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Cognitive remediation in schizophrenia—The view from India

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Abstract

The prevalence and disability due to Schizophrenia (SZ) in India is similar to other parts of the world. Cognitive impairments are also present in a large group of Indian persons with SZ. Interventions to address these impairments – termed cognitive remediation or cognitive retraining – are being tested all over the world. Indian research on remediation in schizophrenia has been eclectic and is reviewed here. Some investigators have focused mainly on symptom control and quality of life, as yoga could be a cost effective and culturally acceptable intervention for remediation and rehabilitation. Although participants were not exhaustively tested for improvement in cognitive function in the majority of such trials, published results are encouraging.

Keywords

Schizophrenia; Cognitive remediation; Yoga; Cognitive impairment

1. Introduction

Cognition denotes information processing and requires a broad range of mental processes (Thara, 2007). Cognitive impairment is an important predictor of functional outcomes including occupational functioning and life satisfaction (Thorsen et al., 2014; Velligan et al., 2000; Bowie et al., 2010). Schizophrenia is associated with deficits in various cognitive processes that result in disorders of complex thinking and ideation, resulting in difficulty in dealing with ‘psychological and social challenges in daily life’ (Lysaker et al., 2015). Drug free or un-medicated patients with schizophrenia show severe cognitive deficits (O’Carroll,

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Conflict of interest

None.

Contribution

Smita N. Deshpande: Concept, design and writing first draft.

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Vishwajit L. Nimgaonkar: Concept, Review of the manuscript.

2000), suggesting that the cognitive impairment cannot be attributed solely to medication effects. Memory dysfunction, disturbance of executive functions, and general cognitive functioning are affected (Tandon et al., 2009; Keefe and Harvey, 2012). Cognitive strategies were developed to address these deficits (Eack et al., 2010; Eack, 2012; Eack, 2012).

2. Cognitive remediation (CR) in schizophrenia

Cognitive rehabilitation is a confluence of therapeutic activities based on brain-behaviour relationships (Hegde, 2014). Functional improvement is achieved by re-establishing or reinforcing previously learned adaptive patterns of behaviour, facilitating improvement in cognitive functions through compensatory mechanisms and sometimes facilitating new patterns of activity through external compensatory mechanisms.

Cognitive remediation aims to improve cognitive functions impaired due to schizophrenia using different techniques. Most CR approaches focus on higher-level cognitive domains, such as attention, memory, and executive function or on increasing and utilizing neuroplasticity through basic tasks, such as early perceptual processing and working memory. The ultimate goal is to improve day to day social functions as well as occupational rehabilitation (Zaytseva et al., 2013). Typically, the remediation relies on reinforcement and learning through repeated sessions. Training sessions can last for 1–2 h and the duration of training varies; some programs last up to six months. Programs combining CR combined with other rehabilitation techniques yielded better results and generalizability to improve functioning (Zaytseva et al., 2013). Therapists used pen and pencil or computerized approaches (Thorsen et al., 2014). Clinically stable patients gained more benefit (Zaytseva et al., 2013).

It is not clear how long the benefits of CR last, and whether ‘booster sessions’ are needed (Shriharsh et al., 2003). The results of CR studies may be affected by randomization and blinding procedures, different numbers of subjects among intervention groups and control groups, effect of concurrent medications especially different types of antipsychotics, generalizability and cost benefit ratio with intensive therapist involvement. All these factors need to be considered before this treatment is recommended for regular use (Thorsen et al., 2014).

