Cognitive impairment in psychosis: What it is and how it is treated

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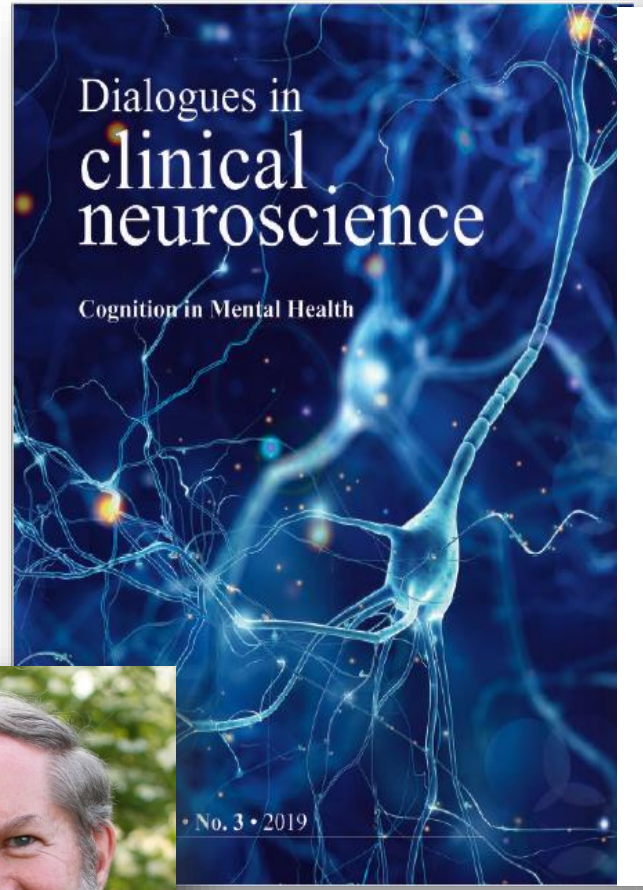
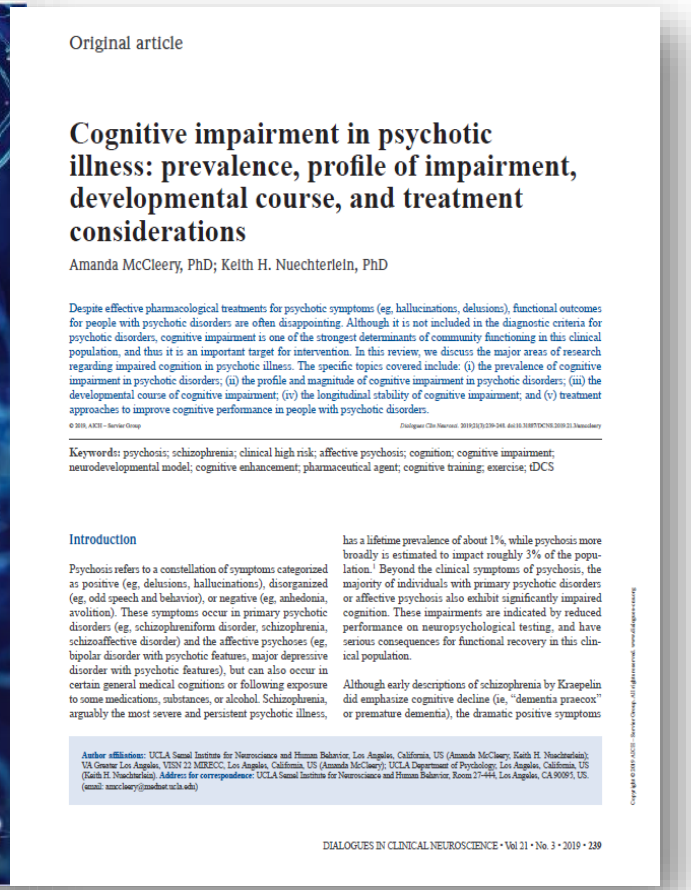
Road map

- Aim:
  - Provide a broad overview of research examining cognitive impairment & the pathway from cognition to daily functioning in people with schizophrenia
  - Provide a broad overview of treatment approaches
- Topics:
  - Disability in schizophrenia
  - Cognitive impairment in schizophrenia
    - Profile of cognitive performance
    - Developmental course
    - Relationship to disability
  - Intervening factors along the pathway from cognition to disability
  - Bridging to clinical practice – treatment approaches





Original article

Cognitive impairment in psychotic illness: prevalence, profile of impairment, developmental course, and treatment considerations

Amanda McCleery, PhD; Keith H. Nuechterlein, PhD

Despite effective pharmacological treatments for psychotic symptoms (eg, hallucinations, delusions), functional outcomes for people with psychotic disorders are often disappointing. Although it is not included in the diagnostic criteria for psychotic disorders, cognitive impairment is one of the strongest determinants of community functioning in this clinical population, and thus it is an important target for intervention. In this review, we discuss the major areas of research regarding impaired cognition in psychotic illness. The specific topics covered include: (i) the prevalence of cognitive impairment in psychotic disorders; (ii) the profile and magnitude of cognitive impairment in psychotic disorders; (iii) the developmental course of cognitive impairment; (iv) the longitudinal stability of cognitive impairment; and (v) treatment approaches to improve cognitive performance in people with psychotic disorders.

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Keywords: psychosis; schizophrenia; clinical high risk; affective psychosis; cognition; cognitive impairment; neurodevelopmental model; cognitive enhancement; pharmaceutical agent; cognitive training; exercise; tDCS

Introduction

Psychosis refers to a constellation of symptoms categorized as positive (eg, delusions, hallucinations), disorganized (eg, odd speech and behavior), or negative (eg, anhedonia, avolition). These symptoms occur in primary psychotic disorders (eg, schizophreniform disorder, schizophrenia, schizoaffective disorder) and the affective psychoses (eg, bipolar disorder with psychotic features, major depressive disorder with psychotic features), but can also occur in certain general medical cognitions or following exposure to some medications, substances, or alcohol. Schizophrenia, arguably the most severe and persistent psychotic illness, has a lifetime prevalence of about 1%, while psychosis more broadly is estimated to impact roughly 3% of the population.[1] Beyond the clinical symptoms of psychosis, the majority of individuals with primary psychotic disorders or affective psychosis also exhibit significantly impaired cognition. These impairments are indicated by reduced performance on neuropsychological testing, and have serious consequences for functional recovery in this clinical population.

Although early descriptions of schizophrenia by Kraepelin did emphasize cognitive decline (ie, "dementia praecox" or premature dementia), the dramatic positive symptoms

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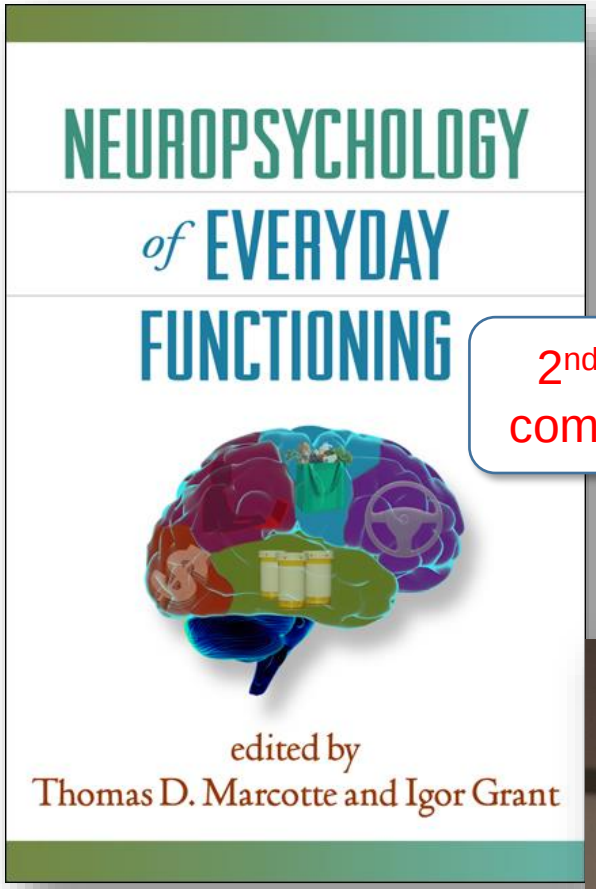
Keith Nuechterlein, Ph.D.



