Cognitive Impairment in Schizophrenia: The Great Unmet Need
Learning Objectives

• Assess and monitor cognitive impairment in patients with schizophrenia over time

• Incorporate evidence-based treatment strategies into the management of cognitive impairment in schizophrenia

• Describe the underlying neurobiology of cognitive impairment in schizophrenia

• Describe novel mechanisms under investigation for the treatment of cognitive impairment in schizophrenia
Schizophrenia is primarily a:

A. Cognitive disorder
B. Psychotic disorder
Pretest Question 1

During adolescence, what general brain changes occur?

A. Pruning of excitatory synapses and proliferation of inhibitory circuits

B. Pruning of both excitatory synapses and inhibitory circuits

C. Proliferation of inhibitory circuits and pruning of excitatory synapses

D. Proliferation of both excitatory synapses and inhibitory circuits
What novel mechanism has the best evidence of efficacy for cognitive symptoms in schizophrenia

A. Anti-inflammatory
B. Cholinergic
C. GABAergic
D. Glutamatergic
Cognitive Impairment in First-Episode, Drug-Naïve Schizophrenia

Cognitive Impairment in Schizophrenia at Baseline of Clinical Trial

Cognitive Functioning Correlates With Functional Ability

N=117 schizophrenia patients. N=77 healthy controls.
Cognitive Impairment Is Pervasive in Schizophrenia

- Majority of schizophrenia patients demonstrate cognitive impairment relative to healthy controls\(^1,2\)
- Small percentage do not, but might still be below expectations
  - Almost all monozygotic twins perform worse than unaffected co-twin\(^3\)
  - 98% of schizophrenia patients have cognitive functioning lower than expected based on mother's education\(^1\)

Low Premorbid IQ Increases Risk of Schizophrenia; Evident by Age 13

*Included participants ages 14–16. Excluding these studies yielded similar results.

Low Premorbid IQ Increases Risk of Schizophrenia; High IQ Is Not Protective


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Premorbid IQ Does Not Correlate With Risk of Affective Disorders

Premorbid Scholastic Achievement Is Poor and Declines During Adolescence


a Iowa Tests of Basic Skills.
b Iowa Tests of Educational Development.
c Significantly lower than median percentile rank (F=5.89, df=1, 45, p<0.05).
d Significantly lower than: median percentile rank (F=7.80, df=1, 45, p<0.01), grade 4 (F=5.04, df=1, 45, p<0.05), grade 8 (F=4.97, df=1, 45, p<0.05).
e Significantly lower than: median percentile rank (F=5.63, df=1, 45, p<0.05), grade 8 (F=6.40, df=1, 46, p=0.01).
f Significantly lower than median percentile rank (F=4.77, df=1, 45, p<0.05).
Specificity of Poor Premorbid Cognitive Function and Decline in Schizophrenia

Decline in Verbal Ability During Adolescence Predicts Risk of Psychosis

4 population-based cohorts of adolescent boys and young men (total N=10,717)

Verbal ability at age 18 did **not** predict schizophrenia or schizoaffective disorder: 0.78 (0.60–1.01), \( P=0.06 \)

Decline in verbal ability from age 13 to 18 **did** predict schizophrenia or schizoaffective disorder: 0.88 (0.42–0.79), \( P<0.001 \)

Cognitive Impairment Remains Stable After Psychosis Onset

82 patients and 107 age/gender-matched controls assessed at baseline and at 1-year follow-up

*Significant time x group interaction

**Significant time effects for patients and controls

Cognitive Impairment Begins Premorbidly and Persists Throughout the Course


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ASSESSING AND TREATING COGNITIVE IMPAIRMENT: CURRENT STANDARD OF CARE
NIMH MATRICS Initiative

• Goals were to create a standardized cognitive battery:
  – As an outcome measure in clinical trials of medications
  – As an outcome measure for studies of cognitive remediation
  – As a measure of cognitive change in repeated testing applications
  – As a cognitive reference point for non-intervention studies of schizophrenia and related disorders

• Led to the MATRICS Consensus Cognitive Battery (MCBB)
# Cognitive Domains Assessed in the MCCB

