Cognitive enhancement therapy in schizophrenia

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Psychosocial treatments in schizophrenia: a historical overview

Fig. 1. Evolution of treatments for schizophrenia.

Tandon, Nasrallah and Keshavan Schiz Res 2010
Cognitive impairment strongly predicts functional outcome.

**Positive symptoms (40-50%)**
- Hallucinations
- Delusions
- Loose associations

**Negative symptoms (60-70%)**
- Avolition
- Anhedonia
- Anergia
- Asociality
- Alogia

**Affective symptoms (40-50%)**
- Depression
- Anxiety
- Stress induced relapses

**Cognitive (80-90%)**
- Working memory
- Selective attention

**Functional Impairment**

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"Cognitive (80-90%)" and "Selective attention" are highlighted in red. The text in black boxes is surrounded by blue arrows pointing towards "Functional Impairment." The cognitive impairment section is expanded below the main text.
Cognitive deficits in Schizophrenia

- Speed
- Memory
- Attention
- Reasoning
- Tact/Social cognition
- Synthesis and Strategy

Cognitive deficits in schizophrenia are
Pervasive
Persistent
Present early
Progress early
Predict functional
disability
IQ Deficits Present in Premorbid & CHR Phases*, In Liu, Keshavan, Tronick & Seidman, 2015, Sz Bulletin

**Cross-sectional studies from 4 meta-analyses – L. Seidman**
Cognitive Impairments are Strong Contributors to Functional Outcome

Green et al., 2001; Sergi et al., 2006
He seems in a bad mood.

Components of social cognition

Emotional temperature taking.

Boss
He must have had a bad day at home.

Perspective taking.
Not a good day to Ask for a vacation..
But I have to!
So how do I do it?

Social Context appraisal.
PERCEIVING FRAGMENTS as parts of a whole can be difficult for people with schizophrenia.
Cognitive deficits in Schizophrenia

- Speed
- Memory
- Attention
- Reasoning
- Tact/Social cognition
- Synthesis
Psychological aspects of schizophrenia vary with the phase of the illness and can be prevented/minimized.

**Premorbid**
- Psychotic
  - Cognitive impairment
  - Social incompetence
  - Stress sensitivity, Depression/ anxiety
  - Denial/ non-compliance
  - Psychosis

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**Prodromal**

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**Transitional**

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**Recovery**

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PRINCIPLES OF COGNITIVE REMEDICATION #1: PRACTICE.

“The more the neurons fire together, the more they wire together”
Pharmacological Treatments for Cognition

Effect Size (Cohen's $d$)

- Antipsychotics (Keefe et al., 2007)
- d-Cycloserine (Buchanan et al., 2007)
- Glycine (Buchanan et al., 2007)
- Galantamine (Buchanan et al., 2008)
- Practice Effect (Goldberg et al., 2007)
Cognitive remediation works!

Til Wykes et al 2011

The meta-analysis (2,104 participants) yielded durable effects on global cognition and functioning.
Cognitive Enhancement Therapy

- **Targeted**
- **Adaptive**
- **Repetition, and Practice.**
- **Generalized to life situations**
- **Engaging (including social engagement)**
- **Tailored** to patient’s cognitive style
- **Scalable**

Cognitive Enhancement Therapy for Schizophrenia

*Effects of a 2-Year Randomized Trial on Cognition and Behavior*

Gerard E. Hogarty, MSW; Samuel Flesher, PhD; Richard Ulrich, MS; Mary Carter, PhD; Deborah Greenwald, PhD; Michael Pogue-Geile, PhD; Matcheri Kechavan, MD; Susan Cooley, MSN; Ann Louise DiBarry, MSN; Ann Garrett, PhD; Haranath Parepally, MD; Rebecca Zoretich, MSEd
Individualizing treatment: The cognitive styles.

The Unmotivational style.
- Not being able to plan or get started.

The Rigid style.
- Not being able to change plan.

The Disorganized style.
- Not being able to stick to plan.
Components of CET

- Support, education, Internal coping
- Neurocognitive remediation
  - Attention, memory, and problem-solving modules (1 – 1.5 hours/week; ~60 hours)
  - Done in pairs; computer exercises; coaching by clinician
- Social-Cognitive Group Therapy
  - Training in perspective-taking, gistfulness,
  - Acting wisely in social situations; Appraising the social context;
  - non-verbal communication, emotional temperature perception, etc
  (1.5 hours/week; about 45 sessions)

CET Groups are structured

- Welcome back
- Assign Chair
- Review
- Module exercise and Feedback
- Teaching
- Homework
CET computer sessions

- Each session has an initial cognitive training based on the Ben-Yishay exercises (e.g. ARC, ZAC, TE) followed by a 10min. interlude with social engagement (SE) between peers

10min. Peer interaction
CET curriculum

• **Module 1: Basic concepts**
  - psychoeducation on psychosis, Medications, early warning signs and cues of stress, strategies to manage stress, Cognitive flexibility, working memory, gistful thinking, etc

• **Module 2: Social cognition**
  - Emotional temperature taking, perspective taking, context appraisal, Emotion management

• **Module 3: CET applications**
  - Consolidating knowledge from prior modules, Construction of recovery plans for implementation after end of CET; addressing common dilemmas in work/ school/ social life; Generalization to daily life and planning for transition to work/ school,
CET is **effective** in chronic schizophrenia as well as early course schizophrenia.

