西部精神医学
四川省西部精神医学协会

SCHIZOPHRENIA AND RELATED PATHOLOGY

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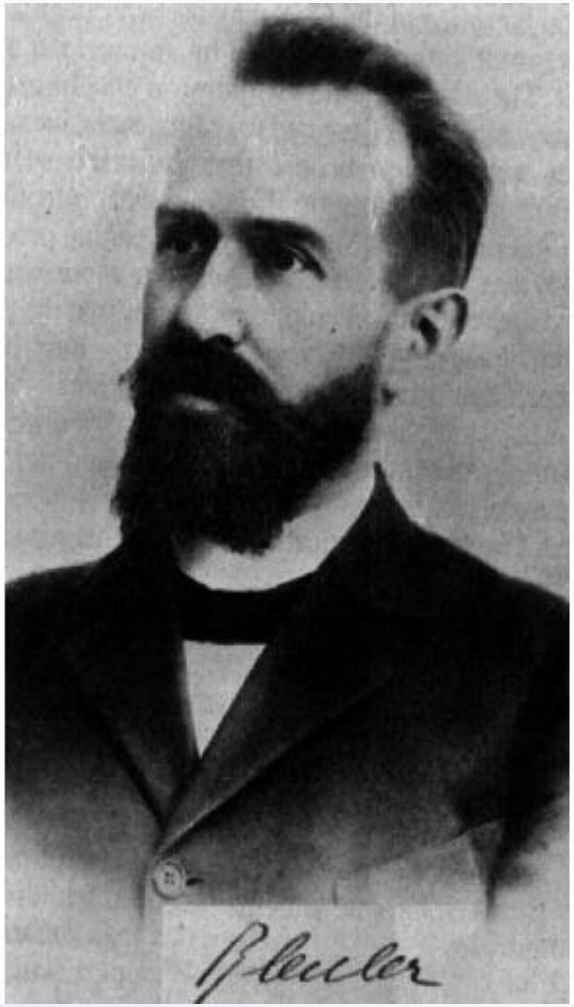
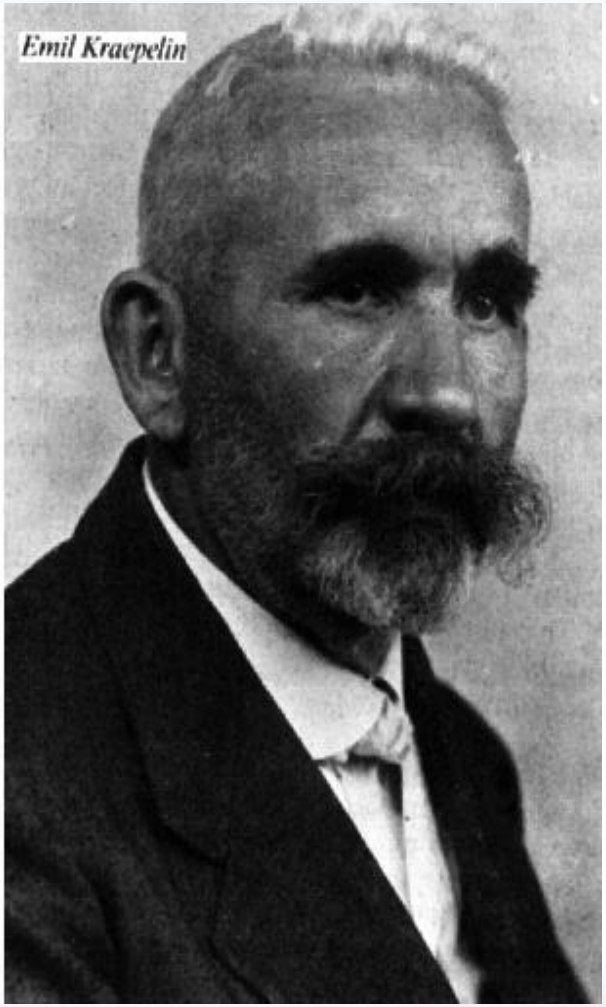
Concepts

- Schizophrenia
- Deconstruction
- Therapeutic Targets
- Prognosis and Course
- First Episode Therapeutics
- Across Diagnosis: Bipolar/Other Psychoses


Bleuler


Emil Kraepelin

Nuclear Schizophrenia Schneider

First Rank Symptoms

Audible thoughts
Somatic passivity
Thought insertion
Thought withdrawal
Thought broadcast
Made feelings
Made impulses
Made volition
Voices arguing
Voices commenting
Delusional percepts

DSM-5 Changes

- Five A Criteria
- Omit subtypes
- Schizoaffective as life course disorder
- Emphasis on heterogeneity
- Dimensions of psychopathology

Domains of Pathology: Strauss, Carpenter and Bartko

--- Disorders of content of thought and perception

--- Disorders of affect

--- Disorders of personal relationships

--- Disorder of form of speech and thought

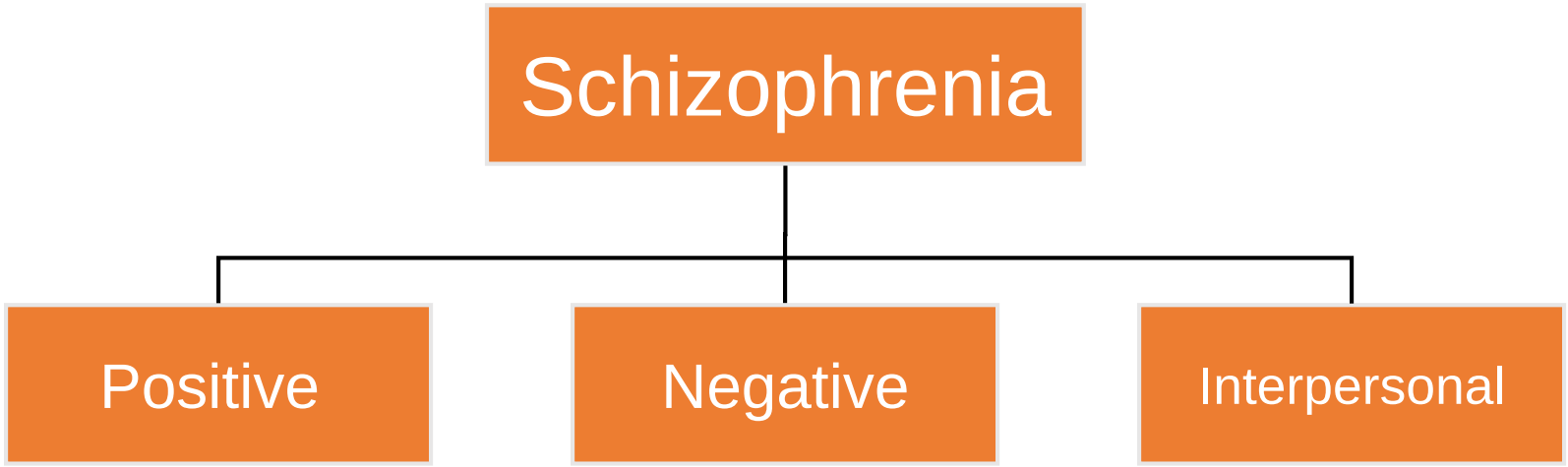
--- Disordered motor behaviors

--- Lack of insight

Schizophrenia Bulletin, 1974

Psychopathological Domains

(1974)



Psychopathological Dimensions: What and How Many?

