Cognitive Functioning & Neuroprotection In Schizophrenia

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Dr. Correll is Chair of the Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany, and Professor of Psychiatry at The Zucker School of Medicine at Hofstra/Northwell, NY, USA. He completed his medical studies at the Free University of Berlin, Germany, and Dundee Medical School, Scotland. He has authored over 500 journal articles and has received over 40 research awards and fellowships for his work. Since 2014, the year of inception of this metric, he has been listed every year by Thomson Reuters/Web of Science as one of the “most influential scientific minds” and “top 1% cited scientists in the area of psychiatry” (https://hcr.clarivate.com).

**René Kahn, M.D., Ph.D.**
Esther & Joseph Klingenstein Professor and System Chair of Psychiatry Icahn School of Medicine, Mount Sinai

Dr. Kahn is the Esther & Joseph Klingenstein Professor and System Chair of Psychiatry at the Icahn School of Medicine at Mount Sinai. Dr. Kahn is an Honorary Lifetime Professor at Jilin University, as well as a Fellow of the American College of Neuropsychopharmacology. Over the past few years, he was named as a Thomson Reuters’ Highly Cited Researcher. Dr. Kahn completed his medical studies in the Netherlands and was trained as a psychiatrist and neurologist in Utrecht and Amsterdam. He completed a research fellowship in biological psychiatry at Albert Einstein College of Medicine, and a psychiatry residency at Mount Sinai Hospital.
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Objectives

• Discuss altered cognition as a core feature of schizophrenia

• Review the trajectory of changes in cognition during the course of illness in patients with schizophrenia

• Explore evidence of the impact of cognitive functioning on clinical outcomes and patient functioning

• Consider the role of strategies to improve cognition and/or mitigate the progressive effects of illness
Altered Cognition In Schizophrenia
Examining The Relationship
What Is Cognition?

A range of brain functions, including the ability to\textsuperscript{1-3}:

- Learn and remember information
- Plan and problem solve
- Accurately perceive the environment
- Understand and use language
- Process new information
- Focus, maintain, and shift attention as necessary

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Cognitive Domains In Schizophrenia

- Processing speed: the speed with which different cognitive operations can be executed based on Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) data

Cognition: A Core Feature Of Schizophrenia

• Cognitive impairment is considered to be a core feature of schizophrenia\(^1\)
  – Studies have reported deficits of 1.5–2.5 standard deviations below healthy controls\(^2\)
  – Nearly all aspects of cognition are impaired\(^2\)
• Severity of cognitive deficits has been suggested to be the primary determinant of functional impairment\(^3\)
• Secondary cognitive impairment due to medications with high anticholinergic burden has also been reported\(^4\)

*Cognitive Deficits in Schizophrenia*

Deficits are:

- Present in the majority of patients\(^3\)
  
  (20-25% of patients have neuropsychological profiles in the normal range)

- Not the result of symptoms or treatment\(^1\)

- Present before symptom onset\(^1\)

- Relatively stable over the course/stage of illness and patient life span\(^1,3\)

- Sometimes seen in attenuated form in unaffected first-degree relatives\(^1\)

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\(^1\) Green MF. J Clin Psychiatry. 2006;67(suppl 9):3.
### Pronounced Characteristics of Cognitive Impairment in Schizophrenia as Compared to Other Neuropsychiatric Disorders

<table>
<thead>
<tr>
<th>SCZ</th>
<th>BP</th>
<th>MDD</th>
<th>PTSD</th>
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**Legend:**
- **Essentially absent**
- **Consistently present, but not pronounced**
- **A common, marked characteristic**
- **A core, severe, and virtually universal characteristic of the disorder**
- **Poorly documented, ambiguous, mild and/or variable**
- **Increased**
- **Intermediate magnitude of deficit**
- **Not clearly evaluated**

**Abbreviations:**
- AD, Alzheimer’s disease; BP, bipolar disorder; MDD, major depressive disorder; PTSD, post-traumatic stress disorder; SCZ, schizophrenia.


