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Cognitive Remediation Therapy (CRT): Improving Neurocognition and Functioning in Schizophrenia

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1. Introduction

Schizophrenia is generally viewed as a chronic disorder characterized by psychotic symptoms and relatively stable neurocognitive and interpersonal deficits. According to the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), to be diagnosed with schizophrenia, three diagnostic criteria must be met (APA 2000):

1. Characteristic symptoms: Two or more of the following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).
   - Delusions
   - Hallucinations
   - Disorganized speech, which is a manifestation of formal thought disorder
   - Grossly disorganized behaviour (e.g. dressing inappropriately, crying frequently) or catatonic behaviour
   - Negative symptoms: Blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)

If the delusions are judged to be bizarre, or hallucinations consist of hearing one voice participating in a running commentary of the patient's actions or of hearing two or more voices conversing with each other, only that symptom is required above. The speech disorganization criterion is only met if it is severe enough to substantially impair communication.

2. Social or occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.
3. Significant duration: Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if symptoms remitted with treatment).

The primary treatment of schizophrenia is antipsychotic medications, often in combination with psychological and social supports. Antipsychotic medication has made it possible to

reduce psychotic symptoms and to prevent relapses, but is it expected that antipsychotic medication could, one day, improve cognition. Frequently, residual cognitive impairments stand as impediments to full recovery from schizophrenia (Bell and Berson, 2001). A number of psychosocial interventions may be useful in the treatment of schizophrenia including: family therapy, supported employment, cognitive remediation, skills training, cognitive behavioural therapy (CBT), token economic interventions, and psychosocial interventions for substance use and weight management. Cognitive Remediation Therapy (CRT) is a promising new treatment designed to improve neurocognitive abilities such as attention, memory and executive functioning. A large body of data on the efficacy of cognitive remediation therapy has been produced, and a number of meta-analyses have shown moderate to large effects on cognitive outcomes. However, experts in the field claim that CRT should not only enhance cognition but also that the improvement in cognition will affect community functioning. Consequently, clinicians are now increasingly concerned with identifying appropriate cognitive targets and ways of promoting secondary improvements in functioning.

2. Neuropsychology in schizophrenia

Current neuropsychological models of schizophrenia assert that cognitive impairments found in patients are simply the expression of some abnormalities in brain functioning. These abnormalities are found mainly in the frontal lobe and lead to a reduced capacity to activate frontal areas when faced with a cognitive challenge. In addition, multiple connectivity abnormalities between different brain regions have also been described. More specifically, it seems that the neural circuits interconnecting the limbic, the temporal and the frontal lobe are irregularly connected (Barch 2005). This model has received considerable support in empirical studies from various disciplines including neuroimaging, electrophysiology, neuropsychology and cognitive psychology (Andreasen, 1997). In an excellent review, Shenton et al. (2001) described the anatomical abnormalities that have been replicated most consistently in schizophrenia research: cavum septum pellucidum (92%), amygdala or hippocampus (74%), lateral ventricles (73%), basal ganglia (68%), superior temporal gyrus (67%), corpus callosum (63%), temporal lobe (61%), thalamus (42%), cerebellum (31%) and brain volume (22%). Nevertheless, the proposed model goes beyond the direct relationship between anatomical abnormalities and neurocognitive impairments. None of the aforementioned brain areas work in isolation. Rather, they work together as a part of different cortico-subcortical circuits linking the frontal cortex with other brain regions, such as the limbic system, basal ganglia and thalamus (Pearlson et al., 1996). This type of "disconnection" between brain areas would involve defective processing of information and be expressed as cognitive impairment (Weinberger & Lipska 1995).

Thus, due to the heterogeneity of the causes of cognitive impairments, it is more common to find different cognitive profiles with selective cognitive impairments than homogeneous, generalized cognitive impairment. Different sorts of dysfunctions have been described in various domains such as attention, vigilance, verbal memory and working memory. Additionally, patients with schizophrenia present serious difficulties in executive functioning: inflexibility, poor self-monitoring, lack of planning, and passive performance due to a lack of cognitive strategies. Problems with motor skills and difficulty in suppressing or inhibiting inappropriate responses are also present. Heinrichs & Zakzanis (1998) conducted a meta-analysis of more than 200 studies and found that between 60-80%

of patients with schizophrenia have neurocognitive impairments that can be classified as moderate or severe. However, it was not possible to find a unique cognitive profile for all patients. Various combinations of impairments including attention, working memory, verbal or visual learning, psychomotor speed and executive function were described (Table 1). Therefore, heterogeneity across all possible conceivable neurocognitive domains is perhaps what best describes the pattern of neurocognitive impairment in schizophrenia. Nevertheless, although the neuropsychological assessment of a patient diagnosed with schizophrenia may reflect an impaired profile through a number of domains such as attention, vigilance, verbal memory and working memory, the presence of attention and executive impairments are the common feature.

MILD IMPAIRMENT 0.5-1 SD below the mean	MODERATE IMPAIRMENT 1-2 SD below the mean	SEVERE IMPAIRMENT <2 SD below the mean
Perceptual skills	Verbal memory	Executive function
Speed processing	Working memory	Verbal fluency
Recognition memory	Recall memory	Verbal learning
Naming	Visuo-motor skills	Motor speed
General Intelligence	Distractibility	Vigilance

Table 1. The severity of cognitive impairments in schizophrenia.

