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«Αποτελεσματικότητα των Παρεμβάσεων Γνωστικής Νευροαποκατάστασης σε Ασθενείς με Σχιζοφρένεια»

ΜΑΡΙΑ ΣΚΩΚΟΥ
Ψυχίατρος

Υπεβλήθη για την εκπλήρωση μέρους των
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Αναπληρωματικό Μέλος:

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Effectiveness of Cognitive Rehabilitation Interventions in Patients with Schizophrenia

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Preface

Schizophrenia is a major burden on global health and economy, owing to its chronic, lifelong nature, and its detrimental effects on patients' functioning, beginning in youth. Neurocognitive deficits, observed in 98% of schizophrenia patients, are at the core of the disease, being evident even from the onset of disease, in the premorbid and prodromal period, and remain or deteriorate throughout the illness course. Social cognition, consisting of theory of mind, social perception, attribution and affective processing, is a further important area, which is more recently researched. Both problems are closely related to the functional outcome of the disease, and, depending on their severity, result in the patient being virtually excluded from occupational and social pursuits, banned from work, family and society.

Treatment of schizophrenia is primarily pharmaceutical. The introduction of neuroleptics a few decades ago revolutionized the treatment of psychosis, but, important symptoms, particularly negative symptoms and cognitive deficits, remain essentially unaffected by currently available agents. Addressing cognitive symptoms, given their relation with functioning and therefore, ultimate recovery, is of paramount importance. Hence, a number of cognitive rehabilitation interventions have been developed, which aim to remediate cognitive symptoms, taking advantage of the brain's neuroplastic properties and the patients' ability for behavioural adaptation. Expanding knowledge and implementation of cognitive remediation programs is imperative, for the sake of recovery, functioning and quality of life; therefore, the exploration of the effectiveness of currently available cognitive rehabilitation interventions seems both important and timely.

Abstract

Introduction: Antipsychotic drugs constitute the basis of schizophrenia therapy, however, available pharmaceutical agents lack efficacy for treating the cognitive deficits caused by the illness. The aim of the present work is to present current data regarding cognitive rehabilitation of schizophrenia, providing information and guidance to health professionals.

Method: A literature search was conducted in the PubMed and Google Scholar Databases from inception up to 1/9/2022. Relevant articles were explored for measures and factors affecting the effectiveness of cognitive rehabilitation interventions, including intervention characteristics, genetics, psychopathology, time in the course of the illness, and drug therapy.

Results: A total of 562 relevant articles were retrieved, 39 of which were selected for the review. Factors contributing to a favorable outcome are young age, early phase of disease, symptomatic control of hostility and conceptual disorganization, lack of negative symptoms, management of drug side effects and cognitive and cortical reserve. Some evidence for a procognitive effect seems to exist for atypical antipsychotics –clozapine, aripiprazole-, memantine, modafinil, d-serine and cycloserine. The Val/Val polymorphism of the COMT gene seems to be associated with worse outcome. Specific remediation strategies include programs such as Cognitive Enhancement Therapy (CET), Cognitive Adaptation Training (CAT), RehaCom Cognitive Therapy Software, among others, all employing a range of techniques, from paper-and-pencil to computer assisted, bottom-up or top-down approaches, and varying neurocognitive targets.

Conclusions: Cognitive symptoms, closely related to functional impairmaint, still remain a therapeutic challenge. Cognitive rehabilitation strategies are as yet the only treatment modality offering cognitive improvement to the patients who struggle to recover.

Key words:

psychosis, functioning, schizophrenia, deficits, remediation

Περίληψη

Εισαγωγή: Τα αντιψυχωτικά φάρμακα αποτελούν τη βάση της θεραπείας της σχιζοφρένειας, όμως δεν είναι αποτελεσματικά για τη θεραπεία των γνωστικών ελλειμμάτων που προκαλεί η νόσος. Σκοπός της παρούσας εργασίας είναι η παρουσίαση σύγχρονων δεδομένων πάνω στην γνωστική νευροαποκατάσταση της σχιζοφρένειας, ώστε να παρασχεθούν πληροφορίες και καθοδήγηση στους επαγγελματίες ψυχικής υγείας.

