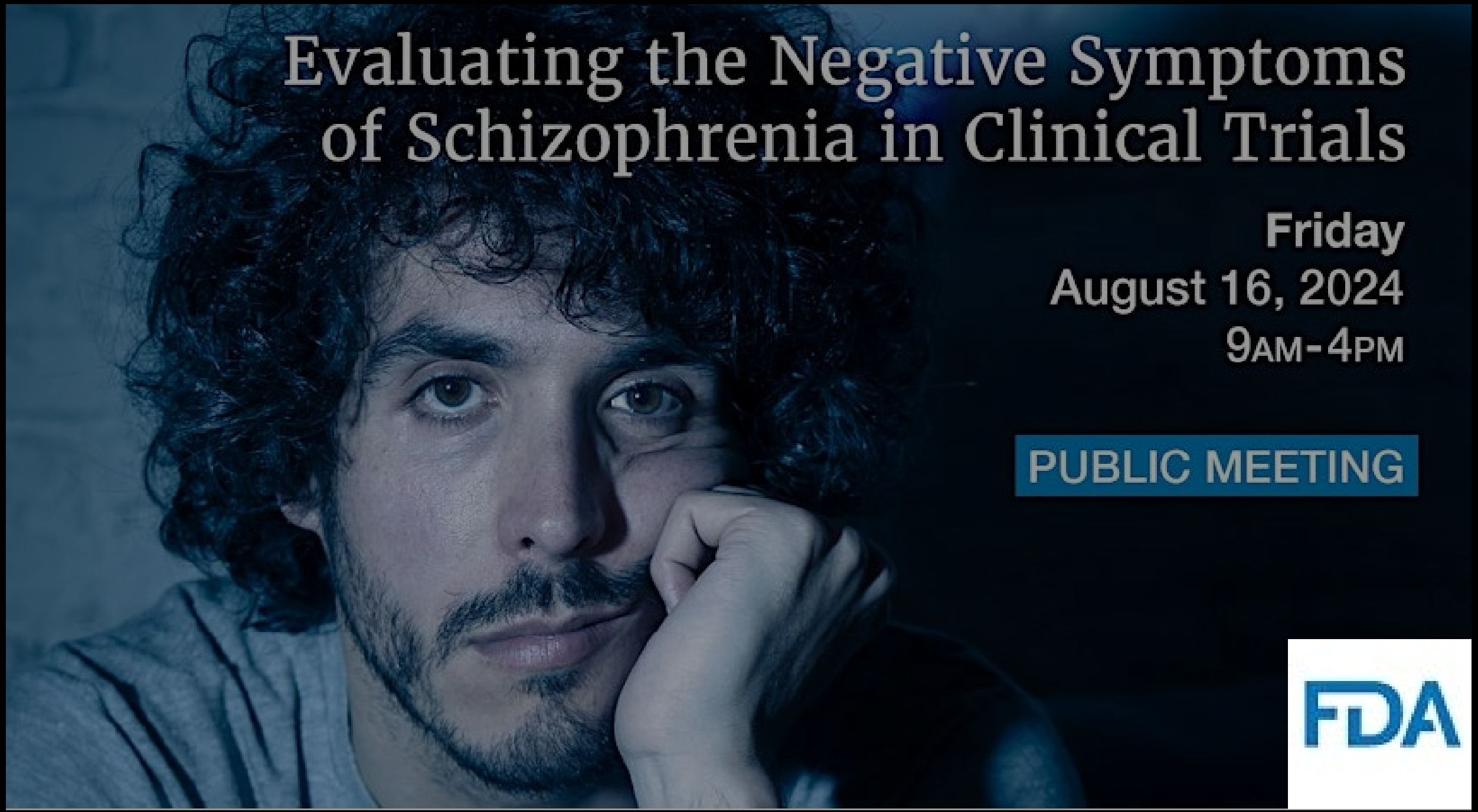

Evaluating the Negative Symptoms of Schizophrenia in Clinical Trials
Friday
August 16, 2024
9AM-4PM
PUBLIC MEETING
FDA

Evaluating the Negative Symptoms of Schizophrenia in Clinical Trials

AUGUST 16, 2024

Welcome

Teresa Buracchio, MD

Director, Office of Neuroscience (ON), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)

Introduction

Bernard A. Fischer, MD
Deputy Director, Division of Psychiatry

U.S. FOOD & DRUG ADMINISTRATION

Introduction to Negative Symptoms

Evaluating the Negative Symptoms of Schizophrenia in Clinical Trials:
A Public Meeting · August 16, 2024

Bernard A. Fischer, MD
Deputy Director, Division of Psychiatry

Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Bernard.Fischer@fda.hhs.gov

Outline

- Early descriptions of negative symptoms
- Origin of the terminology
- What are the negative symptoms?
- Negative symptoms impact on public health
- Describing populations for clinical trials: The 3 Ps
  - Predominant negative symptoms
  - Primary versus /secondary negative symptoms
  - Persistent negative symptoms

Early Descriptions

- Emil Kraepelin description of schizophrenia (dementia praecox)

  "…a weakening of those emotional activities that permanently form the well-spring of volition… The result of this… is emotional dullness, failure of mental activities, loss of mastery over volition…" (p.74)

  Dementia Praecox and Paraphrenia

- Eugen Bleuler (coined term "schizophrenia")

  "Where affect is lacking, there will also be lacking the drive to pursue external and internal processes…" (p.68)

  Dementia Praecox or the Group of Schizophrenias

Positive vs Negative Symptoms

- 1974 John Strauss, Will Carpenter, John Bartko:
  - Positive symptoms “have the appearance of being active processes”
    - For example: delusions, hallucinations
  - Negative symptoms involve an “absence of normal functions”
    - Examples next two slides

Negative Symptoms

- Blunted Affect:
  - Unchanging facial expression
  - Decreased spontaneous movements
  - Lack of expressive gestures
  - Affective nonresponse
  - Poor eye contact
  - Lack of vocal inflection
- Alogia: Poverty of speech

Negative Symptoms

- Avolition/Apathy:
  - Poor grooming/hygiene
  - Physical inactivity
  - Difficulty seeking/keeping employment
- Anhedonia:
  - Few interests/hobbies
  - Decrease in sexual interests (including masturbation)
- Asociality:
  - Few intimate relationships (including with family)
  - Few friends, may appear isolated in social settings

Negative Symptoms

- Single construct? Variable presentation

- Two factors?
  - Emotional Expression (EXP)
    - Blunted Affect, Alogia
  - Motivation and Pleasure (MAP)
    - Anhedonia, Asociality, Avolition

- Five factors?

1. Blunted Affect
2. Alogia
3. Anhedonia
4. Asociality
5. Avolition

Negative Symptoms: Clinical Importance

- Poor functional outcome (work, school, household)
  - Motivation and Pleasure or Amotivation factors
- Low rates of recovery
- Poor subjective quality of life

Three Ps of Negative Symptoms

- Predominant negative symptoms
- Primary negative symptoms
- Persistent negative symptoms

Three Ps of Negative Symptoms

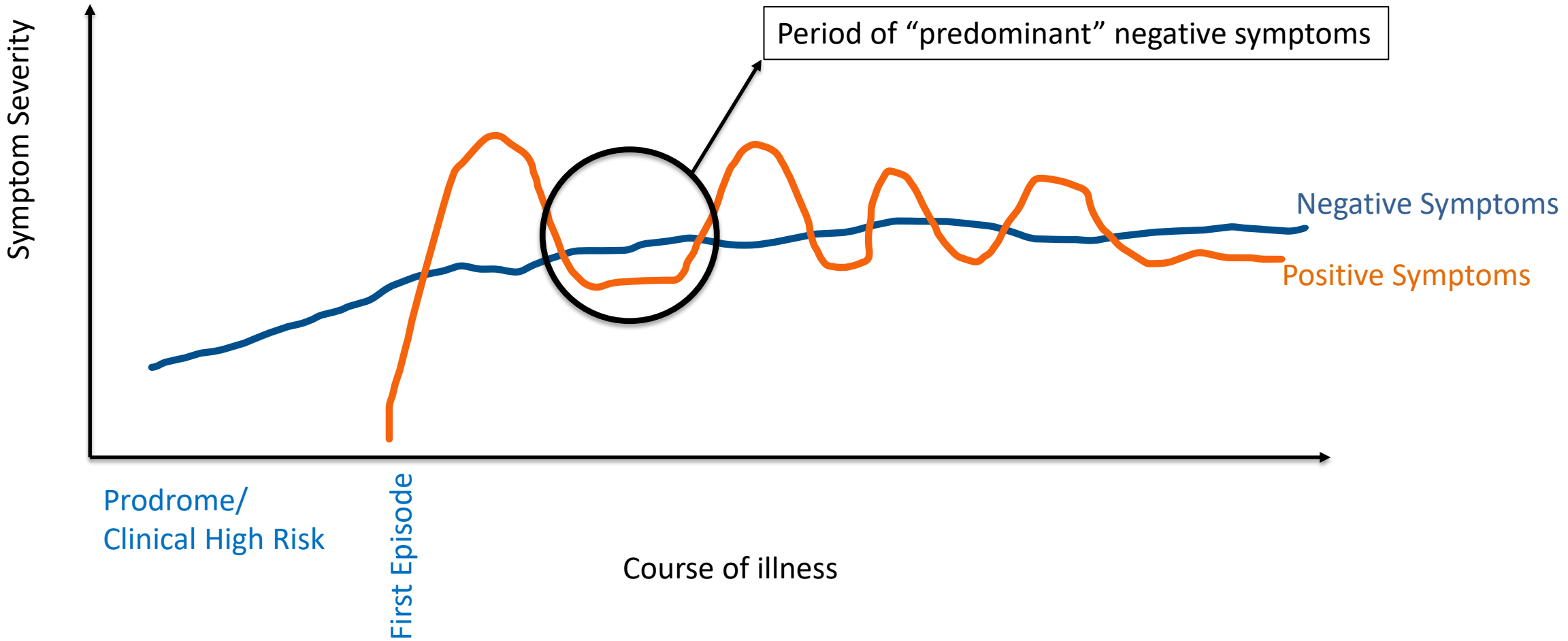
- Predominant negative symptoms (and the relationship to positive symptoms)

- Primary negative symptoms

- Persistent negative symptoms

Predominant Negative Symptoms

- Positive symptoms required for schizophrenia diagnosis
  - Tend to wax and wane
- Negative symptoms independent of positive symptoms
  - More stable
- Predominant negative symptoms are greater severity than positive symptoms
  - Whether negative symptoms predominate depends on:
    - Baseline negative symptom severity
    - Severity of positive symptoms at the moment


Symptom Severity
Period of “predominant” negative symptoms
Negative Symptoms
Positive Symptoms
Prodrome/
Clinical High Risk
First Episode
Course of illness

Three Ps of Negative Symptoms

- Predominant negative symptoms
- Primary negative symptoms
- Persistent negative symptoms

Primary/Secondary Negative Symptoms

- Primary negative symptoms: due to illness of schizophrenia
- Secondary negative symptoms: caused by something else
  - Positive symptoms
    - Paranoia causing social withdrawal
  - Antipsychotic effects
    - Parkinsonism (especially “typical” antipsychotics)
    - Sedation
  - Other mental illness
    - Depression causing anhedonia, lack of motivation
    - PTSD causing avoidance
  - Environmental factors
    - Resource poor environment
    - Internalized stigma (social withdrawal)

Primary/Secondary Negative Symptoms

- Antipsychotics and negative symptoms
  - Antipsychotics may *cause* some secondary negative symptoms
    - Less Parkinsonism with newer, atypical antipsychotics
  - Antipsychotics may *treat* some causes of secondary negative symptoms
    - Examples: depression, paranoia
  - Among people with schizophrenia experiencing an acute exacerbation of positive symptoms, studies show effective antipsychotic treatment decreases negative symptoms...

But after effective antipsychotic treatment, negative symptoms remain

Three Ps of Negative Symptoms

- Predominant negative symptoms
- Primary negative symptoms
- Persistent negative symptoms

Persistent Negative Symptoms

- Negative symptoms often persist after treatment of causes of secondary negative symptoms
  - May be primary, but may also be secondary that failed to respond
    - Difficult to differentiate in most people in the context of a drug trial
- Unmet need that presents a treatment target
- Can be operationalized for a clinical trial
  - At least moderate level of negative symptoms
  - Threshold for low positive symptoms
  - No/low levels of depression/Parkinsonism on rating scale
  - Clinical stability prior to enrollment

Questions for Today

1. What is the target patient population?
   a. Should trials enroll a population based on predominant, primary, or persistent negative symptoms? Is there a better way to define the population of interest?
   b. How should trials ensure the treatment of secondary negative symptoms is optimized before enrollment?

2. How should drug development programs account for real-world antipsychotic use when designing trials?

Questions for Today

3. What is the best way to measure negative symptom improvement in a clinical trial?
   a. Should clinical trials measure negative symptoms as a single score, or should we look at the two factors or five factors separately?
   b. Should we account for cultural differences? If so, how?
   c. What amount of change is meaningful to people? Do we need to see functional improvement?
   d. Are there advantages to using technology in endpoints?

Thank you.

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5. Ahmed AO, et al. Two Factors, Five Factors, or Both? External Validation Studies of Negative Symptom Dimensions in Schizophrenia. Schizophr Bull. 2022;48(3):620-630.
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8. Strauss GP, Harrow M, Grossman LS, Rosen C. Periods of recovery in deficit syndrome schizophrenia: a 20-year multi-follow-up longitudinal study. Schizophr Bull. 2010 Jul;36(4):788-99.

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11. Correll CU, Schooler NR. Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. Neuropsychiatr Dis Treat. 2020;16:519-34.
12. Buchanan RW. Persistent negative symptoms in schizophrenia: An overview. Schizophr Bull. 2007 Jul;33(4):1013-22.

Opening Remarks:
Lived Experience

- How negative symptoms impact people
- What's important to target?

Brandon Staglin, MSHA

President, One Mind (OneMind.org)

Rutherford, CA

Shedding the Chains of Schizophrenia

My Experiences Recovering Volition and Sociality

FDA Evaluating the Negative Symptoms of Schizophrenia in Clinical Trials Meeting

Brandon Staglin, MS

August 16, 2024

My First Episode: A Vortex of Psychotic Dread

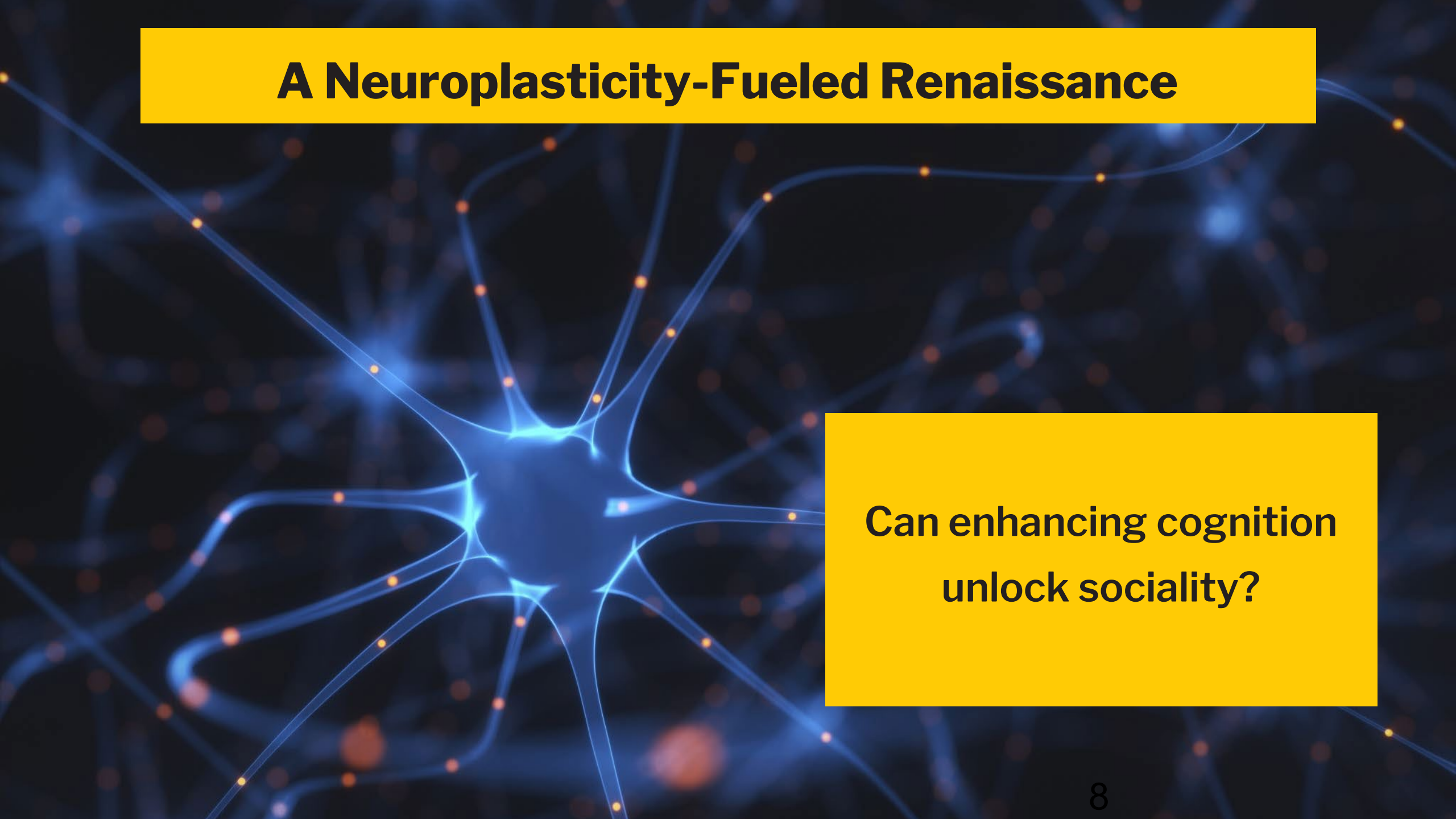
My Second Episode: A Becalmed Backwater

Can enhancing reward anticipation and calming rumination revive volition?

Volition Reignition, No Brakes

Can enhancing cognition help guide volition?

A Neuroplasticity-Fueled Renaissance



Can enhancing cognition unlock sociality?

Music Has Enhanced My Healing

Can musical training treat multiple negative symptoms?

Practicing Sociality Made Me Feel Whole

Take Home Strategies

To strengthen volition, increase reward anticipation and decrease rumination

To improve volition successfully, also strengthen executive function

To improve sociality, enhance cognition then provide opportunities to practice

Negative Symptoms - A Shadow Crisis

Our Challenge Today

Photo Credit: Flying Big Studio

Thank You!
Questions?

Session 1:
Brain Circuits and Relationship to Cognition

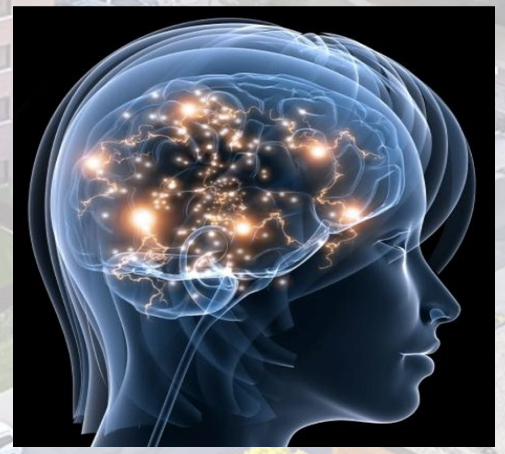
Sophia Vinogradov, MD

Head, Department of Psychiatry & Behavioral Science, Donalf W. Hastings Endowed Chair in Psychiatry, University of Minnesota Medical School

Minneapolis, MN

Negative symptoms:
Cognitive and neural system features

Sophia Vinogradov, MD
University of Minnesota



Disclosures

Boeringer Ingelheim – Advisory Board member

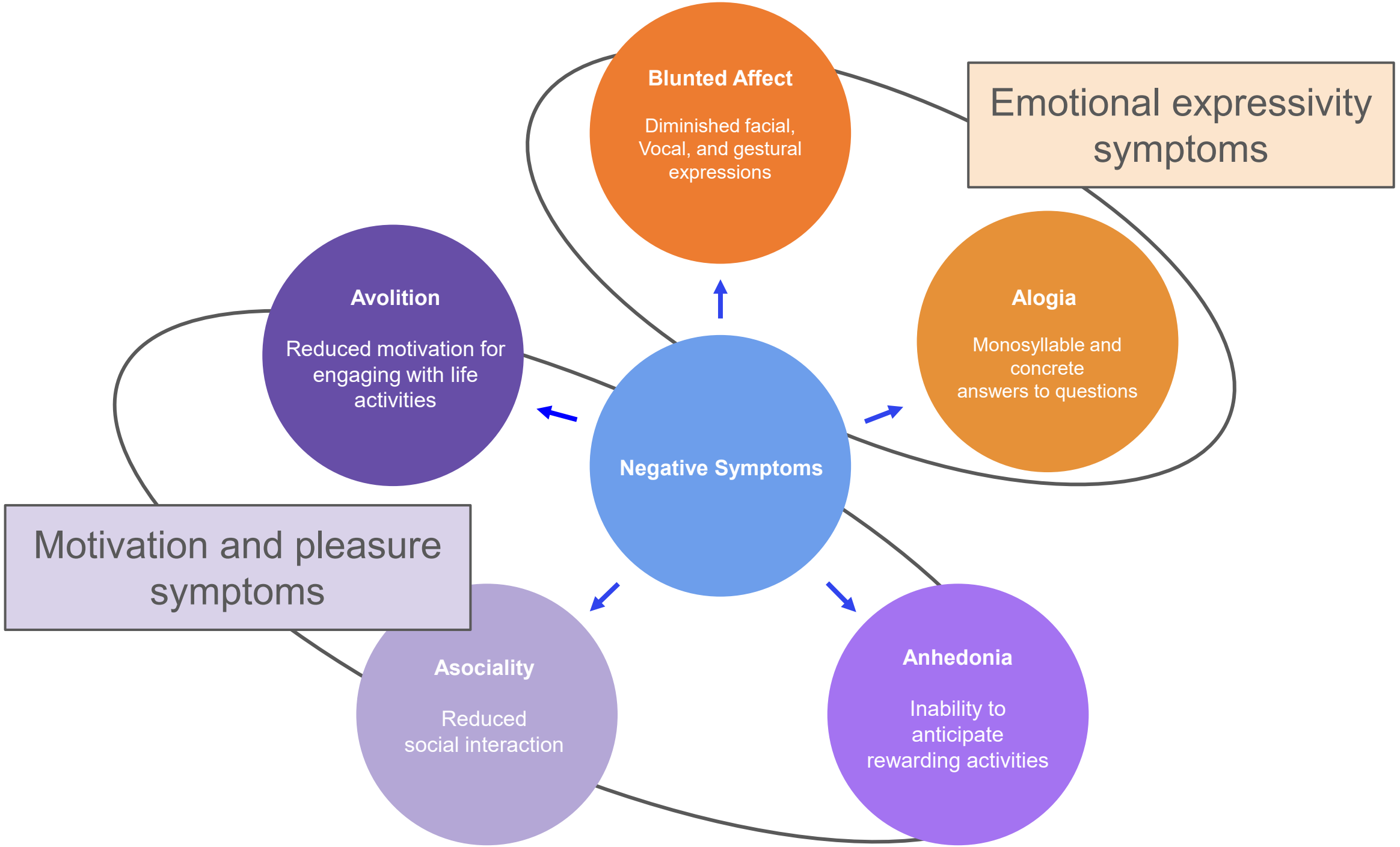
Karuna Therapeutics – Advisory board member