Peralta and Cuesta

Schizophrenia Research, 2001

Eight Major Dimensions

1. Psychosis
2. Disorganization
3. Negative
4. Mania
5. Depression
6. Excitement
7. Catatonia
8. Lack of insight

Paradigm Shift

Psychosis Dx	Delusions
	Hallucinations
	Disorganized Thought
	Psychomotor
	Negative symptoms
	Depression
Cognitive Pathology	Mania

Prognosis/Course

1. Heterogeneous course and outcome
2. Within domain prediction
3. Developmental pathology

Anticipating ICD-11

- Similar to DSM-5
- Attach course types with dimensions
- Maintain schizoaffective as an episode diagnosis

Therapeutic Issues

- Personalized medicine/individualized Rx
- Biopsychosocial medical model
- Integrative therapeutics

Domain Specific Therapy

- Suicide
- Aggression
- Stress
- Thought disorder
- Hallucinations
- Delusions
- Motivation
- Depression/Anxiety
- Sleep disturbance
- Motor

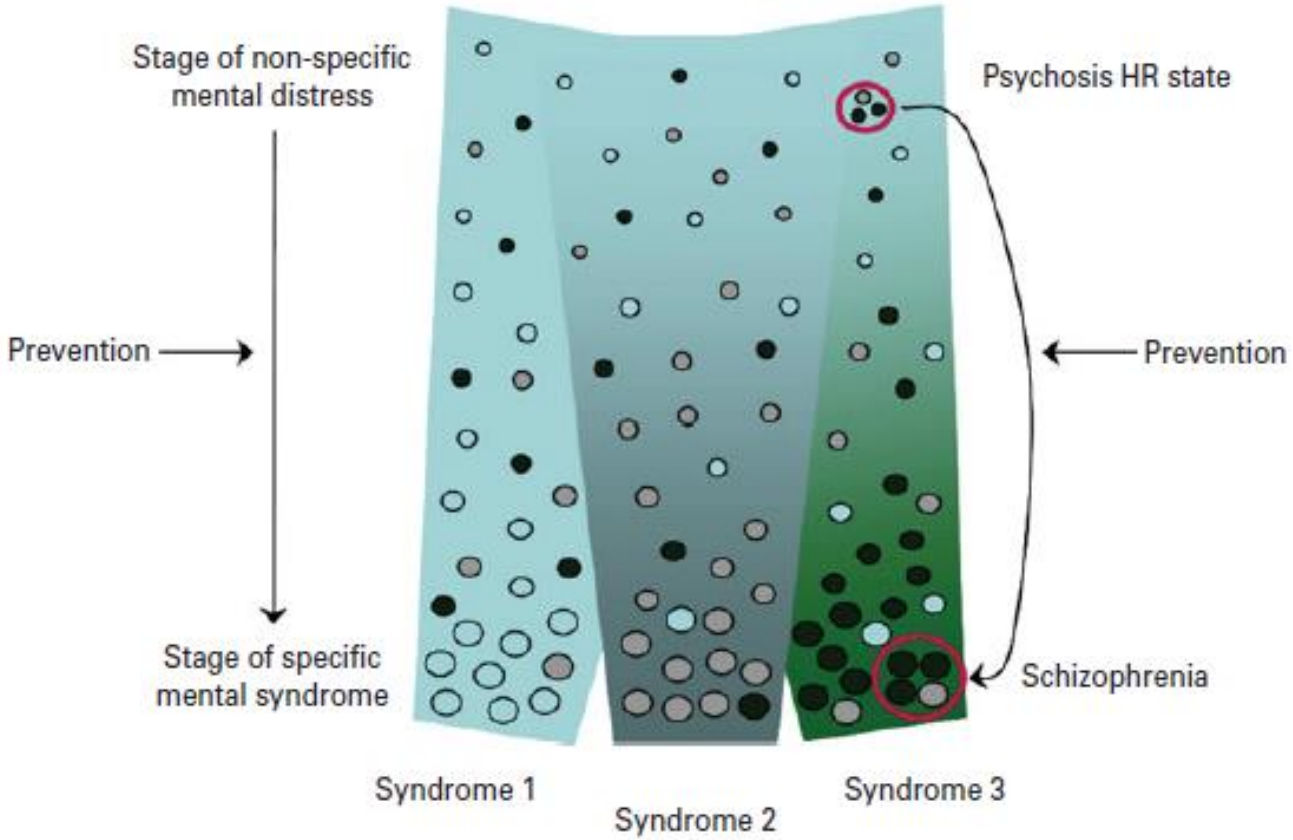
Functional Targets

- Social interactions
- Social withdrawal
- Major role performance
- Stressful interactions
- Sexual dysfunction
- Emotional dysregulation

Treatment: First Episode Psychosis

- Duration of Untreated Psychosis
- Pharmacotherapy
- Psychosocial Therapeutics
- Resilience/Compensatory
- Domain Specific Therapeutics

