International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2015): 6.391

Effects of Cognitive Remediation Therapy in Children with Autism Spectrum Disorder: Study Protocol

Melek Hajri[1,2], Zeineb Abbes[1,2], Houda Ben Yahia[1], Sami Ouanes[1.2], Soumeyya Halayem[1,2], Asma Bouden[1,2], Ali Mrabet[2,3], Isabelle Amado[4].

Child and Adolescent Psychiatry Department- Razi University Hospital – Manouba -Tunisia

[1]Child and Adolescent Psychiatry Department, Razi Hospital, Manouba, Tunisia

[2]El Manar Tunis Univiersity, Faculty of Medicine of Tunis, Tunisia.

[3]Military Center for Health and Environment Protection / General Directorate of Military Health. Tunisia

[4]Hospital practitioner. Sainte-Anne Hospital. Paris. France

Abstract: ***Background: Autism spectrum disorder is known to be associated with cognitive dysfunction. This impairment has an impact on academic difficulties and represents the main treatment target. Cognitive remediation therapy attempts to improve cognitive deficits by teaching information processing strategies through guided mental exercises. The aim of this study is to investigate whether cognitive remediation therapy, a new psychological treatment, improves cognitive function and, in turn school performance in children with autism spectrum disorder. Methods/Design: Children meeting the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) criteria for autism spectrum disorder, and following a regular school curriculum were recruited from clinical population at the Child and Adolescent Psychiatry Department in Razi University Hospital – Manouba - Tunisia. The intervention was individual cognitive remediation therapy delivered over a period of six months with one session per week. The main outcome measures were intellectual abilities, cognitive flexibility, working memory, clinical symptoms and school results. Patients showed significant improvement on intellectual abilities, phonemic fluency, « animal » category of semantic fluency, working memory, clinical symptoms and school results. Discussion: This is one of the first trials to evaluate the effects of cognitive remediation on cognitive function in patients with autism spectrum disorder who encounter cognitive difficulties. Conclusion: Cognitive Remediation Therapy was able to show significant positive effects on neurocognition, clinical symptoms and school results among children with autism spectrum disorder.***

Keywords: Autism spectrum disorder, Cognitive remediation therapy, Remediation, Child, Executive function

1. Background

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by impairments in social interaction and communication and restricted and repetitive interests/behaviors(1).

Children with ASD may have a favorable outcome either in social interactions or in communication, but the outcome in terms of quality of life and skills is still poor(1). One possible explanation is that skills and school performance, although affected detrimentally by high levels of symptoms, are in the longer term associated less with symptoms (which are the current focus of medication) and more with other factors such as cognitive dysfunction, especially executive dysfunction (2-4).

The concept of "executive function" (EF) points out the higher order control processes essential to guide behavior in a continuously changing environment (5). This concept comprises abilities like working memory, response initiation, impulse control, planning, mental flexibility, response inhibition and monitoring of action (6, 7). Neuropsychological and behavioral researches originally associated executive functions to the frontal lobes, especially the pre-frontal cortex.

Cognitive flexibility points out to the skill to shift to distinctive actions or thoughts relying on situational demands (8, 9). Cognitive flexibility intends to develop the participant"s skill to comprehend a variety of situations.

Working memory is a system that enables momentary managing and storing the information essential to execute complex cognitive tasks like reasoning, comprehension and learning. Working memory participates in the initiation, selection and termination of information-processing tasks like, storing, retrieving and encoding data.

Planning is a complex, dynamic operation involved in the evaluation, formulation and selection of a sequence of actions and thoughts to reach a wanted objective (10).

Inhibition includes the following three complementary processes: inhibition of a proponent or dominant response, stopping of a response still in progress and interference control (distractibility) (11).

There is a proof of executive dysfunction in ASD, for the most part regarding planning and flexibility (10). Other researches have investigated the memory functioning and displayed deficits in the long-term memory mainly episodic memory (12). Important disabilities in the inhibition of

proponent responses and attention (13) were in addition stated in children with ASD.

