We aren’t a drug and we aren’t a psychotherapy

Presenter Disclosure

- The cognitive training software described in this presentation was supplied free of charge by Positscience Inc.
- Sophia Vinogradov is a site PI on an NIMH SBIR grant to PositScience Inc., a company with a commercial interest in cognitive training software.
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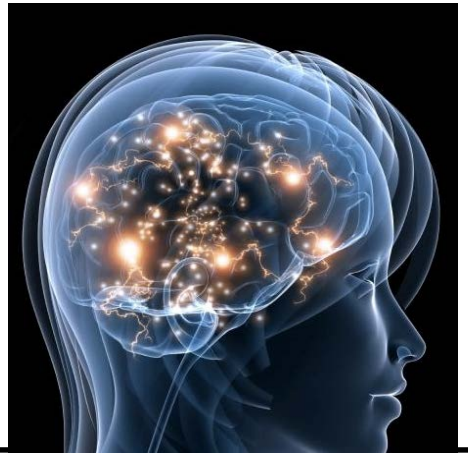


Symptoms

Time

DIAGNOSIS

Trial design and methods issues and solutions are (mostly) well-developed for drug studies and psychotherapy studies

Drug Studies

- Design: placebo-controlled vs. best comparator
- Triple-blind (pt, provider, assessor)
- Dosing worked out in Phase 2 studies– everyone gets same "dose" in terms of mg
- (Measure blood levels)
- Serial measures of response*
- Usually no direct way of knowing which MoAs are engaged or how MoA relates to clinical effects

Psychotherapy studies

- Design: Wait-list control vs. active comparator
- Providers not blind, pts usually not blind
- Ideally use assessors blind to group assignment
- Very difficult to establish optimal dosing or to measure dose
- Use manualized protocols
- Assess fidelity of adherence to protocols
- Ideally use serial measures of response*
- Can assess whether psychological MoA has been engaged (?)
- Cannot rule out other MoA

*Usually rely on self-report; repeated measures raises the issue of practice effects, esp for cognitive measures

But for Cognitive Training Studies…

No such thing as a placebo… so what are the best active comparators?

What kind of blinding is possible?

How to establish optimal dosing? How to measure dose received? Is it the performance threshold reached? The degree of individual improvement? Something else?

Measures of response need to include the cognitive training effects (improvement on the trained skill) as well as the generalized behavioral outcome effects... But what about identifying specific intervention targets and critical underlying MoAs?

And what if practice effects on measures of response are related to MoA?

A tale of two (failed) studies

Dickinson et al. 2009: A randomized controlled trial of computer-assisted cognitive remediation in schizophrenia

Dickinson et al. 2009:

