Cognitive Remediation for Schizophrenia: A Review of Recent Findings

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Opinion statement

Schizophrenia and related psychotic disorders are characterized by deficits in neurocognition. Deficits in domains such as attention, memory, executive functions, and speed of processing, as well as early perceptual processes, typically appear early in the course of the disorder and remain stable over time. Cognitive deficits can cause serious impairments in community functioning (i.e., work, independent living, and social relationships). For this reason, cognitive remediation (CR) is increasingly utilized to improve neurocognition. The empirical support for CR for adults with chronic schizophrenia is encouraging and growing. CR approaches are suitable for widespread dissemination and have been the focus of the majority of recent empirical research in psychoses. There are two broad categories of computerized CR approaches: those that target higher-level cognitive processes, and those that target neuroplasticity using basic auditory and visual processing. Research currently supports the efficacy of both higher-level and neuroplasticity-based CR for improving targeted cognitive domains; however, there is more consistent support for higher-level approaches in terms of generalization to untrained cognitive domains and functional outcomes. To achieve functional outcomes, CR combined with skills training or other psychosocial rehabilitation approaches is likely the most effective approach. The majority of CR interventions allow difficulty to be individually adjusted, which is an important therapeutic feature, and some provide an array of modules to allow personalized interventions. Several CR interventions appear to have durable treatment benefits, but more research is needed to

clarify whether booster sessions, pharmacological augmentation, or other treatments should routinely be incorporated into treatment plans.

Introduction

Neurocognitive impairments are core features of schizophrenia [1, 2]. Patients show large (standardized effect size > 1.0) deficits across the cognitive domains of attention, learning and memory, working memory, speed of processing, and reasoning and problem solving (i.e., executive functions), as well as in basic auditory and visual perceptual processes [3–5]. These deficits are evident in the prodromal phase, tend to worsen around first episode, and subsequently remain stable, typically persisting in the residual phase and after successful amelioration of positive symptoms [6•]. These impairments are also strongly linked to poor functional outcomes across the domains of independent living, work/education, and social relationships. Partly because of their role in determining level of community functioning, there has been an interest over the past 25 years to develop training methods to remediate neurocognitive deficits.

Cognitive remediation (CR) refers to interventions that are based on learning principles that target cognitive deficits and aim to generalize to improvements in functional outcomes (Cognitive Remediation Experts Workshop; CREW, 2010). CR modalities have been developed and evaluated in over 45 independent randomized controlled trials in schizophrenia. Among the various CR approaches, a broad distinction can be made between those focused on higher-level cognition versus neuroplasticity-oriented approaches. Higher-level CR approaches, which directly target cognitive domains such as attention, memory and executive functions, have received the lion's share of research attention. A relatively recent advance in CR over the past 5–10 years is the emer-

gence of neuroplasticity-oriented interventions, which were hoped to be a more effective, neuroscience-based approach to CR. Neuroplasticity refers to the changes in cortical organization and interaction between brain systems in response to learning [7]. Neuroplasticity-based approaches rest on the premise that repetitive high-dosage training in basic perceptual and lower-level cognitive operations facilitates synaptogenesis, which leads to changes in higher-order cognitive functions [8]. Both higher-level and neuroplasticity-based interventions can be administered as stand-alone interventions, or along with additional psychosocial interventions such as skills-training or bridging groups to help the newly acquired cognitive abilities to generalize.

The extensive body of research on CR for schizophrenia has generally demonstrated the promise of improving cognition through training approaches. Indeed, a large meta-analysis in 2011 concluded that CR has durable effects on global cognition and functioning, and that these effects appear to be stronger when CR is combined with psychiatric rehabilitation [9•]. Since the publication of that meta-analysis, trends in treatment and assessment highlight some important updates to our current understanding of CR effectiveness in schizophrenia, and also leave several unanswered questions. In the following sections, we will discuss the firm conclusions we can draw from the recent (past 3 years) empirical trials on higher-level and neuroplasticity-based CR for psychotic disorders. We will then discuss the new research and treatment directions, unanswered questions, and promising future directions.