Besides, executive dysfunction may clarify to some extent impairments in social interactions and communication (12), and repetitive and restricted behaviors (8, 14). That‟s why there is a high-priority clinical necessity for new therapeutic strategies that aim cognitive enhancement in ASD. Now there is an increasing proof from randomized controlled clinical studies that support the effectiveness of the addition of a cognitive remediation therapy, psychological treatment, to pharmacological therapies in improving cognitive deficits (15, 16).

The purpose of cognitive remediation (CR) which is a new psychological treatment is to improve cognitive function, coping and compensation abilities and as a matter of fact, psychosocial function. It has been extensively studied in subjects with schizophrenia and revealed positive results on cognition and on some facets of social functioning (17-19).

In a current meta-analysis of 40 studies demonstrated that CR causes to a durable improvement of social and cognitive function levels in this subject group (effect size=0.32; 95% confidence interval= 0.31 to 0.59) (17).

A small number of researches studied the use of CR in ASD. A research conducted by Weiner et al in 2010, involving two adults, applied a part of the CRT including cognitive flexibility and working memory. The research demonstrated amelioration in tests of flexibility, working memory and self-esteem in one of the patients.

This trial purpose is then, to examine if CR has positive effects on executive function and school performance in children with ASD. We used a modified version of the CRT, adapted to children, who brought his evidence in children with attention deficit/hyperactivity disorder (ADHD)(20).

Hypotheses
The hypotheses of the present study are that CRT will:
1-Improve cognitive flexibility, working memory, intellectual efficiencies
2-Enhance clinical symptoms and school performance.

2. Methods

Study design
Our study was a Cross-sectional one.

Participants and screening
The study was performed by the 12SP20 Research Unit (“Cognitive processes in psychiatric disorders”) - Faculty of Medicine of Tunis.

Subjects were registered from Child and Adolescent Psychiatric Department in Razi University Hospital, Manouba Tunisia. Parents obtained information concerning the study and had the opportunity to ask questions before agreeing to the participation of their children. During the study, additional information was available upon parents‟ request.

The inclusion criteria were:
- Diagnosis of ASD according to the Diagnostic and Statistical Manual, 5th (DSM-5): participants was screened with a psychiatric interview using DSM-5 criteria to confirm diagnosis
- Cognitive difficulties reported by parents
- On a stable dose and type of medication, for at least one month prior to inclusion
- Age between 6 and 21
- Regular school curriculum
- Participants were not included if they had:
- a history of seizures or any other neurological disorder
- a history of a chronic medical condition
- mental retardation

Exclusion criteria were:
- Non achievement of the program
- Non achievement of assessments after finishing the therapy

Assessments
All chosen outcomes had good reliability and validity data.

Outcomes
The main study outcomes (cognitive functions, clinical symptoms and school performance) were measured at baseline and 1 week after finishing the therapy.

Intellectual efficiencies were evaluated using Raven Progressive Matrices (CPM) that assesses general non-verbal intellectual abilities besides the skill of deductive reasoning (21).

We evaluated cognitive flexibility using verbal and semantic Fluency Tests. A maximum number of words had to be said by the participants from a category in a given time (usually 60 seconds) (22). This category can be semantic (like animals) or phonemic. The phonemic fluency task using the initials F, A and S, named FAS, is possibly the most utilized letter fluency task, while “animals” is the most common semantic category (23). The letters used in the test vary relying on the language of the patients and normative data for a number of language versions are available. In our study protocol, we chose the letter “m” ” م “ in Arabic, as neuropsychological research conducted by Aguibi and Bouaziz in 1998 showed that this letter is productive among children aged from 6 to 12. We then adjusted the time to 2 minutes.

We chose both “clothe
s” and “animals” for semantic fluency as stated in a prior Tunisian study (24).
The measure adopted was words number. For each correct response a one point credit was awarded.