N = 34 active, 27 control

Active comparator = computerized “games” with same intensive coaching

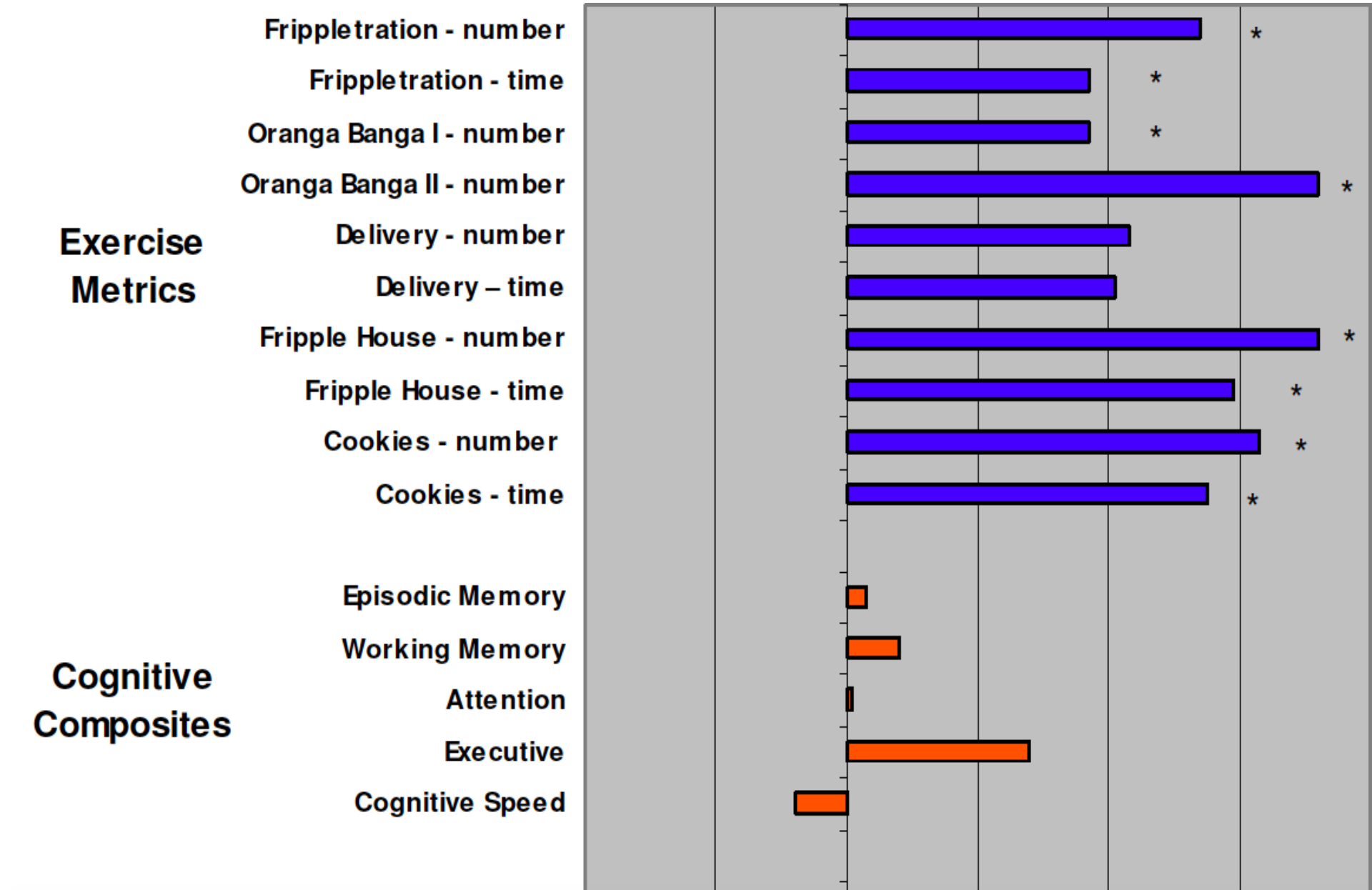
Dosing arbitrarily set at 36 hours of intervention over 4 months

Patients and assessors were blind to group assignment; coaches knew the condition

Range of engaging computerized exercises plus coaching, focused in an unspecified manner on processing speed, attention, working memory, episodic memory, and reasoning/problem solving.

No target or MoA specified.

Control condition: individualized computer activities plus coaching.


Exercise Metrics
Fripplетration - number
Fripplетration - time
Oranga Banga I - number
Oranga Banga II - number
Delivery - number
Delivery – time
Fripple House - number
Fripple House - time
Cookies - number
Cookies - time
Cognitive Composites
Episodic Memory
Working Memory
Attention
Executive
Cognitive Speed
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Funding Opportunity Title	Exploratory Clinical Trials of Novel Interventions for Mental Disorders (R61/R33)

Funding Opportunity Purpose	The purpose of this Funding Opportunity Announcement (FOA) is to support the efficient pilot testing of novel interventions for mental disorders in adults and children through an experimental therapeutics approach. Under this FOA, trials must be designed so that results, whether positive or negative, will provide information of high scientific utility and will support "go/no-go" decisions about further development or testing of the intervention. Studies of novel interventions include, but are not limited to behavioral, pharmacological, biologics-based, cognitive, device-based, interpersonal, physiological, or combined approaches. Support will be provided for up to two years (R61 phase) for preliminary milestone-driven testing of the intervention's engagement of the therapeutic target, possibly followed by up to 3 years of support (R33 phase) for studies to replicate target engagement and relate change in the intervention target to functional or clinical effects. Ultimately, this R61/R33 FOA is intended to speed the translation of emerging basic science findings of mechanisms and processes underlying mental disorders into novel interventions that can be efficiently tested for their promise in restoring function and reducing symptoms for those living with mental disorders.