Hogarty.. et al 2004; 
Eack...Keshavan 2009
The more the brain change, the larger was the improvement in social cognition

Eack et al Arch Gen Psychiatry 2010
The more the brain change, the larger was the improvement in social cognition.

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**Amygdala (L)**

- **CET**
- **EST**

Year

Volume (cc)

Year $p = .001/.008$

**ParaHippocampal Gyrus (L)**

- **CET**
- **EST**

Year

Volume (cc)

Year $p = .008/.048$

**Fusiform Gyrus (L)**

- **CET**
- **EST**

Year

Volume (cc)

Year $p = .007/.048$

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**ΔAmygdala (L) Volume (cc)**

- **CET**
- **EST** $β = .24, p = .031$

ΔSocial Cognition

**ΔParaHippocampal (L) Volume (cc)**

- **CET**
- **EST** $β = .23, p = .036$

ΔSocial Cognition

**ΔFusiform (L) Volume (cc)**

- **CET**
- **EST** $β = .31, p = .034$

ΔSocial Cognition

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Eack et al Arch Gen Psychiatry 2010
Durability of Effects in parent study: 
Neuropsychological Composites

CET benefits are **durable** in early course schizophrenia even after discontinuing treatment

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**ESSENCE study**

Eack..Keshavan Schiz Res 2010
CET has **Real-world** benefits on Functioning and Symptoms (3 year follow up)

- **Functioning (global)**
  - Employment (CET=58%; EST=19%)
  - Social functioning
  - Global adjustment
  - Activities of daily living

- **Symptoms**
  - Negative symptoms
  - Anxiety and depression
  - No effects on positive symptoms, as expected

Eack, Greenwald, Keshavan Psychological Medicine 2010
CET effects are diagnostically non-specific

Autism

Eack et al 2013

Substance abuse and schizophrenia

Eack et al 2015
Goals

• Nature of schizophrenia: pathophysiology and core deficits

• Principles and practice of CET

  • Predictors of treatment response

  • CET in early intervention
Functional connectivity changes

BOLD activation with POP task (cognitive control)


Keshavan et al
Neuroimage 2016
Two-Year Associations Between Changes in Resting State Connectivity and Emotion Processing Outcomes in Early Course Schizophrenia.

Eack et al under review
Baseline brain structure predicts faster response to CET

More gray and white matter (“brain reserve”) to begin with, the better is the early response to CET. Keshavan et al. 2011
CET response predictors

- Baseline verbal memory, but not IQ, may predict neurocognitive benefits with CET.
- Younger age may predict social cognitive benefits with CET.
- Early symptom stabilization may predict cognition and social cognition response to CET.
- Baseline brain structure indexed by gray matter volumes and surface area appears to predict better response to cognitive remediation in early course schizophrenia.
- Patients with low cortical “reserve” may also respond to treatment, but slower than their “high reserve” counterparts.
- Brain’s “functional reserve” may also be a potential predictor of response to cognitive remediation, as indexed by BOLD responses to a cognitive control task.
Importance of Early Cognitive Intervention

• Schizophrenia is characterized by a progressive neurobiologic deterioration (DeLisi, 2008).

• Early treatment may capitalize on an unaffected neurobiologic reserve (Keshavan & Hogarty, 1999).

• Some cognitive domains may be more preserved in early schizophrenia (Braw et al., 2008).
Cognitive Performance Pre and Post Targeted Cognitive Training (TCT)

CHR Post > Pre: ** p<0.05, * p<0.10; HC > CHR: ^^ p<0.05, ^ p<0.10

Hooker, Keshavan and Seidman Schiz Res 2014
Conclusions

• Schizophrenia is associated with cognitive deficits that are prevasive, persistent, present and progress early, and predict poor functional outcome

• CET is an effective, generalizable and durable therapeutic intervention in early course schizophrenia

• Brain mechanisms underlying CET may include protection from gray matter loss, and increased activity and connectivity in key brain circuits

• Predictors of CET response may include younger age, and structural and functional “brain reserve” at baseline

• Social engagement may be a key therapeutic ingredient that needs to be studied further

• CET can potentially be adapted to the clinical high risk populations
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