3. How does cognitive remediation work?

CR is said to influence brain structure as well as function. Brain imaging studies have shown that improvement in neurocognitive performance and neural changes may go together (Thorsen et al., 2014). In support, CR-induced changes including hyper or hypo activity of brain regions and circuits, particularly in prefrontal, middle frontal, parietal, temporal, parahippocampal and limbic areas have been reported (Thorsen et al., 2014). Some areas such as prefrontal cortex (PFC), cortical midline regions, parietal and temporal cortex, insula, and amygdala may show areas of increased activity (Thorsen et al., 2014). CR has also been associated with neuroprotective effects against grey matter loss in temporal brain regions associated with cognition (e.g. hippocampus, parahippocampal gyrus) and with increase of serum brain derived neurotrophic factor (BDNF) levels (Michalopoulou et al., 2015). CR

may strengthen existing or compensatory structures and activity and also promote neuroplasticity. Improvement in brain functioning detected after CR therapy among patients with SZ might be attributable to increase of the interhemispheric information transfer between the bilateral prefrontal cortices via the corpus callosum (Penades et al., 2013). CR affects insular activation to a lesser extent, thus indicating that CR influences cognition more than affective functions.

4. Schizophrenia in India

Schizophrenia (SZ) is as chronic and disabling an illness in India (Math et al., 2007), as it is in other parts of the world (Shankar et al., 1995; Srinivasan and Thara, 1997). In view of its reported beneficial effects in other parts of the world, Indian investigators have also begun to evaluate CR among patients with SZ. These efforts have been constrained by limited resources. Hence investigators have evaluated a number of different approaches. The present review summarizes and evaluates peer reviewed publications published by investigators in Indian settings.

5. Indian studies of cognitive deficits in schizophrenia

Publications from India on cognitive deficits in schizophrenia date back to 1987 (Chandiramani and Varma, 1987) but sampling issues make it difficult to generalize their results. In general, Indian studies reported cognitive deficits similar to those from Western patient populations (Dalal and Sivakumar, 2010). Cognitive deficits were not correlated with current employment status or to level of performance at work in a schizophrenia sample of 100 subjects from Chennai, but negative symptom scores were correlated with social functioning, and employment status was correlated with poor work performance (Srinivasan and Tirupati, 2005). These authors opined that social pressures better accounted for the working status of their subjects than cognitive dysfunction. In a sample from Mumbai (N 50, cases and controls), cognitive deficits were present during remission but did not have a statistically significant relationship to disability (Krishnadas et al., 2007). At Delhi, no statistically significant differences in performance were reported between cases and parents using the Trail Making Test (TMT). Among patients, TMT performance, which assesses attention and working memory, was correlated with severity of auditory hallucinations (Bhatia et al., 2009). Factor analytic studies reported distinct dimensions of neuro cognition and social cognition from Bengaluru (Mehta et al., 2014). Although social cognition is recognized as being distinct from neurocognition, several investigators have focused on social cognition in conjunction with cognitive functions, using a tailored assessment schedule called SOCRATIS (Mehta et al., 2011a,b).

6. Cognitive remediation research in India

The first study to evaluate a combination of pharmacotherapy and cognitive retraining was an international four arm clinical trial conducted at Bengaluru, India and sites in the USA (D'Souza et al., 2013). The four groups were: (1) D-serine (30 mg/kg) + cognitive retraining (CRT) (2) D-serine + control CRT (neutral TV shows), (3) CRT+ placebo, and (4) placebo+ control CRT. The computerized CRT modules targeted attention, memory, verbal-

visuospatial working memory, and executive function. Sessions lasted for 5 h per week, for 2–3 days/week and were supervised by a clinical psychologist. Among the participants, Indian subjects completed assessment at 3 months ($n = 69$) and at six months ($N = 43$). CRT resulted in significant improvement in Verbal Working Memory, and a trend toward improvement in Attention/Vigilance (Table 1).

7. Vocational rehabilitation as cognitive enhancement

Vocational training can improve cognitive functions. The vocational training services available to a study involving Indian subjects were simple ones such as notebook manufacturing, bookbinding, offset printing, carton making, medicine cover making, horticulture (for men) and bookbinding, spinning, and medicine cover making (for women) ($N = 34$) (Suresh Kumar, 2008). Cognitive functions were evaluated using the Mini Mental State Examination (MMSE) only. Subjects who attended the rehabilitation services performed better on orientation, attention, language and total MMSE scores. Better scores on MMSE were positively correlated with occupational functioning and cognitive symptom scores correlated negatively with social functioning in subjects who had availed of vocational rehabilitation.