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Discussion
What Is The Trajectory Of Cognition Through The Course Of Illness?
Theoretical Course Of Illness For Schizophrenia

Adapted from Tandon R et al. Schizophr Res. 2009;110:1–23.

Premorbid phase
Cognitive, motor, or social deficits

Prodromal phase
Brief/attenuated positive symptoms and/or functional decline

Psychotic phase
Florid positive symptoms

Stable phase
Negative symptoms, cognitive/social deficits, functional decline

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Differential Diagnosis Of Primary & Secondary Negative & Cognitive Symptoms In Schizophrenia


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Individuals who later developed a psychotic disorder showed steadily increasing full-scale (p=.02, -1.09 SD), verbal (p=.07, -0.69 SD) and nonverbal (p=.008, -0.94 SD) IQ deficits from infancy to adulthood.

Static & Dynamic Cognitive Deficits In Childhood Preceding Adult Schizophrenia

Representative cohort* from New Zealand (N=1,037) assessed cognitive function in children who later developed schizophrenia

• Reported early cognitive deficits and cognitive lags during childhood†
• Different cognitive functions followed different developmental courses

Early deficits:
Some cognitive impairments‡ by age 7; remained steady throughout puberty

Impairment ranged from 0.4–0.8 mental age¶ years

Later developmental lags:
Additional impairments§ between ages 7–13

Each year between ages 7–13, fell behind by additional 0.17–0.26 mental age¶ years

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*Representative cohort comprised of 1,037 males and females born between 1972 and 1973 who were followed from ages 3–32.
†In individuals who went on to develop schizophrenia as an adult as compared to health controls.
‡Impairments on tests indexing verbal and visual knowledge acquisition, reasoning, and conceptualization.
§Visual-spatial problem solving skills, as assessed by arithmetic and digit symbol tests.
¶Mental age scores express the chronological age for which a given level of performance is normative and can be used to monitor each child’s intraindividual development over time. Reichenberg A, et al. Am J Psychiatry. 2010;167(2):160–169.
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Neuroinflammation In Chronic Schizophrenia: Brain Volume & Structure Association Findings

Meta-analyses have reported progressive reductions in cerebral volume and increases in ventricular volume over the course of illness\(^1\)

Free-water imaging, a diffusion MRI analysis method can differentiate between neuroinflammation and white matter deterioration\(^2\)

Results using this method indicate:

Early stages of disease may be more likely to be associated with a** neuroinflammatory response** and less likely with **white matter deterioration or demyelination**\(^2\)

Conversely, white matter deterioration may play a larger role than neuroinflammation in the chronic stages of schizophrenia\(^2\)

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MRI, magnetic resonance imaging.


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Discussion
Relationship Of Cognition To Clinical Outcomes In Schizophrenia
Cognitive Impairment Is Not Related To Positive Symptoms In Chronic Schizophrenia

**CATIE TRIAL:**
Correlations Between Symptom Dimensions and Neurocognitive Domains

**PANSS**

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<th></th>
<th>Total</th>
<th>Positive</th>
<th>Negative</th>
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<tr>
<td><strong>Pearson Correlation (r)</strong></td>
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<tr>
<td><strong>No relationship</strong></td>
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<tr>
<td><strong>Small to medium correlations</strong></td>
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CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; PANSS, Positive and Negative Syndrome Scale.


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Cognitive Deficits In Schizophrenia Are Reliably & Strongly Predictive Of Functional Outcomes

Neurocognitive Deficits
(Representative associations)

Skill acquisition
Community functioning
Instrumental and problem-solving skills
Work performance
Recovery


