Improving People's Lives Through Innovations in Personalized Health Care

Promoting Cognitive Health Among Youth with Psychosis

Nicholas Breitborde, PhD
Department of Psychiatry and Behavioral Health

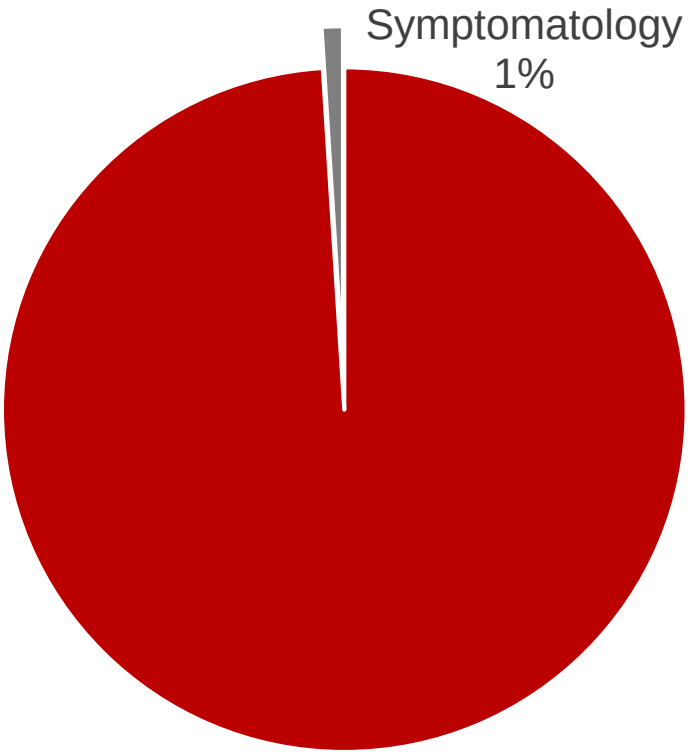
The Ohio State University
Wexner Medical Center

Global Burden of Disease Study 2013

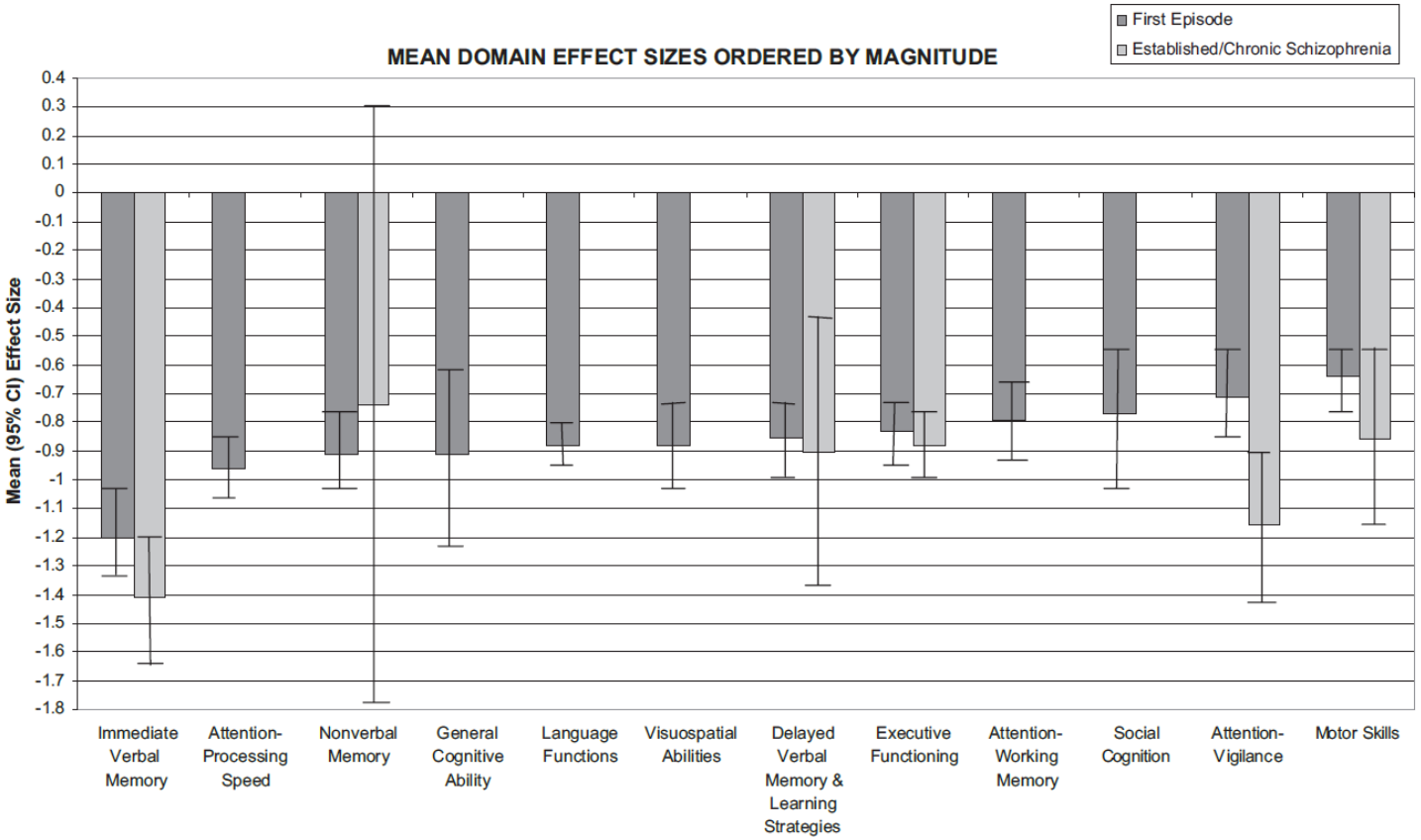
Illness/Injury	Disability Weight
Schizophrenia, Acute State	**0.778**
Spinal cord lesion, At neck: Untreated	0.732
Multiple sclerosis, Severe	0.719
Heroin and other opioid dependence, Moderate to severe	0.697
Major depressive disorder, Severe Episode	0.658
Traumatic brain injury, Long-term consequences, severe, with or without treatment	0.637
Spinal cord lesion, Below neck, untreated	0.623
Spinal cord lesion. At neck, Treated	0.589
Schizophrenia, Residual State	**0.588**
Stroke, Long-term consequences, severe, plus cognitive problems	0.588

