Review

# Cognitive remediation therapy for schizophrenia: what is it and does it work?

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## Abstract

**Impaired cognition is a core feature of schizophrenia (SZ) that precedes, accompanies, and often outlasts a patient's clinical symptoms. The success of new generation antipsychotics, as well as their failure to ameliorate the persistent disabilities associated with the disorder are well documented. Consequently, a number of psychosocial and cognitive interventions have been developed to address specific aspects of disability not adequately alleviated by medication.**

**Among these, interventions adapted from the acquired brain literature that target cognitively based disability (cognitive remediation therapy; CRT) have received significant empirical support both for ameliorating specific deficits in memory, attention and executive function, and improving real world outcome. CRT strategies have focused either on providing drill-based training aimed at increasing capacity or providing behavioural strategies for compensating for cognitive deficits, or a mixture of both. Nonetheless, these interventions have varied widely and several questions remain.**

**This review provides a brief overview of cognitive remediation therapies in psychosis, discusses evidence for its success, and outlines a number of questions that remain about its implementation. Given the current unavailability of cognitive remediation as part of standard care in Irish mental health services, we conclude by describing one such intervention developed within our clinical research group and the questions we hope to address in making this programme more widely available to Irish patients.**


## Introduction

Schizophrenia (SZ) is one of the most disabling disorders in medicine. In a recent World Health Organisation 14-country study of physical and mental disability, active psychosis ranked as the third most disabling condition ahead of paraplegia and blindness.[1] SZ has been estimated to cost between 1.6-2.6% of total healthcare expenditure in western countries and for Ireland has recently been estimated conservatively as €460m in 2006.[2]


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Irish mental health patients have the lowest employment rate of all disability groups;[3] in schizophrenia, only one in four patients are in full-time employment.

Impairments in motivation and cognition, which are strongly associated with long-term disability, respond poorly to current drug treatments, and are a major focus of current pharmacological research.[4] A drought in new drug discovery for SZ is widely acknowledged[5] and has resulted in increased interest in non-pharmacological therapies that can be used in addition to existing pharmacological strategies to minimise the effects of disability in this patient group.[6]

Cognitive remediation therapy (CRT) training has repeatedly been shown to confer significant advantages over current treatments by providing a mechanism for directly treating these deficits in a manner suitable for use by current mental services. Successfully providing CRT in a community-based service represents an important step towards responding to what patients repeatedly articulate as a central cause of disability for them.

Public spending on cognitive remediation therapy research remains low, however, and not just in Ireland. According to Wykes,[7] of the $350m spent on research into SZ by American National Institutes of Health in 2009, only $4.1m (1%) went to cognitive remediation therapy studies. This is to say that by comparison with clinical trials of other therapies for SZ, in particular pharmacological therapies, cognitive remediation therapy has received less focus and attention. Despite this, since the 1990s more than 100 trials of CRT have been reported, with benefits to neuropsychological functions such as attention and memory, and level of social and functional output both reported.

In Ireland and the UK, psychological therapies for psychosis in general have only recently begun to form part of the mental health strategy, with cognitive behavioural therapy (CBT) still not widely available in many services despite significant interest amongst healthcare workers across disciplines. Whether and what place CRT can expect to have given the limited resources available to deliver these services is unclear. However, as with any form of therapy, this discussion must begin with understanding this treatment option, what the 'active ingredients' associated with response are, and what factors explain differences in treatment benefit.

## Cognitive remediation therapy

Adapted primarily from interventions developed for acquired brain injuries, cognitive rehabilitation in SZ has aimed to achieve durable improvements in cognition using a number of techniques. These can be broadly classified into two approaches:[8]

- Cognitive remediation approaches
- Cognitive adaptation approaches.



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In the first approach, cognitive deficits are treated directly through repeated practice and acquisition of compensatory strategy on tasks designed to engage selected aspects of brain function. In the second approach, neurocognitive deficits are addressed through modification of the patient's environment so as to 'bypass' these deficits.

Of the cognitive remediation approach, one of the best-researched early cognitive remediation strategies in SZ was that of Delahunty and Morice,[9] and further developed by Wykes and colleagues (eg. Wykes et al[10]). This intervention was designed to improve executive functioning, in particular, cognitive flexibility, working memory (WM) and planning. It employs a number of techniques to give participants practice on specific tasks and to help them develop an individualised set of problem-solving strategies. These include:

- Verbalising action criteria (saying the strategy and task description out loud); eg. Rossell and David[11]
- Errorless learning techniques (leading the person through the components of the task so that errors rarely occur, eg. Kern et al[12])
- Scaffolding (providing learning support for tasks which increase only slightly in difficulty over time, eg. Young and Freyslinger[13]).

