Cognitive remediation therapy for schizophrenia: an update on efficacy and intervention(s)

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“Community functioning is the ultimate goal….improving cognition in schizophrenia is *not* the end in itself”

Editorial in American Journal of Psychiatry

Michael Green (2009)
Service user views

Personal experiences (Rethink 2010):

“from a bedroom in a hostel to an independent flat with support available if I needed it ”

Greater Independence

“get back to a normal routine….and I hope one day to regain part-time employment”.

Purpose and role

“12 years on, I’m married and content”.

Relationships and support
1. Why is cognition important?

2. What is cognitive remediation therapy (CRT)?

3. What is the evidence that CRT benefits cognition?

4. Do benefits generalise to community functioning?

5. What about mechanisms for transferring therapy gains to community outcomes?
Schizophrenia: a DSM IV perspective

Definition includes

- Social Occupational Dysfunction
- Characteristic symptoms
- Cognitive function

(1887 to present day e.g. DSM V)
Impairment across multiple domains (e.g. Heinrichs et al. 1998; Dickinson et al. 2008)
Impairments tend to be associated with each other (e.g. Dickinson et al. 2004).
Impairments - when defined as “failure to reach expected level” based on maternal education level – affect 98.1% of patients (Keefe et al. 2005)
Present at onset (e.g. Mesholam-Gately. 2009) or earlier (e.g. Cannon et al. 2000) and stable (e.g. Szoke et al. 2008)
“Real World”

Outcomes

Symptoms

Cognitive skills
What Are the Functional Consequences of Neurocognitive Deficits in Schizophrenia?

Michael Foster Green, Ph.D.

Objective: It has been well established that schizophrenic patients have neurocognitive deficits, but it is not known how these deficits influence the daily lives of patients. The goal of this review was to determine which, if any, neurocognitive deficits restrict the functioning of schizophrenic patients in the outside world. Method: The author reviewed studies that have evaluated neurocognitive measures as predictors and correlates of functional outcome for schizophrenic patients. The review included 1) studies that have prospectively evaluated specific aspects of neurocognition and community (e.g., social and vocational) functioning (six studies), 2) all known studies of neurocognitive correlates of social problem solving (five studies), and 3) all

WOS: 150 citations per year
“Real World”
Outcomes

Symptoms

Cognitive skills
“Real World”
Outcomes

Cognitive skills
Cognitive skills $\rightarrow$ “Real World” Outcomes

(0.2–0.4)

Green et al. (1996, 2000)
A group of more recent prospective studies support this link:

(Brekke et al., 2005; Bryson and Bell, 2003; Dickerson et al., 1999; Fujii and Wylie, 2003; Gold, 2004; Jaeger et al., 2003; Prouteau et al., 2005; Smith et al., 2002; Velligan et al., 2000; Woonings et al., 2003)
Symptoms

Depression

Cognitive skills
Via “functional ability”

Community Activities

\[ \sim 10\% \]

\[ \sim 40\% \]

Cross sectional study: Bowie et al. 2006
Symptoms

Depression ~ 20%

Cognitive skills
Via “functional ability” 54%

Work skills

Cross sectional study: Bowie et al. 2006
-ve symptoms 40% Interpersonal outcomes

Cognitive skills 20%
Via “functional ability”

Cross sectional study: Bowie et al. 2006
+ve Symptoms

Subsequent need for care

Cognitive skills / length of illness

1. **Why is cognition important?**

2. **What is cognitive remediation therapy (CRT)?**

3. What is the evidence that CRT benefits cognition?

4. Do benefits generalise to community functioning?

5. What about mechanisms for transferring therapy gains to community outcomes?
Spoilt for choice?

Cognitive remediation programs (some examples):

- Neurocognitive Enhancement Therapy (NET)
- Cognitive Enhancement Therapy (CET)
- Computer Assisted Cognitive Remediation (CACR)
- Neuropsychological Educational Approach to Remediation (NEAR)
- Integrative Psychological Therapy (IPT)
- Posit Science (CRIS)
- Cognitive Remediation Therapy (CIRCuiTS)
Some therapies are computerised.

Practice.. practice..
Some CRTS are focused on teaching strategy plus practice
Other variations….

standard vs. “tailored” tasks

duration (< 10 sessions to 2 years)

transfer of cognitive skills to daily activities, work or social skills via groups (Keefe et al. 2010; Bell et al. 2002; Hogarty et al. 2004; IPT: Brenner, Roder etc)
Defining CRT for schizophrenia

CREW** (2010) definition:

“is a behavioural training-based intervention that aims to improve cognitive processes* with the goal of durable benefits on community functioning”.