3. Relevance of neurocognition in schizophrenia

Neurocognitive impairments in schizophrenia are not trivial because they are consistently associated with low social functioning and worse outcomes. Up to 60% of the variance in social functioning seems to be explained by neurocognitive variables. Performance in tests of attention, working memory, verbal memory, psychomotor speed and executive functions have been shown to be selectively related to different aspects of psychosocial functioning ranging from the level of independence in daily living skills, work performance and use of psychiatric services to the ability to learn new skills. Green (1996) conducted an important meta-analytic study attempting to test the aforementioned putative relationship between neurocognition and functioning. A positive and significant relationship between cognition and functioning was established through the meta-analysis and the various cognitive domains showed significant correlations. More specifically, verbal memory acted as the most robust predictor of functioning including social functioning, social problem solving and learning new skills. This close relationship has been replicated in other studies. Additionally, in former studies other variables including attention, processing speed and executive functions also proved to be strongly related to psychosocial functioning (Table 2). The presence of impairments in both verbal memory and attention span would affect the ability to acquire social skills and might be associated with considerable social dysfunctions.

	Vigilance	Working Memory	Verbal Memory	Executive Function
Social Functioning	+		+	
Vocational Functioning	+	+	+	+
Autonomy		+	+	+

Table 2. Relationship between cognitive performance and functioning.

Furthermore, some specific neuropsychological tests such as the Wisconsin Card Sorting Test (WCST) can be useful in the prediction of concrete aspects of functioning such as work performance (Lysaker et al. 1996). This test has shown an acceptable level of prediction regarding work performance in patients with schizophrenia. Thus, bad performance on the WCST is associated with fewer working hours in a competitive job, increased likeliness of emergent symptoms during the workday and the possibility of new hospital admissions. McGurk & Melter (2003) have pointed to neurocognitive aspects as the most important factors to be taken into account when attempting to return to work. Finally, it should be emphasised that cognitive impairments may interact with negative symptoms. Even further, some authors suggest that the combination of problems, negative symptoms and cognitive dysfunction would themselves generate pervasive social dysfunction. This is especially pernicious as some negative symptoms would prevent the patient being involved in rehabilitation programs.

4. Evidence-based treatments

Initially, neuropsychological rehabilitation programs used in brain injury were the best option for treating cognitive impairment in patients with schizophrenia. Other interventions used in degenerative processes and elderly people were also tried. Nowadays, this practice would not be considered appropriate because cognitive rehabilitation in schizophrenia has its own peculiarities. Therefore, it is highly advisable to use specific interventions, especially those that have been proven to be effective in controlled studies. Various approaches seem to be efficacious and effective alternatives. Interestingly, all these cognitive remediation therapies for schizophrenia have in common that they are types of behavioural training that aim to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization (Crew, 2010). Another important feature of evidence-based cognitive remediation therapies is the aim of enhancing cognition with the expectation that improved cognition will affect community functioning.

4.1 Integrated Psychological Therapy (IPT)

Integrated Psychological Therapy for Schizophrenia (IPT) was probably the first therapy to include neurocognitive elements specially developed to be used with schizophrenia patients (Brenner et al., 1992). It was designed by Professor Hans Dieter Brenner and colleagues at the University of Bern in Switzerland. There are versions in German, English and Spanish, adapted by Professor Volker Roder. The IPT is a structured intervention program that prescribes steps for treating cognitive and behavioural dysfunctions (Roder et al. 2007). It comprises five modules, applied in the following order: cognitive differentiation, social perception, communication, social skills, and interpersonal problem solving (Table 3). Although the main objective is the treatment of neurocognitive disorders, it also includes psychosocial elements, such as social skills training designed to improve social behavior deficit. The duration of the intervention generally ranges between 8 and 12 months although it is not established a priori and depends on the needs and progress of the participants during the course of treatment. It is a group therapy and is implemented twice a week for between 45 and 90 minutes. Ideally, group size is between four and eight participants. Support materials are very simple: a room, a blackboard, projector, paper, and pencils or pens. Learning techniques are frequently used such as token economy, discriminate

learning, social reinforcement, modelling and shaping. Group dynamic techniques are also required including sharing, coaching, role playing, reformulation and positive connotation.

MODULES	TARGETS	INTERVENTION TECHNIQUES
Cognitive Differentiation	Attention Concept formation Abstraction	Card Sorting Verbal concept exercises
Social Perception	Social cognition	Slides depicting social situations Collecting information Interpretation and discussion Assigning a title
Verbal Communication	Communication skills	Literal repetition Paraphrasing W-Questions Topical questions Focused communication
Social Skills	Social Skills	Cognitive analysis Role-playing
Problem solving	Interpersonal problem solving	Problem solving technique Generalisation

Table 3. Modules of the Integrated Psychological Treatment (IPT).

