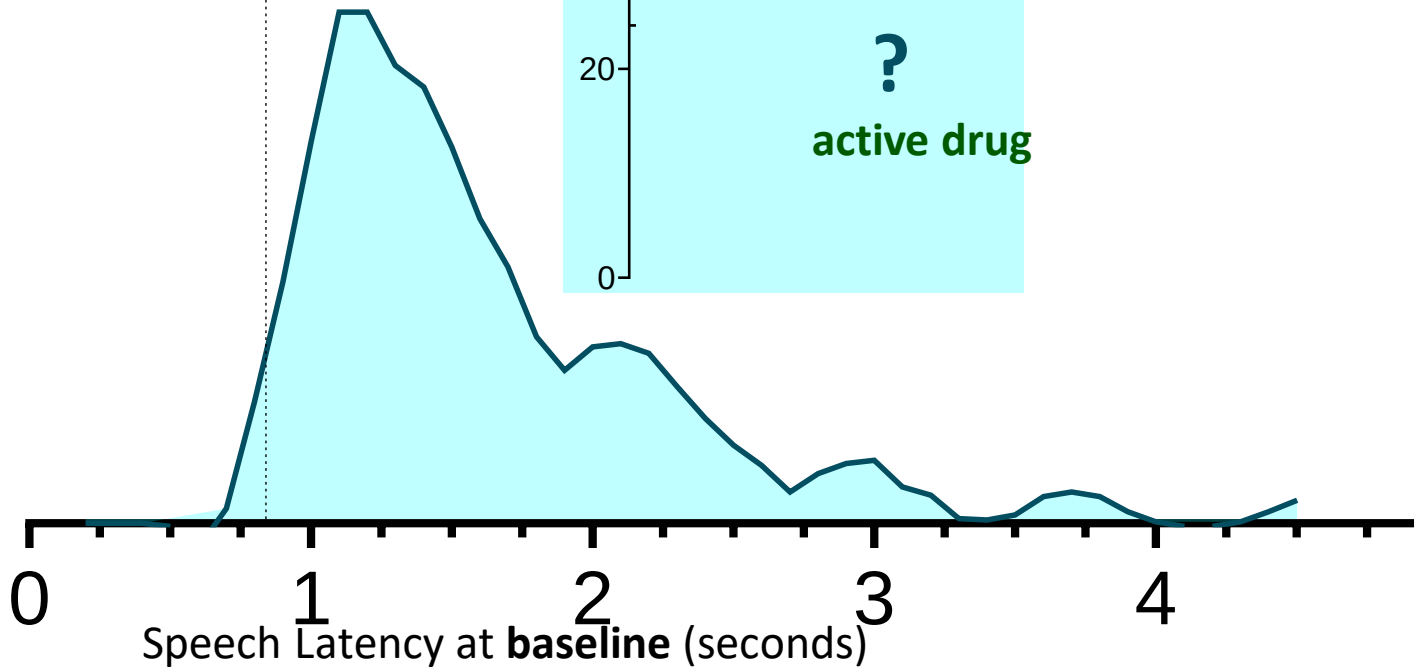


MADRS

getting better



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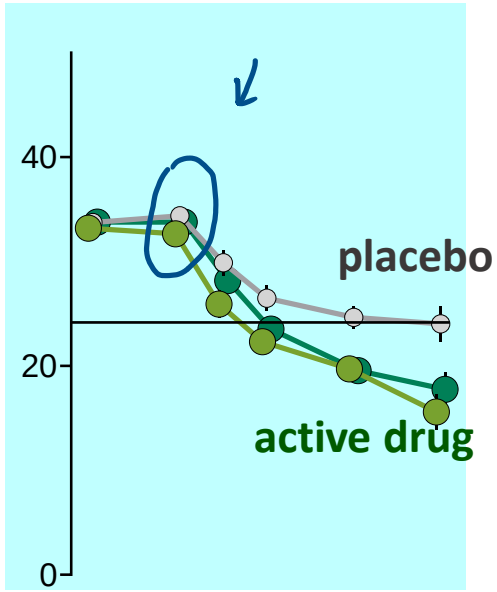
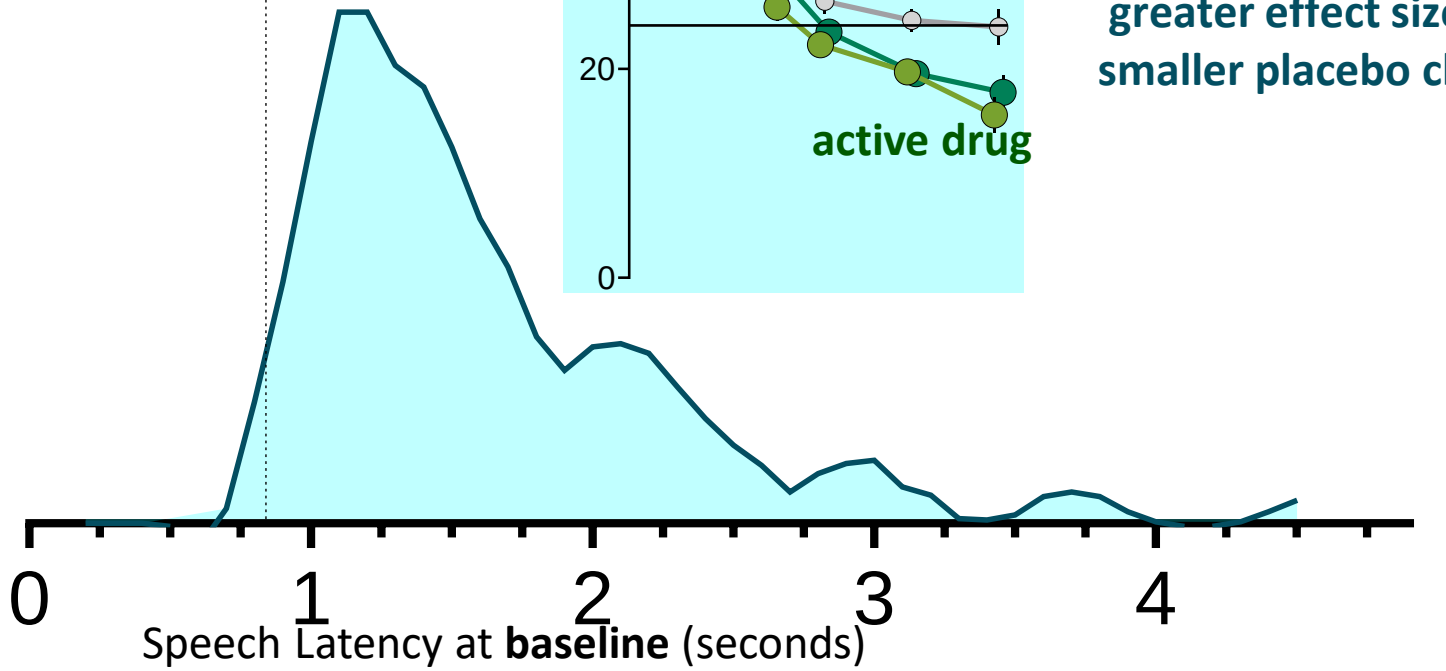