*(attention, memory, executive function, social cognition or meta cognition)

** Cognitive Remediation Expert Working Group
1. Why is cognition important?

2. What is cognitive remediation therapy (CRT)?

3. What is the evidence that CRT benefits cognition?

4. Do benefits generalise to community functioning?

5. What about mechanisms for transferring therapy gains to community outcomes?
A Meta-Analysis of Cognitive Remediation for Schizophrenia: Methodology and Effect Sizes

Til Wykes, Ph.D.
Vyy Huddy, Ph.D.
Caroline Cellard, Ph.D.
Susan R. McGurk, Ph.D.
Pál Czobor, Ph.D.

Objective: Cognitive remediation therapy for schizophrenia was developed to treat cognitive problems that affect functioning, but the treatment effects may depend on the type of trial methodology adopted. The present meta-analysis will determine the effects of treatment and whether study method or potential moderators influence the estimates.

Method: Electronic databases were searched up to June 2009 using variants of the key words “cognitive,” “training,” “remediation,” “clinical trial,” and “schizophrenia.” Key researchers were contacted to ensure that all studies meeting the criteria were included. This produced 109 reports of 40 studies in which ≥70% of participants had a diagnosis of schizophrenia, all of whom received standard care. There was a comparison group and allocation procedure in these studies. Data were available to calculate effect sizes on cognition and/or functioning. Data were independently extracted by two reviewers with excellent reliability. Methodological moderators were extracted through the Clinical Trials Assessment Measure and verified by authors in 94% of cases.

Results: The meta-analysis (2,104 participants) yielded durable effects on global cognition and functioning. The symptom effect was small and disappeared at follow-up assessment. No treatment element (remediation approach, duration, computer use, etc.) was associated with cognitive outcome. Cognitive remediation therapy was more effective when patients were clinically stable. Significantly stronger effects on functioning were found when cognitive remediation therapy was provided together with other psychiatric rehabilitation, and a much larger effect was present when a strategic approach was adopted together with adjunctive rehabilitation. Despite variability in methodological rigor, this did not moderate any of the therapy effects, and even in the most rigorous studies there were similar small-to-moderate effects.

Conclusions: Cognitive remediation benefits people with schizophrenia, and when combined with psychiatric rehabilitation, this benefit generalizes to functioning, relative to rehabilitation alone. These benefits cannot be attributed to poor study methods.

(Am J Psychiatry Wykes et al.; AiA:1–16)
CRT Meta Analysis: Sample

- 2104 participants in 39 CRT trials spanning 37 years (1973 – 2010)

- Outcomes: cognition, functioning and symptom outcomes
CRT Meta Analysis

Data Sources: Electronic databases (Embase, Medline, Current Contents, Web of Science, PsychInfo, and Cochrane Register)

Search Terms: COGNITIVE, TRAINING, REMEDIATION, CLINICAL TRIAL AND SCHIZOPHRENIA
CRT Meta Analysis: Inclusion criteria

1) a intervention is described that aims to improve cognition
2) majority (>70%) of participants had a diagnosis of schizophrenia
3) all participants received standard care including appropriate medication
4) there was a control group and allocation procedure
5) there was a cognitive or functional outcome distinct from the trained tasks.
CRT Meta Analysis

Moderators effects

1. Trial characteristics (training approach, dose [duration and intensity], adjunctive rehabilitation)

2. Participant characteristics (sex, baseline symptoms, age)

3. Methodological rigour >>
Trial methodology

- Used Clinical Trials Assessment Measure (Tarrier and Wykes, 2004) to rated trials on:
  - Method of randomisation
  - Assessment measures, independence and masking
  - Control group
  - Statistical procedures (including drop out)
  - Treatment protocol and fidelity
What are the cognitive outcomes?

- Effect sizes derived from neuropsychological test scores
- 101 outcomes converted into composites
- Classified to MATRICS (2005) consensus:

  (attention, speed of processing, working memory, learning and memory, reasoning / problem solving, social cognition)
What are the other outcomes?