PositScience Inc. – Unpaid scientific collaborator, no financial interest in the company

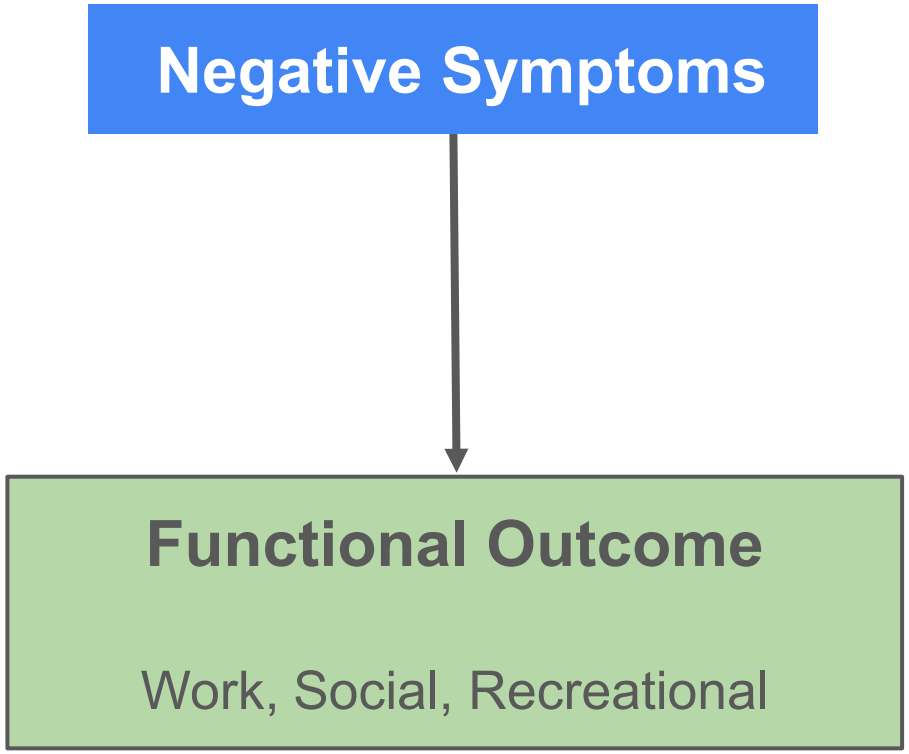
Lynne and Andrew Redleaf Foundation – Research support

National Institute of Mental Health – Research support

Office of Naval Research – Research support


Blunted Affect
Diminished facial, Vocal, and gestural expressions
Emotional expressivity symptoms
Avolition
Reduced motivation for engaging with life activities
Alogia
Monosyllable and concrete answers to questions
Negative Symptoms
Motivation and pleasure symptoms
Asociality
Reduced social interaction
Anhedonia
Inability to anticipate rewarding activities

Functional Impact



Negative symptoms are strongly and consistently associated with poorer functional outcome:

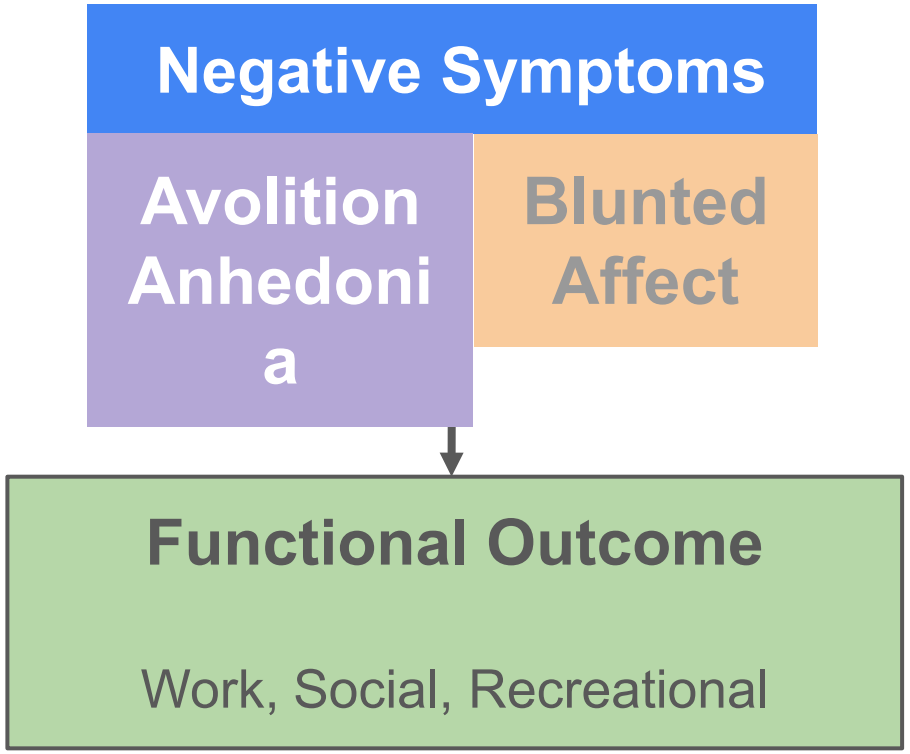
- Even after controlling for secondary neg sx
- Even in people with mild/absent positive sx, depression, anxiety

Fervaha et al, Europ Psychiatry, 2014

Negative symptoms contribute additional variance in predicting real-world functioning, above and beyond cognition and functional capacity

Yang et al, Front Psychiatry, 2021
Schlosser et al, Schiz Res 2015

Domain-specific associations



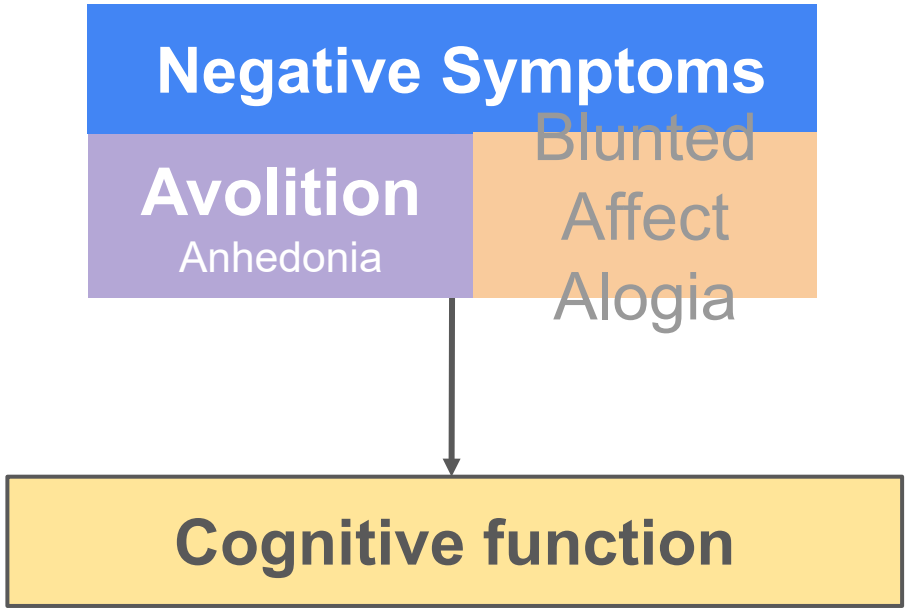
Avolition and anhedonia show strong and consistent domain-specific associations with functional outcome (blunted affect to a lesser degree)

Note: The five domains demonstrate informative domain-specific associations with a range of external validators not revealed by the two-factor approach (N=632)

- Functional outcome
- Psychological measures such as defeatist beliefs
- Cognitive function
- Neural system findings

Ahmed et al., Schiz Bull 2022

Cognitive function



Negative symptoms are associated with disrupted cognitive function in multiple studies, but measurement overlap and clinical confounds must be considered (cognitive observations were included in older negative symptom rating systems)

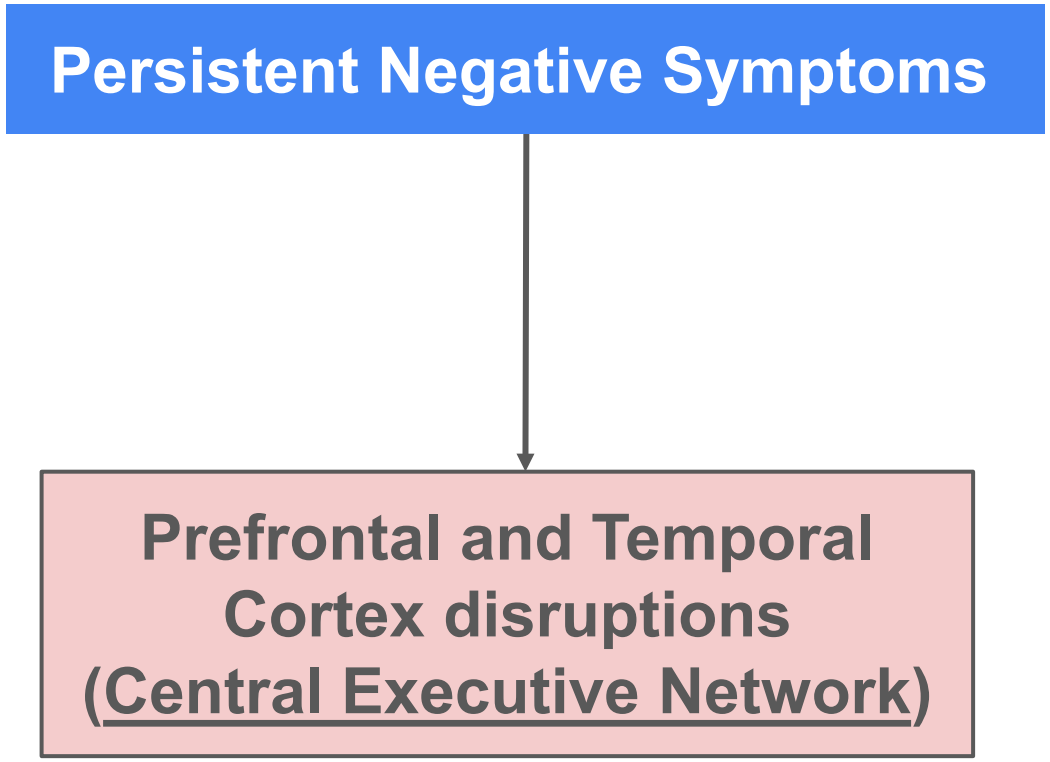
In a recent systematic review of FEP (N=3086), negative symptoms were associated with lower executive function and poorer theory of mind

In Ahmed et al's SEM study of 3 data sets (N= 632) **Avolition** showed a consistent association with disrupted cognition across samples

Associations with Anhedonia, Blunted Affect, and Alogia were also seen

Melillo et al, J Clin Med 2023
Ahmed et al, Schiz Bull 2022

Neural function



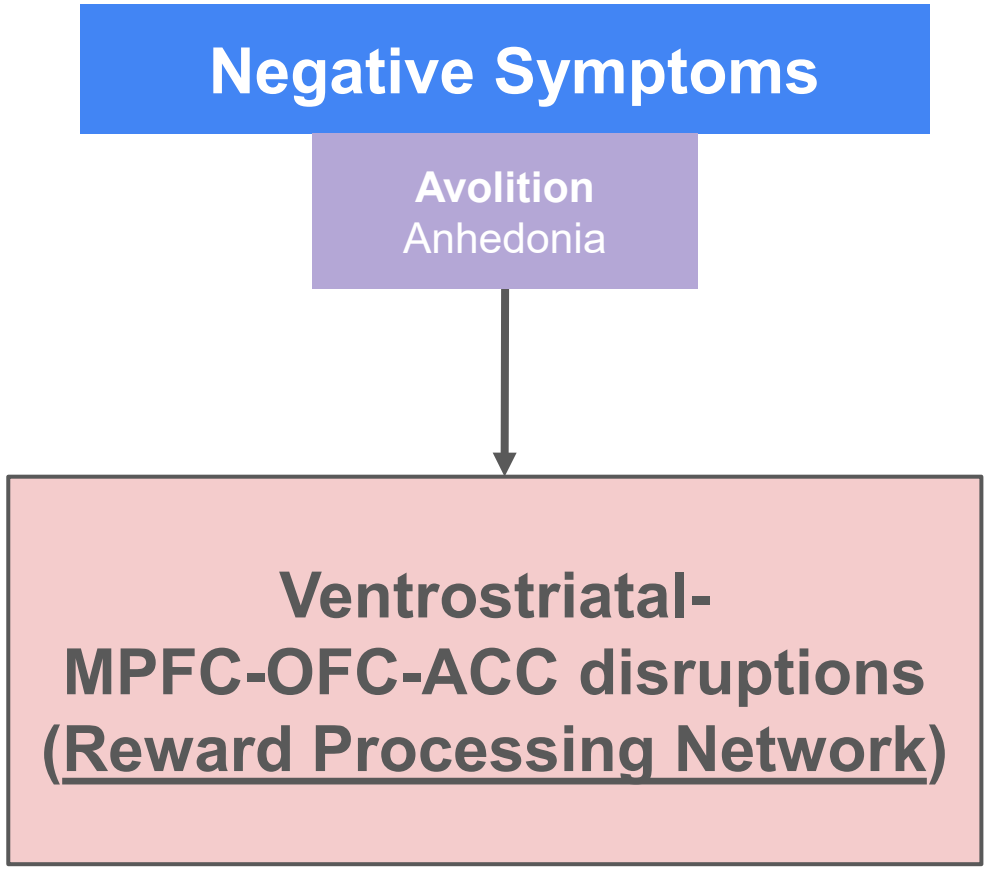
Negative symptoms are associated with disrupted neural function, but findings are inconsistent

Persistent negative symptoms are often associated with structural and functional changes in **prefrontal and temporal cortex.**

In early psychosis, **prefrontal disruptions (e.g., progressive cortical thinning)** are associated with a more severe course of illness, worse functional outcomes, and **increasing negative symptoms**

Hovington & Lepage, Exp Rev Neurother 2012
Tronchin et al, Psychiatry Res: Neuroimaging 2020

Neural function



More recent research “drilling down” into specific domains points to a central role for Avolition and Anhedonia in neural system findings

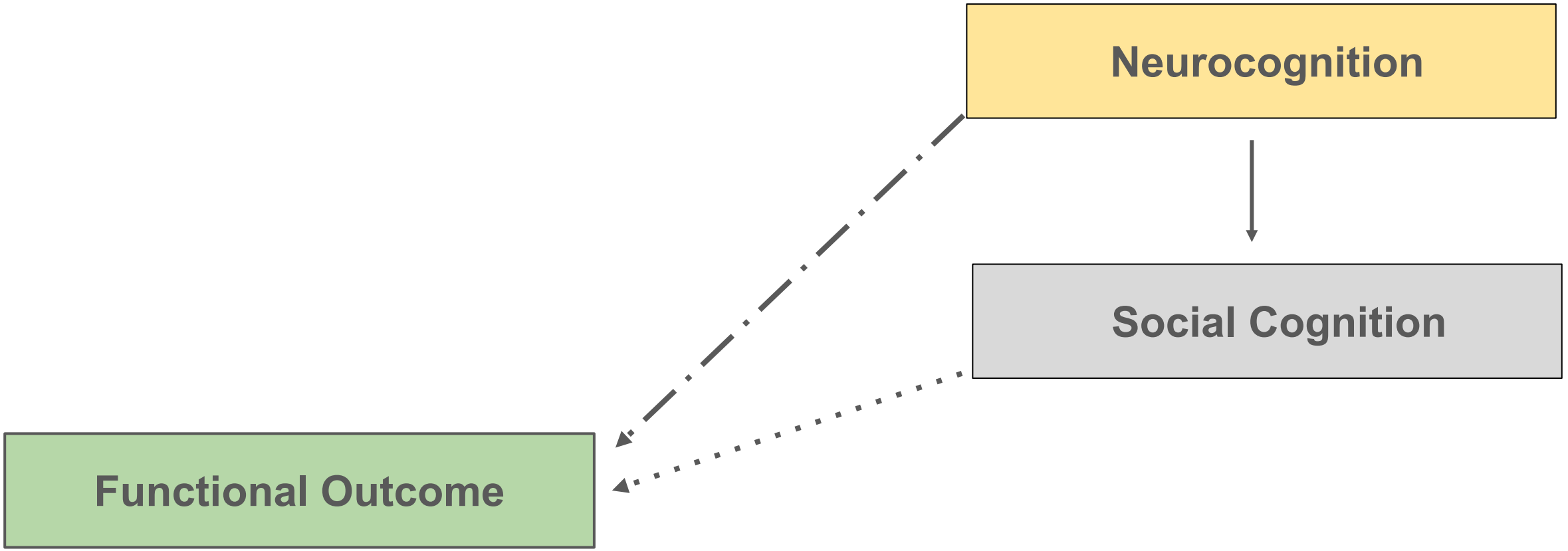
Avolition: Associated with lower glutamate and GABA concentration in anterior cingulate cortex

Avolition: Associated with lower ALFF (intrinsic neural activity) across multiple cortical regions

Avolition and Anhedonia: Associated with reduced ventro-striatal activity and disrupted connectivity between ventral striatum and other regions

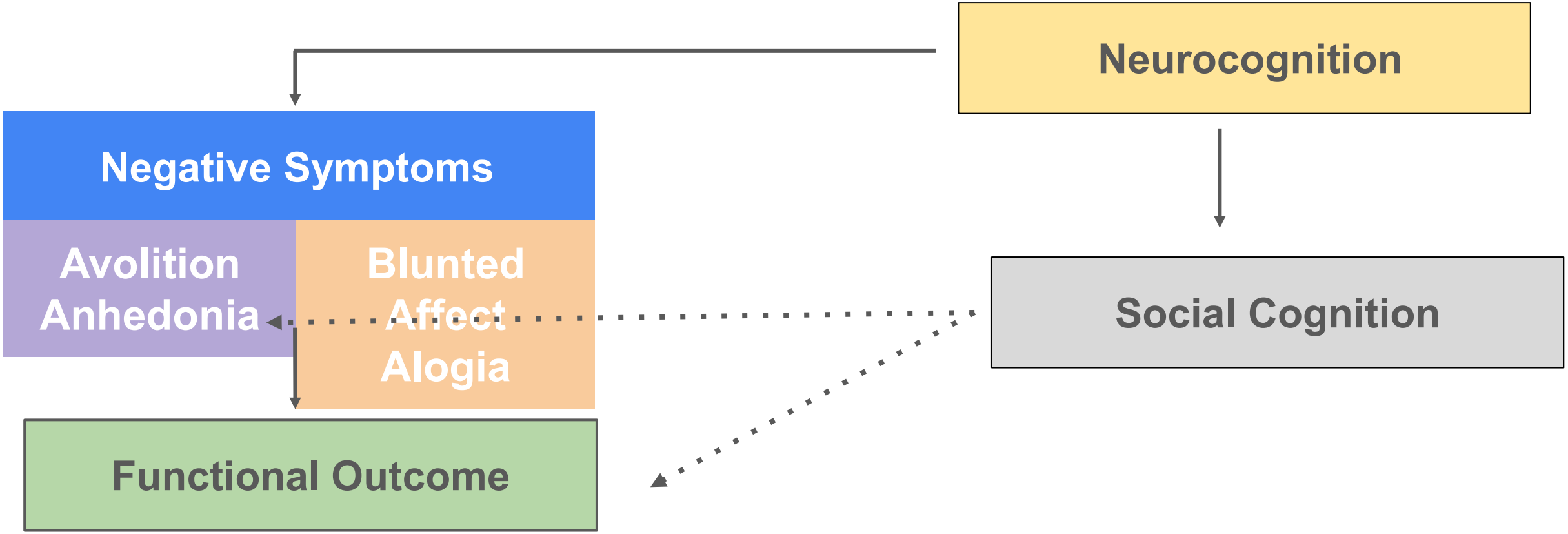
Ahmed et al, Schiz Bull 2022
Cheon et al, Psych Res: Neuroimaging 2023
Blanchard et al, preprint, 2024

Neurocognition plays a key role in functional outcome



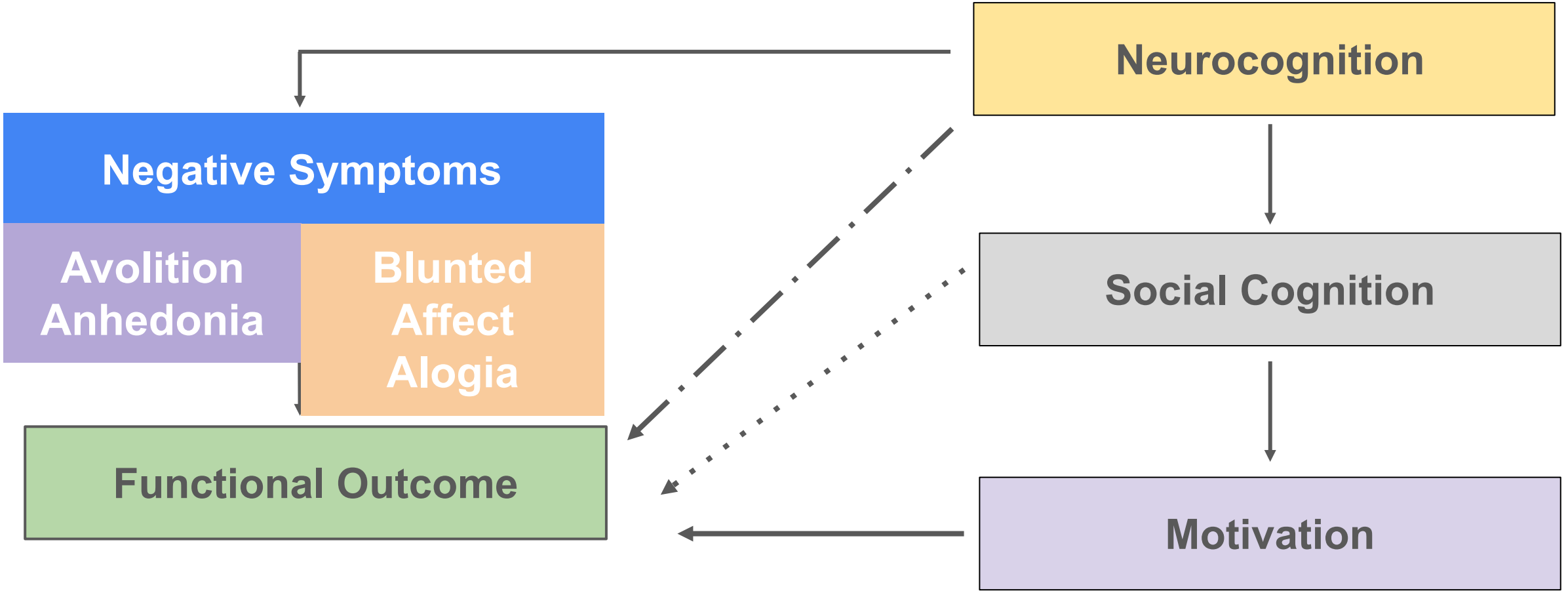
Fett et al, et al. Neurosci Biobehav Rev 2011