Μέθοδος: Έγινε αναζήτηση της βιβλιογραφίας στις βάσεις δεδομένων PubMed και Google Scholar από την αρχή έως την 1η Σεπτεμβρίου 2022. Τα σχετικά άρθρα εξερευνήθηκαν για παραμέτρους της αποτελεσματικότητας των παρεμβάσεων γνωστικής νευροαποκατάστασης, όπως τα χαρακτηριστικά της παρέμβασης, γενετικοί παράγοντες, και παράγοντες που έχουν σχέση με τα συμπτώματα, την πορεία της διαταραχής και τη λαμβανόμενη φαρμακευτική αγωγή.

Αποτελέσματα: Από την αναζήτηση προέκυψαν 562 άρθρα, εκ των οποίων επιλέχθηκαν 39 για τη σύνθεση της ανασκόπησης. Παράγοντες που συμβάλλουν σε θετικό θεραπευτικό αποτέλεσμα είναι η νεαρή ηλικία, η πρώιμη φάση της νόσου, ο έλεγχος συμπτωμάτων όπως η εχθρότητα και η εννοιολογική αποδιοργάνωση. Επίσης, η σχετική έλλειψη αρνητικών συμπτωμάτων, η αντιμετώπιση των παρενεργειών των χορηγούμενων φαρμάκων, όπως και η γνωστική και εγκεφαλική εφεδρεία. Κάποιες ενδείξεις για θετική επίδραση στη γνωστική λειτουργία φαίνεται να υπάρχουν για ορισμένα άτυπα αντιψυχωτικά φάρμακα -κλοζαπίνη, αριπιπραζόλη- για τη μεμαντίνη, τη μονταφινίλη, την d-σερίνη και την κυκλοσερίνη. Από τους γενετικούς παράγοντες, ο πολυμορφισμός *Val/Val* του γονιδίου της κατεχολ-Ο-μεθυλοτρανσφεράσης φαίνεται να συνδέεται με χειρότερη έκβαση. Ειδικές στρατηγικές επανόρθωσης περιλαμβάνουν προγράμματα όπως τα Cognitive Enhancement Therapy, Cognitive Adaptation Training, RehaCom Cognitive Therapy Software, μεταξύ άλλων, κάθε ένα από τα οποία επιστρατεύει ποικλία τεχνικών, από μολύβι-και-χαρτί έως υποβοήθηση από υπολογιστή, ανωφερή (bottom up) ή κατωφερή (top-down) προσέγγιση, και μπορεί να στοχεύει σε διαφορετικό φάσμα νευρογνωστικών λειτουργιών.

Συμπέρασμα: Τα γνωστικά συμπτώματα, στενά συνδεόμενα με το βαθμό της λειτουργικής έκπτωσης, ακόμη παραμένουν πρόκληση για τη θεραπεία. Τα προγράμματα γνωστικής νευροαποκατάστασης αποτελούν μέχρι τώρα τη μόνη θεραπευτική προσέγγιση που είναι ικανή να προσφέρει βελτίωση των γνωστικών λειτουργιών στους ασθενείς που προσπαθούν να πετύχουν την ανάρρωση.

Λέξεις-Κλειδιά:

Ψύχωση, λειτουργικότητα, σχιζοφρένεια, ελλείμματα, αποκατάσταση

General Part

Chapter 1 Schizophrenia

1.1 General considerations

Schizophrenia is a major burden on global health and economy, owing to its chronic, lifelong nature, and its detrimental effects on patients' functioning. Beginning commonly in youth, it is one of 25 causes of disability globally (1). It is frequently associated with significant distress and impairment in personal, family, social, educational, occupational, and other important areas of life. People with schizophrenia are 2 to 3 times more likely to die earlier than the general population. Reduced life expectancy is often accounted for by physical illnesses, such as cardiovascular, metabolic, and infectious diseases(2), as well as limited access to health services, due to stigma and social isolation. Health costs of schizophrenia are immense, escalating at about US$94 million to US$102 billion annually, depending on parameters related to a given country (3).