Salomon et al., 2015

Disease-Related Burden in First-Episode Psychosis



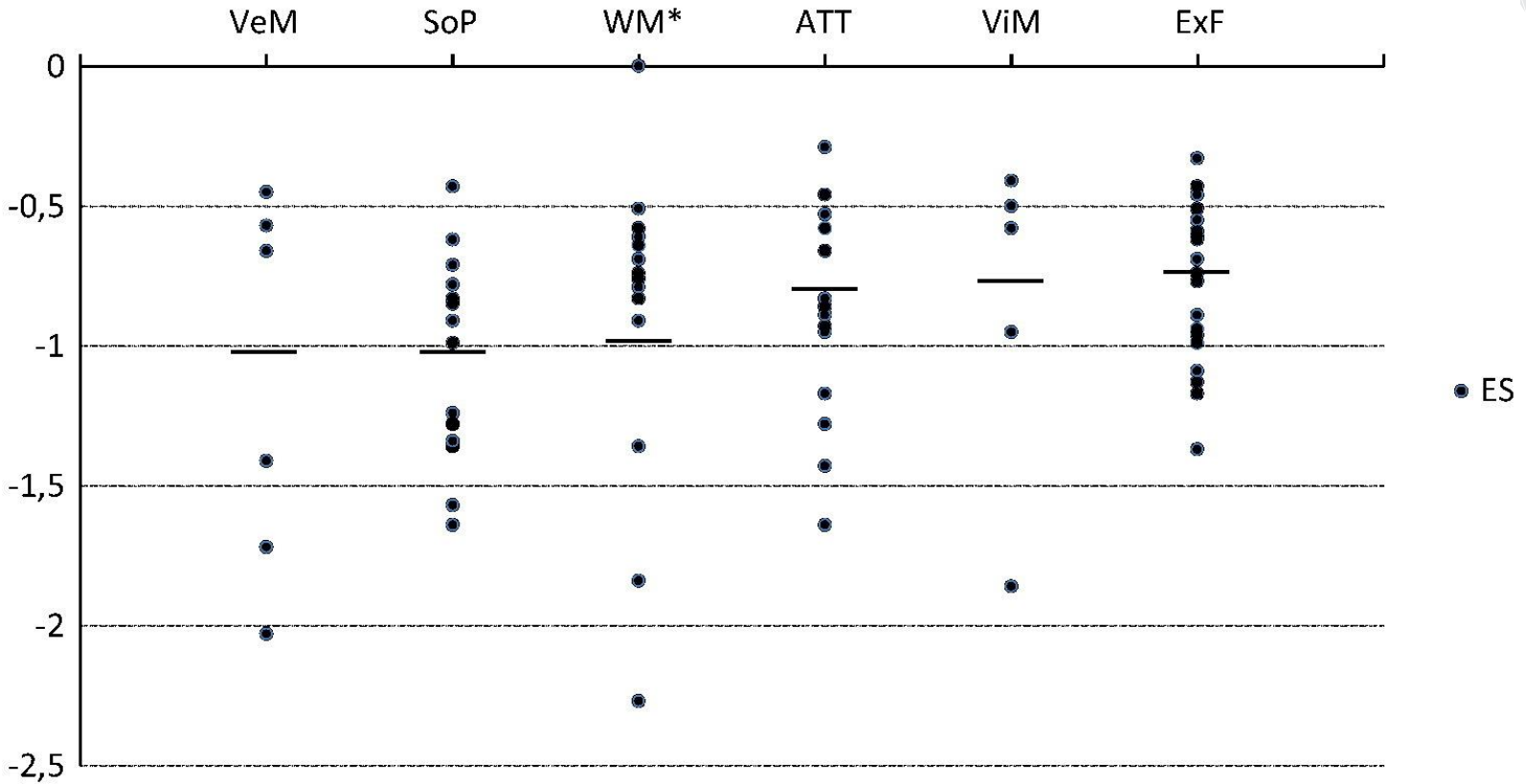
Moe et al., In Progress



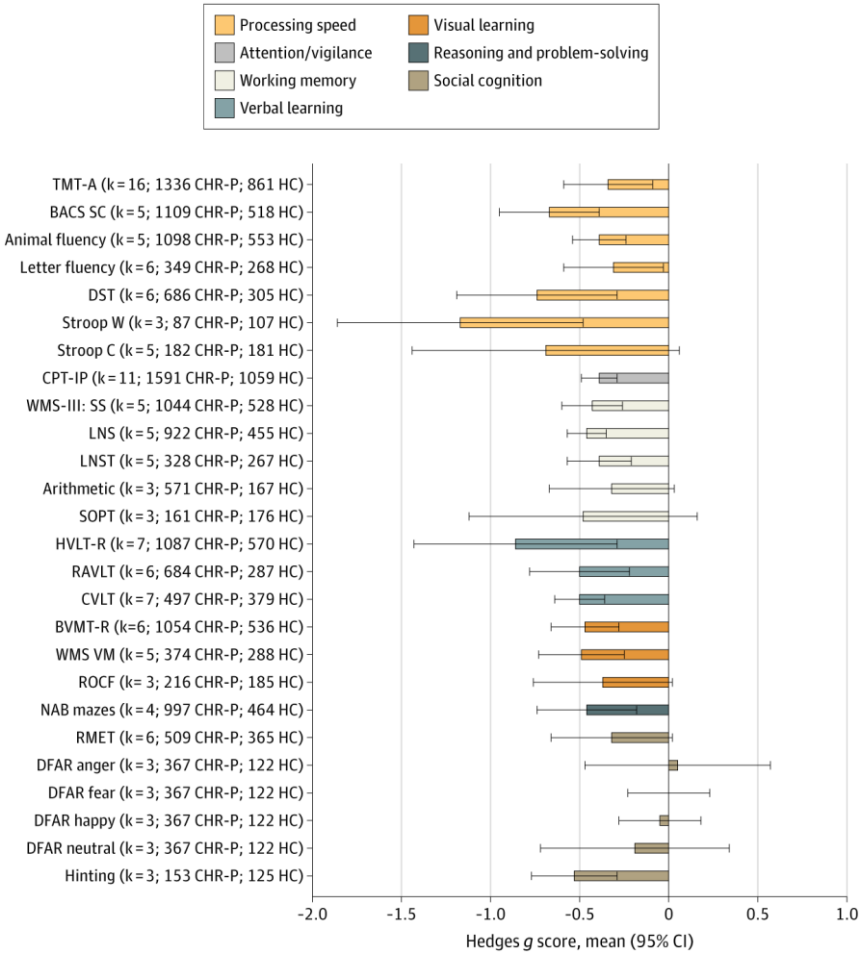
Mesholam-Gately et al., 2009

Cognitive measure	First-episode schizophrenia (FES)	Youth-onset schizophrenia (YOS)	Late-onset schizophrenia (LOS)	$Q_{between}$	FES *v.* YOS *v.* LOS[a]
Full-scale IQ	0.89 (0.04)	1.77 (0.07)	1.61 (0.15)	121.64***	FES < YOS, FES < LOS, YOS=LOS
Verbal IQ	1.31 (0.08)	1.19 (0.13)	1.34 (0.16)	0.75	–
Performance IQ	1.73 (0.09)	1.25 (0.15)	2.07 (0.23)	11.75**	FES=YOS=LOS
Global measure of cognition	0.67 (0.10)	–	1.67 (0.11)	45.74***	FES < LOS
Digit symbol coding	1.46 (0.05)	1.46 (0.09)	0.29 (0.22)	27.18***	FES=YOS, LOS < FES, LOS < YOS
Tower of London and similar tests	0.78 (0.05)	0.57 (0.08)	0.97 (0.15)	8.18*	FES=YOS=LOS
Visual memory	0.85 (0.03)	0.95 (0.10)	1.12 (0.09)	9.46**	FES=YOS=LOS
Verbal general memory	1.03 (0.03)	0.98 (0.07)	1.11 (0.13)	0.86	–
Vocabulary	1.02 (0.05)	1.18 (0.11)	0.42 (0.19)	11.76**	FES=YOS, FES=LOS, LOS < YOS
Arithmetic	0.99 (0.07)	1.37 (0.12)	0.24 (0.26)	17.74***	FES=YOS, FES=LOS, LOS < YOS
Fluency	0.87 (0.03)	0.96 (0.10)	1.47 (0.14)	17.50***	FES=YOS, FES < LOS, YOS=LOS
Visual attention	0.72 (0.03)	0.66 (0.08)	1.51 (0.15)	26.72***	FES=YOS, FES < LOS, YOS < LOS
Stroop test	0.86 (0.04)	1.14 (0.13)	1.76 (0.27)	14.20**	FES=YOS=LOS
Continuous Performance Test	0.83 (0.04)	0.73 (0.08)	–	1.17	–
Visuospatial construction	0.83 (0.03)	0.98 (0.08)	1.41 (0.18)	12.97**	FES=YOS=LOS
Trail making test B	0.77 (0.05)	1.12 (0.10)	–	9.82**	FES < YOS
Verbal special memory	0.94 (0.03)	1.18 (0.06)	1.20 (0.12)	15.04***	FES < YOS, FES=LOS, YOS=LOS
Trail making test A	0.66 (0.04)	0.70 (0.10)	–	8.82*	FES < YOS
Wisconsin card sorting and similar tests	0.76 (0.03)	2.00 (0.08)	1.13 (0.12)	231.41***	FES < YOS, FES=LOS, LOS < YOS
Psychomotor speed of processing	0.65 (0.02)	0.92 (0.06)	1.01 (0.21)	19.68***	FES < YOS, FES=LOS, YOS=LOS
Auditory attention	0.61 (0.08)	0.53 (0.12)	1.95 (0.27)	23.47***	FES=YOS, FES < LOS, YOS < LOS
Digit span	0.64 (0.04)	0.85 (0.10)	0.87 (0.12)	6.69*	FES=YOS=LOS