Negative symptoms are a mediator



Giordana et al, Frontiers Psychiatry 2024

Neurocognition also affects functional outcomes directly through social cognition and motivation



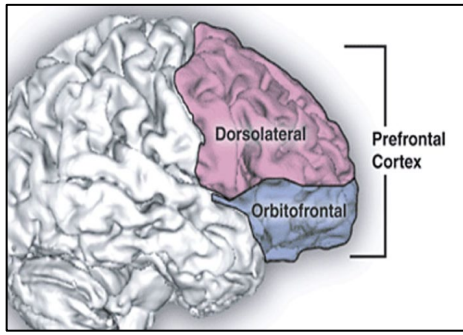
Foussias et al, et al. Europ Neuropsychopharm 2014

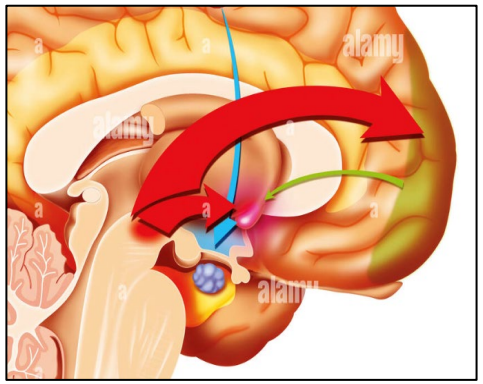
A few more thoughts about Motivation (Volition)

Relies on the interaction of two major neural systems:

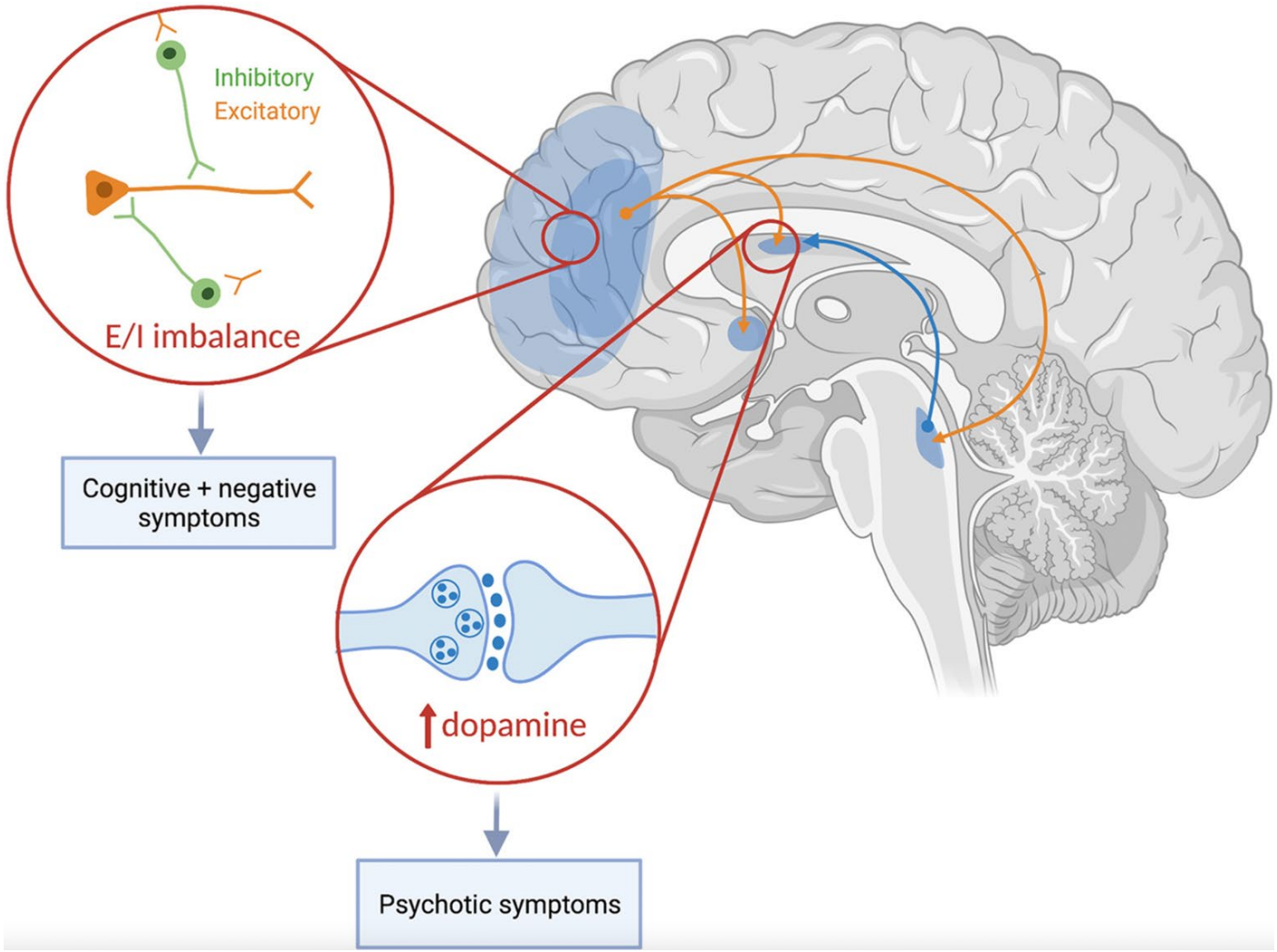
- Dorsal "**Central Executive**" network: DLPFC and dorsal caudate
  - Encoding of action-outcome contingency
  - Representation of the expected reward value of action
  - Functional overlap with cognitive control and attention

- Ventro-striatal "**Reward Processing**" network: Ventral striatum, OFC, ACC, insula, medial prefrontal cortex (mPFC)
  - Reward anticipation and valuation
  - Representation of stimulus-reward associations
  - Functional overlap with value-based decision making and social cognition



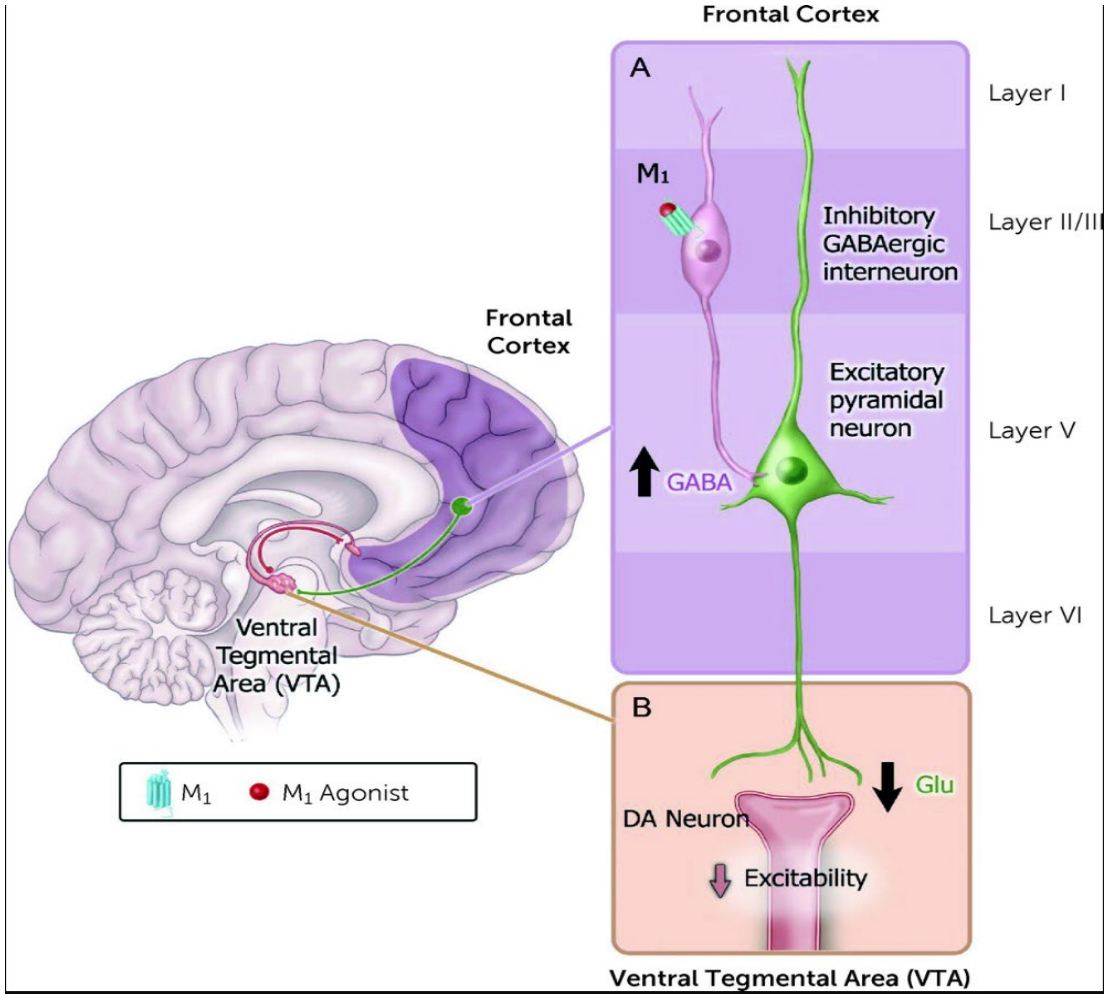


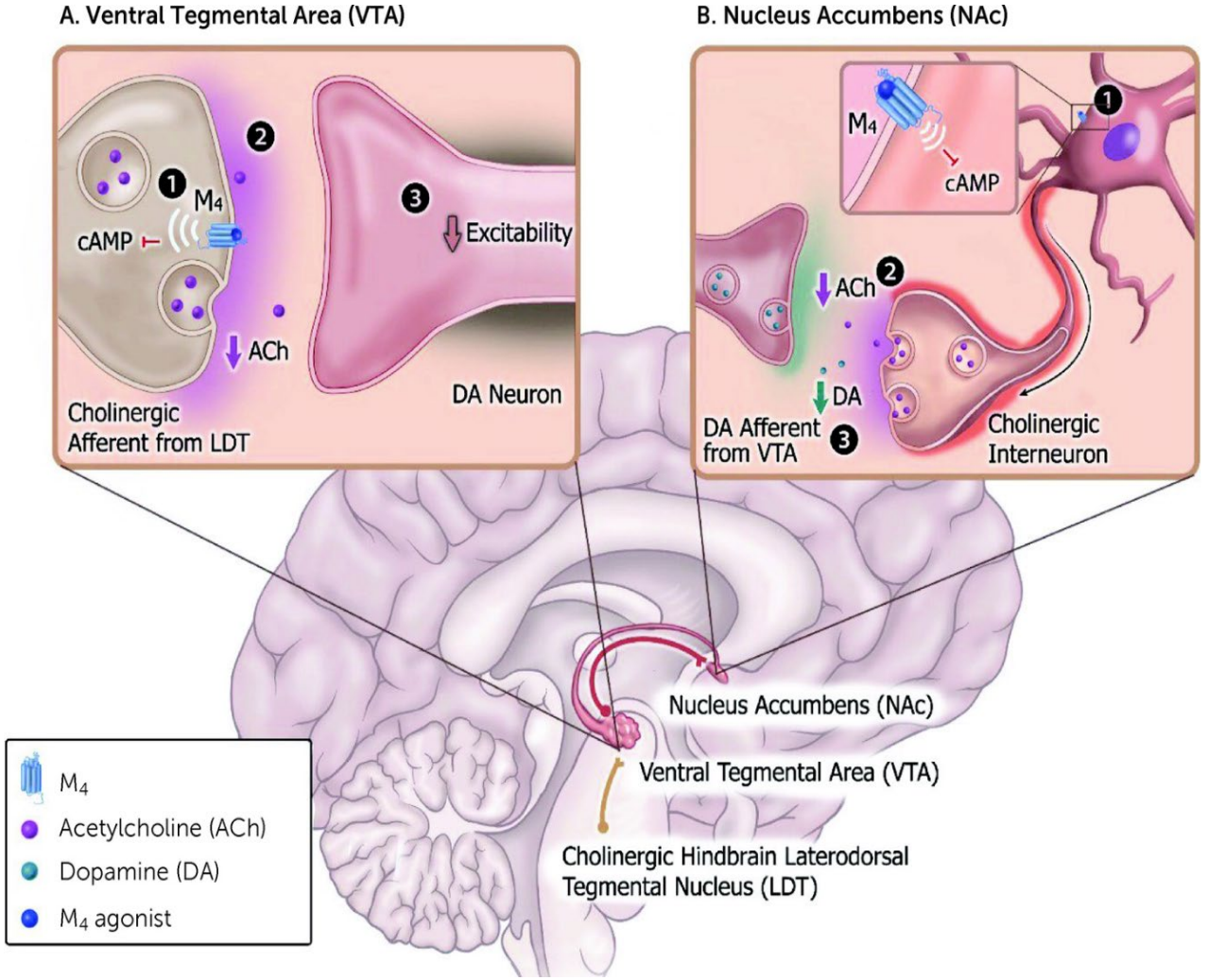
Requires the interplay of cortical excitation/inhibition (glutamate-GABA) and subcortical and cortical dopamine modulation



Howes & Shatalina 2022, Biol Psych

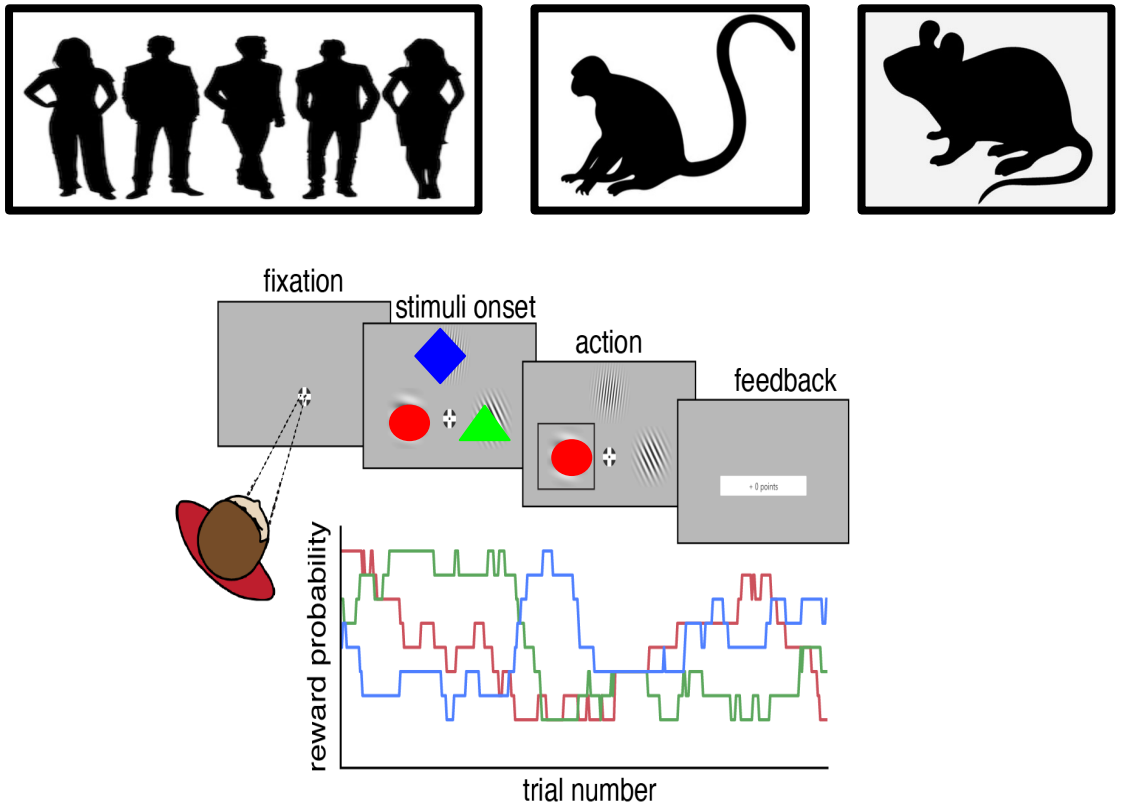
Muscarinic modulation affects these systems

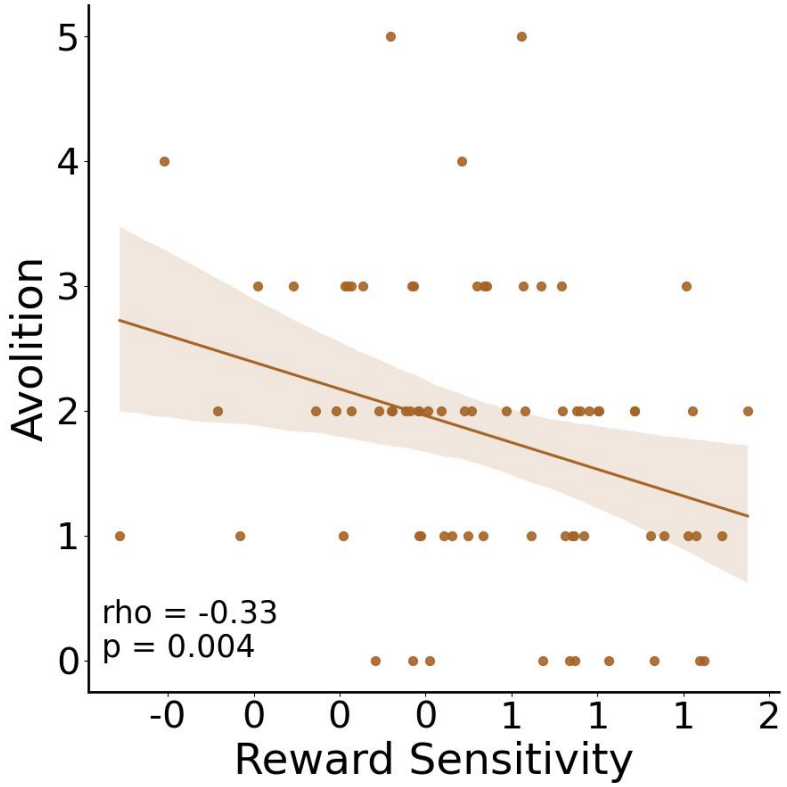




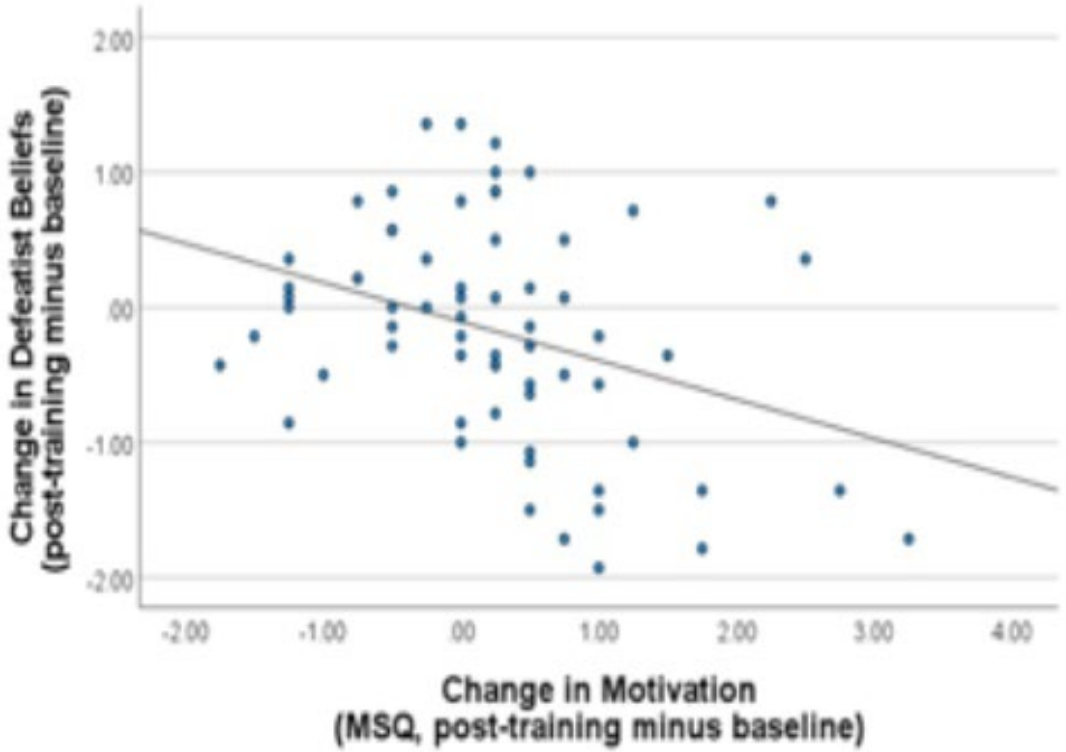
Paul et al, Am J Psych 2022

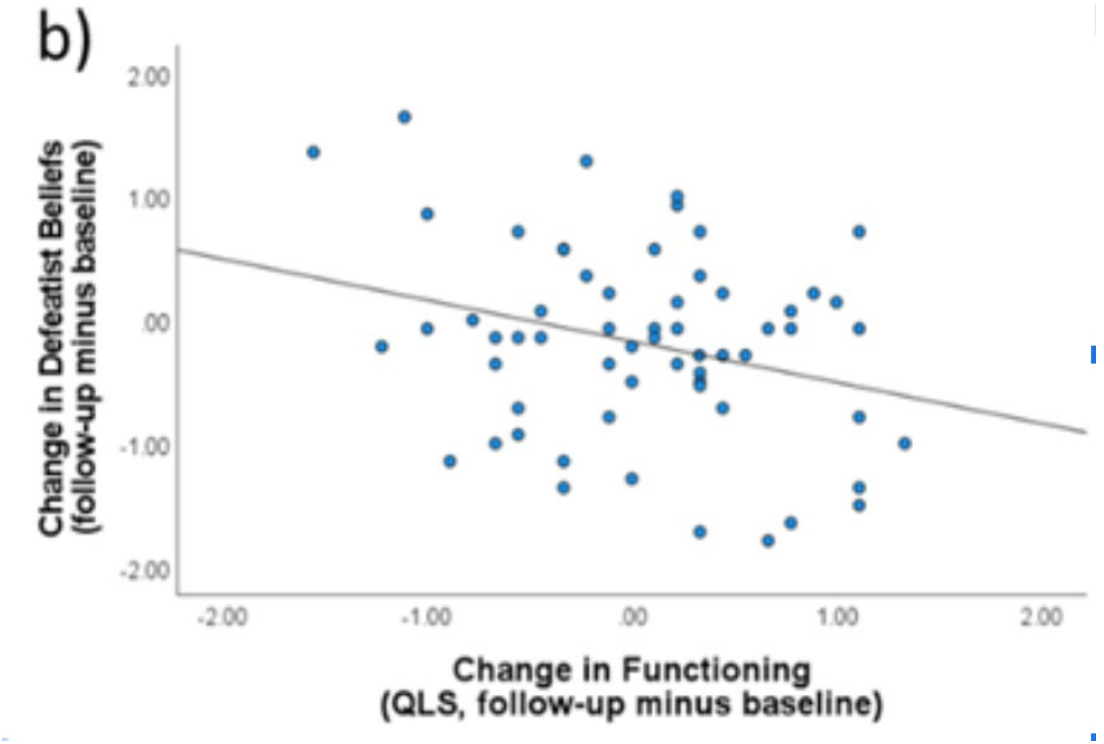
Computational analyses of reward-based trial-by-trial behavior can provide translational models for experimental therapeutics





Intensive social cognitive training drives changes in motivation measures that correlate with changes in defeatist beliefs and are in turn associated with changes in functioning 6 months later





Fisher et al, JMIR 2023

In sum:

- Negative and cognitive symptoms are considered separate domains of psychopathology… BUT consistent associations and shared features suggest overlapping neurobiological origins
- Negative symptoms in general and Avolition/Amotivation specifically mediate aspects of the relationship between cognition and function
- The Fronto-Parietal Central Executive Network is implicated in persistent negative symptoms and worse outcomes
- The Ventral-Striatal Reward Network is strongly implicated in Avolition and Anhedonia symptoms
- Computational modeling shows promise for bridging our understanding of the interplay between neural systems and performing translational studies
- Well-designed social cognitive training can improve motivation measures and functioning; cognitive and metacognitive factors affect the expression and impact of negative symptoms

THANK YOU!