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Michael Green, Ph.D.
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Psychosis: symptoms of schizophrenia

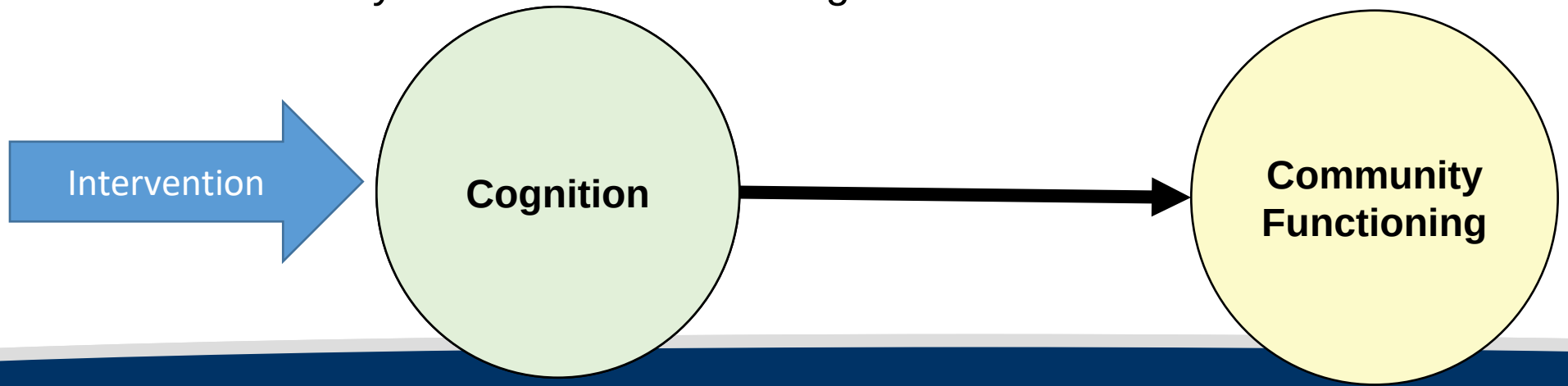
Distortions in

- Perception
- Thought content
- Communication
- Behavior

Image source: https://www.verywellmind.com/positive-symptoms-in-schizophrenia-2953124

We have a problem

- We have effective treatments for symptoms of psychosis
  - Introduction of antipsychotic medications - big impact on **clinical remission** (Braslow, 1997)
- Why aren't **functional outcomes** better for people with schizophrenia?
  - Social relationships, occupational success, independent living, enrichment activities
  - Leading cause of disability, accounts for ~1.5% DALYs in younger adults (WHO Global Burden of Disease, 2019)
- Positive symptoms are distressing and capture clinical attention
  - However, weak relationship with community functioning (Best et al., 2020; Ventura et al., 2009)
  - Functional recovery depends on other factors (e.g., cognition)
  - Recovery-oriented treatment target



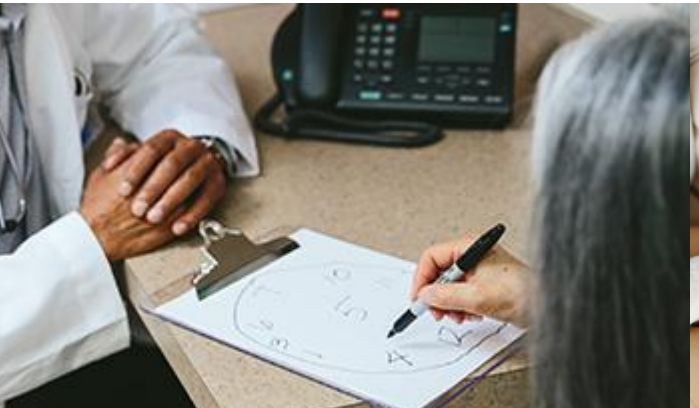
Rethinking schizophrenia

- Paradigm shift: Recognition that schizophrenia is a **cognitive disorder**
- Impaired cognition is not included in the DSM criteria
- Estimated ~80% of people with schizophrenia are impacted (Palmer et al., 1997; Keefe et al., 2007; Reichenberg et al., 2009)
- If unimpaired, performance tends to fall below expectations (Goldberg et al., 1990; Keefe et al., 2005; Kremen et al., 2000, Gray et al., 2013; Vaskinn et al., 2014; Wilk et al., 2005)
  - Twin studies
  - Comparing to expected performance based on pre-illness functioning
  - People with schizophrenia and superior intellectual ability

Is there an objective test to determine cognitive dysfunction?

Cognitive assessment

- In a clinical setting: “neuropsychological evaluation”
  - Aim of the assessment is to answer a specific referral question
  - Conducted by clinical psychologist with specialized postdoctoral training in neuropsychology (“neuropsychologist”)
  - Comprehensive battery of standardized and validated cognitive tests
    - Gather information about cognitive strengths and weaknesses
    - Tests of memory, motor skills, attention, reasoning, verbal abilities, etc.
    - Completed over several hours/testing sessions
  - Individualized feedback and recommendations in a written report



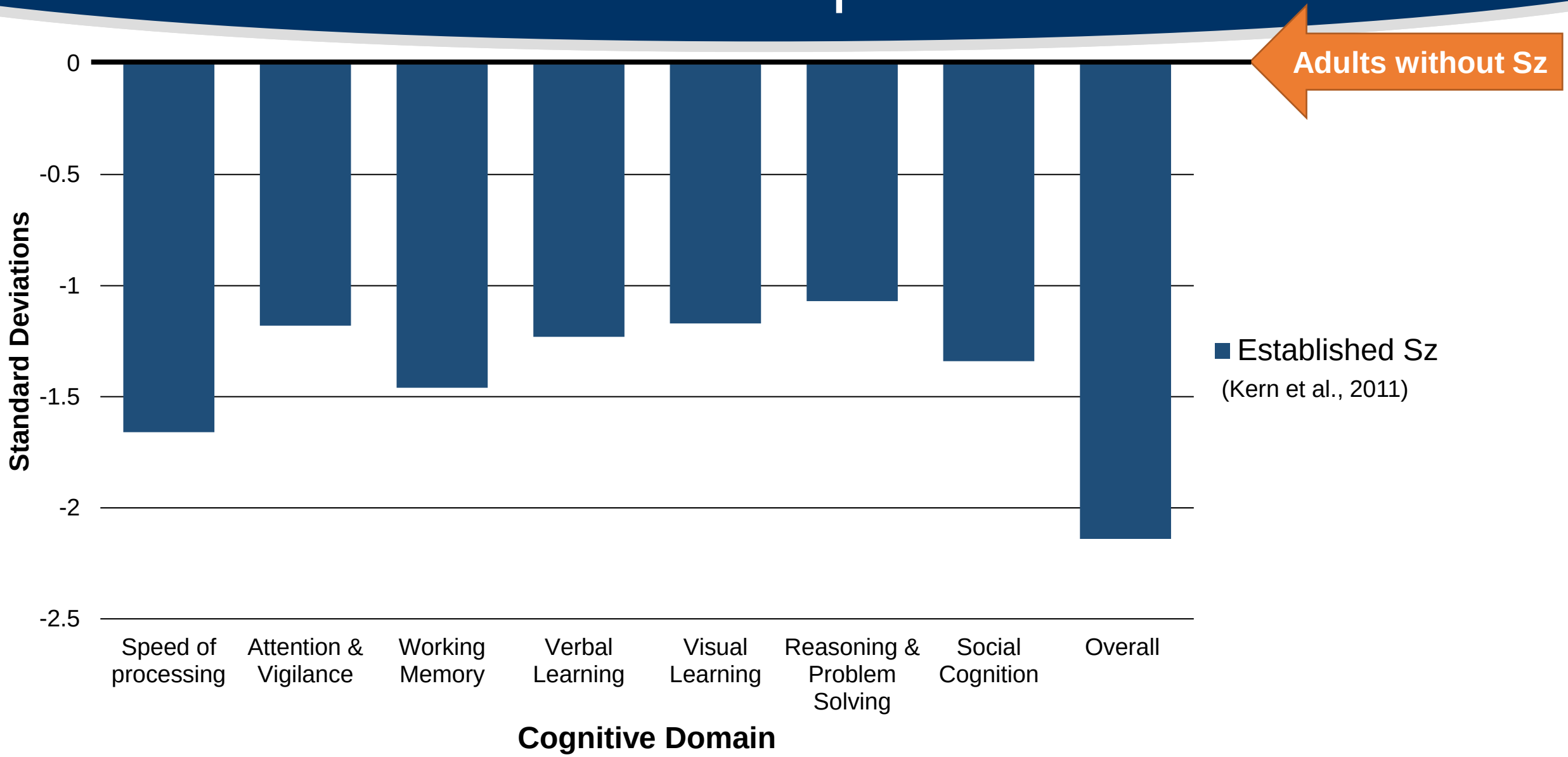

How do we define cognition and how do we assess it in research settings?

- Problem:
  - Progress limited by lack of consensus regarding best practices for assessment of cognition in research studies
    - Which domains of cognition are important to measure?
    - How best to measure the important cognitive domains?
  - Difficult to compare findings across studies
- Solution: NIMH Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Initiative
- Consensus regarding important domains to assess in research (Nuechterlein et al., 2004)
- MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein & Green, 2006)

Cognitive domains identified in MATRICS

		Domain	Skills assessed
"NEUROCOGNITION"	OVERALL COGNITION	Speed of Processing	Process simple information quickly and accurately
		Attention and Vigilance	Focus and sustain attention on a task over a long period of time
		Working Memory	Hold on to information for brief periods and manipulate the information
		Verbal Learning	Acquire and retain new information that has been presented verbally
		Visual Learning	Acquire and retain new information that has been presented visually
		Reasoning & Problem Solving	Plan ahead, consider potential obstacles and overcome them (AKA "executive functions")
		Social Cognition	Understand the emotions and mental states of others, and to use the social information adaptively