Training consisted of approximately 40 hours of 1:1 therapy taking place on at least three days a week and focused on cognitive flexibility (being able to switch between two tasks), working memory (being able to hold and mentally manipulate information) and planning (being able to organise/sequence information to obtain a goal).

Wexler and Bell[14] have suggested that efforts to remediate, rather than circumnavigate, the cognitive deficits observed in schizophrenia are likely to in part reflect a remediation of 'disuse atrophy' whereby activities that involve areas of deficits are avoided and unrewarded. Therapeutic exercise or practice of these functions and activation of the associated neural centers could, they argued, reverse such atrophy and, at best, decrease the initial deficit. They also argue that this 'use-it-or-lose-it' may also partly explain why cognitive remediation appears to be more successfully implemented with patients who are already engaged in vocational rehabilitation (eg. having some hours of work each week), hence having an opportunity to apply and extend the 'brain' benefits of CRT in their daily lives.

## Recent developments in CRT

More recent developments in CRT have focused on using 'adaptive training' to improve memory and attentional capacity in which task difficulty is dynamically adjusted during the training on a trial-by-trial basis. Based on the patient's response accuracy, the amount of information presented is changed so that it is close to the capacity of the subject. The approach differs from earlier training approaches in several ways.

First, the training was not designed to teach explicit strategies, such as rehearsal techniques or meta-cognitive strategies. Second, rather than taking a broad focus on cognitive deficits in general, this kind of approach generally targets a specific aspects of cognition (eg. working memory; WM). Previous interventions typically used WM tasks as part of training batteries that included other types of executive functions tasks, which decreased the overall time spent on WM tasks. Third, the use of computerised tasks rather than typical one-on-one testing made it possible to have longer training times and to change the WM load on a trial-by-trial basis in response to patient's progress.

Several research groups have developed their own type of computerised task on which to provide such training. In general, the standard procedure involves participants learning to keep in mind a constant stream of verbal or visual information, looking initially for immediate repetitions, then repetitions but one, then repetitions but two, and so on. In neuropsychology this is often described as an 'n-back' task. Progression to the next level of difficulty is contingent on meeting a criterion at the current one. In the non-SZ literature, this kind of working memory training has recently been the focus of enormous interest since its benefits have been shown to generalise to improved cognitive functions including in older adults and children with ADHD, even after relatively brief treatment.[15-17]

In young volunteers dopamine D1 receptor density in prefrontal cortex is shown to increase with this type of training.[18] CRT programs for SZ that target working memory (WM) deficits appears important for the following reasons: Firstly, WM deficits are strongly correlated with the general cognitive deficits observed and are influenced by several putative genetic risk factors for SZ. Secondly, WM deficits are predictive of functional outcome[19] and treatment of these deficits has been shown to strongly correlate with functional improvements following CR training.[20,21]

Several other developments in CRT can be found in the literature. This includes, for example, programmes that focus first on sensory level deficits in patients before honing higher-level cognitive processing such as working memory. Proponents of this approach have argued that this kind of 'bottom-up' approach is crucial, given the sensory difficulties that come with schizophrenia. Training sensory processing frees patients to work on higher-level cognitive tasks. For example, in a study by Fisher et al,[22] 55 clinically stable schizophrenia patients were randomly assigned to either 50 hours of computerised auditory training or a control condition using computer games. Those receiving auditory training engaged in daily computerised exercises that placed implicit, increasing demands on auditory perception through progressively more difficult auditory-verbal working memory and verbal learning tasks. Relative to the control group, subjects who received active training showed significant gains in global cognition, verbal working memory, and verbal learning and memory.

Fisher et al[22] found that these benefits correlated significantly with the improved psychophysical performance, ie. ability to attend to 'signal' instead of 'noise' when attending to auditory information.

## Effectiveness of CRT in schizophrenia

Almost 40 randomised controlled studies of CRT have been reported to date. These include 26 randomised trials included in a meta-analysis by McGurk et al,[23] a further 12 studies reviewed by Wykes and Huddy,[24] and at least three additional studies since then.[25-27]

McGurk et al's[23] meta-analysis, based on 1,151 patients, investigated the effects of CRT on three main outcome variables: cognitive performance, psychosocial functioning, and symptoms. They found that across studies CRT was associated with significant improvements across all three outcomes,



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with a medium effect size for cognitive performance (0.41), a slightly lower effect size for psychosocial functioning (0.36), and a small effect size for symptoms (0.28).