THE EXPERIMENTAL MEDICINE MODEL: TARGET DEFINITION, TARGET ENGAGEMENT, ASSOCIATION OF TARGET ENGAGEMENT TO DESIRED OUTCOME

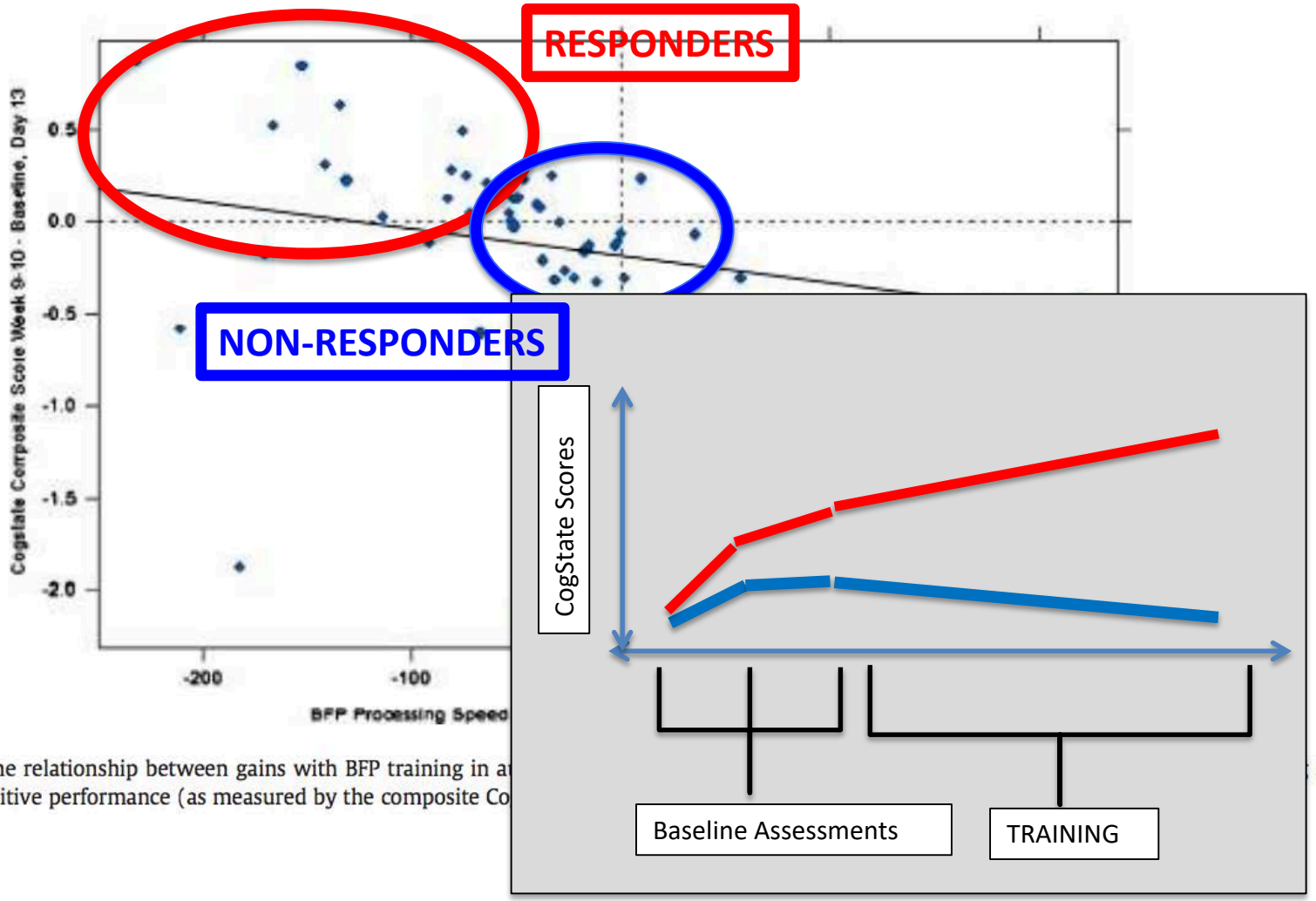
Define the target: Develop experimental hypothesis about pathophysiologic mechanisms (treatment targets) that are related to clinical outcome

