

# International Society for CNS Clinical Trials and Methodology

**Satellite Meeting on the NIMH Initiative  
Regarding Treatment Development for  
Negative Symptoms**

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# Defining Negative Symptoms

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# Defining Negative Symptoms

- **Working Definition**
- **Relationship to other domains**
- **Negative Symptoms as an area of therapeutic need**

# Negative Symptoms

## -Larry Alphas Definition

- **Negative symptoms represent the reduction or absence of behaviors normally present in a healthy person. These include, but are not limited to, behaviors related to personal, social and affective, functioning. Specifically, negative symptoms of schizophrenia are considered to include reduction in emotional expression and perception, reduction in the fluency and productivity of thought and speech, reduced desire for social involvement and reduced social interaction with others and a loss or lack of goal-directed behavior.**

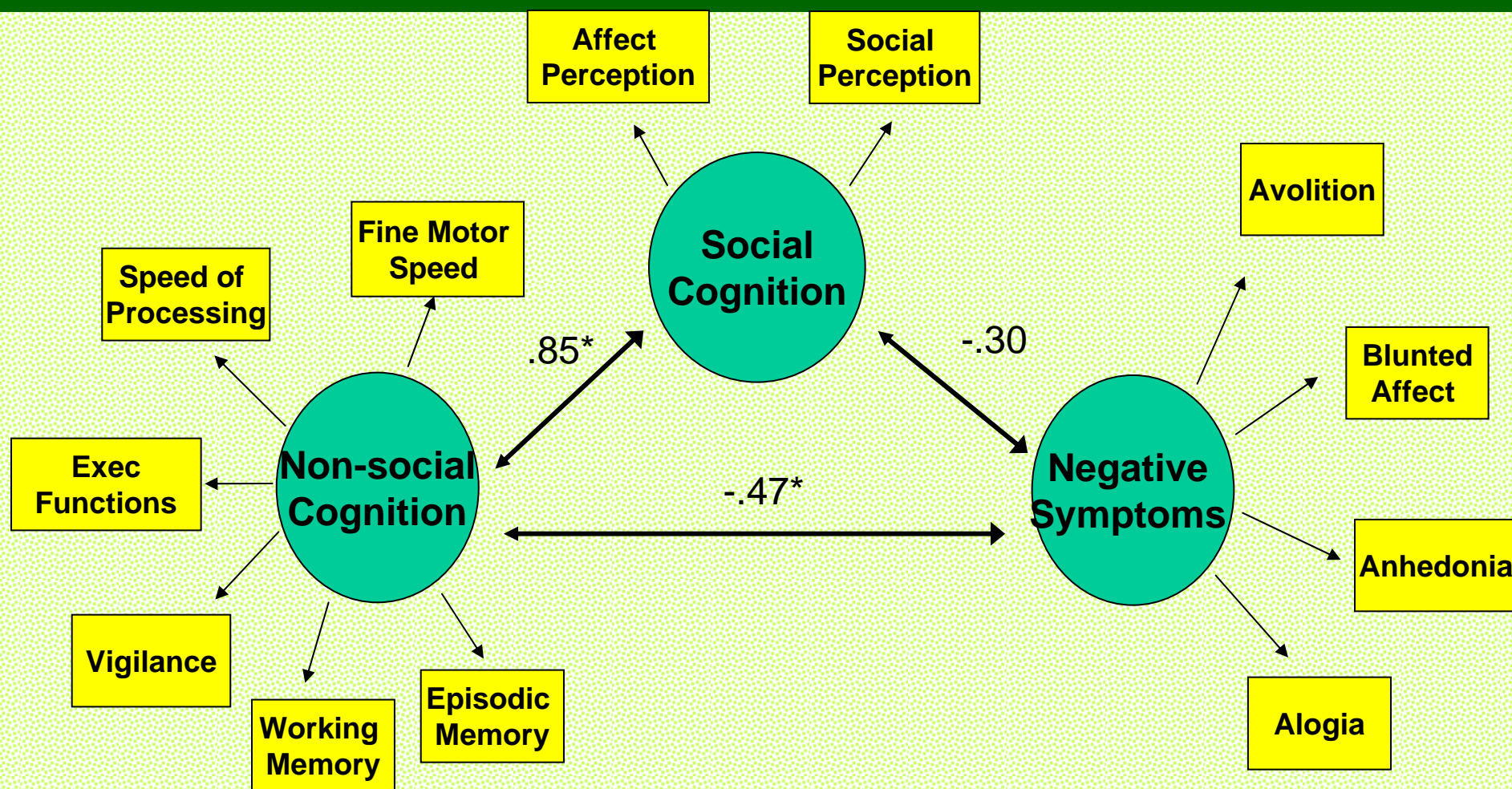
# Negative Symptoms and Neurocognition

- **Negative symptoms have moderate overlap with cognitive performance impairment (10-20% of the variance)**
- **Unclear if cognitive impairment and negative symptoms are associated with different types of outcome**

