Improving cognition in people with schizophrenia: Medication, physical exercise, cognitive remediation, and functional skills training

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Learning Objectives

• Identify cognitive deficits commonly present in people with schizophrenia
• Review medication approaches to cognitive symptoms of people with schizophrenia
• Review brain responses to physical exercise, and improvement in cognitive function
• Clinical experience in supported employment and education
• Review evidence on cognitive remediation

Neurobiology of Schizophrenia

• Neurodevelopmental dysregulation
• Neurodegeneration
• Regional brain volume changes
• Reduced neuronal connectivity
• Cognitive symptoms typically present early

Schizophrenia: Ventricular Enlargement
Suddath et al 1989 Monozygotic Twin Study

Dendritic Spine Reduction in Schizophrenia

Dendritic spines: area 46
Non-schizophrenic individual
Schizophrenic individual #1
Schizophrenic individual #2

Symptom Clusters in Schizophrenia

• Psychotic (positive)
• Disorganized
• Negative (deficit)
• Cognitive
• Mood


Cognitive Symptoms of Schizophrenia

- Working memory
- Vigilance and attention
- Verbal learning and memory
- Visual learning and memory
- Reasoning and problem solving
- Speed of processing
- Social cognition

Assessment of Cognitive Symptoms

- Distinguish symptoms from side effects
- High antipsychotic dose associated with cognitive impairment
- Anticholinergics, antiepileptics
- Distinguish cognitive symptoms from distraction by psychosis or loss of initiative
- Evaluate impact on functioning
- Evaluate coping strategies

Pharmacologic Approaches to Cognitive Symptoms

- Antipsychotic medication
- Specific medication for cognition
- Nutrition and supplements
- Targets:
  - Dopamine
  - Acetyl Choline
  - Norepinephrine
  - Glutamate

Dopamine Circuits in People with Schizophrenia


Global Neurocognitive Improvement

- OLZ > CLZ & HAL
- RSP > HAL
- OLZ: improved general and attention
- RSP: memory (> CLZ & HAL)
- CLZ: improved motor domain

CATIE Cognition Outcomes

- Modest improvements in cognitive measures
  - Risperidone: $z = 0.26$ ($P < 0.001$)
  - Perphenazine: $z = 0.25$ ($P < 0.001$)
  - Quetiapine: $z = 0.18$ ($P < 0.001$)
  - Olanzapine: $z = 0.13$ ($P < 0.002$)
  - Ziprasidone: $z = 0.12$ ($P < 0.06$)
- 2 and 6 months: No significant differences
- 18 months: PPZ > OLZ, RSP

Model Pharmacology for People with Schizophrenia

Antipsychotic medication
+ Anti-negative symptom medication
+ Pro-cognitive medication

Medication Trials for Cognition

- Atomoxetine
- Memantine
- MK-0249 (H3 inverse agonist)
- Nicotine
- Oxytocin
- Glutamate modulators
- Lurasidone
- Donepezil
- amphetamines

Subjective Responses to Exercise

- Clear thinking
- Improved mood, energy, concentration
- Improved sleep
- Wellbeing
- Reduced substance use
- Higher functioning
- Independent motivation
- Spontaneous exercisers study

Trials Evaluating the Effect of Exercise on Cognition

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Van Uffelen et al</td>
<td>Supervised aerobic walking vs supervised flexibility classes for 1 year</td>
<td>Improved memory in subgroup with good adherence</td>
<td>Included vitamin B substitution, no effect for vitamin B</td>
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<tr>
<td>Lautenschlager et al</td>
<td>Moderate-intensity walking vs health education for 6 months</td>
<td>Delayed recall and whole ADAS Cog significantly improved</td>
<td>18-month followup, patients with subjective complaints</td>
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<tr>
<td>Baker et al</td>
<td>Two types of aerobic exercise (eg, treadmill, bicycling) vs stretching and balancing exercises for 6 months</td>
<td>Executive functioning in women, less than in men</td>
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<td>Baker et al</td>
<td>Two types of aerobic exercise (eg, treadmill, bicycling) vs stretching and balancing exercises for 6 months</td>
<td>Executive functioning</td>
<td>Subgroup of participants with impaired glucose tolerance</td>
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<tr>
<td>Anderson-Hanley et al</td>
<td>Chair and standing exercises with small weights (non-aerobic) vs wait list for 4 weeks</td>
<td>Improved working memory and executive function</td>
<td>Small group</td>
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<td>Schwenk et al</td>
<td>Dual task-based exercise training vs unspecific low-intensity training for 13 weeks</td>
<td>Improved dual task performance</td>
<td>Impaired patients with mild to moderate dementia</td>
</tr>
<tr>
<td>Erickson et al</td>
<td>Supervised aerobic walking vs unsupervised stretching and toning for 1 year</td>
<td>Increased hippocampal volume + improved spatial memory</td>
<td>Followup 1-2 years</td>
</tr>
<tr>
<td>Yagüez et al</td>
<td>Movement training vs standard care for 6 weeks</td>
<td>Improved memory tasks</td>
<td>Pilot study, tested directly after intervention ended</td>
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Association Between APOE Status and Exercise Engagement for the Mean Cortical Binding Potential