8. Home based unsupervised cognitive retraining

Hegde reported a 2 month home based CR program, based on a prior pilot study (Hegde et al., 2007, 2012). She developed booklet based tasks to be practiced weekly as an easier and cheaper alternative to one on one CR programs ($n = 45$ first episode schizophrenia patients, duration of illness less than two years, 12 subjects and 11 controls for final assessment) (Hegde et al., 2012). While only half her subjects were employed, all the controls were in full time employment. Controls received treatment as usual and psychoeducation, but no cognitive remediation. All participants received treatment as usual and three sessions of psychoeducation. Home based cognitive tasks (graded difficulty over time, could be done unsupervised, weekly timetable) consisted of number connection, letter symbol substitution, grain sorting, rearrangement of jumbled words, design fluency, word generation, colouring designs, completing mazes, essay writing, letter and number cancellation tasks, dotted designs, embedded figures tracing, proverb illustration and memory for designs. She tested participants at baseline, immediately after CR training and after six months following the intervention. Cognitive functions such as divided attention, planning, concept formation and set shifting ability improved with large effect sizes. Negative symptoms also improved. It would be important to attempt replication of these promising results.

9. Yoga as cognitive enhancement therapy

Yoga, the ancient art of physical and mental practices is increasing in popularity and acceptability across the world, and is undergoing a renaissance in India as well. Indeed, the number of yoga therapists exceeds the number of mental health professionals in India (Jagannathan et al., 2015). The practice of yoga emphasizes body awareness and involves focusing one's attention on breathing or specific muscles or parts of body, so yoga may improve more general attentional abilities. Indeed, the Yoga Sutra, the ancient text

describing the practice of yoga states, “Yoga is the control of the whirls of the mind” (Saper et al., 2004; Feuerstein, 2005). Could yoga practices be regularly used as alternative and/or complementary treatment for various psychiatric disorders? Yoga is practicable, acceptable, cost effective with few adverse effects, and can be practiced at home. Several studies have described the positive effects of yoga (translated as a union of body, mind and spirit) on various psychiatric disorders and symptoms (Jagannathan et al., 2015). Prominent among them are studies on anxiety and depression as syndromes (Rao et al., 2013) and as symptoms (e.g. Yeung et al., 2014).

Several studies have been published from two centres- National Institute for Mental Health and Neurosciences (NIMHANS), Bengaluru and Ram Manohar Lohia Hospital (RMLH), New Delhi on yoga as an adjunctive intervention for schizophrenia. The NIMHANS studies focussed on symptom control, quality of life, social functioning (Duraismamy et al., 2007; Varambally and Gangadhar, 2012; Jayaram et al., 2013; Gangadhar, 2014; Talwadkar et al., 2014). Talwadkar and colleagues conducted a randomized controlled study in elderly and studied the effects of Trataka in comparison with wait listed patients (Talwadkar et al., 2014 from Gangadhar, 2014). Neuropsychological test performance in Trataka group was better after exposure. These studies have been summarised in a Cochrane review (Broderick et al., 2015) and will not be discussed further here.