# Can negative symptoms be separated from cognition and depression?

- **NIMH Consensus Meeting**
  - *Negative symptoms and cognitive impairments represent separate domains. Aspects of interaction and overlap may be defined in the future, but documentation of substantial separation is available in current data.*
- **Factor analyses of psychopathologic dimensions in schizophrenia have consistently found that these factors can be separated (including data from Liddle, Kay, Marder and others)**

# Social Cognition, Non-social Cognition, and Negative Symptoms



\*  $p < .05$

Sergi et al., unpublished

Comparative Fit Index (CFI) = .97

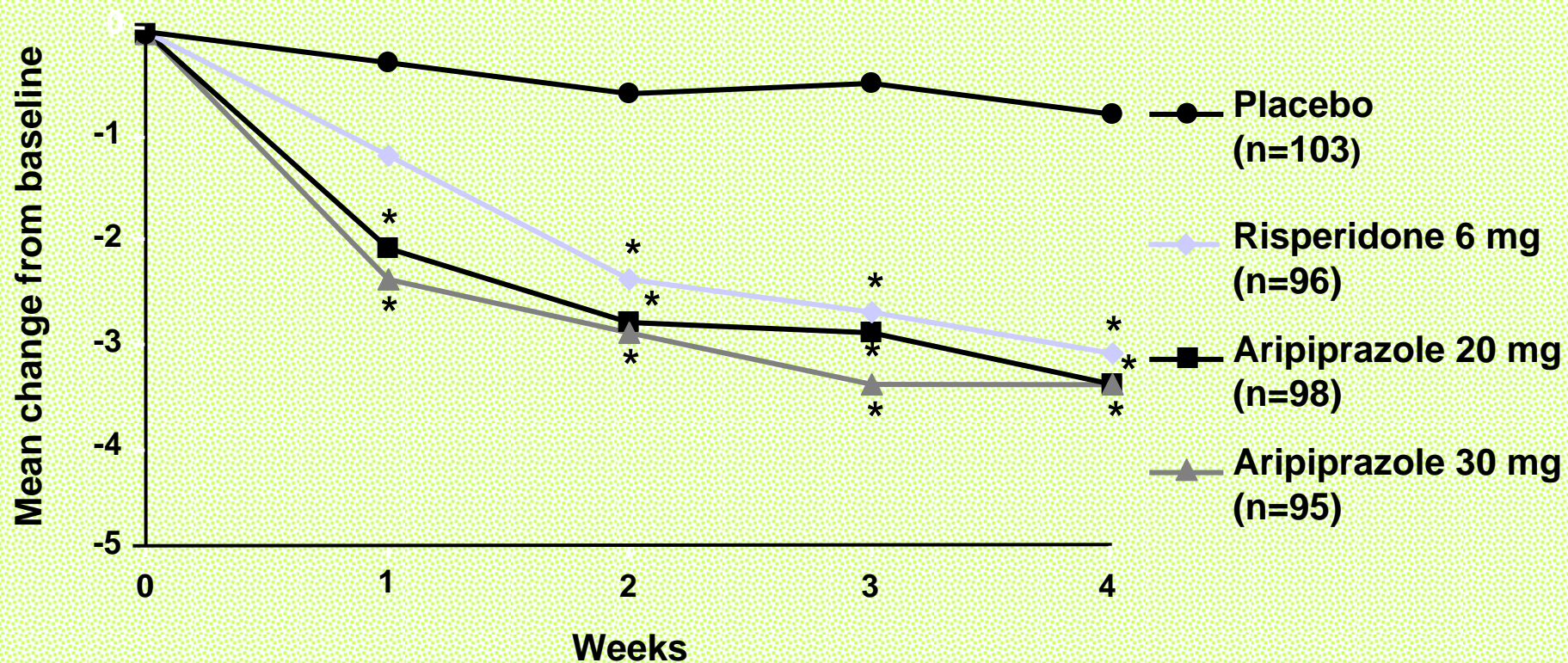
# Why focus on negative symptoms

- **Association with functional outcome**
- **Ineffectiveness of current treatments**
  - **Poor design has led to false positive findings**
- **Uncertainty regarding its domains**