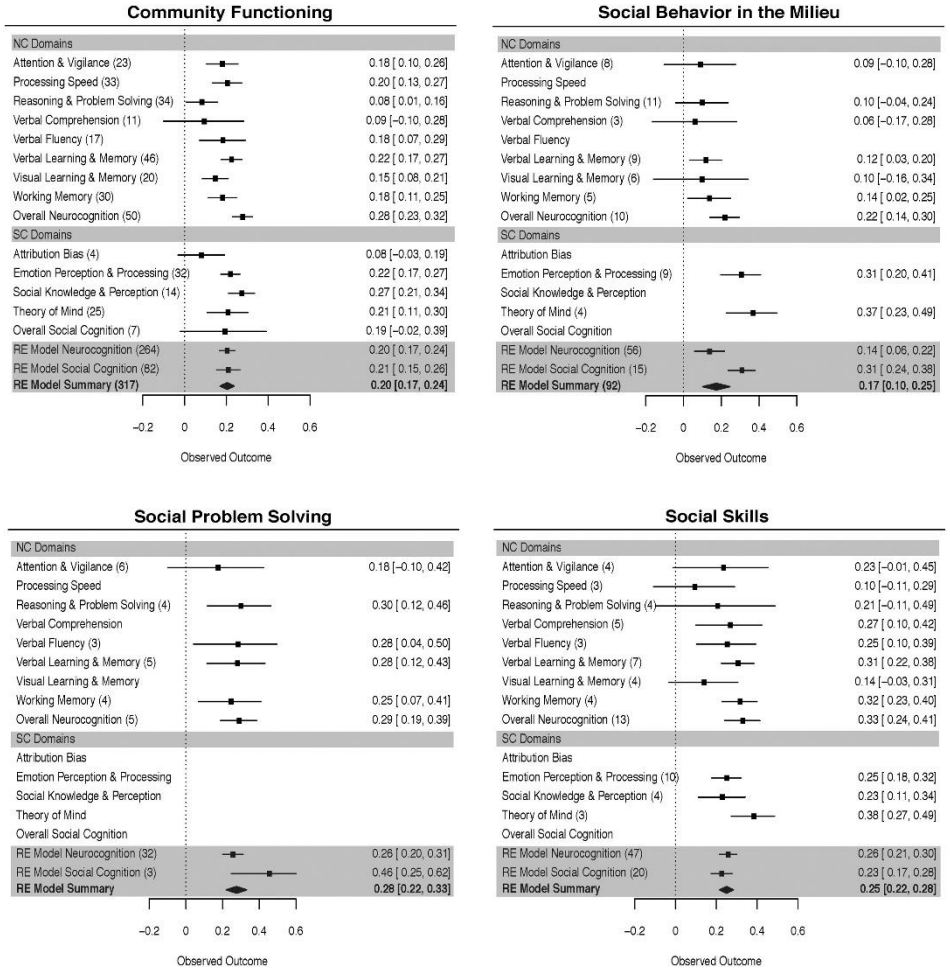
Rajji et al., 2009



Fatouros-Bergman et al., 2014



Catalan et al., 2021



Halverson et al., 2019

Special Communication

Schizophrenia Is a Cognitive Illness
Time for a Change in Focus

René S. Kahn, MD, PhD; Richard S. E. Keefe, PhD

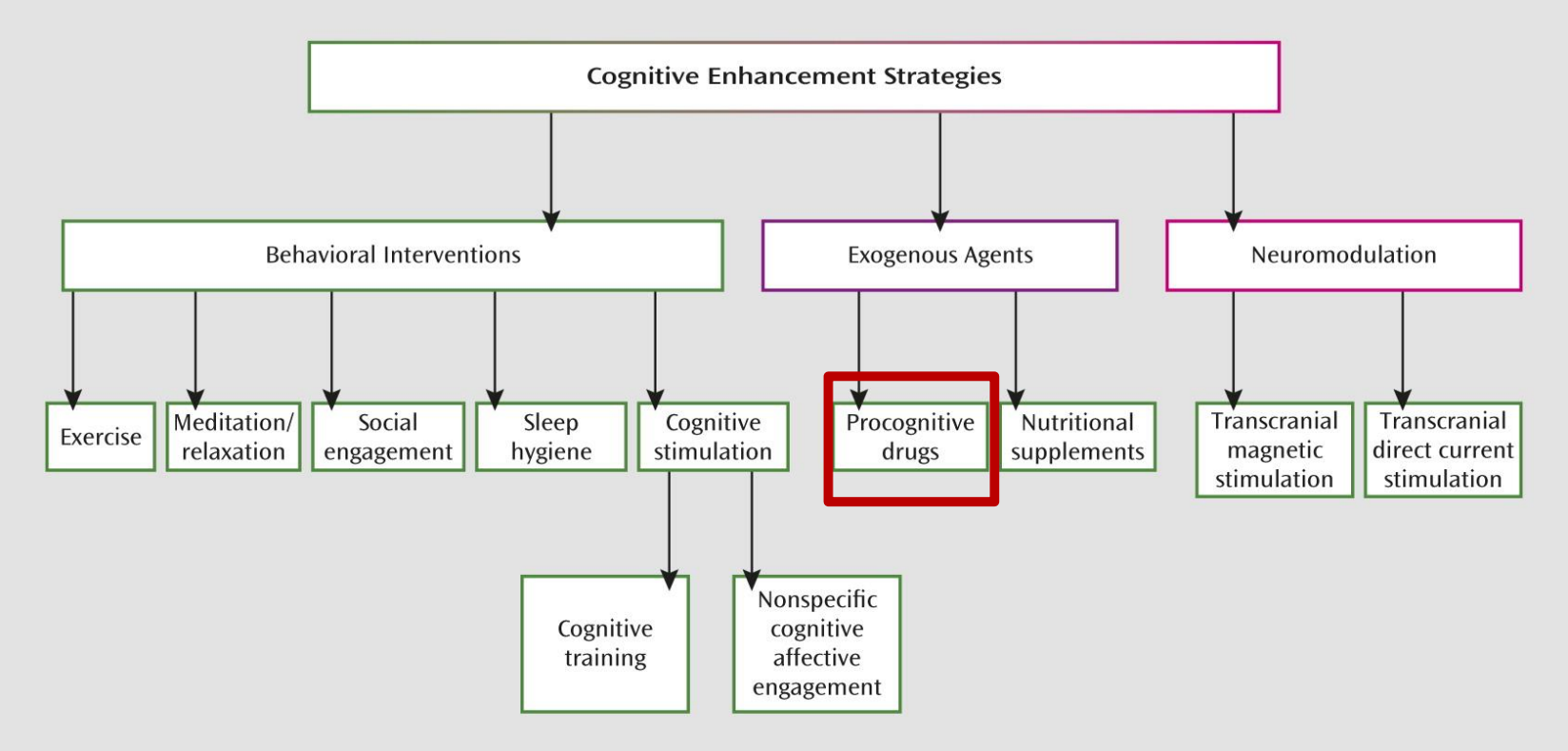
Schizophrenia is currently classified as a psychotic disorder. This article posits that this emphasis on psychosis is a conceptual fallacy that has greatly contributed to the lack of progress in our understanding of this illness and hence has hampered the development of adequate treatments. Not only have cognitive and intellectual underperformance consistently been shown to be risk factors for schizophrenia, several studies have found that a decline in cognitive functioning precedes the onset of psychosis by almost a decade. Although the question of whether cognitive function continues to decline after psychosis onset is still debated, it is clear that cognitive function in schizophrenia is related to outcome and little influenced by antipsychotic treatment. Thus, our focus on defining (and preventing) the disorder on the basis of psychotic symptoms may be too narrow. Not only should cognition be recognized as the core component of the disorder, our diagnostic efforts should emphasize the changes in cognitive function that occur earlier in development. Putting the focus back on cognition may facilitate finding treatments for the illness before psychosis ever emerges.

JAMA Psychiatry. 2013;70(10):1107-1112. doi:10.1001/jamapsychiatry.2013.155
Published online August 7, 2013.

Editorial page 1009

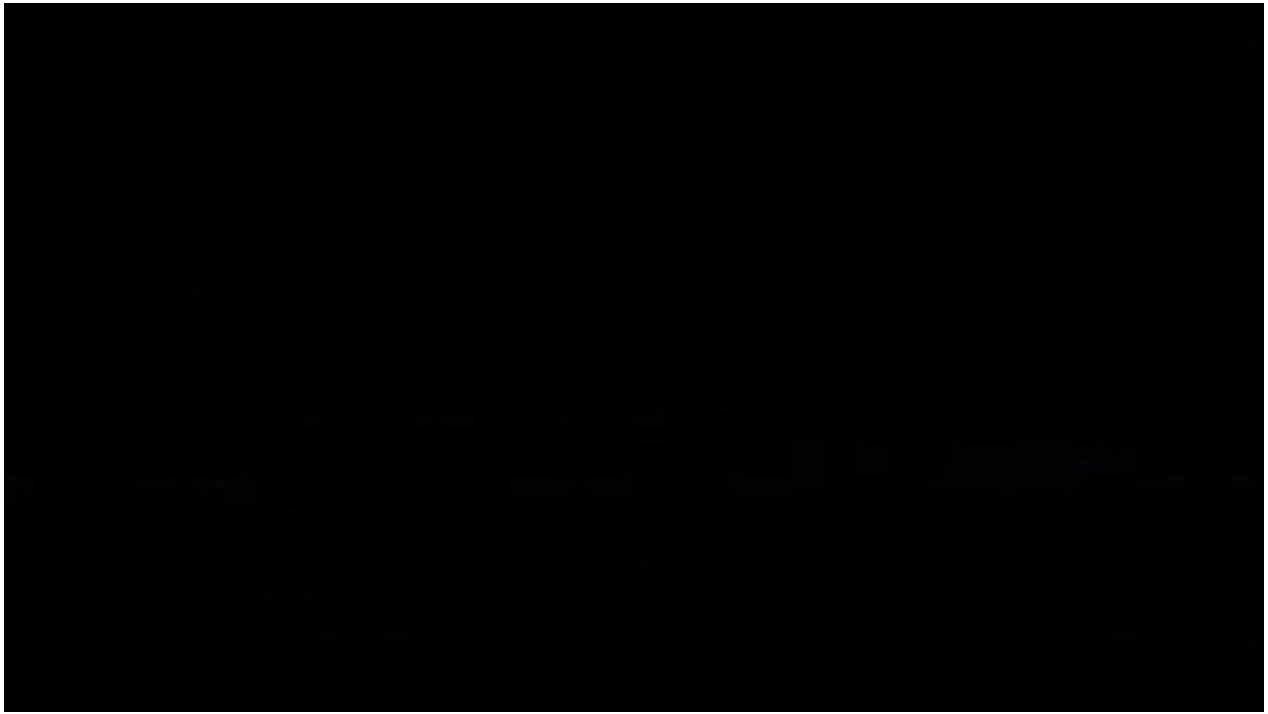
Author Affiliations: Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, UMC Utrecht, Utrecht, the Netherlands (Kahn); Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina (Keefe).

Corresponding Author: René S. Kahn, MD, PhD, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, UMC Utrecht, Utrecht, Heidelberglaan 100, 3508 GA Utrecht, PO Box 85500, the Netherlands (r.kahn@umcutrecht.nl).