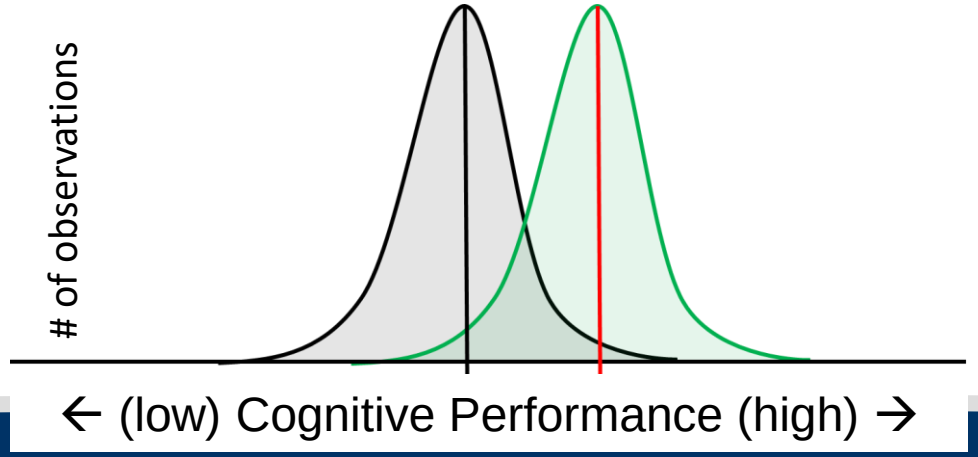
MATRICS profile



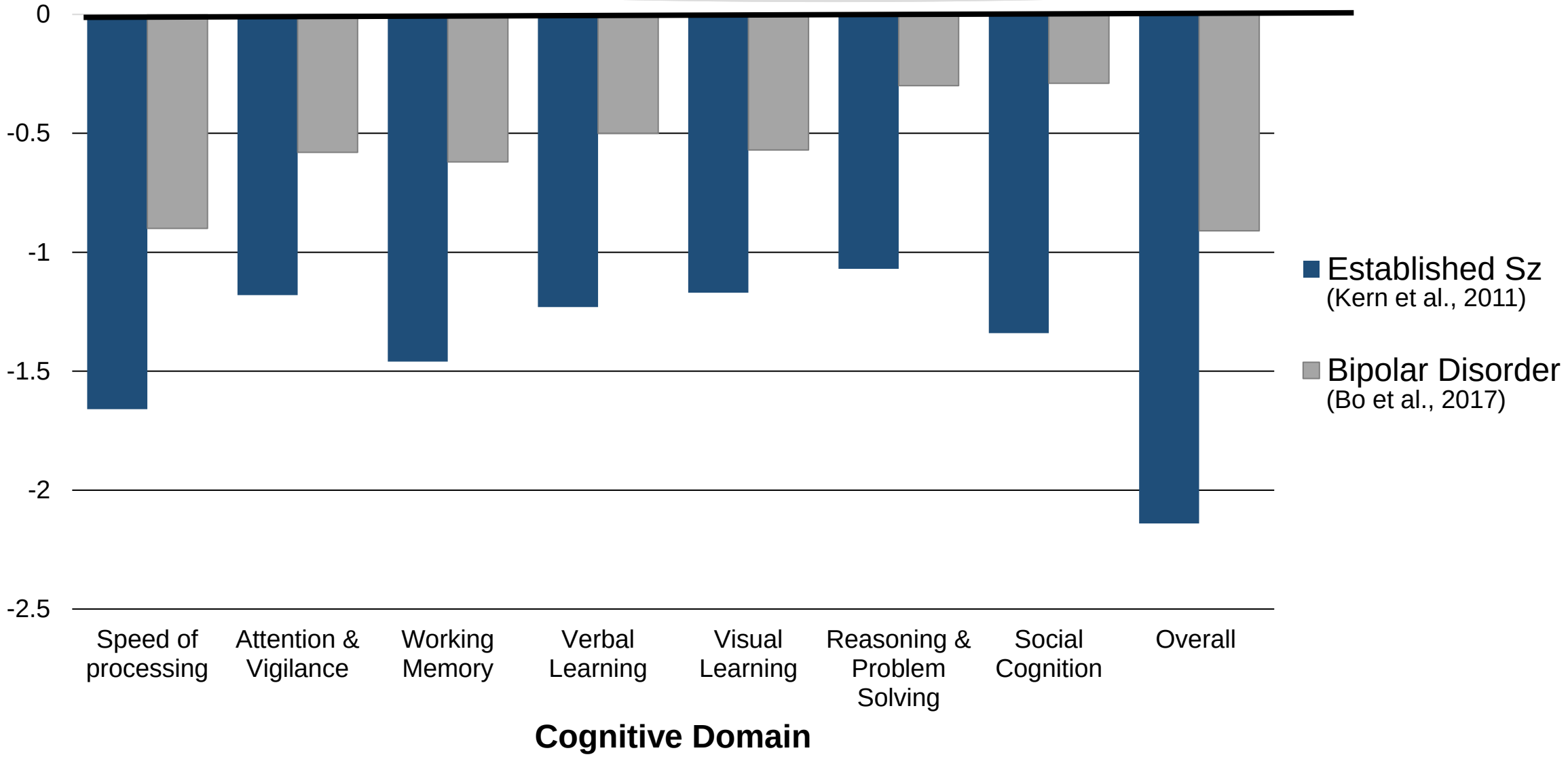
Does the cognitive profile of schizophrenia look the same or different from other mental health conditions?

Profile of cognitive performance

- Diffuse pattern, range of domains impacted
- Meta-analytic reviews report large effect sizes across domains (Fioravanti et al., 2005, 2012; Heinrichs & Zakzanis, 1998; Schaefer et al., 2013)
- Not substantially impacted by clinical factors, medication status, and observed among medication naïve (Schaefer et al., 2013)
- Group differences and heterogeneity within groups
  - Tend to see less impaired performance in affective psychoses



MATRICS profile



Pathophysiology of cognitive impairment

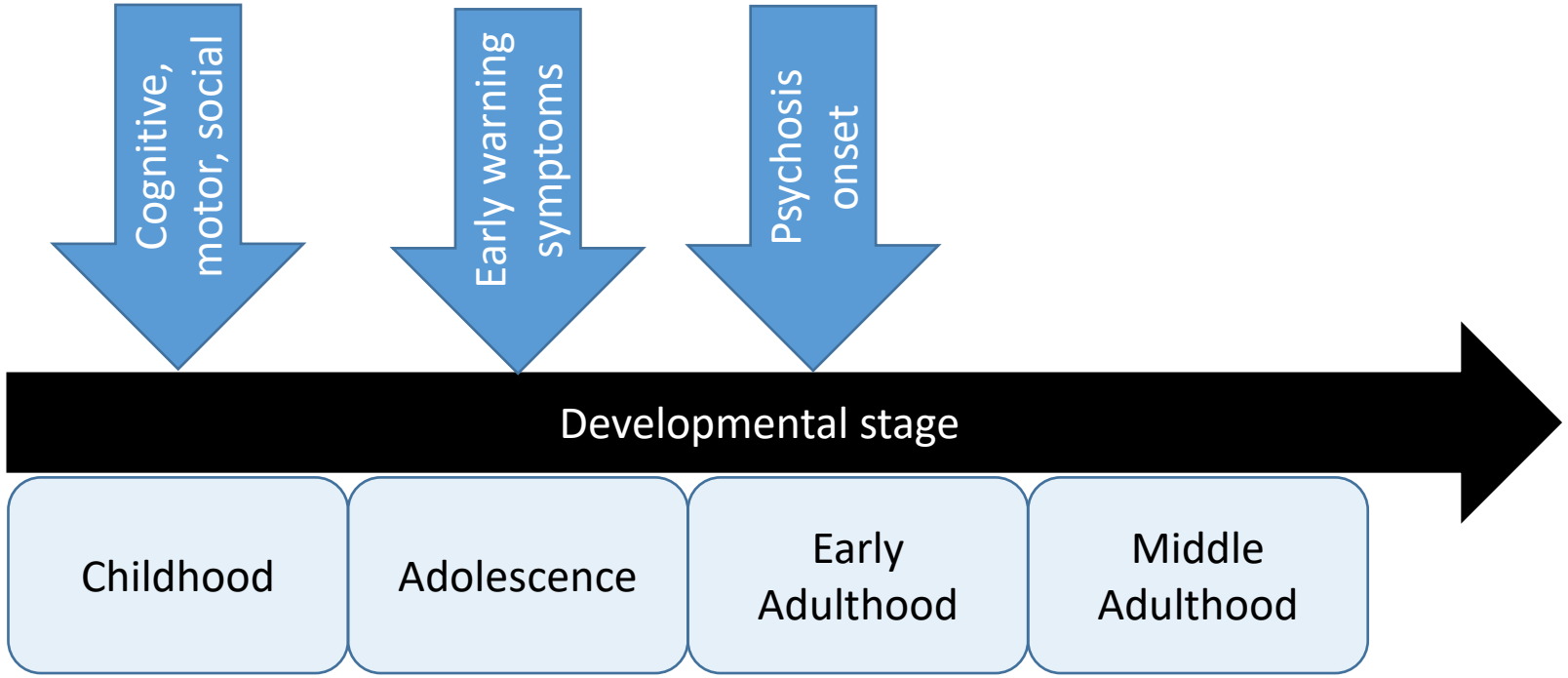
Why is cognition impaired?

- Altered neurodevelopment impacting:
  - Synaptic receptors, neurotransmitter systems (e.g., glutamatergic, cholinergic), and neuroplasticity
  - Structure and function of neurons, circuits, and brain regions
  - Coordination between brain circuits/regions

When do impairments appear? Are the impairments neurodevelopmental or neurodegenerative in nature?