Clinical High Risk



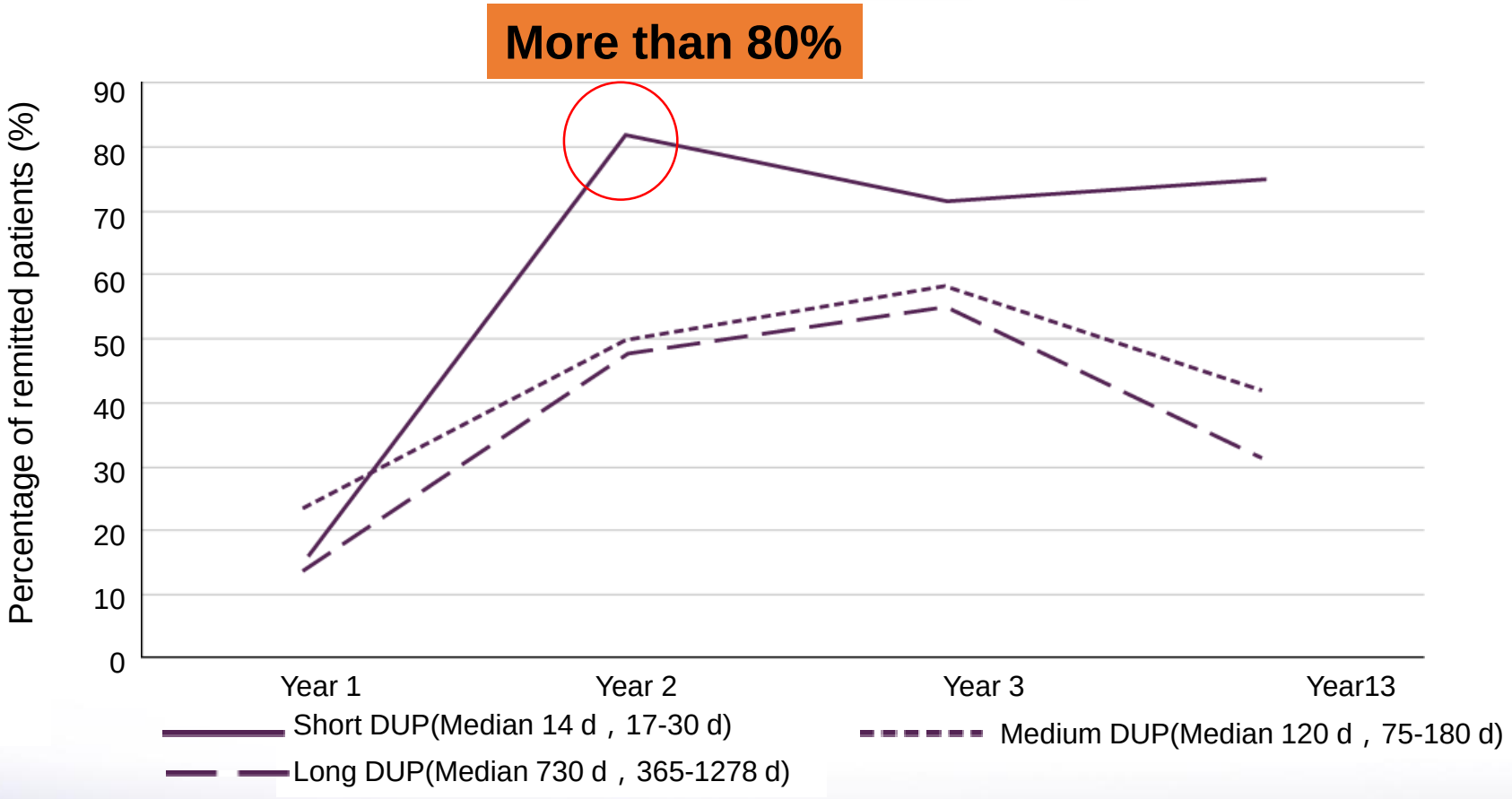
RCT for First-episode Psychosis

Study	Intervention	Control	Treatment group(N)	Control group (N)	Follow-up (months)	Outcome
Craig et al[98]	Specialized integrated early intervention (antipsychotics, cognitive behavior therapy, family counseling, vocational help)	Treatment as usual in community care	71	73	18	No difference in relapse, reduced psychiatric hospitalization and disengagement
Kuipers et al[99]	Specialized integrated early intervention (atypical antipsychotics, cognitive behaviour therapy, family intervention, vocational help)	Treatment as usual in community care	32	27	12	No significant benefits including psychiatric hospitalization
Grawe et al[100] Sigrúnarson et al[101]	Specialized integrated early intervention (family psychoeducation and therapy home crisis management, cognitive behaviour therapy, antipsychotics)	Treatment as usual in community care	30	20	24 168	At 24 months, reduced negative and positive symptoms; no benefits on psychiatric hospitalization or recurrences. No substantial long-term effects.
Petersen et al[102] Bertelsen et al[103] Secher et al[104]	Specialized integrated early intervention (family psychoeducation, social skills training, antipsychotics)	Treatment as usual in community care	275	272	12,24 60 120	At 12 months, reduced hospitalization. At 24 months, improvement on positive and negative symptoms, substance abuse, treatment adherence; lower dosage of antipsychotic medication, higher satisfaction with treatment, reduced burden to the family; no effect on psychiatric hospitalization. At 60 months, many positive effects disappeared; more patients living independently. At 120months, most positive effects had diminished or vanished.
kane et al[105]	Specialized integrated early intervention (family psychoedication, resilience focused individual therapy, supported employment and education, antipsychotics)	Treatment as usual in community care	223	131	24	Reduced disengagement, greater improvement in quality of life, wellbeing and total psychopathology, greater involvement in work and school, no effect on psychiatric hospitalization

Randomized Clinical Trial

Ruggeri et al[106]	Specialized integrated early intervention (cognitive behaviour therapy, family intervention, case management, antipsychotics)	Treatment as usual in community care	272	172	9	Reduced total symptom severity, improved functioning and emotional well-being; no effect on psychiatric hospitalization or disengagement
Srihari et al[107]	Specialized integrated early intervention (antipsychotics, family education, cognitive behaviour therapy, vocational support)	Treatment as usual in community care	60	57	24	Reduced psychiatric hospitalization, positive and total psychotic symptoms, improved vocational engagement, no effect on functioning
Chang et al[108] Chang et al[109]	3-year specialized integrated early intervention (psychosocial interventions, cognitive behaviour therapy, antipsychotics)	2-year specialized intefrated early intervention and 1-year step-down care	82	78	12	Better functioning, reduced negative and depressive symptoms and disengagement, no effect on psychiatric hospitalization
Ando et al[110]	Specialized integrated early intervention	Treatment as usual in community care	34	34	9	No effects on disengagement, functional remission, psychiatric hospitalization, self-harm, suicide attempt, social relationship