One of the strongest findings of the study was that the effects of cognitive remediation on psychosocial functioning were significantly stronger in studies that provided adjunctive psychiatric rehabilitation than in those that provided cognitive remediation alone. This finding, echoed in other reviews[14] appears to be one of the strongest findings in the field of CRT for schizophrenia, and a major determinant of trial outcome. Many other variables are likely to mediate the efficacy of CRT, including patients related factors, the kind of approach taken, treatment duration and durability, and the treatment context and motivational factors; these are described briefly next.

## Factors associated with variation in response to CRT

*1. Patient-related variables*

In addition to differences in sample size, other patient related variables have included age, inpatient versus outpatient status, and baseline level of function. The meta-analysis by McGurk et al[23] found that neither age nor inpatient status significantly moderated the effects of CR. It might be surprising that inpatient status, which usually indicates greater symptom severity, might not be associated with differences in outcome; however, the benefits of CR have consistently been shown to have only small effects on symptomatology, possible reflecting the relative independence between clinical symptoms and cognitive ability reported in the literature.[28] Moreover, inpatient status may have the benefit of increasing therapy attendance. For age, Wykes and Huddy[24] argue that the relative lack of variation in age across studies (mean 36.3 years) may have lessened the impact of this variable; a study by their group[29] found that younger patients (< 40 years) tended to benefit more from CR training than older patients. In terms of baseline level of function, Bell et al[30] have shown that CRT had a stronger effect (measured in terms of later employment) in those with a poor level of cognitive functioning at baseline.

*2. The CR approach taken*

As already noted, modes and focuses of CR have varied widely across studies. Perhaps inevitably treatment has increasingly made use of computerised training, an important advantage of which is to provide training at a level that dynamically changes in response to patient's baseline performance and subsequent improvements. Most studies have focused particularly on one training package, each of which varies in terms of the type of training provided and the specific aspect or aspects of cognition targeted. For example, intervention targets have included executive functioning and problem solving, attention and vigilance, visual and verbal memory, working memory function, and processing speed. Specific treatment strategies also vary, to include on task rehearsal (drill and practice), strategy training, and enhancement of meta-cognitive skills.

What was perhaps most surprising in the McGurk et al[23] meta-analysis was that the treatment effect size for changes in general cognitive function were largely independent of cognitive function selected, with the exception of verbal learning which seemed to require a particular focus to establish improvements. A meta-analysis carried out since then by Wykes et al[31] based on ~2,100 participants similarly observed the absence of a specific effect associated with the individual CRT approach taken.

*3. Treatment duration and durability*

In a recent consensus statement on cognitive remediation from US-based clinical researchers,[6] a strong recommendation was that CR duration be of a minimum of 30 hours over a sufficiently short period (eg. two to three months) to ensure adequate dosage. This is somewhat longer than cognitive remediation being trialed in the non-SZ literature; a review of CR of working memory[32] reported that 30-45 min/day five-week programmes of CR focusing on working memory were sufficient to bring about significant changes in both behavioural and neuro-imaging measures in patients with ADHD and healthy controls.

In the SZ CRT meta-analysis by McGurk et al,[23] variation in effect size did not appear to be explained by treatment duration despite the massive differences in duration reported (mean 12.8 weeks; SD = 20.9, range = 1–104). An important issue raised by McGurk et al was whether treatment duration was a more significant determinant of the durability of CR effects; testing this hypothesis is made difficult by the paucity of studies that have investigated longer-term benefits (> one year following treatment). Of those that have, Eack et al[26] found that CR was associated with maintained/enhanced grey matter volume one to two years post treatment. Eack et al's MRI study of the effects of CRT is one of only a few such studies in the SZ literature; further studies in this area are sorely needed.

*4. The treatment context and motivational factors*

While inpatient versus outpatient status may be less significant to CR treatment outcome, one factor consistently associated with treatment outcome has been the opportunity to apply the benefit of new training to real life situations. Studies in which patients have an opportunity to apply newfound skills to work and other areas of daily functioning consistently show larger effects than studies in which CR is provided in isolation. Moreover, CR interventions were more likely to show effects that generalised to improvements on measures of social and occupational functioning if the opportunity to practice such skills was made part of the programme.

Medalia and Choi[33] argue that in addition to providing further learning and practice, opportunities to apply learning from CR had a direct benefit for enhancing intrinsic motivation to learn by making CR personally relevant and more apparently useful. In addition to providing opportunities to apply new skills, several interventions explicitly teach generalisation techniques and motivation enhancement. Silverstein[34] argues that this is particular essential in SZ research given the unusually low intrinsic motivation often associated with the disorder.

