

Improving People's Lives Through Innovations in Personalized Health Care

Promoting Cognitive Health Among Youth with Psychosis

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The Ohio State University

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Global Burden of Disease Study 2013

Illness/Injury	Disability Weight
Schizophrenia, Acute State	<u>0.778</u>
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	<u>0.588</u>
Stroke, Long-term consequences, severe, plus cognitive problems	0.588



Salomon et al., 2015

Disease-Related Burden in First-Episode Psychosis









E First Episode Established/Chronic Schizophrenia

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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









Processing speed
 Visual learning
 Attention/vigilance
 Working memory
 Verbal learning







Community Functioning

NC Domains	:				
Attention & Vigilance (23)	-				0.18 [0.10, 0.26]
Processing Speed (33)	-				0.20 [0.13, 0.27
Reasoning & Problem Solving (34)	1	-			0.08 [0.01, 0.16]
Verbal Comprehension (11)	-	•			0.09 [-0.10, 0.28]
Verbal Fluency (17)	: .				0.18 [0.07, 0.29]
Verbal Learning & Memory (46)	1				0.22 [0.17, 0.27]
Visual Learning & Memory (20)	:				0.15 [0.08, 0.21]
Working Memory (30)	1				0.18 [0.11, 0.25]
Overall Neurocognition (50)	1		-		0.28 [0.23, 0.32]
SC Domains	1				
Attribution Bias (4)	+ +				0.08 [-0.03, 0.19]
Emotion Perception & Processing (3	ż)				0.22 [0.17, 0.27]
Social Knowledge & Perception (14)	1		-		0.27 [0.21, 0.34]
Theory of Mind (25)	-		02		0.21 [0.11, 0.30]
Overall Social Cognition (7)	-				0.19 [-0.02, 0.39]
RE Model Neurocognition (264)	-				0.20 [0.17, 0.24]
RE Model Social Cognition (82) RE Model Summary (317)		+			0.21 [0.15, 0.26] 0.20 [0.17, 0.24]
	Т				
-0.2	0	0.2	0.4	0.6	
	Obs	erved Out	come		

Social Behavior in the Milieu

NC Domains	
Attention & Vigilance (8)	0.09 [-0.10, 0.28]
Processing Speed	
Reasoning & Problem Solving (11)	0.10 [-0.04, 0.24]
Verbal Comprehension (3)	0.06 [-0.17, 0.28]
Verbal Fluency	
Verbal Learning & Memory (9)	0.12 [0.03, 0.20]
Visual Learning & Memory (6)	0.10 [-0.16, 0.34]
Working Memory (5)	0.14 [0.02, 0.25]
Overall Neurocognition (10)	0.22 [0.14, 0.30]
SC Domains	
Attribution Bias	
Emotion Perception & Processing (9)	- 0.31 [0.20, 0.41]
Social Knowledge & Perception	
Theory of Mind (4)	 0.37 [0.23, 0.49]
Overall Social Cognition	
RE Model Neurocognition (56)	0.14 [0.06, 0.22]
RE Model Social Cognition (15)	- 0.31 [0.24, 0.38]
HE woder summary (92)	0.17 [0.10, 0.25]
-0.2 0 0.2	0.4 0.6
Observed Outo	ome

Social Problem Solving

NC Domains	
Attention & Vigilance (6)	0.18 [-0.10, 0.42]
Processing Speed	
Reasoning & Problem Solving (4)	0.30 [0.12, 0.46]
Verbal Comprehension	
Verbal Fluency (3)	- 0.28 [0.04, 0.50]
Verbal Learning & Memory (5)	0.28 [0.12, 0.43]
Visual Learning & Memory	
Working Memory (4)	0.25 [0.07, 0.41]
Overall Neurocognition (5)	0.29 [0.19, 0.39]
SC Domains	
Attribution Bias	
Emotion Perception & Processing	
Social Knowledge & Perception	
Theory of Mind	
Overall Social Cognition	
RE Model Neurocognition (32)	0.26 [0.20, 0.31]
RE Model Social Cognition (3)	0.46 [0.25, 0.62]
RE Model Summary	0.28 [0.22, 0.33]
	1
-0.2 0 0.2 0.4	0.6