# Effectiveness of antipsychotics for negative symptoms

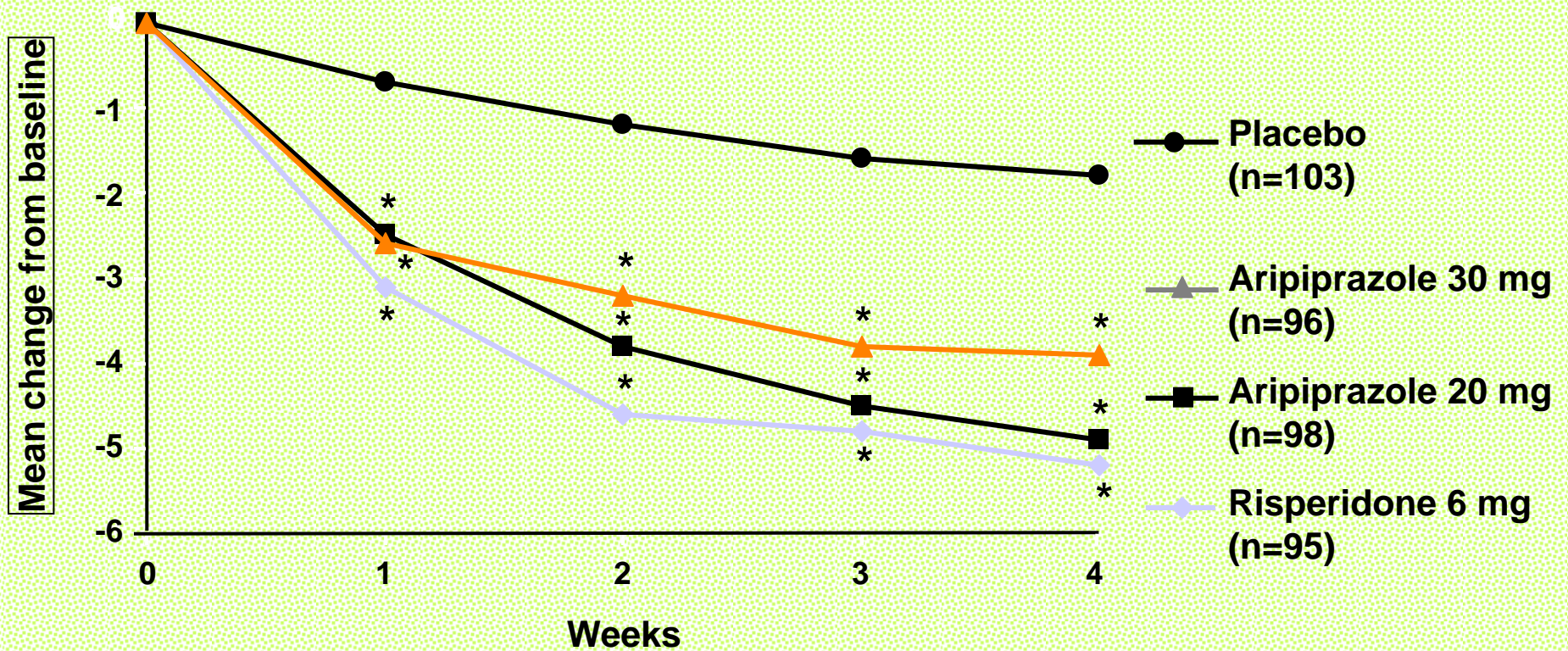
- **Virtually all studies find that antipsychotics improve negative symptoms in acute patients**
- **Differences between 1<sup>st</sup> and 2<sup>nd</sup> generation drugs are small**
- **Improvement with antipsychotics may be secondary to other improvements**