Session 1:
Q&A

10-Minute Break

10:10am

Session 2:
Study Design

Christoph Correll, MD

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Hempstead, NY, USA

Investigator, Center for Psychiatric Neuroscience, Feinstein Institute for Medical Research

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Considerations for Drugs Designed to be Adjunctive to Antipsychotics for Negative Symptoms in Schizophrenia

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Professor of Psychiatry and Molecular Medicine

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Professor of Child and Adolescent Psychiatry

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1

Disclosures: Christoph U. Correll, MD

I have an interest in relation with one or more organizations that could be perceived as a possible conflict of interest in the context of this presentation. The relationships for the past 5 years are summarized below:

Interest	Name of organization
Grants	Boehringer Ingelheim, Einstein Foundation, Berlin, German Ministry of Health, German Research Foundation, Innovationsfond Germany, Janssen, National Institute of Mental Health (NIMH), Patient Centered Outcomes Research Institute (PCORI), Takeda, Thrasher Foundation
Shares (options)	Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Medlink, Mindpax, Quantic, Terran
Consultant, honoraria and advisory boards	AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Eli Lilly, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, MedLink, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Saladax, Sanofi, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Terran, Tolmar, Vertex, Viatris and Xenon

2

Overview

- Negative Symptom Considerations
- Negative Symptom Treatment Considerations
- Negative Symptom Trial Design Considerations
- Negative Symptom Trial Design Recommendations
- Conclusions

3

Negative Symptom Considerations

4

Negative Symptoms: Target

Negative Symptoms	Proposed Definition
Predominant	**Clinically relevant negative symptoms of greater relative severity than co-occurring positive symptoms; unspecified duration**
Prominent	Pronounced and clinically relevant negative symptoms without clear prominence of either positive or negative symptoms; unspecified duration
Primary	**Negative symptoms thought to be intrinsic to the underlying pathophysiology of schizophrenia**
Secondary	Negative symptoms thought to be related to other factors, i.e., psychiatric or medical comorbidities, adverse effects, or environmental factors
Persistent (enduring)	**Primary negative symptoms or secondary negative symptoms that have not responded to treatment for ≥6 months, interfere with normal role functioning, and persist during periods of clinical stability**

Correll CU and Schooler. NR Neuropsychiatr Dis Treat. 2020 Feb 21;16:519-534.

5

Transdiagnostic Presence of "Negative Symptoms"

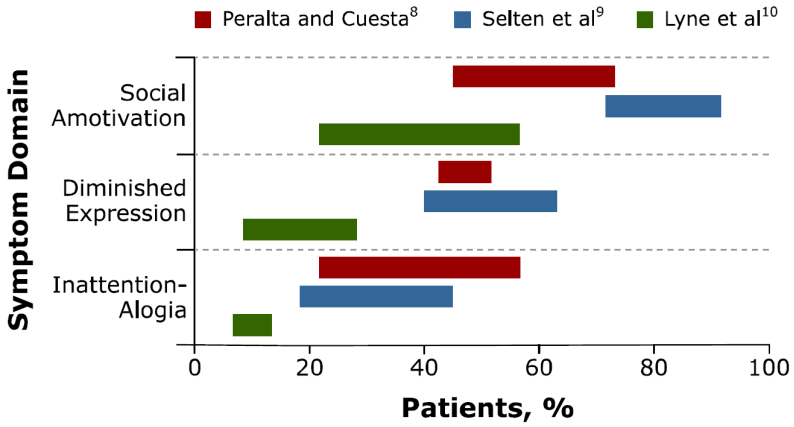
Negative Symptom Domain					
Asociality	Avolition	Anhedonia	Alogia	Blunted Affect	Disorder
X	X	X	X	X	1. Schizophrenia
X	X	X	X	X	2. Schizoaffective disorder
X	X	X	X	X	3. Schizophreniform disorder
X		X		X	4. Schizotypal personality disorder
X	X	X		X	5. Schizoid personality disorder
X					6. Paranoid personality disorder
X					7. Avoidant personality disorder
X	X	X		X	8. Bipolar disorder (I and II)
X	X	X		X	9. Major depressive disorder
	X			X	10. Persistent depressive disorder (dysthymia)
X	X				11. Premenstrual dysphoric disorder
			X		12. Selective mutism
X					13. Social anxiety disorder
	X				14. Separation anxiety disorder
X				X	15. Reactive attachment disorder
X	X	X			16. Posttraumatic stress disorder
		X			17. Depersonalization/derealization disorder
X			X	X	18. Autism spectrum disorder
X	X	X	X	X	19. Neurocognitive disorders

Strauss GP, Cohen AS. Schizophr Bull. 2017 Jul 1;43(4):712-719.

6

Enrichment? Specificity?

According to 3 studies, social amotivation is the most prevalent negative symptom, followed by diminished expression, and then inattention-alogia



Correll CU. *J Clin Psychiatry*. 2013;74(2):e04.
See www.cmeinstitute.com/psychlopedia/Documents/psychosis/5cpem/sec3/psy5-3_AV2.htm. Accessed August 10, 2017.

7

Differentiation between Depression and Negative Symptoms

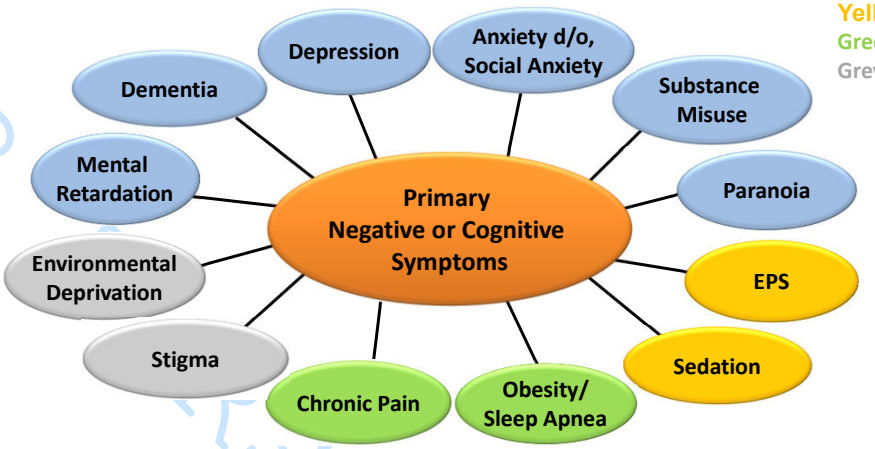
Symptom	Depressive symptoms	Depressive and negative symptoms	Negative symptoms
Anhedonia		X	
Emotional blunting		X	
Anergia		X	
Amotivation		X	
Asociality		X	
Avolition		X	
Low mood	X		
Pessimism	X		
Suicidal ideation	X		
Observed sadness			X
Alogia			X
Poor attention and concentration			X
Blunted affect			X
Social withdrawal			X

Krynicki CR, et al. Acta Psychiatr Scand. 2018 May;137(5):380-390.

8

Differential Diagnosis of Primary and Secondary Negative and Cognitive Symptoms in Schizophrenia

Blue: Psychiatric morbidity
Yellow: Side effects
Green: Physical morbidity
Grey: Environment



Adapted from: Carbon M and Correll CU. CNS Spectr. 2014 Dec;19 Suppl 1:35-53.

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Negative Symptom Treatment Considerations

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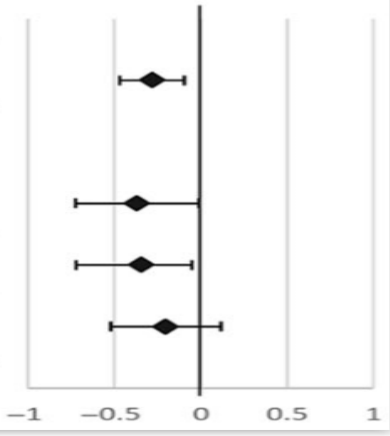
Antidepressant Augmentation in Schizophrenia: Small Benefits for Negative Symptoms

	No of studies	SMD	95%CI lower limit	95%CI lower limit	*P*-valve
All studies	34	−0.28	−0.47	−0.09	**0.003**
Focus of study					
Total symptoms	11	−0.37	−0.73	−0.01	0.046
Negative symptoms	17	−0.34	−0.63	0.04	0.025
Depressive symptoms	3	−0.20	−0.52	0.12	0.216



42 studies, n = 1934, mean duration: 10.1±8.7 weeks. Superiority regarding negative symptoms was confirmed in studies augmenting first-generation antipsychotics (SMD = 0.42, 95% CI = -0.77, -0.7, P = 0.019), but not second-generation antipsychotics (P = 0.144).

Galling B, et al. Acta Psychiatr Scand. 2018 Mar;137(3):187-205.

11

JAMA Psychiatry | Original Investigation | META-ANALYSIS

Efficacy of 42 Pharmacologic Cotreatment Strategies Added to Antipsychotic Monotherapy in Schizophrenia
Systematic Overview and Quality Appraisal of the Meta-analytic Evidence

Christoph U. Correll, MD; Jose M. Rubio, MD; Gabriella Inczedy-Farkas, MD; Michael L. Birnbaum, MD; John M. Kane, MD; Stefan Leucht, MD

RESULTS Of 3397 publications, 29 meta-analyses testing 42 combination strategies in 381 individual trials and among 19 833 participants were included. For total symptom reductions, 32 strategies that augmented any antipsychotic drug and 5 strategies that augmented clozapine were examined. Fourteen combination treatments outperformed controls (standard mean difference/Hedges *g*, −1.27 [95% CI, −2.35 to −0.19] to −0.23 [95% CI, −0.44 to −0.02]; *P* = .05). No combination strategies with clozapine outperformed controls. The quality of the methods of the meta-analyses was generally high (mean score, 9 of a maximum score of 11) but the quality of the meta-analyzed studies was low (mean score, 2.8 of a maximum score of 8). Treatment recommendations correlated with the effect size (correlation coefficient, 0.22; 95% CI, 0.35-0.10; *P* < .001), yet effect sizes were inversely correlated with study quality (correlation coefficient, −0.06; 95% CI, 0.01 to −0.12; *P* = .02).

to −0.02]; *P* = .05). No combination strategies with clozapine outperformed controls. The quality of the methods of the meta-analyses was generally high (mean score, 9 of a maximum score of 11) but the quality of the meta-analyzed studies was low (mean score, 2.8 of a maximum score of 8). Treatment recommendations correlated with the effect size (correlation coefficient, 0.22; 95% CI, 0.35-0.10; *P* < .001), yet effect sizes were inversely correlated with study quality (correlation coefficient, −0.06; 95% CI, 0.01 to −0.12; *P* = .02).

Hillside Hospital, Psychiatry Research, Northwell Health, Glen Oaks, New York (Correll, Rubio, Inczedy-Farkas, Birnbaum, Kane); Hofstra Northwell School of Medicine, Hempstead, New York (Correll, Birnbaum, Kane); The

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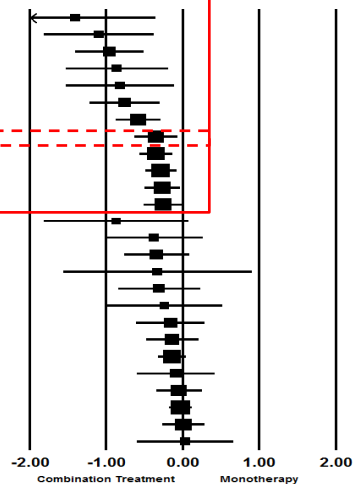
Psychopharmacologic Co-Treatment of Any Antipsychotic: Negative Symptoms

Drug Added to AP (Publication)	Type of agent	Std diff in means	Lower limit	Upper limit	p-Value	N/n	AMSTAR-Plus
SNRIs (Galling '16)	Antidepressant	-1.40	-2.44	-0.36	0.01	1/40	3
Serotonin 3 Rec Ant (Kishi '14)	Miscellaneous	-1.10	-1.81	-0.39	0.00	5/261	3
Lamotrigine (Premkumar '06)	Mood Stabilizers	-0.96	-1.40	-0.52	0.00	3/98	2
AchEsterase Inhib (Singh '12)	Miscellaneous	-0.86	-1.52	-0.20	0.01	1/31	4
Testosterone (Heringa '15)	Hormones	-0.82	-1.52	-0.12	0.02	1/30	3
Minocycline (Solmi '16)	Antioxidants	-0.76	-1.21	-0.31	0.00	5/299	3
Topiramate (Zheng '16)	Miscellaneous	-0.58	-0.87	-0.29	0.00	8/236	4
Antipsychotics (Galling '16)	Antipsychotic	-0.35	-0.63	-0.07	0.01	12/672	3
Estrogen action (Heringa '15)	Hormones	-0.35	-0.56	-0.14	0.00	13/863	4
Any antidepressant (Galling '16)	Antidepressant	-0.29	-0.49	-0.09	0.00	27/1233	4
Modafinil (Andrade '14)	Stimulants	-0.27	-0.50	-0.04	0.02	6/342	3
SSRIs (Galling '16)	Antidepressant	-0.26	-0.50	-0.02	0.04	18/922	4
NMDA rec ant (Matsuda '13)	Miscellaneous	-0.87	-1.81	0.07	0.07	8/245	4
Pregnenolone (Heringa '15)	Hormones	-0.38	-1.01	0.25	0.24	5/222	3
Oxytocin (Oya '15)	Hormones	-0.34	-0.76	0.08	0.11	6/214	2
SARI (Galling '16)	Antidepressant	-0.33	-1.56	0.90	0.60	1/26	3
Carbamazepine (Leucht '14)	Mood Stabilizers	-0.31	-0.84	0.22	0.25	1/53	0
MAO-B Inhibitors (Galling '16)	Antidepressant	-0.24	-0.99	0.51	0.53	2/83	2
NaSSA (Galling '16)	Antidepressant	-0.16	-0.60	0.28	0.48	7/207	3
DHEA (Heringa '15)	Hormones	-0.14	-0.48	0.20	0.42	3/160	3
Adenosine mod (Nitta '15)	Miscellaneous	-0.14	-0.31	0.03	0.12	7/484	2
Azapirones (Kishi '13)	Miscellaneous	-0.09	-0.60	0.42	0.73	4/149	2
Varenicicline (Kishi '15)	Miscellaneous	-0.05	-0.34	0.24	0.74	2/190	4
NSAIDs (Nitta '13)	Antioxidants	-0.03	-0.17	0.11	0.68	8/774	5
Lithium (Leucht '15)	Mood Stabilizers	0.01	-0.26	0.28	0.94	7/259	1
NRIs (Galling '16)	Antidepressant	0.03	-0.59	0.65	0.92	3/132	3



*Only for augmentation with partial D2 agonist.
Adapted from Correll CU, et al. *JAMA Psychiatry*. 2017;74(7):675-684.

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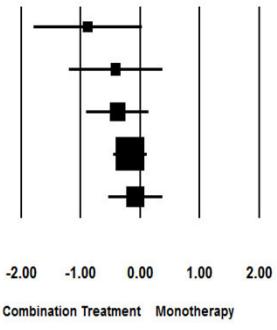
Psychopharmacologic Co-Treatment of Clozapine: Negative Symptoms

Study name	Std diff in means	Lower limit	Upper limit	p-Value	N/n	AMSTAR
CZP+ Antidepressant (Veerman '14)	-0.87	-1.77	0.03	0.06	4/111	3
CZP+Topiramate (Veerman '14b)	-0.40	-1.18	0.38	0.32	4/152	2
CZP+Lamotrigine (Veerman '14b)	-0.37	-0.89	0.15	0.16	6/185	3
CZP+Antipsychotic (Veerman '14)	-0.16	-0.44	0.11	0.25	11/599	3
CZP+Glycine (Veerman '14b)	-0.07	-0.52	0.38	0.76	3/68	3



CZP = clozapine.
Correll CU, et al. *JAMA Psychiatry*. 2017;74(7):675-684.

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However, Poor Study Quality in High-Quality Meta-analyses Hampers Interpretation and Application

- Umbrella review of 29 meta-analyses of 42 cotreatments (trials=381, n=19,833)
- For negative symptoms, 12 of 26 meta-analyzed augmentation strategies outperformed placebo (effect sizes = 0.26 -1.40)
- The quality of the meta-analyses was high
- The quality of the meta-analyzed studies was low (AMSTAR-Content scores 0-5/8 and 2-4/8 for significant agents)
- The lower the study quality, the higher the pooled effect sizes
- The largest meta-analyzed study did not confirm the pooled results

Correll CU, et al. *JAMA Psychiatry*. 2017;74(7):675-684.

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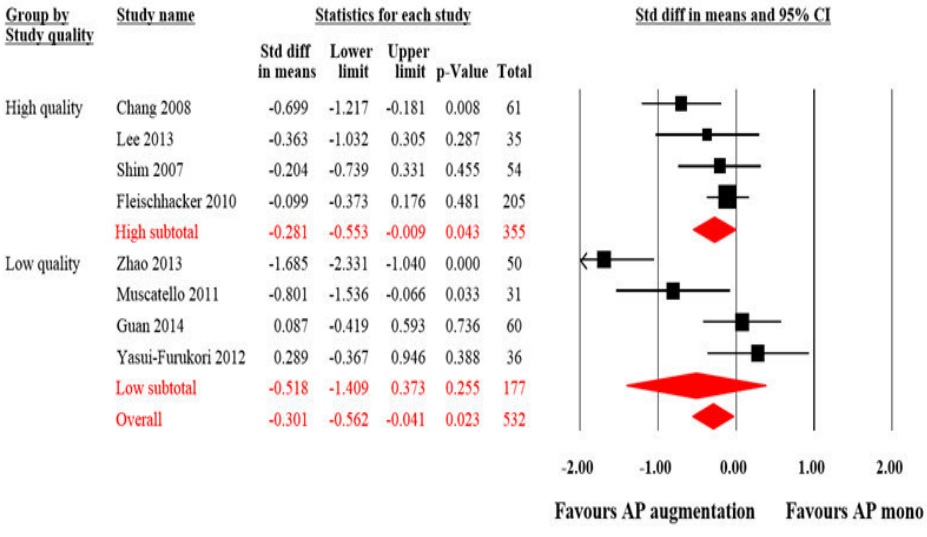
Improvement of Negative Symptoms When Adding a Partial D2 Agonist to a Full D2 Antagonist



High Quality = Double Blind and mITT Galling B et al. World Psychiatry. 2017 Feb;16(1):77-89.

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Negative Symptom Trial Design Considerations

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General Design Considerations in Negative Symptom Trials

- **Population**: age, setting, recruitment frame, cultural differences, wish to participate/change
- **Illness**: stage, duration, comorbidities (anxiety/social anxiety, cannabis)
- **Treatment**: prior treatment duration, type, wash out, cotreatment (augmentation vs co-initiation)
- **Negative symptoms**: predominant vs prominent, persistence (duration), enrichment (severity cut off, sx type), stability, trial duration
- **Assessment**: source (rater, patient, informant, passive/interactive digital monitoring (EMA), speech/facial/GPS assessments), scales (2nd vs 1st generation – which one(s)
- **Pseudospecificity/dampening**: EPS, sedation, depression (sum score/specific sxs?), co-treatments (background, trial-related), clinical stability (last hospitalized, duration, pro/retrosp.)
- **Additional outcomes: c**ognition, functioning, QoL, trial burden
- **Placebo response**: trial effects (type/frequency of contact, number/type of assessments), recruitment frame, expectation bias, enrichment, lead-in, number of trial arms, psychosocial & pharmacological cotreatments
- **Other**: Retention, adherence, functional unblinding

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Specific Design Considerations for Adjunctive Trials

- **Population**: age, setting, recruitment frame, cultural differences, wish to participate/change
- **Illness**: stage, **duration**, **comorbidities** (social) anxiety, cannabis) **[dual effect?]**
- **Treatment**: prior treatment duration, **type [less D2 blockade?]**, wash out **[?]**, cotreatment (**augmentation vs co-initiation**)
- **Negative symptoms**: predominant vs **prominent [dual effect?]**, persistence (duration), enrichment (severity cut off, sx type **[specific efficacy?]**), stability, trial duration **[longer?]**
- **Assessment**: source (rater, patient, informant, passive/interactive digital monitoring (EMA), speech/facial/GPS assessments), scales (2nd vs 1st generation – which one(s)
- **Pseudospecificity/dampening**: EPS, sedation **[additive/neutralizing effect?]**, depression (sum score or specific sxs?) **[dual effect?]**, co-treatments (background, trial-related) **[DDI?]**, clinical stability (last hospitalized, duration, pro-/retrosp.)
- **Additional outcomes:** cognition, functioning, QoL, trial burden
- **Placebo response**: trial effects (type/frequency of contact, number/type of assessments), recruitment frame, expectation bias, enrichment, lead-in **[double-/triple-blind PBO lead-in, variable add-on time]**, number of trial arms, psychosocial & pharmacological cotreatments
- **Other**: Retention, adherence, functional unblinding **[AE profile, unique vs subdued?]**

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Negative Symptom Trial Design Recommendations

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Trial Design Considerations: Set Items

Recommendation	Domain of Concern/Benefit
1. **Severity**: Subjects should have ≥2 negative symptoms with ≥1 rated ≥moderate	Enrichment, Room for Change/Ceiling
2. **EPS:** Exclude subjects with notable EPS	Pseudospecificity
3. **EPS:** Include scales measuring EPS	Pseudospecificity
4. **Antipsychotics**: Include subjects on first- and second-generation antipsychotics when testing adjunctive agents	Generalizability
5. **Cognition**: Include an assessment battery to measure cognition	Biological Colocation, Added Benefit
6. **Outcome**: Ratings for negative symptoms should include a single global score	Statistical power, Clinical Relevance
7. **Outcome:** Ratings for negative symptoms should include global scores for major domains, i.e., expressiveness and apathy/asociality	Precision, Interpretability
8. **Clozapine**: Subjects treated with clozapine should not be excluded when testing adjunctive agents	Generalizability(?), Clinical Need

Marder SR, et al. Schizophr Res. 2013 Nov;150(2-3):328-33.