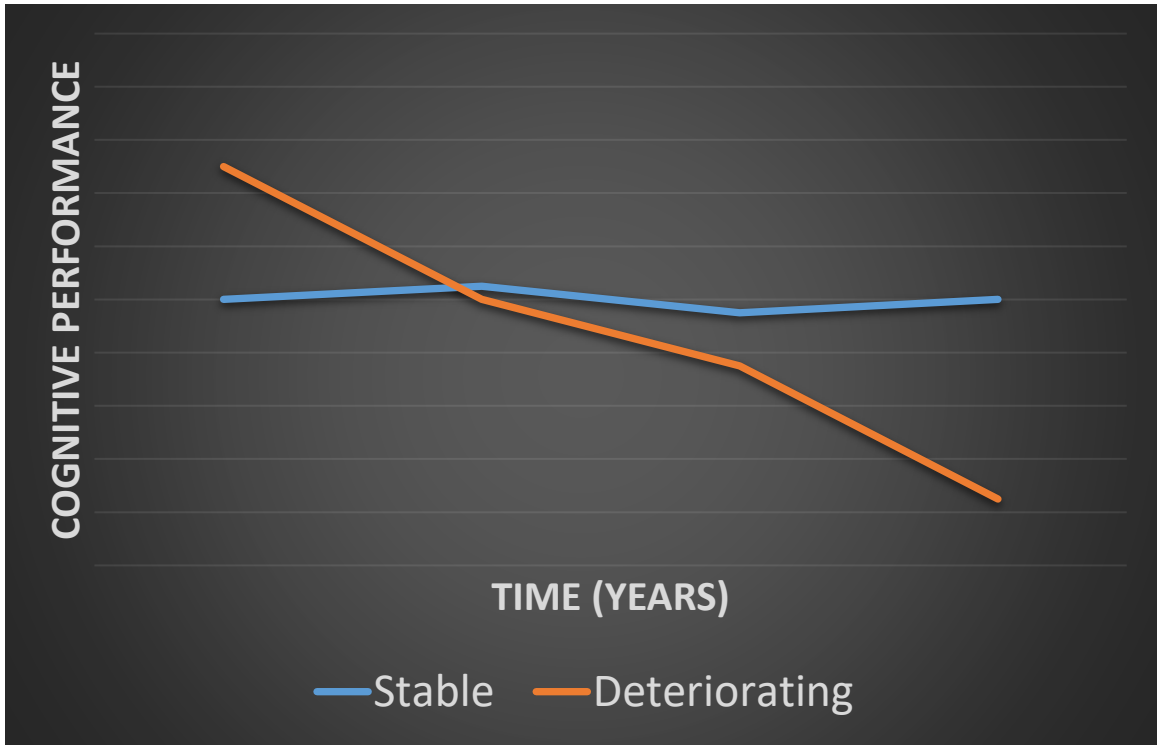
Rethinking schizophrenia

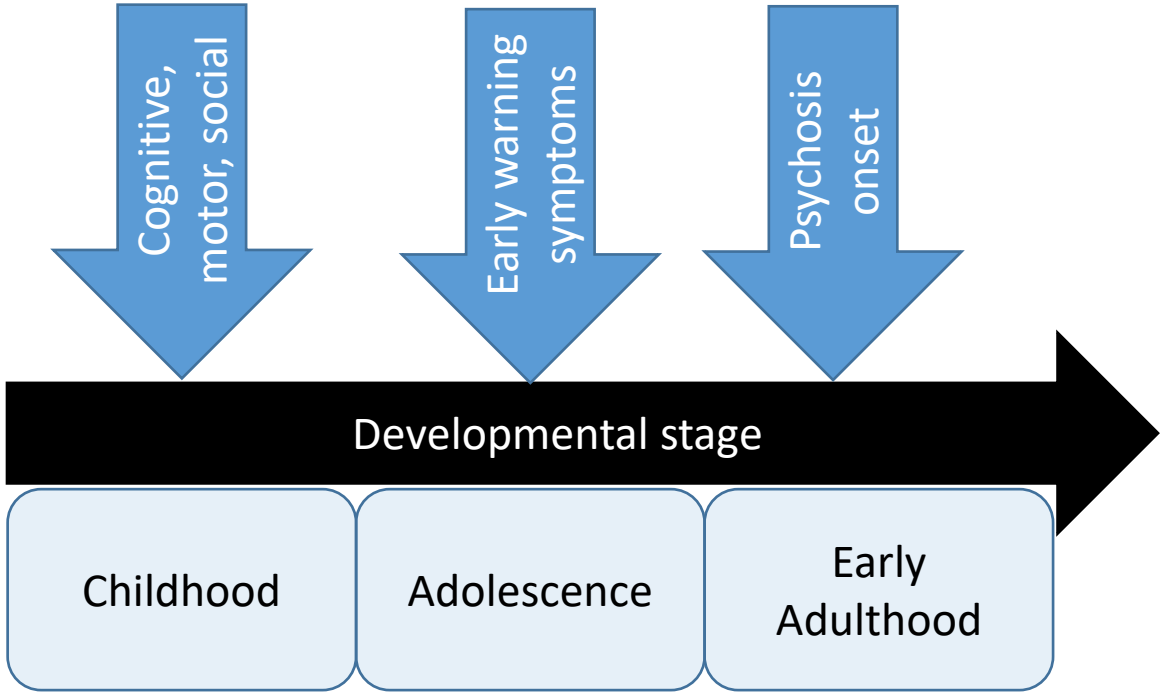
- Another paradigm shift: Recognition that schizophrenia is a neurodevelopmental disorder
- Symptoms of psychosis emerge in late adolescence/early adulthood
- Subtle early disturbances in cognitive, motor, and social development



Developmental course of cognition in schizophrenia

1. Stable or deteriorating course?
2. When in illness course do cognitive impairments appear (before, at the onset, or after onset of psychosis)?





Developmental course of cognition in schizophrenia

Stable or deteriorating course?

Evidence for stability:

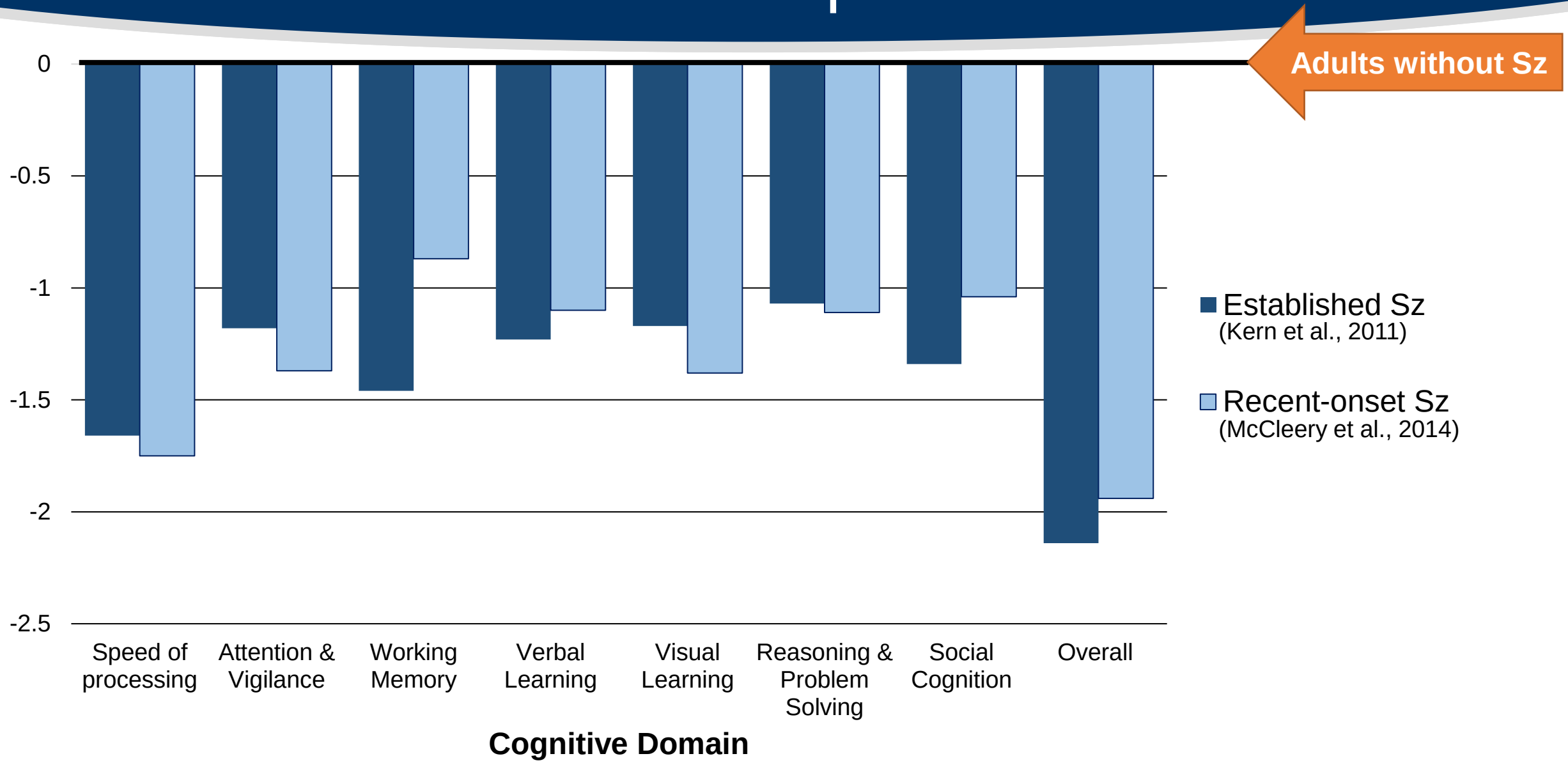
- Meta-analysis (53 studies) no significant decline over ~1 year in established schizophrenia (Szöke et al., 2008)
- Late-life change: small effect sizes (*d* = -0.10, 14 studies) for change in cognitive functioning over ~ 2-year follow-up in older adults with schizophrenia (Irani et al., 2011)
- However, evidence for declining course in late-life for a subset of individuals (Friedman et al., 2001; Harvey et al., 2003, 2010)

Developmental course

When do cognitive impairments appear (before, at the onset, or after onset of psychosis)?

