International Journal of Recent Technology and Engineering (IJRTE)
ISSN: 2277-3878 (Online), Volume-8 Issue-6, March 2020

Effect of Computerized Cognitive Remediation in Patients with Schizophrenia

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Abstract: ***The objective of this study is to evaluate the effect of computerized cognitive remediation through 3 months randomized controlled trial in Indian patients with schizophrenia. Nineteen chronic schizophrenic patients were recruited and randomized into Cognitive Training (CT) and Treatment as Usual (TAU) groups. Neuropsychological assessments were done before and after 3 months of cognitive training on the developed program. As compared to TAU, the CT group exhibited significant improvement in speed of processing (p= 0.031, 95% Confidence Interval CI [-90.36 to -29.64], large effect size Φ = 0.7) and sustained attention (digit span - time, (p= 0.015, 95% CI [-99.40 to -41.60], large effect size Φ = 0.7)). The outcome of this study shows that the computerized cognitive training is feasible and useful in treating cognitive deficits in Indian patients with schizophrenia.***

Keywords: Schizophrenia, Cognition, Cognitive remediation, cognitive training.

I INTRODUCTION

Computers have been used in psychiatry for long to provide cognitive remediation in different psychiatric disorders. The technological advancements have allowed health care programs to be effective, accessible and sustainable. Mobile-based cognitive programs in the form of "Applications (Apps)" are now widely utilized for screening and assessment of persons with disability [1][2]. Some studies have shown the utility of mobile-based administration can induce higher interest in patients with mental disorder [3][4]. Watts *et al.* (2013) achieved positive results with a software program (The Get Happy Program) on mobile phones for patients with depression [5]. Dagoo *et al.* (2014) successfully conducted mobile phone-based administration of Cognitive Behavioural Therapy (mCBT) for social anxiety disorder [6]. Oliveira *et al.* (2014) successfully assessed cognitive functions of stroke patients through a virtual reality-based mobile application [7]. Bless *et al.* (2014) reported improvements in fMRI-BOLD regional activations with the potential use of a mobile application for self-supervised training of auditory attention inhealthy subjects [8].

Manuscript received on February 10, 2020.
Revised Manuscript received on February 20, 2020.
Manuscript published on March 30, 2020.
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To the best of our knowledge, very few studies have provided insight into the usage of mobile applications for assessment and training of patients with schizophrenia. The available studies largely involve ambulatory interventions for people with severe mental illnesses. In a pilot study, Granholm *et al.* (2012) presented Mobile Assessment and Treatment for Schizophrenia
(MATS) to improve outcomes in patients by low-intensity mobile phone text messaging intervention [9]. For the purpose, MATS typically imply ambulatory monitoring and cognitive behavioural therapy to target medication adherence, socialization and auditory hallucinations. The whole procedure is based on self-reporting paradigm. The subjects are supposed to report at least one benefit of medications, being social and a coping strategy used by the subject to control auditory hallucinations. The methodology had some limitations such as 1) false reporting by subjects 2) different phone configurations 3) problems faced in the reading of text messages. Ben-Zeev *et al.* (2014) developed a smartphone intervention "FOCUS" for management of illness in real time. The application assist in symptom management, medication adherence, mood regulation, social functioning and help in achieving better sleep [10]. FOCUS home screen lists items such as medication, voices, social, mood, medication and sleep for respective assessments. The users can click on any icon they like. After answering to brief assessment questions, either a positive response or some friendly advice is received. Following the intervention, participants were reported to have better-Brief Assessment of Cognition in Schizophrenia (BACS) scores, reduced positive and negative symptoms (PANSS), and changes in beliefs about medication. Palmier-Claus *et al.* (2012) showed successful ambulatory monitoring of symptoms by patients several times a day using smartphone software application "ClinTouch"[11]. In this application, the subjects were required to respond to statements regarding their symptoms whether they agree or disagree on an analogue scale. Along similar lines, an application named "CrossCheck" is under development with the main focus on relapse prevention in schizophrenia patients [12]. Well, these applications mainly focus on services such as ambulatory monitoring, reporting and management and do not strictly target the cognitive deficits. Dang *et al.* (2014) tested the feasibility of iPad assisted cognitive training (working memory-N Back task) for first-episode schizophrenic patients [13]. The subjects were engaged for 60 minutes a day; 5 days per week. Patients were reported with significant improvements in the accuracy and reaction time at 1, 2-Back tests after training. From the literature, it is certain that the capacity to impart some treatment via mobile applications may turn out to be a small but revolutionary step in the delivery of mental health.

Hegde *et al.* (2017) presented the review on the current studies of Cognitive Remediation (CR) in Indian schizophrenic population [16]. Conventional methods such as paper pencil methods, yoga therapy and integrated psychological therapy to cognitive remediation are largely prevalent in Indian psychiatry setups.