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of processing</td>
<td>Category Fluency</td>
</tr>
<tr>
<td></td>
<td>BACS Symbol Coding</td>
</tr>
<tr>
<td></td>
<td>Trial Making A</td>
</tr>
<tr>
<td>Attention/Vigilance</td>
<td>Continuous Performance Test</td>
</tr>
<tr>
<td>Working Memory</td>
<td>Letter-Number Span</td>
</tr>
<tr>
<td></td>
<td>WMS-III Spatial Span</td>
</tr>
<tr>
<td>Verbal Learning and Memory</td>
<td>Hopkins Verbal Learning Test-R</td>
</tr>
<tr>
<td>Visual Learning and Memory</td>
<td>Brief Visuospatial Memory Test-R</td>
</tr>
<tr>
<td>Reasoning and Problem Solving</td>
<td>NAB Mazes</td>
</tr>
<tr>
<td>Social Cognition</td>
<td>MSCEIT Managing Emotions</td>
</tr>
</tbody>
</table>
Comprehensive Cognitive Performance Assessments

**ADVANTAGES**

- Address all 7 MATRICS cognitive domains
- Sufficient items to generate test-retest reliability
- Associated with change index to calculate amount of change that will define improvement/worsening

**DISADVANTAGES**

- Significant time to administer and score
- Require tester training and credentials
- Acquisition costs
- Missing data create scoring challenges

MATRICS Consensus Cognition Battery (MCCB)
CogState
Cambridge Neuropsychological Test Automated Battery (CANTAB)

Keefe RSE et al. Schizophr Bull 2015;Epub ahead of print.
Brief Cognitive Performance Assessments

ADVANTAGES
• Address most domains yet take less time
• Evidence that shorter tests are equally sensitive
• Lower cost

DISADVANTAGES
• Shorter tests often have less reliability
• Reduced number of domains tests
• Testers require training and supervision

Brief Assessment of Cognition in Schizophrenia (BACS)
Brief Cognitive Assessment (BCA)

Keefe RSE et al. Schizophr Bull 2015;Epub ahead of print.
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Interview-Based Measures of Cognition

Schizophrenia Cognition Rating Scale (SCoRS)
Cognitive Assessment Interview (CAI)
Measure of Insight into Cognition

**ADVANTAGES**
- Brief (~15 min per interview)
- Good relationship to real-word function
- Good test-retest reliability
- High correlation with some performance-based measures of cognition

**DISADVANTAGES**
- Weak relationship to objective cognitive and functional measures
- Validity and correlations with performance-based measures depend on availability of informant
- Some training required

Keefe RSE et al. Schizophr Bull 2015;Epub ahead of print.
## Performance-Based Measures of Functional Capacity

<table>
<thead>
<tr>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Able to predict failures to achieve milestones</td>
<td>• Relationship to cognitive change may be indirect</td>
</tr>
<tr>
<td>• May correlate more strongly with real-world functioning than cognitive measures</td>
<td>• Comprised of functional tasks that are not consistently required across cultures</td>
</tr>
<tr>
<td>• Easily tolerated</td>
<td>• Lack alternate forms; practice effect in real world?</td>
</tr>
<tr>
<td>• High test-retest reliability and minimal practice effects in large-scale clinical trials</td>
<td>• Ceiling effect for high-functioning patients</td>
</tr>
</tbody>
</table>

UCSD Performance-Based Skills Assessment (UPSA)
Test of Adaptive Behavior in Schizophrenia (TABS)
Independent Living Scale (ILS)

Keefe RSE et al. Schizophr Bull 2015;Epub ahead of print.
Interview-Based Assessments of Real-World Functioning

Specific Levels of Functioning (SLOF)

**ADVANTAGES**
- Assesses social functioning, vocational and non-vocational productive functioning, and residential independence and self-care
- Functional scales are acceptably correlated with performance-based measures

**DISADVANTAGES**
- Requires input of informants
- Changes are likely to take longer to detect

Keefe RSE et al. Schizophr Bull 2015;Epub ahead of print.
Cognitive Remediation Therapy