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Trial Design Considerations: New Items

Recommendation	Domain of Concern/Benefit
2. **Predominant vs Prominent**: Predominant in Ph2/POC, but may study both	Pseudospecificity (lack of agreement)
3. **Depression**: exclude based on symptoms not overlapping with depression or comorbid MDD diagnosis, but not based on cutoff on total depression rating scale	Pseudospecificity
4. **Functional outcome**: Due to face-validity no co-primary outcome, but desirable	Clinical Relevance
5. **Informants**: Desirable but nor necessary	Validity, Clinical Relevance
6. **Trial Duration**: Ph2/POC: 12 weeks, Ph3: 6 months	Sensitivity to change
7. **Clinical Stability:** retrospective confirmation for a period of 4 to 6 months	Signal-to-noise differentiation
8. **Stability of negative sxs:** prospective confirmation for ≥4 weeks	Generalizability

Marder SR, et al. Schizophr Res. 2013 Nov;150(2-3):328-33.

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Conclusions

- Augmentation with antipsychotic and non-antipsychotic agents has suggestive efficacy, but there is:
  - Frequent lack of consideration of individual agents
  - Pseudo-specificity (positive symptoms, depression, EPS, functional unblinding)
  - Publication bias
- Partial dopamine agonists may have benefits for negative symptoms, but unclear if for primary neg sxs
- Potential subgroup and/or illness phase specificity need to be investigated
- For augmentation treatments, consider specifically:
  - Specific underlying antipsychotic agent(s), incl. D2 blockade below EPS threshold, sedative effects
  - Illness and treatment duration effects
  - Comorbidities and potential for dual effect
  - Potentially reduced effect size and/or slower effects vs monotherapy
  - Functional unblinding
  - Expectation bias
  - Trial effects
  - Symptom enrichment and lead-in options
  - Digital, EMA, novel clinical biomarker for patient selection or as outcomes

23

Stephen Brannan, MD

Chief Medical Officer, Karuna Therapeutics

Boston, MA

Considerations for Drugs Designed to be Monotherapy

By

Stephen Brannan, M.D.

Disclosures

- Former CMO at Karuna
- Previously also worked at Forum Pharmaceuticals, Takeda, Novartis, Cyberonics, and Eli Lilly
- Currently consulting with:
  - Seaport Therapeutics
  - EMA Wellness
  - Kynexis
  - Engrail Therapeutics

General issues with Negative Symptom Trials

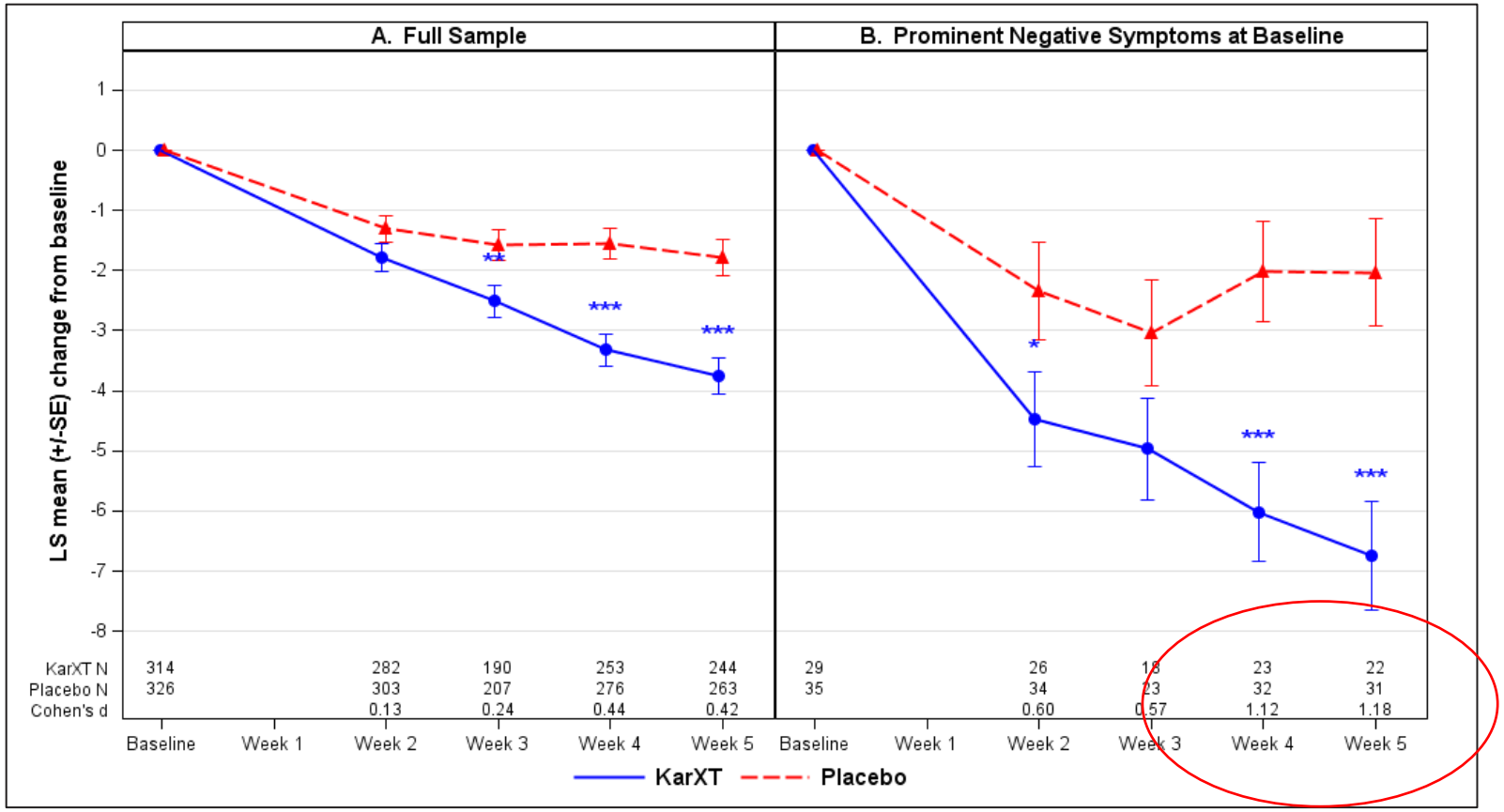
- Duration of the trial?
  - Neg Sx purportedly take longer to respond
- How stable do subjects need to be regarding Neg and Pos Sx?*
  - Neg Sx- “stable and persistent”
  - Recent hospitalizations? Recent Sx changes?
- Relapses/Rescues
- Enrichment- a threshold for Neg Sx? Relative to Positive Sx?
- Exclusions- subjects with significant Depression or EPS?*
- Where do the study subjects come from?
  - Role of site and Regional differences?
- Also assess for cognition?*
- Age range (18-65)?*
- Placebo issues

* Denotes an issue covered by Dr. Correll

Enrichment and Relapse Issues

- Enrichment
  - General consensus has been to exclude actively psychotic individuals, such as those seen in most acute schizophrenia studies
  - And for excluding subjects lacking “stable” Sx
  - Should one exclude any subject scoring above a certain threshold for certain (Positive Sx) PANSS items?
  - Study only stable subjects with predominant Negative Sx
  - Are European sites/patients favored?
  - Add a standardized vocational rehab and social opportunity
- Relapse
  - For patient safety, what “rules” should trigger when a subject should be withdrawn?
    - Can some fluctuation be tolerated w/o withdrawing the subjects?
  - How frequent are relapses?
    - Is there a subgroup of patients less prone to relapse?
  - What should be the role of a support network? Informants?
  - What is the role/need for a DSMB/Safety Board

PANSS Marder Negative Symptoms score

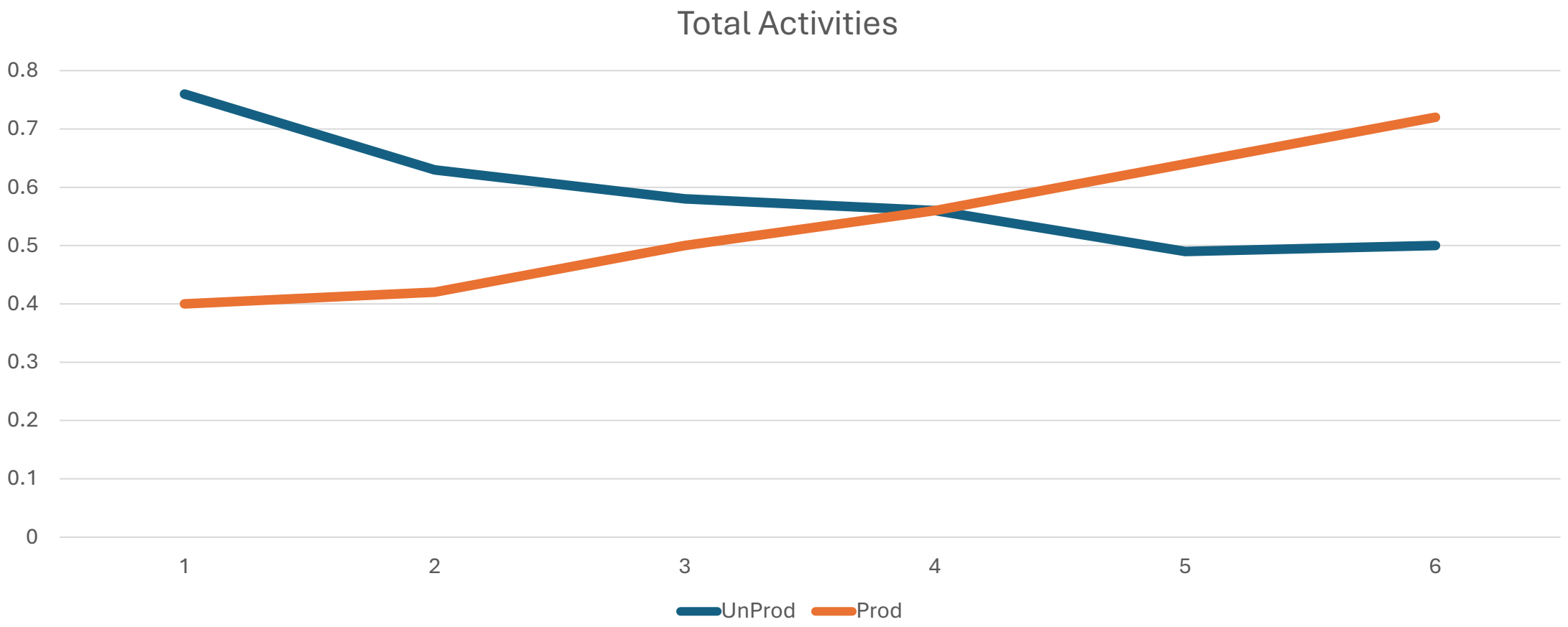


- Criteria for predominant negative symptoms
- ≥24 PANSS Marder Negative Factor score
- ≤19 PANSS Mohr positive symptom subscore
- ≥4 on at least 2 of the following PANSS core NS items: blunted affect (N1), passive/apathetic social withdrawal (N4), or lack of spontaneity and flow of conversation (N6).

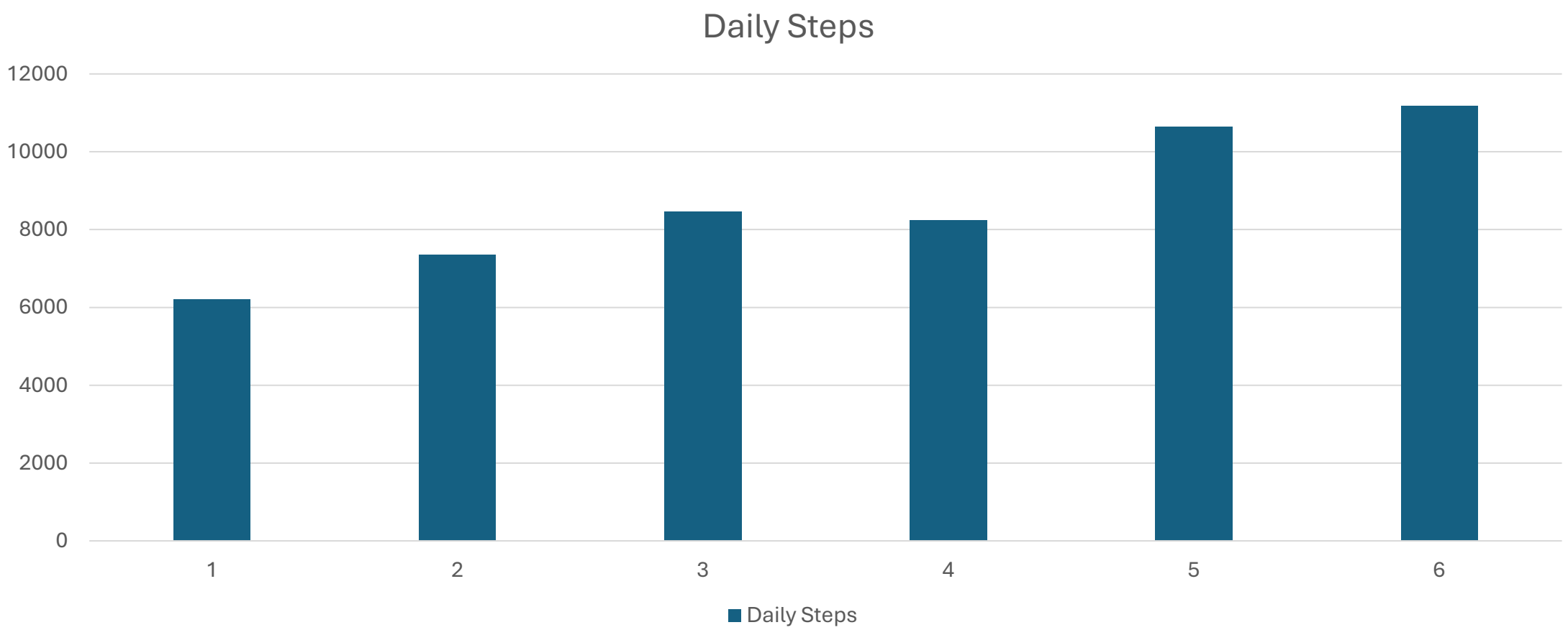
Outcome Measure issues

- Will primarily leave this to our fellow presenters during session 4, especially what the better primary scales are…
- Relative consensus that Functional co-primary is not needed
- Should a global scale be included? (e.g. CGI-Sch)
- Does one look for Neg Sx dimensions?
  - Expressive? Experiential?
- Need for depression and EPS scales? (to r/o confounds)
- Issues regarding accurate/stable ratings?
  - Need for informants??
  - Several of the scales are not easy to rate consistently (based on previous studies)
- Use and role of non-rater measurements
  - Direct speech and facial measurement
  - The role of EMA? Actigraphy?

Home- Based Activities



Daily Steps


Daily Steps
12000
10000
8000
6000
4000
2000
0
1
2
3
4
5
6
Daily Steps

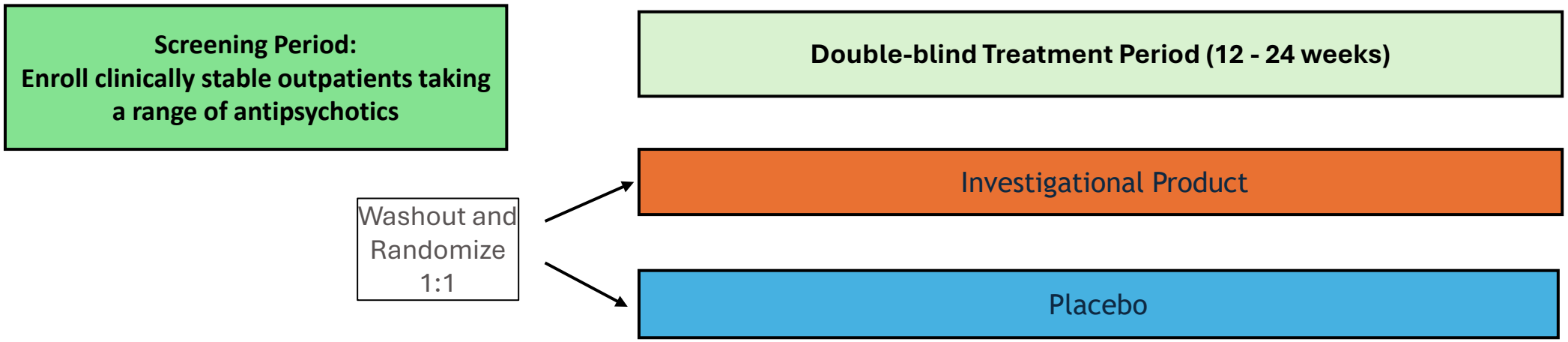
Placebo Issues

- Increased number of trial arms and large number of sites is associated with larger placebo responses
- The need for Rater surveillance
- Issue of “staff attention”, especially for Neg Sx patients
- The need for Blinded data analytics?
- Having strong drug effects likely helps (duh)

Issues pertaining to Monotherapy trials

- Comparator arm- role of Placebo? Role of Psychosocial interventions? Role of other comparators?
- Against placebo
  - Safeguards for subjects on placebo for longer durations
    - Define Sx worsening well
    - Need for an (active) Safety Board
    - Need for study subjects who are “non-relapsers” (stable Sx, no h/o relapse, have a good support network)
- Against comparator
  - Should be a drug with minimal EPS
  - Pragmatically one cannot use all antipsychotics, so which one(s)?

1. Placebo-controlled trial



Placebo control considerations:

- Notable relapse risk: data loss
- High potential for symptom fluctuation: complicates interpretation of treatment benefit for IP and pseudospecificity
- Potential patient/caregiver reluctance to participate: psychosocial disruption, neurotoxicity; extends timelines to enroll

Use of Placebo Comparator (2-arm)

- Duration of trial
  - Patients on placebo have an increased risk for relapse, risk increases with time off treatment
- Positive findings due to drug effect (improvement) or placebo effect (worsening) or <u>both</u>

- Ethical considerations
- E.g. Minerva trial
  - Acadia also ran such a trial,

but will not be discussed here

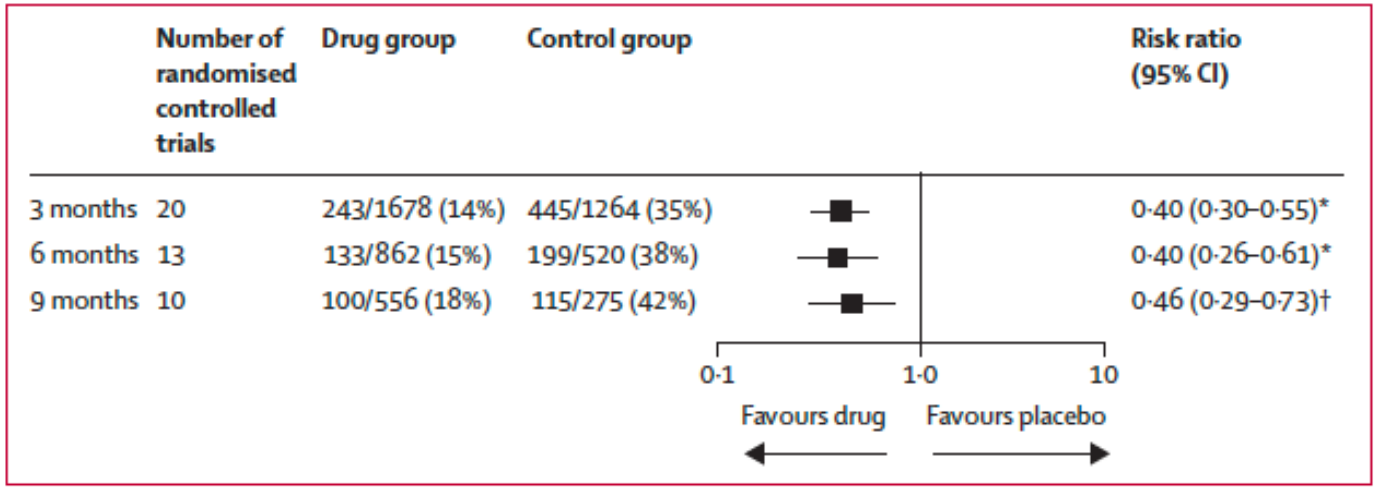


Figure 4: **Sensitivity analysis of subsequent relapse risk after specific lengths of time without a patient relapsing**
Data are n/N (%) unless otherwise stated. The random effects model by DerSimonian and Laird[17] was used throughout, with weights calculated by the Mantel-Haenszel method. *p<0·0001. †p=0·0009.