## Important questions for the use of CRT in the treatment of schizophrenia

Despite replicated evidence of success with CR in SZ several questions remain. These include:

*1. The cost effectiveness of CR in addition to treatment as usual*

Only one study has directly addressed the economics of CR interventions, and reported that, at least in the short term (< six months post therapy), economic costs (in terms of overall service utilisation), were comparable for those receiving



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CRT and those receiving treatment as usual. The longer-term economic costs have yet to be evaluated.

*2. The effects of CR interventions on brain structure and function*

An impressive aspect of cognitive training in the non-sz literature has been the effects on brain structure and function. A recent study[32] highlights the effects of brief working memory training across 10 different studies on changes in brain activation in multiple brain regions, including cingulate cortex, dorsolateral cortex, parietal cortex, and occipital cortex. Much less is currently known about the effects on brain structure and function following CR interventions in SZ, as only two studies to date have investigated the effects of CR on either brain structure[26] or brain function.[35]

Particularly interesting in the Eack et al study were the benefits of CR to grey matter volume one to two years post treatment. This study appears to highlight brain plasticity in SZ despite chronic disability, and the possibility of bringing about brain-related recovery in brain structures and functions associated with cognition; replication of these results, particularly over an extended follow-up period is clearly a priority for the field.

*3. Role of genetic variants in predicting outcome following CR*

Despite the advances in understanding the genetic architecture of SZ and associated cognitive deficits, very little investigation of the role of genetic variants in predicting outcome following CR has been undertaken, with unreplicated association between the COMT MET allele and better outcome being the single study undertaken to date;[36,37] further studies of schizophrenia and cognition related genes are required to further determine the effect of genetics on brain plasticity and treatment response (eg. DTNBP1, G72, NRG1).

*4. Does treatment type influence the duration of treatment required?*

While the meta-analysis by McGurk et al,[23] and a more recent meta-analysis by Wykes et al,[31] suggested comparability between CR interventions, it is still unclear whether treatment type influences the duration of treatment required, ie. does a more specific or more general cognitive remediation treatment lead to more rapid treatment outcomes.

*5. Acceptability to patients*

Finally, little is know about the acceptability of CR interventions to patients and the factors that contribute to acceptability. Addressing these questions is critical in seeking to make interventions that augment current approaches to treatment in combating disability.

## CRT for schizophrenia in the Irish context

As noted, while the efficacy of CRT for schizophrenia has been confirmed by almost 40 independent studies, CRT for schizophrenia has not been available in Ireland until now. In partnership with SHINE, the national organisation for patients with enduring mental health disorders (previously called Schizophrenia Ireland), we are engaged in delivering a working memory focused CRT programme developed at Trinity College Dublin to community-based patients with schizophrenia. Key features of this CRT intervention include:

- This CR intervention is a computerised programme
- Training level is dynamically varied to suit patients' individual ability level; The cognitive function targeted is working memory, an aspect of function that closely relates to both general cognitive ability[32] and, in SZ, level of social function[20]
- Motivation to learn and generalisation to real world function are a particular focus of the intervention and supported with ongoing therapist interaction in addition to personal training
- The context for training is an urban community-based outpatient rehabilitation and support setting based on a recovery model and focused on promoting independence and better integration.

After initial training with the programme, patients will be able to access training remotely through the internet. As access to the internet falls below 20% for this patient group, internet access is facilitated by providing patients with a laptop computer and a mobile internet connection.

In setting up the project, which is funded by the Genio Trust, a key objective was to take the program out of hospital based services and locate it in the community beside social and occupational rehabilitation services. The rationale for this was two fold: firstly, to make accessing the programme less stigmatising; secondly, to maximise the likelihood that training benefits will be synergistically facilitated by the potential to generalise skills learnt in social and occupational settings.

This project is not specific to any one catchment area: during the course of the project any individual with a diagnosis of schizophrenia/schizoaffective disorder in a stable phase of their illness and who has some social or occupational activity can apply to participate. Enquires about the project can be made to the first author.

## Conclusion

The recent NIMH position paper[6] on the role of CRT in treating schizophrenia concluded by stating that a multisite trial of a cognitive remediation intervention using a network of diverse research sites would be of great scientific value. Rather than suggesting only one kind of treatment over another, the authors argued that various interventions could be employed for this multisite trial, given the evidence of success across interventions. However, whatever the strategy, Keefe et al stressed the need to address key motivational and interpersonal aspects of cognitive remediation, as well as the importance of applying their newly acquired cognitive skills to everyday life. In effect, this report concludes that while different interventions may be associated with different outcomes, the single most important determinant of outcome is how well patients are engaged in the programme, whether they remain engaged for the duration of the course, and whether they then have an opportunity to put into practice what they've learned.

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