Higher-level CR approaches

Our review of the higher-level studies published between 2011 and 2013 (see Table 1) includes 16 peer-reviewed studies of CR for schizophrenia. The majority of studies in this review were randomized, controlled trials. The patient sample sizes range from 17 to 107 with a mean of 63; three studies included a healthy control sample. Two studies also included follow-up assessments, at least 1-year post intervention, to examine durability of treat-

Table 1. Higher-level CR approaches

Author/ Year	Stand-alone (Y/N)	Study Design, Dose	Sample (N) Controlled (Y/N)	Results	Generalizability (Y/N)
Bor et al. 2011	Yes	Design: Randomly assigned to CR vs. TAU Dose: RehaCom CR administered in 14 2-hour sessions over 7 weeks	Sample: 17 Scz; 15 NC Controlled: Yes	CR group: over-activations in the left inferior/middle frontal gyrus, & cingulate gyrus, & inferior parietal lobule for the spatial task; significant improvement in attention and reasoning CR group and combined CR + skills-training: significant gains in neurocognition and real-world functioning.	Yes – fMRI improvements; neurocognitive gains
Bowie et al. 2013	Followed by skills-training in sequential condition	Design: Randomly assigned to CR vs. skills training vs. combined treatment Dose: Thinking Skills for Work Program administered over 12 weeks	Sample: 107 Scz Controlled: Yes	CR group: at 6 and 12 months, significant improvement in attention, verbal memory executive functioning; interpersonal relationships CR group: significant improvements on reward and punishment sensitivity and WCST performance. CR group: significant improvement in attention/vigilance, verbal working memory and verbal learning memory, and reasoning/	Yes – the CR group showed significant gains in neurocognition. The combined group showed significant gains in social and functional competence, and real-world community activities and work skills Yes – neurocognition and community functioning
Bucci et al. 2013	Yes	Design: Randomly assigned to CR vs. SST Dose: RehaCom CR administered in 48 1-hour sessions over 6 months	Sample: 72 Scz Controlled: No	CR group: at 6 and 12 months, significant improvement in attention, verbal memory executive functioning; interpersonal relationships CR group: significant improvements on reward and punishment sensitivity and WCST performance. CR group: significant improvement in attention/vigilance, verbal working memory and verbal learning memory, and reasoning/	Yes – CR improves sensitivity to reward and punishment Yes and No – CR led to improvements in some domains of cognition but not others; no gains for functional outcome measures
Cella et al. 2013	Yes	Design: Assigned to CR vs. TAU Dose: CRT administered in 36 1-hour sessions	Sample: 37 Scz; 34 NC Controlled: Yes	CR group: significant improvements on reward and punishment sensitivity and WCST performance. CR group: significant improvement in attention/vigilance, verbal working memory and verbal learning memory, and reasoning/	Yes – CR improves sensitivity to reward and punishment Yes and No – CR led to improvements in some domains of cognition but not others; no gains for functional outcome measures
d'Amato et al. 2011	Yes	Design: Randomly assigned to CR vs. active control Dose: RehaCom administered in 36 1-hour sessions over 12–15 weeks	Sample: 77 Scz Controlled: No	CR group: significant improvement in attention/vigilance, verbal working memory and verbal learning memory, and reasoning/	Yes and No – CR led to improvements in some domains of cognition but not others; no gains for functional outcome measures

Table 1. (Continued)

Author/ Year	Stand-alone (Y/N)	Study Design, Dose	Sample (N) Controlled (Y/N)	Results	Generalizability (Y/N)
Deppen et al. 2011	Yes	Design: Assigned to 1–3 CR modules Dose: Recos administered in 20 1-hour sessions over 20 weeks	Sample: 28 Scz Controlled: No	problem solving; no significant benefits of cognitive remediation on non-verbal working memory and learning, speed of processing or functional outcome measures CR group: significant improvement in the domains targeted (chosen based on pre- treatment cognitive testing); improvement in targeted domains was greater but gains in untrained domains also significant	Yes – gains in trained domains as well as untrained domains, but significantly more improvement in the targeted areas
Franck et al. 2013	Yes	Design: Randomly assigned to CRT or RECOS Dose: Both CRs administered in 42 1-hour sessions over 14 weeks	Sample: 138 Scz Controlled: Yes	RECOS (specific remediation) and CRT (general remediation) globally showed similar efficacy	No
Garrido et al. 2013	Yes	Design: Randomly assigned to CR or active control Dose: CACR administered in 48 1-hour sessions	Sample: 67 Scz Controlled: Yes	CR group: significant improvements in speed of processing, working memory, reasoning and problem-solving, self-esteem and quality of life measures	Yes – overall cognition, functional outcomes
Gharaeipour & Scott, 2012	Yes	Design: Randomly assigned to CR or control Dose: CRT administered in 40 1-hour sessions	Sample: 42 Scz Controlled: Yes	CR group: significant improvement in neuropsychological functioning, depression, and negative symptoms	Yes – overall cognition, clinical symptoms