An open pilot trial of yoga was initially conducted at RMLH using a computerized battery that reduced assessment bias (Bhatia et al., 2012). A 21 days yoga training protocol which included one-hour daily sessions of yoga exercise (Asanas) and breathing exercises (pranayama) using a manualized protocol, designed by yoga experts, was imparted to successive consenting persons affected with schizophrenia (N = 65), bipolar disorder (BPD, n = 40) and major depressive disorder (MDD, n = 37), as well a comparison group of stable patients attending Cardiology outpatient clinics (n = 68). Cognitive functions of all four groups were assessed at baseline, after 21 days (i.e. immediately after yoga training) and two months later, using the Penn Computerized Neuropsychological Battery (CNB, Gur et al., 2001). Another group of participants with SZ (n = 23) received only treatment as usual (TAU). The yoga group as a whole showed significantly greater improvement in attention (speed) estimates compared with the TAU group (p = 0.025). In the schizophrenia group, the CNB test for abstraction and mental flexibility (accuracy) and parameters of attention improved. Unlike the SZ group, where the improvements were most marked for speed, the cardiac outpatient group showed improvement in accuracy for attention (ES = 0.35), face memory (0.615), spatial memory (0.35) and spatial ability (0.28). The patients with BPD and MDD had different patterns of changes. Thus, persons with major mental illnesses, as well as relatively older persons with cardiac disorders, could benefit cognitively from simple yoga exercises (Bhatia et al., 2012).

The aforementioned yoga study was a non-randomized open trial. Based on positive results from our earlier study, a randomized controlled trial to evaluate the effects of adjunctive yoga training on cognitive functions in schizophrenia was initiated (Bhatia et al., 2014). Subjects with schizophrenia are randomly assigned to one of the three groups – TAU alone, TAU with adjunctive yoga training, or TAU with adjunctive physical exercise. Participants

are assessed at baseline, after 21 days, 3 months and 6 months on cognitive domains using CNB, with the rater blind to the type of supplementation provided to the participant, if any.

There are several practical considerations when interpreting studies of yoga. Like other behavioural paradigms, blinding for assessment (double or single) is difficult to implement (Gangadhar, 2014). The need for daily initial training under personal supervision is a barrier that needs to be addressed if yoga supplementation is envisaged as cognitive intervention; further it is uncertain whether and how yoga can be used as a complementary treatment for SZ (Jagannathan et al., 2015). Whether yoga should be advised for brief or on continued practice is also uncertain. Still, a meta analysis of 5 RCTs in SZ found moderate evidence for a beneficial effect of yoga on quality of life in the short term (Cramer et al., 2013). It was noted that the results of RCTs could be biased and the safety of the intervention has not been proved. It should be noted that only one RCT in the meta analysis evaluated outcomes other than clinical severity; this study evaluated face emotion recognition, but not cognitive function (Behere et al., 2011). A study in Hong Kong also compared effect of yoga and aerobic exercise on cognition among women with early psychosis; yoga enhanced attention better than aerobic exercise (Lin et al., 2015).

10. Conclusions

Cognitive remediation could improve functional outcomes and brain plasticity among people with SZ (Penades et al., 2013). Intensive CR protocols available in developed countries are difficult to implement in India in view of the multiple ethnic groups, cultural practices and above all, a scarcity of mental health professionals. Thus, it is important to develop innovative CR approaches that can be implemented with brief training (Hegde et al., 2012). CR research in India is gathering momentum. Indian studies report on CR approaches used in western countries, as well as indigenous approaches such as yoga. Yoga, a culturally acceptable, low cost, and practicable at home, is appealing as a CR strategy. Other novel approaches need to be tested through well-planned RCTs.

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Table 1

Indian studies of cognitive remediation in schizophrenia.