- Broad based functioning outcomes (Work skills, functional performance measures, observational measures, GAF scores, work performance and hours, QOL)
- Also, symptom outcomes (e.g. PANSS scores, BPRS)
### Figure 1: Forest Plot of Global Cognition Among Studies in Cognitive Remedia\-tion Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Size</th>
<th>Weight [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logie and van der Velde 2003</td>
<td>0.64 (0.36 to 0.92)</td>
<td>1.9</td>
</tr>
<tr>
<td>Offit and Murgatroyd 1999</td>
<td>0.25 (0.15 to 0.35)</td>
<td>2.2</td>
</tr>
<tr>
<td>Benecke et al. 1994</td>
<td>0.55 (0.14 to 0.96)</td>
<td>2.3</td>
</tr>
<tr>
<td>van der Gaag et al. 2002</td>
<td>0.12 (0.09 to 0.17)</td>
<td>2.6</td>
</tr>
<tr>
<td>Lecointre et al. 2009</td>
<td>0.01 (0.00 to 0.02)</td>
<td>1.4</td>
</tr>
<tr>
<td>Medaska et al. 1998</td>
<td>0.29 (0.25 to 0.33)</td>
<td>3.0</td>
</tr>
<tr>
<td>Field et al. 1997</td>
<td>0.85 (0.65 to 0.95)</td>
<td>0.9</td>
</tr>
<tr>
<td>Medaska et al. 2001</td>
<td>0.56 (0.47 to 0.65)</td>
<td>2.4</td>
</tr>
<tr>
<td>Medaska et al. 2000</td>
<td>-0.03 (-0.04 to 0.02)</td>
<td>2.5</td>
</tr>
<tr>
<td>Ueland and Sand 2004</td>
<td>-0.10 (-0.06 to 0.04)</td>
<td>1.9</td>
</tr>
<tr>
<td>Perksley et al. 2009</td>
<td>0.34 (0.35 to 0.35)</td>
<td>2.3</td>
</tr>
<tr>
<td>Carvalho et al. 2009</td>
<td>0.23 (0.20 to 0.26)</td>
<td>3.5</td>
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<tr>
<td>Graedel and Harris 1989</td>
<td>1.02 (0.75 to 1.29)</td>
<td>1.7</td>
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<tr>
<td>Hodge et al. 2010</td>
<td>0.29 (0.27 to 0.31)</td>
<td>2.5</td>
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<tr>
<td>Burda et al. 1994</td>
<td>0.57 (0.46 to 0.68)</td>
<td>3.2</td>
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<tr>
<td>Hinde-Lidor, et al. 2011</td>
<td>1.67 (1.32 to 2.01)</td>
<td>2.9</td>
</tr>
<tr>
<td>Silberstein et al. 2005</td>
<td>-0.18 (-0.29 to 0.05)</td>
<td>2.2</td>
</tr>
<tr>
<td>Medkenbaum and Cameron 1975 1</td>
<td>2.35 (0.97 to 3.73)</td>
<td>0.8</td>
</tr>
<tr>
<td>Lack et al. 2009</td>
<td>0.60 (0.37 to 0.83)</td>
<td>3.0</td>
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<tr>
<td>Lindenmayer et al. 2008</td>
<td>0.24 (0.21 to 0.26)</td>
<td>3.4</td>
</tr>
<tr>
<td>Hogan et al. 2004</td>
<td>0.92 (0.80 to 1.04)</td>
<td>4.0</td>
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<td>Medkenbaum and Cameron 1975 2</td>
<td>2.35 (0.86 to 3.84)</td>
<td>0.9</td>
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<td>Bell et al. 2001–2005</td>
<td>0.47 (0.10 to 0.84)</td>
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<td>Greg et al. 2007</td>
<td>0.31 (0.19 to 0.43)</td>
<td>3.1</td>
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<tr>
<td>Wykes et al. 2007</td>
<td>0.13 (0.05 to 0.22)</td>
<td>2.3</td>
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<tr>
<td>Vauth et al. 2005</td>
<td>0.90 (0.38 to 1.42)</td>
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<tr>
<td>Bellucci et al. 2002</td>
<td>0.46 (0.23 to 0.69)</td>
<td>2.3</td>
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<tr>
<td>Herranz et al. 1981</td>
<td>0.46 (0.43 to 0.49)</td>
<td>1.7</td>
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<tr>
<td>Saino et al. 2005</td>
<td>0.50 (0.44 to 1.28)</td>
<td>2.6</td>
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<tr>
<td>Kurtz et al. 2007</td>
<td>0.36 (0.25 to 0.47)</td>
<td>2.6</td>
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<tr>
<td>Nocentini et al. 2005</td>
<td>0.44 (0.30 to 0.58)</td>
<td>2.7</td>
</tr>
<tr>
<td>Pons et al. 2006</td>
<td>2.02 (1.92 to 1.13)</td>
<td>2.2</td>
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<td>0.09 (0.04 to 0.14)</td>
<td>2.9</td>
</tr>
<tr>
<td>Willet et al. 2005</td>
<td>-0.26 (-0.34 to 0.03)</td>
<td>2.3</td>
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<tr>
<td>Spaulding et al. 1999</td>
<td>0.22 (0.20 to 0.24)</td>
<td>3.6</td>
</tr>
<tr>
<td>Dickinson et al. 2010</td>
<td>0.06 (-0.43 to 0.55)</td>
<td>3.2</td>
</tr>
<tr>
<td>Wykes et al. 2007</td>
<td>0.04 (-0.37 to 0.45)</td>
<td>3.5</td>
</tr>
<tr>
<td>Overall</td>
<td>0.45 (0.31 to 0.59)</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Does CRT change cognition?