1.2 Epidemiology

Schizophrenia has a point prevalence of 0.5%, ranging from 0.27 to 0.83%, in studies of various populations, depending on the proportion of young persons in the sample; in cases where this percentage is higher, point prevalence gets lower values(4). It affects approximately 24 million people or 1 in 300 people (0.32%) worldwide. Lifetime prevalence is commonly assumed to be around 1%, however, it is different in diverse countries around the globe, and a recent systematic review concluded to the figure of 0.42%(5), being higher in countries of the developing world. The incidence of schizophrenia is about 0.20/1000/year (4). Male to Female ratio is 1.4 to 1 (6).
The disease most often begins at a young age of 15-25 in males, and 25-35 in females. In the latter, there exists a second peak of age of onset, beyond 35 years of age (7). Typically, a prodromal period develops, comprising a constellation of non-specific and negative symptoms first, and positive attenuated symptoms later, escalating to the outbreak of the first psychotic episode of the illness(8). Children who later present with schizophrenia, are frequently found to have minor physical abnormalities and soft neurological signs, as well as adaptation and social problems, therefore the premorbid period, before the occurrence of the first prodromal symptom, is not actually free of abnormality(9). The course of the illness progresses with relapses and remissions, with each episode being heavier, demanding higher antipsychotic dosages, and leaving residual symptoms to the patient. The chronic phase of the disease is characterized by residual symptoms of the disease, usually negative, and cognitive deficits, resulting in functional deterioration and social isolation(10).

Risk factors identified are, among others, season of birth, perinatal complications, parental age, particularly age of the father, and infections(4). The causes of schizophrenia, in spite of intensive efforts, have not been elucidated yet. However, there seems to be an interaction between genes conferring risk for the disorder and environmental factors. Heritability of the disorder is estimated at 75%, that is, 75% of the etiology of the illness is attributed to genetic factors(11) .

1.3 Psychopathology

According to DSM-5, there are five characteristic symptoms of schizophrenia, included in criterion A, two of which are required to be present so as to make the diagnosis. These symptoms are 1) Delusions 2) Hallucinations 3) Disorganized speech 4) Grossly disorganized or catatonic behavior, 5) Negative symptoms, i.e., affective flattening, alogia, or avolition(10). Delusions are defined as fixed believes that are not amenable to change in light of conflicting evidence(12). Hallucinations, that is perceptions in any sensory modality in the absence of external stimuli, are typically auditory, but frequently also visual; kinesthetic, tactile, olfactory and gustatory hallucinations have also been reported. Disorganized speech manifests as loosening of associations or incoherence, whereas abnormal behaviour may include purposeless or inappropriate behaviour, posturing, waxy flexibility, catatonic agitation or immobility. Negative symptoms are demonstrated as diminished affective expression and loss of motivation and interests. A number of studies have examined the factorial structure of schizophrenia, and have extracted dimensions of psychopathology. Such are the positive, negative, disorganized and affective (depressive and manic) dimensions (13). At the core of the illness, cognitive symptoms inflict a major burden on the patient (14).

1.4 Cognitive deficits

Cognitive deficits are a prominent aspect of the psychopathology of schizophrenia. Research over the past two decades has substantially elucidated the nature and significant relevance of cognitive impairments in schizophrenia, which follow a developmental pattern of declining cognition over the years prior to onset of psychosis, and continue throughout the lifelong course of the disease(10)

Cognitive symptoms comprise a range of deficits, such as working memory, attention, processing speed, verbal learning, visual learning, and executive functions which include reasoning, planning, problem solving, abstract thinking, inhibition and mental flexibility. Observed in 98% of schizophrenia patients, they are at the core of the disease, evident from the onset of disease, in the premorbid and prodromal period, whereas they remain and/or deteriorate

throughout the illness course. The neurobiological background largely seems to involve frontal functions and disruption of cortico-thalamo-cerebellar-cortical circuits. Areas involved include the prefrontal cortex, anterior cingulate cortex, temporal structures -superior temporal gyrus, medial temporal lobe, hippocampus- amygdala, basal ganglia, thalamus, cerebellum, and inferior parietal lobule. Social cognition, consisting of theory of mind, social perception, attribution and affective processing, is a further important area, which is more recently researched.

1.5. Treatment

Treatment of schizophrenia is primarily pharmaceutical, with significant contribution of psychosocial interventions. The introduction of neuroleptics a few decades ago revolutionized the treatment of psychosis, attaining at least partial resolution of positive symptoms, i.e., delusions and hallucinations. Effective neuroleptics share D2 antagonism properties, and are classified as typical (D2 antagonists) and atypical (D2 plus 5-HT2A antagonists) antipsychotics. Despite initial expectations, atypical antipsychotics do not substantially ameliorate negative, neither cognitive symptoms. Clozapine, the first atypical antipsychotic discovered, seems to promote cognitive recovery (15) and aripiprazole, but not risperidone, showed a synergistic effect with cognitive rehabilitation(16). Evidence base for other agents' effectiveness on cognitive deficits is rather weak, and they are not routinely prescribed for this indication.

. On the other hand, it can cause restlessness and

Addressing cognitive symptoms, given their relation with functioning and therefore, ultimate recovery, is of paramount importance. Hence, a number of cognitive rehabilitation interventions have been developed for this group, at first emanating from previous experience with neurologically inflicted patients.

Chapter 2 Neurocognitive rehabilitation

2.1 General Considerations

Neurocognitive rehabilitation is defined as a set of interventions aiming to restore or compensate for deficits that have been caused by brain damage. It is a systematical, functoning-oriented, delivery of therapeutic activities, based on the assessment and understanding of the patients' brain function and behavioural deficits, that aims to make the client or patient and his/her family to live, manage, circumvent, ameliorate or compromise with the cognitive deficits which have been caused by a brain injury or damage (17). Brain damage inflicts cognitive deficits on the

patient, which are mirrored in functional impairments in activities of daily living, and cause disability. In other cases, although disability is not present, the injury may result in some handicap of the person, due to special life circumstances; for example, a pianist may become handicapped by an otherwise minor deficit in attention or processing speed. At first employed for people who had sustained traumatic brain injury, the implementation of cognitive rehabilitation has readily expanded to many pathological conditions affecting brain function, for example, neurological disorders including stroke, multiple sclerosis, and others, and psychiatric disorders(18).

Rehabilitation interventions succeed their goals by employing two main approaches: Restoration/restitution and compensation. Both are possible by taking advantage of the brain's neuroplastic properties and the patients' ability for behavioral adaptation. Restoration or restitution refers to the re-establishing and strengthening of damaged neural pathways, as well as reorganization, i.e. developing and strengthening of new neural pathways. Compensation, on the other hand, is based on the intact abilities of the patient, without using the damaged neural pathways, so as to manage and overcome his/her problems, by means of learning new strategies. There are two types of such strategies, internal and external. Internal strategies reinforce the conscious control and awareness of the deficient function, with the aim of controlling thought, behaviour and affect, finally resulting in completing a given task without external cues. External strategies depend on the use, by the patient, external cues or aids, (diaries, clocks, notebooks, electronic devices and others) in order to overcome a deficient function.

2.2. Neuroplasticity

Neuroplasticity is the ability of the brain- either intact or damaged- to reorganize its neural pathways, as a result of experience, and constitutes the basis of learning. It occurs at all levels of brain structure, - molecular, synaptic, cellular, neural circuit, macroscopic- throughout the lifespan, and depends on neurogenesis and long term potentiation(LTP). For neuroplastic changes to occur, certain conditions must be met, and these are 1) Practice of a given task or function, 2) Effortful reinforcement of the function 3)Specificity of experience 4) Repetition 5) Intensity 6) Time point and duration of practicing 7) Salience of the experience. Younger age promotes neuroplasticity. Neuroplastic effects can lead to the acquirement of additional, similar behaviors, or interfere with the achievement of other behaviors (19).

2.3 Phases of neurocognitive rehabilitation

The first step in the process of rehabilitation is a thorough and careful neuropsychological assessment. This will allow the identification of functional deficits, of potential strengths, and will make possible a conversation with the patient and management of possible lack of awareness of the deficits, feelings of depression, shame or inadequacy after the occurrence of the damage, and set the context of the intervention. Defining the specific targets of the rehabilitation, deciding the desired outcome, the setting of a personalized therapeutic plan, and the stepwise achievement of tactical and long-term goals in this direction, completes the first stage of the rehabilitative intervention (20). Contributing treatment modalities are the psychoeducation of the patient and his/her family, psychotherapy for behavioral and affective issues, occupational rehabilitation, learning skills for independent living.

The second phase of the intervention consists of three hierarchical stages: Acquisition, Application, Adaptation. The patient learns practices the targets and the processes of the selected task, practices, and, as a favourable outcome, adapts and expands the learned skills in the real world environment, at home, at work, in the community (21).

2.4 Outcome

Considering the progress achieved by the patient, there are 4 possible levels of outcome:

1) The patient does not ever develop that awareness or motive required to become independent in compensating his/her deficits. He/she only learn to undergo simple routines and sequencies of action.

2) The patient achieves to employ external cues/aids so as to compensate, being capable of executing some activities with internal strategies, but still in need of external guidance.

3) The person becomes able to internalize the learned strategies and can independently apply them without external help in specific situations/tasks.

4) The patient is able to generalize the learned skills to a range of situations and/or tasks.

Special Part

Chapter 3 Aim and Methods

3.1 Aim of the study

The aim of the present work, is to illustrate and discuss the current state of the implementation of neurocognitive rehabilitation interventions in the treatment of patients with schizophrenia, with the purpose of informing clinicians and health professionals who manage psychotic patients in the clinic, community and housing facilities, and encourage them to integrate neurocognitive remediation in their care. In the end, every such patient, with challenging and multiple therapeutic needs, should be offered the opportunity to improve his/her cognitive function for a better outcome, and the best possible quality of life.

3.2 Method

A literature search was conducted, from inception to 1/9/2022, in the PubMed and Google Scholar databases. Key words used were “schizophrenia” AND “cognitive remediation” OR “cognitive rehabilitation” AND “outcome”. Data that were looked for and presented included cognitive remediation programs, as well as factors influencing cognitive function and the outcome of cognitive rehabilitation efforts.

Chapter 4 Results

The literature search, after removal of duplicates, yielded 562 articles, out of which 62 were selected.

4.1. Factors affecting cognition and cognitive rehabilitation in patients with schizophrenia

4.1.1 Genetics

It seems that working memory and global intelligence are the cognitive domains with the highest heritability. Of the researched genes, *DISC1* (Disrupted in Schizophrenia 1) has been found to be involved in neuronal growth, expanding and immigration in the developing brain(22), and *Akt1* has been implicated to the neurogenesis occurring in the hippocampus(23). *NRG 1* (neuregulin) and *ZNF804A* are related to synaptic plasticity and the connectivity between dorsolateral prefrontal cortex and the hippocampus,

respectively(24,25). Polymorphisms of dystrobrevin binding protein 1 *(DTNBP1)* seem to be implicated in the general cognitive capacity(26).

Regarding genetic effects on the outcome of cognitive remediation efforts, most data exist for the catechol-O-methyltransferase (COMT) gene polymorphisms, although study results are somehow mixed. It seems that the Val/Val polymorphism has the worst performance on cognitive remediation programs, compared with the Val/Met and Met/Met genotypes (27).

4.1.2 Illness stage and age

Time in the illness course, and age of the patient seem to matter, as demonstrated in an RCT conducted by Corbera et al. (28). After applying a computer assisted cognitive remediation intervention to 3 groups of different age ranges and illness durations, those who were older than 40 years and had mean illness duration 18.2 years, tended to have worse outcomes after the intervention (28). Intervening in young patients early in the disease seems to carry the best opportunity for remediating cognitive deficits, and this is mirrored to functional outcome in the real world work skills (29).

4.1.3. Symptoms

Certain symptoms of the illness, i.e. conceptual disorganization, negative symptoms and hostility, predict a poor outcome of cognitive remediation, as expected (30,31). Depressive symptoms, producing fatigue, low motivation, and pessimistic views of the self and the future, should be promptly treated before the intervention(32).

4.1.4 Pharmaceutical agents enhancing or inhibiting cognitive function and recovery

Memantine has shown some promising results as add-on therapy to risperidone, at a dosage of 20mg per day, in a recent RCT (33), yet, on the other hand, it can cause restlessness and has an abuse potential (34). A study that combined modafinil with cognitive remediation yielded negative results (35). Some favorable effects have been found with d-serine (36) and cycloserine (37). Further, adverse drug reactions, including anticholinergic effects on cognition, as well as hypotension and sedation, can compromise cognitive function, and the effectiveness of any cognitive rehabilitative intervention (38). In essence, present evidence for substantial gains in cognitive improvement from

pharmaceutical agents is weak and solid improvements are not to be expected at the moment.

4.1.5 Other factors related to the patient

Physical exercise, mostly aerobic, or cycling outdoors, and generally exercise involving the legs (39,40) enhances positive results. Cognitive reserve has been found to reduce risk for occurrence of schizophrenia, and confers better functional and cognitive performance through the disease course, although its presumably positive effect on neurocognitive remediation efforts is not yet unequivocally supported(41). Accordingly, cortical reserve, in terms of cortical surface and gray matter, can accelerate cognitive improvement, as demonstrated by a study that employed Cognitive Enhancement Therapy (CET) (42).

4.2. Cognitive rehabilitation interventions

4.2.1. General considerations

Cognitive training approaches in schizophrenia have varying characteristics, ranging from paper-and pencil to computer assisted, from drill-and-practice to therapist-guided strategy coaching, from bottom-up- starting from basic neurocognitive skills such as attention and perceptual skills- to top-down techniques- beginning with higher order executive functions (43). Training usually takes place several times a week, for 1-2 hours each time, combined with weekly therapy sessions, and includes tasks in the cognitive domains of verbal and visual memory, language, visuo-motor skills, processing speed, orientation, vigilance, attention, executive function and others (43). There has been reported generalizability of the effects, to some extent; an Australian study reported improvement of other cognitive domains than those targeted, namely verbal memory and social cognition, but also in symptoms and social functioning (44).

An important issue to consider is the definition of improvement an normalization concepts based on observable changes in the cognitive status, in the context of rehabilitation. An threshold of 0.5 SD (standard deviation) of the variable measured must be achieved, in the direction of amelioration, to be considered as improvement. An improvement by 1 SD is thought to represent normalization of function (45–47). Significant improvements, ranging from 40% to even 70% in at least one of cognitive domains, corresponding to around 0.5 SD in cognition measures, are observed in

schizophrenic patients undergoing neurocognitive rehabilitation(48). Percentages of patients showing improvement or normalization have been estimated around 46%-50% and 32%-43%, respectively (32,45,49).

4.2.2. Specific interventions

There are several specific interventions for the administration of cognitive remediation to schizophrenia patients. One of the most frequently used is the Cognitive Enhancement Therapy (CET). This constitutes a multi-component approach, providing enriched cognitive tasks through integrated and targeted training, containing neurocognitive and social cognitive components. It employs bottom up processing of critical stimuli and top down executive control over distractions and emotional arousal. The technique is computer-assisted, and has been proved effective, with durable improvements, in a number of studies (50–53). Another program used is the Neuropsychological Educational Approach to Rehabilitation (NEAR). This training technique is computer-based and delivers training in a step-wise manner. The participants discuss the strategies learned in view of real world activities (54).

Cognitive Adaptation Training (CAT) is a cognitive remediation strategy that is provided remotely through computer, at the patients' home. It focuses on solving daily life problems, individually for each patient (55,56). Another strategy, the Brain Fitness Program (BFP), is targeted to the restoration and enhancement of auditory perception and working memory. It employs 6 exercises of increasing complexity, containing mastery acquisition of phonemes, words and sentences, memorizing verbal instructions and processing of real world scenarios (57).

The use of Fully Immersive Virtual Reality (VR) (58,59) offers a quasi-real, very enriched cognitive experience, that has been proved to be effective for general cognitive function, planning and sustained attention. Other programs include the RehaCom Cognitive Therapy Software (60-63), the REHACOP rehabilitation cognitive program (64), CogRehab (65)and others (Table 1).

Table 1. Frequently used cognitive rehabilitation interventions in schizophrenia.

Intervention	Target	Duration	Setting	Type
CogPack	Cognitive functions	Variable	Individual	Computer assisted
CET	Γνωστικές λειτουργίες και κοινωνική Νόηση	45 min sessions, 2/week, 24 months	Individual	Computer assisted and non-computer assisted sessions
NEAR	Cognitive functions – Problem solving	60 min sessions, 2/week, 4 months	Individual/group	Computer assisted and non-computer assisted sessions
NET	Cognitive functions -social cognition	45 min sessions, 5/week, 6 months	Individual/group	Computer assisted and non-computer assisted sessions
CAT	Cognitive functions	30 min sessions 1/week, variable duration	Individual	non-computer assisted sessions
RehaCom	Cognitive functions	50-60 min sessions, 2 /week, variable duration	Individual	Computer assisted

4.2.3 Effectiveness of cognitive remediation programs

Numerous studies have addressed the question of effectiveness and outcome of cognitive rehabilitation interventions, with varying remediation programs, patient characteristics, and outcomes. For example Kurtz et al., 2001(66), included 11 studies on a total of 181 patients and found significant improvement of executive function, with the use of Wisconsin Card Sorting Test(66). Revell et al. (67) found significant improvement in psychosocial, but not in neurocognitive function, after the use of varying remediation modalities, on a population of 615 patients derived from 11 studies. An extensive presentation of various studies can be found in Kim et al., 2018 (68).

Apart from cognitive gains per se, neurocognitive rehabilitation has been shown to enhance vocational interventions (69,70), psychosocial treatments(71) and negative symptoms (72). Further, improved neurocognition increases time to relapse, particularly through improved executive function and problem solving, which is very important in terms of illness course as well as health costs (73).

4.2.4 Durability of cognitive gains

Few studies have examined the time course of cognitive improvements following rehabilitation. In one study, patients who completed 40 hours of Auditory Training remotely, versus a control group with 40 hours of video gaming, showed durability of positive effects on global cognition, problem-solving and processing speed, at a 6-month follow-up (74). Eack et al. (75) demonstrated maintenance of the functional outcome of CET, with a retention rate of 72%, one year after termination of the intervention. It should be mentioned, that both studies employed samples of patients early in the course of the disease.

Chapter 5 Discussion

Current state of the field has many achievements to demonstrate, although a lot remain to be done. Most important is the functional outcome in real world situations and the management of the patient in an individualized and holistic manner. The clinician must take into account a great range of issues, including the symptoms' remission, the premorbid condition of the patient, social and financial issues that affect motivation and access to therapy. Young patients early in the disease have the most to gain, which is an important consideration for early intervention efforts. Economic studies assessing cost effectiveness of the rehabilitation methods, would hopefully convince policy makers and stakeholders to have cognitive rehabilitation programs reimbursed by public health insurance. There are a few studies that have succeeded to demonstrate the cost effectiveness of cognitive rehabilitation interventions, compared with traditional psychosocial ones (44–46). Expanding the implementation of cognitive remediation programs could bring results not only beneficial and relieving for patients, families, and society, but also, in a broad sense, life saving.

Chapter 6 Summary

Schizophrenia is a lifelong debilitating disorder, characterized by profound changes in functioning and cognitive deterioration. It affects almost every aspect of cognition, most evidently working memory, attention, processing speed, verbal memory, executive function. The management of these core manifestations, given the inefficiency of currently available pharmaceutical agents, demands the use of cognitive remediation interventions.

A variety of intervention methods have been developed, computer-assisted or with non-computer sessions, employing bottom-up or top-down approaches, of varying durations and specific domain targets. Significant improvements ranging from 40% up to 70% in a given cognitive domain, have been observed, reflected in functional enhancement. Most data show that cognitive rehabilitation interventions are a potent tool in the treatment of this challenging condition, and every effort should be made to have such interventions broadly available, to all patients that could benefit from them.

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