greater effect size, smaller placebo change



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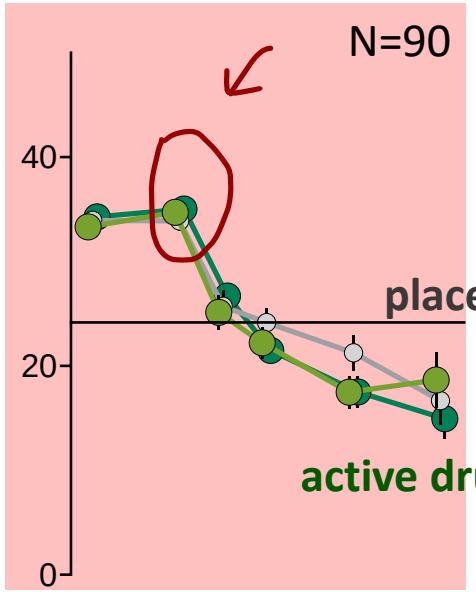

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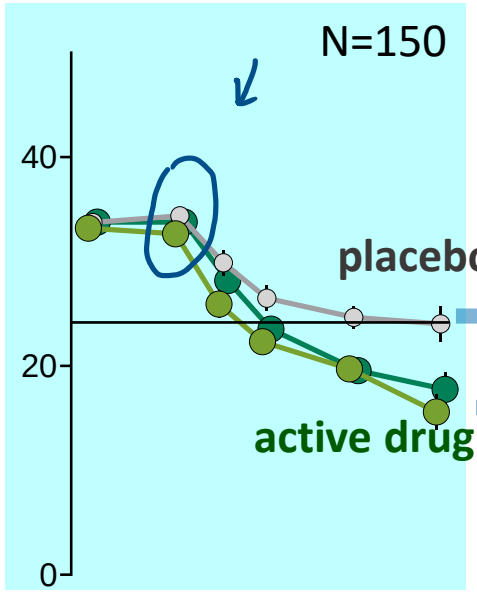