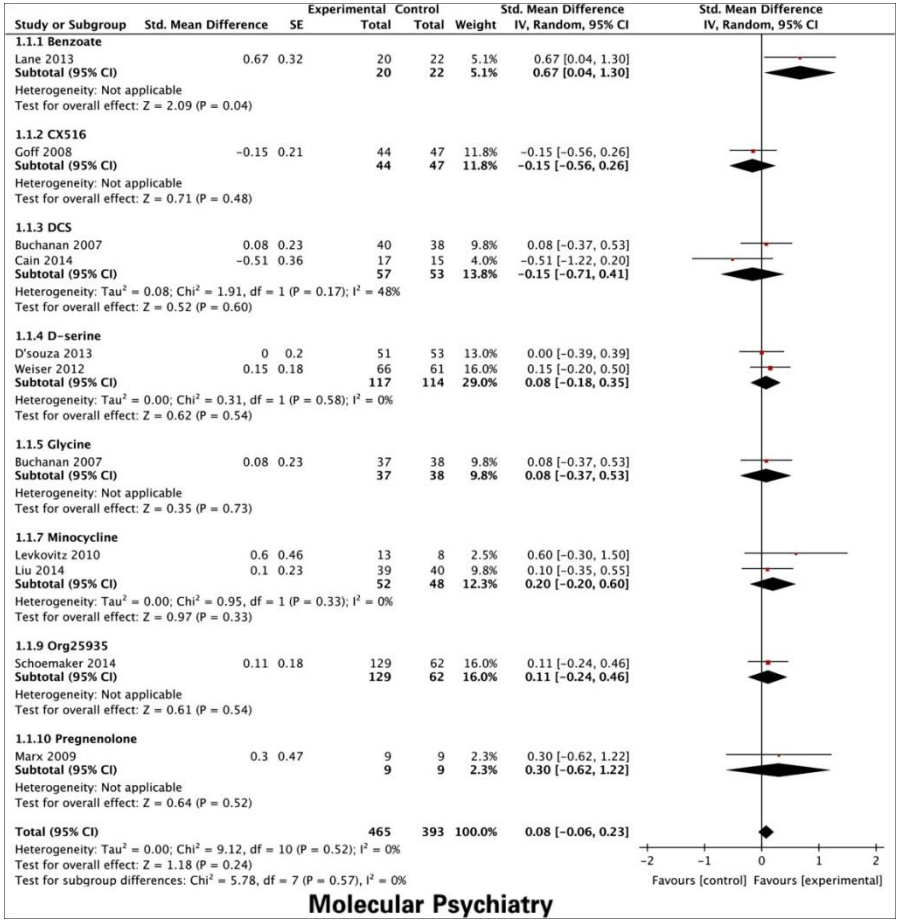


Keshavan et al., 2014

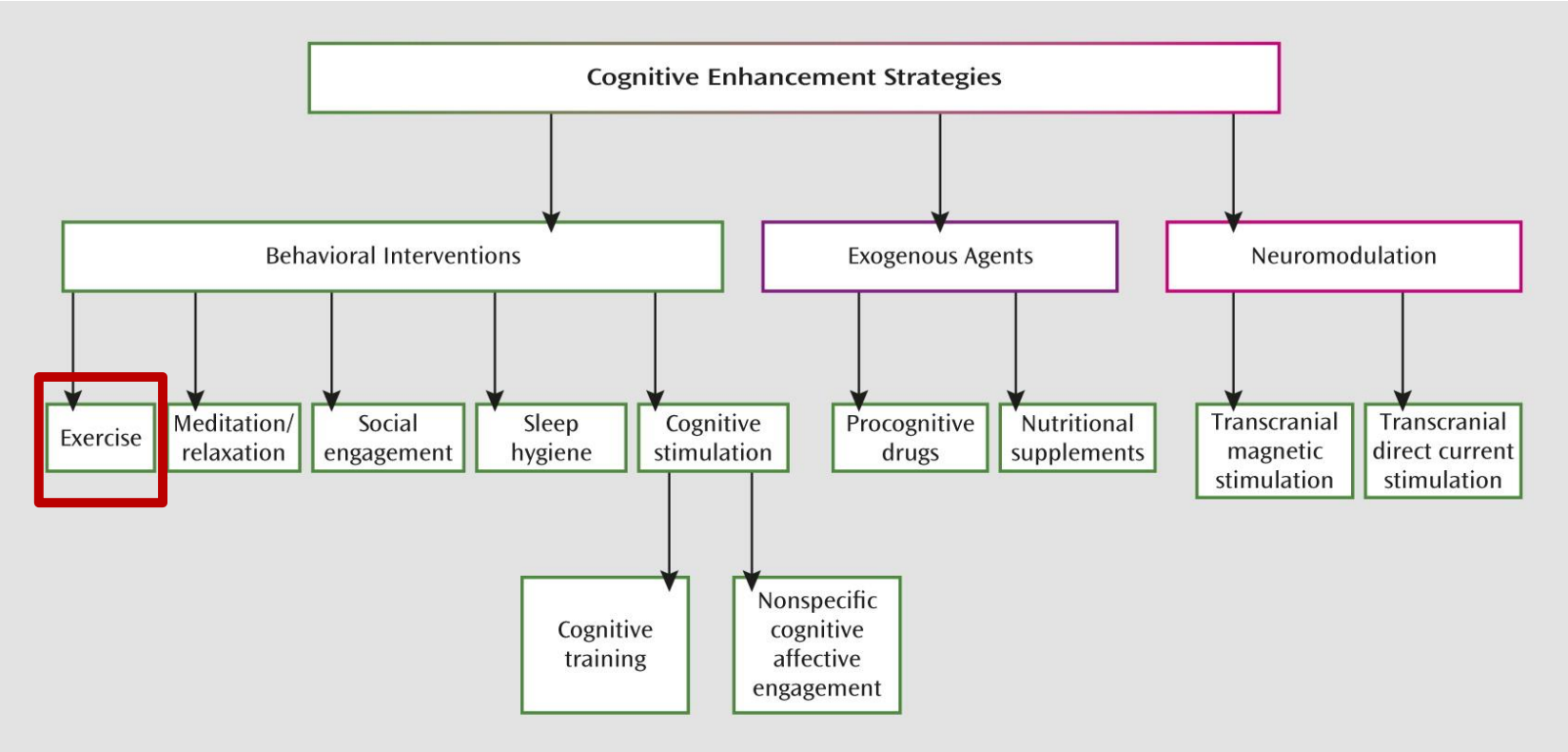
Glutamate Modulators and NMDA Receptors



Citrome, 2013



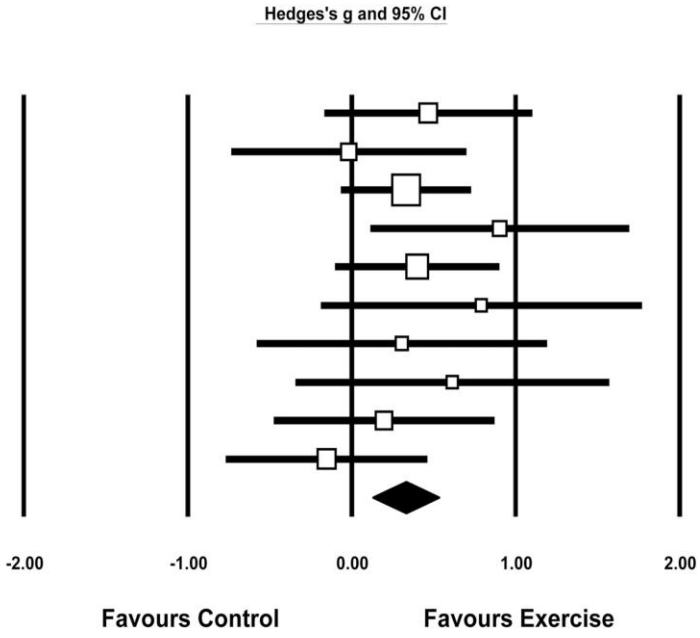
Iwata et al., 2015



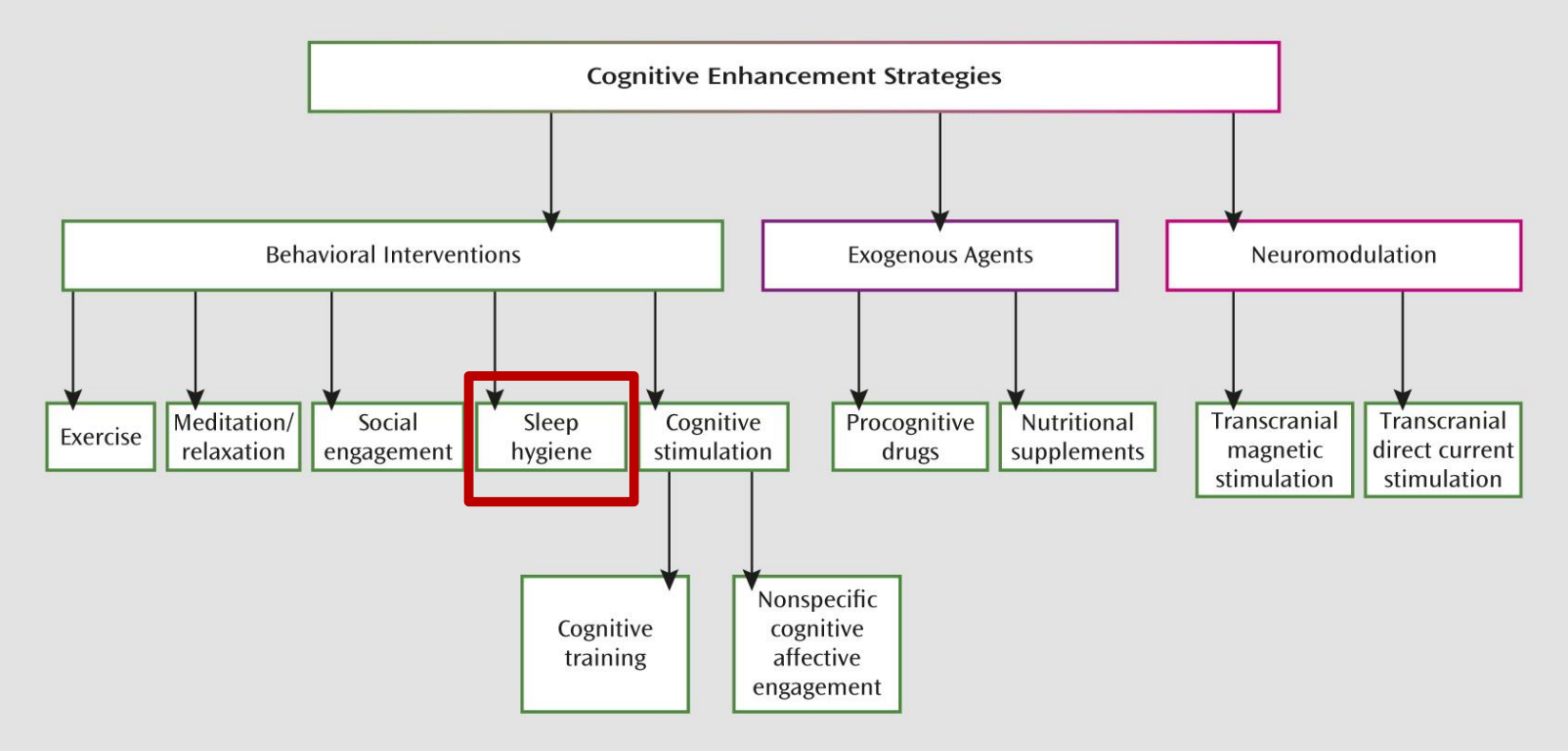
Keshavan et al., 2014

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	Total	p-Value
Behere et al. 2011	0.469	0.321	0.103	-0.160	1.097	1.461	39	0.144
Campos et al. 2015	-0.016	0.363	0.132	-0.727	0.695	-0.044	29	0.965
Ho et al. 2016	0.333	0.200	0.040	-0.059	0.725	1.665	100	0.096
Kimhy et al. 2015	0.905	0.400	0.160	0.121	1.689	2.262	26	0.024
Lin et al. 2015	0.402	0.253	0.064	-0.093	0.897	1.590	64	0.112
Nuechterlein et al. 2016	0.792	0.497	0.247	-0.181	1.766	1.595	16	0.111
Oertel-Knochel et al. 2014	0.308	0.449	0.202	-0.572	1.187	0.685	19	0.493
Pajonk et al. 2010	0.615	0.485	0.235	-0.336	1.566	1.267	16	0.205
Svatkova et al. 2015	0.199	0.341	0.116	-0.468	0.867	0.585	33	0.558
Malchow et al. 2015	-0.151	0.311	0.097	-0.760	0.458	-0.487	41	0.626
	0.334	0.102	0.010	0.134	0.533	3.279	383	0.001

Statistics for each study



Firth et al., 2017



Keshavan et al., 2014

Sleep Medicine Reviews 31 (2017) 25–38

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

A systematic review of the nature and correlates of sleep disturbance in early psychosis

Gabriel Davies [a, b, *], Gillian Haddock [a, b], Alison R. Yung [c, d], Lee D. Mulligan [d], Simon D. Kyle [e]

[a] School of Psychological Sciences, University of Manchester, UK
[b] Manchester Mental Health and Social Care NHS Trust, Manchester, UK
[c] Institute of Brain, Behaviour and Mental Health, University of Manchester, UK
[d] Greater Manchester West NHS Trust, Manchester, UK
[e] Sleep and Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, UK

Schizophrenia Research 221 (2020) 44–56

Contents lists available at ScienceDirect

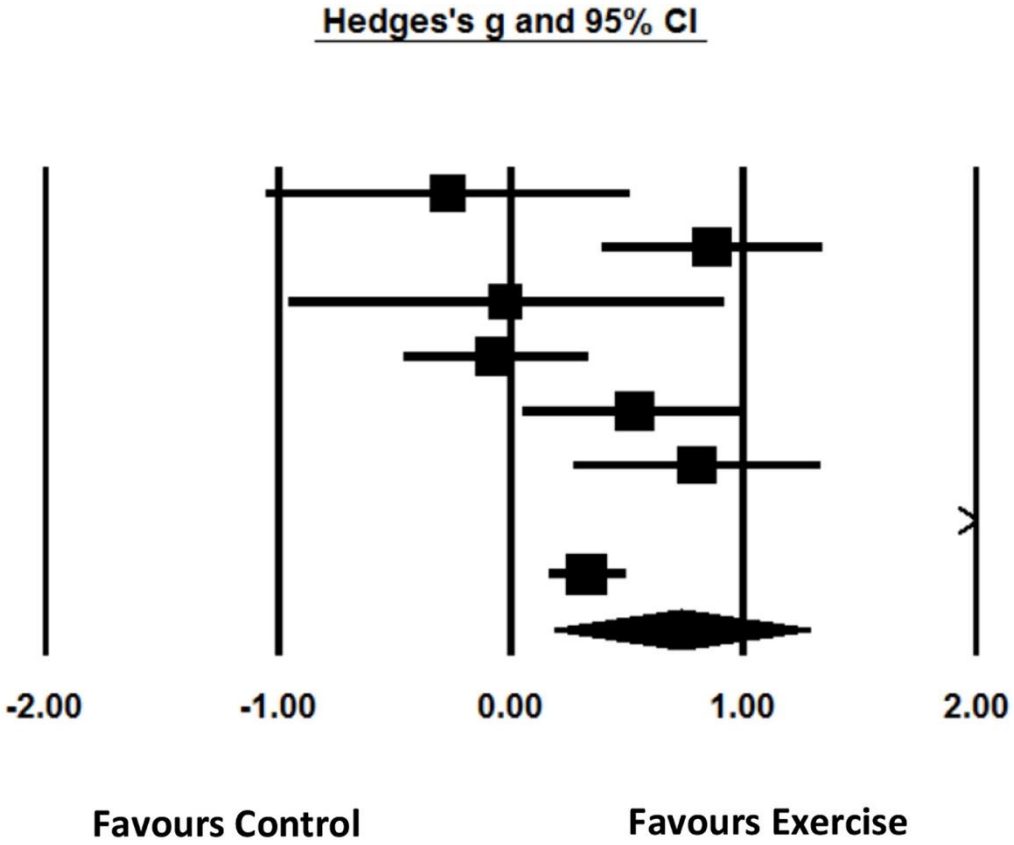
Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