Exercise in Schizophrenia

- Benefits for comorbidities
- Metabolic benefits
- Core symptoms (psychosis, deficit)
  - Growing evidence
- Cognition
  - Growing evidence
Exercise Capacity and Symptom Severity

- 93 inpatients with schizophrenia
- Functional exercise capacity: 6-minute walk test
- Positively correlated: GAF
- Negatively correlated:
  - Negative symptoms
  - Depression
  - Cognitive symptoms
  - BMI
  - Smoking
  - Dose of antipsychotic medication

Vancampfort et al., Acta Psychiatr Scand. 2012 May;125(5):382-7

Effect of Exercise on BDNF

- 33 outpatients with schizophrenia in Taiwan
- Behavioral weight loss program
  - Physical exercise
- 10 weeks
- Significant increase in serum BDNF levels

Kuo et al., Psychiatry Res. 2012

Effects of Exercise on Hippocampal Plasticity

- Cycling (aerobic exercise) vs foosball (control) x 3 months
- 8 healthy controls: +16% hippocampal vol with exercise
- Male outpatients with schizophrenia
  - 8 aerobic: +12% hippocampal vol, +35% metabolic activity
  - 8 sedentary: -1% hippocampal vol
- Hippocampal vol x ↑ V̇O₂max (P<0.003)
- Hippocampal vol x ↑ short-term memory (P<0.05)
- Negative and cognitive symptoms improved in the group with schizophrenia who exercised

Pajonk F-G et al. Arch Gen Psychiatry. 2010;67(2):133-143.

Effects of Exercise on Brain Volumes

- 63 people with schizophrenia, 55 controls
- Aerobic/strength training vs. OT
- Twice/week x 6 months
- PANSS total and positive, disorganization, excitement and emotional distress factors improved in the group with schizophrenia who exercised
- Cardiorespiratory fitness improvement:
  - Increased grey matter volume and reduced ventricular volumes in patients
  - Thickening cortex in left frontal, temporal and cingulated areas in patients and controls


How Does Exercise Exert Beneficial Effects?

- Neurotransmitter effects
  - Endorphins, endocannabinoids (AEA)¹
  - Norepinephrine, serotonin, dopamine²
- Neurotrophic effects
  - BDNF¹
- Glycogen storage in astrocytes
  - Frontal cortex + hippocampus³
- Tighter glucose regulation⁴


Review: Brain Effects of Exercise

- Improved perfusion
- Neurotrophin release – BDNF
- Neurogenesis - hippocampus
- Neuproliferation
- Neurotransmitter release
- Immunoinflammatory
- Insulin sensitivity

BDNF, brain-derived neurotrophic factor
Exercise Recommendations for Psychiatric Care

- Consider current capacity
- 30 to 60 min, 3 to 7 days/week
- More is better, to a point
- Mix strength and aerobic
- Intensity: 60% to 85% HRmax (220 - age)
- Have client choose activity
  - Access, cost, familiar, enjoyment
  - Variation vs. repetition

Case Example: Exercise and Cognition

- 22-year-old male, schizophrenia
- Randomized to clozapine, 75 mg/day → remission
- 25 lb early weight gain
- Running, health club - triathlon
- Complete reversal of weight gain
- Remission from substance abuse
- Full-time work
- Full time college

Supported Employment & Education

- Individual Placement and Support
- Competitive job placement
- Workplace skills

Subjective Responses to Work & School

- Pride & self-esteem
- Hope
- Reason to be well
- Access to social networks
- External anchor for attention
- Cognitive challenges
- Meaningful roles & responsibilities - recovery

Cognitive Remediation

- Paper & pencil
- Computerized
- 80 hrs, 3-4 hrs/week
- Neurocognition, social cognition
- Drill & practice
- Strategy teaching
- Methods to address beliefs and motivation

Cognitive Remediation + Functional Adaption Skills Training

- N = 114
- 12 weeks CR v. 12 weeks ST v. 12 wk CR + 12 wk ST
- CR – improved neurocognition but not real world behavior
- ST – improved social competence but not neurocognition
- CR + ST
  - greatest ↑ functional competence
  - Significant ↑ community & household activities and work skills
  - NNT = 3 improved functional skills

Cognitive Remediation

• Improves cognitive domains and social adjustment
• Interventions integrating range of cognitive skills
• CR + CBT and/or group particularly effective
• Integration with psychosocial rehab enhances functional outcomes

Summary

• Cognitive deficits are common in people with schizophrenia and drive functional impairment
• Medication trials disappointing to date
  • others in development
• Physical exercise promising
• Supported employment and education clinically helpful
• Cognitive remediation demonstrating positive effects

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