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Discussion
Strategies To Improve Cognition &/Or Mitigate Progressive Effects Of Illness
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<table>
<thead>
<tr>
<th>Strategy</th>
<th>Possible Impact in Schizophrenia</th>
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<tr>
<td><strong>Pharmacological approach</strong></td>
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<td><strong>Treatment with SGA antipsychotics</strong></td>
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</table>
| Meta-analysis comparing efficacy of SGAs vs FGAs in FES\(^1\) (11 studies; n=1932\(^*\)) | • Pooled SGAs superior to pooled FGAs in improving cognitive composite scores at 3–6 months  
  • Cognitive function (Hedges’ g=0.25, 95% CI: 0.10 to 0.40, P<0.01) |
| **Nonpharmacological approach** | |
| **Cognitive remediation therapy** | |
| Meta-analysis assessing effect on cognition outcomes\(^2\) (40 studies; n=2104\(†\)) | • Small to moderate durable effect on cognition and functioning  
  • Global cognition effect: 0.45, 95% CI: 0.31–0.59  
  • Significant effect sizes from 0.25–0.65 on all but 2 domains\(‡\)  
  • Authors recommended adjunctive therapy, with strategic CRT approach |
| **Aerobic exercise** | |
| Meta-analysis of controlled trials assessing cognitive outcomes\(^3\) (10 studies; n=383\(§\)) | • Significantly improved global cognition (g=0.33, 95% CI: 0.13–0.53, P=0.001) vs control conditions  
  • Effect size in 7 RCTs: g = 0.41, P<0.001  
  • Significantly improved cognitive domains of working memory (g=0.39, P=0.024), social cognition (g=0.71, P=0.002), and attention/vigilance (g=0.66, P=0.005)\(¶\)  
  • Dose effect of exercise (β=0.005, P=0.065) and activity supervision (g=0.47, P<0.001) on global cognition |

\(*\text{Cognitive data for pooled SGAs vs pooled FGA included 11 studies across 1932 patients.}  
\(†\text{Overall meta-analysis included 2,104 participants in 39 reports on 40 independent studies.}  
\(‡\text{Nonsignificant cognitive domains were visual learning and memory and continuous performance test ratings.}  
\(§\text{Included 10 eligible trials with cognitive outcome data for 385 patients with schizophrenia.}  
\(¶\text{Effects on processing speed, verbal memory, visual memory and reasoning and problem solving were not significant.}  
\(\text{CI, confidence interval; CRT, cognitive remediation therapy; FES, first-episode schizophrenia; FGA, first-generation antipsychotics; RCT, randomized controlled trial; SGA, second-generation antipsychotics.}  

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Co-Treatment Strategies To Improve Cognition: Meta-Analyses

Meta-analysis of 29 meta-analyses of RCTs reporting effect sizes for the efficacy of antipsychotic augmentation with any pharmacological agent in schizophrenia

Improvement of cognitive symptoms by antipsychotic augmentation was assessed for:

- Glutamate positive modulators
- Azapirones
- Mood stabilizers
- AchE inhibitors
- Glutamatergic agonists
- NMDA receptor antagonists
- Antidepressants

Only augmentation with NMDA antagonists or antidepressants exhibited an effect on cognitive symptoms:

**NMDA receptor antagonists:** SMD*: −0.77, 95% CI: −1.26 to −0.28, p < 0.01

**Pooled antidepressants:** SMD*: −0.10, 95% CI: −0.17 to −0.02, p = 0.01

*SMD expresses the mean difference between the intervention and control groups in standard deviation units with 95% confidence intervals. Generally an |SMD| < 0.2 is considered negligible, ≥ 0.2 and < 0.5 is small, ≥ 0.5 and ≤ 0.8 is medium, and > 0.8 is large.

AchE, acetylcholinesterase; NMDA, N-methyl-d-aspartate; RCT, randomized controlled trial; SMD, standardized mean difference.

Correll CU et al. JAMA Psychiatry. 2017;74(7):675-84.
Discussion
Questions
Closing
### Upcoming Webinars*

<table>
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<th>Event</th>
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| Using Holistic Strategies To Improve Outcomes In Mood Disorders | • Saundra Jain, MA, PsyD, LPC  
• Michael Thase, MD | July 11, 2019 | 12:00 –1:00pm ET |

*Register for these programs at https://www.PsychU.org/events*
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