- Approaches: Cross-sectional, longitudinal
- Cross-sectional studies of recent-onset schizophrenia:
  - Cognitive impairment is present at illness onset, with large effect sizes across cognitive domains (d = -0.74 to -1.20, 47 studies) (Mesholam-Gately et al., 2009)
- Longitudinal studies:
  - Stability reported over 1-10 years (Barder et al., 2013; Bergh et al., 2014; Bora et al., 2014; Hoff et al., 2005; Rund, 1995)
- Upshot: Impairment present at onset of illness, and evidence for stability during transition between early and established phases of schizophrenia

MATRICS profile

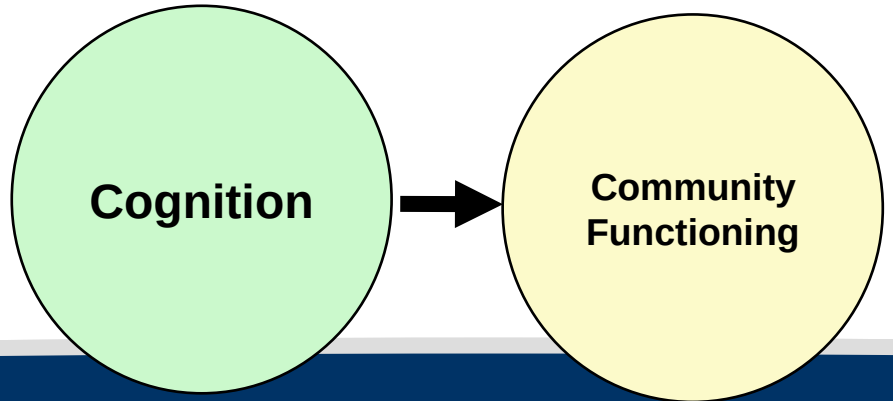


Developmental course of cognitive impairment

- What about before illness onset?
  - Clinical high-risk (i.e., putatively prodromal)
- Cross-sectional studies indicate intermediate cognitive performance
  - Small to med. effect sizes across domains (*g* = -0.18 to -0.40, 19 studies) (Fusar-Poli et al., 2012)
  - Heterogeneity of clinical outcomes
  - Few studies compare “converters” to “non-converters”, but some evidence for similar impairment in converters and recent-onset schizophrenia (e.g., Carrion et al., 2018)
- Longitudinal:
  - Studies of short-term (2 years) and long-term (10 years) follow-up do not provide significant evidence for progressive decline (Allott et al., 2019, Bora et al., 2014; Lam et al., 2018)
- Upshot: Cognitive impairment evident at the onset, likely precedes the onset, and appears to be relatively stable over time after the first episode

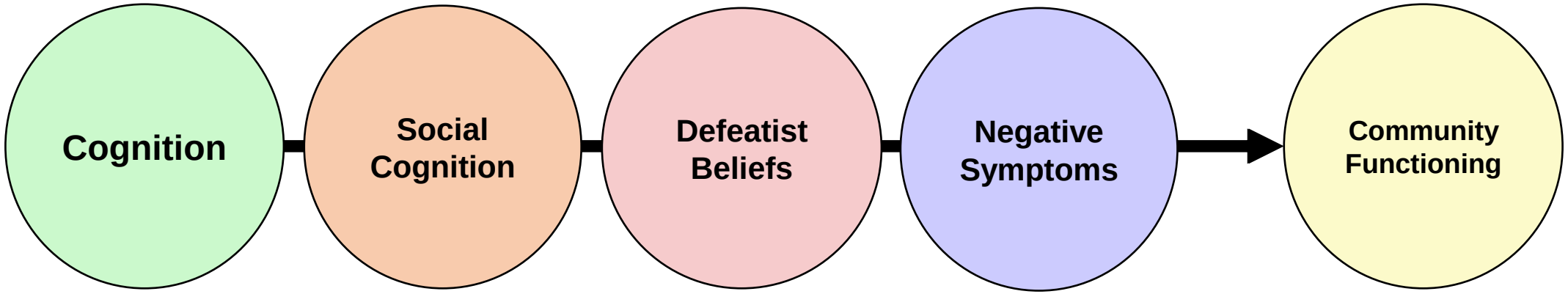
Cognition and community functioning

- Significant relationship between cognition and daily functioning
  (Fett et al., 2011; Green, 1996; Green et al., 2000, 2004, Halverson et al., 2019)
- The strength of association small to moderate for individual cognitive domains (r = 0.06 to 0.39), stronger for composite scores
  (Fett et al., 2011; Green et al., 2000; Halverson et al., 2019)
- The relationship is evident early in illness and in clinical high risk
  (Carrión et al., 2011; Grau et al., 2016; Niendam et al., 2006)
- Cognitive impairment predicts later community functioning (e.g., 6-mo to 4-yr follow-up) (Carrión et al., 2013; Dickerson et al., 1999; Friedman et al., 2002; Gold et al., 2002; Green et al., 2004; Robinson et al., 2004; Stirling et al., 2003)
- Intervention target to improve functional outcome!



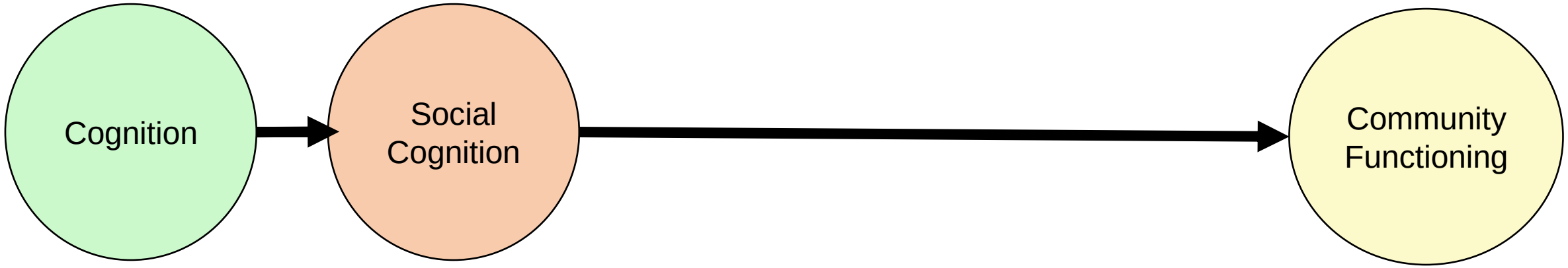
Pathway between cognition and disability

- Link between cognition and functioning is well-established
- Potential mechanisms?
- Important intervening factors along the pathway have been identified: social cognition, defeatist beliefs, and negative symptoms



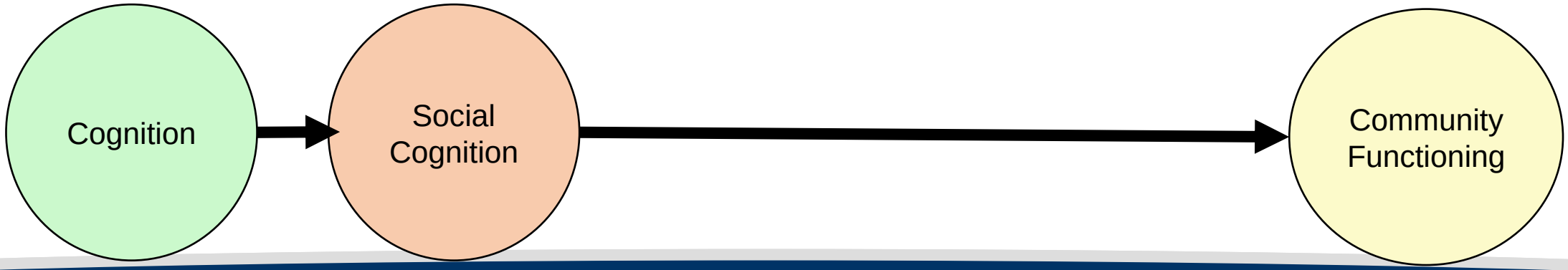
Intervening factors

- Social cognition:
  - The mental operations that underlie social interactions
  - Includes emotion processing, theory of mind, social perception, and attributional style (Green et al., 2005, 2008)
  - Marked impairment across domains in schizophrenia ($g \geq 0.80$) (Savla et al.,2013)



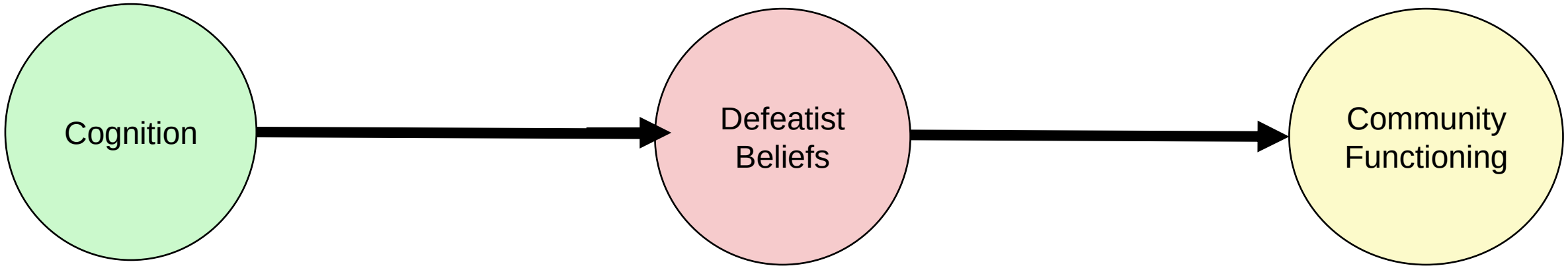
Social cognition

- Associated with community functioning:
  - Small, but significant association between all domains of social cognition and functional outcomes (r = 0.24, 119 studies) (Halverson et al., 2019)
  - Relationship sustained over time, e.g., follow-up periods of 1 to 5 years (Horan et al., 2012; McCleery et al., 2016)
- Meta-analytic reviews support significant mediation
  - Explains ~ 10 to 25% variance in functioning (Halverson et al., 2019; Schmidt et al., 2011)