Observed Outcome

Social Skills

NC Domains	
Attention & Vigilance (4)	0.23 [-0.01, 0.45]
Processing Speed (3)	0.10 [-0.11, 0.29]
Reasoning & Problem Solving (4)	0.21 [-0.11, 0.49]
Verbal Comprehension (5) -	0.27 [0.10, 0.42]
Verbal Fluency (3) -	0.25 [0.10, 0.39]
Verbal Learning & Memory (7)	0.31 [0.22, 0.38]
Visual Learning & Memory (4)	0.14 [-0.03, 0.31]
Working Memory (4)	0.32 [0.23, 0.40]
Overall Neurocognition (13)	0.33 [0.24, 0.41]
SC Domains	
Attribution Bias	
Emotion Perception & Processing (10)	0.25 [0.18, 0.32]
Social Knowledge & Perception (4) -	0.23 [0.11, 0.34]
Theory of Mind (3)	
Overall Social Cognition	
RE Model Neurocognition (47)	0.26 [0.21, 0.30]
RE Model Social Cognition (20)	0.23 [0.17, 0.28]
RE Model Summary	• 0.25 [0.22, 0.28]
-0.2 0	0.2 0.4 0.6
Obser	ved Outcome



Halverson et al., 2019



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 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.

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Glutamate Modulators and NMDA Receptors





Citrome, 2013

		E	xperimental C	ontrol	5	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Std. Mean Difference	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 Benzoate		-					
Lane 2013 Subtotal (95% CI)	0.67	0.32	20 20	22 22	5.1% 5.1%	0.67 [0.04, 1.30] 0.67 [0.04, 1.30]	
Heterogeneity: Not ap Test for overall effect	oplicable : Z = 2.09 (P = 0.04)						
1.1.2 CX516							
Goff 2008 Subtotal (95% CI)	-0.15	0.21	44 44	47 47	11.8% 11.8%	-0.15 [-0.56, 0.26] -0.15 [-0.56, 0.26]	
Heterogeneity: Not ap Test for overall effect	plicable : Z = 0.71 (P = 0.48)						
1.1.3 DCS							
Buchanan 2007	0.08	0.23	40	38	9.8%	0.08 [-0.37, 0.53]	
Cain 2014 Subtotal (95% CI)	-0.51	0.36	17 57	15 53	4.0% 13.8%	-0.51 [-1.22, 0.20] -0.15 [-0.71, 0.41]	
Heterogeneity: Tau ² = Test for overall effect	= 0.08; Chi ² = 1.91, df = : Z = 0.52 (P = 0.60)	1 (P =	0.17); I ² = 48%				
1.1.4 D-serine							
D'souza 2013	0	0.2	51	53	13.0%	0.00 [-0.39, 0.39]	
Weiser 2012 Subtotal (95% CI)	0.15	0.18	66 117	61 114	16.0% 29.0%	0.15 [-0.20, 0.50]	
Heterogeneity: Tau ² = Test for overall effect	= 0.00; Chi ² = 0.31, df = : Z = 0.62 (P = 0.54)	: 1 (P =	0.58 ; $I^2 = 0\%$				
1.1.5 Glycine							
Buchanan 2007 Subtotal (95% CI)	0.08	0.23	37 37	38 38	9.8% 9.8%	0.08 [-0.37, 0.53] 0.08 [-0.37, 0.53]	-
Heterogeneity: Not ap Test for overall effect	plicable : Z = 0.35 (P = 0.73)						
1.1.7 Minocycline							
Levkovitz 2010	0.6	0.46	13	8	2.5%	0.60 [-0.30, 1.50]	
Liu 2014	0.1	0.23	39	40	9.8%	0.10 [-0.35, 0.55]	
Subtotal (95% CI)			52	48	12.3%	0.20 [-0.20, 0.60]	-
Heterogeneity: Tau ² = Test for overall effect	= 0.00; Chi ² = 0.95, df = : Z = 0.97 (P = 0.33)	1 (P =	0.33); l ² = 0%				
1.1.9 Org25935							
Schoemaker 2014 Subtotal (95% CI)	0.11	0.18	129 129	62 62	16.0% 16.0%	0.11 [-0.24, 0.46] 0.11 [-0.24, 0.46]	
Heterogeneity: Not ap Test for overall effect	oplicable : Z = 0.61 (P = 0.54)						
1.1.10 Pregnenolone							
Marx 2009	0.3	0.47	9	9	2.3%	0.30 [-0.62, 1.22]	
Subtotal (95% CI)			9	9	2.3%	0.30 [-0.62, 1.22]	
Heterogeneity: Not ap Test for overall effect	plicable : Z = 0.64 (P = 0.52)						
Total (95% CI)			465	393	100.0%	0.08 [-0.06, 0.23]	•
Heterogeneity: Tau ² =	= 0.00; $Chi^2 = 9.12$, df =	= 10 (P =	= 0.52); I ² = 0%				
Test for subgroup dif	L = 1.10 (P = 0.24) ferences: Chi ² = 5.78, d	f = 7 (P	$= 0.57), I^2 = 05$	6			Favours [control] Favours [experimental]
		1	Molecul	ar P	sychi	iatry	







Study name	Statistics for each study							
	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

Hedges's g and 95% Cl



-2.00



Firth et al., 2017





Sleep Medicine Reviews 31 (2017) 25-38



Contents lists available at ScienceDirect

Sleep Medicine Reviews

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



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



sleepmedicin

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Sleep and schizophrenia: From epiphenomenon to treatable causal target



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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



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

		Gene	eral Co	gnition				Func	tional o	utcome						
Study name	Statistics for each study Hedges's g and 95% Cl		Statistics for each study Hedges				Study name	Stat	istics for	each st	udy	ļ	Hedges	's g and	95% (
	Hedges's g	Lower limit	Upper limit	p-Value			Hedges's g	Lower limit	Upper limit	p-Value						
Burda et al. 1994	-0.36	-0.84	0.12	0.139		d'Amato et al. 2011	-0.17	-0.61	0.27	0.448		-				
Bellucci et al. 2003	-0.28	-0.94	0.38	0.402		Horan et al. 2011	0.09	-0.53	0.71	0.777				-		
Horan et al. 2011	-0.01	-0.64	0.62	0.966		Vita et al. 2011	0.67	0.15	1.19	0.012			-	■┼		
Vita et al. 2011	0.41	-0.11	0.92	0.121		Man et al. 2012	0.04	-0.47	0.56	0.870			-	-		
Rass et al. 2012	-0.02	-0.68	0.63	0.945		Byrne et al. 2013	0.90	0.17	1.62	0.015				-	-	
Cavallo et al. 2013	1.21	-0.03	2.45	0.055		Cavallo et al. 2013	0.19	-0.93	1.31	0.739						
D'Souza et al. 2013	0.08	-0.46	0.61	0 781		D'Souza et al. 2013	0.40	-0.14	0.93	0.149			=	_		
Pitschel et al. 2013	0.12	-0.26	0.50	0.545		Comar of al. 2015	-0.12	-0.01	0.30	0.002		-				
Linke et al. 2017	-0.03	-0.51	0.45	0.906		Linko ot al 2017	0.24	-0.23	0.70	0.520				_		
	0.03	-0.17	0.23	0.748			0.19	-0.01	0.39	0.069			•			
					-2.00 -1.00 0.00 1.00 2.00 Control Cognitive remediation						-2.00	-1.00 Control	0.00 _{Cog}	1.00 niti ve remedia	2.0 ation	



Prikken et al., 2019

Cognitive Remediation in Early Psychosis

				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Std. Mean Difference	SE	Weight	IV, Random, 95% CI	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: Tau ² = 0.00;	Chi ² = 8.23, df = 10 (P =	: 0.61); I ^z	= 0%	H	
Test for overall effect: Z = 1.	.49 (P = 0.14)			-2	Favours control Favours CR



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 <i>Cognitive</i> <i>Attentional Syndrome</i> (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 				



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



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
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MCR Improves Metacognition





Pine et al., 2021



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



Social Functioning: CCR





Social Functioning: MCR





Intrinsic Motivation



Breitborde et al, 2018



Therapeutic Alliance





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

