ISBP
Israel Society of Biological Psychiatry
האיגוד הישראלי לפסיכיאטריה ביולוגית

בית ספר קיץ של האיגוד הישראלי לפסיכיאטריה ביולוגית:

מבט נוירופסיכיאטרי על פסיכוזה וסכיזופרניה

4 ביולי 2019

ד"ר רננה איתן וד"ר בת שבע חדד

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נוירופסיכיאטריה מאגדת את המדעים הקליניים של הקשר בין המח וההתנהגות

ועוסקת בשלושה מימדים עיקריים:

1. **הממשק שבין קוגניציה, רגשות, התנהגות, תחושה ותנועה**
2. **נוירוביולוגיה של הפרעות פסיכיאטריות**
3. **הביטויים הנפשיים של מחלות נוירולוגיות**

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מטרת בית ספר הקיץ של האיגוד השנה הינה קידום יישום קליני של הידע הנוירוביולוגי בהפרעות פסיכוטיות ובסכיזופרניה, תוך הבנת הממשק שבין קוגניציה, רגשות, התנהגות, תחושה ותנועה במטופלים הסובלים מסכיזופרניה.

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דברי פתיחה

פרופ' יואב כהן, יו"ר האיגוד לפסיכיאטריה ביולוגית

ד"ר שולה גלרשטיין, יאנסן

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

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האוניברסיטה העברית בירושלים
The Hebrew University of Jerusalem

The Role of Neuropsychiatry in Schizophrenia

Renana Eitan

July 4th 2019 ; ISBP – Summer School

Louis Wain
(1860 –1939)

Symptoms of Schizophrenia

* Schizophrenia is a chronic complex clinical syndrome that involves a range of emotional, behavioral and cognitive dysfunctions
* Schizophrenia is the most puzzling of psychiatric syndromes and one of its most debilitating - people with the illness suffer greatly
* Although its phenomenology is fascinating, its pathophysiology and etiology remain unclear

Epidemiology of Schizophrenia - Mortality

Cause	Prevalence % *	No. of deaths attributable to mental disorders **	Pooled relative risk for deaths attributable to mental disorders (95% CI)
All mental	26.1	8,000,000	2.22 (2.12-2.33)
Mood disorders	10.6	2,740,000	1.86 (1.73-2.00)
Anxiety disorders	14.3	2,410,000	1.43 (1.24-1.64)
Schizophrenia	**1.04**	**350,000**	**2.54 (2.35-2.75)**

* Median lifetime prevalence of illness, estimates from the World Heath Organization

** Based on the World Health Organization estimate of deaths worldwide in 2012

Adjusted from: Reisinger Walker et al, JAMA Psychiatry, 2015
Mortality in Mental Disorders and Global Disease Burden Implications; A Systematic Review and Meta-analysis

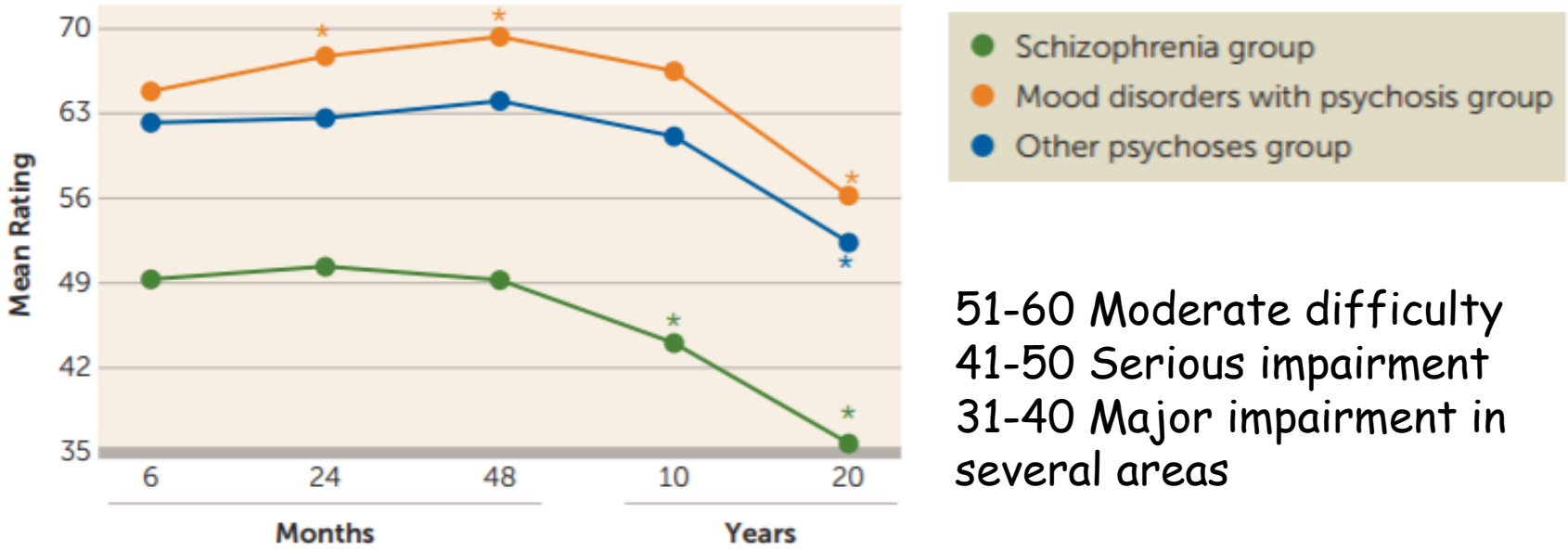
Epidemiology of Schizophrenia – Social and Economic Burden

* Annual costs for patients with schizophrenia are ~$20,000 and are 10-fold higher (~$200,000) for patients with treatment resistant schizophrenia;
  - unemployment (38%)
  - productivity loss due to caregiving (34%)
  - direct health care costs (24%)
* Most patients with schizophrenia need formal or informal daily living supports

Kennedy et al, Int Clinical Psychopharm, 2014
The social and economic burden of treatment-resistant schizophrenia: a systematic literature review

Declining Clinical Course of Schizophrenia

Global Assessment of Functioning (GAF)



51-60 Moderate difficulty
41-50 Serious impairment
31-40 Major impairment in several areas

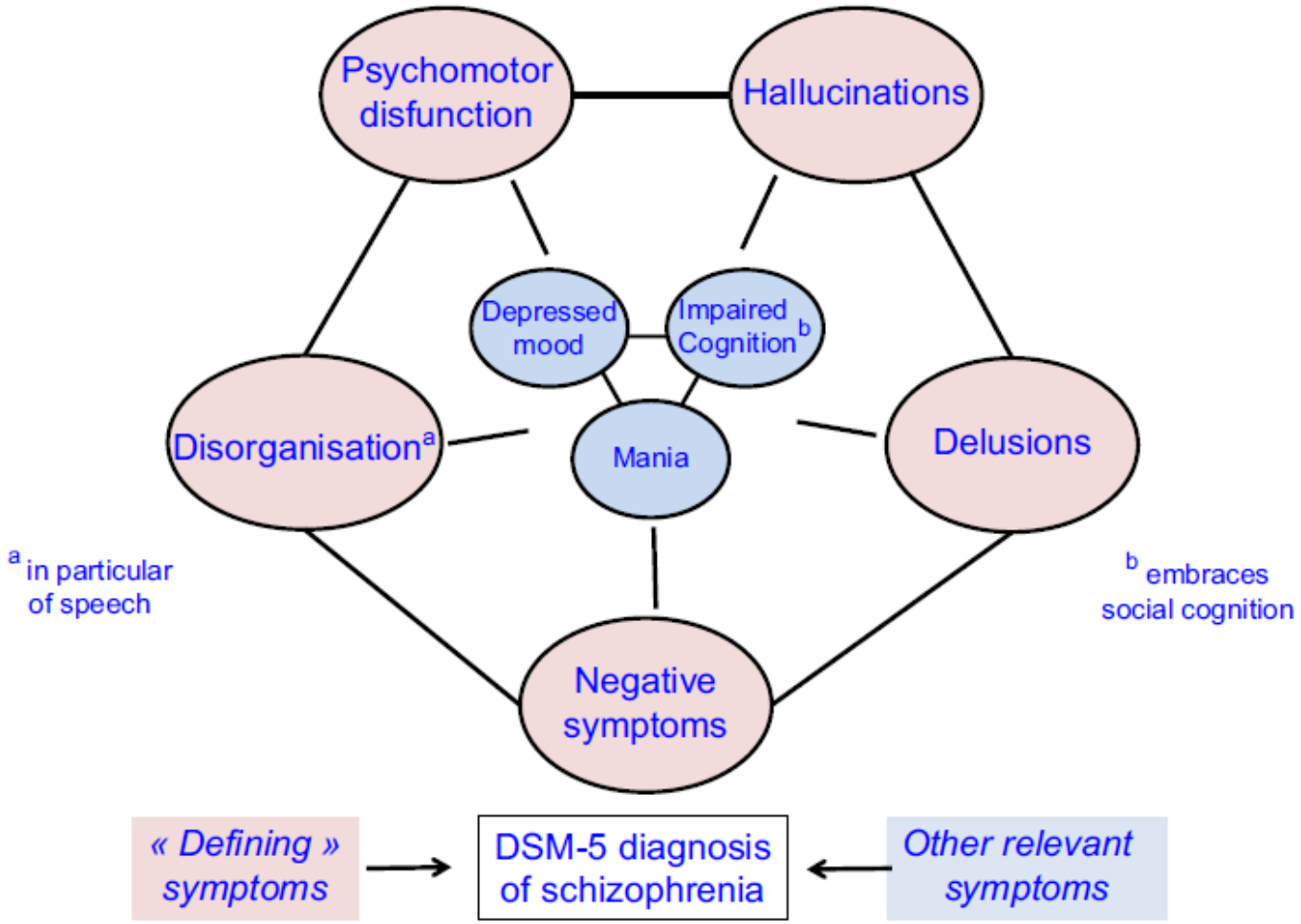
Kotov , Am J Psychiatry. 2017 Aug

Declining Clinical Course of Psychotic Disorders Over the Two Decades Following First Hospitalization: Evidence From the Suffolk County Mental Health Project.

Declining Clinical Course of Schizophrenia

What are the main causes of functional impairment in schizophrenia?

Five Diagnostic Pillars in DSM-5



Millan et al, European Neuropsychopharmacology, 2014

Positive +
Presence of problematic behavior

1. Delusions
(imaginary beliefs)

catatonic behavior

Negative -
Absence of healthy behavior

1. Affective flattening
(no emotion showing)
2. Alog[illegible]ech)
3. Amo[illegible]
(less[illegible]ive,
focu[illegible]
4. Anhedonia
(no feeling of enjoyment)
5. Asociality
(reduced social interaction)

Negative Symptoms of Schizophrenia

Table 1 Characteristics of the five major sub-domains of negative symptom.