The Cognitive Differentiation module seeks to improve attention (selective attention, focused attention, sustained attention, alternating attention, etc.) and also conceptualization skills (abstraction, concept formation, conceptual discrimination, etc.). The exercises consist of sorting cards; managing verbal concepts; elaborating definitions; managing words in different contextual meanings, and so on. The use of reinforcement is especially important in this part of the program to overcome motivational problems and negative symptoms. The Social Perception module seeks to improve the analysis and understanding of psychosocial information. This is neurocognitive work but focused on the social cognition processes. Different slides displaying social interaction situations are shown to the patients to be analyzed and interpreted. Each slide gives the opportunity for some analysis, coding, integration and understanding of social information. Therapists try to stimulate patients' abilities to discriminate between relevant and informative parts and the irrelevant stimuli. To achieve these targets, therapists use a variety of techniques including shaping, modelling and coaching. The Communication module targets relevant aspects of communication and interpersonal behavioural skills. It is designed to work with the three basic processes of language: listening, understanding and speaking. A series of verbal exercises are proposed in order to determine the effects of cognitive impairment on communication. These move from the literal repetition of sentences, formulation of questions and answers, to free communication exercises which gradually involve patients in interactive communication exercises. The Social Skills module aims to practice the necessary skills that enable patients to have satisfactory psychosocial functioning. The authors emphasize that learning through

role-play requires memorization and analysis of social behaviour. Both processes may be altered as a consequence of cognitive impairments. Therapists encouraged the practice of these skills in real contexts to compensate for cognitive difficulties. Finally, the Problem Solving module brings the program to an end. The main objective is to increase the likelihood of solving the typical problems that appear in usual contexts. The intention is to allow the patient to be able to identify problems, to develop a rational attitude towards them and to focus on solutions rather than the problem itself so ultimately, fostering a thinking style that anticipates and takes into account the consequences of the chosen solutions. As is well known, all of these skills require a high degree of self-management that is not frequently found in patients suffering from executive dysfunction. A recent meta-analysis has confirmed the effectiveness of this therapy (Roder et al. 2006).

4.2 Cognitive Enhancement Therapy (CET)

The Cognitive Enhancement Therapy (CET) program was described by Hogarty & Flesher (1999 a, 1999 b). It was designed to be applied to patients with schizophrenia who show significant social and functional disability following pharmacological stabilization. CET has two complementary targets: neurocognitive rehabilitation and improvement of social cognition. It is intended that patients develop the cognitive and social skills that will be required for proper functioning in real interpersonal settings. It is primarily based on cognitive strategy instruction through computer tasks and group socialization experiences.

The program consists of two distinct parts: a neurocognitive training module and a social cognition module. Neurocognitive training is done individually and assisted with computer programs. It should be stressed that the exercises are done on the computer with the help of a peer and guided by a therapist. The social cognition training is done in groups through structured exercises and the practice of social interactions in real-life situations. Individual neurocognitive training is done through a series of exercises of increasing difficulty using computer programs on a PC. The training lasts about 60 hours and in each session performance on various tasks is discussed with another patient and the therapist who will carry out the necessary coaching. In terms of content, training is divided into attention, memory and problem-solving modules. Attention training is performed using computerized tasks from other programs such as the Orientation Remediation Module Ben-Yishay (1980) and the Bracy Computer Program (1987). Additionally, memory training aims to practice a number of skills that are supposed to improve memory performance. Categorization ability, use of abstract thinking and a flexible cognitive style on spatial and verbal tasks are all encouraged. Finally, improvement in problem-solving capacity is done through the practice of analytical thinking, planning, generation of alternatives and social intuition by reading clues.

The other component of the program is training in social cognition. This training is conducted in groups and aims to improve the cognitive skills required for effective interpersonal behaviour. Groups consist of 6 to 8 patients participating in 45 weekly sessions lasting one hour. Examples of the session topics are: understanding the others point of view, reading nonverbal signals or adjusting personal behaviour to the norms and rules of the social context. Group exercises are a way of generating real experiences to facilitate the learning of a variety of skills such as taking others' perspectives), interpreting contextual variables, solving potential social conflicts, and practicing emotion recognition, cognitive flexibility, abstract thinking and planning. The group exercises include categorization

guidelines, construction of verbal messages, initiation and maintenance of a conversation, and extracting the central message from the opinion pages of a newspaper (the authors used the online version of USA Today). In other tasks, therapists encourage participants to interpret ambiguous scenes in interpersonal contexts in terms of social and emotional content. Participants are asked to interpret the intentions of various actors in a scene and to produce a written report highlighting the most relevant leading roles. This program was tested in a methodologically rigorous study, with a 2 year follow-up, and showed improvements in verbal memory, processing speed, social cognition and social adjustment (Hogarty et al. 2004).

4.3 Cognitive Remediation Therapy (CRT)

Initially developed in Australia by Ann Delahunty and reformulated by Til Wykes in the United Kingdom, this rehabilitation program aims to remediate cognitive impairments in schizophrenia patients by targeting executive functions. The program is applied individually, using mainly paper and pencil tasks and is based on cognitive strategy instruction. Ann Delahunty & Morice Rodney (1993) developed the first version of the program, the Frontal/Executive program, based on the specific process model. The tasks are designed to directly activate the frontal and prefrontal neural systems of the patient. The program consists of three modules: cognitive flexibility, working memory and planning (Delahunty et al. 1993, 2002).