**Effect size (d)**

- Cognition 41
Is there an effect on function and symptoms?
Is there an effect on function and symptoms?

- Cognition: 41
- Function: 18
- Symptoms: 20
Is methodology important?

- Cognition: 41
- Function: 18
- Symptoms: 20

Effect size (d)
Is methodology important?

![Bar chart showing effect sizes for Cognition, Function, and Symptoms.

- Cognition: 41 (11)
- Function: 18 (8)
- Symptoms: 20 (7)

* Symptoms not significant

Better Methodology^
Is methodology important?

Better Methodology^

* Symptoms not significant

<table>
<thead>
<tr>
<th>Category</th>
<th>Effect Size (d)</th>
<th>Count (Std Dev)</th>
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</thead>
<tbody>
<tr>
<td>Cognition</td>
<td>0.5</td>
<td>41 (11)</td>
</tr>
<tr>
<td>Function</td>
<td>0.45</td>
<td>18 (8)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.2</td>
<td>20 (7)</td>
</tr>
</tbody>
</table>

*Symptoms not significant
Is it durable?
Data at 6 months (average)

![Graph showing effect size (d) for Cognition, Function, and Symptoms]
Is it durable?
Data at 6 months (average)

<table>
<thead>
<tr>
<th>Effect size (d)</th>
<th>Post treat</th>
<th>Durability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td>0.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Function</td>
<td>0.35</td>
<td>0.4</td>
</tr>
<tr>
<td>Symptoms*</td>
<td>0.15</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Symptoms not significant
Is CRT acceptable to service users?

- 85% of trials have a drop out rate of less than 20%.
- Average 5% therapy drop out overall.
- Rose et al. (2008) participatory study:
  - CRT is acceptable and valued.
  - But side effect.. benefits of CRT on self esteem were linked with improvement on tasks...if clients felt they hadn’t improved self esteem scores were lower.
Do *client characteristics* influence improvement?

- Higher symptoms associated with small cognitive improvement.

- Trials that included only impaired participants showed higher effect size (0.53 versus 0.35)

- Age not significant in meta analysis (but narrow age range?)

- ...two trials suggest younger people do better (McGurk, 2008, Wykes et al. 2009).
And *therapy characteristics*?

- Little evidence of effects on *cognition outcome* with:
  - comparison against active control treatment
  - Variable dose (intensity or length of therapy)
  - Approach (strategy based or drill / practice)
  - When adjunctive rehabilitation included in the package of care

- But for the functioning outcomes >
But therapy effects on functioning....
But therapy effects on functioning....

Those with psychiatric rehabilitation (N = 4)
CRT: summary

- Moderate - and durable effect - on cognitive skills

- Cognitive improvement *generalises* to moderate effects on functioning

- Larger effect on functioning outcomes when
  - a strategy training approach was used and
  - in particular when combination with a rehabilitation package

- Negligible effect on symptoms
“there was little consistent advantage of cognitive remediation over standard care and attentional controls.....

.....given this finding and the variability in both the methodological rigour and effectiveness of cognitive remediation studies, it was the opinion of the GDG that further UK-based research is required”. 
Progress since NICE (2009)

- NICE review included 17 trials
- Included trials of cognitive adaptation
- Excluded trials
  1. with concurrent vocational rehabilitation
  2. without a functioning outcome
  3. durability data for cognition
- 20 trials published since 2004 - only 4 which included in NICE review
Half the total trials published 2005 - 2010
PORT
(US: Patient Outcomes Research Team)

“rigorous clinical trials are still a minority of studies”
PORT
(US: Patient Outcomes Research Team)

“rigorous clinical trials are still a minority of studies”

<table>
<thead>
<tr>
<th></th>
<th>Methodology score (out of 100)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBTp</td>
<td>61.2 (18.0)</td>
</tr>
<tr>
<td>CRT</td>
<td>57.0 (12.5)</td>
</tr>
</tbody>
</table>

Not significantly different: \( t(72) = 1.2 \ p > 0.05 \)

*Clinical Trials Assessment Measure (Tarrier and Wykes, 2004)
PORT
(US: Patient Outcomes Research Team)

“variation among cognitive remediation models and programs is too great to allow identification of key elements of the intervention”
PORT
(US: Patient Outcomes Research Team)

“variation among cognitive remediation models and programs is too great to allow identification of key elements of the intervention”

Message: there is a Need for a coherent model!
1. Why is cognition important?