Minerva Trial (roluperidone)

- 12 weeks duration w/ 24 mo OLE
- 18-60 y/o
- 234 Subjects
- Neg Sx stable for 3 mo
- Excluded if: BMI >35
- Primarily European sites

FIGURE 2. Change From Baseline in PANSS Total Scores in Patients With Schizophrenia Treated With MIN-101 or Placebo[a]

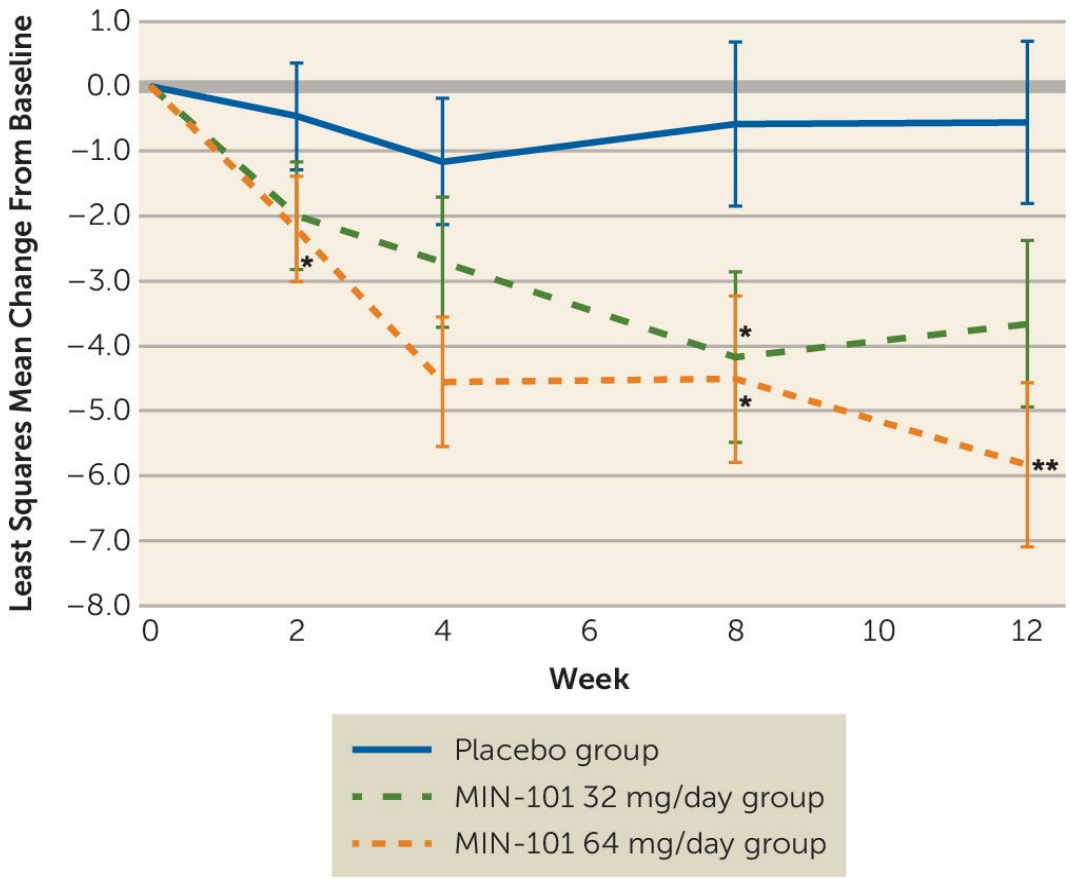
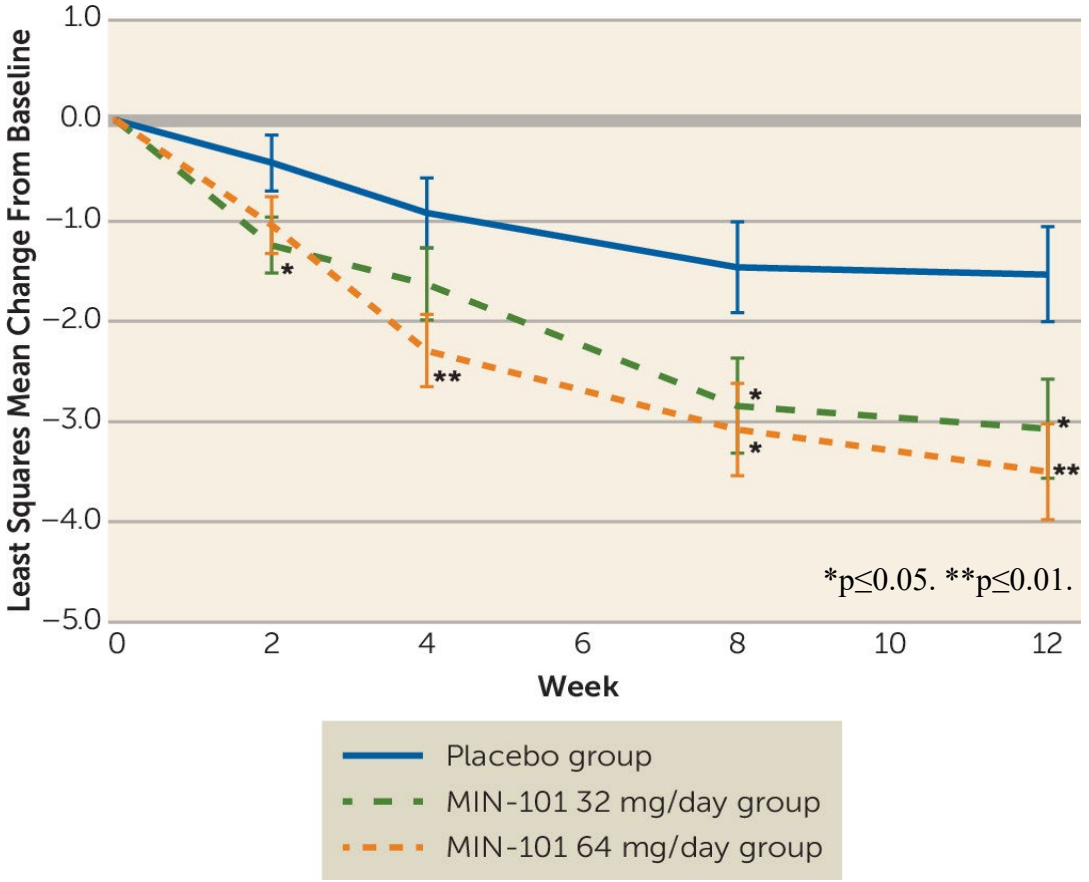
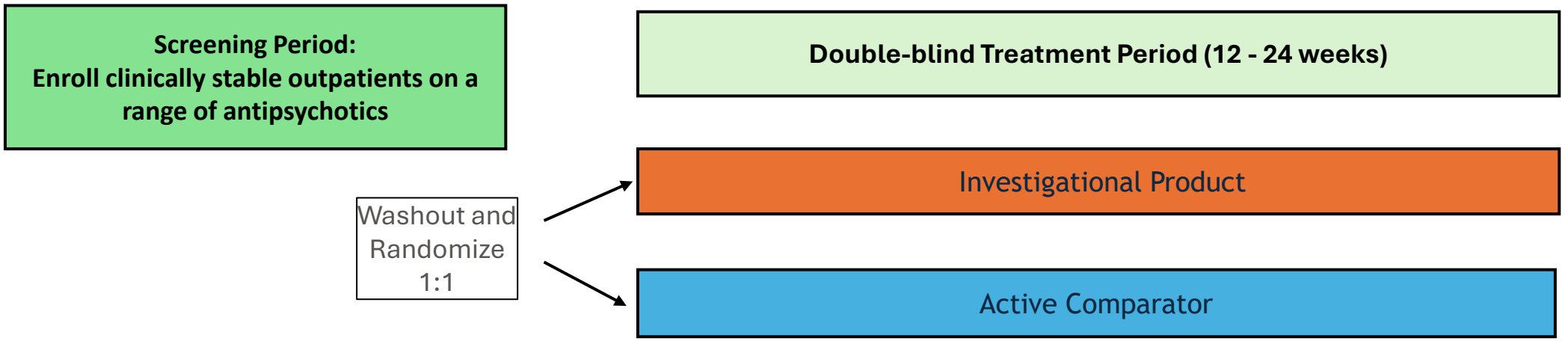


FIGURE 1. Change From Baseline in the Five-Factor PANSS Negative Subscale Scores in Patients With Schizophrenia Treated With MIN-101 or Placebo[a]



DOI: (10.1176/appi.ajp.2017.17010122)

1. Superiority trial versus active comparator



Considerations:

- Comparator should be an approved treatment for positive symptoms that is neutral with regard to negative symptoms (e.g., risperidone, olanzapine, quetiapine)
- Exposes all subjects to treatment change and possible relapse/ symptom fluctuation
- Possible risk of functional unblinding with approved treatments antipsychotics (e.g., sedation, weight gain)
- Only a single-drug comparison: could contribute to disagreements about labeling if the benefit is superior to only one available antipsychotic
- Note: large studies and meta-analyses suggest most antipsychotics are equivalent in their lack effects on NS. Requiring the already understood lack of NS benefit be proven repeatedly with separate trials seems impractical (possibly unethical)

Use of Active Comparator (2-arm)

- Fundamental assumption: comparator drug adequately controls positive symptoms without impacting negative symptoms (positively or negatively)
- Positive trial due to investigational drug positive effects, active comparator negative effects, or both?
- May be more ethically and operationally feasible to conduct
- E.g. Cariprazine trial

Cariprazine trial (Gedeon Richter)

- 26 weeks duration
- Stable Schizophrenia (2 yrs) and Negative Sx (6 mo)
- Run at European sites
- Versus (flex dose) risperidone
- 461 patients randomized

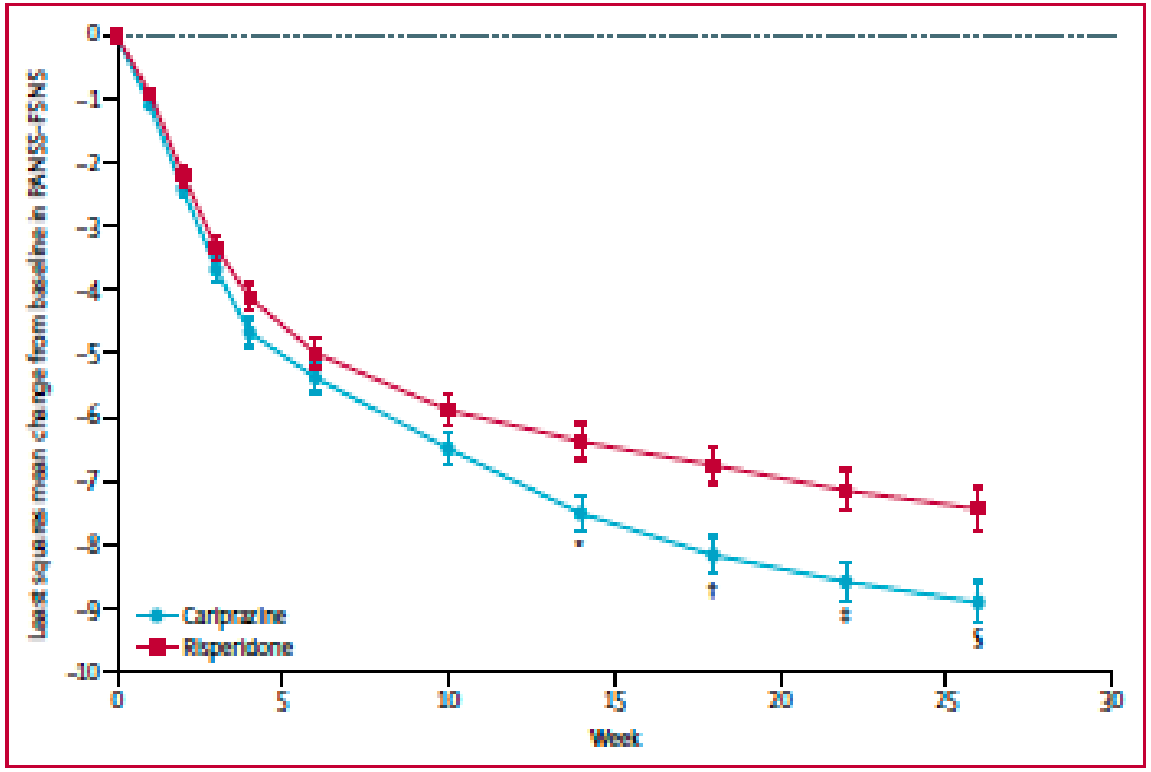


Figure 2: Mean change from baseline to week 26 in PANSS-factor score for negative symptoms
p=0·0092 for the overall treatment effect of cariprazine versus risperidone. PANSS-FSNS=Positive and Negative Syndrome Scale factor score for negative symptoms. *p=0·0079. †p=0·0011. ‡p=0·0016. §p=0·0022.

6-month Head-to-Head Comparison of Cariprazine vs Risperidone: No "Pseudospecificity"

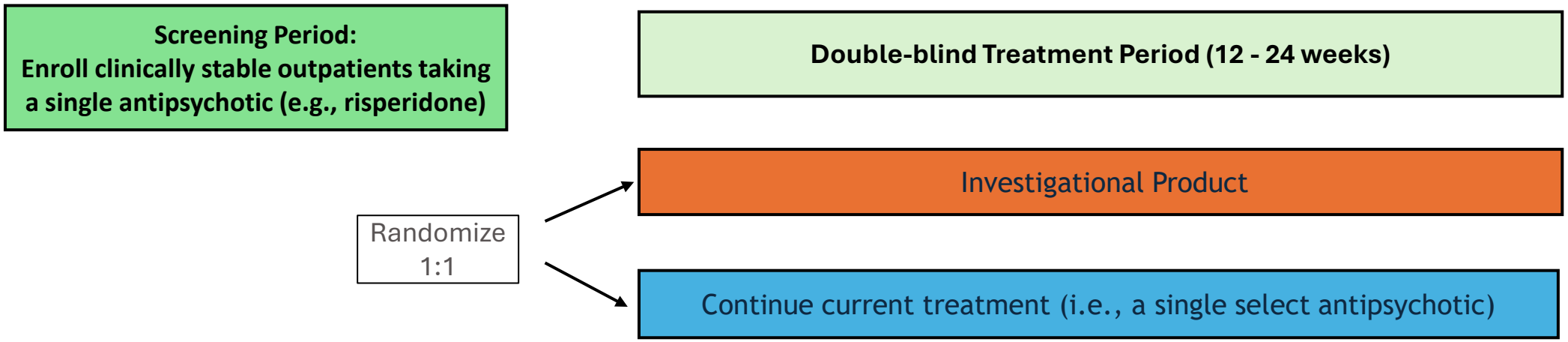
	Cariprazine group (n=227)	Risperidone group (n=229)	LSMD (95% CI)	p value
Additional efficacy (repeated measures ANCOVA mixed effects model)*				
CGI-S score	−0·95 (0·05)	−0·74 (0·05)	−0·21 (−0·36 to −0·06)	0·0052
PANSS				
Total score	−16·90 (0·80)	−14·80 (0·81)	−2·10 (−4·34 to 0·13)	0·065
Negative subscale score	−8·63 (0·32)	−7·16 (0·34)	−1·48 (−2·38 to −0·57)	0·0015
Positive subscale score	−1·40 (0·21)	−1·41 (0·16)	0·01 (−0·52 to 0·54)	0·96
General	−7·14 (0·41)	−6·42 (0·42)	−0·72 (−1·86 to 0·43)	0·22
Pseudospecificity measures (repeated measures ANCOVA mixed effects model)*				
PANSS-FSPS	−1·07	−1·08	0·01 (−0·43 to 0·45)	0·96
CDSS total score	−0·28	−0·22	−0·06 (−0·33 to 0·21)	0·66
SAS items 1–8	0·01	0·05	0·05 (−0·21 to 0·12)	0·58

CDSS = Calgary Depression Scale for Schizophrenia; PANSS-FSPS = Positive and Negative Syndrome Scale – Factor Scale Positive Symptoms; SAS = Simpson Angus Scale for the Measurement of Extrapyramidal Symptoms

Németh G, et al. *Lancet*. 2017;389(10074):1103-1113.

Other Potential designs

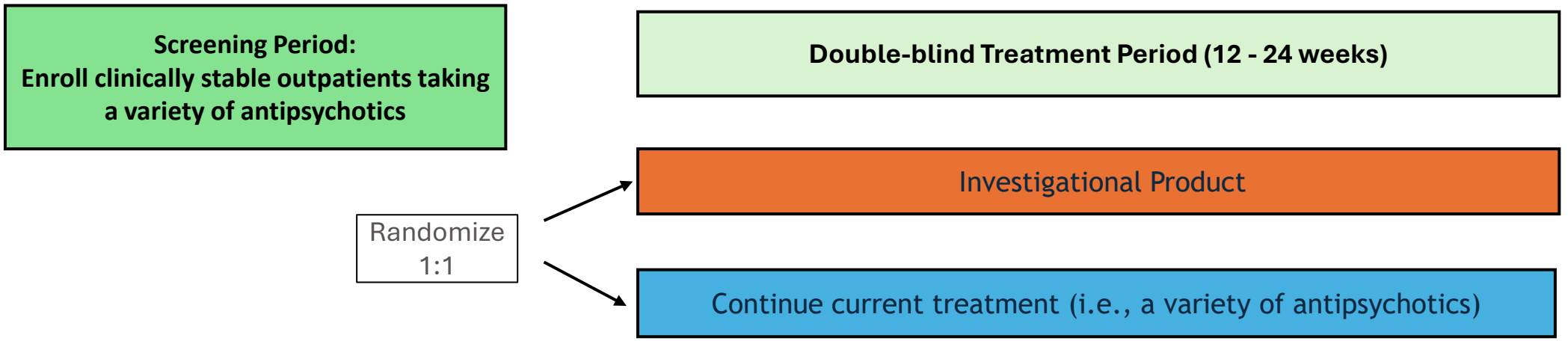
3. Stay/switch design: focused on a single approved antipsychotic



Considerations:

- 50% of patients would not be at risk to develop clinical instability on a new agent, reducing attrition risk
- Possible symptom instability for patients who switch to new monotherapy
- Recruitment challenges: limited to population taking a select antipsychotic
- Increased potential for unblinding?

4. Stay/switch design: allowing multiple approved antipsychotics



Considerations:

- 50% of patients would not be at risk to develop clinical instability on a new agent, reducing attrition risk
- Addresses potential labeling concern associated with using a single active comparator
- Possible symptom instability for patients who switch to new monotherapy
- Potential complications if there is an expectation to examine effects for different comparators (power/sample sizes considerations for sub-analyses)
- Increased potential for unblinding?

Summary

- There are important issues that relate to both adjunctive and monotherapy trials of Negative Sx in Schizophrenia
- Important considerations regarding Monotherapy trials center around the choice of comparison (placebo versus antipsychotic)
- One can also envision the need/use of Psychosocial intervention within the trial, prior to randomization or throughout the trial
- There are a variety of choices one can take depending on the specific aims of the trial in question
- Regardless of choice- concerns around practicality and the threat of high placebo responses should be important considerations

Panel Discussion

- Tiffany R. Farchione, MD

  Director, DP, ON, OND, CDER, FDA

- Peiling Yang, PhD

  Office of Biostatistics, CDER, FDA

- Robert W. Buchanan, MD

  Professor, Department of Psychiatry

  University of Maryland School of Medicine

  Maryland Psychiatric Research Center

  Baltimore, MD

- Michael Sand, PhD

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  Faculty Network Member of the Duke Institute for Brain Sciences
  Behavioral Medicine & Neurosciences Division
  Duke University School of Medicine
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- Nina R. Schooler, PhD

  Professor of Psychiatry and Behavioral Sciences
  State University of New York
  Downstate Health Sciences University
  Brooklyn NY

Lunch

11:40am

Session 3: Outcomes Part 1, Meaningfulness

Eric Jarvis, MD

Associate Professor of Psychiatry, McGill University, Director of the Cultural Consultation Service, the First Episode Psychosis Program, and the Culture and Psychosis Working Group at the Jewish General Hospital

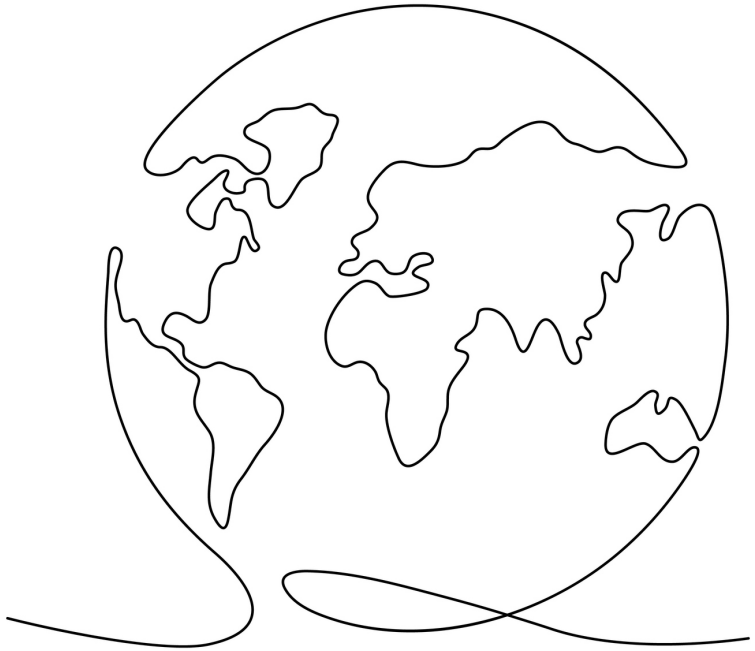
Montreal, Quebec, Canada

Cultural Considerations When Rating Negative Symptoms

G. Eric Jarvis, MD

FDA Public Meeting

August 16, 2024



Positionality Statement of G.E. Jarvis, MD

- Transcultural Psychiatrist and Director of Cultural Consultation Service and Culture and Early Psychosis Program
- Associate Professor, McGill University
- Research Focus - cultural adaptation of services for minority patients and their families
- Publishes about mental health effects of racism and discrimination
- Born in the U.S.A and lives in Canada. British, German and Danish ethnic origins and a member of The Church of Jesus Christ of Latter-day Saints (Mormon)

Focus of this presentation

PAPERS PUBLISHED IN THE UNITED STATES

MEMBERS OF AFRICAN AMERICAN COMMUNITIES

PEOPLE WITH SCHIZOPHRENIA

Negative symptoms of schizophrenia

- Affective flattening or blunting
- Alogia
- Avolition – Apathy
- Anhedonia – Asociality
- Attention

(From the Survey for the Assessment of Negative Symptoms, Andreasen, 1983)

The problem

- Negative symptoms in members of ethnic minorities are not as well studied as positive symptoms (Morgan et al., 2019)
- This may be due to beliefs that negative symptoms represent damage to brain structures and are therefore difficult to change (Weisman de Mamani & Caldas, 2013)
- Negative symptoms may in fact be confused with depression (Trierweiler et al., 2006), avoidance of stigma, and/or the effects of social adversity (Strauss, 2024)
- This may lead to misdiagnosis and improper interventions, especially in minority populations (Vega & Lewis-Fernández, 2008)