The "Cognitive Shift Module" aims to address flexibility in thinking and information-set maintenance both of which presumably require the capacity to effectively engage and disengage activated neural network processing. It consist of a package of 6 to 8 training sessions of one hour targeting cognitive inflexibility and attention difficulties. Tasks are designed to provide some practice in exercises that help patients to get used to switching from one task to another and being able to keep in mind the information relevant to each task 'set'. It is practiced with visual, conceptual and motor information (Table 4). To ensure maintenance and the switch to the appropriate 'set' for each task, the therapist tries to use verbal instructions as a cue. Rather than performing the tasks themselves, patients should practice the connection between thought and behaviour. The therapist's task is to force the patient to pay attention to all stimuli, to ask the patient to identify what the current 'set' is and to show the patient whether their performance speed is appropriate. Finally, the therapist should promote open and covert verbal mediation of the task and not allow the patient to hesitate about what 'set' has to be used.

AREA	TARGET	INTERVENTION TECHNIQUE
Visual-motor training	Psychomotor coordination	Line bisection Cancelation tasks
Perceptual Flexibility	Alternative perceptions	Figure/Ground pictures, overlapping figures
Conceptual Flexibility	Alternative concepts	Card sorting, number shift, visual illusions, Stroop exercises
Psychomotor training	Speed Accuracy	Finger tap, hand flip, palm lifting.

Table 4. Components of the 'Cognitive shift' module.

The "Working Memory Module" aims to target the executive processes central to memory control, and has patients work with as many as two to five information sets at a time. It focuses on variables such as attention, sequencing, working simultaneously with multiple tasks, and delayed verbal and visual memory information. Working memory is defined as the ability to maintain or manipulate different sets of data. In schizophrenia, poor memorization is interpreted as a consequence of executive impairment rather than primary memory impairment per se. Thus, improving executive functions might be an important factor in enhancement of memory functioning. The module consists of two parts: A and B. Both consist of eight sessions of one hour and are designed to be used over several weeks. Part A introduces a series of working memory tasks ranging from one to four information sets. Part B provides additional exercises to Part A tasks with special emphasis on sequencing and dual tasks.

Finally, the primary target of the "Planning Module" is self-ordered, goal-oriented, set/schema formation and manipulation, that is, the application of the practiced processes, such as Working Memory, to tasks requiring planning. The goal of the tasks is to improve cognitive functioning by using active cognitive strategies including active coding, sequencing and chunking, and using internal and external verbal mediation in multitasking performance. The Planning Module also includes two parts: A and B. The first is a package of twelve sessions of one hour and part B involves about eight training sessions. Both modules provide practical exercises that facilitate the formation and manipulation of sets of information or goal-oriented schemes, with special emphasis on generating cognitive strategies and self-control. We work on control processes relating to the skills of attention, sequencing, organizing information, practical reasoning, formation of sub-objectives, and self-monitoring. Part B of the Planning Module provides more complex tasks requiring the application of effective executive skills. All tasks set out in Part B are designed to involve abstraction with more complex and complementary material. Finally, some everyday tasks like using a recipe or reading a map are used as complementary exercises.

The theoretical formulation of cognitive remediation therapy by Til Wykes and Clare Reeder (2005) also represents a major overhaul of the Frontal/Executive program. Although it uses the same treatment modules, it requires that the therapist proceed in a new way. The most important innovations are the emphasis on meta-cognition, and the use of techniques such as errorless learning and scaffolding. Scaffolding is a learning technique in which the therapist tries to teach the patient to solve problems taking their cognitive limitations into account. This involves an instructor extending a learner's ability by providing support in those aspects of a task which the learner cannot accomplish, while removing assistance in those areas where competence has been achieved. Exercises become an opportunity to practice cognitive strategies and also to learn new ones. All this learning is done through an errorless learning approach using tasks of progressive complexity and with the problem being set, as far as possible, at the subject's own pace. Subsequently, further practice is necessary to achieve the over-learning of the new cognitive strategies. The same procedure applied throughout the modules will be used to solve everyday problems of working memory, planning and, to some degree, cognitive flexibility. All in all, the treatment guidelines proposed by Wykes (2008) are based on the following principles:

1. Initial assessment
2. Identification of personal goals

3. Personal therapeutic relationship to promote self-esteem
4. Tailoring of sessions
5. Reflective learning (metacognition)
6. Use of scaffolding
7. Using errorless learning
8. Development of cognitive strategies
9. Generalization to everyday life

This program has been tested in controlled studies and has shown positive effects on cognition and on some aspects of social functioning (Wykes et al. 1999, 2007; Penadés 2006).

4.4 Studies of efficacy

The first review of cognitive remediation was performed by Kurtz et al. (2001). Because of its thoroughness and the fact that it was the first review that used meta-analytic methodology, it can be considered as a pioneering study even though, in this analysis, the authors mixed results from 'laboratory' and clinical studies. The review was conducted on three distinct cognitive domains according to the target of the neurocognitive intervention: executive function, attention and memory. Starting with executive function, a fairly statistically significant (effect size = 0.96) effect was found. Various intervention techniques produced a reduction in neurocognitive deficits such as committing perseverant errors. Furthermore, the interventions facilitate cognitive flexibility and improve patients' categorization ability. This effect remained similar in other studies despite the differences in intervention strategies. Although the meta-analysis confirmed these positive findings, the effect size obtained in clinical settings was always somewhat lower than in research conditions. Additionally, the meta-analysis showed that both reinforcement learning and teaching cognitive strategies were effective in improving performance on attention tests. Results regarding the method of repeated practice were contradictory, so their role in improving performance on attention tasks is unclear. Finally, the studies focusing on memory impairments showed that cognitive remediation is capable of enhancing memory function in a clear and consistent way, especially when the intervention is based on the teaching of coding strategies. In summary, the Kurtz study was the first to establish that cognitive intervention can produce lasting and valuable improvements in neurocognition in schizophrenia patients.