Working memory was evaluated utilizing the digit-span task: Participants were provided with a number string and requested to repeat it in the same presentation order (Digit Span Forward) or backward (Digit Span Backwards). The interest measure was the digit correct for every condition. For every trial, numbers were chosen randomly from the group of 1 to 9 (25). The trials were different in length from

2 to 8 digits. The next restrictions applied: no consecutive digits followed each other, no numbers were repeated in a trial, and sequences of digits with mnemonic cues (e.g., phonological similarity) were avoided.
We evaluated clinical symptoms with the Childhood Autism Rating Scale (CARS). It is a technique of diagnostic assessment that rates patients on a scale from one to four for different criteria, varying from normal to severe, and presents a composite score varying from non-autistic to mildly autistic, moderately autistic, or severely autistic. The scale is used to observe and subjectively rate 15 items (relationship to people, imitation, emotional response, body, object use, adaptation to change, visual response, listening response, taste-smell-touch response and use, fear and nervousness, verbal communication, non-verbal communication, activity level, level and consistency of intellectual response, general impressions). This scale can be done by a parent or clinician or teacher relying on the subjective monitoring of the child‟s behavior (26, 27).

✓ School performance was evaluated by school results.

Interventions

Cognitive remediation therapy
This program of rehabilitation was first elaborated by Ann Delahunty in Australia (28), then modified by Til Wykes in the United Kingdom. By aiming executive functions, the program tried to ameliorate cognitive functioning in subjects with schizophrenia.

This program is implemented on an individual basis, using mainly paper and pencil tasks. An errorless learning approach is adopted in tasks of progressive complexity and the problem is set, as far as was possible, at the subject's own pace. The main instructional technique is scaffolding. This involves an instructor extending a learner's ability by providing support in those aspects of a task which the learner cannot accomplish, while removing assistance in those areas where competence has been achieved (18, 28, 29).

CRT comprises three modules, delivered in the following order: cognitive flexibility, memory and planning.

i The cognitive flexibility module targets to approach flexibility in thinking and information-set maintenance, the two apparently need the capability to adequately engage and disengage activated neutral network processing. Verbal instructions as a cue are used by the therapist to guarantee maintenance and the switch to the suitable “set” for every task. The mission of the therapist is to push the patient to pay attention to every stimuli, to request the subject to recognize what the present „set‟ is and to show the subject if their performance speed is suitable. Lastly, the therapist ought to encourage covert and open verbal mediation of the task and do not permit the subject to be uncertain about what „set‟ has to be utilized (30).
Suggested tasks:
- Bisecting lines
- Superposed figures
- Collection
- Stroop Like
- Manipulation of shapes, numbers and letters
- Card Games
- Sorting of coins
- Chip sorting
- Manual exercises

ii The working memory module aims the executive processes central to memory control, it has subjects work with up to two to five information sets at the same time. It emphasizes on variables like sequencing, attention, multitasking, and delayed visual and verbal memory information (30-32).
Suggested tasks:
- Multiple visual search
- Copying symbols
- Delayed Answers
- Sequential search
- Visual analysis: "part-whole"
- Stroop like exercises
- Sequence of tokens

iii „‟Planning Module” aims goal-oriented, self-ordered, set/schema manipulation and formation, meaning the implementation of the practiced processes, like Working Memory to tasks that need planning. The tasks target is to ameliorate cognitive functioning using active cognitive strategies involving active sequencing, coding and chunking, and utilizing external and internal verbal meditation multitasking performance (30).

Suggested tasks:
- Divided attention
- Serial Search
- Sequencing
- Construction of cubic
- Categories
- Verbal Analogies
- Verbal Associations
- Understanding
- Visual search
- Superposed Figures

Everything considered, the therapy guidelines presented by Wykes (2008) (33) are founded upon these rules:
1. Initial assessment
2. Identification of personal goals
3. Personal therapeutic relationship to promote self-esteem
4. Tailoring of sessions
5. Reflective learning (metacognition)
6. Use of scaffolding
7. Using errorless learning
8. Development of cognitive strategies
9. Generalization to everyday life

Program progress
The sessions are divided between the various modules as follows: 8 sessions of cognitive flexibility, 8 sessions of memory and 8 planning sessions delivered 45-minutes weekly over 6 months. However, this duration could be adapted to each child‟s level. In our study, other tools were utilized and a modification of some tasks to children was created, turning them simpler and “funnier”. Besides, for children that do not speak French, Arabic exercises were

comprised and those done with French letters of alphabet were modified by changing letters to images.