Hence, this experimental study aims to test feasibility of computer assisted cognitive remediation in chronic Indian schizophrenic patients through a randomized controlled trial.

II MATERIAL AND METHODS

The study design is a longitudinal, randomized, controlled and single–blind. The study procedure was approved by the concerned institutional research and ethics boards. All the subjects gave written, informed consent to participate in the study in the presence of their caregivers. No financial compensation or incentive in any form was given to subjects for participation in training and assessment. Nineteen patients diagnosed with schizophrenia were recruited from Disability Assessment and Rehabilitation Triage (DART) rehabilitation facility, Department of Psychiatry, Government Medical College and Hospital (GMCH), Sector 32, Chandigarh, INDIA. The inclusion criteria for the study was (a) Age: 18 - 60 years (b) Duration of illness: minimum 2 years (c) No head injury (d) No co-morbid illness (e) No substance abuse. All the subjects were clinically stable at the time of recruitment and were on regular maintenance medication as decided by treating psychiatrist. Subjects in CT group underwent computerized cognitive training for a period of 3 months, at a frequency of 4 days per week. All the participants in the TAU group received standard treatment during the study duration, which involved continuous psychiatric treatment and daycare activities in the DART clinical facility. At baseline, the two groups did not differ significantly in any of the demographic parameters as specified in Table 1. All the participants were assessed on NIMHANS (National Institute of Mental Health and Neurosciences) Neuropsychological Battery which includes Indian adaptation of standard neuropsychological tests [17]. The entire battery includes paper-pencil tests. The tests were performed under the supervision of clinical psychologist.

Table 1. Socio demographic profile of the participants

Demographic Variable	Cognitive Training (N=10)	TAU (N=9)	t or x^2	df	*p*
Age*	35.1 (7)	39.7(6)	1.529	17	0.144
Education (Years)*	16.9(3.20)	18.3(3.17)	-0.957	17	0.352
Gender					
Male	3	5	}1.269	1	0.259
Female	7	4			
Handedness					
Right	10	10	No diff.		
Left	0	0			
Duration of Illness*	10.5(8)	11.1(8)	0.163	17	0.872
Occupation					
Employed	0	0	No diff.		
Unemployed	10	10			
Socio-Economic Status					
(0-3500) Rs	2	4	}1.6185		
(3500-7000) Rs	2	2			
(7000) Rs or above	6	3		2	0.445
Antipsychotic Profile					
Typical	0	0	No diff.		
Atypical	10	10			

***** mean(standard deviation) values are given for the parameter

III RESULTS AND DISCUSSION

Neuropsychological test were performed before treatment and after treatment on 19 chronic schizophrenic patients. The test scores for each patient were compared with the Indian context normative data available in the NIMHANS Neuropsychological Battery. The normative values are available on the basis of subject age group (below 30 / 31-50 / 51-65 years), gender (Male/ Female) and education (literate-[school/college], illiterate). In the battery, the scores below the 15 percentile have been set as the threshold to define cognitive deficit. Hence, all those patients who scored below 15 percentile in the psychological test were considered to be cognitively deficient in the respective cognitive domain. For analysis, the results of the test were further coded as '1' for scores less than 15 percentile (deficit-present) and coded as '0' for scores greater than 15 percentile (deficit-not present) and McNemar Chi-square test was applied to confirm whether there is a significant change in cognitive profile of subjects from pre to post treatment.

A. McNemar chi-square test

McNemar's chi-square is a form of chi-square test for repeated measures designs. It is applied using a 2×2 contingency table with the dichotomous variable at two time points: before and after treatment as shown in table 2. It checks if a statistically significant change in proportions has occurred on a binary dependent variable at two time points on the same population.

Table 2. Contingency table (2 x 2)

COGNITIVE DEFICITS ?	After Treatment		
Before Treatment	***Absent***	***present***	ROW SUM (PROPORTIONS - %)
absent	**A**	**b**	**a +b** ((a + b) / n)%
present	**C**	**d**	**c + d** ((c + d) / n)%
COLUMN SUM (PROPORTIONS- %)	**a + c** ((a + c) / n)%	**b +d** ((b + d) / n)%	**n**

The McNemar chi square statistic is calculated as

$$\chi^2 = \frac{(b-c)^2}{(b+c)} \quad (1)$$

If, P_1 = Probability (*BeforeTreatment_absent*=0, *AfterTreatment_present* =1) and,

P_2 = Probability (*BeforeTreatment_present*= 1, *AfterTreatment_absent* = 0)

Hence, it is hypothesized that

H_0: $P_1 = P_2$ (before treatment equal after treatment)