A Higher Symptomatic Remission Rate Was Observed In Patients With Shorter DUP

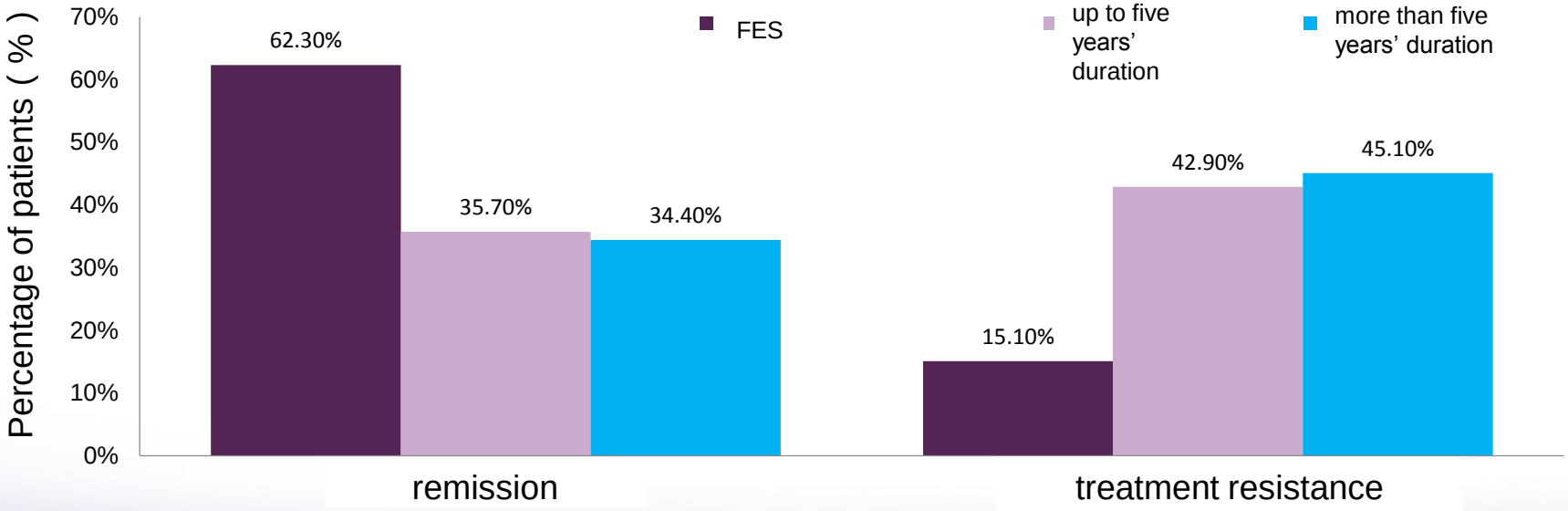


A prospective study of a cohort of 153 first-episode psychosis patients in Hongkong at the 13-year follow-up to explore the relationship between DUP (duration of untreated psychosis) and long term symptomatic remission.

Tang JY, et al. Schizophr Res. 2014 Mar;153(1-3):1-8.

FES seems to be the critical period to improve outcome, and should be given the optimal treatment

This study of 203 inpatients at the 5-year follow-up investigated whether clinical and psychopathological differences exist between first-episode schizophrenia (FES) and multiple-episode patients in an inpatient setting.



Ortiz BB, et al. Compr Psychiatry. 2017;73:93-96.

Some SGAs outperformed FGAs in FES patients in terms of treatment discontinuation, symptom reduction and treatment response

Pooled effect sizes (95% confidence interval in parenthesis) of short-term primary outcome variables in comparison of SGAs and FGAs

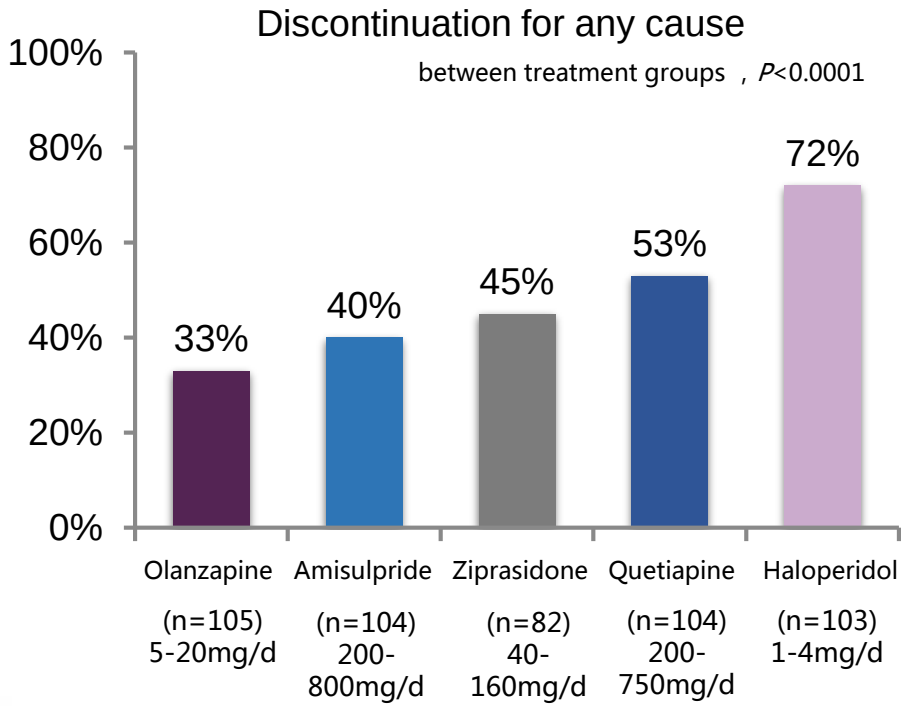
SGA	FGA	studies	n	All-cause Discontinuation Rate (RR)	Symptom Reduction (Hedges' g)	Response Rate（RR）
Olanzapine	Haloperidol	5	689	**0.53（0.37~0.77）****	**0.26（0.05~0.47）***	**1.29（1.05~1.58）***
Risperidone	Haloperidol	5	1146	0.79（0.63~0.97）*	-0.04（-0.19~0.11）	1.04（0.90~1.20）
Quetiapine	Haloperidol	1	207	0.81（0.63~1.05）	0.26（-0.02~0.53）	1.30（0.92~1.84）
Ziprasidone	Haloperidol	1	185	0.89（0.68~1.15）	0.22（-0.07~0.51）	1.11（0.76~1.64）
Amisulpride	Haloperidol	1	207	0.63 (0.47~0.85)**	0.40 (0.13~0.68)**	1.56 (1.13~2.15)**
Pooled SGAs	Pooled SGAs	12	1952	0.74 (0.62~0.87)**	0.11 (-0.02~0.24)	1.13 (0.99~1.27)