# Aripiprazole and Risperidone: Change in PANSS Negative Score



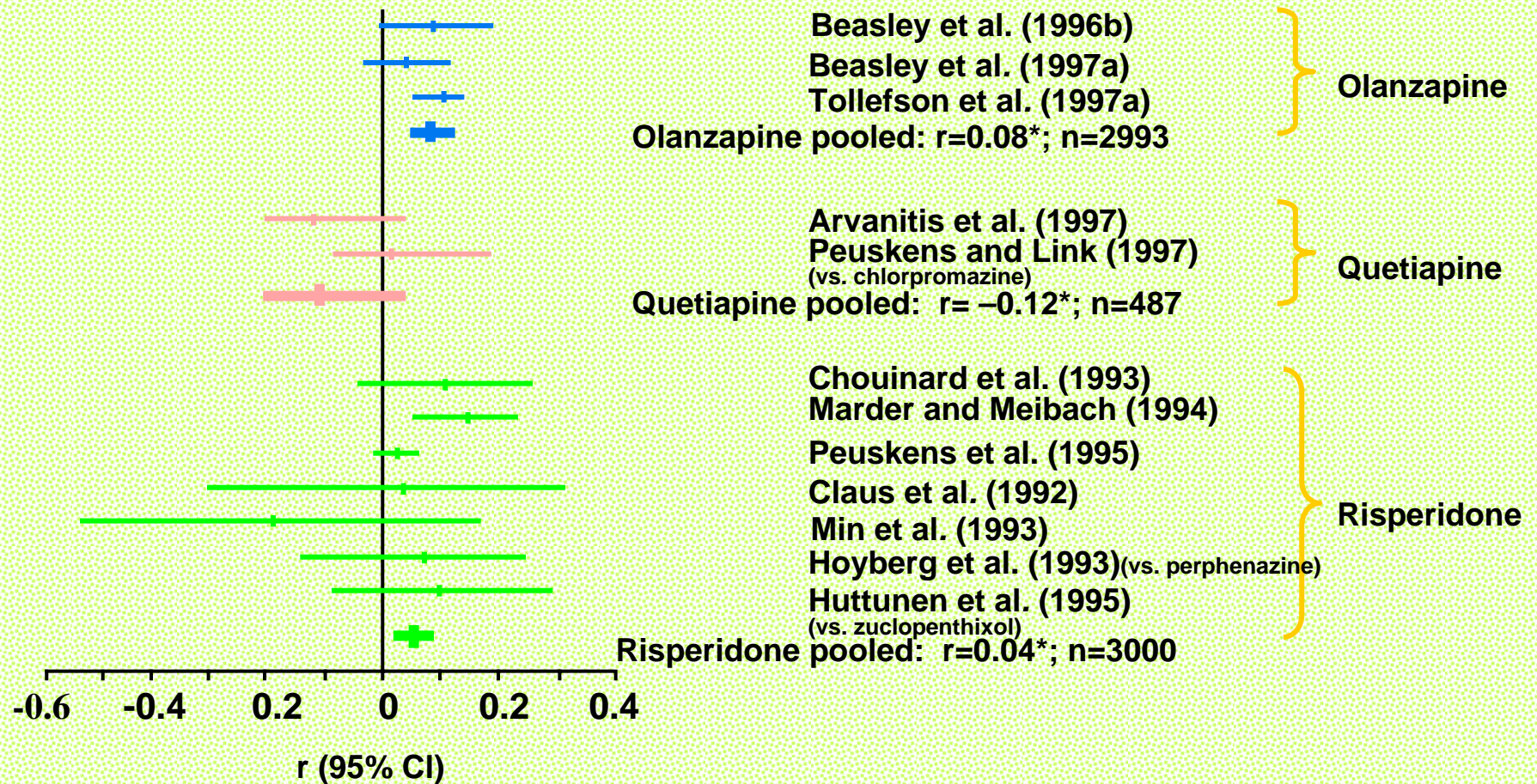
\*Significantly different from placebo, LOCF,  $P < 0.05$ .  
Baseline mean scores ranged from 23.0-24.3.  
Potkin et al. *Arch Gen Psychiatry*. 2003. In press.

# Aripiprazole and Risperidone: Change in PANSS Positive Score



\*Significantly different from placebo, LOCF,  $P<0.05$ .  
Baseline mean scores ranged from 23.7-24.6.  
Potkin et al. *Arch Gen Psychiatry*. 2003. In press.

# Mean Change in Negative Symptoms: New Antipsychotics vs. Haloperidol



\*Statistically significant

# Obstacles for finding treatments for negative symptoms

- 1. Lack of consensus regarding the domains of negative symptoms**
- 2. Lack of consensus regarding the best measures for change in negative symptoms**
- 3. Overlap with cognitive and positive symptoms**
- 4. Uncertainty about relevant neuropharmacological targets**

## There are important differences between treatment development for negative and cognitive symptoms

- Negative symptoms are not as prevalent
- Negative symptoms are more likely to be secondary to other symptoms
- Negative symptoms are more difficult to measure precisely – require pt self-report and rater observation
- It is uncommon for patients themselves to complain of negative symptoms