Intervening factors

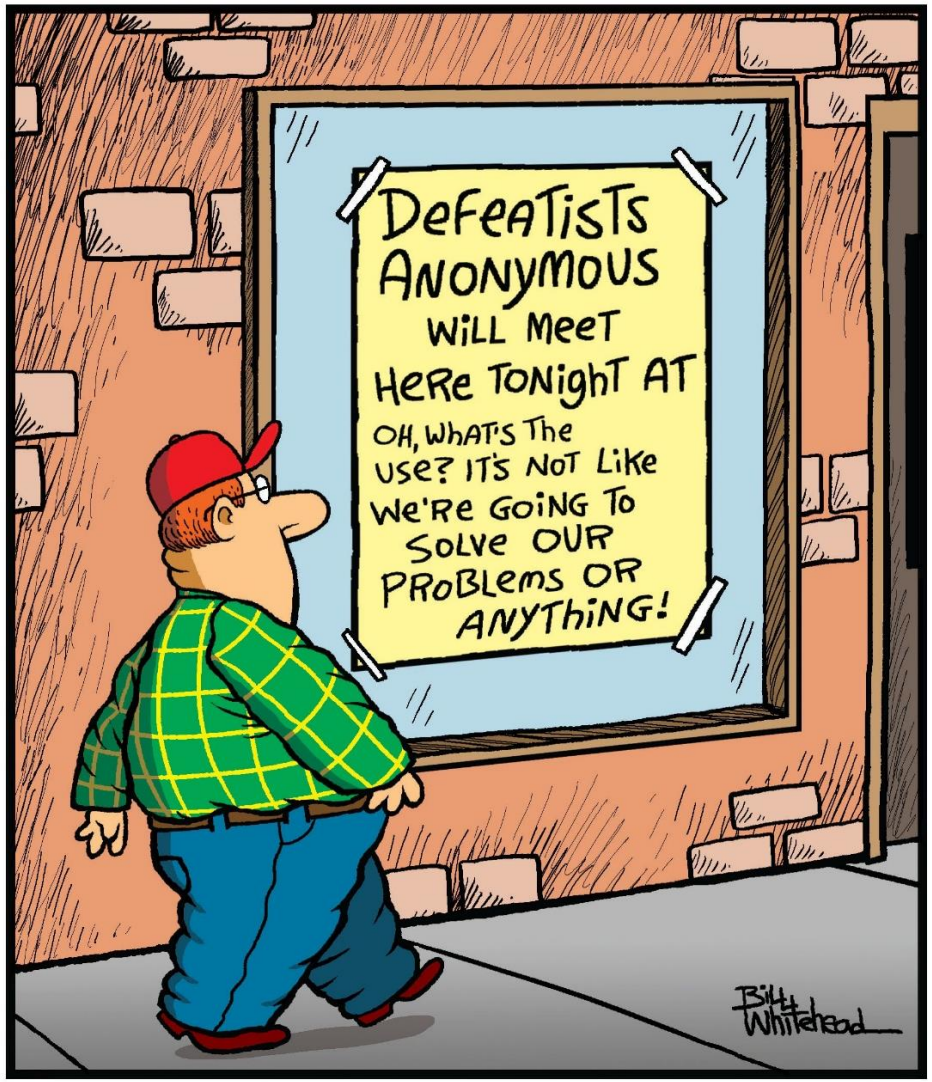
- Defeatist beliefs: a type of dysfunctional attitude in which an individual holds generalized negative beliefs about their ability to successfully perform tasks
  (Couture et al., 2011; Grant & Beck, 2009)



Defeatist beliefs

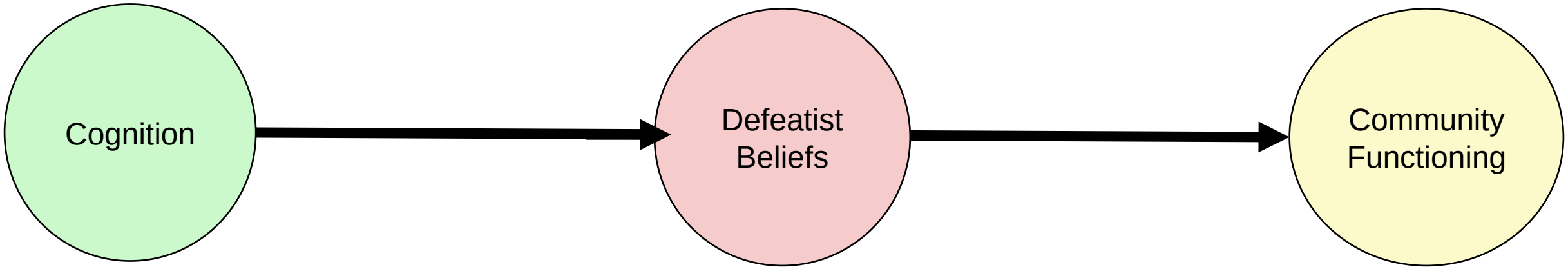
If I do not do as well as other people, it means I am an inferior human being

People should have a reasonable likelihood of success before undertaking anything



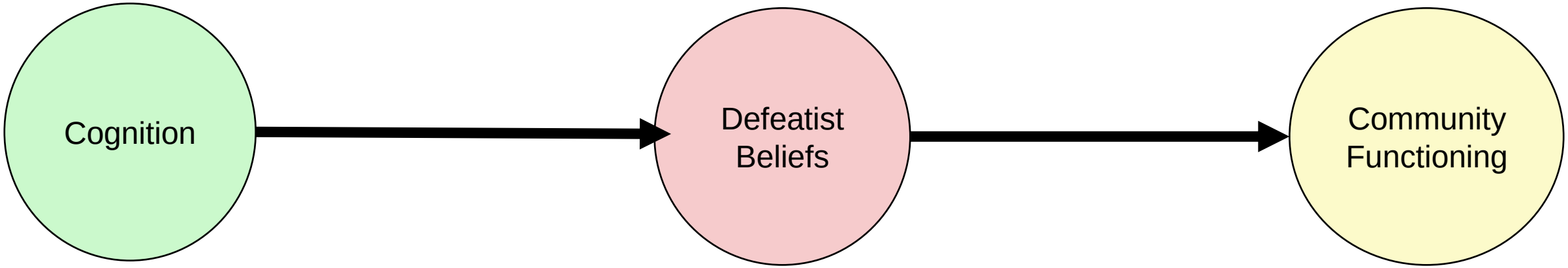
Defeatist beliefs

- Dr. Aaron T. Beck's cognitive model of schizophrenia:
  impaired ability → negative life experiences → defeatist beliefs
  (Beck & Rector, 2005; Rector, Beck, & Stolar, 2005)
- Beliefs contribute to reduced motivation to engage and to poor daily functioning



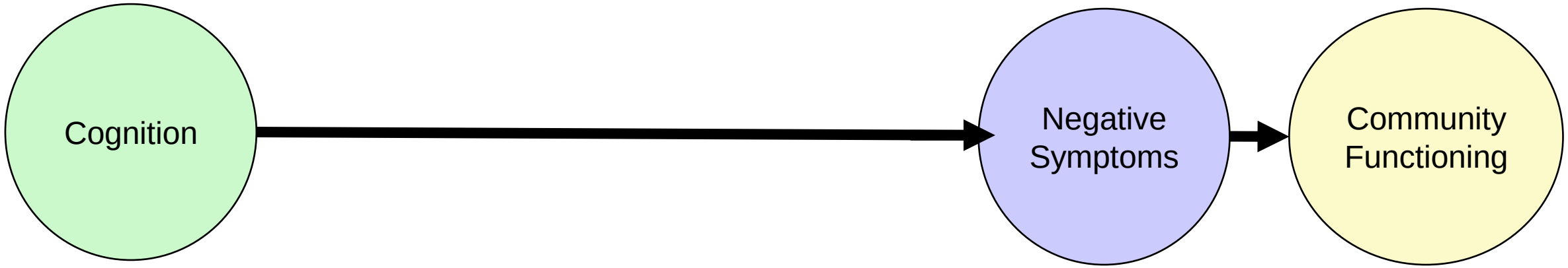
Defeatist beliefs

- Association with functioning:
  - Small, but significant association between defeatist beliefs and daily functioning (r = -0.27, 8 studies) (Campellone et al., 2016)
- Link to cognition and functioning:
  - Beck et al. found support for significant mediation by defeatist beliefs (Grant & Beck, 2009)
- Intervening factors, e.g., negative symptoms (Green et al., 2012; Quinlan et al., 2014; Thomas et al., 2017)
  - Small, but significant association between defeatist beliefs and negative symptoms (r = 0.24, 10 studies) (Campellone et al., 2016)



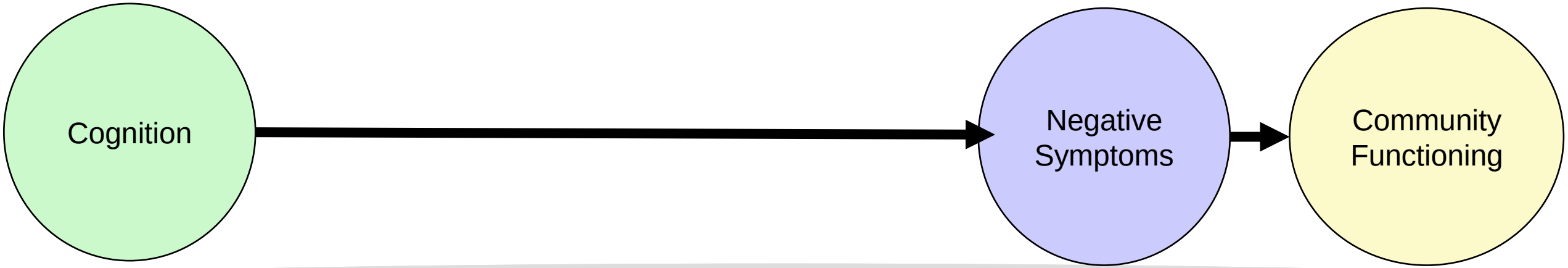
Intervening factors

- Negative symptoms:
  - Expressive: outward expression of emotion is diminished
    - Facial expressions, tone of voice, movements
  - Experiential: motivation and drive to engage are diminished
    - Disinterest, avolition, and anhedonia impacting activities, socialization, self-care, etc.