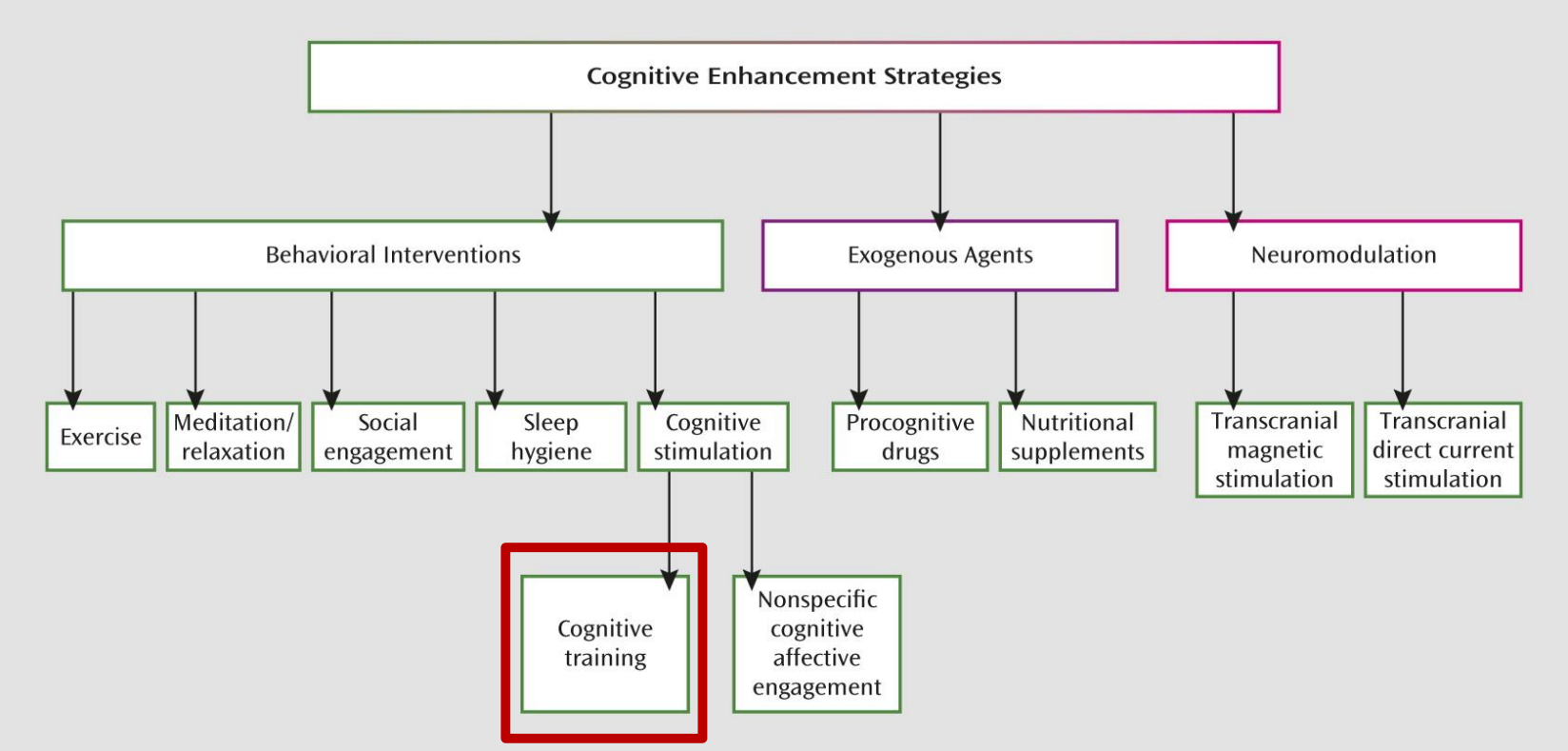
Sleep and schizophrenia: From epiphenomenon to treatable causal target

Felicity Waite [a,b,c,*], Bryony Sheaves [a,b,c], Louise Isham [a,b], Sarah Reeve [d], Daniel Freeman [a,b,c]

[a] Department of Psychiatry, University of Oxford, UK
[b] Oxford Health NHS Foundation Trust, UK
[c] Sleep and Circadian Neuroscience Institute, University of Oxford, UK
[d] University College London, UK



Lederman et al., 2019



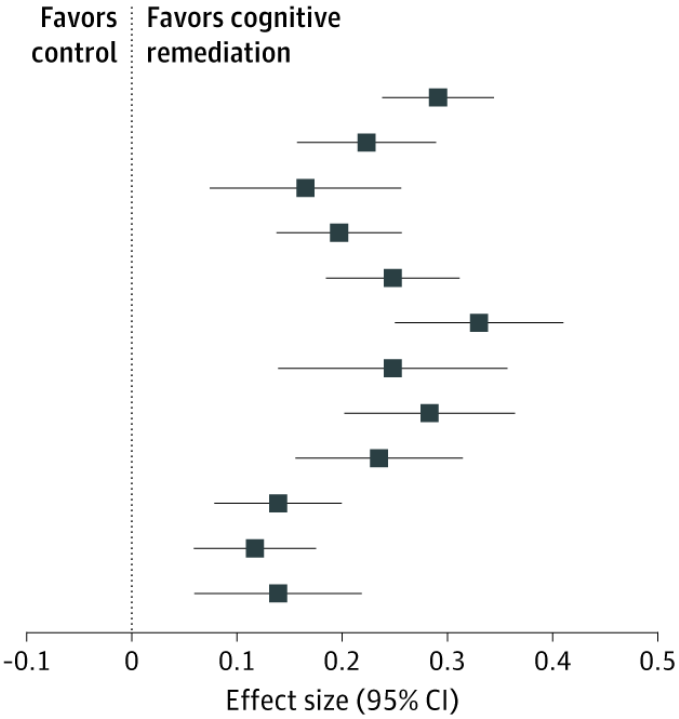
Keshavan et al., 2014

Cognitive Remediation Therapy

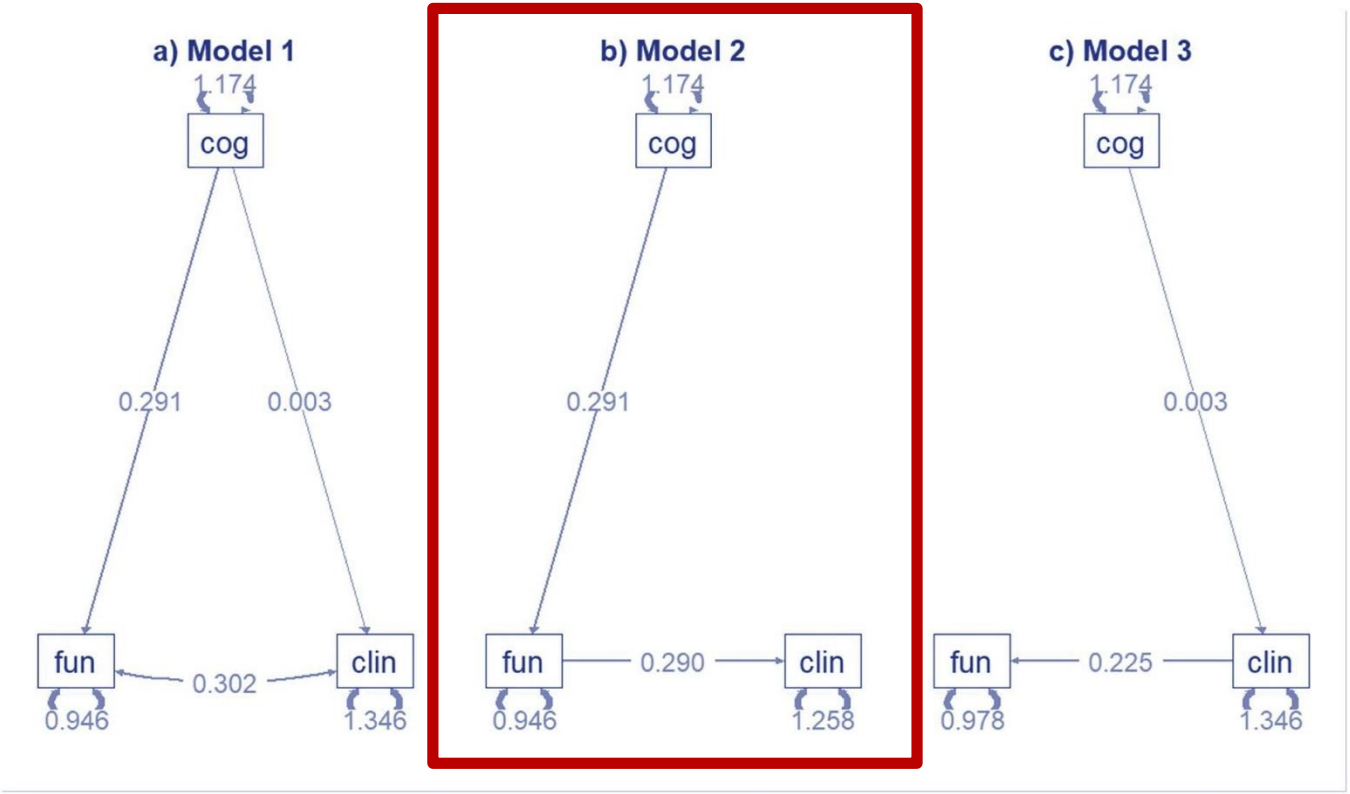
- Development of cognitive strategies
- Repeated practice of cognitive exercises
- Promotion of skills transfer to real world
- Delivered by a trained and active therapist