The second meta-analysis to be published was conducted by Krabbendam and German (2003). It differed considerably from the previous one in that it was the first meta-analysis performed only with controlled trials using standardized intervention protocols, comprehensive neurocognitive assessment batteries, real patients and healthy controls. The authors conducted a systematic review and chose 12 of 19 controlled studies. The main result of the analysis was that cognitive remediation was effective and produced a result considered to be a medium effect (effect size = 0.45). This finding is more or less the same as that obtained in the other review. Again, effect size was somewhat smaller in studies performed in clinical settings than in laboratory studies. Improvements were described in the majority of cognitive domains such as attention, learning and memory, verbal fluency, abstraction ability, and executive functions. On the other hand, the results were higher for programs using learning strategies than the programs using repeated practice only, although this finding did not reach statistical significance. With the publication of this study, new evidence for the efficacy neurocognitive rehabilitation was added. Specifically that neurocognitive improvement can also be obtained

in clinical settings and is detectable not only in the laboratory but also in clinical neuropsychological testing. However, it still left the open question of the relevance of this improvement to daily functioning and the durability of the improvements achieved.

Almost simultaneously, Twamley et al. (2003) published another important study. These authors conducted a systematic review and decided to include only protocol-controlled studies, involving formalized intervention protocols and preferably studies carried out in clinical settings. They added another important inclusion criterion; the studies should to be randomized and assessment of the outcomes should be performed in masked conditions. Thus, it became the first meta-analysis of cognitive rehabilitation in schizophrenia with all the features of evidence-based medicine. A systematic search was conducted using these criteria with only 17 studies being selected among all studies published. In addition to efficacy on neurocognition, they compared other interesting aspects such as the type of intervention (repeated practice versus learning strategies) or whether the intervention was assisted by computer or only with paper and pencil tasks. The authors found that different types of rehabilitation were effective in improving cognitive performance and they were able to improve not only cognitive functioning but also some of the negative symptoms and daily functioning of patients. On the other hand, the programs based on computer tasks did not add better results to the use of paper and pencil tasks. However, remediation programs based on teaching strategies were more efficacious that those based only on repeated practice. As such, this meta-analysis added support to the reported efficacy of cognitive remediation programs in patients with schizophrenia, and this time the analysis was done with high-quality studies. Unfortunately, the question of whether the improvement following cognitive remediation was clinically or functionally relevant to the patient still remained an open question.

The most recent meta-analytic study was conducted by Susan McGurk et al. (2007), adding important secondary analysis to the more general analysis. It included only randomized and controlled trials, and the authors monitored neurocognition outcomes as well as clinical symptoms and psychosocial functioning. In addition, questions concerning the characteristics of rehabilitation programs were also analyzed, such as the required number of hours of intervention, the usefulness of cognitive rehabilitation programs with broader psychosocial intervention, and the importance of the patients' demographic characteristics. Other technical issues, such as the kind of control group (active or passive), were also analyzed. A total of 26 controlled studies were selected, including 1,151 patients with a diagnosis of schizophrenia. The authors underline the need for a new meta-analytic study stating that apart from the inclusion of new studies published since the last meta-analysis, previous reviews paid little attention to the effects of neurocognitive rehabilitation on psychosocial functioning.

The study confirms that cognitive remediation is effective in improving cognitive impairments in schizophrenic patients, obtaining a robust effect size (0.51), which can be considered a medium effect. This is consistent with previous studies; additionally it concluded that cognitive remediation produced an improvement in social functioning. Although the effect size was a somewhat smaller change (0.36), it can be still considered significant and medium in size. Finally, a positive effect on symptoms was also found, suggesting that there is a reduction in symptoms after rehabilitation, although the effect size is now considered only small (0.28). Thus, the study provided the first meta-analytic evidence for the impact of cognitive remediation in domains other than neurocognition. Improvements in various factors such as social functioning, quality of life, and personal autonomy were the

main results. Moreover, an intuitive but previously undemonstrated hypothesis was confirmed. By adding cognitive remediation therapy to psychosocial rehabilitation, functional outcomes improved significantly. For instance, by adding cognitive remediation to vocational rehabilitation work, performance was improved and a higher level of work performance and longer-lasting jobs were generally achieved. By and large, cognitive remediation impacts on functioning only when the intervention is part of a broader psychosocial rehabilitation program. In other words, the effects of cognitive remediation therapy are higher (0.47) when acting as a part of a broader psychosocial rehabilitation than when applying cognitive remediation therapy as an isolated intervention (0.05). On the other hand, other studies have shown that cognitive remediation is clearly superior to other interventions such as occupational therapy, vocational rehabilitation programs, leisure groups, supportive therapy, watching videos, and treatment as usual. More specifically, cognitive remediation programs were more efficacious (0.62) when based on cognitive learning strategies (coaching strategy) than when the programs were based on progressive exercises or repeated practice (0.24). Learning strategies are usually based on the learning of memory strategies and cognitive abilities such as solving problems. Finally, it also was noted the improvements were shown to be maintained over periods ranging from six months to two years.