Sub-domain (alternative terms)	Core characteristics
Blunted affect (affective flattening, blunted expression)	Reduced intensity and range of emotional expression as manifested *via* vocal and non-verbal modes of communication including intonation (prosody), facial expression, hand-gestures and body movements.
Alogia (poverty of speech)	Decreased quantity of speech, reduced spontaneous speech and loss of conversational fluency.
Amotivation (loss of volition)	Deficits in the initiation and maintenance of goal-directed behaviours like work, study, sport, personal hygiene and daily tasks, especially when requiring an effort (cognitive or physical) and significant organisation. Also deficits in desire to undertake such activities. Related to apathy and lack of energy.
Anhedonia (reduced ability to experience or anticipate pleasure)	The looking forward to a reward, recreational or other pleasurable experience ("wanting") is more markedly and consistently impaired (*anticipatory anhedonia*) than the appreciation ("liking") of the experience itself (*consummatory anhedonia*).
Asociality (social withdrawal)	Diminished interest in, motivation for, and appreciation of social interactions with others, like family and friends. Also, loss of interest in intimate (sexual) relationships independent of any somatic problems. For children, may correspond to loss of interest in playing together.

Millan et al, European Neuropsychopharmacology, 2014

Negative Symptoms of Schizophrenia

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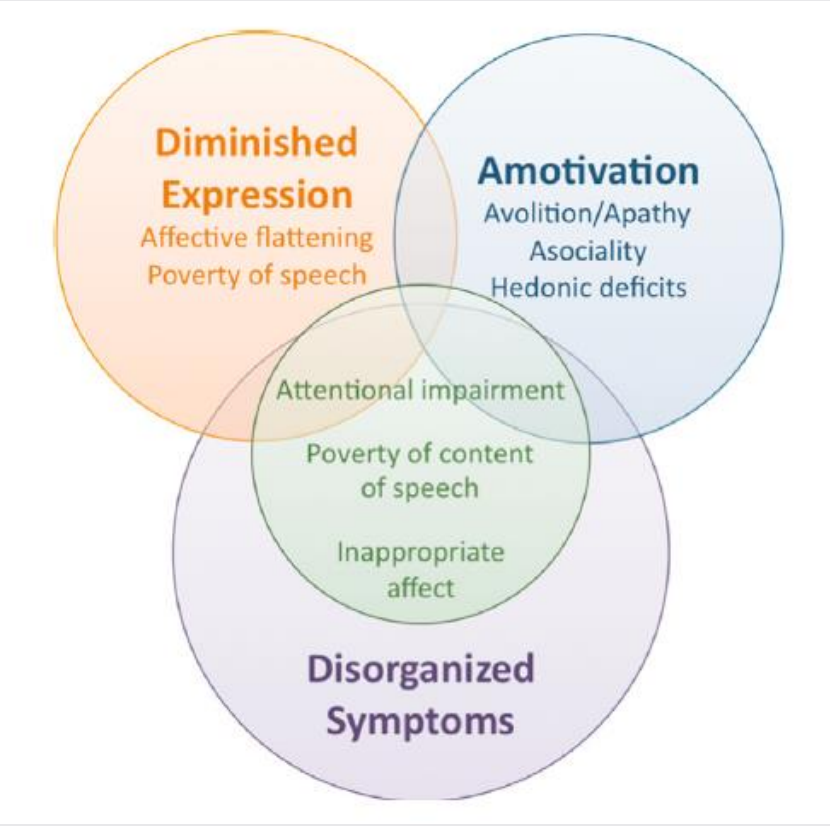

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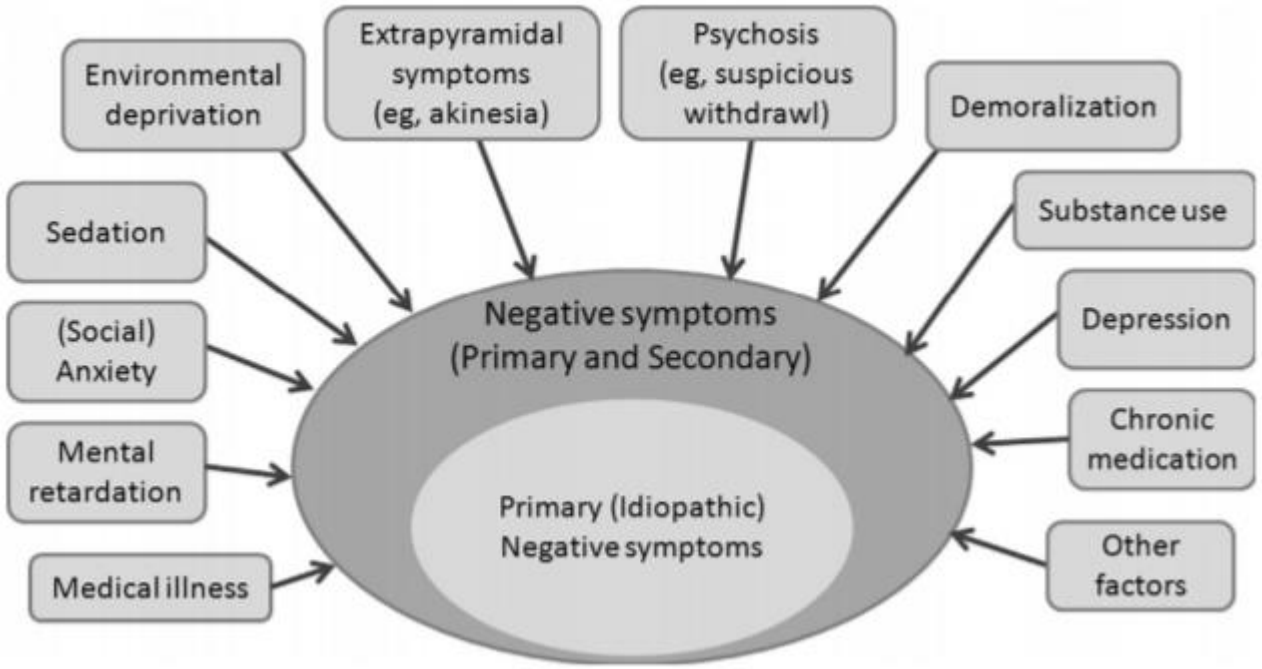
Millan et al, European Neuropsychopharmacology, 2014

Foussias et al, European Neuropsychopharmacology, 2014

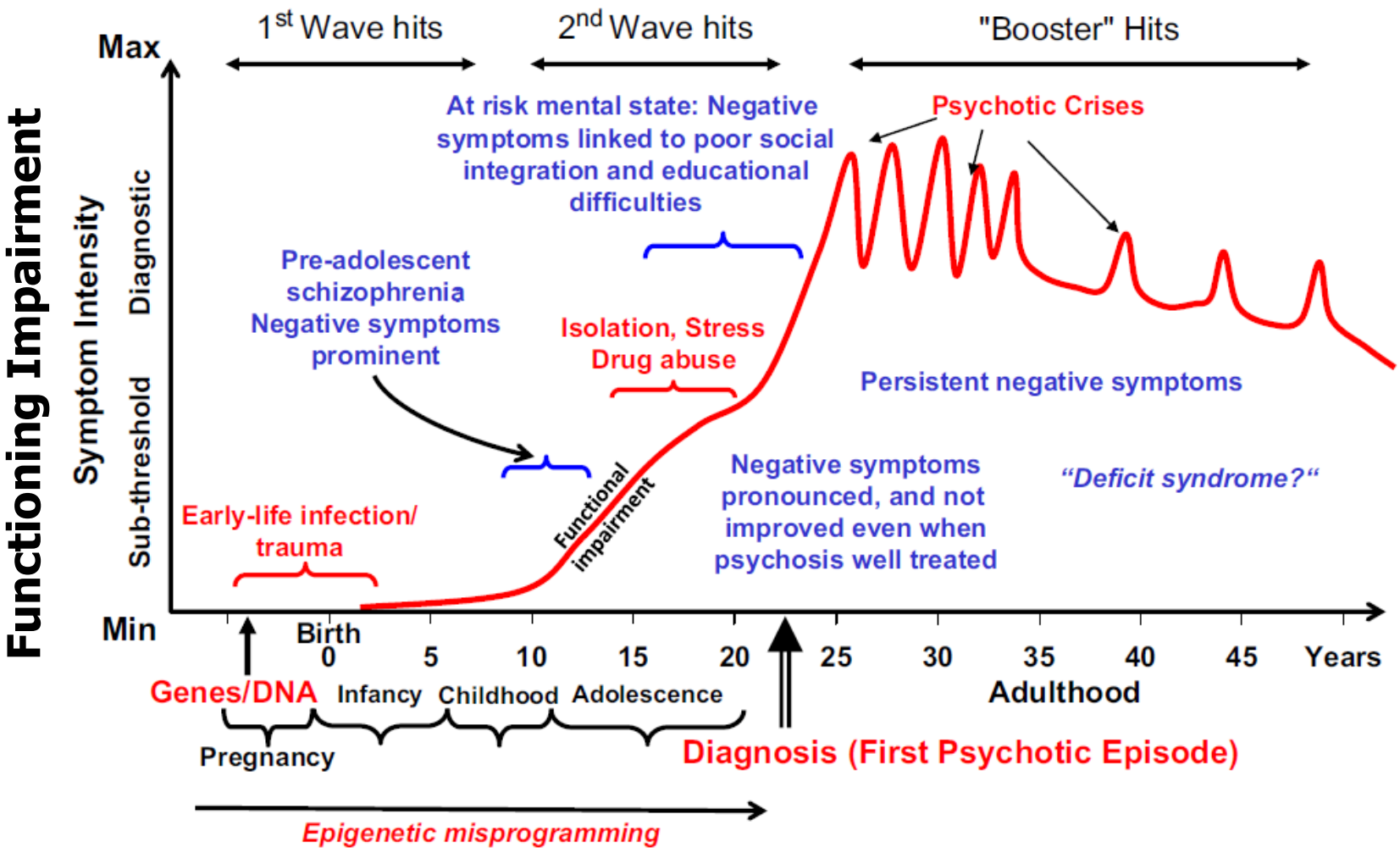
Primary and Secondary Negative Symptoms



Fervaha et al, European Psych, 2014

Impact of primary negative symptoms on functional outcomes in schizophrenia

'Natural' History of Negative Symptoms



Millan et al, European Neuropsychopharmacology, 2014

Prevalence of Negative Symptoms

Summary of each symptom domain course (n = 127).

	Diminished Expression	Diminished Motivation
The symptom occurred[a]	**87 (68.5)**	**121 (95.3)**
The symptom was present continuously[b]	**7 (5.5)**	**20 (15.7)**
When present, mean time to initial remission[c]	**18.8 (28.4)**	**28.4 (40.7)**
Mean proportion of time present (total sample)[d]	**.14 (25)**	**.33 (.35)**

Note: Figures in parentheses indicate percentage for categorical variables and standard deviation for continuous variables.