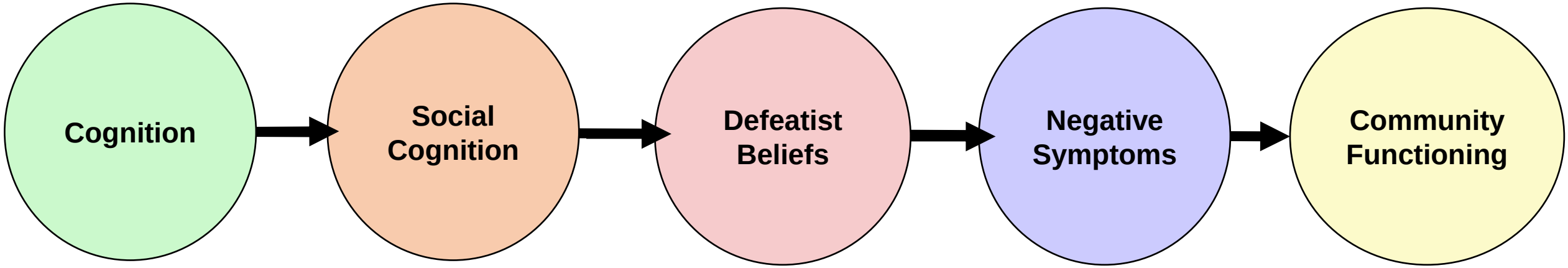
Negative symptoms

- Negative symptoms are associated with cognition and daily functioning (Ventura et al., 2009)
  - Small, but significant association with cognitive performance (r = -0.24, 53 studies)
  - Moderate association with daily functioning (r = -0.42, 23 studies)
  - Negative symptoms partially mediate the relationship between cognition and daily functioning



Intervening factors

- This is **NOT** an exhaustive list of intervening factors!
- Multi-step models, multi-path models, bidirectional relationships, etc.
- Additional important factors that we have not discussed today (e.g., stigma, mood, social support, etc.)



Can cognitive impairments be treated? Can they be prevented?

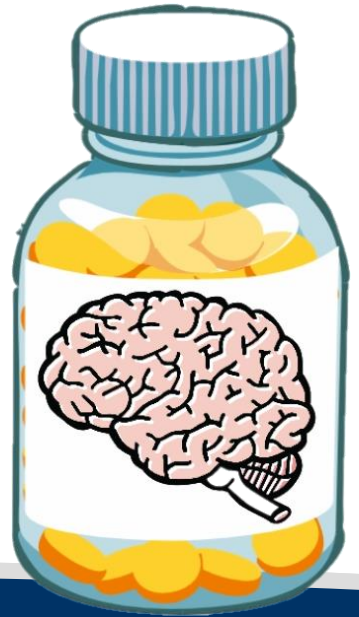
What can we do to improve functioning?

- Targeting impaired cognition:
  - Pharmacological agents
  - Cognitive training
  - Physical exercise
  - Neurostimulation
- Targeting the proposed mechanisms:
  - Social cognition skills training
  - CBT for defeatist beliefs
  - Psychotherapy for negative symptoms

Bridging to clinical practice

Targeting impaired cognition with pharmacological agents (“cognitive enhancers”)

- Main idea:
  - Target neurotransmitter systems that are disrupted in schizophrenia and are believed to be associated with cognitive performance
  - Comparison condition – e.g., placebo
  - Immediate (challenge studies) vs. enduring effects (treatment trials)



Bridging to clinical practice

Targeting impaired cognition with pharmacological agents

- Combined across NT systems (e.g., cholinergic, glutamatergic, serotonergic, dopaminergic, GABA-ergic, noradrenergic):
  - Small effects of cognitive enhancers on overall cognition (g = 0.10, 51 studies), and no significant effects on individual cognitive domains (Sinkeviciute et al., 2018)
- Cholinergic agents (cholinesterase inhibitors) may impact working memory (g = 0.26, 6 studies)
- Glutamatergic agents may impact overall cognition (g = 0.19, 17 studies) and working memory (g = 0.13, 20 studies)
- Limitations: few studies, studies tend to be underpowered, brief treatment duration
- Possible that pharmacological agents may be more effective when combined with the opportunity to learn!

What about antipsychotic medications? Can they help or hinder cognitive performance?

Antipsychotic medication and cognition

Cognitive impairment in schizophrenia is primary, not secondary to antipsychotic medications

- Cognitive impairment is evident in first episode psychosis prior to treatment with antipsychotic medications
- Cognitive impairment is evidence among medication naïve with established illness

May yield modest benefits for cognitive performance (Woodward et al., 2005; Keefe et al., 2007), and atypicals and LAIs may be neuroprotective (Bartzokis et al., 2011; 2012; Chen & Nasrallah, 2019)

However, antipsychotic medications may negatively impact cognition through sedation, dosing (e.g., high D2 occupancy level), polypharmacy, or with certain adjunct medications (Hori et al., 2006; Sakurai et al., 2013)

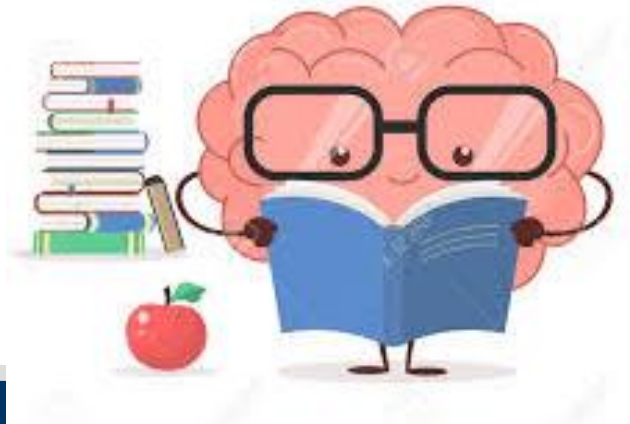
What about supplements, alternative medicine, etc.?

Check with your physician and reliable sources (e.g., Cochrane Reviews, peer-reviewed research)

Bridging to clinical practice

Targeting impaired cognition with cognitive training (CT)

- Main idea: Train the brain with structured activities to improve cognitive performance
  - “Restorative approach” to shore up impaired cognitive skills – neuroplasticity based
  - “Compensatory approach” to use strategies and environmental supports to side-step impairments
  - Low vs. high level processes
  - Often computerized, but not always
  - Group or individual format
  - May include a “bridging” component



Bridging to clinical practice

Targeting impaired cognition with cognitive training (CT)

- Cognitive training is an empirically-supported treatment for schizophrenia (https://div12.org/treatment/cognitive-remediation-for-schizophrenia/)
- Across different CT approaches and formats: moderate effects on overall cognition (g = 0.28, 70 studies) and small to moderate effects on individual cognitive domains (g = 0.12 to 0.27, 23 to 50 studies) (Kambeitz-Ilankovic et al., 2019)
  - Gains on trained tasks/domains, but near and far transfer is a challenge
  - Small effect on community functioning (g = 0.16, 49 studies)
- More work needed to:
  - Increase methodological rigor of treatment trials
  - ID characteristics of effective CT programs
  - Factors associated with optimal treatment response
  - Enhance transfer of gains

Bridging to clinical practice

- Targeting cognition through physical exercise
- Main idea: exercise may support cognition through mechanisms such as increased neurogenesis, improved cerebrovascular and cardiovascular fitness, reducing inflammatory processes
  - Different approaches – HIIT, cardio, weight training, walking, yoga, etc.
- Encouraging findings in schizophrenia, but a small literature (Firth et al., 2017)
  - Moderate effects of aerobic exercise for:
    - Overall cognition (g = 0.33, 10 studies)
    - Working memory (g = 0.39, 7 studies)
  - Moderate to large effects for:
    - Social cognition (g = 0.71, 3 studies)
    - Attention/vigilance (g = 0.66, 3 studies)

Bridging to clinical practice

Combining CT with exercise (CT + E)

- Main idea: optimize learning potential (E-induced neurogenesis and enhanced plasticity) + the opportunity to learn (CT)
- An initial study compared CT alone and CT + E in recent-onset schizophrenia at the UCLA Aftercare Research Program has yielded promising results
  - Improved cognition, improved community functioning, and structural and functional brain changes

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Bridging to clinical practice