To sum up, taking into account all the current scientific evidence, we may conclude that cognitive remediation therapy is an effective treatment tool for psychiatric rehabilitation. It has been established that neurocognitive impairments can be ameliorated and some improvement in social functioning can also be expected. To achieve these results it is necessary that cognitive remediation therapy is based on the teaching of cognitive strategies and also involves some cognitive practice. Cognitive remediation therapy needs to be carried out in the context of broader psychosocial rehabilitation involving the learning of other communication, social, and self-control skills.

5. The Neuro-cognitive-behavioural approach

The majority of empirical findings, including the meta-analysis, challenge the assumption that simply improving cognitive functioning in schizophrenia will spontaneously lead to better psychosocial outcomes. Moreover, the results of previous studies suggest that cognitive remediation is probably the best option to optimize the response of some patients to psychiatric rehabilitation programs. So CRT is not likely to be implemented as a stand-alone therapy but as a part of a broader psychosocial rehabilitation program. Unfortunately, little is known about how to integrate the different rehabilitation tools in a broader rehabilitation program. Furthermore, even though these interventions show good efficacy in increasing the chances of functional improvement, only few specialized centres offer these interventions. Regrettably, they are neither standardized nor available in routine care in the majority of clinical settings.

Taking into account the published data, an evidence-based guideline for delivering cognitive remediation with other psychological treatments is presented in Figure 1. This guideline is based on the principals of the neuro-cognitive-behavioural approach established elsewhere by Penadés & Gastó (2010):

- It is an empirical approach that incorporates any sort of methodologies, learning techniques, rehabilitation programs, software or paper and pencil tasks provided that their efficacy has previously been demonstrated in controlled studies

- Rehabilitation treatment should focus on improving neurocognition but the main target is to ameliorate associated psychosocial disability
- Rehabilitation treatment must be customized for each patient and should focus on those targets considered to be important by the patient
- Rehabilitation targets should be agreed with the patient based on their capabilities, their needs and their current social environment
- This approach is called "neuro-cognitive-behavioural" since it proposes comprehensive treatment of neurocognitive aspects but does not overlook emotional, functional and psychological ones

Thus, in order to implement integrated psychosocial rehabilitation programs including CRT and evidence-based psychological therapies a flowchart has been proposed (Figure 1).

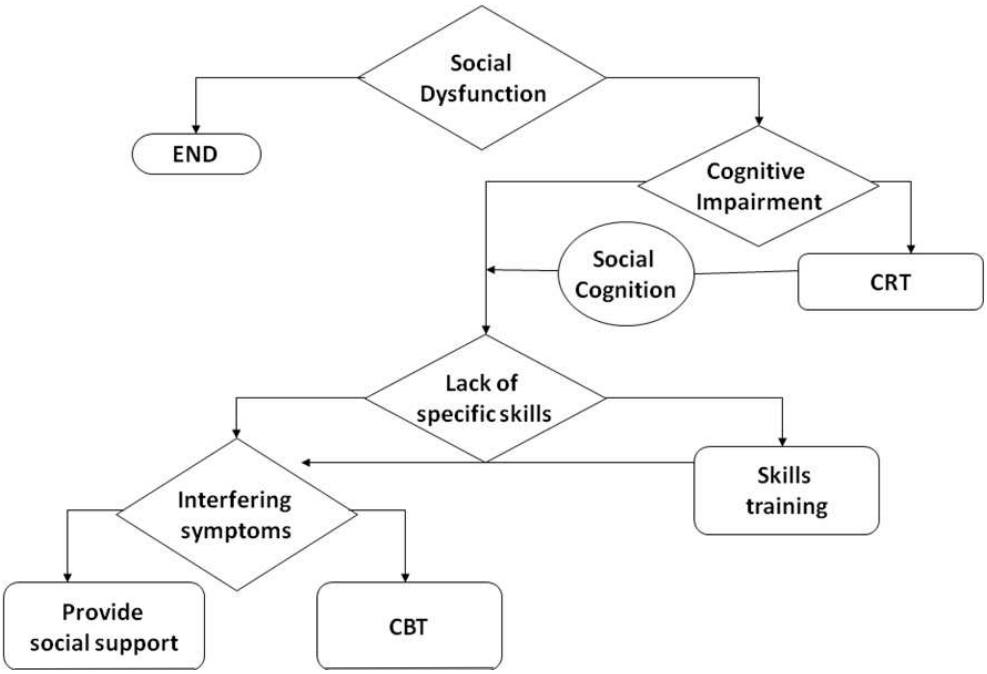

Fig. 1. Flowchart for the Neuro-cognitive-behavioural approach.

6. Improving outcomes and promoting recovery with CRT

As has been suggested before, we have some evidence that improved cognitive function can lead to improved social functioning in the context of psychological interventions. However, another concern is the identification of the cognitive domains that need to be targeted to improve functioning. In a pioneering study, Spaulding et al. (1999) investigated Integrated Psychological Therapy (IPT) (Brenner et al., 1994) and found some improvements in attention, memory, and executive function as well as improvements in social competence. However, as IPT is a multimodal program with cognitive-oriented modules and psychosocial-oriented modules, the exact role of cognitive change in overall functional

improvement was not clear. In order to clarify the specific impact of cognitive change on social functioning, a controlled trial was designed (Penadés et al., 2003) using only the cognitive modules (cognitive differentiation and social perception). In this trial, memory, executive functions and social functioning showed improvement. Interestingly, changes in neurocognition were associated with changes in functional outcome, particularly in personal autonomy and general functioning.