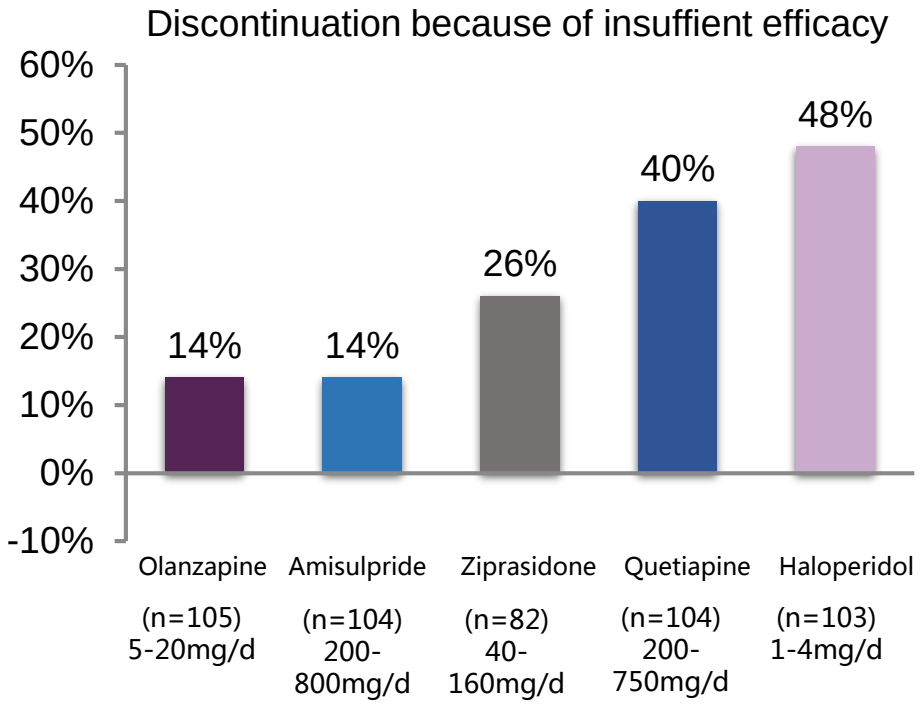
*P < 0.05， **P < 0.01

This meta-analysis includes 13 studies (n=2509) comparing efficacy and safety profile of individual second-generation antipsychotics (SGAs) with first-generation antipsychotics (FGAs) in FES.

Int J Neuropsychopharmacol. 2013 Jul;16(6):1205-18.

EUFEST study showed that SGAs vary in treatment discontinuation in first-episode schizophrenia and schizophrenia disorder

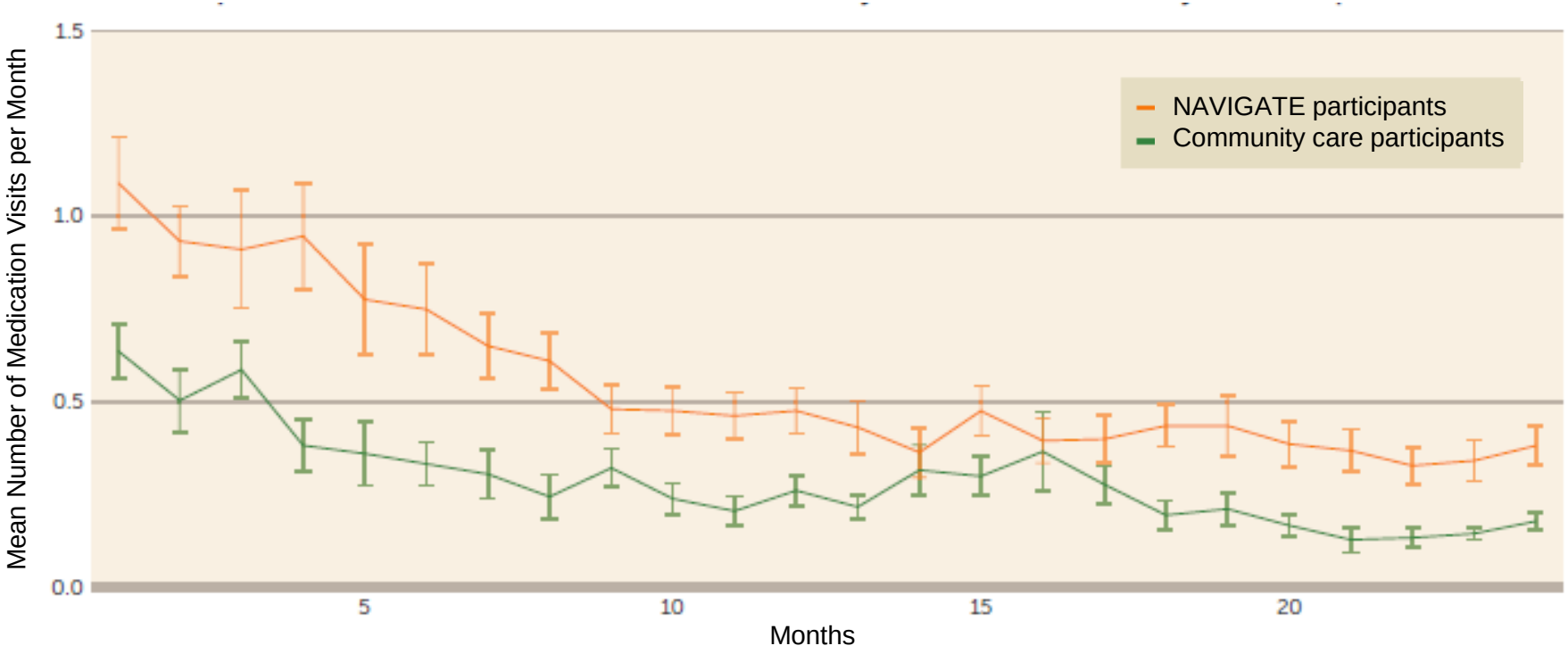




EUFEST study : An open randomised controlled trial of haloperidol versus second-generation antipsychotic drugs in 50 sites, in 14 countries. Eligible patients were aged 18–40 years, and met diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. 498 patients were randomly assigned by a web-based online system to haloperidol (1–4 mg per day; n=103), amisulpride (200–800 mg per day; n=104), olanzapine (5–20 mg per day; n=105), quetiapine (200–750 mg per day; n=104), or ziprasidone (40–160 mg per day; n=82); follow-up was at 1 year. The primary outcome measure was all-cause treatment discontinuation. **The results showed that there are significant differences in treatment discontinuation among different therapeutic agents for various reasons during follow-up.**

Lancet. 2008 Mar 29;371(9618):1085-97.

FIGURE 1 Least Squares Mean Estimates of Number of Medication Visits by NAVIGATE and Community Care Participants Over 2 years[a]



Specific Prescriptions

	Months of Prescription			
	Community Care		NAVIGATE	
Prescribed Medication	N	% of Follow up	N	% of Follow up
Medication Class				
Any antipsychotic	1,901	74.6	3,193	86.6
Antipsychotic conforming to NAVIGATE first-line principles	1,065	41.8	1,873	50.8
Any antidepressant	997	39.1	1,044	28.3

	Community Care		NAVIGATE	
Prescribed Medication	N	% of Follow up	N	% of Follow up
Selected Specific Agents				
Oral antipsychotics				
Aripiprazole	245	9.6	839	22.8
Clozapine	45	1.8	174	4.7
Haloperidol	169	6.6	76	2.1

	Community Care		NAVIGATE	
Prescribed Medication	N	% of Follow up	N	% of Follow up
Long-acting formulations				
Any	328	12.9	659	17.9
Haloperidol decanoate	131	5.1	91	2.5
Paliperidone palmitate	166	6.5	376	10.2
Risperidone microspheres	18	0.7	139	3.8

Medication	Modal Daily Dose (mg)	
	Community Care Mean	**NAVIGATE Mean**
Aripiprazole	9.90	11.79
Clozapine	433.08	330.05
Haloperidol	6.36	7.41
Olanzapine	16.29	16.10
Paliperidone	6.46	6.17
Quetiapine	252.72	302.35
Risperidone	3.36	2.88
Ziprasidone	92.35	114.65