Historical stereotypes

(Jarvis, 2008)

African Americans are

- More prone to paranoia
- More prone to schizophrenia
- Intellectually inferior
- These stereotypes may encourage perception of negative symptoms of schizophrenia

Schizophrenia in ethno-racial minorities

Traditional position:

“Compared with Caucasians, African Americans, especially men, are less likely to receive a diagnosis of a mood disorder and more likely to receive a diagnosis of schizophrenia. African Americans with schizophrenia are also less likely to receive a diagnosis of a comorbid affective or anxiety disorder. While it is possible that such differences may reflect actual illness variation among racial/ethnic groups, there is growing evidence that cultural differences in symptom and personal presentation, help seeking, interpretation of symptoms and clinical judgments by (usually Caucasian) clinicians, and treatment referral are likely causing race-linked biases in diagnosis and therefore in treatment”

(APA Guidelines 2004/2010, p. 49)

Schizophrenia in ethno-racial minorities

Literature:

- *Gara et al. (2019)* confirmed the 2004 APA conclusions, but did not study negative symptoms per se
- Cultural mistrust (or paranoia), as ways to cope with histories of oppression, may bias toward the diagnosis of negative symptoms *(Whaley, 2001)*
- In Europe, high rates of schizophrenia in migrants, especially from the Caribbean and Sub-Saharan Africa *(Selten et al., 2020)*
- In the U.S., a new discourse is emerging that higher diagnosed rates of schizophrenia in African Americans may not just be due to clinician bias but also the effects of systemic and structural racism *(van der Ven et al., 2024)*

Negative symptoms in ethno-racial minorities

- African Americans and Mexicans may experience more negative symptoms than other groups *(Dassori et al., 1998; Barrio et al., 2003; Chang et al., 2011)*
- Chinese Americans may have fewer psychotic symptoms overall *(Chang et al., 2011)*
- Native Americans are less studied generally *(Taparra et al., 2024)*
- Findings have been mixed *(Brekke & Barrio, 1997)*

General Rating Problems

1. The nature of psychotic symptoms – They don't arise from brain processes alone but are experiences that are filtered and shaped by context for patients and their evaluators, whether in clinical or research settings
2. Broad ethno-racial categories – white, Black, Hispanic, Asian – need to be reconsidered, even discarded – they are not very helpful concepts
3. Lack of culturally adapted instruments

Specific rating problem: **Affect**

- Negative symptoms require careful assessment in context:

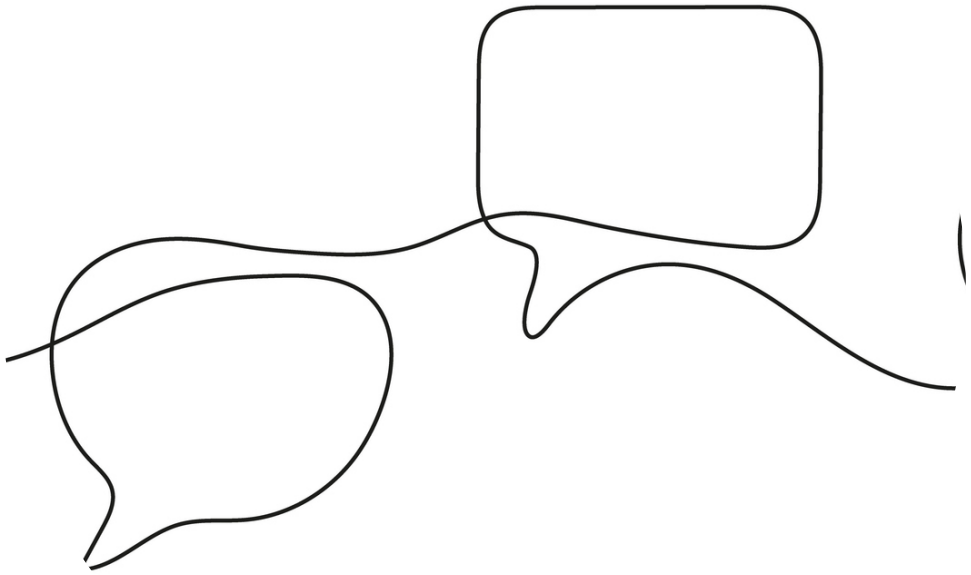
  Affective flattening or blunting

  -unchanging facial expression

  -poor eye contact

Specific rating problem: **Alogia**

- Poverty of speech
- Poverty of content of speech

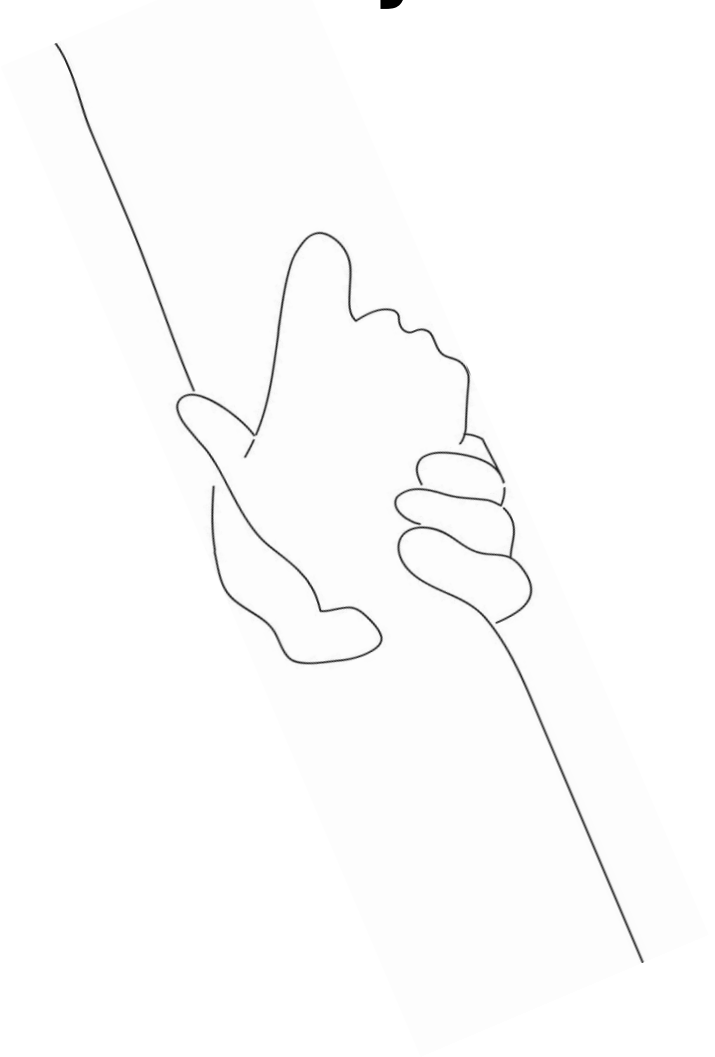


Specific rating problem: **Avolition-Apathy**

- Lack of grooming and hygiene
- Impersistence at work or school

Specific rating problem: **Anhedonia-Asociality**

- Recreational interests and activities
- Sexual interest and activity
- Ability to feel intimacy and closeness
- Relationships with friends and peers



Specific rating problem: **Attention**

- Social inattentiveness
- Inattentiveness during mental status testing

Negative Symptoms in Cultural Context

Overlap between depression and negative symptoms may be especially problematic for some ethnic minority groups in which depression is already diagnosed at an excessively low rate:

"Just as manics and psychotic depressives are likely to have delusions and hallucinations, so too depressives are likely to have some negative symptoms such as alogia or affective blunting" *(Andreasen 1989, p. 49)*

Negative Symptoms in Cultural Context

Social adversity may explain or contribute to apparent negative symptoms:

"Thus, after experiencing the illness for many years, it is possible that indirect environmental factors (economy, mass media, politics, government laws)…begin to exert a greater effect on their ability to perform recreational, goal-directed, and social activities that are the foundation of negative symptoms"

(Strauss, 2024, p. 1173)

Case Example

Depression versus Negative Symptoms

18-year-old African Canadian

- Possible FEP in 2020, with auditory and tactile hallucinations, emotional blunting, avolition, paranoia for one year – then no symptoms for three years
- No current medication or substance use
- Psychiatric evaluation in Dec 2023 – “recurrent depression but not currently depressed”
- “However, through multiple subsequent individual psychotherapy sessions, [we] strongly believe that the patient would benefit from an in-depth evaluation…to r/o psychosis due to persistent negative/cognitive psychotic symptoms.”

Specific concerns of the clinical team

“Since 2020 he began experiencing restricted affect, less ability and desire to communicate with others, and less anticipatory pleasure about things that he used to look forward to. As a result, he has found it harder to maintain relationships with others. He has also found it more difficult to feel attraction and romantic interest towards others.”

Specific concerns of the clinical team

“We would appreciate your expert assessment…to help determine if there is enough evidence to appropriately consider that he suffered a psychotic period and may continue to struggle with the negative symptoms of schizophrenia.”

What can be done?

1. Culturally adapt surveys and instruments
2. Train clinicians, researchers and raters in cultural humility
3. Make sure to include diverse participants in clinical trials and other studies
4. Include members of diverse communities in the research process and follow their recommendations and suggestions
5. Community outreach and qualitative studies

More data needed, especially ethnographic data

Cautionary note

(Rogers et al., 2024, p. 221)

“...practitioners should always evaluate whether psychotic-like experiences may be better explained via ethno-cultural context”

Conclusions

- Negative symptoms of schizophrenia are understudied in members of minority groups
- Rates of negative symptoms likely vary by ethnic group, but how much of this is due to cultural variation of illness expression is unknown
- Clinicians and researchers need to adopt a position of cultural humility in their work with minority groups
- Members of minority groups need to be part of our research teams, and their recommendations need to be implemented

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Laura Swett, PhD

Reviewer, Division of Clinical Outcome Assessment, CDER, FDA

U.S. FOOD & DRUG ADMINISTRATION

Evaluating the Negative Symptoms of Schizophrenia in Clinical Trials

Public Workshop

August 16, 2024

Regulatory Considerations for Assessing Clinically Meaningful Within-Patient Change

Disclaimers

Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position.

Determining a Clinically Meaningful Within-Patient Change in NSS

1. Are clinical rating scales enough?
   (Why consider a patient-perspective for measurement?)

2. Regulatory considerations for defining clinically meaningful within-patient change in NSS.

3. Types of COA's that might contribute to the measurement of clinically meaningful within-patient change.

Are clinical rating scales enough?

Disease/Condition	COA Context of Use	Concept	COA Tool & Type	Drug Name/Approval Date/ Qualification Link
Schizophrenia	Adults with schizophrenia	Severity of schizophrenia symptoms	Positive and Negative Syndrome Scale (PANSS): **ClinRO**[1,2,3,4,5,6]	1. Aristada (aripiprazole lauroxil) *October 5, 2015* 2. Vraylar (cariprazine) *September 17,2015* *November 9, 2017* 3. Latuda (lurasidone hydrochloride) *October 28, 2010* *January 27, 2017** 4. Saphris (asenapine) *August 13, 2009* 5. Fanapt (iloperidone) *May 6, 2009* 6. Invega (paliperidone) *December 19, 2006* 7. Invega Sustenna (paliperidone palmitate) *December 20, 2017*
		Positive symptoms of psychosis	Brief Psychiatric Rating Scale derived (BPRSd): **ClinRO**[3,5]	
		Global clinical impression of severity	Clinical Global Impression-Severity: **ClinRO**[2,3]	
		Personal and social functioning	Personal and Social Performance (PSP) scale: **ClinRO**[6]	
		Relapse of psychosis	**ClinRO**[2,7]	

Source: Center for Drug Evaluation and Research; Clinical Outcome Assessment Compendium, (June 2021) p. 49.

Why Consider a Patient-Perspective for Measurement?

- Concepts of Interest
- Treatment Goal
- Aspects/Attributes of concepts:
  - *Presence/Absence
  - *Frequency
  - *Intensity
  - *Duration

Regulatory Considerations for Defining Meaningful Change

1. Do the concepts comprising NSS move together or separately? (What drives the change?)

2. Are all concepts considered to be important from a clinician vs. patient vs. caregiver perspective?

3. What are the most important concepts to treat from the patient/caregiver perspective?

Regulatory Considerations for Defining Meaningful Change

4. Do patients or caretakers consider some concepts more important/ more bothersome or less important or less bothersome, than others?

5. Which domains might your MOA be targeting?

6. When do we consider clinically meaningful change at the group level (e.g., inferences regarding a population) versus at the individual level (i.e., establishing that a certain proportion of patients benefitted from treatment)

How Do you Define Meaningful Change?

6. How much change is considered to be meaningful (improvement or worsening) within each key concept?

7. How does this translate to lived experiences?

What are other ways meaningful change data can be captured?

Digital Health Technologies (DHT)

E.g., Virtual Reality Functional Capacity Assessment (VRFCAT) or measurement of other aspects of functioning such as Remote or Wearable Patient Monitoring Devices)

Observer Reported Outcomes (ObsRO's)

E.g., Caregiver Reported Outcome Measures

Videos

E.g., of conducting tasks directly linked to a negative symptom) and utilization of centralized raters


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Panel Discussion

- Matthew Racher, CRPS
  Certified Peer Specialist
  Miami, FL
- Deanna L. Kelly, PharmD, BCPP
  Dr. William and Carol Carpenter Professor of Psychiatry for Mental Illness Research
  MPower Professor of Psychiatry
  University of Maryland Strategic Partnership: MPowering the State
  Acting Director, Maryland Psychiatric Research Center
  Chief Treatment Research Program
  University of Maryland School of Medicine
  Baltimore, MD
- Mark G. Opler, PhD, MPH
  Chief Research Officer
  Clinical Research Solutions
  New York, NY
- Bonnie Kaiser, PhD, MPH (virtual)
  Associate Professor, jointly appointed in the Department of Anthropology and the Global Health Program
  University of California San Diego
  San Diego, CA

10-Minute Break

1:50 pm

Session 3:
Outcomes Part 2,
Scales and Other Measures

Jack J. Blanchard, PhD

Associate Provost for Enterprise Resource Planning and Professor
Department of Psychology, University of Maryland

College Park, MD, USA

Clinical Assessment Interview for Negative Symptoms: Background and Current Status

Jack J. Blanchard, Ph.D.
Associate Provost & Professor
University of Maryland, College Park

Next Generation Negative Symptom Assessment: Historical Context

1980's scale development :

- Scale for the Assessment of Negative Symptoms (SANS, 1984)
- Positive and Negative Syndrome Scale (PANSS, 1987)
- Negative Symptom Assessment (NSA, 1989)

Problems With Older Scales

Emotional Range

- NSA: "reduced emotional range" reflects both anhedonia and aspects of emotion that are not part of negative symptoms including the lack of anxiety, sadness, or anger.

Cognitive Functioning

- SANS: "attention"; PANSS "abstract thinking"

Relying on behavior to infer experiential deficits

- PANSS: "interest," "affect," "empathy" and "closeness" items do not have probes to assess experiential states but rely on observation of behavior and reports for social behavior.

Poor reliability

Unclear anchors, lack of interview guide, manuals, or training materials.

(Blanchard et al., 2011; Horan et al., 2006; Kirpatrick et al., 2006)

Next Generation:

NIMH Negative Symptom Consensus Development Conference (2005).

Multistage collaborative approach

- Extensive literature review
- Collaborative development of initial item pool
- Preliminary beta measure circulated to garner feedback from clinical researchers and industry representatives.
- Two different approaches and two different measures
    1. Clinical Assessment Interview for Negative Symptoms (CAINS)
    2. Brief Negative Symptom Scale (BNSS)

Collaboration to Advance Negative Symptom Assessment in Schizophrenia

Jack Blanchard

Bill Horan

Ann Kring

Raquel Gur

Blanchard, Kring, Horan, & Gur (2011). *Schizophrenia Bulletin*.
Kring, Horan, Gur, & Blanchard (2013). *American J. Psychiatry*.
NIMH 1R01MH082890, 1R01MH082839, 1R01MH082783, 1R01MH082782

Clinical Assessment Interview for Negative Symptoms (CAINS)

Modifications to address in new measure:

1. Remove item content not conceptually related to negative symptoms
2. Assess experiential deficits (e.g., pleasure, interest) independent of current functioning.
   - Consider two aspects of hedonic experience: Consummatory, Anticipatory
3. Begin with broad content (23 items) and then refine iteratively and transparently using data-driven approach (not clinical fiat).
4. Utilize state of the art psychometrics (e.g., Item Response Theory, IRT) to examine such features as optimal number of anchor points.
5. To ensure rater agreement, cross-site consistency, and wide adoption:
   - Develop standardized interview probes and use comprehensive and descriptive anchor points, detailed rating manual and standardized training videos.

Initial CAINS 23 Item Pool

Domain	Content	Items
Anhedonia (9 items)	• Consummatory pleasure Intensity and frequency • Anticipated pleasure	1. Social Activities 2. Physical Sensations 3. Recreational/Vocational Activities
Asociality (3 items)	Internal experience & behaviors considered	1. Family 2. Romantic Relationships 3. Friends
Avolition (4 items)	Internal experience & behaviors considered	1. Social Interactions 2. Work/Vocational/School Activities 3. Recreation/Hobbies 4. Self-care
Blunted Affect (5 items)	Based on interview observations and following questions that elicit both positive & negative emotion	1. Facial Expression 2. Vocal Expression 3. Expressive Gesture 4. Eye Contact 5. Spontaneous Movements
Alogia (2 items)	• No specific probes • Based on entire interview	1. Quantity of Speech 2. Spontaneous Elaboration

CAINS Iterative Development

Forbes et al. (2010)

CAINS-beta: 23-items, 7-point scale
N = 37
Examined rater agreement, item redundancy, response options, validity.

Horan et al. (2011)

- CAINS-beta2: 23-items, 5-point scale
- *N* = 281
- Examined latent structure, rater agreement, item redundancy, response options, validity.
- Revised items, rating anchors, and shortened scale based on data analysis.

Kring et al. (2013)

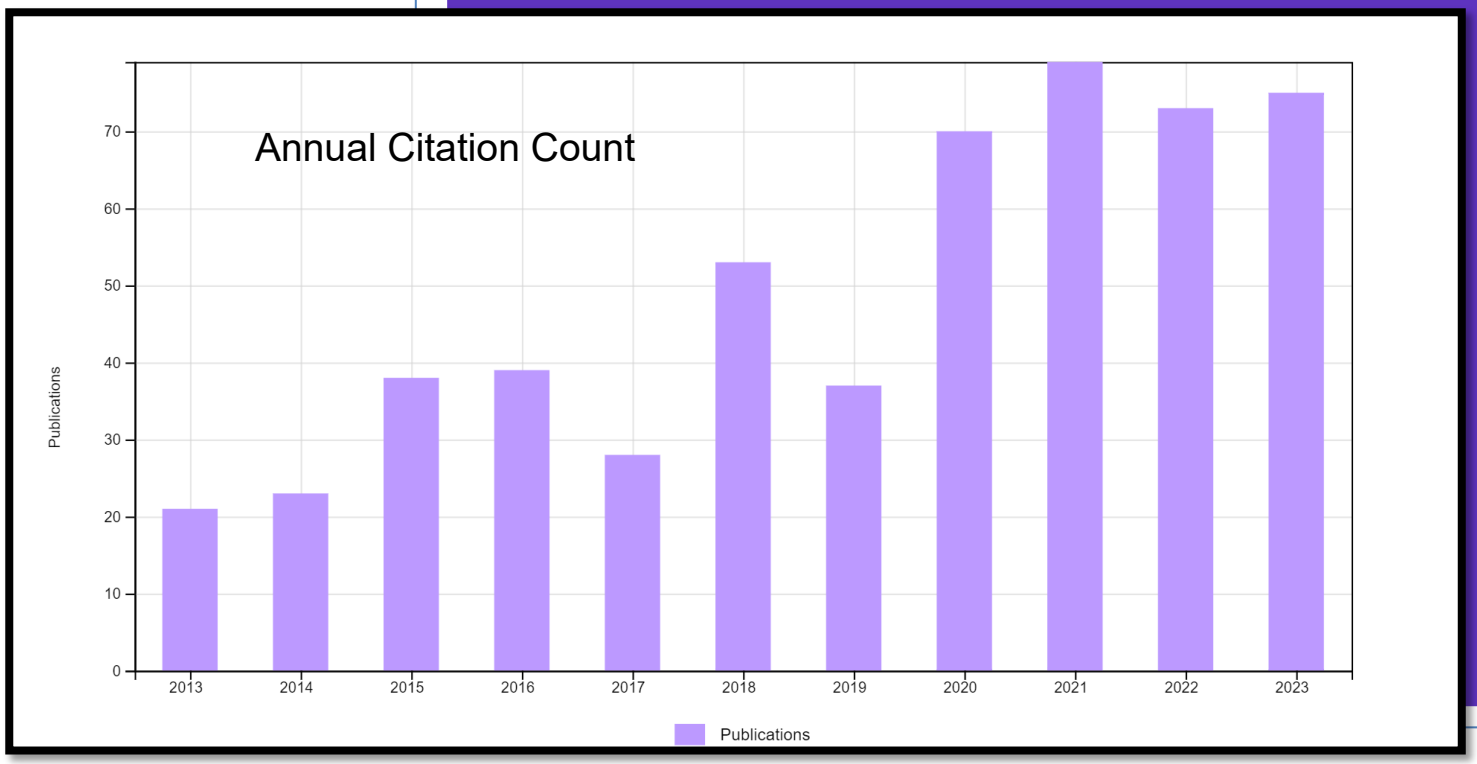
- CAINS 16 items trimmed to 13
- *N* = 162
- Established reliability, rater agreement, convergent and discriminant validity.
- Determined that scale performed similarly across gender and ethnicity.
- Test-retest stable over 2-3 weeks.

Final 13-item CAINS	Subscales
Motivation for Close Family/Spouse/Partner	**Motivation and Pleasure**
Motivation for Close Friendships/Romantic	**Motivation and Pleasure**
Frequency of Pleasurable Social Activities (Past)	**Motivation and Pleasure**
Frequency of Expected Pleasurable Social	**Motivation and Pleasure**
Motivation for Work & School	**Motivation and Pleasure**
Frequency of Expected Pleasurable Work/School	**Motivation and Pleasure**
Motivation for Recreational Activities	**Motivation and Pleasure**
Frequency of Pleasurable Recreational Activities (Past)	**Motivation and Pleasure**
Frequency of Expected Pleasurable Activities	**Motivation and Pleasure**
Facial Expression	**Expressivity**
Vocal Expression (prosody)	**Expressivity**
Expressive Gestures	**Expressivity**
Quantity of Speech	**Expressivity**

Reliability ✓
Convergent Validity ✓
Discriminant Validity ✓
Short-Term Test-Retest ✓
Administration time: 15-30mins

Kring, Gur, Blanchard, Horan, & Reise (2013). *American Journal of Psychiatry*.