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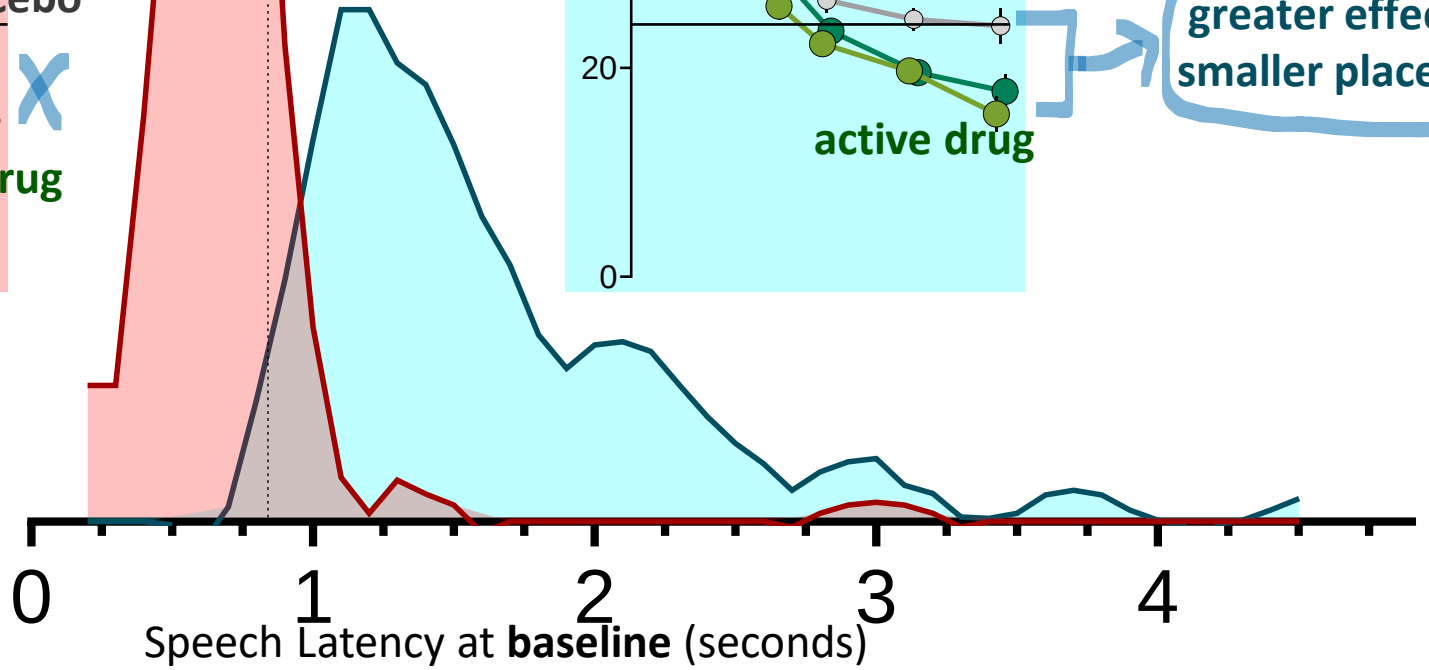
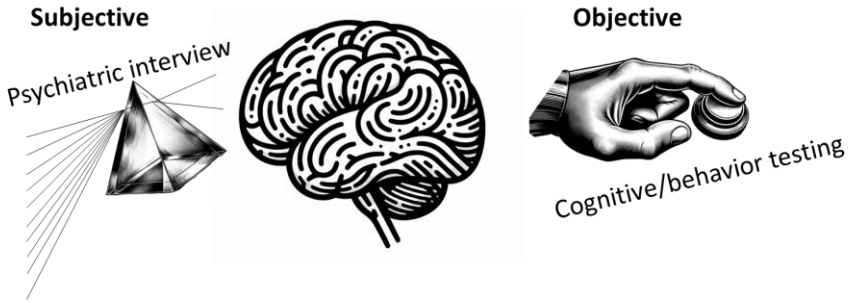


reduce burden



enrichment

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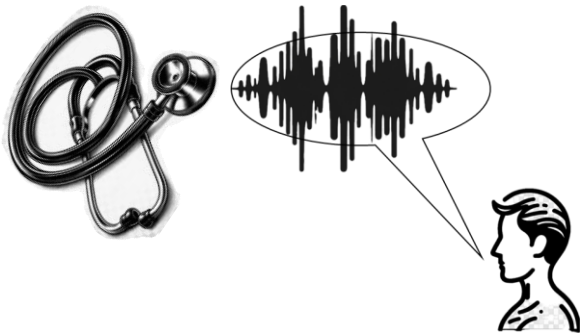
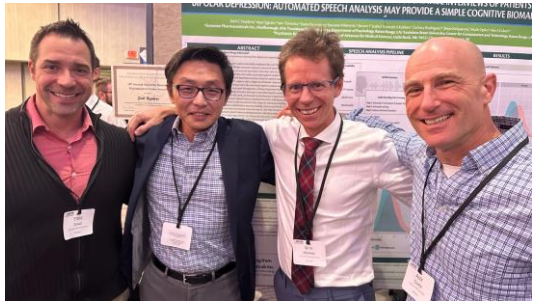
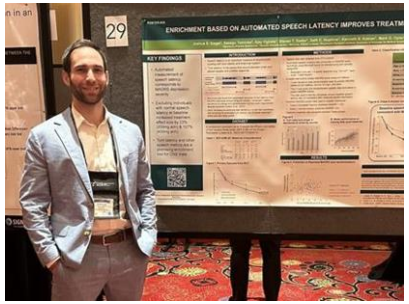
drug-device



Ken Koblan
Steve Szabo
Josh Siegel
Ajay Ogirala
Daria Piacentino
Snezana Milanovic
Sam Tomioka
Carson Tao





Steve Sam Seth Alex Josh

Alex Cohen
Mark Opler
Brian Kirkpatrick

Anzar Abbas