- Designed to improve neurocognitive abilities, including attention and memory
- Pencil/paper tasks; computer exercises; can be tailored to address individual areas of weakness
- Improvement in executive functioning predicts improved daily functioning
- FOCUS (Function and Overall Cognition in Ultra-high risk States) trial

Cognitive Remediation Therapy: Meta-analysis

- 2,104 participants
- Durable effects on global cognition and functioning
  - Effect size 0.45 (95% CI 0.31–0.59)
- No treatment element (remediation approach, duration, computer use, etc.) was associated with cognitive outcome
- More effective when patients were stable
- More effective when combined with psychiatric rehabilitation

Auditory Cortical Plasticity Drives Training-Induced Cognitive Changes in Schizophrenia

Dale CL. Schizophr Bull 2015;Epub ahead of print.
PREMORBID SCHIZOPHRENIA: IS THE EARLIEST MANIFESTATION A DISRUPTION IN BRAIN DEVELOPMENT/CONNECTIVITY?
Brain Development/Connectivity: What Are the Implications for Cognitive Impairment?

Cognition Requires Proper Signaling Throughout the Brain

- attention
- reasoning
- problem solving
- planning
- organizing
- working memory
- decision making
- response inhibition
- learning
- semantic memory
- sensory processing
- visual processing
- episodic memory

Brain Changes During Normal Development

birth

age 5

age 20

Brain Changes During Normal Development

Competitive elimination of synapses (loss of dendritic arborization)

Prefrontal excitatory synapses

Prefrontal DA innervation

Prefrontal inhibitory synapses

The "At-Risk" Brain

- Competitive elimination of synapses (loss of dendritic arborization)

- Prefrontal excitatory synapses
- Prefrontal inhibitory synapses
- Prefrontal DA innervation

- Increased striatal DA synthesis and release capacity; predictive of conversion (Howes 2009 & 2011, Bonoldi 2013)
- Increased glx (glutamate and glutamine) (de la Fuente-Sandoval 2013 & 2011)
- Decreased volume in frontal and temporal areas (similar to but less than in schizophrenia) (Wood 2013)

Progressive Brain Changes in Schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>Premorbid</th>
<th>Prodrome</th>
<th>First episode</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial volume</td>
<td>Decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gray matter</td>
<td></td>
<td>Decreased*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White matter</td>
<td></td>
<td>Decreased**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glx</td>
<td></td>
<td></td>
<td>Increased***</td>
<td></td>
</tr>
</tbody>
</table>

*Most pronounced in frontal and temporal areas

**Twin studies suggest it reflects genetic risk rather than the effects of the illness

***In medicated first-episode patients, glx is normal

The "At-Risk" Brain

Competitive elimination of synapses
(loss of dendritic arborization)

Prefrontal excitatory synapses
Prefrontal inhibitory synapses
Prefrontal DA innervation

Competitive Elimination: Normal Development

- **Normal synapse strengthening**
  - Glu
  - NMDA-R
  - AMPA-R
  - LTP
  - Strong synapse survives competitive elimination

- **Weak synapse weakening**
  - Low activity
  - Weak synapse is competitively eliminated
NMDA, Brain Development, and Proper Signaling

NMDA receptors are comprised of 4 subunits. During brain development, the subunit composition of NMDA receptors switches.

Ideally, this makes the receptor more suitable for optimal timing of firing and thus swifter integration of environmental stimuli.

Timing of switch differs by brain region and may coincide with risk windows.

Abnormalities in a mature NMDA receptor subunit profile may affect LTD and LTP such that pruning in adolescence becomes random.