Targeting cognition through neurostimulation

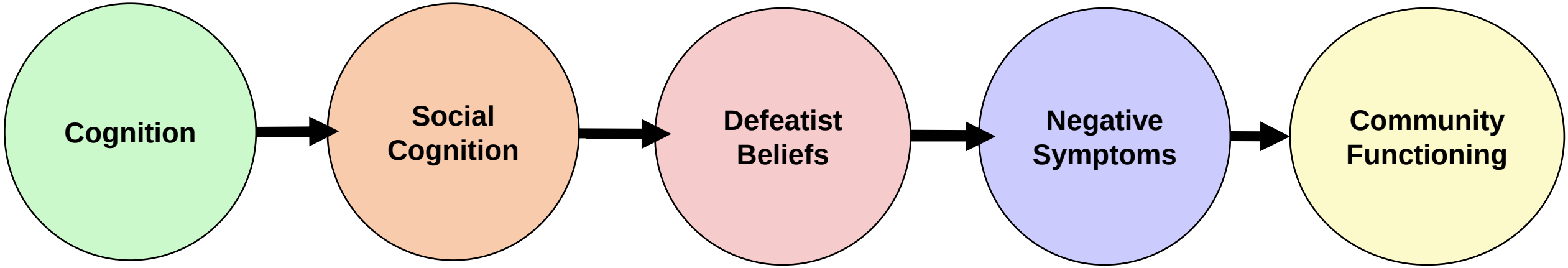
- Main idea: apply electrical (e.g., tDCS) or magnetic (e.g., TMS) stimulation to alter potential for cell firing and to modulate synaptic plasticity in a particular brain region
- Considerations:
  - Target sites
  - Immediate vs. enduring effects
  - Single session vs. repeated

Bridging to clinical practice

- tDCS:
  - Multi-session, prefrontal tDCS associated with a moderate effect on working memory (*SMD* = 0.49, 9 studies) (Narita et al., 2020)
    - When single session and AC studies are included, effects are minimal ($g \leq 0.08$, 13 studies) (Sloan et al., 2020)
- TMS:
  - Repeated TMS applied to dorsolateral prefrontal cortex associated with moderate effects on working memory (*SMD* = 0.34, 9 studies)
  - Evidence for enduring effects over ~ 2-12 week follow-up (Jiang et al., 2019)
- Upshot: Promising findings, but a very small literature – more work is needed

Bridging to clinical practice

- Targeting the intervening factors:
  - Social cognition
  - Defeatist Beliefs
  - Negative symptoms



Bridging to clinical practice

- Social Skills Training (SST) is an empirically supported treatment for schizophrenia (https://div12.org/treatment/social-skills-training-sst-for-schizophrenia/)
  - Emphasis on interpersonal skills – instruction, role plays, etc.
- Social cognition training:
  - Similar to CT, but focuses on improving processing of social stimuli
  - Main idea: training social cognition through instruction and repeated practice
  - May be individual or in groups, live or computerized, include bridging activities

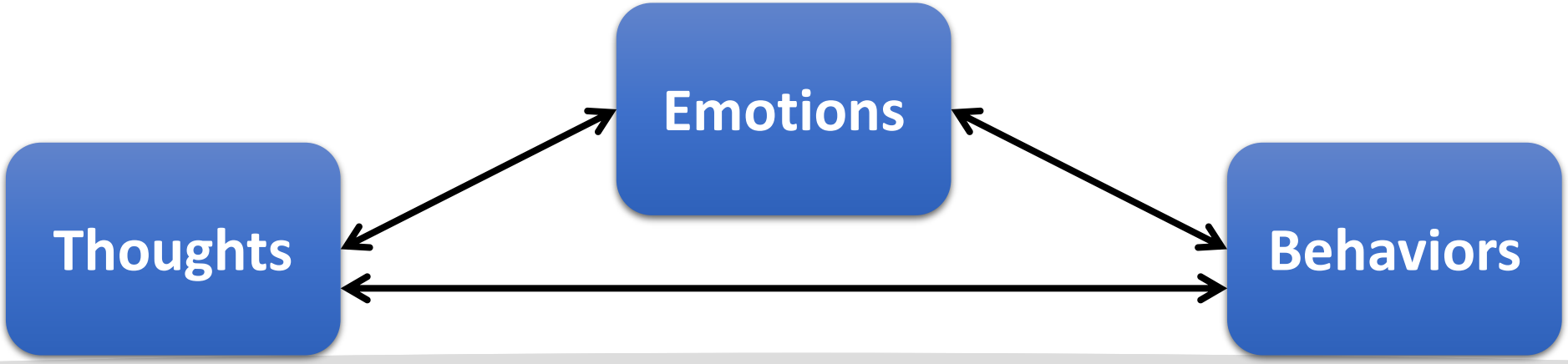
Bridging to clinical practice

- Social cognition training:
  - Medium-to-large improvements in emotion identification performance (*d* = 0.84, 12 studies), theory of mind (*d* = 0.70, 13 studies), social perception (*d* = 1.29, 4 studies) (Kurtz et al., 2015)
  - Moderately large effect on functioning (*d* = 0.78, 6 studies), but significant heterogeneity (Kurtz & Richardson, 2012)
- Potential benefit of augmenting learning in social cognition training with oxytocin (Davis et al., 2014)

Stephen Marder, MD
2016 BBRF Lieber Prizewinner

Bridging to clinical practice

- Defeatist beliefs may be amenable to change through cognitive behavioral therapy (CBT)
  - Few studies, but moderate to large effect sizes for reduction in defeatist beliefs (*d* = 0.53 to 0.95) (Granholm et al., 2014; Mervis et al., 2017; Staring et al., 2013)
  - Change in defeatist beliefs are associated with improvements in functioning (Granholm et al., 2013, 2014, 2018; Mervis et al., 2017)



Bridging to clinical practice

Targeting negative symptoms

- Challenging!
- CBT has been tested as a potential intervention
  - Small-med effect on functional outcome (*d* = 0.28, 25 studies) (Laws et al., 2018) and very small effect on negative symptoms (*g* = 0.16, 30 studies) (Velthorst et al., 2015)
- Promising results from a novel intervention combining motivational interviewing with CBT to improve negative symptoms (Reddy et al., 2019; Reddy et al., under review)

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I would like to get involved in a treatment study (or other types of research) – how can I participate?

clinicaltrials.gov/ct2/results?recrs=ab&cond=Schizophrenia&term=cognition&cntry=US&state=&city=&dist=

COVID-19 Information

Public health information (CDC) | Research information (NIH) | SARS-CoV-2 data (NCBI) | Prevention and treatment information (HHS) | Español

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾ PRS Login

Home > Search Results

Modify Search Start Over

49 Studies found for: **cognition | Recruiting, Not yet recruiting Studies | Schizophrenia | United States**

Also searched for **Cognitive function**. See Search Details

Applied Filters: ☑ **Recruiting** ☑ **Not yet recruiting**

List | By Topic | On Map | Search Details

Hide Filters

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Status

Recruitment :

- ☑ Not yet recruiting
- ☑ Recruiting
- ☐ Enrolling by invitation
- ☐ Active, not recruiting
- ☐ Suspended
- ☐ Terminated
- ☐ Completed
- ☐ Withdrawn
- ☐ Unknown status†

Showing: 1-49 of **49** studies 50 studies per page

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Recruiting	Reducing Hippocampal Hyperactivity and Improving **Cognition** in **Schizophrenia**	• **Schizophrenia**	• Drug: Levetiracetam • Drug: Placebo	• Rocky Mountain Regional VA Medical Center Aurora, Colorado, **United States**
2	☐	Recruiting	Target Engagement and Response to Oxytocin	• **Schizophrenia**	• Drug: Oxytocin nasal spray • Behavioral: Social **Cognition** Skills Training • Behavioral: Health Management • Drug: Placebo nasal spray	• UCLA Los Angeles, California, **United States**
3	☐	Recruiting	Effects of Brain Stimulation on **Cognition**, Oscillations and GABA Levels in **Schizophrenia**	• **Schizophrenia**	• Device: Transcranial Direct Current Stimulation	• Imaging Research Center Sacramento, California, **United States**
4	☐	Recruiting	Effects of Low-dose Levetiracetam on Clinical Symptoms, **Cognition** and Hippocampal Hyperactivity in **Schizophrenia**	• **Schizophrenia**	• Drug: Levetiracetam • Drug: Placebo	• University of Colorado Anschutz Medical Can Aurora, Colorado, **United States**
5	☐	Recruiting	Restoration of **Cognitive Function** With TDCS and Training in **Schizophrenia**	• **Schizophrenia**	• Device: TDCS • Device: Sham Stimulation	• Minneapolis VA Health Care System, Minnea Minneapolis, Minnesota, **United States**
6	☐	Recruiting	Effects of Brain Stimulation on Higher-Order **Cognition**	• **Schizophrenia**	• Device: Transcranial Direct Current Stimulation	• Imaging Research Center

Clinicaltrials.gov is a searchable database of active treatment studies

Consider joining a research registry at your local university and/or psychiatric institute

Directory of early psychosis treatment programs in the US:

- https://med.stanford.edu/peppnet.html

My client is planning to return to work or school. What strategies would be helpful?

https://div12.org/treatment/supported-employment-for-schizophrenia/

Summary

- Schizophrenia is associated with significant disability and cognitive impairment
- Impaired cognition is evident at illness onset, and is present before onset to some degree
- Cognitive impairment is relatively stable from first episode forward, with a subset of individuals exhibiting a deteriorating trajectory late in life
- Impaired cognition is associated with functional impairment
- Intervening factors along the pathway to functioning include social cognition, defeatist beliefs, and negative symptoms
- Recovery-focused interventions targeting impaired cognition, and the intervening factors, are promising, but more work is needed to understand the mechanisms, refine the treatments, and improve generalizability of effects