H_1: $P_1 \neq P_2$ (before treatment not equal after treatment)

For p-value lesser than reasonable $\alpha = 0.05$ (two-sided) was accepted as if there exists a significant difference between the two proportions. The Cramer's Phi Φ, a measure of effect size for chi-square statistics for n observations is also calculated as shown in equation 2.

$$\Phi = \sqrt{\frac{\chi^2}{n}} \quad (2)$$

Table 3 presents the estimates of p-values, confidence intervals and effect size after the McNemar chi-square test has been applied on post hoc treatment data of CT and TAU group. The key findings are detailed as follow:

a) Statistical Significance: The subjects in the CT group were associated with significant cognitive improvements in Speed of Processing (p= 0.031, 95% Confidence Interval CI [-90.36 to -29.64], large effect size Φ =0.7) and Sustained Attention (digit span - time, (p= 0.015, 95% CI [-99.40 to -41.60], large effect size Φ =0.7)) than those who participated in TAU Group (Table 3). In the CT group 60% participants showed reduction of deficits in speed of processing and 70% improved upon sustained attention (digit span-time). The results of TAU group did not achieved statistically significance in the test performed. These results suggest that cognitive training on a computerized platform, tablet in our case, helped in improving the ability to maintain attention for longer time and the speed of information processing in individuals with schizophrenia. In both the groups, no statistically significant improvement was achieved for any other cognitive domain.

b) Clinical Significance: From Table 3, it has been observed that the p-values for some test lie in the proximity of the defined significance limit (0.05). For example, the p-value for the Sustained Attention

Table 3. Cognitive assessment at pre-post training

Primary Outcomes	CT (Pre - Post)				TAU (Pre-Post)			
	p value	95% Confidence Interval	Diff. (%)	Phi- Φ, Effect Size	p value	95% Confidence Intervals	Diff. (%)	Phi- Φ, Effect Size
Mental Speed								
• Digit Symbol Substitution	**0.031***	-90.36 to -29.64	-60	**0.7(L)**	1.000	- 31.64 to 9.42	-11	0.3(M)
Sustained Attention								
• Digit Span –Time	**0.015***	-98.40 to -41.60	-70	**0.8(L)**	0.500	- 49.38 to 4.94	-22	0.4(M)
• Digit Span -Error	0.062	-80.99 to -19.01	-50	**0.7(L)**	1.000	- 30.80 to -30.80	0	0(S)
Focused Attention								
• Trail A Time	1.000	-27.72 to 27.72	0	0 (S)	1.000	- 31.64 to 9.42	-11	0.3(M)
• Trail B Time	1.000	-43.38 to 23.38	-10	0.1(S)	1.000	- 9.42 to 31.64	-11	0.3(M)
Divided Attention								
• Triad Test-Error	0.125	-70.36 to -9.64	-40	**0.6(L)**	1.000	-30.80 to 30.80	0	0(S)
Verbal Working Memory								
• 1 Back Hits	0.125	-70.36 to -9.64	-40	**0.6(L)**	1.000	-48.13 to 25.90	-11	0.1(S)
• 1 Back Error	0.125	-70.36 to -9.64	-40	**0.6(L)**	0.500	-49.38 to 4.94	-22	0.4(M)
• 2 Back Hits	0.625	-57.19 to 17.19	-20	0.3(M)	0.375	- 76.89 to 10.22	-33	0.4(M)
• 2 Back Error	0.250	-58.40 to -1.60	-30	0.3(M)	1.000	-48.13 to 25.90	-11	0.1(S)