More specifically, a number of Cognitive Remediation Therapy (CRT) studies have shown that neurocognitive improvements are associated with improvement in functioning (McGurk et al., 2007). In one of the first randomized, controlled trials comparing CRT with a control therapy, Wykes et al. (1999) found differential improvements in cognitive flexibility and memory in favour of the CRT group. When these cognitive changes reached a certain threshold, a reduction in social problems was also apparent. Furthermore, other randomized, controlled trials with CRT have shown various improvements in functioning ranging from improvements in obtaining and keeping competitive jobs (McGurk et al., 2005; Vauth et al., 2005), to the quality of, and satisfaction with, interpersonal relationships (Hogarty et al., 2004; Penadés et al., 2006) and the ability to solve interpersonal problems (Spaulding et al., 1999). These findings reinforce the assumption that neurocognition and functioning are strongly related and that CRT is useful in improving functioning.

The impact of CRT on functioning is important because the primary rationale for cognitive remediation in schizophrenia is to improve psychosocial functioning (Wykes and Reeder, 2005). Surprisingly, the majority of clinical studies of CRT did not test this hypothesis until recently and focused primarily on cognitive performance (McGurk et al., 2007). Studies have rarely investigated specific treatment mechanisms or the particular cognitive targets that are related to social improvements. Obviously, an understanding of the links between cognitive change and functional improvement is crucial in identifying appropriate cognitive targets for treatment leading to functional improvement.

In two studies, Reeder et al. (2004) published some surprising results. Cognitive functions which usually show significant cross-sectional associations with social functioning are not the same as those associated with improvement in functioning in the context of CRT. In the first study, it was found that while the "response inhibition speed" factor was associated with social functioning at baseline, change in a different factor predicted social functioning change following Cognitive Remediation Therapy (CRT). In the second study (Reeder et al., 2006), a relationship at baseline was found between social functioning and various cognitive domains such as verbal working memory, response inhibition, verbal long-term memory and visual-spatial long-term memory, but not schema generation. Surprisingly, it was the improvement in schema generation which predicted improved social functioning.

From the two studies, it can be concluded that cross-sectional associations between cognitive functions and social functioning may not be an appropriate approach for selecting cognitive targets for intervention. Even though selecting the cognitive targets of CRT on the basis of cognitive skills that appear to predict functional outcome in schizophrenia sounds logical, it could be misleading. Thus, while it has been generally assumed that improved cognition will lead to improved functional outcome, the nature of this putative link is far from clear.

Penadés et al. (2010) conducted research to investigate the neurocognitive changes occurring in the context of CRT and tried to identify which of those changes led to improvements in daily

functioning. This study used data collected as part of a randomized, controlled trial investigating a CRT program in a partner study (Penadés et al., 2006). The trial recruited 52 schizophrenia patients between the ages of 27 and 42 who had been in contact with psychiatric services for at least 10 years; composing a truly chronic schizophrenia sample with predominant negative symptoms and cognitive impairments. Of these participants, 40 were randomized to receive either CRT or control psychological treatment (Cognitive Behavioral Therapy; CBT) where neurocognition was not targeted. CRT was based on the Frontal/Executive program (Delahunty and Morice, 1993). At baseline, daily functioning was significantly associated with verbal memory. Surprisingly, improvement in executive function, but not in verbal memory, predicted improved daily functioning among those with chronic schizophrenia who had current negative symptoms and evidenced neuropsychological impairments. Notwithstanding, the statistical mediation model found that social improvement caused by executive changes is expressed indirectly through improvement in verbal memory.

The direct model, as the name suggests, represents the prediction of social improvement from the change in executive function directly. The mediated model indicates that social improvement caused by executive changes is expressed indirectly through improvement in verbal memory. All variables were correlated and reached statistical significance ($\alpha > 0.05$), as can be seen in Fig. 2. None of the executive other cognitive measures, such as change in psychomotor speed (t=0.846, P=0.405), change in nonverbal memory (t=0.934, P=0.358), or change in working memory (t=1.402, P=0.172) add significant explanatory power to the effect of executive change in the social improvement function equation.