Bowie et al., 2019

Outcome	Studies	Participants	Effect size (95% CI)
Global cognition	135	7813	0.29 (0.24-0.34)
Global functioning	95	6091	0.22 (0.16-0.29)
Attention	40	2483	0.17 (0.07-0.26)
Processing speed	80	4917	0.20 (0.14-0.26)
Working memory	93	5493	0.25 (0.19-0.31)
Verbal memory	81	4954	0.33 (0.25-0.41)
Visual memory	43	2970	0.25 (0.14-0.36)
Executive functions	86	5196	0.28 (0.20-0.36)
Social cognition	55	3389	0.24 (0.16-0.32)
Global symptoms	76	4735	0.14 (0.08-0.20)
Positive symptoms	79	4700	0.12 (0.06-0.18)
Negative symptoms	82	4892	0.14 (0.06-0.22)



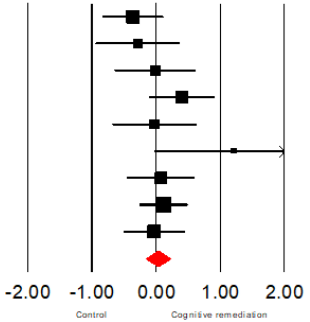
Vita et al., 2021



Kambeitz-Ilankovic et al., 2019

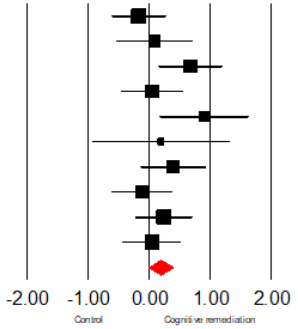
General Cognition

Study name	Hedges's g	Lower limit	Upper limit	p-Value
Burda et al. 1994	-0.36	-0.84	0.12	0.139
Bellucci et al. 2003	-0.28	-0.94	0.38	0.402
Horan et al. 2011	-0.01	-0.64	0.62	0.966
Vita et al. 2011	0.41	-0.11	0.92	0.121
Rass et al. 2012	-0.02	-0.68	0.63	0.945
Cavallo et al. 2013	1.21	-0.03	2.45	0.055
D'Souza et al. 2013	0.08	-0.46	0.61	0.781
Pitschel et al. 2013	0.12	-0.26	0.50	0.545
Linke et al. 2017	-0.03	-0.51	0.45	0.906
	0.03	-0.17	0.23	0.748



Functional outcome

Study name	Hedges's g	Lower limit	Upper limit	p-Value
d'Amato et al. 2011	-0.17	-0.61	0.27	0.448
Horan et al. 2011	0.09	-0.53	0.71	0.777
Vita et al. 2011	0.67	0.15	1.19	0.012
Man et al. 2012	0.04	-0.47	0.56	0.870
Byrne et al. 2013	0.90	0.17	1.62	0.015
Cavallo et al. 2013	0.19	-0.93	1.31	0.739
D'Souza et al. 2013	0.40	-0.14	0.93	0.149
Lee 2013	-0.12	-0.61	0.38	0.652
Gomar et al. 2015	0.24	-0.23	0.70	0.320
Linke et al. 2017	0.04	-0.44	0.52	0.867
	0.19	-0.01	0.39	0.069



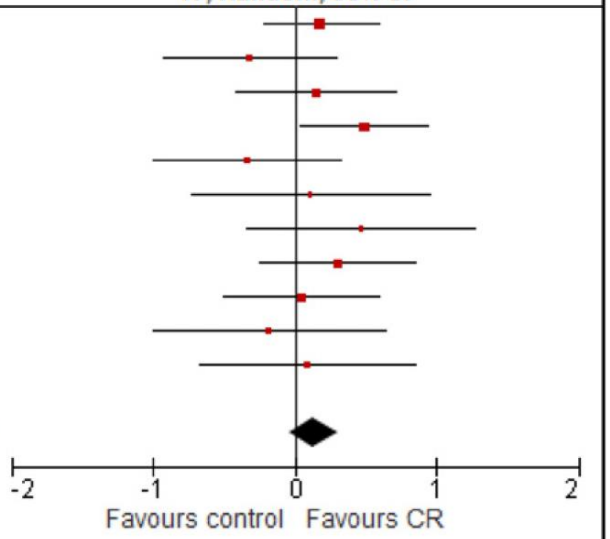
Prikken et al., 2019

Cognitive Remediation in Early Psychosis

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Christensen et al (2014)	0.1833	0.2068	19.1%	0.18 [-0.22, 0.59]
Drake et al (2013)	-0.32	0.31	8.5%	-0.32 [-0.93, 0.29]
Eack et al (2009)	0.15	0.29	9.7%	0.15 [-0.42, 0.72]
Fisher et al (2014)	0.49	0.23	15.5%	0.49 [0.04, 0.94]
Holzer et al (2014)	-0.34	0.34	7.1%	-0.34 [-1.01, 0.33]
Lee et al (2013)	0.11	0.43	4.4%	0.11 [-0.73, 0.95]
Mendella et al (2015)	0.47	0.41	4.9%	0.47 [-0.33, 1.27]
Ojeda et al (2011)	0.3	0.28	10.4%	0.30 [-0.25, 0.85]
Puig et al (2014)	0.05	0.28	10.4%	0.05 [-0.50, 0.60]
Ueland & Rund (2004)	-0.18	0.42	4.6%	-0.18 [-1.00, 0.64]
Wykes et al (2007)	0.09	0.39	5.4%	0.09 [-0.67, 0.85]
Total (95% CI)			**100.0%**	**0.13 [-0.04, 0.31]**

Heterogeneity: Tau² = 0.00; Chi² = 8.23, df = 10 (P = 0.61); I² = 0%

Test for overall effect: Z = 1.49 (P = 0.14)



Revell et al., 2015

Targeting Metacognition

- Cognitive abilities can be enhanced through improving metacognitive awareness/abilities (Schraw et al., 2006)

- Metacognitive abilities may moderate association between cognitive functioning and real-world functioning (Koren et al., 2006)

METACOGNITIVE INTERVENTIONS

AIM	• targeting metacognitive content by raising awareness and understanding of own thoughts and feelings and those of others • enhancing metacognitive capacities by gaining more flexibility in the attention, monitoring, control, and regulation of cognitive processes • alleviating disorder-specific and individual symptoms		
APPROACH	• individual problem formulation based on a metacognitive model of illness • goal-oriented treatment		
	METACOGNITIVE THERAPY	**METACOGNITIVE TRAINING**	**METACOGNITIVELY-ORIENTED INTEGRATIVE PSYCHOTHERAPIES**
DEFINITION OF META-COGNITION	• beliefs about cognition • strategies used to control attention and thinking	• capacity to think about their thinking • patients' awareness of their cognitive biases	• ability to understand and make sense of own mental states and the mental states of others
MODEL OF ILLNESS	• inflexible metacognitions (= positive and negative beliefs about cognition) • result in disorder-specific *Cognitive Attentional Syndrome* (CAS)	• disorder-specific cognitive biases	• inability to construct and develop a coherent personal narrative
KEY INTER-VENTIONS	• challenging inflexible metacognitive beliefs in order to modify CAS	• educating patients about cognitive processes and their negative consequences • promote alternative thinking strategies	• encouraging reflection • enriching narratives • constructing integrated sense of self and others

Phillip et al., 2020

Metacognition—What is it?

- Metacognitive knowledge
  - Stored knowledge about cognitive processes of self and others
- Metacognitive experiences
  - Reflection/awareness about cognitive processes of self and others
- Goals/Tasks
  - Recognition of utility/desire to evaluate metacognitive experience
- Actions/Strategies
  - Activity employed to evaluate metacognitive experience

Flavell, 1979

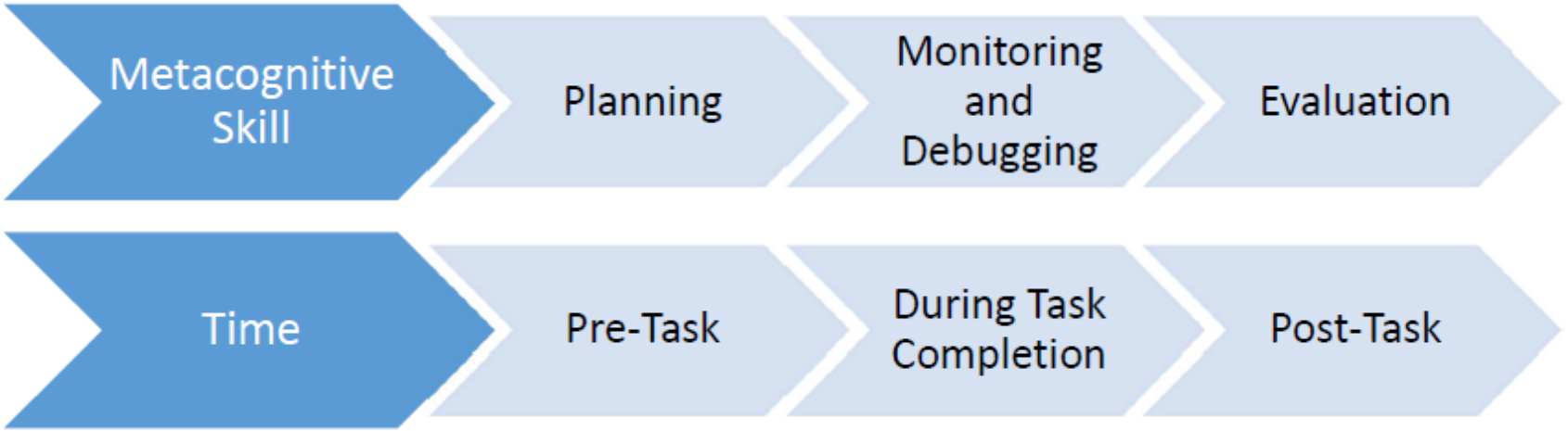
MCR sessions

- Pairing of computerized cognitive remediation with metacognitive skills development exercises
  - Identification of strategies to enhance knowledge of cognition
  - Identification of strategies to enhance regulation of cognition
  - Exploration of intervening factors that may interfere with or enhance task knowledge/regulation of cognition
  - Real-world application of strategies

Knowledge of Cognition

- GOAL = Improve knowledge of problem-solving skills for cognitive tasks:
  - Declarative Knowledge
    - “What Strategies Can I Use to Complete This Task?”
  - Procedural Knowledge
    - “How Do I Use Each Specific Strategy to Complete the Task?”
  - Conditional Knowledge
    - “Why Would This Strategy Work Best In A Specific Situation?”
- Exploring Real-World Applications

Regulation of Cognition



Intervening Factors

- Provide training in evidence-based strategies to address factors that may interfere with application of problem-solving strategies
  - Arousal Regulation
  - Mood Regulation
  - Self-Efficacy and Motivation