Outcome assessments
The main outcome measures (executive functioning, clinical symptoms and school performance) were calculated at baseline and one week after therapy achievement.

Data analysis
Data will be entered and analyzed using statistical logiciel. Comparisons of two independent quantitative variables will be performed using parametric or non-parametric tests as the Mann-Whitney test. Comparisons of several independent quantitative variables will be performed using non-parametric Kruskal-Wallis test or the Pearson's chi-squared test.

Ethical considerations
The study was approved by Razi Hospital Ethical Committee, and supported by the 12SP20 Research Unit ("Cognitive processes in psychiatric disorders") - Faculty of Medicine of Tunis.

Preliminary results
From the 25 involved subjects, 18 had attained the end of the program. From them, 16 achieved the neuropsychological evaluations tests after CRT, consequently forming our final sample. Their mean age was 10.87 (±3.55 years). The average number of the performed sessions was 22.38 (±1.99 sessions).

Intellectual efficiency:
Subjects displayed important improvement concerning intellectual efficiency ($p<10^{-3}$). IQ was 27.6 before CRT and 28.5 after finishing this program.

Mental flexibility:
The mean score in "animals" category was 13.16 before CRT and 17 after it (p=0.045). Concerning the "clothes" category, the mean score increased from 10.47 to 12 after completion of the program (p=0.382). Higher scores of phonemic fluency (7) were also found after CRT in comparison with baseline mean scores (4.27), this improvement was not significant (p=0.032). Patients committed more repetitive errors in "animals" category, the mean score ranged from 0.56 before CRT to 0.94 after it (p=0.277). In "clothes" category, the mean score increased from 0.6 to 0.87 after completion of the program (p=0.277). Higher scores of repetitive errors were also found in phonemic fluency (0.2) after CRT in comparison with baseline mean scores (0.07), this increase was not significant (p=0.621).

As for intrusive errors, scores in "animals" category ranged from 0.44 to 0.25 after achievement of CRT program. This improvement was not significant (p=0.851). In "clothes" category, the mean score increased significantly (p=0.019) from 0.93 to 1.2 after completion of the program. In phonemic fluency, patients committed fewer errors (1.87 before CRT and 0.87 after it). This improvement was not significant (p=0.661) (Table 1).

Working memory:
Significant improvement (p=0.001) was observed on forward digit span. In fact, score increased from 3.38 before CRT to 4 after achievement of the program. Regarding backward digit-span, the average score raised from 2.21 prior to CRT to 3.09 afterwards. This was a significant improvement (p=0.006).

Clinical symptoms:
We noticed lower scores (26.81) after CRT comparing with baseline average score (27.87). This was a significant improvement (p=0.001).

School results:
There was a raise in the average score 10.57/20 before CRT to 11.08/20 afterwards, with a significant improvement (p=0.001).

3. Discussion

This trial is pioneering the examination of CRT effects on ASD executive functions, clinical symptoms and school performance. Data from research involving patients with schizophrenia as well as with ADHD indicated positive effects (17, 20).

Besides, the current trial is practical to meet the clinical requirement for more in-depth and specific examinations of CRT effects on ASD patients‟ executive functions.

4. Limitations

The research presented a few limitations. First, there was an emphasis on the direct result of the interventions, then we cannot extrapolate our findings to long-term result. To make clear this issue follow-up data are required. Second, a control group was not included due to ethical considerations: the control group would have had to come to the hospital weekly in order to practice games, at the expense of their school hours and multidisciplinary care sessions including occupational and speech therapy. Additional limitation was the limited number of the subjects, making results extrapolation hard. Actually, acquiring large numbers of patients was not realistic. Besides, pharmacological therapy could have an effect on cognition and/or the chance to CRT response.