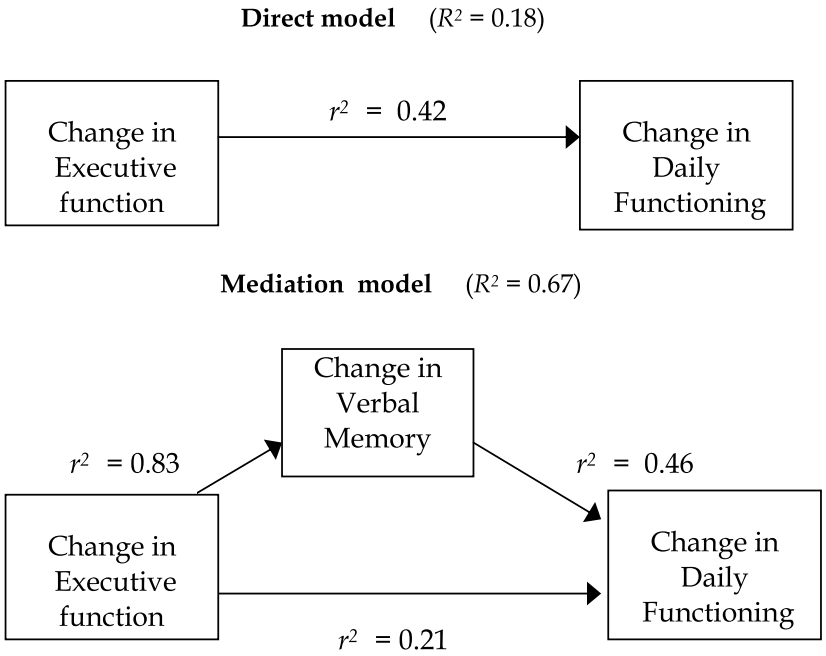

Fig. 2. Diagrams of direct and mediated models of change in daily functioning after the CRT intervention.

Thus, it was found that improvements in cognitive functions that were not significantly associated with daily functioning at baseline led to improved daily functioning. These results confirm that there is no evidence for a simple direct relationship between cognition and the different aspects of social functioning. Consequently, even if people have impairments in multiple cognitive domains, executive functioning still needs to be the intervention target. Data are consistent with findings from previous studies (Reeder et al., 2004, 2006) where it is concluded that baseline correlations may not therefore provide basic targets for intervention and may fail to highlight potential targets. In these studies, where improvements in a number of aspects of executive functioning are present, such as schema generation or response inhibition, CRT leads to improvements in social functioning regardless of baseline cognitive associations. Furthermore, it is suggested that verbal memory changes are associated with social improvements when they mediate the executive improvements. Not surprisingly, memory impairment in long-term schizophrenia can be considered as a consequence of executive impairment and not necessarily more severe cognitive impairment (Bryson et al., 2001).

7. Conclusion

Links between neurocognition and functioning have encouraged efforts to develop new pharmacological agents and novel psychological interventions targeting these variables directly. These interventions rely on the assumption that changes in neurocognition will simply improve life skills in patients with schizophrenia. This assumption is strengthened by the results of numerous studies showing that neurocognitive impairments can produce impaired social functioning. Many of these studies even suggest that neurocognitive deficits, particularly verbal memory and executive functions, are more closely linked to functional outcome than psychiatric symptoms.

However, while the role of impaired cognition in accounting for functional outcome in schizophrenia is generally established, the relationship between cognitive and functional change in the context of treatments is far from clear. In a recent study we tried to identify which cognitive changes lead to improvements in daily functioning among persons with chronic schizophrenia who had current negative symptoms and evidenced neuropsychological impairments. Cognitive Remediation Therapy (CRT) had been compared with a control therapy, involving similar length of therapist contact but different targets. At the end of treatment, CRT conferred a benefit to people with schizophrenia in cognition and functioning. Subsequently, analyses of covariance (ANCOVA) were conducted with baseline and cognitive change scores as covariates to test whether cognitive change predicted change in functioning. Additionally, statistical tests to establish the mediation path with significant variables were performed.

At baseline, daily functioning was significantly associated with verbal memory. Surprisingly, improvement in executive function, but not in verbal memory, predicted improved daily functioning among persons with chronic schizophrenia who had current negative symptoms and evidenced neuropsychological impairments. Notwithstanding, the statistical mediation model found that social improvement caused by executive changes is expressed indirectly through improvement in verbal memory. Thus, we have found that improvements in cognitive functions that were not significantly associated with daily functioning at baseline led to improved daily functioning. These results confirm that there is

no evidence for a simple direct relationship between cognition and the different aspects of social functioning. Consequently, in order to improve daily functioning through CRT it is crucial to target executive function even if persons have more severe impairments in other cognitive domains. Additionally, it is important to remark that in order to achieve generalization of the CRT effects to daily functioning it is necessary to include CRT in broader programs in conjunction with other psychosocial interventions.

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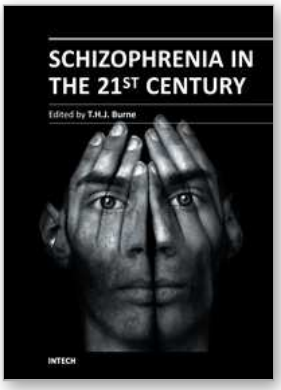

Schizophrenia in the 21st Century
Edited by Dr. T.H.J. Burne

ISBN 978-953-51-0315-8
Hard cover, 180 pages
Publisher InTech
Published online 23, March, 2012
Published in print edition March, 2012

Schizophrenia is a poorly understood but very disabling group of brain disorders. While hallucinations and delusions (positive symptoms of schizophrenia) feature prominently in diagnostic criteria, impairments of memory and attentional processing (cognitive symptoms of schizophrenia) are attracting increasing interest in modern neuropsychiatry. Schizophrenia in the 21st Century brings together recent findings on this group of devastating disorders. We are still a long way from having effective treatment options, particularly for cognitive symptoms, and lack effective interventions and ways to prevent this disease. This volume covers various current options for therapy, clinical research into cognitive symptoms of schizophrenia and preclinical research in animal models.

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