Real-World Applications

- Bridging MCR Strategies to Real-World Situations

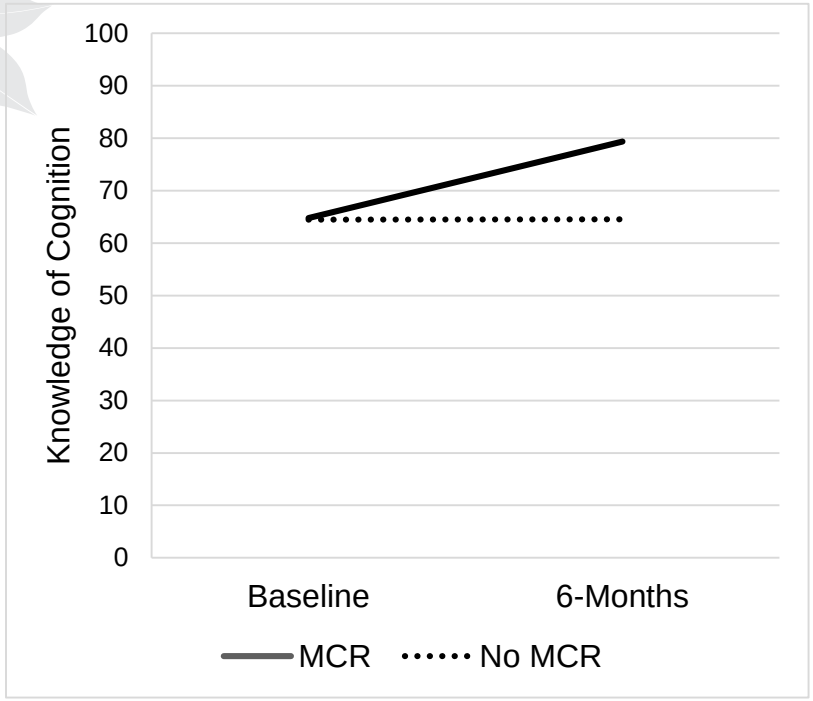
- Low Road vs High Road Transfer (Salomon & Perkins, 1989

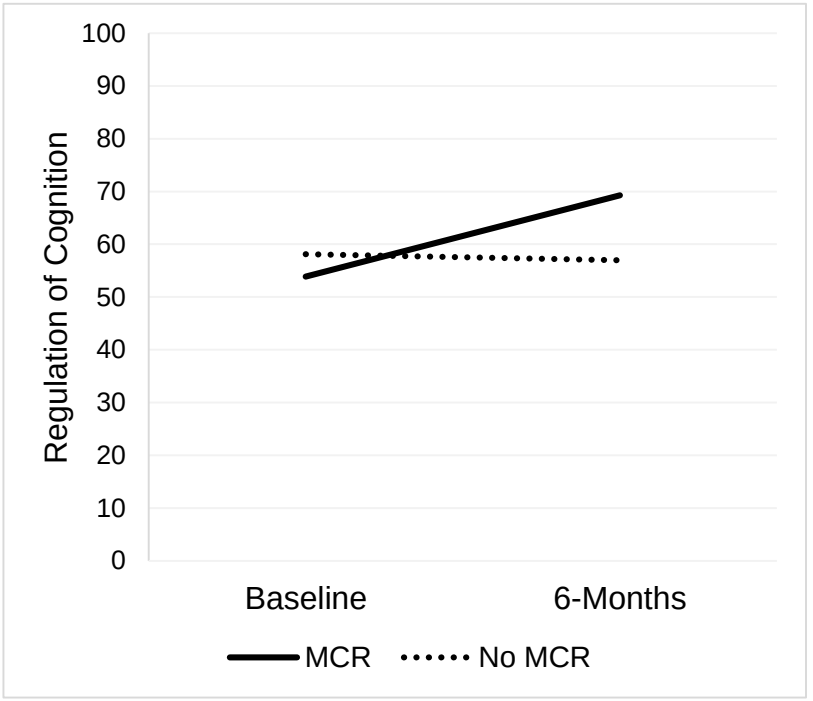
Is MCR Metacognitive?

- Metacognitive knowledge
  - Enhance knowledge of problem-solving strategies and intervening factors that influence their success
- Metacognitive experiences
  - Increase ability to monitor implementation of problem-solving strategies
- Goals/Tasks
  - Enhance motivation to evaluate implementation of problem-solving strategies
- Actions/Strategies
  - Develop/master strategies to evaluate whether problem-solving strategies are achieving their goal

MCR Outcomes

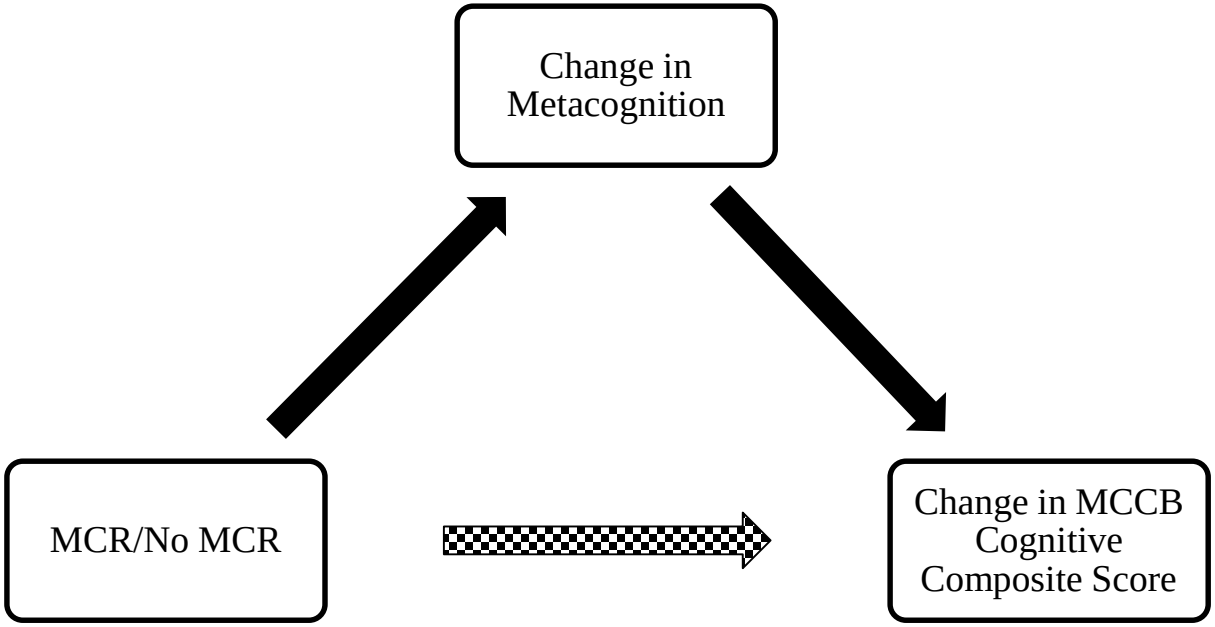
MCR Improves Metacognition





Pine et al., 2021

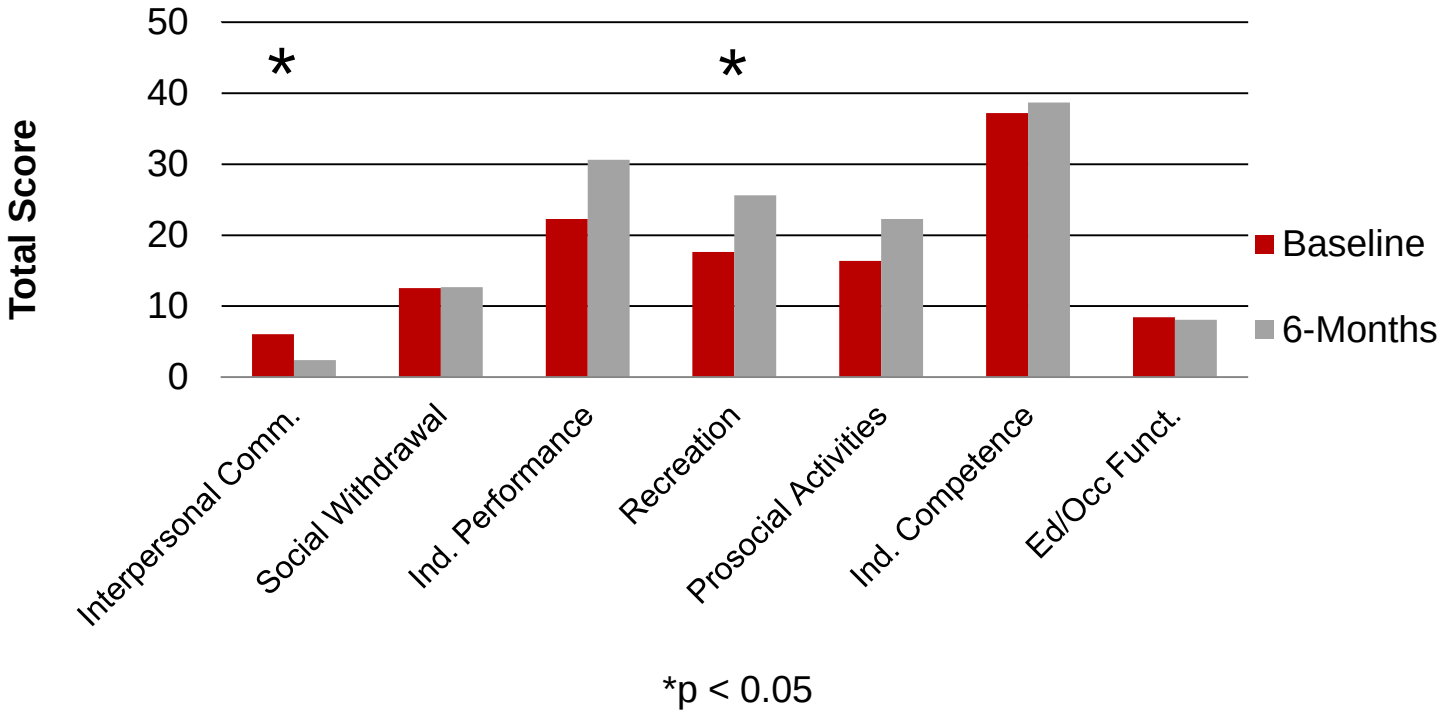
MCR Mechanisms of Change



(*indirect effect* = 1.89; *95% CI* = 0.07–5.20)