Least Squares Mean Estimates of Number of Medication Side Effects in the NAVIGATE Program and in Community Care

Assessment	Community Care Mean	NAVIGATE Mean	Difference of Means *p*
Baseline	7.09	6.89	0.581
3 months	6.03	4.96	0.042
6 months	6.17	4.36	<0.001
12months	5.61	4.19	0.007
18months	5.10	4.12	0.075
24months	5.20	4.09	0.063

Issues in Treatment

- Unmet needs
- Superiority and marketing
- Novel mechanism
- Treatment advancement

Mechanisms

- Pathophysiology
- Common final pathways
- Compensatory
- Resiliency

Unmet Therapeutic needs

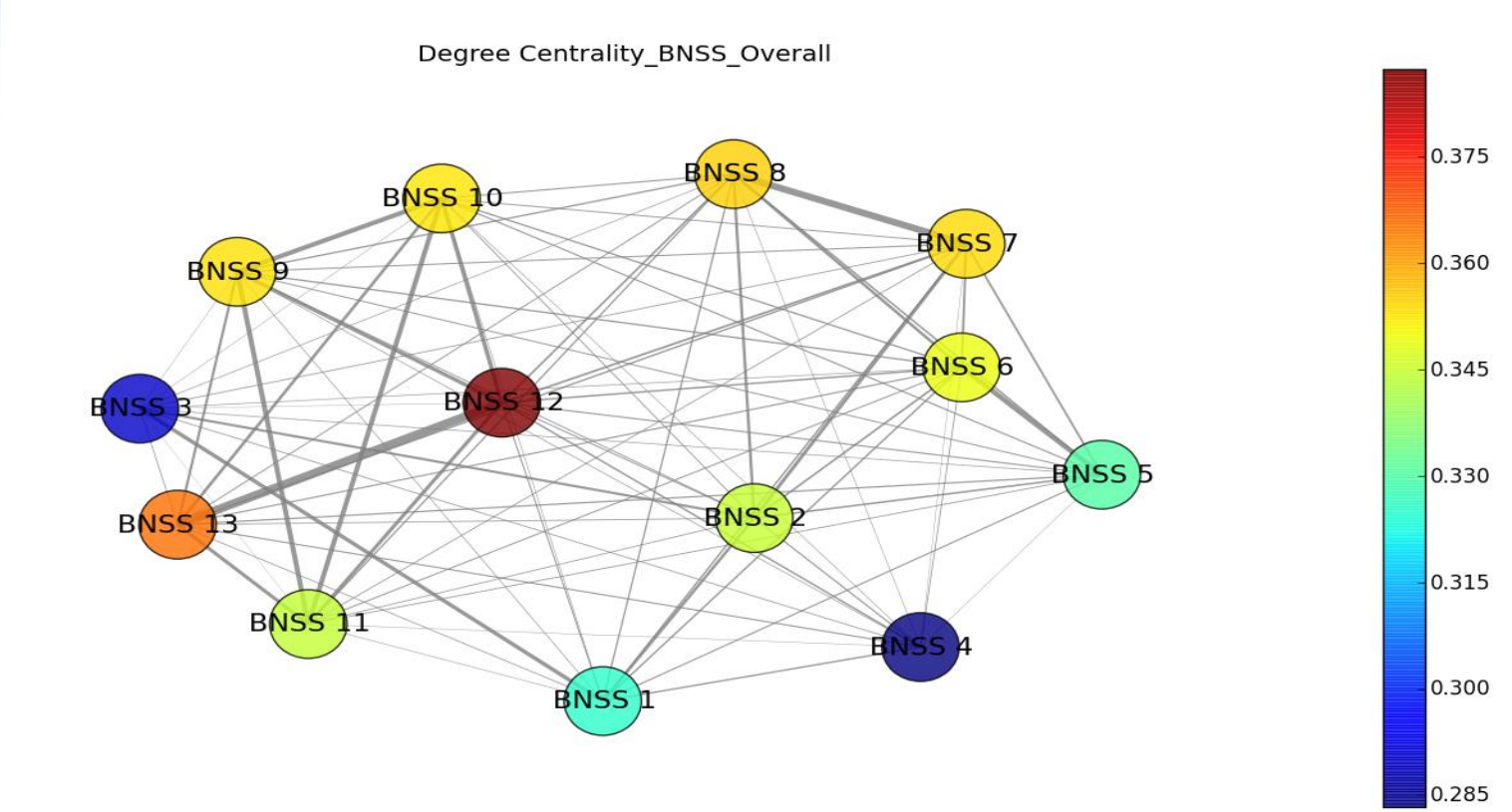
- Negative symptoms
- Impaired cognition

Negative Symptom Construct: Five Domains

- Psychopathology that separates from reality distortion, disorganized thought, and depression/anxiety

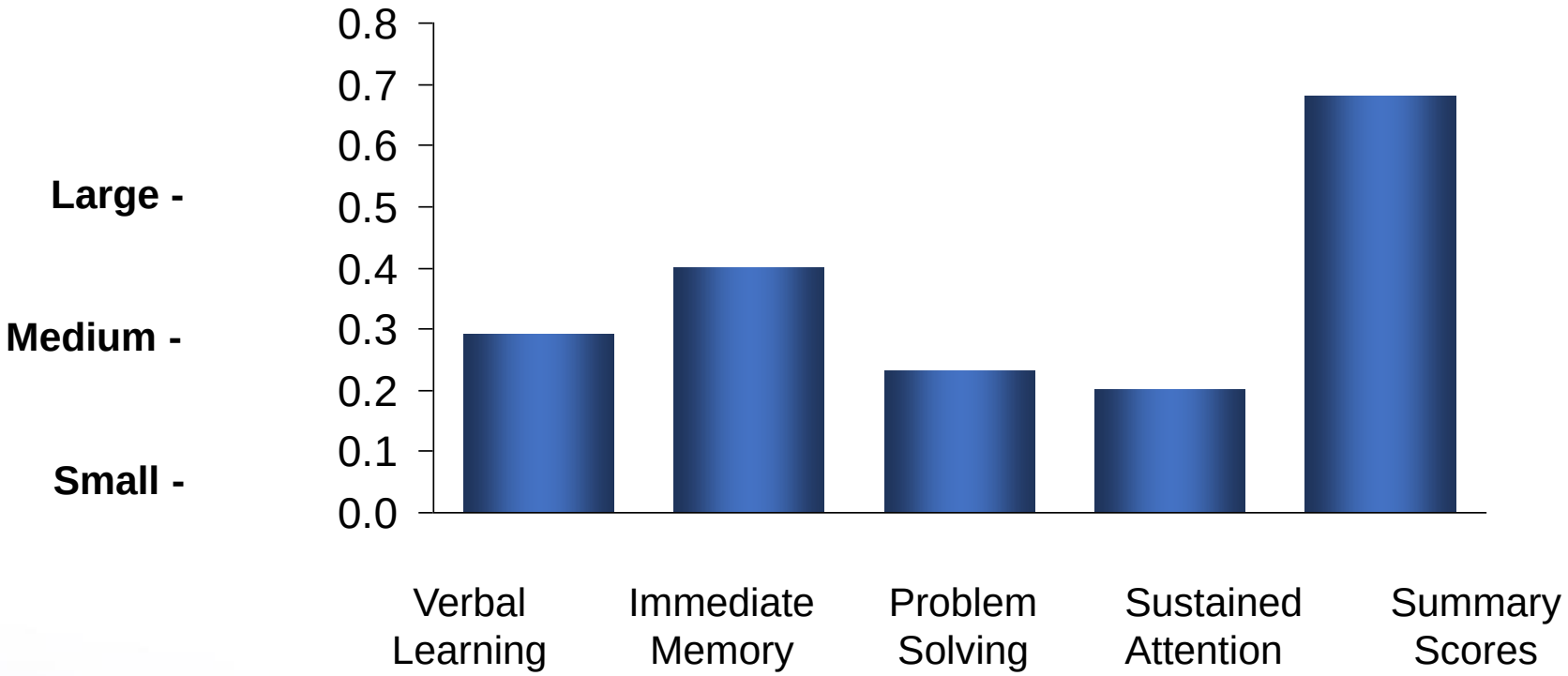
- Five domains, two factors
  - Diminished expression
    Diminished verbal output
  - Anhedonia
    Diminished interest
    Diminished social engagement