Develop an experimental intervention that engages the hypothesized target (MoA)

Assess whether the intervention moves the target and the outcome measures in the desired direction

Determine whether target engagement shows a relationship to desired clinical outcome: Comfirm/disconfirm the hypothesis

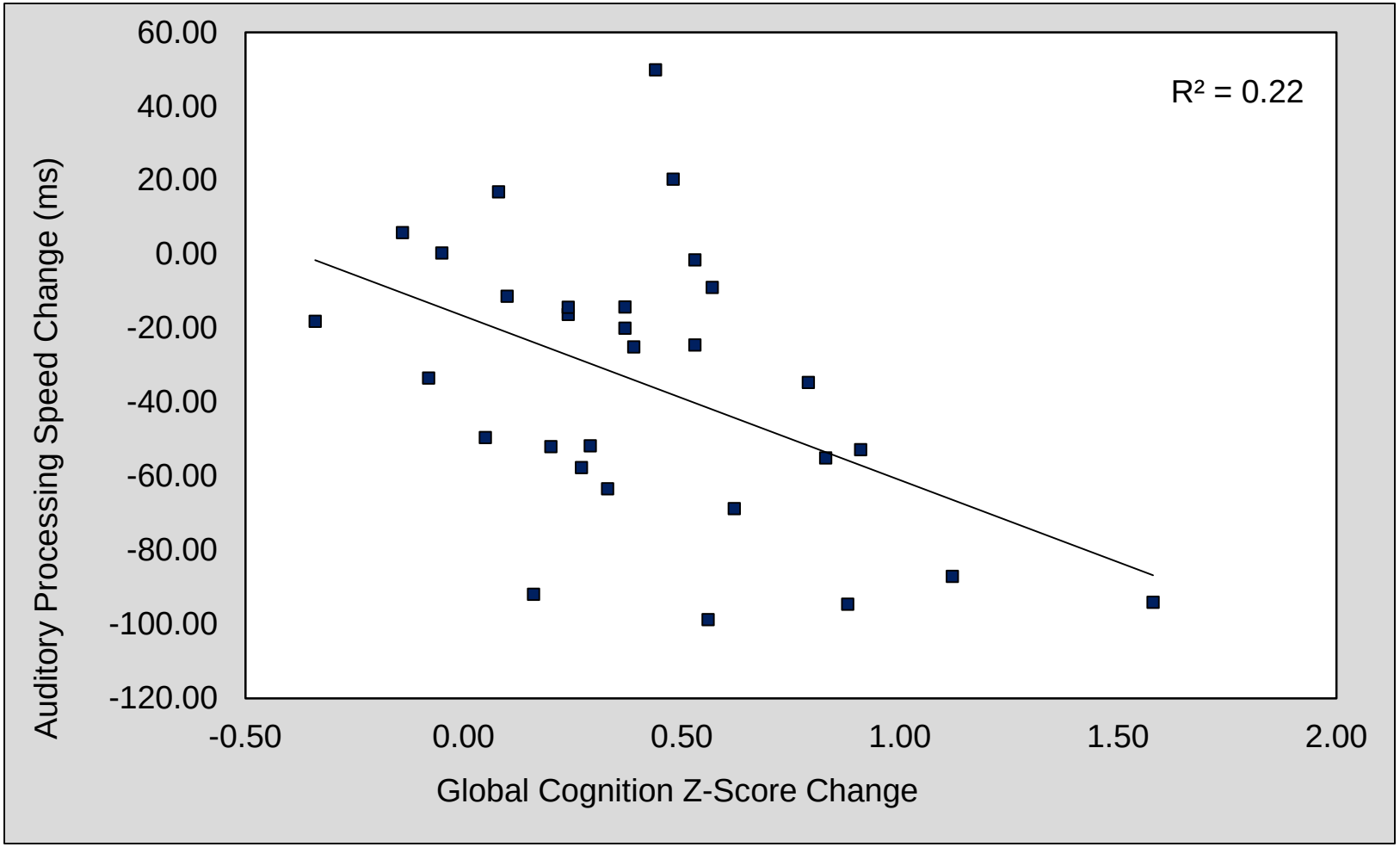
Murthy et al. 2012: Computerized cognitive remediation training for schizophrenia: An open label, multi-site, multinational methodology study