Premorbid NMDA and GABA Receptors

- **Glu** (glutamic acid)
- **GABA-R** (GABA receptor)
- **Hypo-functional NMDA receptor and synapse**
- **GAD67** (glutamic acid decarboxylase)
- **Alpha 2 GABA-R**

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Mesocortical Pathway to DLPFC

- Hypofunctional NMDA glutamate synapse
- DA neuron

Symptoms:
- Negative symptoms
- Cognitive symptoms

Temperature:
- Normal
- Low
Mesolimbic Pathway

- hypofunctional NMDA glutamate synapse
- overactivation
- positive symptoms
- normal
- high

DA neuron
Neuroinflammation and NMDA Receptor Dysfunction

- Epidemiological studies consistently show increased risk of schizophrenia following pre- and perinatal infections
- Microglial activation: reduced neurotrophic function, production of proinflammatory cytokines, production of free radicals, and increased glutamate
- NMDA-R activation: antioxidant production
- NMDA-R hypofunction: leaves brain vulnerable to neurotoxicity
- Activation of IL-6/NOX2 pathway can induce loss of parvalbumin-containing interneurons, which would increase activation/desynchrony of the second glutamate cortical neuron
  - Could inflammation be a cause of increased glutamate in at-risk/first-episode patients rather than (or in addition to) NMDA-R hypofunction?

Cholinergic System Modulates DA, Glutamate, and GABA

- **VTA**
  - DA neuron
  - Stimulation activates Glu release
  - Glu stimulation activates DA release

- **PFC**
  - Glu neuron

- **PPT/LDT**
  - ACh neuron

**Abbreviations**

- **VTA**: ventral tegmental area
- **PPT**: pedunculopontine tegmental nucleus
- **LDT**: laterodorsal tegmental nucleus
- **ACh**: acetylcholine
- **GABA**: gamma-aminobutyric acid
- **DA**: dopamine

**Receptors**

- α7
- α4β2
Multiple Susceptibility Genes Converge on NMDA Synapses in Schizophrenia
FROM NEUROBIOLOGY TO CLINICAL PRACTICE: NOVEL TREATMENT MECHANISMS
Clinical Translation: Treatment Mechanisms Beyond Dopamine

• Neurobiological data: rationale for why current antipsychotics don't seem to improve cognition
• Prospect of novel mechanisms
  – Glutamatergic
  – GABA-ergic
  – Cholinergic
  – Anti-inflammatory
Novel Treatment Mechanisms: Glutamate

- **glutamate neuron**
- **glial cell**

**AMPA modulators**
- CX-516
- piracetam
- cyclothiazide
- LY404187

**direct acting glycine site agonists**
- d-cycloserine
- d-serine
- glycine

**glycine transporter inhibitors**
- sarcosine
- bitopertin (RG1678)

**glycine transporter**

**mGlu receptor modulators**
- LY354740
- LY2140023
Glutamate Positive Modulators: Results Not Promising for Cognition

- Meta-analysis of 17 studies (N=1,391)
- Measure: standardized mean differences (SMDs) between active drug and placebo (added to antipsychotic)
- No significant effect on overall cognitive function (total or each individual agent)
  - 11 studies, n=858; SMD=0.08, 95% CI -0.06–0.23
- No significant effect on each of 8 cognitive domains
  - n=367–940; SMD=-0.03–0.11

Iwata Y et al. Mol Psychiatry 2015;Epub ahead of print.
Novel Treatment Mechanisms: GABA

GABA binding site

BZ binding site

alpha 2/3 selective

MK-0777

negative results

Novel Treatment Mechanisms: Cholinergic

Nicotinic receptor agonists: alpha 7
- nicotine
- DMXB-A
- encenicline
- TC-5619
- RG-3847

Muscarinic 1/4 receptors agonist
- xanomeline

Nicotinic receptor agonists: alpha 4 beta 2
- varenicline

Cholinesterase inhibitors
- donepezil
- rivastigmine
- galantamine

VTA DA neuron
PFC glur neutron
PPT/LDT ACh neuron
GABA inter-neuron

Cognitive domains

Attention (1 RCT, n=73, MD 1.20 95% CI 0.14–2.26)

Visual memory (2 RCTs, n=48, MD 1.90 95% CI 0.52–3.28)

Verbal memory and language (3 RCTs, n=42, MD 3.46 95% CI 0.67–6.26)

Executive functioning (1 RCT, n=24, MD 17.10 95% CI 0.70–33.50)
## Galantamine: Also a Nicotinic PAM