Blanchard JJ and Cohen AS. *Schizophr Bull*. 2006;32:238-245.



1. Intensity of pleasure during activities
2. Frequency of pleasurable activities
3. Intensity of expected pleasure from future activities
4. lack of normal Distress
5. Asociality: Behavior
6. Asociality: Internal experience
7. Avolition: Behavior
8. Avolition: Internal experience
9. Facial expression
10. Vocal expression
11. Expressive gestures
12. Quantity of speech
13. Spontaneous elaboration

Cognition and Functional Outcome in Schizophrenia: Strengths of Relationships[a]



[a]Effect size based on Cohen's r.

Green MF et al. *Schizophr Bull.* 2000;26(1):119-136.

Overview of Rx Modalities

- Pharmacology
- Family Education/stress reduction
- CBT
- Cognitive remediation
- Supportive Psychotherapy
- Neurostimulation/inhibition
- Supported Employment
- Exercise

Treatment Summary

- Modest advances in Drug and Psychosocial Rx
- Emphasis on integration of Rx, multiple clinical targets, and individualized
- Early recognition and Rx of first episode psychosis
- Secondary prevention in clinical high risk

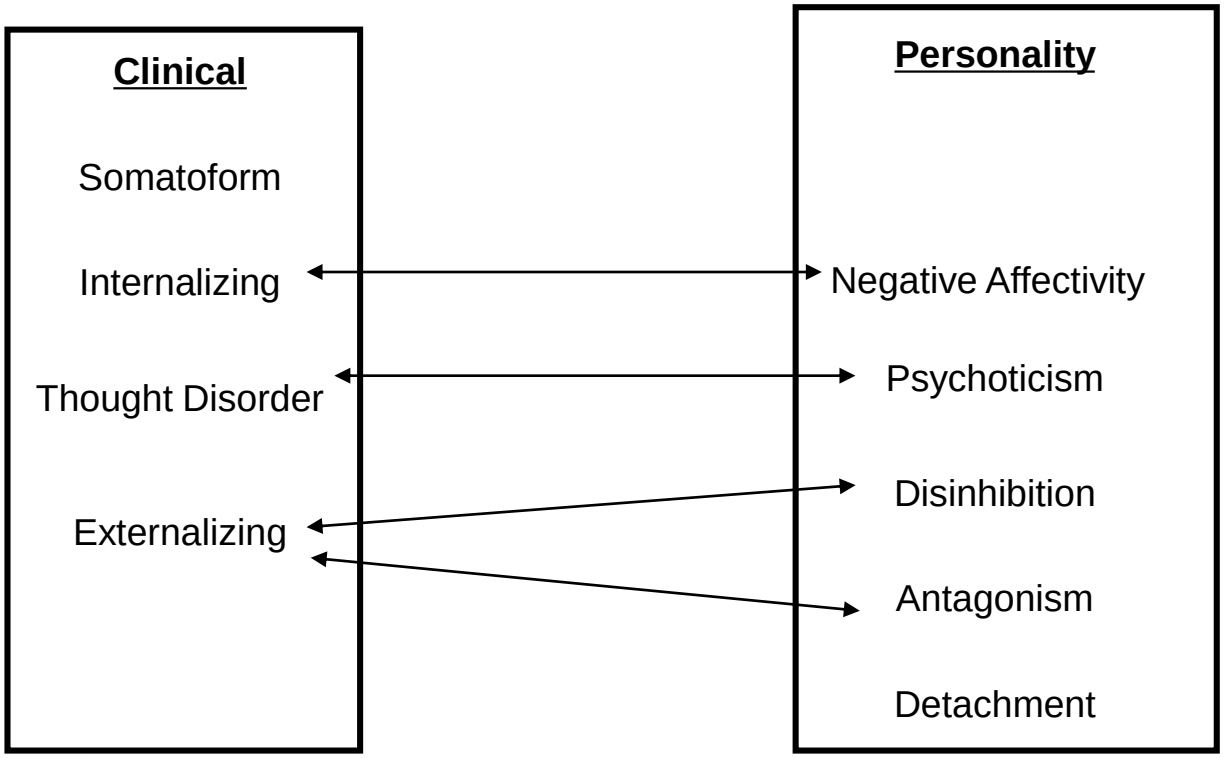
New Directions in Therapeutic Discovery

- Genetics : molecular targets
- Brain Imaging: network targets
- Focus: unmet needs
- Across diagnoses indications
- New paradigms: RDoC, SyNoPsis, HiTOP

New Approaches to Psychopathology

- HiTOP: Hicharctical Typology of Psychopathology
- SyNoPsis: Systems Neuroscience of Psychosis
- Extended Psychosis Phenotype
- Research Domains Criteria—a paradigm for research