rplot showing the relationship between gains with BFP training in a spe
baseline in cognitive performance (as measured by the composite Co

Murthy et al Schiz Res 2012

Auditory system target engagement at 20 hrs correlates with training-induced cognitive gains at 40 hrs



Fisher et al Schiz Bull 2014

Auditory system target engagement is best defined as "learning" (plasticity) over time

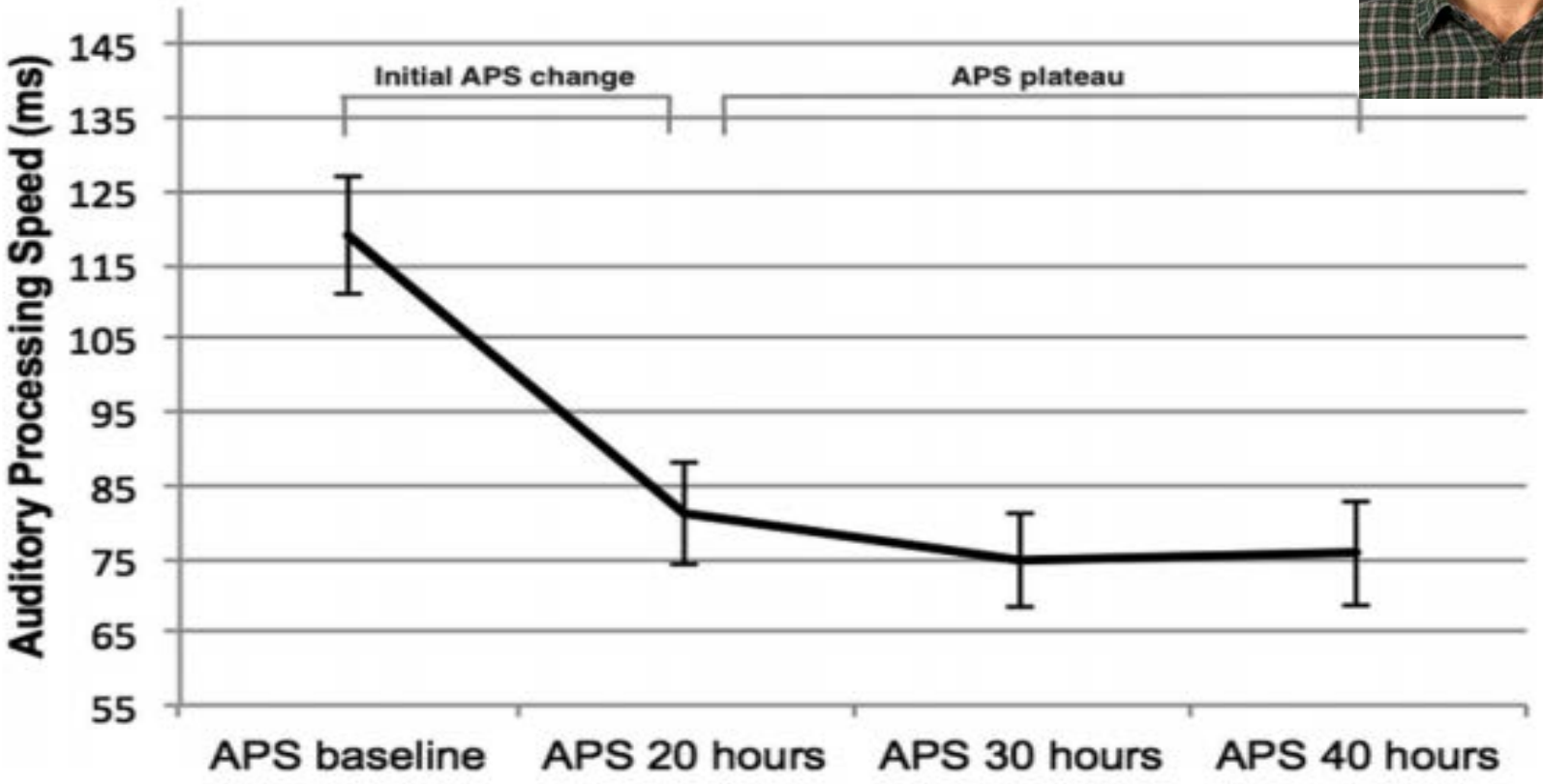
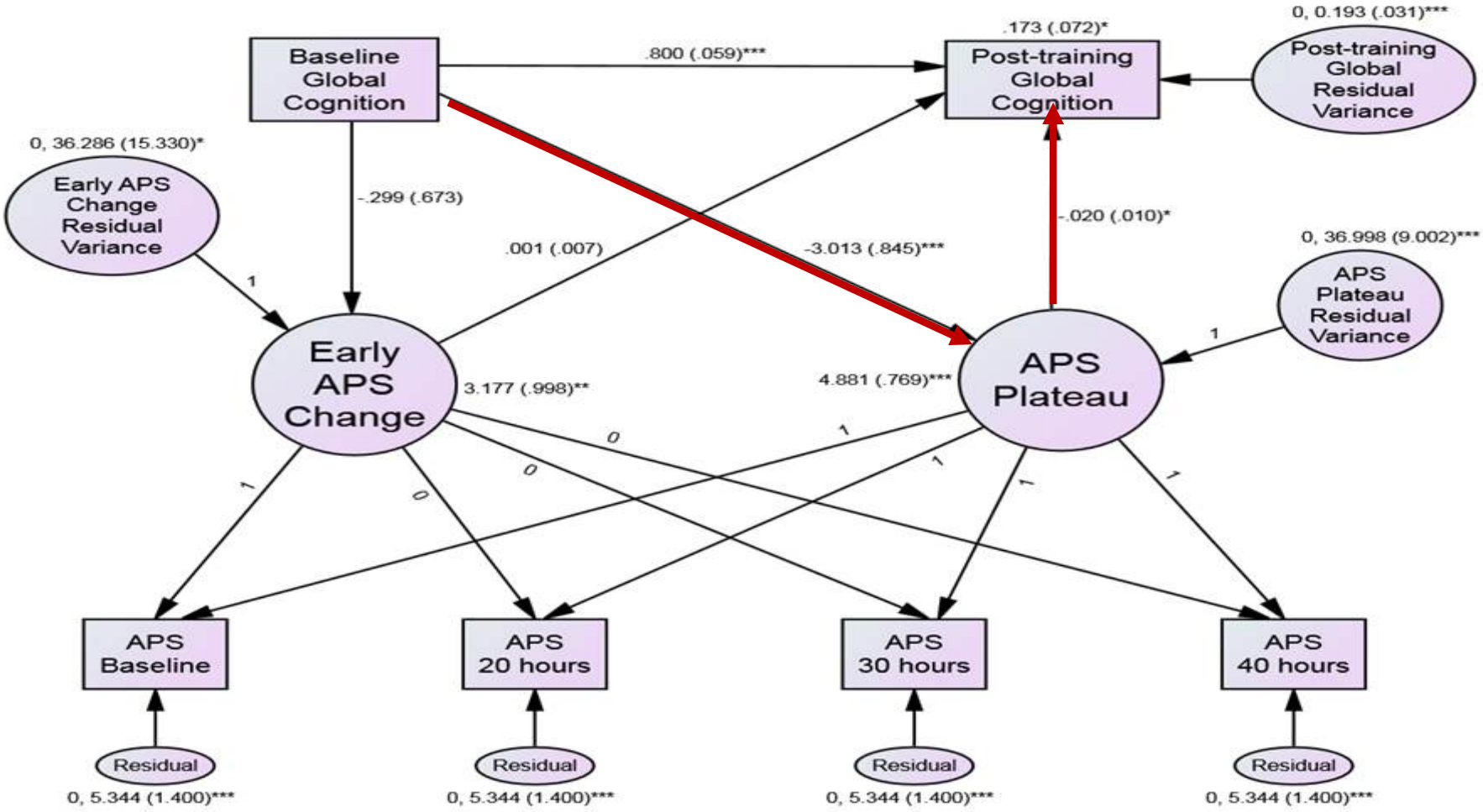