Table 1. (Continued)

Author/ Year	Stand-alone (Y/N)	Study Design, Dose	Sample (N) Controlled (Y/N)	Results	Generalizability (Y/N)
Lee 2013	Yes	Design: Randomly assigned to CR or TAU Dose: CogTrainer administered in 20 1-hour sessions over 3 months	Sample: 60 Scz Controlled: Yes	CR group: significant improvement in attention, concentration, working memory, and work quality on WBI	Yes – cognition and work outcomes. No improvement in clinical symptoms
Lindenmayer et al. 2013	Integrated with social cognition training and both treatment groups in the context of psychosocial rehabilitation	Design: Randomly assigned to COGPACK or COGPACK + MRIGE Dose: Both CRs administered in 36 1-hour sessions over 12 weeks	Sample: 59 Scz Controlled: Yes	CR + MRIGE: significant improvement on all measures of social cognition; both groups showed gains on MCCB	Yes – social functional gains
Penadés et al. 2013	Yes	Design: Randomly assigned to CRT or SST Dose: CRT administered in 40 1-hour sessions over 4 months	Sample: 30 Scz; 15 NC Controlled: Yes	CR group: significant improvement in executive functions and memory; improvement in efficiency of CEN and DMN during tasks, increase in white matter integrity in the genu of the corpus callosum	Yes – improved neural network efficiency
Royer et al. 2012	Yes	Design: Randomized to CRT or TAU Dose: CRT administered in 40 1-hour sessions	Sample: 59 Scz Controlled: Yes	CR group: significant improvement in memory and executive function; also show improvement on community functioning and social activity	Yes – functional outcomes
Trapp et al. 2013	Yes	Design: Randomly assigned to CR or occupational therapy Dose: X-Cog administered in 12 60-minute sessions in 3 weeks	Sample: 60 Scz Controlled: Yes	CR group: significant improvement in memory, attention and executive performance. At five-year follow-up, verbal memory and problem-solving skills predicted lower rates of relapse	Yes – cognitive functioning and functional outcomes

Table 1. (Continued)

Author/ Year	Stand-alone (Y/N)	Study Design, Dose	Sample (N) Controlled (Y/N)	Results	Generalizability (Y/N)
Tan & King, 2013	Integrated into vocational training or day rehabilitation programs	Design: Randomly assigned to CR or physical exercise Dose: CogRehab administered in 60 hours	Sample: 70 Scz Controlled: Yes	CR group: significant improvement in all neurocognitive domains. Furthermore, the cognitive remediation group achieved greater attainment of vocational or independent living skills and better functional outcomes at post-intervention and at the end of the 1-year follow-up	Yes – cognitive functioning and functional outcomes
Vita et al. 2011	All participants were involved in rehabilitative programs targeting social skills, social relationships or work abilities, individually tailored in relation to clinical needs and personal preferences	Design: Randomly assigned to IPT-cog or CogPack or active control Dose: Both CRs administered in 48 45-min sessions over 24 weeks	Sample: 90 Scz Controlled: Yes	IPT: significant improvement in processing speed and working memory compared to control. CogPack: significant improvement in psychosocial functioning. Both CR groups improved in clinical symptoms and GAF	Yes – cognition, symptoms, functional outcomes

CR: cognitive remediation; TAU: treatment as usual; Scz: schizophrenia; NC: normal controls
 CRT: cognitive remediation therapy
 MRIGE: mind reading: interactive guide to emotions
 CACR: computer assisted cognitive remediation
 Recos: cognitive remediation for schizophrenia

ment effects. The general impression is that many research laboratories are examining the efficacy and effectiveness of CR for psychotic disorders. We included only studies that looked at cognition as the primary outcome, although some studies implemented CR to target social cognition or another related functional ability. There are three salient issues across all recent CR studies: first, whether treatment gains generalize across domains of cognition and to functional outcomes; second, the extent to which CR gains impact neural structures and functions; and third, determination of a “best” methodology for treatment delivery.