2. What is cognitive remediation therapy (CRT)?

3. What is the evidence that CRT benefits cognition?

4. Do benefits generalise to community functioning?

5. What about mechanisms for transferring therapy gains to community outcomes?
Too simple?

Cognition  --  Thrive in job
CRT: summary

• Moderate - and durable effect - on cognitive skills

• Cognitive improvement *generalises* to moderate effects on functioning

• Larger effect on functioning outcomes when
  – a strategy training approach was used and
  – in particular when combination with a rehabilitation package

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CRT: summary

• Moderate - and durable effect - on cognitive skills

• Cognitive improvement generalises to moderate effects on functioning

• Larger effect on functioning outcomes when
  – a strategy training approach was used and
  – in particular when combination with a rehabilitation package

• Negligible effect on symptoms
CRT Work
(e.g. sorting items in a clothes shop)
CRT

Work
(e.g. sorting items in a clothes shop)

Practice categorising complex arrays

“easier to sort stuff ...
but it slows me down”

Plan a CRT session time

Plan shift time
Ability to monitor / regulate: (e.g. monitor performance; e.g. notice errors and respond)

Develop Knowledge about thinking ("I'm impulsive at times") and strategies ("its useful to stop and plan")

Notice similarities and draw analogies between CRT tasks and real world tasks and vice versa.

Meta cognitive skills
Meta cognitive skills on WCST
(Koren et al. 2005; Stratta et al. 2008)

Meta cognitive skills more closely associated with clinical insight (Koren et al. 2005) and social functioning (Stratta et al. 2008) than conventional measures.
CRT aimed at meta cognitive skills should...

1. Awareness of strengths / weaknesses
2. Database of strategies

Thrive in Job

REGULATION
When and where to apply strategies

KNOWLEDGE ABOUT THINKING

What about meta cognitive skills in CRT?

Computerised Interactive Remediation of Cognition – Training for Schizophrenia

Institute of Psychiatry, King’s College London
<table>
<thead>
<tr>
<th>Key</th>
<th>从点化本文格只中电将来用业向即三内脑在说户级</th>
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<tr>
<td></td>
<td>abcdefghijklmnopqrstuvwxyz</td>
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<td>企面种片</td>
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<td>Message</td>
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<tr>
<td>Type Your Answer Here:</td>
<td></td>
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</tbody>
</table>
# Before you start...

**Task Difficulty**

How difficult do you think this task will be? (1=easy to 5=difficult)

1 2 3 4 5

**Task Length**

How many minutes do you think this task will take?

0-1 1-3 3-9 9-15 15+
Well done, you've finished the task!
You used the hint 0 times.

How difficult did you find this task?
EASY-----------------HARD
1 2 3 4 5

It took you 0 minutes.
Your initial estimation was 2 minutes.

How useful were the strategies?
Highlight the code
1 2 3 4 5
Other
1 2 3 4 5
Instructions
Where are you? Click on the correct marker to show your position.
Feasibility study

- Clients (N = 5) rated circuits as:
  1. Attractive
  2. Culturally appropriate
  3. Age appropriate
  4. Clear and understandable
- The same participants also bug tested and suggested numerous design changes.
Circuits

- Provides additional measures of the “process” of change in response to CRT
- Easily transportable – can operate without an internet connection.
- Potentially less therapist (and client) fatigue
- Administering a computerised therapy requires less specific training for therapists……..however……..
Circuits

**Therapists have a key role in CRT**

- Facilitate training > promote metacognition
- Facilitate goal setting and monitoring.
- Develop and use *working alliances* with people who have either frequently suffered stigma in educational contexts or have been socially excluded, or both.
- Trust, mutual confidence and acceptance are important for engagement.
1. Is cognition important? ✓

2. Does CRT benefit cognition? ✓

3. Do benefits generalise to community outcomes? ✓

4. Do we know how generalisation takes place? ?