Figure 2. Trajectory of auditory processing speed (APS) over time, as indexed by APS scores at baseline, and after 20, 30 and 40 hours of auditory TCT (n = 131). Error bars represent standard errors of the means.

Biagianti et al Neuropsychol 2016

Latent growth curve modeling indicates that auditory system "learning" (plasticity) mediates training-induced cognitive gains



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THE EXPERIMENTAL MEDICINE MODEL: TARGET DEFINITION, TARGET ENGAGEMENT, ASSOCIATION OF TARGET ENGAGEMENT TO DESIRED OUTCOME

Define the target: Develop experimental hypothesis about pathophysiologic mechanisms (treatment targets) that are related to clinical outcome

→

- Target: Impaired operations in auditory processing
- Hypothesis: Improving these operations will drive gains in cognition

Develop an experimental intervention that engages the hypothesized target (=mechanism of action)

→

PERFORM AUDITORY SYSTEM TRAINING

USE A RIGOROUS CONTROL

Assess whether the intervention moves the target and the outcome measures in the desired direction

→

- Assess auditory system operations before, during, and after the 2 conditions
- Assess cognition before and after the 2 conditions

Determine whether target engagement shows a relationship to desired clinical outcome: Comfirm/disconfirm the hypothesis

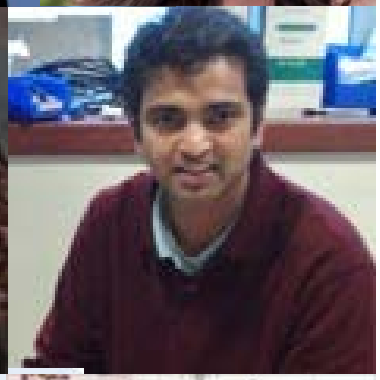
→

- Auditory system processing efficiency is impaired at baseline, improves during training, and is significantly better after training (but not in control condition)
- Training induces cognitive gains compared to control condition
- Auditory system changes mediate cognitive gains

Methods issues unique to cognitive training trials

- ~~What are the best active comparators?~~
- ~~How do we achieve "blinding"?~~
- ~~How do we determine optimal dose?~~
- How do we define treatment target(s) and MoA? (E.g., WM can be a target, but is the MoA for enhancing WM better representation of salient stimuli? Better suppression of task-irrelevant stimuli? Increased overall capacity? etc.)
- How do we demonstrate target engagement?
- How do we incorporate key dynamic features of learning rate or "plasticity capacity" into our measures of target engagement and our measures of response outcomes?



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