First, the studies support the notion that improvements in specific targeted cognitive domains generalize to other untrained domains. All sixteen studies reported gains in several cognitive domains, and in general cognition. One study found gains in all cognitive domains, but significantly greater ones in trained domains [10]. Another study compared higher-level training that targets specific deficit areas (Recos) to general higher-level CR training and found both groups improved on executive functioning, and there was no evidence to support either a specific or general approach to higher-level CR [11]. Regarding generalization to functional outcomes, the recent research also indicates that gains tend to generalize to real-world skills. Ten of the sixteen studies found supportive evidence of generalizability to functional outcomes [12–21]. One study [22] reported no improvement in functional outcome and another study [12] found that functional outcomes improved when skills-training followed CR, but not after CR alone. Although it is not a focus of this review, a few studies observed improvements in clinical symptoms after CR and posit that neurocognitive impairment is closely associated with negative symptoms [23]. Thus, the conclusion across studies is that higher-level CR results in improved neurocognition across domains, and generalizes to work, social, and independent living skills.

A recent trend is the examination of CR impact on neural functioning. There is some evidence that higher-level CR training impacts neural functioning. Two of the 16 studies in the table [24, 25] used magnetic resonance imaging (MRI) to assess white matter integrity and functional MRI (fMRI) to measure regional brain activity of relevant brain regions; both showed positive results. In studies of higher-level computerized CR not included in this review because of publication date, repeated structural MRI assessments show CR resulted in significantly greater preservation of gray matter volume [26] and increased activation in attention and working memory networks (dorsolateral prefrontal cortex, anterior cingulate, and the frontal pole) [27]. Furthermore, these preservations mediated the effects of the CR to predict better cognitive outcomes. However, few studies have examined such effects and larger studies are needed for clarification of the structural and functional changes.

An ongoing debate in this area is whether there is an optimal approach to delivering CR. The primary methods include drill and practice (either administered by a trained therapist or via computerized modules), and drill and practice combined with adjunctive psychiatric rehabilitation. The recent research does not resolve this issue, as gains are apparent in studies with and without adjunctive treatments. Only four of the recent 16 studies reported systematic integration of higher-level approaches with structured approaches for psychosocial treatment [12, 17, 20, 21]. These studies all yielded positive

results for functional outcomes, including work outcomes and social skills. Six of the 12 studies that did not implement adjunctive psychosocial rehabilitation treatment also showed generalization to functional outcomes. Previous meta-analyses found more robust gains for integrated treatments [28], and our current review does not support one side of this argument.

Neuroplasticity-based approaches

As summarized in Table 2, we identified five neuroplasticity-oriented intervention studies published between 2011 and 2013. There were significantly fewer studies of neuroplasticity-based CR than there were studies of higher-level approaches. Three of the five studies were controlled trials with random assignment and one was a multi-site trial [29]. The patient sample sizes ranged from 14 to 55 with a mean of 41. One of the five studies included a healthy control sample and one of the five studies was primarily seeking to establish feasibility. Two of the studies included electrophysiological measurement of treatment effects. Two of the studies included adjunctive psychosocial treatment, and one study directly compared neuroplasticity-based with a higher-level approach. Again, we included only studies that looked at cognition as the primary outcome. We review the same three salient issues in relation to recent neuroplasticity-based CR that we examined above.

First, we examined the evidence with regard to generalizability to untrained cognitive domains and functional outcomes. The five recent studies all found that neuroplasticity-based interventions do not generalize across domains of cognition. Of the five studies we reviewed, two observed definite gains on tasks related to training exercises [30, 31], one study reported trend-level improvements on overall cognition [29], and one study observed gains in the three areas of cognition that were assessed (immediate and delayed recall and working memory) [32]. One study assessed generalization to functional outcomes, but did not find support [30]. Overall, this is a small sample of studies and the negative findings are in contrast to two studies with positive results outside of our time period [33, 34] that found evidence of generalizability to neurocognition and functional outcomes (i.e., work skills).