Hierarchical Topography of Psychopathology



Internalizing

Distress Components

Dysphoria

Anhedonia

Insomnia

Suicidality

Fear Components

Enclosed spaces

Psychological panic

Traits

Emotional lability

Hostility

Thought Disorder

Components

Psychotic

Disorganized

Inexpressivity

Avolition

Traits

Cognitive/perceptual dysregulation

Unusual beliefs and experiences

Fantasy proneness

Mania components

Euphoric activation

Hyperactive cognition

Reckless overconfidence

Disinhibited Externalizing

Components

Alcohol problems

Marijuana problems

Traits

Problematic impulsivity

Distractibility

Risk taking

Antagonistic Externalizing

Traits

Attention seeking

Callousness

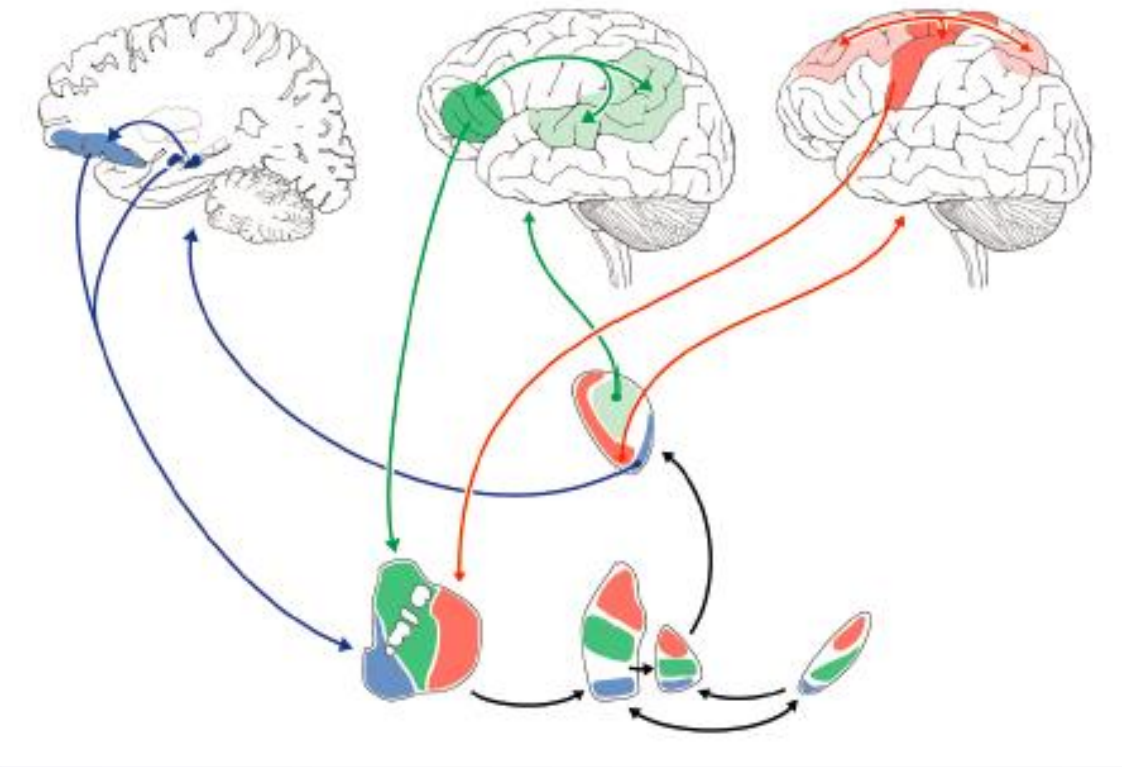
Grandiosity

Manipulativeness

Egocentricity

Dominance

SyNoPsis



Research Domains Criteria

Five RDoC domains have been proposed that are thought to cut across current DSM diagnostic categories:

RDoC Dimensions
Negative Valence
Positive Valence
Cognitive Systems
Systems for Social Processes
Arousal/Regulatory Systems

RDoC: Candidate Domains/Constructs and Units of Analysis (v. 2.1)

v.3.1,6/30/2011	DRAFT RESEARCH DOMAIN CRITERIA MATRIX							
	UNITS OF ANALYSIS							
DOMAINS/CONSTRUCTS	**Genes**	**Molecules**	**Cells**	**Circuits**	**Physiology**	**Behavior**	**Self-Reports**	**Paradigms**
Negative Valence Systems								
Acute threat("fear")								
potential threat ("anxiety")								
Sustained threat								
Loss								
Frustrative nonreward								
Positive Valence Systems								
Approach motivation								
Initial responsiveness to reward								
Sustained responsiveness to reward								
Reward learning								
Habit								
Cognitive Systems								
Attention								
Perception								
Working memory								
Declarative memory								
Language behavior								
Cognitive (effortful) control								
Systems for Social Processes								
Imitation, theory of mind								
Social dominance								
Facial expression identification								
Attachment/separation fear								
Self-representation areas								
Arousal/regulatory Systems								
Arousal & regulation (multiple)								
resting state activity								

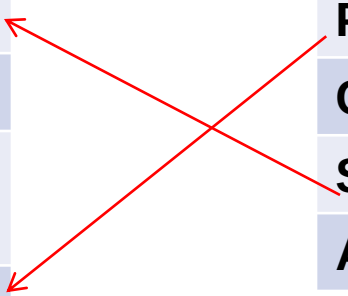
Two criteria for a Construct: Empirical support for (1) a functional dimension of behavior and (2) an implementing brain circuit).

Mapping RDoC to DSM-V

How to map DSM-V onto RDoC?

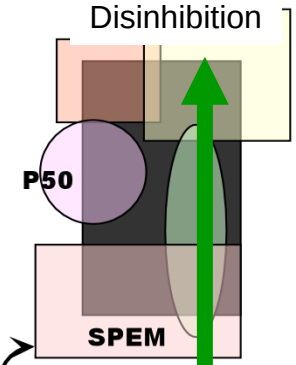
DSM-V Dimensions
Hallucinations
Delusions
Disorganized Speech
Abnormal Psychomotor Behavior
Negative Symptoms (diminished emotional expressivity; avolition)
Cognitive Impairment
Depression
Mania

RDoC Dimensions
Negative Valence
Positive Valence
Cognitive Systems
Systems for Social Processes
Arousal/Regulatory Systems



Clinical Dx of Schizophrenia **encompasses** **Multiple phenotypes**

Proof of Concept drug study



Drug A

Drug B

Drug C

Molecular Target 1

Molecular Target 2

Molecular Target 3

Molecular Target 4

Gene/Phene Project

PIK4CA
COMT
dysbindin

Retinoid x
G72
Neuroregulin
DRD3

GABA Ab

Brain tissue

Hot spots based On linkage studies

??

Final Thoughts: Concepts

- Psychopathology versus clinical syndromes
- Individual differences
- Slow progress and unmet Rx needs
- New paradigms for discovery
- Neurobiology informing Rx discovery

Final Thoughts: Treatment

- AP drugs and symptoms
- AP drugs and relapse prevention
- CBT (e.g., amotivation)
- Transcranial stimulation (e.g., hallucinations)
- Cognitive remediation

Bipolar Disorder: Differential Rx

- Lithium/Valproic Acid
- Circadian stability
- Emotional dysregulation
- Anti-depressive drugs
- Role for AP drugs

Citations

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- RDoC https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml