

# Cognitive Deficits in Schizophrenia: Understanding the Biological Correlates and Remediation Strategies

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Cognitive deficits are one of the core symptoms of schizophrenia that evolve during the course of schizophrenia, after being originated even before the onset of illness. Existing pharmacological and biological treatment modalities fall short to meet the needs to improve the cognitive symptoms; hence, various cognitive remediation strategies have been adopted to address these deficits. Research evidences suggest that cognitive remediation measures improve the functioning, limit disability bettering the quality of life. The functional outcomes of cognitive remediation in schizophrenia are resultant of neurobiological changes in specific brain areas. Recent years witnessed significant innovations in cognitive remediation strategies in schizophrenia. This comprehensive review highlights the biological correlates of cognitive deficits in schizophrenia and the remedial measures with evidence base.

**KEY WORDS:** Cognitive symptoms; Schizophrenia; Cognitive remediation; Neurobiology.

## INTRODUCTION

Dysfunctions in working memory, attention, processing speed, visual and verbal learning with substantial deficit in reasoning, planning, abstract thinking and problem solving have been extensively documented in schizophrenia.<sup>1)</sup> According to some estimates, almost 98% of patients suffering from schizophrenia have such impairments and they fall short of their predicted cognitive function, based on pre-morbid intelligence and parental education levels.<sup>2)</sup> Neurocognitive impairment profile of patients of schizophrenia, depicts underlying disruption of cortico-cerebellar-thalamic-cortical circuits.<sup>3)</sup> A large scale retrospective study showed cognitive deficits to be among one of the first signs in individuals who were later diagnosed with schizophrenia.<sup>4)</sup> Cognitive deficits, therefore denote a trait marker for schizophrenia.<sup>5)</sup> Further, the evidence of cognitive impairments in both prodromal

phases as well as throughout the course of schizophrenia justifies the inclusion of cognitive decline as a core element of this illness. Significant correlation is shown between functional outcome of deficits with that of employment, independent living, social and community cognition and functions.<sup>6-10)</sup> Cognitive deficits are prominent, despite clinical stability in patients with schizophrenia and it probably attribute to disability.<sup>11)</sup> Social cognition refers to the ability to correctly process information as carried by socially relevant stimuli and to use it to generate socially appropriate response in situations.<sup>12)</sup> It includes perception of emotions, assigning people to specific mental states and decision making. Difficulties in social functioning leading to social isolation, interpersonal problems exacerbate symptoms, and hence promote relapses. These can further significantly impair quality of life and interfere with rehabilitation processes and vocation.<sup>13)</sup>

Cognitive training programs are interventions that seek to enhance the neurocognitive and socio-cognitive skills in patients relevant to their recovery goals.<sup>14)</sup> There are varieties of the cognitive remediation programs available at present. To explain the cognitive remediation programs, three different terms are often used—“Cognitive Remediation”, “Cognitive Rehabilitation”, and “Cognitive Training”.<sup>15)</sup> The aim of this selective review is to examine basic

**Received:** February 15, 2017 / **Revised:** June 22, 2017

**Accepted:** July 16, 2017

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principles, underlying conceptual basis and methodology of the existing major cognitive remediation programs. Evidence base for effectiveness of these programs is also discussed.

## UNDERSTANDING THE NEUROBIOLOGY OF COGNITIVE DEFICITS IN SCHIZOPHRENIA

Earlier, it was assumed that neurogenesis or neuronal multiplication as process restricted to intrauterine life and early childhood years; however, there are evidences that the process of neurogenesis continues through adulthood to late life, though the process gets restricted to certain confined brain areas like olfactory bulb, hippocampus, and periventricular areas.<sup>16,17</sup> Schizophrenia is believed to be a disorder of abnormal neurodevelopment. Abnormalities in neurodevelopment might be responsible for the cognitive deficits in schizophrenia.

In schizophrenia, abnormality of brain development begins as early as in the prenatal life, which intensifies during childhood and continues till adulthood, explaining the genesis of schizophrenia in the neurodevelopmental background.<sup>18,19</sup> Abnormalities are found in many brain areas in schizophrenia; most consistent brain changes are in the parts like prefrontal cortical areas, inferior parietal lobule, amygdala, superior temporal gyrus, medial temporal lobe, basal ganglia, thalamus, corpus callosum and cerebellum.<sup>18,19</sup> The neurodevelopmental hypothesis is falling short to explain the extensive brain changes in schizophrenia. The brain changes can rather be explained as the cumulative effect of neurodevelopmental abnormality, change in neuroplasticity and alteration in neuronal maturation.<sup>18</sup> The core symptoms of schizophrenia like negative symptoms and executive dysfunction directly result from altered neuroplasticity.<sup>20</sup> Brain derived neurotrophic factor (BDNF) is associated with the hippocampal neuroplasticity, which is involved in cognitive processing.<sup>21</sup> Schizophrenia causes neurodevelopmental changes, which alters the BDNF mediated hippocampal neuroplasticity, attributing to the cognitive deficits.<sup>21</sup>

Cognition is also largely influenced by the genetic factors.<sup>22</sup> Among the various domains of cognition, heritability is maximal with working memory and intelligence.<sup>23</sup> Gene-environmental interaction affects brain develop-

ment as well as cognition. Working memory deficits in schizophrenia can be explained largely, based on the genetic influence.<sup>23</sup>

The disrupted in schizophrenia 1 (*DISC1*) gene associated with schizophrenia also affects the neuroplasticity.<sup>24,25</sup> The *DISC1* gene regulates the process of neuritic growth, expansion and migration in the developing brain.<sup>24,26,27</sup> Neuregulin 1 (*NRG 1*) is a candidate gene, involved in schizophrenia have some role in regulating synaptic plasticity in schizophrenia.<sup>28</sup> This gene may attribute to the cognitive deficits resulting from abnormal neuroplasticity. Another gene "*Akt1*" is found to play an important role in neuronogenesis in hippocampus.<sup>29</sup> The level of phosphorylated Akt was found to be low in patients with schizophrenia.<sup>29</sup> A gene called human dystrobrevin binding protein 1 (*DTNBPI*) gene is also associated with schizophrenia and is known to determine the general cognitive ability.<sup>30</sup> Single nucleotide polymorphisms in the *DTNBPI* gene influence the cognitive ability in patients with schizophrenia.<sup>30</sup> A genome-wide association study in Irish population revealed the association of *ZNF804A* gene with schizophrenia.<sup>31</sup> It is known to modulate the coupling of dorsolateral prefrontal cortex with hippocampus and maintaining the binding sites for several neurotrophic factors.<sup>31,32</sup> Similar genome-wide association studies also revealed involvement of *ITIH3/4*, *CACNA1C* and *SDCCAG8* genes in schizophrenia, which are involved in modulation of various neuro-circuitry and are likely to influence cognition.<sup>33</sup>

In recent studies revealed that neuronal glycoprotein M6a has a role in facilitating neurite outgrowth, synaptogenesis and neuroplasticity.<sup>34</sup> Patients with schizophrenia develop aberrant connection in the brain resulting from abnormal synaptic plasticity leading to dysconnectivity in brain neuronal network.<sup>35</sup> Dysconnectivity due to abnormal synaptic plasticity, results in impairment of learning and information processing, which is manifested in the form of cognitive deficits in schizophrenia.<sup>35</sup> Some important neuromodulatory neurotransmitters like dopamine, acetylcholine, and serotonin play a major role in abnormal synaptic plasticity.<sup>35</sup> Impairment of memory is well reported in schizophrenia. The extent of impairment has little association with the duration of illness, severity of psychopathology, medication used and age of the patient.<sup>36</sup> Working memory deficits are one of the core cognitive deficits in schizophrenia.<sup>37</sup> The deficits in

working memory is associated with dysfunction of certain brain areas like left dorsolateral prefrontal cortex, medial prefrontal cortex as well as visual cortex.<sup>38)</sup> Imbalance in dopaminergic, glutamatergic and gamma-aminobutyric acid (GABA) activity in the above functional brain areas are might be responsible for working memory deficits in schizophrenia.<sup>38)</sup>

## HISTORICAL ASPECTS

Since the earliest description of schizophrenia by Kraepelin as “dementia praecox”, cognitive deficits have been noted as core components of the illness.<sup>14)</sup> Recently the symptoms of schizophrenia are classified as positive symptoms, negative symptoms, cognitive symptoms, and affective symptoms. Cognitive symptoms are recognized as a major symptom domain. Efforts have been taken to address the cognitive symptoms in the management of schizophrenia. However, the conventional pharmacological, biological as well as psychological interventions fall short to adequately address the cognitive deficits. Hence, attempts have been taken to design specific strategies that improve the cognitive deficits.

The history of cognitive remediation or rehabilitation techniques date back to times when drill and practise restoration methods were the only behavior modification techniques in use. It was borrowed from the drill and practise restorative philosophy behind neuropsychiatric rehabilitation for brain traumatic injury. These exercises later evolved into more complex, computerized patterns.<sup>39,40)</sup> Complexity of stimuli used was modified; several non-cognitive and social cognitive aspects were included. These further paved the way for “neuroplasticity-based treatment”.<sup>41)</sup>

Neuroplasticity refers to the ability of neuronal circuits to alter their structure, function and connectivity in response to experience and conditioning. Repeated and persistent stimulation of the post-synaptic cell by the pre-synaptic cell enhances the functional strength of the synapse. The demonstration of this process of “synaptic plasticity” in experimental settings is termed “long-term potentiation” and is central to the phenomena of both normal and abnormal learning and memory.<sup>42)</sup>

A study of neural plasticity using transcranial magnetic stimulation showed abnormal plasticity in schizophrenia.<sup>43)</sup> Electrophysiological recordings in response to au-

ditory conditioning in schizophrenia patients also revealed reduced plasticity. While earlier techniques would aim at cognitive rehabilitation through environmental and adaption modification,<sup>44,45)</sup> recent “neuroplasticity-based treatments” manipulate early sensory processing to improve signal-to-noise ratio in schizophrenia.<sup>41)</sup>

## DEFINITIONS

Cognitive remediation for schizophrenia is defined as “an intervention based on behavioral training that intends at mending the cognitive processes (executive functions, attention, memory, social cognition or metacognition) in terms of its durability and making it more generalized”.<sup>46)</sup> The recent definition of cognitive remediation emphasizes at improvement of functional outcomes by addressing the cognitive deficits through the scientific principles of learning enhancement in the effectiveness of cognitive remediation can be achieved through delivering the therapy in various contexts to improve functioning of daily activities.<sup>46)</sup>

Keshavan *et al.*<sup>47)</sup> has defined cognitive training as an intervention that uses specifically designed and behaviorally constrained cognitive or socio-affective learning events, delivered in a scalable and reproducible manner, to potentially improve neural systems operation.

## BASIC PRINCIPLES OF COGNITIVE REMEDIATION

Based on target deficits in neuro-cognition, remediation training includes training in areas such as attention, memory, executive functioning, speed of processing and abstraction etc. Socio-cognition deficits commonly involve five domains within this constructs which includes emotional processing, social perception, social knowledge, attribution bias and theory of mind.

There are different ways of classifying cognitive remediation techniques. Wykes and Reeder<sup>48)</sup> has divided the training programs in to drill and practice methods. Drill and practice methods involve repeated exercises in progressively difficult tasks and participant learns by trial and error. There are no predetermined explicit strategies.

Drill and strategy coaching involves teaching a predetermined strategy to accomplish a particular task in graded difficulty level. This involves modelling, ex-

planation or role-play and involves both explicit learning (strategy) as well as implicit learning (drills).

Cognitive remediation techniques can also be divided into two main groups based on the understanding of neurocognitive science, i.e. *compensatory* and *restorative* models. *Compensatory* model try to overcome or circumvent cognitive deficits to improve broader aspects of functioning by utilizing the intact cognitive parameters or installing the desired behavior of interest through training by using environmental resources.<sup>49)</sup> Teaching compensatory skills requires that participants to have insight into their difficulties, assessing individuals strengths and weaknesses as well as understanding learning style/learning preferences best suited for the person. On the other hand, *restorative* methods are based on the knowledge derived from cognitive neurosciences and neural plasticity research. These strategies involves attempt to correct a specific neural deficit using the capacity of the brain to develop and repair throughout the whole life.<sup>14)</sup>

Another way of classifying cognitive remediation techniques is *top-down* and *bottom-up* techniques. *Top-down* (feedback) approach involves improving single and specific neurocognitive complex skills like strategy coaching, training of higher order metacognitive skills and executive functions. *Bottom-up* (feed-forward) approaches start with basic neurocognitive skills like attention, pre-attentive perceptual biasing and perceptual skills. Successful cognitive training program involve varying combination of above two approaches. These two processes are not so distinct as previously thought and often they act synergistically more so in impaired brain in patients of schizophrenia.<sup>47,50)</sup>

Cognitive training also utilizes various learning strategies like errorless learning, scaffolding, massed practice, positive reinforcement and information processing strategies.<sup>48)</sup> In errorless learning, training task is broken down into smaller components to start training with simple tasks and then to continue with more complex ones. To prevent occurrence of any error during training, various methods of teaching are used and reinforced. Through this, implicit error encoding can be avoided. Another way of errorless learning is scaffolding. It minimizes errors through careful regulation of complex task to be learnt. The learner is encouraged to use previously established areas of competence, whilst help is provided with new aspects of learning. Massed practice consists in

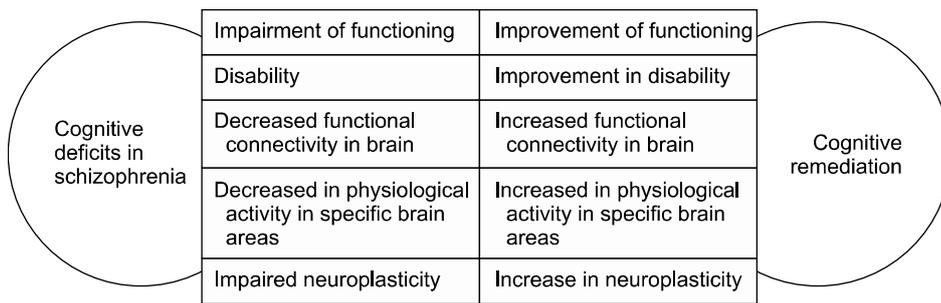
the frequent exercise of a repeated task (at least 2-3 times per week) in order to encourage the retention and application of the skills developed.<sup>50)</sup>

Compensatory training programs are using strategies to improve information processing. Information processing strategies include verbalization (repeating important information mentally or physically to remember), information reduction (focusing only on key aspect of information), breaking and simplifying the task into smaller steps, providing written prompts, chunking (systematically dividing information in to smaller groups based on common characteristics), self-monitoring, mnemonic strategies, categorization (sorting information into classes), organization, and planning.<sup>50)</sup>

## SPECIFIC TECHNIQUES OF COGNITIVE REMEDIATION IN SCHIZOPHRENIA

Cognitive training is now used for a various psychiatric illnesses. Its evidence base has also been proved. Efficacy of interventions in the targeted cognitive domains shows range of outcomes. Although few long-term studies show effect till the end of treatment. Several remediation approaches have been developed, ranging from computer-administered to paper and pencil and drill-and-practice to therapist-guided strategy coaching.<sup>51)</sup> These therapies are based on a range of basic cognitive processes, including perception, working memory, attention, and social cognition, along with combinations of these functions to improve cognitive function and optimize well-being in these disorders. However, currently it is very early to draw definite conclusions and suggest the best method. Study outcomes have shown varying efficacy in the targeted cognitive domains, while others have shown generalization or transfer to untrained domains and to functional outcome; only a few have examined issues of durability beyond the end of treatment.<sup>51)</sup>

Cognitive training, either computerized using CogRehab software (Psychological Software Services, Indianapolis, IN, USA),<sup>51)</sup> or therapist guided pen and pencil training includes tasks in the following cognitive domains: verbal and visual memory, language, visuo-motor skills, orientation, vigilance, processing speed, and so forth. This training is carried out by patients usually for 1 to 2 hours per day multiple times in a week. It is integrated with weekly therapy sessions.



**Fig. 1.** Impact of cognitive deficits and role of cognitive remediation in schizophrenia.

Cognitive enhancement therapy (CET) is a multi-component cognitive remediation approach. It is designed in a way to provide enriched cognitive experiences through targeted and integrated neurocognitive and social-cognitive training. The main focus is on enhancing both “bottom-up” processing of critical social stimuli, with “top-down” executive control over distracting information and emotional arousal.<sup>49,50,52</sup> By integrating computer-based cognitive exercises involving attention training and problem-solving, with an active social-cognitive group experience to facilitate perspective-taking, processing of information, and social context appraisal, CET provides the requisite experiences required to enhance neural processing and achieve adult cognitive milestones.<sup>49,50,52</sup> The intervention involves once per week sessions for up to two years. Evidences show that CET can successfully improve both, social and non-social cognitive impairments in schizophrenia. Hogarty *et al.*,<sup>52</sup> in a randomized-controlled study demonstrated significant improvements in cognitive measures such as neuro-cognition, processing speed, and cognitive style in patients with chronic schizophrenia, receiving CET in comparison to those receiving enriched supportive therapy. This difference was evident in the first year of training and even persisted in the subsequent two years of training. Recent evidences also support the beneficial role of long term cognitive remediation therapy.<sup>53</sup> A similar study demonstrated the role of CET in improving cognitive measures in patients with early-course schizophrenia or schizoaffective disorder. CET demonstrated only moderate beneficial effect size ( $d=0.46$ ) in improving neurocognitive function but strong differential effects ( $d>1.00$ ) favoring CET on social cognition, cognitive style, and social adjustment composites were observed.<sup>54</sup> These findings echoed a previous study demonstrating improve improvements in social cognition following CET in early course schizo-

phrenia.<sup>6</sup> Improvement in the employment rates of patients in the CET cohort suggests that the benefits of CET extend beyond formal testing to daily functioning as well.<sup>54</sup> This functional improvement was mediated by neurocognitive improvements, primarily in executive functioning, and social-cognitive gains in emotion management.<sup>55</sup> Figure 1 shows the effect of cognitive deficits in the life of patients with schizophrenia and role of cognitive remediation to overcome these deficits.

Plasticity of fronto-temporal areas, i.e., areas implicated for cognition, plays a huge role for the effects of CET. It has been observed that various brain areas like grey matter volume in the left hippocampus, Parahippocampal gyrus, fusiform gyrus, and grey matter in the left amygdala are more preserved in patients with schizophrenia, treated with CET as compared with those given enriched supportive therapy.<sup>6,56</sup> Probably they activate the mentioned pathways. It has also been seen that the cortical reserves i.e. the areas and volume of brain before treatment does affect the benefits of CET. Greater reserve in temporal cortex showed a rapid response to CET. The initial response appears to come from the use of already present ‘surplus’ neural activity and the later response is due to increased connections.<sup>6,56</sup> The therapeutic effects of CET may capitalize on brain plasticity processes to provide neuroprotection and improved brain functioning of the fronto-temporal areas that are implicated in cognitive impairment.<sup>55</sup> Improved cognition was associated with intact grey matter density in left parahippocampal and fusiform gyrus as well as increase in grey matter density in the left amygdala.<sup>56</sup> These structural changes seem to be mediated through neuroplasticity, which might be responsible for the therapeutic effects of CET. Interestingly, pre-treatment whole brain cortical surface area and grey matter volume (“cortical reserve”) significantly affects the effects of CET on social cognition, but not much on

neurocognition.<sup>57)</sup> Greater cortical reserve, particularly in the temporal cortex, predicted a rapid social-cognitive response to CET in the first year of treatment. Patients with less neurobiological reserve achieved a comparable social cognitive response by the second year of cognitive intervention. It is possible that the early response is due to recruitment of “surplus” neural capacity, while later developing changes are due to the increased connectivity of the networks underlying these functions.<sup>57)</sup>

A step wise training approach has been used in neuropsychological educational approach to rehabilitation (NEAR) method. Followed by the computerized session of training, participants discuss in detail the strategies that they have learned while practicing cognitive tasks and how these skills may be helpful in real life activities.<sup>58)</sup>

Various new techniques using cognitive remediation strategies are now available. Cognitive adaptation training (CAT) is a home delivered cognitive rehabilitation strategy which is designed to train cognition in order to solve daily life problems, specific and concrete to each individual.<sup>59)</sup>

Brain fitness program (BFP) is a way of practicing, improves brain plasticity. BFP restores and amplifies auditory perception and working memory processing using six exercises of increasing complexity. Initially formants in speech like phenomes, words and sentences are to be mastered. Verbal instructions in are remembered in sequences and then processing of the real world scenarios is done.<sup>60)</sup> Table 1 summarizes various cognitive remediation programmes in schizophrenia.

## EVIDENCE BASE FOR COGNITIVE REMEDIATION

Various published meta-analyses have demonstrated the efficacy of cognitive remediation for improving cognitive outcomes targeted by these interventions. In an initial review, Pilling *et al.*<sup>61)</sup> had reported that cognitive remediation was of no use. But in last few years, several quantitative reviews have demonstrated that cognitive remediation reduces cognitive deficits and improves functional outcome with long-term benefits in schizophrenia.<sup>62-64)</sup> A meta-analysis of 40 studies conducted over 35 years period (between 1973 and 2009), found modest efficacy of cognitive remediation therapy, in overall cognitive performance, with long term effects, as shown in follow up studies (effect size=0.43). Moreover, significant small-to-medium effect was also found on functional outcomes at both post-treatment and follow-up assessment (effect size=0.37).<sup>65)</sup>

Evidences suggest that significant improvement in social functioning occurs when cognitive training and other psychosocial rehabilitation programs administered together in addition to adoption of strategy coaching approach based on learning strategies.<sup>66)</sup> Studies, where cognitive remediation was combined with other forms of rehabilitation and when it included strategy coaching, demonstrated significantly better functional outcomes.

Computer-assisted cognitive remediation (CACR) techniques have been shown to improve various cognitive domains and social cognition in schizophrenia.<sup>62,67)</sup> Another

**Table 1.** Cognitive remediation programmes in schizophrenia

Cognitive training	Target	Duration	Setting	Type	Mechanism used
CogPack	Cognitive function	Sessions are variable in duration and frequency	Individual	Computer assisted	Restorative/bottom-up/drill and practice/individually tailored
CET	Cognitive functions and social cognition	Biweekly sessions (about 90 min every week) for 24 mo	Group	Computer assisted and non-computer assisted sessions	Restorative/top-down/bottom-up/drill and practice/strategy coaching
NEAR	Cognitive functions and problem solving	Sessions of 60 min twice a week (about 4 mo)	Individual/group	Computer assisted and non-computer assisted sessions	Restorative/top-down/strategy coaching/individually tailored
NET	Cognitive functions and social cognition	Sessions of 45 min, at least 5 times a week (about 6 mo)	Individual/group	Computer assisted and non-computer assisted sessions	Restorative/bottom-up/drill and practice/individually tailored
CAT	Cognitive functions	Variable (short weekly visits at home, lasting about 30 min)	Individual	Non-computer assisted sessions	Compensatory/individual tailored

CET, cognitive enhancement therapy; NEAR, neuropsychological educational approach to rehabilitation; NET, neurocognitive enhancement therapy; CAT, cognitive adaptation training.

study comparing short-term outcomes of CACR in adolescents with psychotic disorders or at high risk of psychosis<sup>68)</sup> revealed significant differences between baseline and follow-up in executive function and reasoning abilities, with better performances at follow-up only in the CACR group. Prediction of positive response and personalization of treatment individualization of such techniques is must as these are labour intensive approaches. Kurtz and Richardson<sup>63)</sup> performed a meta-analysis, specifically on social cognitive interventions, proved the greatest effect of treatments on facial affect recognition, with a moderate-to-large effect size for affect identification and a large effect size for affect discrimination. Moderate effect size for theory of mind and a large impact on measures of observer-rated community and institutional functioning was also reported.<sup>63)</sup> A randomized controlled trial (RCT) which investigated the effects of CET on social cognition was the first step in this path.<sup>6)</sup> It demonstrated a significant superiority of CET over a non-specific treatment. Another RCT, evaluated the effectiveness of CET delivered over two years.<sup>54)</sup> Subjects receiving cognitive remediation showed improvements in dysfunctional style of cognition as well as social cognition improving social adjustment and symptomatology in comparison to the control group after one year. At the end of two years of cognitive remediation therapy, improvement in cognitive style, social cognition, social adjustment, as well as symptomatology was reported in the group receiving cognitive remediation than the control group. Cognitive remediation is able to bring appreciable changes in

the functional connectivity, neurophysiological activity as well as neuroplasticity of specific brain regions of the frontal lobe, cingulate cortex, occipital cortex.<sup>69,70)</sup> Working memory task in cognitive remediation intervention causes activation of left lateral prefrontal cortex.<sup>70)</sup> Training on neurocognition and social cognition has additive effect on the modulation of neuronal networks.<sup>69)</sup> Social cognition training in patients with schizophrenia improves facial emotion recognition, theory of mind, social intelligence, attribution style, social perception and social behavior.<sup>71)</sup>

A randomized control trial was performed by Wykes *et al.*,<sup>72)</sup> to study the effects of cognitive remediation therapy (CRT) versus usual treatment in subjects with a recent diagnosis of early-onset schizophrenia (onset prior to the age of 19 and duration of illness of less than 3 years).

All cognitive tests showed better results in the CRT group, but the effect was significant only for the Wisconsin Card Sorting Test. Effect of CET was studied with focus on impact of cognitive training on different outcome measures as well as brain morphology.<sup>6,54,73)</sup>

McGurk and Mueser<sup>74)</sup> found that clients younger than 45 years age reported better improvement in cognitive functioning than those more than 45 years of age and hence suggested for modification in the cognitive training programs for the older people to have comparable outcome .

A long-term follow-up study was performed in order to verify the durability of the effects of CET.<sup>73)</sup> Results from intent-to-treat analyses indicated that effect of CET on

**Table 2.** Factors predicting positive response to cognitive remediation therapy

Domain	Variable	Predictors of better response to cognitive remediation
Patient related	Age	Adolescents
	Genotype	COMT Met carriers Presence of 8 SNPs at the 3' end of the COMT gene Presence of BDNF polymorphisms in case of older adults
	Cognitive and brain reserve	Better pre-treatment neurobiologic reserve Faster processing speed, superior verbal and visual learning
	Motivation and emotional state	Positive mood and high level of motivation Less severe positive symptoms
Treatment related	Pro-cognitive agents	Glycine agonist (D-serine), GlyT1 inhibitor (sarcosine), Ampakines Metabotropic mGlu2/3 agonists, GABAergic agent (MK-0777) Modafinil, d-amphetamine Dopaminergic and cholinergic agents
Others	Adjunctive cognitive-enhancing interventions	Aerobic exercises
	Brain neuromodulation	Transcranial magnetic stimulation, transcranial direct current stimulation, and vagal nerve stimulation

COMT, catechol-O-methyl transferase; Met, methionine; SNP, single nucleotide polymorphism; BDNF, brain derived neurotrophic factor.

functional outcome was broadly maintained one-year post treatment and that patients receiving CET continued to demonstrate highly significant differential functional benefits, compared with the control group. Bowie *et al.*<sup>75)</sup> evaluated the short-term and long-term effectiveness of cognitive remediation as well as its impact on functional competence and everyday functioning in patients with schizophrenia. The early course group had greater improvements in processing speed and executive functions, in adaptive competence, and real-world work skills.

Effect of cognitive remediation techniques in the prodromal phase of schizophrenia or in subjects at risk for schizophrenia has also been studied.<sup>68,76)</sup> Rauchensteiner *et al.*<sup>76)</sup> studied the differential effects of CogPack (Marker Software, Ladenburg, Germany) in prodromal patients, compared with patients with fully manifested schizophrenia and indicated that prodromal patients can improve their long-term verbal memory, attention, and concentration after cognitive training. Interventions are likely to be more effective when the skills trained resemble those needed in daily life. Presence of certain factors predicts positive treatment response with CRT (Table 2<sup>55,73-84)</sup>).

## FUTURE DIRECTIONS

Research on cognitive intervention (training) in the coming days need to focus on the domains where results are ambiguous among which are the specific and un-specific effects of treatment. Neural mechanisms underlying cognitive remediation, its generalization and real-world applicability, and approaches for dissemination of cognitive remediation in practice settings, the role of motivation, understanding of metacognition and social cognition for treatment outcome are the focus of current research. Most studies discuss cognitive remediation in the context of management of cognitive symptoms of schizophrenia. Recent evidences from a network meta-analysis revealed the role of cognitive remediation in negative symptoms of schizophrenia, thought beneficial effect is small to moderate.<sup>85)</sup> It will be too early to accept the outcome solely as the result of cognitive interventions. Various other factors influence the outcome. Evidences also exist that even after cognitive intervention; there is no noticeable improvement in the outcomes. There is a need

to understand the gaps in intervention and hindering factors. Evidences also suggest that effect size of these interventions have little role determining the utility of these interventions.<sup>86,87)</sup> If the individual receiving the cognitive remediation gets adequate opportunities to use the acquired skills, it is more crucial in the real world functioning.<sup>87)</sup>

Future research need to evaluate the role of cognitive remediation in other symptoms of schizophrenia. It will be important to develop cognitive remediation that can be delivered in community settings and to train clinicians for its implementation. Robust evidences exist regarding the effectiveness of combined treatment of cognitive remediation and other psychosocial treatments, such as social skills training and supportive employment. Hence further work is needed to develop comprehensive approaches to cognitive remediation that incorporate key therapeutic principles from a variety of treatment modalities. Pharmacological interventions in schizophrenia that caused improvement in cognition did not report any noticeable improvement in community functioning.<sup>88)</sup> It is highly essential to see the replicability of the effective cognitive interventions in real world functioning.

## CONCLUSION

Benefits of CRT are especially relevant for chronic and severe patients with schizophrenia. Current evidence indicates that it results in significant improvements in a wide range of outcomes, including memory, attention, problem-solving, cognition, social cognition, independent living skills, and social adjustment. These developments are promising as the conventional pharmacological treatment falls short to bring noticeable changes in cognitive as well as socio-affective processing. Cognitive trainings are safe, preventive remedial measures for individuals at younger ages and at earlier stages of illness. Early detection of psychosis and early cognitive intervention may restrict the development of deficits and likely to improve the real-world functioning. There may even be the possibility of primary prevention of mental disorders if neural biomarkers of vulnerability can be found and improved through computed tomography, although ethical issues related to “labelling” of individuals without overt symptoms will need to be addressed cautiously.

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