Regarding the question of whether CR has a detectable impact on brain functioning, two of the five studies measured changes at the neural level. One reported significant effects, in terms of normalized magnetoencephalography (MEG) sensory gating (M50 ratio) following neuroplasticity-based CR training [32]; in a separately published re-examination of the data, the researchers found normalized alpha desynchronization mediated the effects of improved auditory gating [35]. The other study concluded there were no gains in neurocognition and no changes in electroencephalogram (EEG) measures following 40 hours of BrainFitness training [36]. Two other studies [37, 38] that were published before our publication period showed improved verbal memory and auditory neural responses (M100) after intensive auditory training. The MEG findings contradict Rass et al.'s study [36], but are in line with the original neuroplasticity-based studies from Fisher and colleagues [34, 39], which reported significant improvements in verbal learning and memory and global cognition, and maintenance of treatment gains at 6-

Table 2. Neuroplasticity-based CR approaches

Author/ Year	Stand-alone	Study Design, Dose	Sample (N) Controlled (Y/ N)	Results	Generalizability (Y/N)
Keefe et al. 2012	Integrated: drill- and-practice + strategy coaching	Design: Randomly assigned to CR or active control Dose: PositScience + NEAR administered in 40 1-hour sessions over 12 weeks	Sample: 53 Scz Controlled: Yes	CR group: feasibility established and non-significant trend of improvement greater than control group on MCCB	No
Murthy et al. 2012	Yes	Design: Pre-post Dose: Brain Fitness Program (BFP) administered in 32 1- hour sessions over 8- 10 weeks	Sample: 55 Scz Controlled: No	CR group: significant treatment effect on a training exercise task (auditory processing speed), but no improvement on neurocognitive assessment or functional outcome measures	No
Popov et al. 2011	Yes	Design: PositScience CE vs. CogPack Dose: CE: 20 60-min sessions; CogPack: 12 60–90-minute sessions	Sample: 39 Scz; 28 NC Controlled: Yes	Gating ratios decreased after CE but not after Cogpack. Cognitive test performance improved more after CE than after Cogpack	Yes – changes in neural sensory gating and cognitive function
Rass et al. 2012	Yes	Design: Random assignment to CR vs. active control vs. TAU Dose: BFP administered in 20 2- hour sessions over 10 weeks	Sample: 44 Scz Controlled: Yes	CR group: no significant gains on cognitive measures or EEG measures	No
Surti et al. 2011	Integrated into vocational rehabilitation program	Design: Post-hoc analysis Dose: PositScience CCR: Brain Fitness Program (BFP), visual (Insight) and cognitive control exercises (Aristotle) administered between 5 hours and 12 months	Sample: 14 Scz Controlled: No	Visual training performance predicts visual memory improvement. No effect on visual working memory requiring significant manipulation of the presented information (i.e. Spatial Span) or auditory verbal learning and memory	No

CR: cognitive remediation; TAU: treatment as usual; Scz: schizophrenia; NC: normal controls

NEAR: neuropsychological educational approach to remediation

CCR: computer-based cognitive remediation

month follow-up. Thus, the limited data available for this review suggest neuroplasticity-based interventions likely impact functional brain changes associated with basic perceptual/cognitive processes.

Finally, similar to higher-level intervention studies, neuroplasticity-based approaches have been implemented in two formats: drill and practice, and drill and practice integrated with another psychosocial treatment. One of the five studies combined neuroplasticity-based CR with NEAR strategy-coaching “bridging” groups and another study used adjunctive vocational rehabilitation. Neither found significant treatment gains in cognition or functional outcomes. Of the three studies that did not include adjunctive psychiatric rehabilitation, two studies observed gains on tasks similar to those used in training, and one study found no improvements in the treatment group. Thus, the data from the five studies included in this review do not indicate an observable benefit of adjunctive treatment.