Authors and Publication	Subjects/controls	Inclusion criteria	N, period, sampling	Instruments	Intervention	Final results
D. C. D'souza, R. Radhakrishnan, E. Perry, S. Bhakta, N.M. Singh, R. Yadav, D. AbiSaab, B. Pittman, S. K. Chaturvedi, M.P. Sharma, M. Bell, C. Andrade; Neuropsychopharmacology (2013) 38, 492–503	DSM-IV schizophrenia or schizoaffective disorder, aged 18–65 years with 8 years school education, clinically stable, healthy, on stable doses for one month, total treatment period six months, no significant extrapyramidal symptoms, no depression + other criteria		India: 104 randomized, 69/82 completed 12-week active treatment phase. Mixed, double-blind, placebo-controlled, parallel-group design, stratified random sampling by IQ. Assessments: at 12 and 24 weeks	Continuous Performance Test (CPT); WAIS-III Digit Symbol coding and Trail Making Test part A; WAIS-III Digit Span and WAIS-III Letter/Number Sequencing; WAIS-III Spatial Span; Hopkins Verbal Learning Test-Revised (HVLTR); WAIS-III Logical Memory; Tower of London (TOL) and Wisconsin Card Sorting Test (WCST), plus others	(1) D-serine plus CRT, (2) Placebo D-serine plus CRT; (3) D-serine plus control CRT (video viewing), or (4) Placebo D-serine plus control CRT Medication: D-serine (30 mg/kg) or placebo for 12 weeks; Duration: 12 weeks + Computerized (20 computer-assisted tasks – 4 tasks per cognitive domain- for attention, memory, verbal and visuospatial working memory, executive functions.) or control (TV viewing) CRT for 5 h per week spread across 2–3 days/week.	CRT improved measures of attention/vigilance and verbal working memory only, high placebo response. No effect of CRT on global cognitive index.
P. N. Suresh Kumar, Indian J Psychiatry 50(4), Oct–Dec 2008	DSM IV schizophrenia with 2 years duration of illness, speak Malayalam, attending vocational rehabilitation for 6 months, controls: no vocational rehabilitation		Subjects: 34 Controls: 40 From 08-02-2006 to 21-03-06, Non-probability purposive sampling	Sociodemographic, SCARF Social Functioning Index, Mini Mental State examination, Positive and Negative Syndrome Scale	Vocational activities, full day, as per ability, in the hospital	Cognitive functioning positively correlated with occupational role in patients and negative correlation in controls.
S. Hegde, S. L. Rao, A. Raguram, B.N. Gangadhar, Indian Journal of Psychiatry 54(1), Jan–Mar 2012	First episode schizophrenia: ICD 10 criteria, duration of illness <2 years Spoke English or Kannada or Hindi fluently, had adequate visual and hearing ability, minimum education up to 5th grade. Excluded: mental retardation, neurosurgical or neurological condition, electroconvulsive therapy in the past 6 months.		Subjects+ controls-45; 12 subjects and 11 controls completed study. Randomized controlled design Assessments: at baseline (prior to the intervention), post-assessment (after the intervention), and at 6-month follow-up (4 months after completion of the intervention).	Positive and Negative Syndrome Scale (PANSS), WHO Disability Assessment Schedule-II (WHODAS-ID), several psychological tests of cognitive ability. Caregivers: General Health Questionnaire (GHQ-28), Scale for Assessment of Family Distress (AFD).	2-month-long home-based cognitive retraining program with treatment as usual (TAU); psychoeducation and drug therapy) for subjects, only TAU; psychoeducation and drug therapy for controls.	Cognitive retraining: improved cognition; better performance on motor speed, verbal working memory, concept formation and set-shifting ability, verbal learning, visuo-constructive ability, divided attention, planning, and reduced negative symptoms. Improvement sustained at six months. No difference in measures of family health or distress.

Authors and Publication	Subjects/controls	Inclusion criteria	N, period, sampling	Instruments	Intervention	Final results
T. Bhatia, A. Agarwal, G. D. Shah, J. Wood, J. Richard, R.E. Gur, R.C. Gur, V.L. Nimgaonkar, S. Mazumdar, S. N. Deshpande. Acta Neuropsychiatr. 2012; 24(2): 91–100.	DSM-IV schizophrenia, outpatients, over 18 years of age, no comorbidity,		Subjects: 65 Open, non-randomized study among patients with SZ. February 2006 to August 2009 Assessments: at baseline 21 days after yoga therapy, and two months following completion of YT	University of Pennsylvania Computerised Neurocognitive Battery (CNB)	Structured 21 days, daily one hour yoga protocol (combinations of Asanas and Pranayam), or treatment as usual	Significant improvement in attention (speed) index of CNB with attendant improvement in efficiency. Improvement in abstraction and mental flexibility (accuracy).