Pine et al., 2021

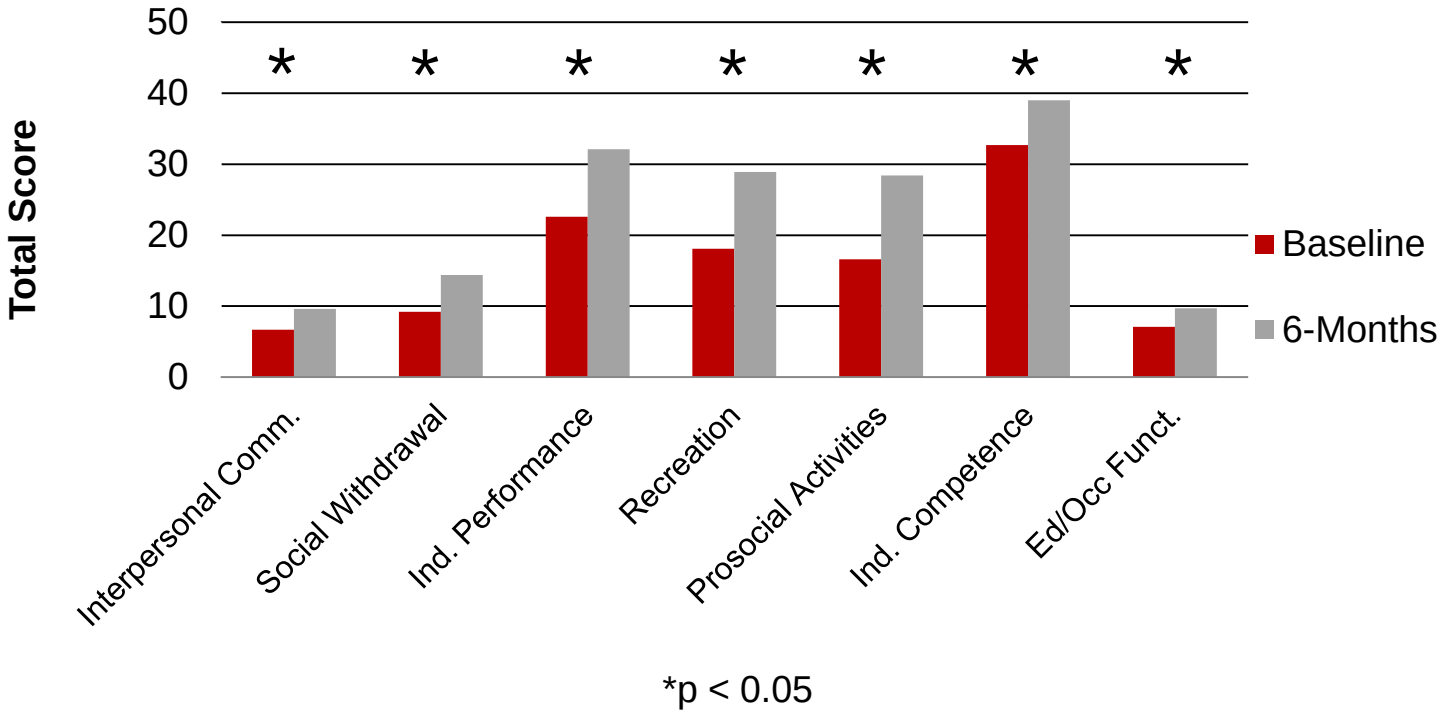
Social Functioning: CCR



*p < 0.05

Breitborde et al., 2017a

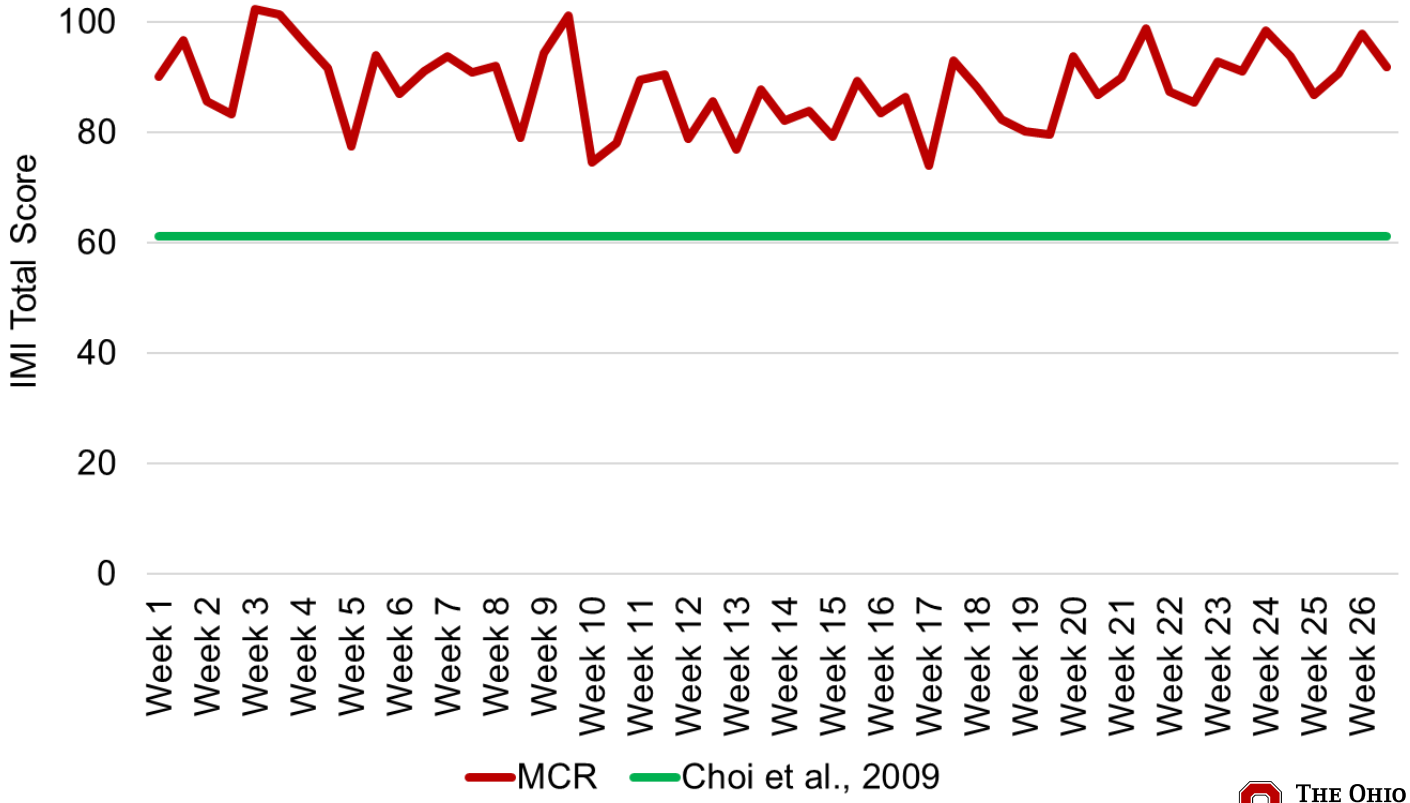
Social Functioning: MCR



*p < 0.05

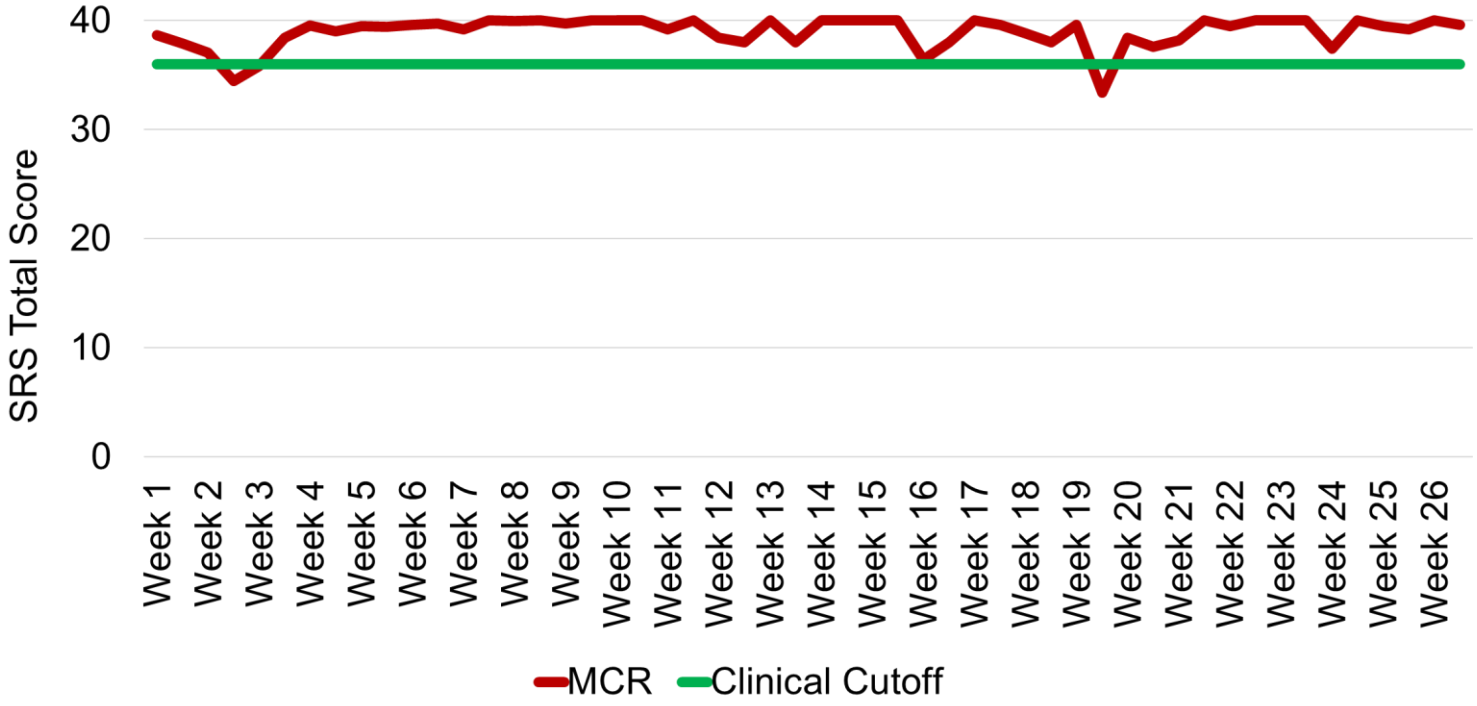
Breitborde et al., 2017a

Intrinsic Motivation



Breitborde et al, 2018

Therapeutic Alliance



Breitborde et al, 2018

Conclusions

- Cognitive deficits are a core feature of psychotic disorders
- Multiple interventions of varying intensity show promise in addressing these cognitive deficits
- Not all cognitive remediation interventions may be effective for youth with psychosis