Impact of CAINS (Kring et al., 2013)
Citation Count > 500



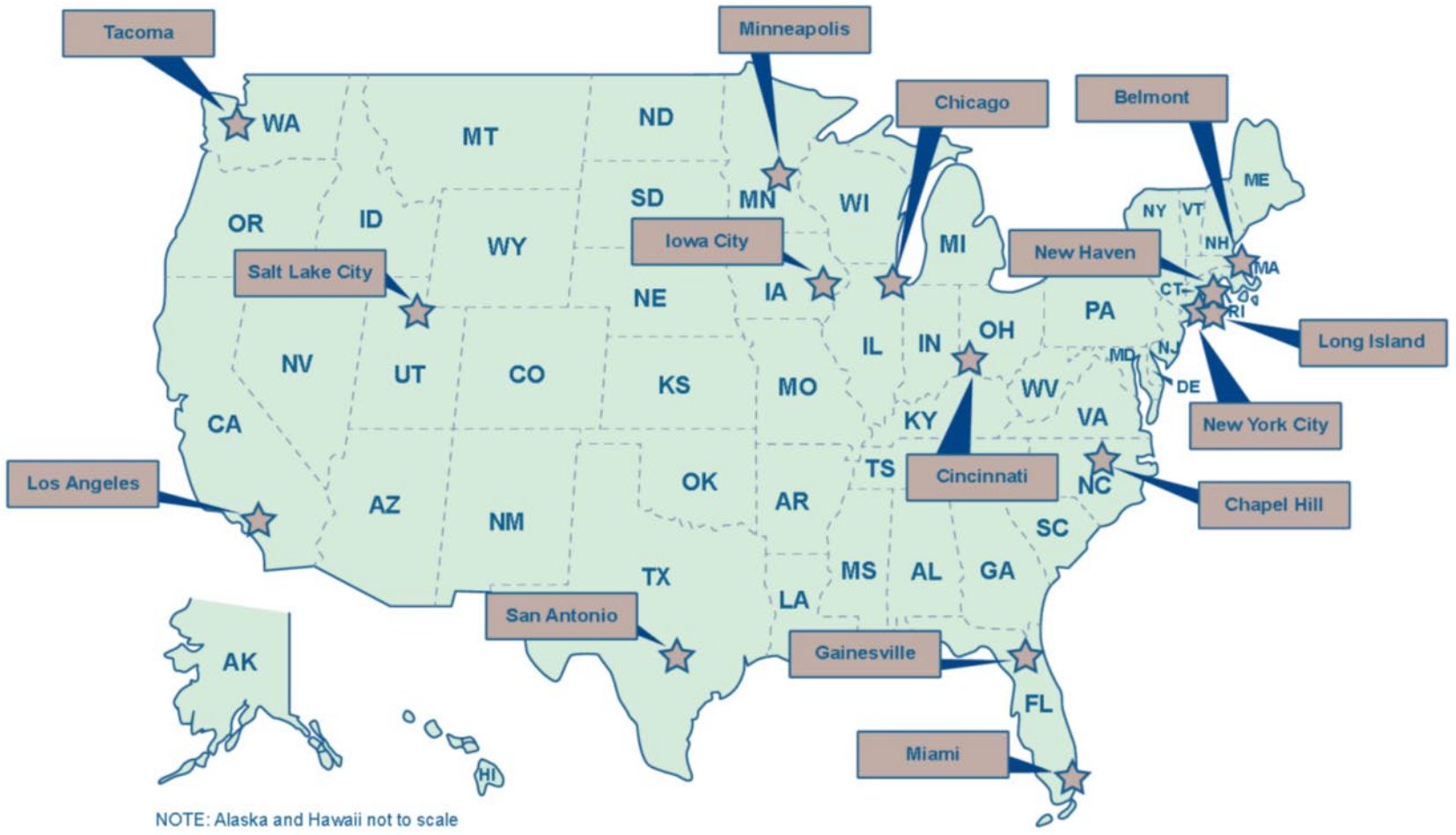
Interrogating the Validity of the CAINS

Other Evidence

- **Replication**
- Patient Reported Experiences
- Real-World Experience (in the moment)
- Behavior
- Neural Responding
- Sensitivity to Treatment

Management of Schizophrenia in Clinical Practice (MOSAIC): 501 Participants across 15 Centers

Figure 1. Geographic location of the Patient Assessment Centers



Blanchard et al. (*2017*). *Schizophrenia Research*

CAINS Structure and Stability

Two-factor solution for the CAINS items at baseline.

CAINS item	Factor 1	Factor 2
9. MAP: Expected pleasure recreation	0.85	
8. MAP: Pleasure from past recreation	0.80	
7. MAP: Motivation for recreation	0.75	
4. MAP: Expected pleasure social	0.73	
3. MAP: Pleasure from past social	0.72	
6. MAP: Expected pleasure work/school	0.55	
2. MAP: Motivation for friendship/romantic	0.53	
5. MAP: Motivation for work/school	0.50	
1. MAP: Motivation for family/spouse/partner	0.46	
11. EXP: Vocal expression		0.93
12. EXP: Expressive gestures		0.91
10. EXP: Facial expression		0.89
13. EXP: Quantity of speech		0.71

Note: CAINS = Clinical Assessment Interview for Negative Symptoms; MAP = Motivation and Pleasure; EXP = expressivity.

Scale Reliability ✓
Convergent Validity ✓
Discriminant Validity ✓
3-month Test-Retest ✓
- MAP: r = .80**
- EXP: r = .75**

Blanchard et al. (*2017*). *Schizophrenia Research*

Interrogating the Validity of the CAINS

Other Evidence

- Replication
- **Patient Reported Experiences**
- Real-World Experience (in the moment)
- Behavior
- Neural Responding
- Sensitivity to Treatment

Clinician-Rated CAINS and Patient Reported Experience

Patient Report	CAINS-MAP	CAINS-EXP
Quality of Life: Social (worse)[a]	**.35*** **	.04
Quality of Life: Motivation & Energy (worse)[a]	**.36*** **	.05
Social Anhedonia[b]	**.29** **	.07
Social Closeness[b]	**-.36** **	-.01
Loneliness[c]	**.38** **	**.29** **
Social – Emotional Support	**-.47*** **	**-.25** **
Affiliative Feelings toward Social Partner[c]	**-.33** **	**-.19***
Size of Social Network[c]	**-.56*** **	**-.25** **
Social Functioning[c]	**-.41** **	**-.33** **

[a]Blanchard et al. (*2017*). *Schizophrenia Research*
[b]Kring et al. (2013). *American Journal Psychiatry*.
[c]Blanchard et al. (2024). *Clinical Psychological Science*.

Interrogating the Validity of the CAINS

Other Evidence

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- **Real-World Experience (in the moment)**
- Behavior
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CAINS and Real-World Experience: Ecological Momentary Experience (EMA)

Merchant, Moran & Barch (2022)

- Schizophrenia or Schizoaffective Disorder
- CAINS MAP
- EMA over 7 days
- Anticipatory and Consummatory Pleasure

Results

- MAP severity related to **decreased EMA anticipatory pleasure** (independent of depression).
- MAP unrelated to consummatory pleasure.

Abel, Vohs, Salyers, Wu & Minor (2024)

- Schizophrenia
- CAINS MAP
- EMA over 5 days
- Social Pleasure

Results

- MAP severity related to **decreased EMA anticipated social pleasure**.
- MAP severity related to lower consummatory pleasure at trend level.

Interrogating the Validity of the CAINS

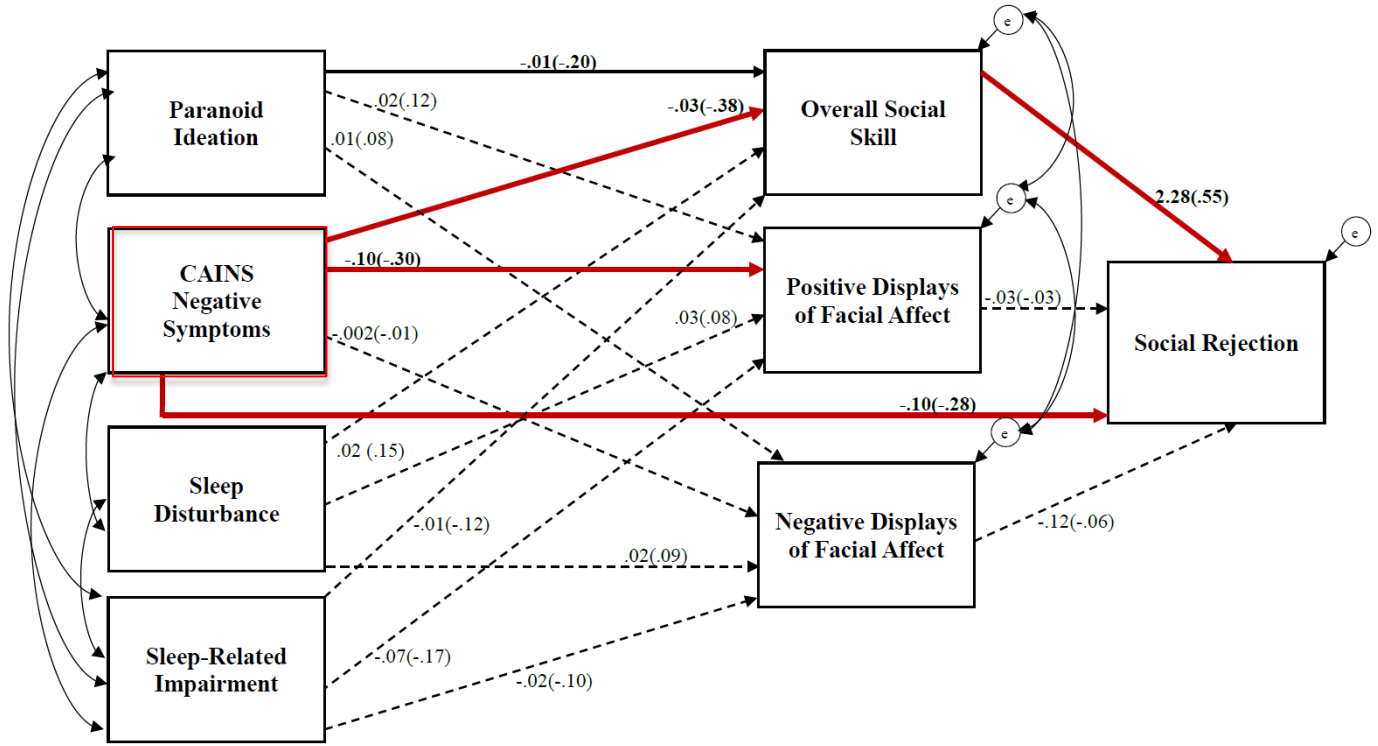
Other Evidence

- Replication
- Patient Reported Experiences
- Real-World Experience (in the moment)
- **Behavior**
- Neural Responding
- Sensitivity to Treatment

Interpersonal Consequence of Negative Symptoms

CAINS negative symptoms are related to poorer behavioral social skills and social rejection.

Parameter Estimates of the Respecified Model



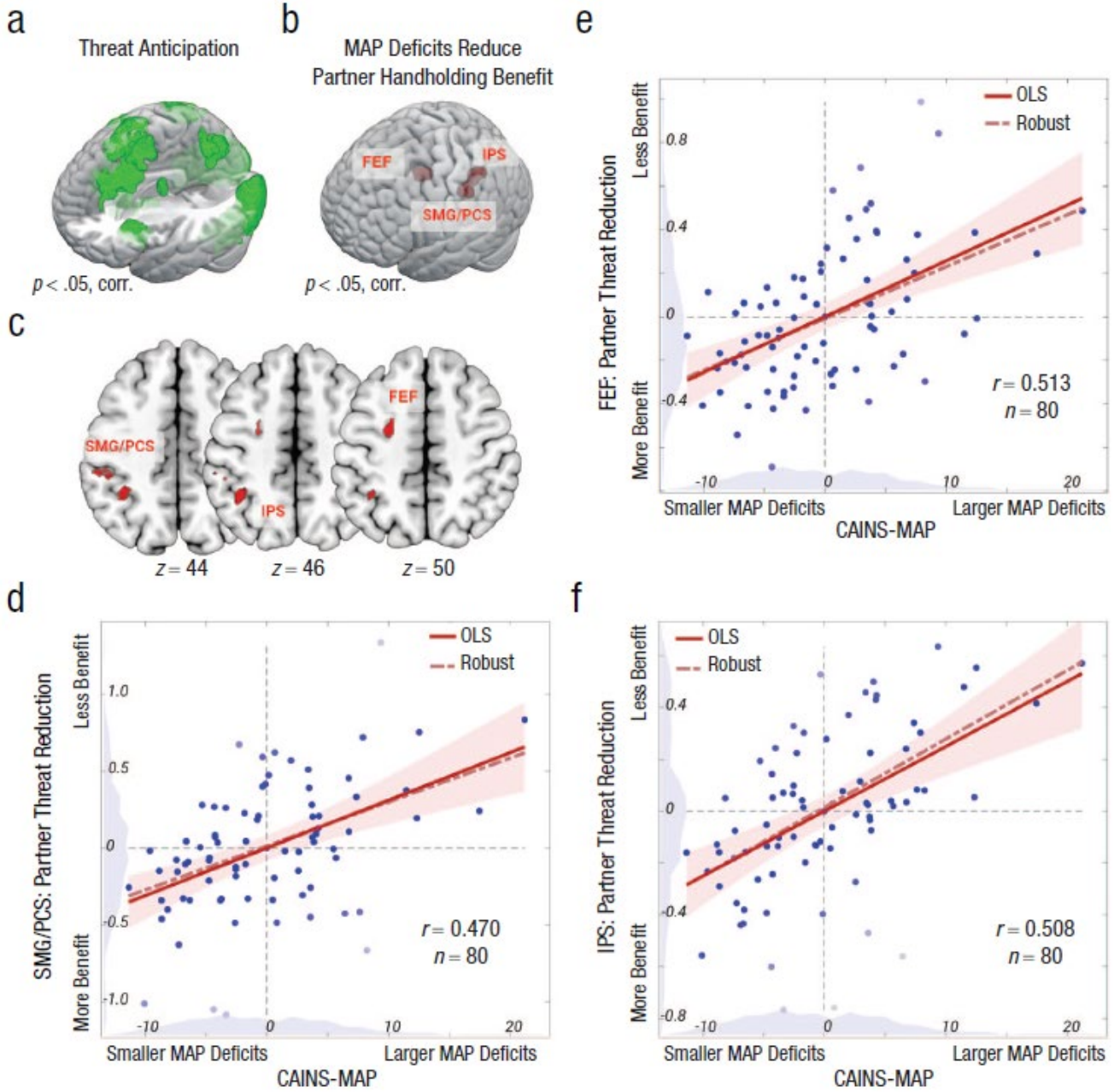
Note. Unstandardized (and standardized) parameter estimates for the respecified model. Significant parameter estimates are in bold ($ps < .05$). Dotted lines indicate non-significant paths ($ps \geq .05$).

Savage et al. (2024). *Journal of Psychiatric Research*.

Interrogating the Validity of the CAINS

Other Evidence

- Replication
- Patient Reported Experiences
- Real-World Experience (in the moment)
- Behavior
- **Neural Responding**
- Sensitivity to Treatment



CAINS MAP Symptoms undermine the neural benefits of social affiliation in psychosis-spectrum transdiagnostic sample.

Blanchard et al. (2024) *Clinical Psychological Science*.

CAINS MAP symptoms are related to blunted ventral striatum reactivity to naturalistic social (but not monetary) reward in psychosis-spectrum transdiagnostic sample.

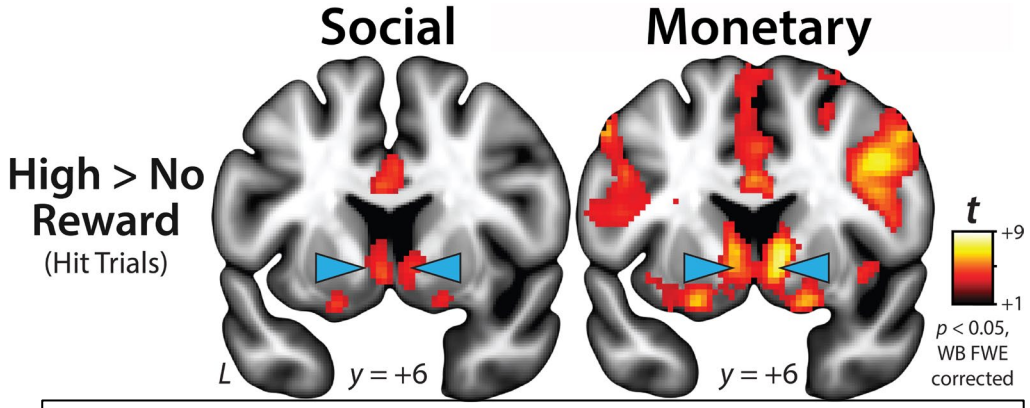
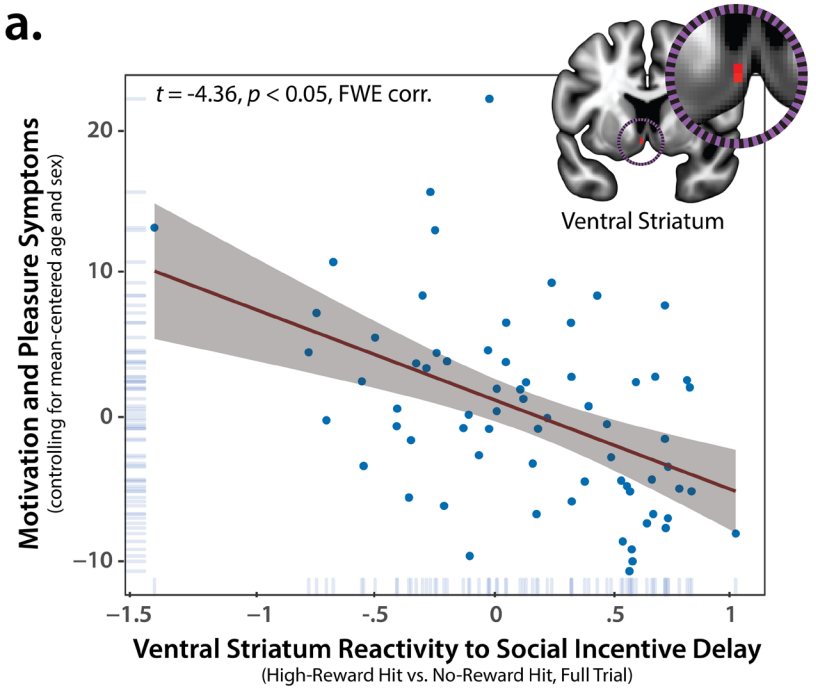
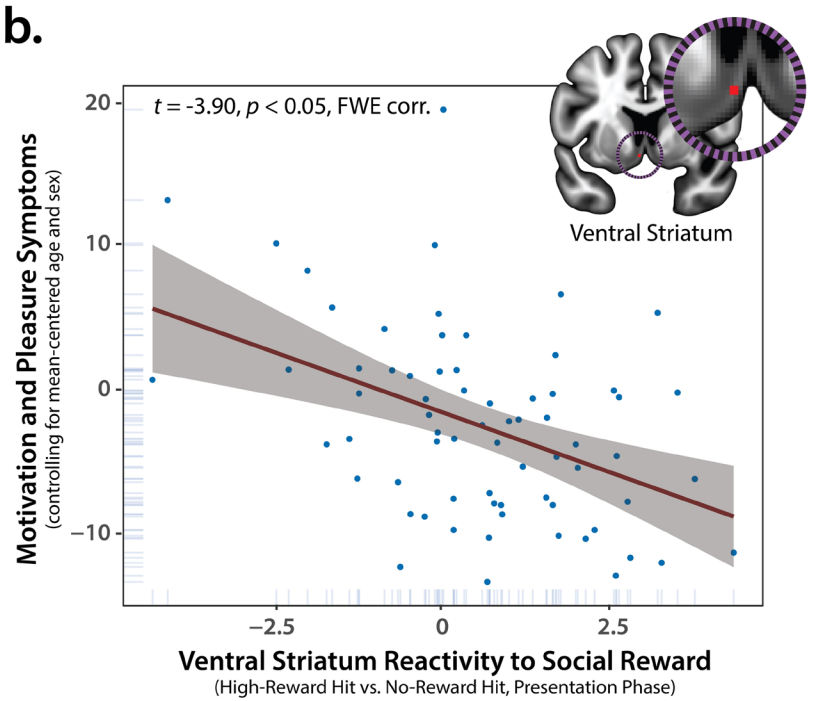


Figure depicts regions showing significantly greater activation during High-Reward compared to No-Reward hit trials for the Social (left) and Monetary (right). Blue arrows indicate the ventral striatum.

Blanchard et al. (2024) *under review*.





Interrogating the Validity of the CAINS

Other Evidence

- Replication
- Patient Reported Experiences
- Real-World Experience (in the moment)
- Behavior
- Neural Responding
- **Sensitivity to Treatment**

The CAINS Is Sensitive to Treatment Effects

Study	Intervention	Duration	Negative Symptoms
Oh et al. (2023)	Behavioral Activation vs Treatment as Usual (TAU)	10-weeks	CAINS-Total, ***p* = .01*** BNSS, *ns* PANSS-N, *ns*
Reddy et al. (2023)	Motivational Interviewing and CBT vs Control	12 weeks	CAINS-MAP, ***p* = .01***
Luther et al. (2020)	Mobile Enhancement of Motivation vs Control	8 weeks	CAINS-MAP(4), ***p* = .03***
Granholm et al. (2020)	Mobile assisted CBT (open single arm)	24 weeks	CAINS-MA, ***p* = .004*** CAINS-EXP, *ns*
Velligan et al. (2015)	Motivation and Enhancement Training vs TAU	9 months	CAINS-Total, ***p* < .04*** NSA, $p < .02$* BNSS, *ns*
Ivanov (2022)	Cariprazine (open label)	4 weeks	CAINS-Total, ***p* < .001*** PANSS-N, $p < .05$*

CAINS Translations (unofficial)

- German*
- Chinese*
- Korean*
- Turkish*
- Swedish*
- Portuguese
- Russian
- Greek

French*
Serbian
Spanish*
Albanian
Macedonian*
Danish
Polish
Lithuanian

*Translation has published convergent/discriminant validity.

Summary of CAINS Characteristics

Characteristic	
Only Negative Symptom Scale to Follow Recommended Iterative Development	✓
Psychometrically Sound	✓
Temporal Stability	✓
Discriminant Validity	✓
Convergent Validity	✓
Sensitivity to Treatment Effects	✓
Manual and Training Videos	✓
Translated into Multiple Languages	✓

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Adjourn