Conclusions

Taken together, studies from the past 3 years shed additional light on some of the salient issues in the literature on CR in schizophrenia. Regarding the first question of whether apparent treatment benefits generalize to other neurocognitive domains and functional outcome, the majority of recent studies using higher-level approaches reported generalizability of cognitive gains to other domains of cognition and to functional outcomes. In contrast, few of the recent neuroplasticity-based interventions found evidence of generalization to abilities apart from those directly related to the training exercises. The multi-site trial can be viewed as partial support for neuroplasticity-based interventions and cognitive change because the results were significant at the midpoint but not the endpoint. More studies are needed to fully understand the generalizability of neuroplasticity-based CR. In contrast, the evidence of generalizability has grown stronger for higher-level CR interventions. Regarding the second question about impact on brain functioning, there is a small amount of evidence for higher-level approaches and mixed findings for neuroplasticity-based CR. Changes at the level of structural or functional imaging, or MEG and EEG, will be more meaningful if they are observed in concert with cognitive or functional gains. Regarding the third question of whether these approaches are best administered as stand-alone vs. integrated treatments, the jury is still out. Conceptually, it makes sense that gains from CR would augment gains from skills training or vocational rehabilitation; however, the current review suggests patients benefit with or without adjunctive psychosocial rehabilitation, at least on the functional measures included in the present studies. The study by Bowie and colleagues [12] is the one exception among recent studies to this conclusion: they found that persons receiving CR only showed improvements in neurocognition and those in the combined CR + skills-training showed gains in social and functional competence, real-world community activities, and work skills. These findings are important and suggest a highly specific effect of CR alone versus CR +

adjunctive training, but it is the only higher-level study in our update with a controlled experimental design to specifically make this comparison. Thus, there is currently no clear evidence that neuroplasticity-based CR provides more benefits than traditional higher-level approaches. Only one study has directly compared these approaches by randomly assigning 39 schizophrenia patients to either 20 60-minute sessions of BrainFitness CE or 12 60–90-minute sessions of CogPack [32]. In this study, between-group comparisons were mixed and both treatment groups had significant improvements in cognition, but the neuroplasticity-based group had larger effect sizes for cognitive gains.

The current update reveals notable recent trends and advances in CR research, such as the integration of adjunctive psychiatric rehabilitation and increased utilization of neuroscience assessment techniques. There are a few important areas where future research should be directed. First, additional studies are needed to examine minimally necessary and sufficient dosage and frequency for treatment gains. The dosage requirements will likely depend on individual characteristics including level of baseline deficits. Second, the technique of adjusting difficulty level to match ability level has been supported in reviews, but never empirically compared to a general format with preset difficulty levels. To date, only one intervention (Recos) applied CR to specific domains dependent on baseline deficits of an individual patient. A third issue is that it is difficult to compare results across studies since a wide variety of assessment methods have been used. Future research would be benefited by the use of standardized assessments and well-normed neurocognitive batteries. The MATRICS Consensus Cognitive Battery (MCCB) [40] is accepted for use in clinical trials and facilitates comparisons across interventions and across samples. It would help to develop similar standardized methodologies for domains of community functioning and that was the goal of the NIMH VALERO study [41]. Finally, there is some hope that cognitive remediation might help with the large problem of medication adherence in schizophrenia. However, the literature on cognition and adherence is inconsistent, and some of the larger studies paradoxically find that better cognition is associated with poorer medication adherence [42, 43]. Hence, medication adherence will be an elusive target for cognitive remediation, as its causes are complex. One related question is whether patients with better medication adherence demonstrated stronger improvements with CR, and studies are currently underway to address that issue.

Next steps for CR include clinical implementation and dissemination. Several studies support the implementation of CR in real-world clinical settings [17, 20, 21, 44], although there remains uncertainty about the specific parameters of implementation (e.g., duration, approach, dosage, etc.). As stated above, computerized programs can ease the burden of dissemination in that they require less staff training, and enhance standardization of procedures. The current CR literature suggests CR interventions are efficacious for people with schizophrenia. Further information regarding dosage, individually tailored treatments, and standardization of assessments will enable the field to move forward with effectiveness studies to establish benefits across diverse settings and patient groups. In looking forward to future directions of CR research,

current research trends suggest that combining CR with new approaches, such as social cognitive remediation and cognitive enhancing medication, will be increasingly important. These are active research areas with several trials currently underway.

Compliance with Ethics Guidelines

Conflict of Interest

Carol Jahshan, L. Felice Reddy and William P. Horan declare no conflict of interest. Michael F. Green reports previous work as a consultant for Brain Plasticity, which produces cognitive remediation software, outside of the submitted work.

Human and Animal Rights and Informed Consent

This article does not contain any studies with animal subjects performed by any of the authors.

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