5. Advantages

Our research was the first large scale one. Outcome measures were easy to use, accustomed to children. Besides, we attempted to create a relation between executive functions and school performance. Research naturalistic‟s sitting enabled us to investigate the CRT effects in "real" subjects.

6. Perspectives

If it is proven that CRT is effective, it may effortlessly be used in ASD‟s future therapy to ease subjects‟ executive function and then possibly better their educational achievement.

7. Trial Status

The recruitment of subjects began in July 2012 and is still continued. Twenty five subjects were recruited so far. Sixteen finished evaluation one week after finishing the therapy.

8. Abbreviations

ADHD: Attention deficit/hyperactivity disorder; ASD: Autism spectrum disorder; CR: Cognitive remediation; CRT: Cognitive remediation therapy; EF: Executive functions.

9. Author's Contributions

MH, ZA, HBY and SO conceived the trial. MH authored the first version of this article, which was then revised and optimized by AM, AB and IA.

10. Acknowledgements

We thank the patients participating in this study, as well as their parents.

11. Conflicts of interest

The Authors declare that there is no conflict of interest.

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Table 1: Comparison of flexibility results before CRT and after it

		Before CRT			After CRT		
		Score	Repetitions	Intrusions	Score	Repetitions	Intrusions
Semantic fluency	Animals	13,94	0,56	0,44	17	0,94	0,25
	Clothes	10,47	0,6	0,93	12	0,87	1,2
Phonemic fluency		4,27	0,07	1,87	7	0,2	0,87

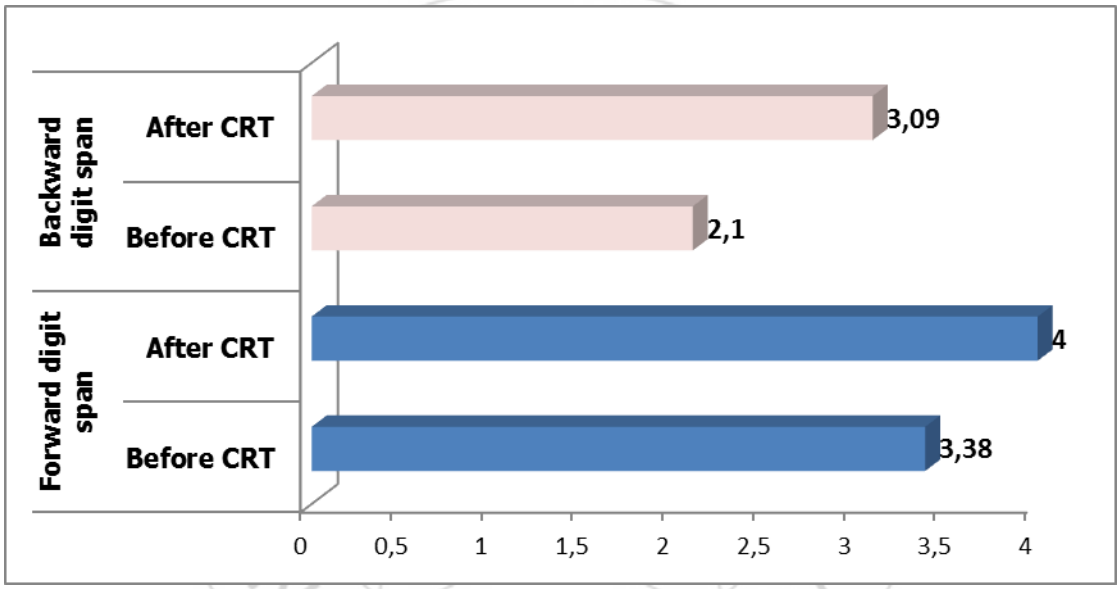

Figure 1 : Comparison of digit span results before CRT and after it