<table>
<thead>
<tr>
<th>Duration</th>
<th>Dosage</th>
<th>Participants</th>
<th>Measures</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 weeks</td>
<td>24 mg/d</td>
<td>14 schizophrenia or schizoaffective patients (8 galantamine, 6 placebo)</td>
<td>RBANS</td>
<td>Significant effect on composite score (attention and delayed memory)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>16 mg/d</td>
<td>24 schizophrenia patients (12 galantamine, 12 placebo)</td>
<td>Several</td>
<td>Significant effect on RCFT (recognition)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>24 mg/d</td>
<td>86 schizophrenia patients (42 galantamine, 44 placebo)</td>
<td>Several</td>
<td>Significant effect on digit symbol and verbal memory WAIS-III</td>
</tr>
<tr>
<td>12 months</td>
<td>24 mg/d</td>
<td>32 schizophrenia or schizoaffective patients (15 galantamine, 17 placebo)</td>
<td>Several</td>
<td>No significant effects</td>
</tr>
</tbody>
</table>

PAM: positive allosteric modulator.

Nicotinic Modulators

• Nicotine (nasal spray, gum, or patch)
  – Significant enhancing effect on working memory, attention, and novelty detection (placebo-controlled trials)
  – Seen in tobacco users and non-tobacco users
• DMXB-A (alpha 4 and 7 partial agonist)
  – 1 positive study, 1 negative study
• Alpha 7 agonists
  – TC-5619: 1 positive study, 1 negative study
  – RG-3487: negative study
  – Encenicline: 2 positive studies
Encenicline: Positive Effects on EEG Biomarkers

Cognitive processing markers: Mis-Match Negativity (p=0.02) and p300 (p=0.008)
Early sensory processing marker: p50 (p=0.07)

0.3 mg: n=8 1.0 mg: n=9 Placebo: n=4

Alpha 7 Nicotinic Receptor Agonist: Encenicline

Keefe RS et al. Neuropsychopharmacol 2015;Epub ahead of print.
Is Social Cognition a Separate Entity?

Encenicline Post Hoc Re-analysis

Original Analysis (Keefe et al., 2015)
MATRICS Consensus Cognitive Battery (MCCB), 7 domains

- 0.27 mg vs. placebo: p=0.142, ES=0.17
- 0.9 mg vs. placebo: p=0.069, ES=0.28

Post Hoc Re-analysis (Ho et al., 2015)
MATRICS Consensus Cognitive Battery (MCCB), 6 domains

- Placebo
- Encenicline 0.27 mg: p=0.038, ES=0.55
- Encenicline 0.9 mg: p=0.024, ES=0.57

54 early-phase schizophrenia patients were randomly allocated in a 2:1 ratio to minocycline 200 mg/day. Adjunct antipsychotics were initiated no more than 14 days prior to study entry. Antipsychotics included risperidone, olanzapine, quetiapine, and clozapine (200–600 mg/day chlorpromazine-equivalent doses).

Personalized Medicine?

Neuroimaging for DA striatal synthesis? Frontal glx? Microglial activation?

Demjaha A et al. Biol Psychiatry 2014;75(5):e11-3;
From Neurobiology to Clinical Practice: Summary

- Currently, best evidence may be for cholinergic strategies (nicotinic)

- Interpreting negative study results
  - NMDA/GABA changes occur premorbidly
    - Importance of biomarkers to identify—and ideally treat—before psychosis onset; staging treatment?
  - Most completed trials included predominantly older, chronic, male patients
  - Ongoing trials have more diverse patient populations
Summary

• Cognitive impairment
  – Is a risk factor for schizophrenia
  – Precedes psychosis onset by several years
  – May continue to progress after psychosis onset
  – Determines functional outcomes
  – Is generally unaffected by current antipsychotics

• Best current treatments
  – Cognitive intervention combined with rehabilitation programs
Hope for the Future

• Near term
  – Best data exist for cholinergic strategies
  – Promising novel cognitive training interventions

• Longer term
  – Biomarkers, new cognitive tools, and other factors for earlier detection and treatment implementation
  – Glutamatergic, GABA-ergic, cholinergic, and/or anti-inflammatory mechanisms