Norman et al, Schizophrenia Research, 2015

The course of negative **symptoms over the first five years of treatment**: Data from an early intervention program for psychosis

Prevalence of Deficit Syndrome is ~30%

Study	Sample size	Deficit syndrome (%)	95% CI	Weight (%) Fixed	Weight (%) Random
Ahmed et al.[11]	789	19.392	16.688 to 22.326	37.53	8.83
Dantas et al.[26]	85	34.118	24.175 to 45.202	4.09	7.76
Ekinci et al.[27]	121	33.058	24.776 to 42.191	5.80	8.09
Kitis et al.[28]	29	37.931	20.687 to 57.740	1.43	6.20
Kösger et al.[29]	71	42.254	30.612 to 54.562	3.42	7.56
Mete et al.[30]	110	35.455	26.567 to 45.146	5.27	8.01
Nkam et al.[31]	51	21.569	11.289 to 35.321	2.47	7.13
Rethelyi et al.[32]	280	54.643	48.610 to 60.576	13.35	8.57
Santos et al.[33]	302	27.152	22.217 to 32.542	14.39	8.60
Scala et al.[34]	40	27.500	14.601 to 43.888	1.95	6.75
Szendi et al.[35]	50	28.000	16.231 to 42.491	2.42	7.10
Vogel et al.[36]	67	22.388	13.106 to 34.223	3.23	7.50
Yu et al.[37]	97	41.237	31.335 to 51.689	4.66	7.89
Total (fixed effects)	2,092	29.589	27.645 to 31.590	100.00	100.00
Total (random effects)	2,092	**32.646**	**25.394 to 40.341**	100.00	100.00

Test for heterogeneity [I^2=91.31% (95% CI=86.97 to 94.20) p<0.0001]

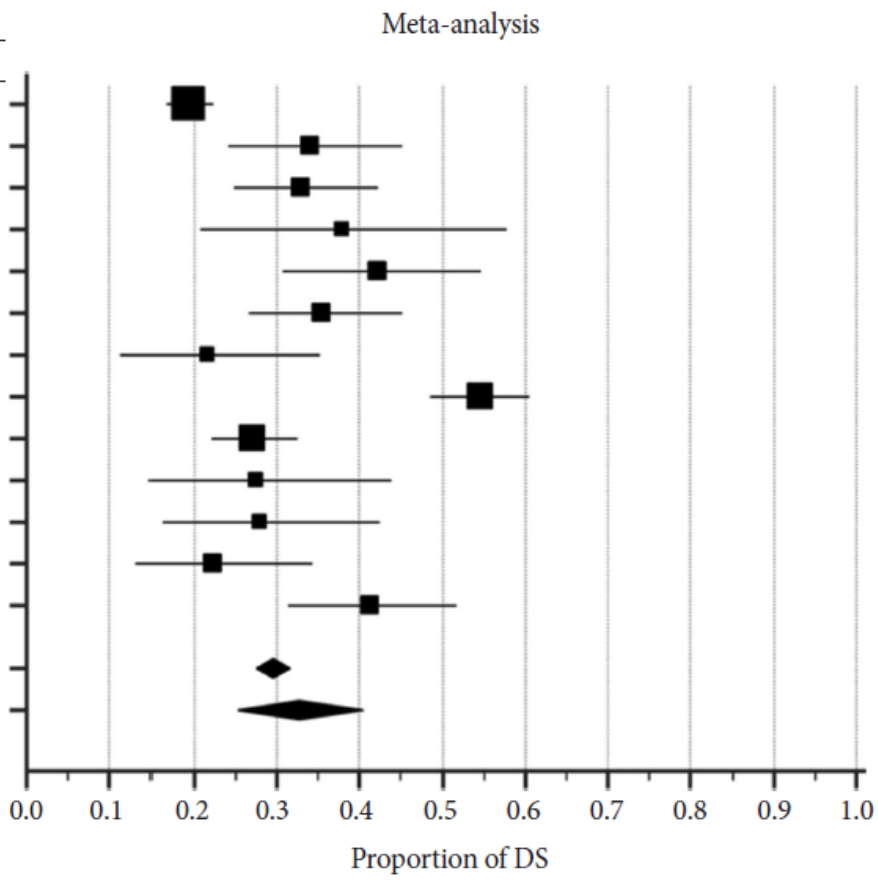
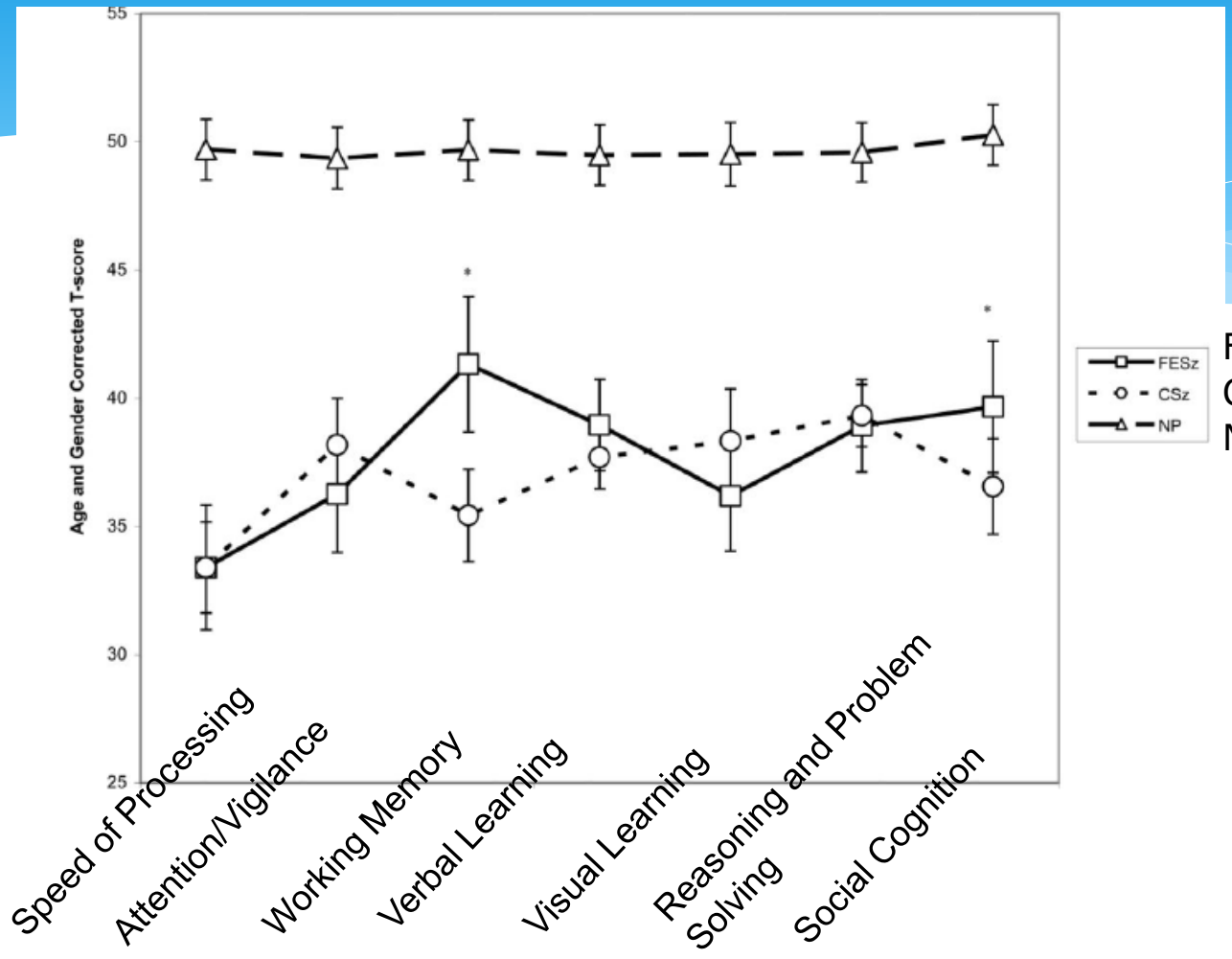


Figure 2. Pooled prevalence of the deficit syndrome in schizophrenia by random effects meta-analysis. CI: confidence interval, DS: deficit syndrome.

Lopez-Dias et al, Psychiatry Investig, 2018

Cognitive Symptoms of Schizophrenia



First episode
Chronic SCZ
Normal

McCleery et al, Schizophrenia Research, 2014

Functioning in First-Episode Schizophrenia: MATRICS Consensus Cognitive Battery (MCCB) Profile of Impairment

Cognitive Symptoms of Schizophrenia DSM 5

* Cognitive deficits in schizophrenia are common and are strongly linked to vocational and functional impairments.
* These deficits can include decrements in declarative memory, working memory, language function, and other executive functions, as well as slower processing speed.
* Abnormalities in sensory processing and inhibitory capacity, as well as reductions in attention, are also found.
* Some individuals with schizophrenia show social cognition deficits, including deficits in the ability to infer the intentions of other people (theory of mind), and may attend to and then interpret irrelevant events or stimuli as meaningful, perhaps leading to the generation of explanatory delusions.

DSM-5

Cognitive Symptoms of Schizophrenia ICD-11

Schizophrenia is characterized by disturbances in multiple mental modalities, including

* thinking (e.g., delusions, disorganization in the form of thought),
* perception (e.g., hallucinations),
* self-experience (e.g., the experience that one's feelings, impulses, thoughts, or behaviour are under the control of an external force),
* cognition (e.g., impaired attention, verbal memory, and social cognition),
* volition (e.g., loss of motivation)
* and affect (e.g., blunted emotional expression).

Psychomotor disturbances, including catatonia, may be present.

- WHO site, ICD-11 beta site, https://icd.who.int/dev11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1683919430
- Gaebel et al, Die Psychiatrie, 2015, Psychotic Disorders in ICD-11

Correlation Between Cognitive and Negative Symptoms

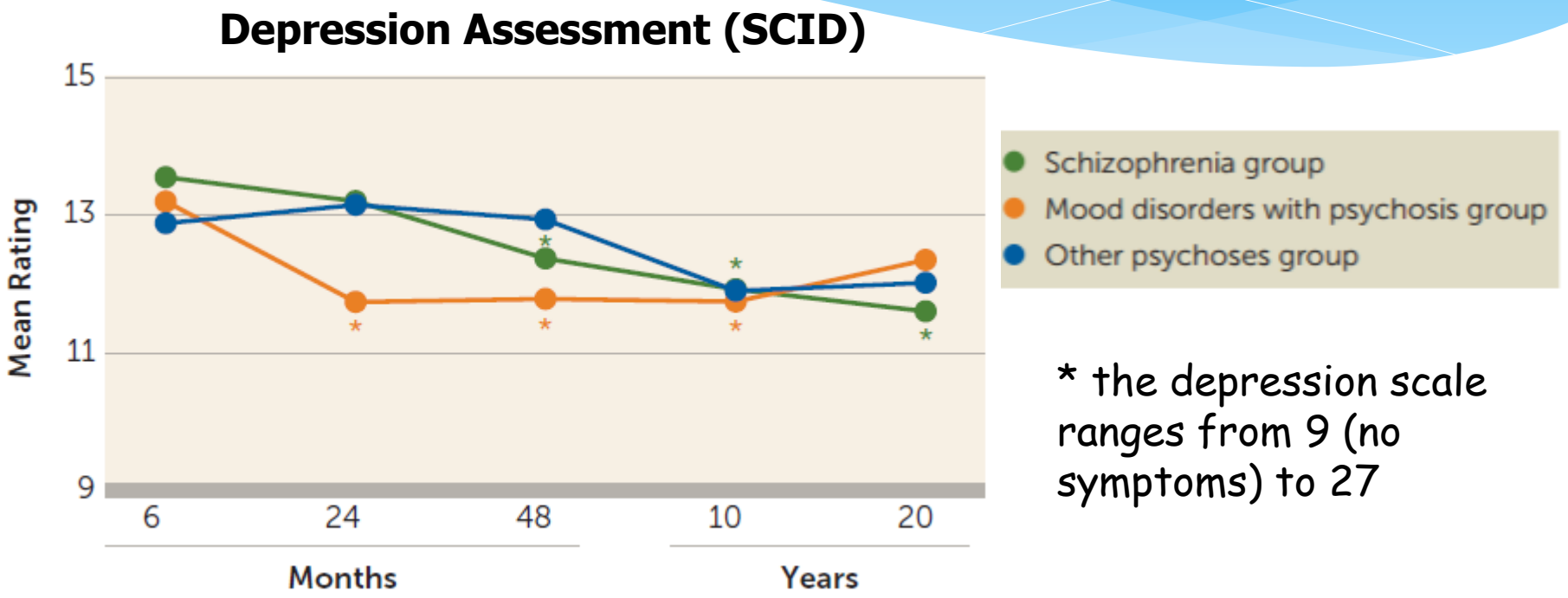
Table 8 Correlation Matrix of CATIE Neurocognitive Domains and Composite Score with Clinical and Demographic Factors

Domain	Theoretical composite ($N = 1332$)	Verbal memory ($N = 1332$)	Vigilance ($N = 1212$)	Processing speed ($N = 1332$)	Reasoning and problem solving ($N = 1331$)	Working memory ($N = 1331$)
Total PANSS	−0.166	−0.162	−0.108	−0.126	−0.074	−0.159
PANSS positive	−0.031	−0.054	0.005	0.025	−0.007	−0.073
PANSS negative	−0.271	−0.235	−0.196	−0.268	−0.133	−0.209
PANSS general	−0.108	−0.111	−0.073	−0.069	−0.043	−0.112

The *N* for the correlations varied based upon the neurocognitive measures. The symptom and demographic measures had very few missing cases, and are thus not reported for each correlation. All correlations greater than 0.10 are significant at $p < 0.0001$.
Duration of illness defined as number of years since first prescribed antipsychotic medication; WRAT-3 = wide range achievement test, third edition; CGI = clinical global impression; PANSS = positive and negative syndrome scale.

Kefee et al, Neuropsychopharmacol, 2006
Baseline Neurocognitive Deficits in the CATIE Schizophrenia Trial

Depression Course of Schizophrenia



* the depression scale ranges from 9 (no symptoms) to 27

Kotov , Am J Psychiatry. 2017 Aug 4

Declining Clinical Course of Psychotic Disorders Over the Two Decades Following First Hospitalization: Evidence From the Suffolk County Mental Health Project.

Contributions of Negative Symptoms to Explaining the Functioning Variance

TABLE 6. Relationship Between Negative Symptom Severity at Intake and the Outcome Measures for 99 Subjects With First-Episode Schizophrenia Followed on Average for 7 Years

Outcome Variable	Univariate F (df=1, 97)	p	R^2
Global psychosocial function	11.95	0.0008	0.11
Relationship impairment	6.73	0.01	0.065
Recreation impairment	5.69	0.02	0.055
Work impairment	6.12	0.01	0.059

Milev , Am J Psychiatry. 2005

Predictive Values of Neurocognition and Negative Symptoms on Functional Outcome in Schizophrenia: **A Longitudinal First-Episode Study With 7-Year Follow-Up.**

Contributions of Cognitive Domain to Explaining the Functioning Variance

TABLE 5. Relationships Between Cognitive Domains and Outcome Measures in 99 Subjects With First-Episode Schizophrenia Followed on Average for 7 Years

	Verbal Memory			Processing Speed and Attention		
Outcome Variable	Univariate F (df=1, 97)	p	R^2	Univariate F (df=1, 97)	p	R^2
Global psychosocial function	11.29	0.001	0.104	7.57	0.007	0.072
Relationship impairment	6.51	0.01	0.063	1.00	0.30	0.010
Recreation impairment	10.48	0.002	0.098	4.44	0.04	0.044
Work impairment	3.64	0.06	0.036	7.19	0.009	0.069

Milev , Am J Psychiatry. 2005

Predictive Values of Neurocognition and Negative Symptoms on Functional Outcome in Schizophrenia: **A Longitudinal First-Episode Study With 7-Year Follow-Up.**

Contributions of Cognitive and Negative Symptoms to Explaining the GAF

TABLE S3. Changes in symptoms explain contemporaneous changes in GAF[a]

	Schizophrenia		Mood Disorders With Psychosis		Other Psychoses	
	β	p	β	p	β	p
Inexpressivity	**–0.11**	0.0005	**–0.11**	0.0005	0.00	0.9965
Apathy-asociality	**–0.45**	<0.0001	**–0.49**	<0.0001	**–0.53**	<0.0001
Reality distortion	**–0.25**	<0.0001	**–0.05**	0.0414	**–0.29**	<0.0001
Disorganization	**–0.18**	<0.0001	**–0.08**	0.0195	–0.07	0.1521
Depression	**0.07**	0.0167	–0.02	0.5919	–0.02	0.6760
Excitement	**0.09**	0.0081	**–0.06**	0.0441	–0.03	0.5355

[a] To evaluate contributions of individual symptoms to global outcome, we constructed a multilevel model (with random intercept and slopes) for GAF regressed on the six symptom dimensions treated as time-varying predictors. The predictors entered the model simultaneously. All predictors were converted to z-scores prior to analysis to ensure comparability of effect sizes. Sample size is N=175 for schizophrenia, 137 for mood disorders with psychosis, and 61 for other psychoses.
p<0.05 effects are bolded.

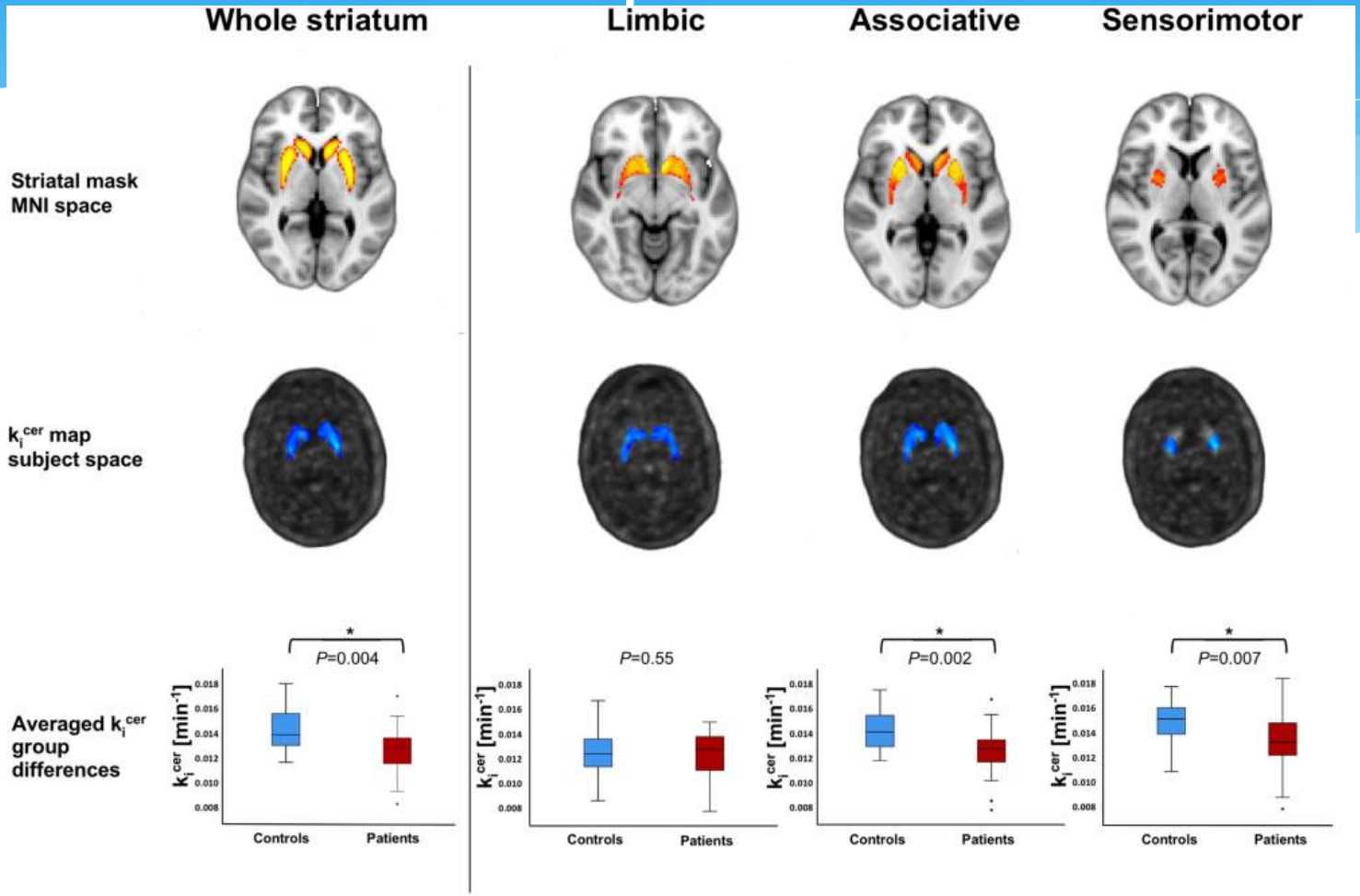
Kotov , Am J Psychiatry. 2017 Aug 4

Declining Clinical Course of Psychotic Disorders Over the Two Decades Following First Hospitalization: Evidence From the Suffolk County Mental Health Project.

Brain Circuits Correlates of Schizophrenia

* The most consistent observation in schizophrenia is the **normal macroscopic appearance** of the postmortem brain
* Negative symptoms:
  ventral prefrontal cortex and ventral striatum
* Positive symptoms:
  medial prefrontal cortex, amygdala, and hippocampus / parahippocampal region
* Disorganization symptoms:
  dorsolateral prefrontal cortex

Reduced Striatal Dopamine Synthesis in Schizophrenia

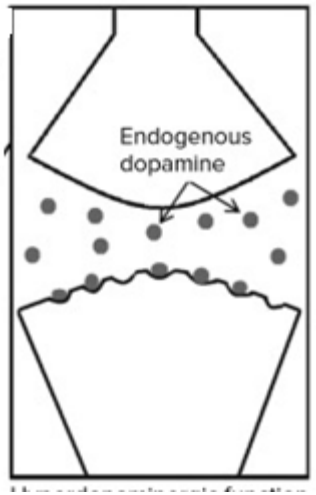


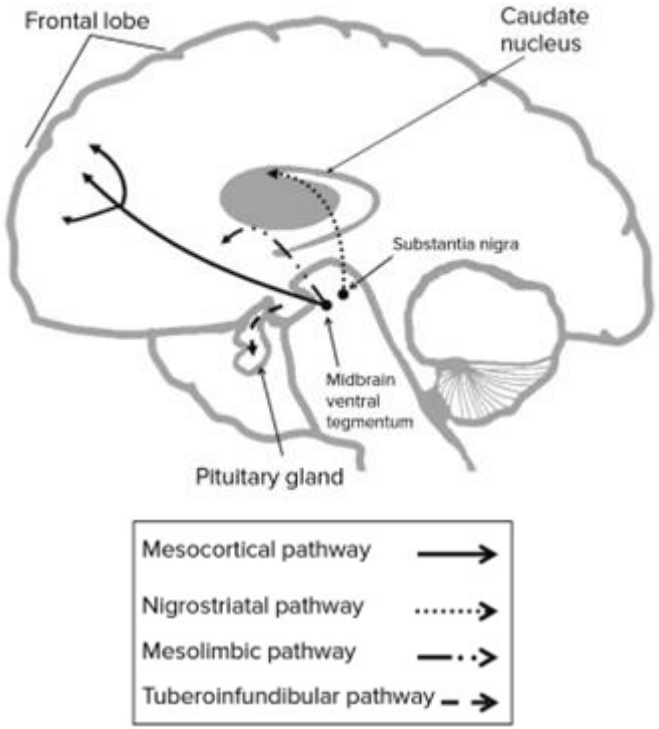
Avram et al, Brain, 2019

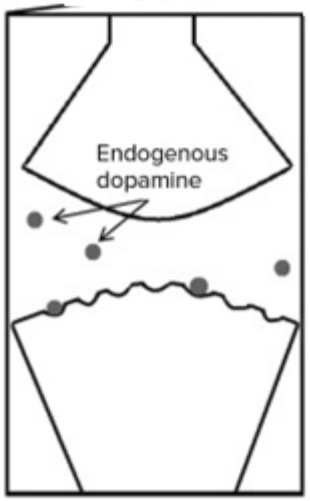
Reduced striatal dopamine synthesis capacity in patients with schizophrenia during remission of positive symptoms

Positive +
Presence of problematic behavior

Negative -
Absence of healthy behavior







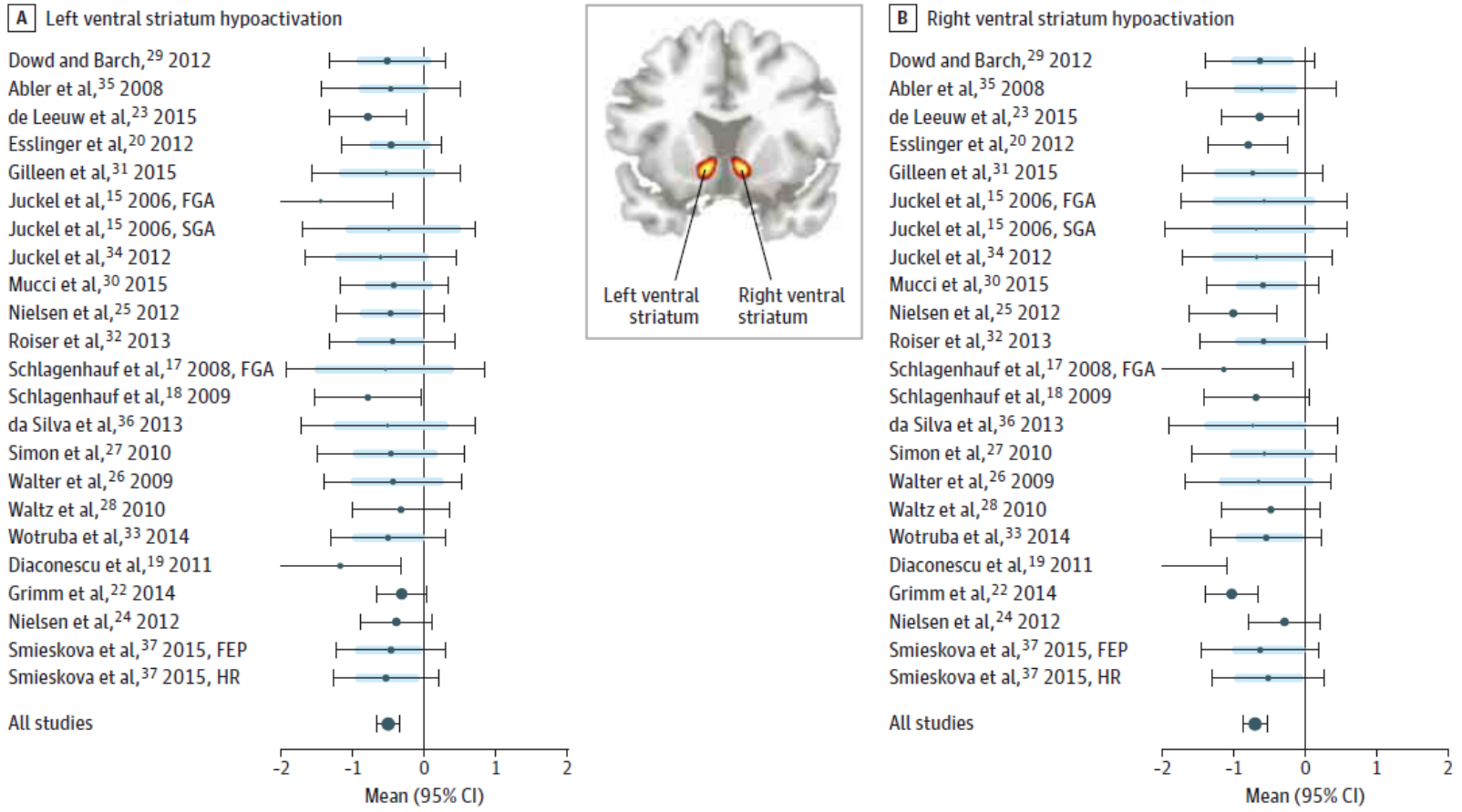
Hyperdopaminergic function in the **caudate nucleus** is the cause of positive symptoms of schizophrenia

Hypodopaminergic function in the **frontal cortex** is the cause of negative symptoms and cognitive impairment in schizophrenia

Adapted from Patel et al, P&T, 2014.

fMRI Meta-analysis: Reward in Schizophrenia

Figure. Forest Plots of the Ventral Striatum Response to Reward Anticipation in Psychosis

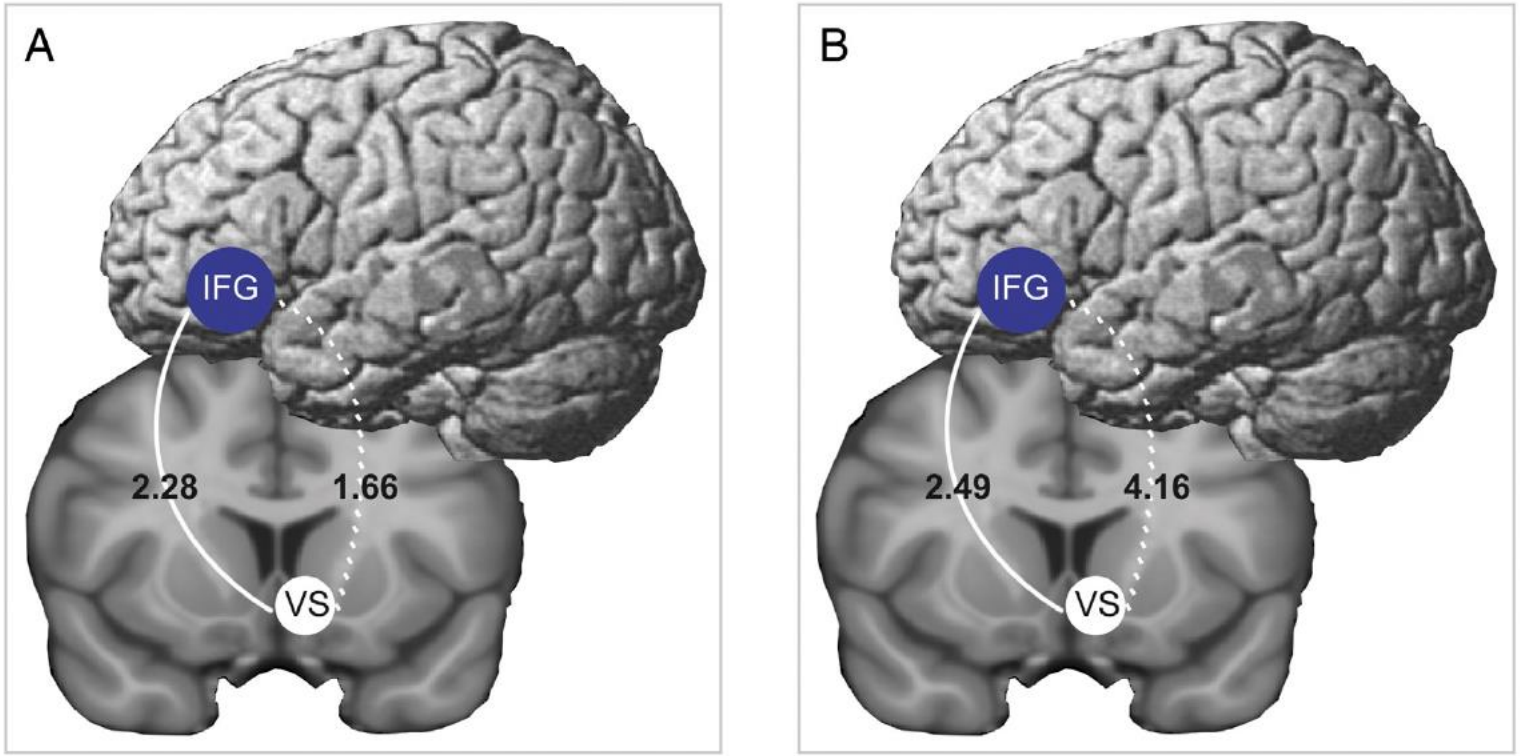


Radua et al, JAMA Psychiatry, 2015
Ventral Striatal Activation During Reward Processing in Psychosis

Reward in SCZ – Striato-Cortical Connectivity

(A) healthy controls

(B) patients with schizophrenia.



mean connectivity strength between the right VS and left IFG in the motivation (solid line) and neutral (dashed line)

Reckless et al, NeuroImage: Clinical 8, 2015
Negative symptoms in SCZ, striato-cortical connectivity, reward task

Cognitive Functions in Schizophrenia are Correlated with Anti-NMDA Receptor Ab levels

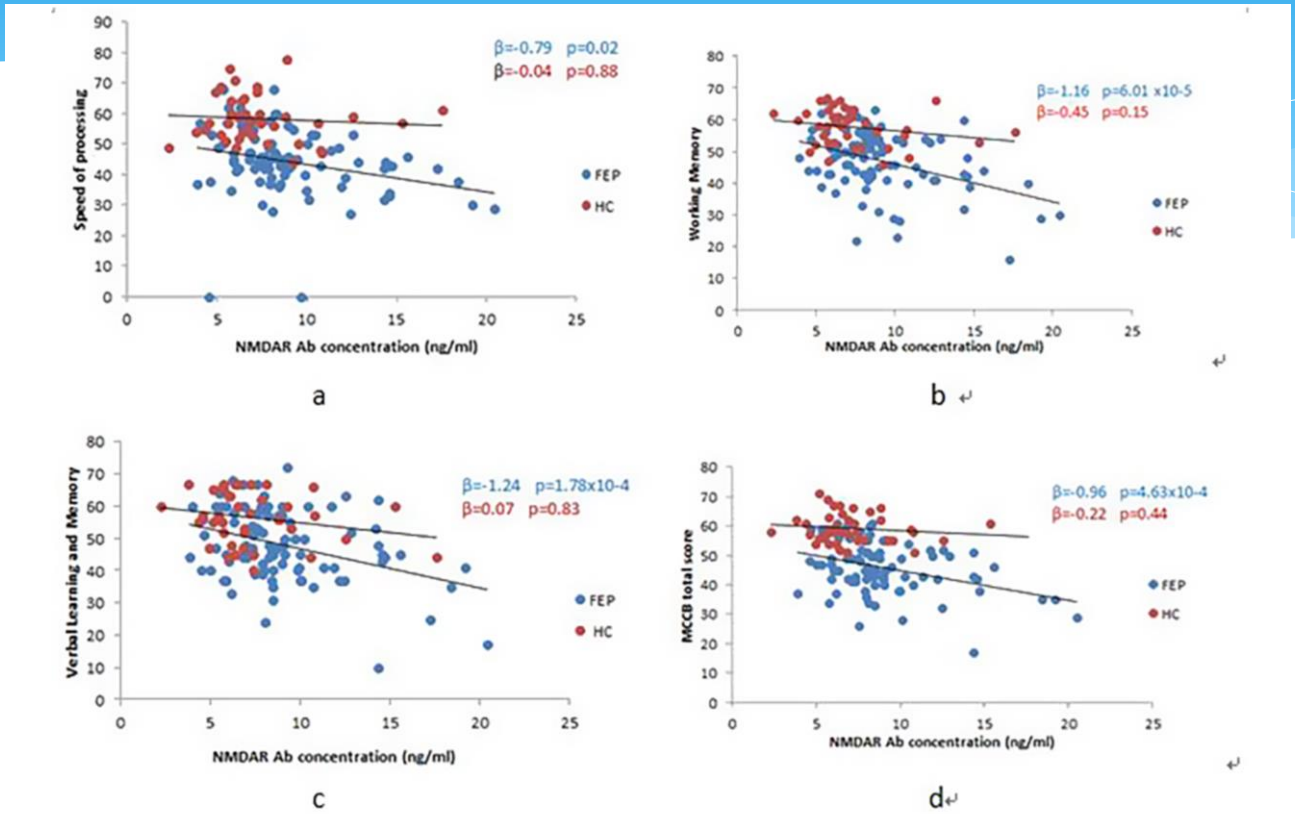


Fig. 2. Correlation between Anti-NMDAR Ab concentration and cognitive performance. a: Correlations between NMDAR Ab level and speed of processing. b: Correlations between NMDAR Ab level and working memory. c: Correlations between NMDAR Ab level and verbal learning and memory. d: Correlations between NMDAR Ab level and MCCB total score. The FEP was represented by blue dots while the HC was represented by res dots. The associations were significant at $P < 0.05$ after adjusting for age, sex, education level.

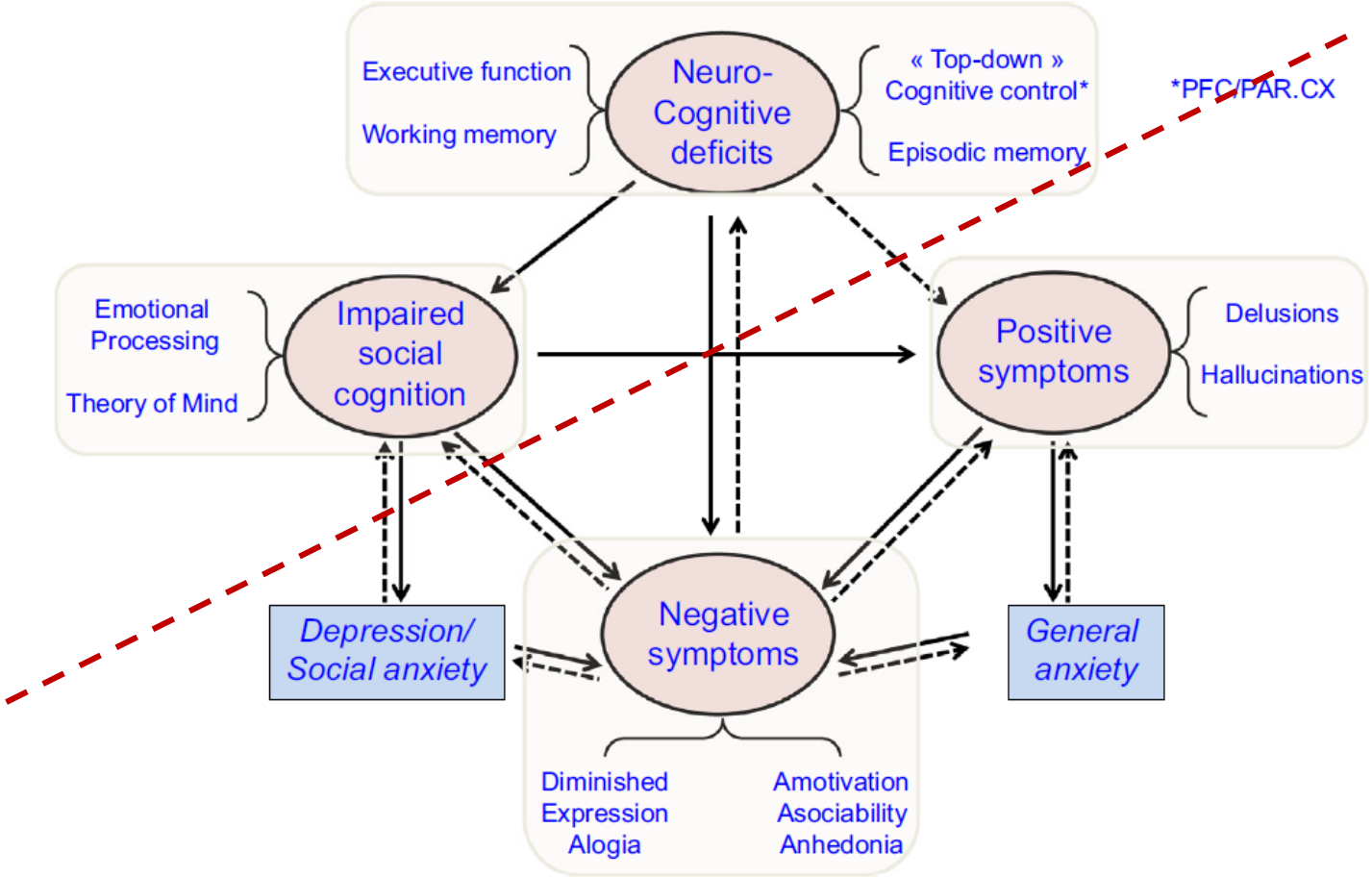
Tong et al, Brain Behav Immun. 2019

Elevated serum anti-NMDA receptor antibody levels in first-episode patients with schizophrenia.

Negative Symptoms and Cognitive Deficits are Core Features of Schizophrenia

* Presence before the onset of psychotic symptoms
* Presence in schizophrenia patients who are in a psychosis-remitted state
* Mainly contribute to functional impairment
* Present in attenuated form in unaffected first-degree relatives of patients
* Correlated with specific brain functions and pathophysiology processes in schizophrenia

Re-defining the Core Facets of Schizophrenia



* Millan et al, European Neuropsychopharmacology, 2014

The Role of Neuropsychiatry in Schizophrenia

Classification, measurement and treatment of the negative and cognitive symptoms are essential to the care of schizophrenia patients

Evaluations of Negative Symptoms

- Traditional scales for negative symptoms:
  - Assessment of Negative Symptoms (SANS)
  - Positive and Negative Symptoms Scale (PANSS)
  - Negative Symptom Assessment Scale (NSA)
- Newer scales negative symptoms:
  - Brief Negative Symptom Scale (BNSS)
  - Clinical Assessment Interview for Negative Symptoms (CAINS)

Classification of Schizophrenia by Negative Symptoms ?

"Class analysis supported a three-class model of schizophrenia that included deficit, persistent, and transient negative symptom subgroups…

Findings suggest that schizophrenia encapsulates qualitatively distinct negative symptom subgroups that differ in their demographic, symptomatic, neuropsychological, and functional profiles…"

- Ahmed et al, J Psych Reserach, 2018, Schizophrenia heterogeneity revisited: Clinical, cognitive, and psychosocial correlates of statistically-derived negative symptoms subgroups

MATRICS Consensus Cognitive Battery tests

Domain	Test
Speed of Processing	BACS Symbol Coding Test (BACS SC)
	Category Fluency Test, Animal Naming (Fluency)
	Trail Making Test, Part A (TMTA)
Attention/Vigilance	Continuous Performance Test, Identical Pairs (CPT-IP)
Working Memory	WMS 3rd ed., Spatial Span (WMS-III SS)
	Letter-Number Span Test (LNS)
Verbal Learning	Hopkins Verbal Learning Test – Revised (HVLT-R)
Visual Learning	Brief Visual Memory Test – Revised (BVMT-R)
Reasoning & Problem Solving	NAB Mazes Subtest (NAB Mazes)
Social Cognition	MSCEIT Managing Emotions Branch (MSCEIT-ME)

Differential Diagnosis of Schizophrenia

Late Onset Schizophrenia

Implications for clinical practice.

Implications for differential diagnosis
• Intellectual deterioration is present in LOS and VLOSLP, whereas levels of premorbid intelligence are average
• There is diffuse but less severe impairment noticeable in several cognitive domains in LOS and VLOSP compared with normally aging individuals and AOS
• Consolidation is more preserved than learning in LOS and VLOSP as opposed to AD
• Language is equally impaired in LOS/VLOSP and in AD
• Executive dysfunction in LOS compared with FTD is characterized by deficits in working memory, as opposed to verbal fluency, abstraction and cognitive flexibility

Van Assche et al, Neuroscience and Biobehavioral Reviews, 2017
The neuropsychology and neurobiology of late-onset schizophrenia (LOS) and very-late-onset schizophrenia-like psychosis (VLOSLP): A critical review

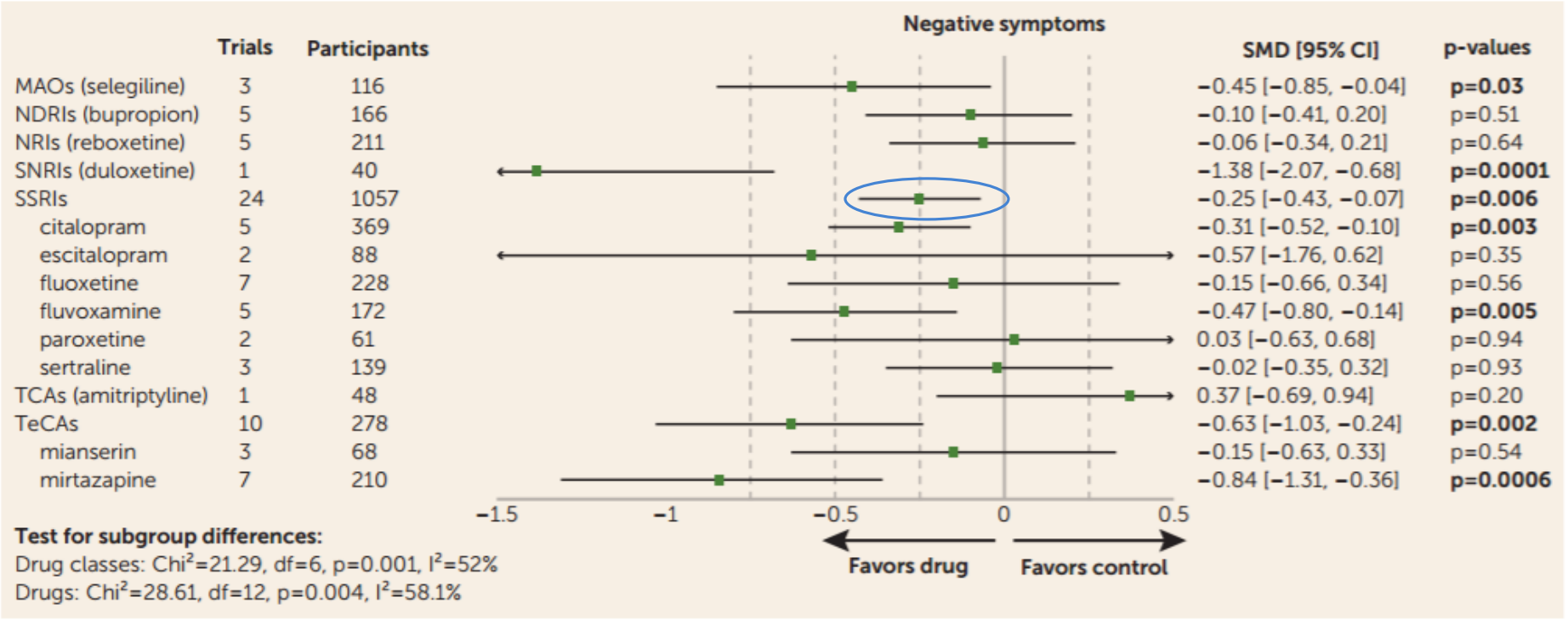
Treatments in Schizophrenia

* Positive symptoms or psychosis are controlled in most patients by antipsychotic drugs (dopamine D2 receptor blockers)
* **Although negative and cognitive symptoms determine the prognosis and functioning of schizophrenic patients, no effective treatment is available**

* Typical and atypical antipsychotic drugs, antidepressants
* Glutamatergic neuromodulators, anticholinergics,, anticonvulsants, psychostimulants, modafinil, 5-HT3 receptor antagonists
* Psychological therapies / cognitive remediation
* Brain Stimulation

Tsapakis et al, Pharmacol Ther, 2015
Clinical management of negative symptoms of schizophrenia: An update.

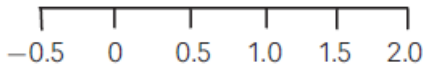
Antidepressants for Negative Symptoms



Helfer et al, Am J Psychiatry, 2016
Efficacy and Safety of Antidepressants Added to Antipsychotics for Schizophrenia: A Systematic Review and Meta-Analysis

Cholinergic and Glutamatergic Treatment for Negative Symptoms

Study	Adjunctive medication	Pharmacological targets	Effect size	(95% CI)	*n*	%
Dyer *et al* (2008)[17]	Galantamine	AChEI	−0.06	(−0.94 to 0.82)	20	4.5
Schubert *et al* (2006)[15]	Galantamine	AChEI	0.21	(−0.79 to 1.2)	16	3.6
Akhondzadeh *et al* (2008)[44]	Donepezil	AChEI	1.37	(0.56 to 2.11)	30	6.7
Fagerlund *et al* (2007)[9]	Donepezil	AChEI	0.62	(−0.71 to 1.84)	11	2.5
Friedman *et al* (2002)[10]	Donepezil	AChEI	0.34	(−0.52 to 1.18)	26	5.8
Buchanan *et al* (2007)[21]	D-cycloerine	Glutamate agonist	0.75	(0.34 to 1.15)	104	23.4
Tsai *et al* (1998)[20]	D-serine	Glutamate agonist	0.85	(0.06 to 1.59)	29	6.5
Goff *et al* (1999)[49]	D-cycloerine	Glutamate agonist	0.78	(0.16 to 1.37)	46	10.3
Goff *et al* (2001)[51]	CX516	Glutamate agonist	1.49	(0.36 to 2.48)	18	4.0
Tsai *et al* (1999)[22]	D-serine	Glutamate agonist	0.96	(−0.01 to 1.85)	20	4.5
Goff *et al* (2008)[50]	D-cycloerine	Glutamate agonist	−0.07	(−0.48 to 0.34)	92	20.7
Goff *et al* (2008)[52]	CX516	Glutamate agonist	0.68	(−0.05 to 1.37)	33	7.4



Choi et al, BJPsych, 2013
Adjunctive pharmacotherapy for cognitive deficits in schizophrenia: meta-analytical investigation of efficacy

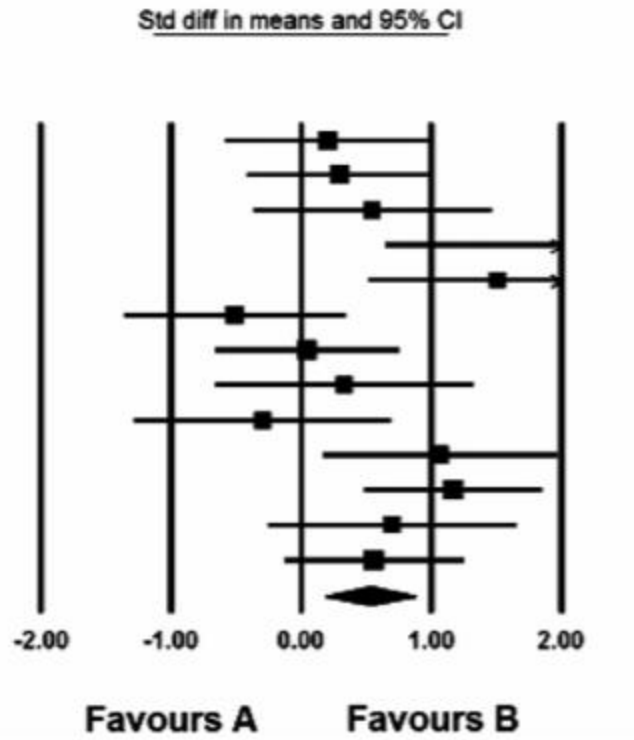
Targets and compounds currently in clinical development

Compound	Mechanism of action	Example	Target symptoms	Development stage/status
Glycine site agonist	Stimulates NMDAR at glycine; D-serine binding site	Glycine; D-serine	Persistent negative symptoms; neurodegeneration in early psychosis	Phase II/ ongoing studies
Glycine reuptake inhibitor	Increases synaptic glycine levels by blocking Glycine Type 1 Transporters	Bitopertin	Suboptimally controlled symptoms; neurodegeneration in early psychosis	Phase III; No significant effects on negative symptoms; ongoing studies for suboptimal response
Metabotropic type 2; 3 receptor agonist	Inhibits presynaptic glutamate release by stimulating presynaptic mGluR	Pomeglumetad	Early psychosis; neurodegeneration	Phase II/III; No significant effects on total symptoms; potential effects in early psychosis
Metabotropic type 5 receptor agonist	Potentiates postsynaptic NMDAR function	VU0092273 [95]	Negative symptoms; cognition	Preclinical
Alpha7 nicotinic agonist	Stimulates presynaptic glutamate release	EV-6124	Negative symptoms; cognition	Phase III for Cognitive Impairment Associated with schizophrenia

Javitt et al, Curr Treat Options Psychiatry, 2015
Current and emergent treatments for symptoms and neurocognitive impairment in schizophrenia

rTMS for Negative Symptoms

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Barr et al. 2012	0.207	0.401	0.161	-0.580	0.994	0.516	0.606
Cordes et al. 2010	0.299	0.358	0.128	-0.403	1.001	0.834	0.404
Fitzgerald et al. 2008	0.551	0.465	0.216	-0.360	1.462	1.186	0.236
Goyal et al. 2007	2.227	0.805	0.648	0.649	3.805	2.767	0.006
Hajak et al. 2004	1.518	0.508	0.258	0.523	2.513	2.991	0.003
Holi et al. 2004	-0.504	0.433	0.188	-1.353	0.345	-1.164	0.245
Klein et al. 1999	0.050	0.359	0.129	-0.655	0.755	0.139	0.889
Mogg et al. 2007	0.335	0.504	0.254	-0.651	1.322	0.666	0.505
Novak et al. 2006	-0.291	0.503	0.253	-1.276	0.694	-0.579	0.563
Prikryl et al. 2007	1.073	0.456	0.208	0.179	1.967	2.353	0.019
Prikryl et al. 2013	1.175	0.346	0.120	0.497	1.852	3.397	0.001
Saba et al. 2006	0.705	0.486	0.236	-0.247	1.657	1.451	0.147
Schneider et al. 2008	0.562	0.350	0.122	-0.123	1.247	1.607	0.108
	0.532	0.174	0.030	0.191	0.874	3.057	0.002



- Shi et al, Psychiatry Res., 2014
  Revisiting the therapeutic effect of rTMS on negative symptoms in schizophrenia: A meta-analysis

- Dougall N, Maayan N, Soares-Weiser K, McDermott LM, McIntosh A Cochrane review, 2015. TMS for schizophrenia (Review)

Balance Antipsychotics btw Positive and Secondary Negative Symptoms

Outcome Measure and Assessment Point	Schizophrenia	
	N	%
Use of antipsychotics		
Baseline	152	86.9
6 months	148	84.6
24 months	136	79.5
48 months	122	70.1
10 years	142	87.1
20 years	117	81.8
Illness pattern over 20 years		
Single episode	1	0.6
Multiple episodes	43	25.3
Continuous illness	126	74.1

Kotov et al, Am J Psychiatry. 2017 Aug 4

Declining Clinical Course of Psychotic Disorders Over the Two Decades Following First Hospitalization: Evidence From the Suffolk County Mental Health Project.

Balance Antipsychotics btw Positive and Secondary Negative Symptoms

SUPPLEMENTARY TABLE S5. Adjunctive Aripiprazole for Schizophrenia-Spectrum Disorders: Secondary Outcomes

Secondary outcomes	N[a] Patients (RCTs)	SMD or WMD[b] (CI)	I^2 (%)	p[c]
PANSS/BPRS Positive symptom sub-score	2223 (29)	-0.01 (-0.26, 0.25)	88	0.95
PANSS/BPRS Negative symptom sub-score	2294 (30)	-0.61 (-0.91, -0.31)	91	**<0.0001**
PANSS General symptom sub-score	1138 (13)	-4.02 (-7.23,-0.81)	99	**0.01**

BPRS, Brief Psychiatric Rating Scale; CI, 95% confidence interval; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein; PANSS, Positive and Negative Symptoms Scale; RCT, randomized clinical trial; SMD, standardized mean difference; TESS: Treatment Emergent Symptom Scale; WMD, weighted mean difference.

[a]Patients refers to the total number of individuals included in the statistical analysis. In parentheses, the number of RCTs from which these patients come.

[b]WMDs were calculated in these analyses.

[c]P-values <0.05 are bolded.

Zheng et al, J Clin Psychopharmacol. 2016

Efficacy and Safety of Adjunctive Aripiprazole in Schizophrenia: Meta-Analysis of Randomized Controlled Trials..

Psychotherapy, CBT, Cognitive Remediation for Negative and Cognitive Symptoms

* participants in the CBT+CR condition worked significantly more hours and had a more positive trajectory of improving global work performance and work quality across the study compared with the CBT alone and vocational support condition.
* Compared to the other conditions, CBT+CR also had a significant increase in overall neurocognition that continued to the 12 month follow-up, particularly in the domains of verbal learning and social cognition.

Kukla et al, Schizophrenia Research, 2018 Feb 5
A randomized controlled trial examining a cognitive behavioral therapy intervention enhanced with cognitive remediation to improve work and neurocognition outcomes among persons with schizophrenia spectrum disorders.

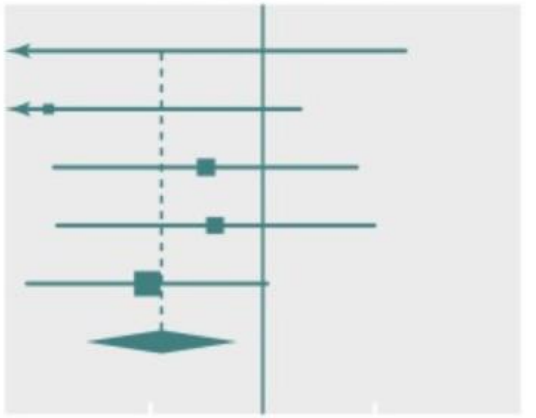
Early Interventions to Prevent Psychosis

Transition to Psychosis for Participants Receiving Psychotherapy

Study	Events/total CBT	Events/total Supportive counselling	Risk ratio (95% CI), M-H, random	Weight (%)	Risk ratio (95% CI), M-H, random
Addington 2011a	0/16	3/15		2.6	0.13 (0.01 to 2.40)
Morrison 2004	2/35	5/23		9.1	0.26 (0.06 to 1.24)
Morrison 2011	7/144	10/144		24.9	0.70 (0.27 to 1.79)
Phillips 2009	7/44	6/28		22.7	0.74 (0.28 to 1.98)
Van der Gaag 2012	9/94	20/102		40.6	0.49 (0.23 to 1.02)
Total (95% CI)	25/333	44/312		100.0	0.54 (0.34 to 0.86)

Test for heterogeneity: $\tau^2=0.00$, $\chi^2=2.51$, df=4, P=0.64, $I^2=0\%$

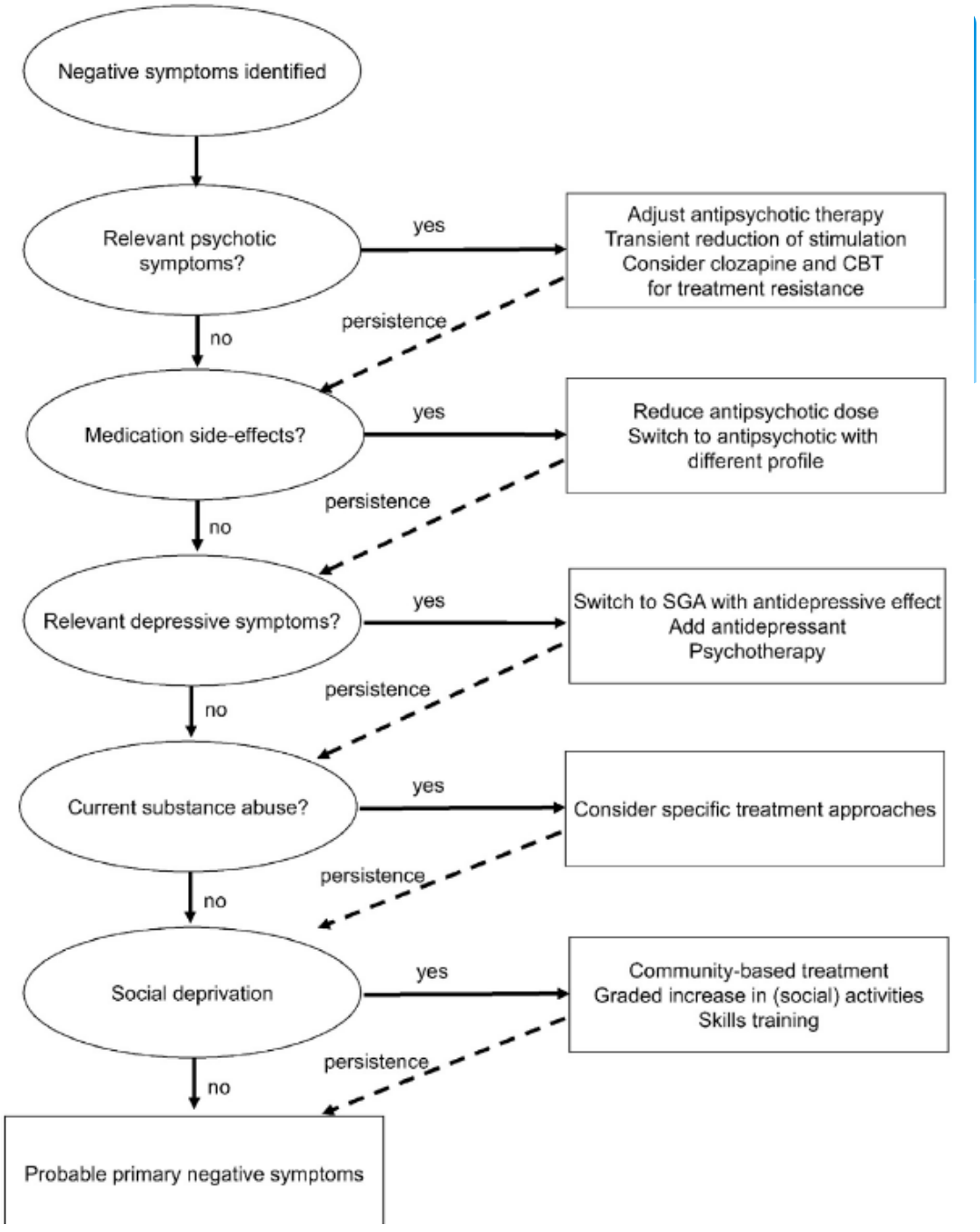
Test for overall effect: z=2.60, P=0.009



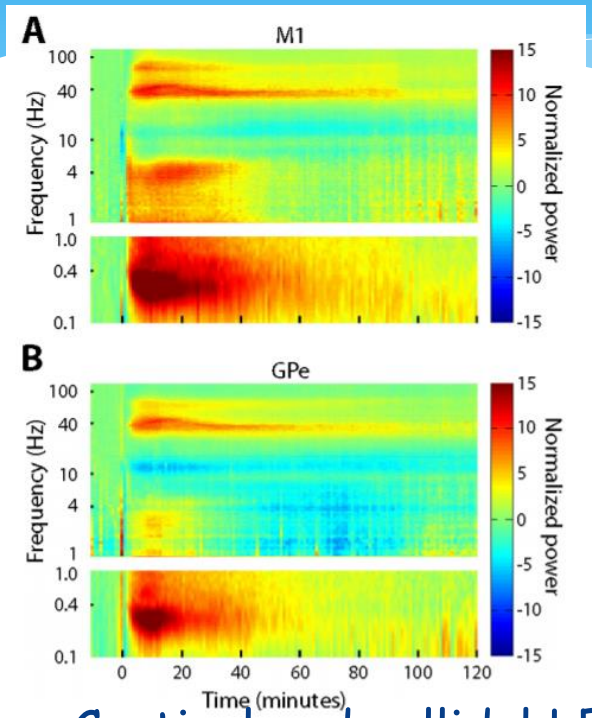
- Stafford et al, BMJ, 2013
  Early interventions to prevent psychosis: systematic review and meta-analysis

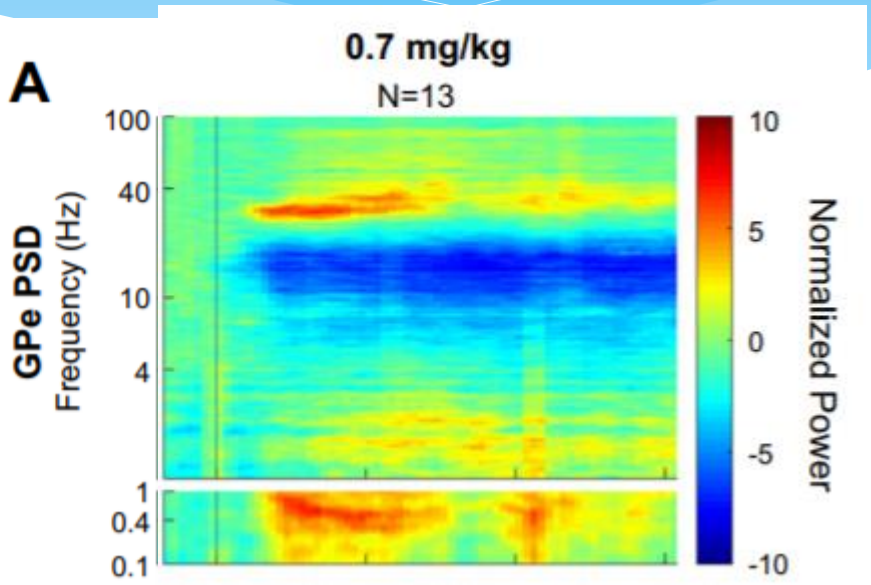
Balance Antips
Secondar

- Carpenter et al, Schizophr. Bull, 1985. Treatment of negative symptoms.
- Kirshner et al, Schizophrenia Research, 2016. Secondary negative symptoms — A review of mechanisms, assessment and treatment



Primate Schizophrenia Model – NMDA Receptor Antagonists Ketamine & PCP





* Cortical and pallidal LFPs exhibit changes in multi-frequency bands following ketamine administration
* PCP induces spectral and coherence changes in a dose dependent manner

Maya Slovik et al, J of Neurophysiology, 2017
Ketamine induced converged synchronous gamma oscillations in the cortico-basal ganglia network of nonhuman primates.

The Role of Neuropsychiatry in the Diagnosis, Treatment and Research of Cognitive and Negative Symptoms

- Routine evaluations of negative symptoms, cognition and social cognition
- Differential diagnosis of cognitive and negative symptoms
- Use old & new treatments for patient-specific symptoms
- Balance antipsychotics between positive and secondary negative symptoms
- Explore the interface of motivation and cognition
- Consider early intervention to prevent psychosis
- Apply neuropsychiatry knowledge and research skills to develop new treatments
- …