Visual Working Memory								
• 1 Back Hits	0.500	-44.79 to 4.79	-20	0.4(M)	0.500	-49.38 to 4.94	-22	0.4(M)
• 1 Back Error	0.250	-58.40 to -1.60	-30	**0.5(L)**	1.000	-37.04 to -59.26	-11	0.1(S)
• 2 Back Hits	0.250	-58.40 to -1.60	-30	**0.5(L)**	0.218	-89.19 to -0.30	-44	**0.5(L)**
• 2 Back Error	1.000	-27.72 to 27.72	0	0 (S)	1.000	-49.13 to 25.90	-11	0.1(S)
Verbal Fluency - COWA								
• Average New Words	0.453	-78.41 to 18.41	-30	0.3(M)	1.000	-31.64 to 9.42	-11	0.3(S)
Category Fluency Animal Naming								
• Total No Words	1.000	-39.20 to 39.20	0	0(S)	1.000	-30.80 to 30.80	0	0(N)
Tower of London								
• TPNMM	0.500	-44.79 to 4.79	-20	0.4(M)	1.000	-31.64 to 9.42	-11	0.3(M)
Set Shifting								
• Perseverative Responses	0.625	-57.19 to 17.19	-20	0.3(M)	1.000	- 30.80 to -30.80	0	0(N)
• No of Categories Completed	0.250	-58.40 to -1.60	-30	**0.5(L)**	1.000	-9.42 to -31.64	-11	0.3(M)
• Complete 1st Category	1.000	-8.59 to 28.59	10	0.3(M)	0.500	-4.94 to 49.38	22	0.4(M)
• Failure to maintain Set	1.000	-23.38 to 43.38	10	0.1(S)	1.000	-31.64 to 9.42	-11	0.3(M)
Response Inhibition								
• Stroop Effect	0.687	-66.38 to 26.38	-20	0.2(S)	0.500	-49.38 to 4.94	-22	0.4(M)
Comprehension								
• Token Test	0.125	-70.36 to -9.64	-40	**0.6(L)**	0.625	-63.29 to 18.84	-22	0.3(M)
Auditory Verbal Learning Test								
• Immediate Recall	0.125	-70.36 to -9.64	-40	**0.6(L)**	1.000	-9.42 to 31.64	11	0.3(M)
• Delayed Recall	0.125	-70.36 to -9.64	-40	**0.6(L)**	0.500	-4.94 to 49.38	22	0.4(M)
Logical Memory								
• Immediate Recall	0.250	-58.40 to -1.60	-30	**0.5(L)**	1.000	-25.90 to 48.13	11	0.4(M)
• Delayed Recall	1.000	-28.59 to 8.59	-10	0.3(M)	1.000	-48.13 to 25.90	-11	0.1(S)
Visual Learning and Memory								
• Immediate Recall	0.500	-44.79 to 4.79	-20	0.4(M)	1.000	-9.42 to 31.64	11	0.3(M)
• Delayed Recall	0.625	-57.19 to 17.19	-20	0.4(M)	1.000	-9.42 to 31.64	11	0.3(M)

- **Diff.(%)**:- The difference of proportions (in percentage) with 95 % confidence interval**.**
- **Phi (Φ) Effect Size:-** S – Small (0.1), M – Medium (0.3) , L – Large (0.5), N - No effect.

(digit span error) was p = 0.062 in the CT group showing a marginally significant effect of the treatment. As there is little difference in evidence for p-values of 0.05 and 0.06, the clinically relevant information about the subjects' improvement is also of greater value. So in contrast to p-values, values for Confidence Intervals (95%) and Effect Size (Cramer's Phi Φ) were obtained to estimate the magnitude and direction of the treatment effect. If the confidence interval does not contain the value of zero effect, it can be assumed to be a clinically significant outcome. For Cramer's Phi Φ, a value of 0.1 is considered a small effect, 0.3 a medium effect and 0.5 a large effect [19]. On the basis of 95 % CI values and effect sizes obtained, the CT group as compared to TAU was associated with clinically meaningful improvements in Sustained Attention (digit span-errors, CI [-80.99 to -19.01, large effect size Φ = 0.7]), Divided Attention (Triad test-errors, CI [- 70.36 to -9.64, large effect size Φ = 0.7]), Verbal Working Memory (1 Back Hits and Errors, CI [- 70.36 to -9.64, large effect size Φ = 0.6]) ,Comprehension (Token Test, CI [-70.36 to -9.64, large effect size Φ = 0.6]), Auditory Verbal Learning (Immediate and Delayed Recall- CI [-70.36 to -9.64, large effect size Φ = 0.6]) and Logical Memory (Immediate Recall- CI [-58.40 to -1.60, large effect size Φ = 0.5]). So far the subjects in the training group were able to achieve improvements in lower order cognitive functions.

IV CONCLUSION

This experimental study was conducted to test the feasibility of computerized cognitive training in Indian patients with schizophrenia. Pre and post psychological tests were conducted on participants in the Cognitive Training (CT) group and Treatment as Usual (TAU) group. The subjects in the CT group were associated with significant cognitive improvements in speed of processing and sustained attention. The improvements were achievable because all the speed and attention training tasks demanded the subjects to respond accurately and quickly as possible every time the stimuli is presented. Medium to large effect sizes were also achieved in the CT group in divided attention, verbal working memory, comprehension, auditory verbal learning and logical memory. TAU group could not achieve significance level in any of the test scores.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

ACKNOWLEDGMENT

The authors acknowledge Director, Government Medical College and Hospital and UIET, Panjab University Chandigarh, India for providing a facility for carrying out this research work. Mr. Jaskirat Singh acknowledges University Grant Commission (UGC), INDIA for providing UGC-BSR Ph.D. scholarship-(F-7-379/2012 (BSR).

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