

# Improving neurocognitive functioning in schizophrenia by addition of cognitive remediation therapy to a standard treatment of metacognitive training

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## Abstract

Cognitive dysfunctions are a common clinical feature of schizophrenia and represent important indicators of outcome among patients who are affected. Therefore, a randomized, controlled, monocentric, single-blind trial was carried out to compare two different rehabilitation strategies adopted for the restoration and recovery of cognitive functioning of residential patients with schizophrenia. A sample of 110 residential patients were selected and, during the experimental period, a group of 55 patients was treated with sets of *domain-specific* exercises (SRT+CRT), whereas an equal control group was treated with sets of *non-domain-specific* exercises (SRT+PBO) belonging to the Cogpack® software. The effects on the scores (between T0 and T1) of the variables *treatment* and *time* and of the interaction *time X treatment* were analyzed: for the total BACS, the *main effect* of the *between-factors* variable *treatment* is statistically significant ( $F=201.562$   $P=0.000$ ), as well as the effect of the *within-factors* variable “*time*” ( $F=496.68$   $P=0.000$ ). The interaction of these two factors is also statistically significant ( $F=299.594$   $P=0.000$ ). The addition of cognitive remediation therapy (CRT) to a standard treatment of metacognitive training (MCT) resulted in a significant improvement in global neurocognitive functioning and has reported positive effects with regard to the strengthening of *verbal* and *working memory*, *selective* and *sustained attention* at T1. A relevant result is the statistical significance of “*time X treatment*” for all the tests administered: we can assume that the *domain-specific* cognitive training amplifies the effects of SRT, as the primary and secondary goals of the present study were achieved.

## Introduction

It is estimated that schizophrenia affects approximately 0.4-1% of the worldwide population, and although there has been important progress recognizing genetic and environmental risk factors, it has not been possible to unequivocally shed light on the mechanism underlying these gene-environment interactions. The presence of biological markers in association with poor cognitive performances in subjects with schizophrenia is attested from several studies, and it has recently been suggested that an inflammatory process could be the basis of cognitive deterioration.<sup>1</sup> Specifically, cytokines such as interleukins 1 and 6 (IL-1, IL-6) and tumor necrosis factor (TNF) seem to play a fundamental role in the maintenance of special molecular biological characteristics, such as synaptic plasticity, neurogenesis and neuro-modulation, and of cellular mechanisms involved in global cognitive functioning and activities.<sup>2</sup>

Cognitive dysfunctions are considered a common and disabling feature of schizophrenic disorder: they are already present in the prodromal phase and tend to be stable over time, affecting approximately 85% of subjects with schizophrenia and reducing cognitive abilities by 90% compared to healthy subjects.<sup>3</sup> Cognitive deterioration in schizophrenia negatively affects different cognitive domains,<sup>4</sup> with more feedback on *input information processing speed*, *working memory*, *verbal learning*, *executive functions* and *social cognition*,<sup>5</sup> with inevitable consequences for *psychosocial functioning*.<sup>6</sup> Currently, although antipsychotic D2 receptor antagonists represent the most frequently used pharmacological strategy for schizophrenia treatment, their effective action has been shown to be limited to positive symptoms. They do not produce significant effects on negative and cognitive symptoms,<sup>7,8</sup> which are more detrimental to a patient's life when compared to psychotic symptoms, as Green suggested.<sup>9</sup> The low efficiency of antipsychotics was confirmed in a study in which 30% of patients continues to show psychotic symptoms even after targeted antipsychotic medications. This condition led to the definition of *treatment-resistant schizophrenia* (TRS).<sup>10</sup> During the International Society for CNS Clinical Trials and Methodology (ISCTM) meeting in March 2014, a particular emphasis was placed on the importance of cognitive dysfunctions and functional disability in schizophrenia, recognizing them as intervention targets of equal importance.<sup>11</sup> Cognitive dysfunction is still associated with limits in obtaining rehabilitation improvements: cognitive remediation therapy (CRT) was

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intended as a cognitive deficits-based and patient-centered remedy.<sup>12</sup> It was carried out according to intensive treatment methods on each deficit and patient-tailored so as to promote restoration and recovery of the most damaged functions, and to provide resources capable of maintaining and enhancing residual and partially undamaged skills. Moreover, the negative outcomes produced by cognitive deterioration in terms of prognosis and health cares encouraged the use of cognitive remediation rehabilitative strategies.<sup>13</sup> In fact, this kind of therapy helped to reduce hospitalizations compared to other rehabilitative strategies.<sup>14</sup> In particular, the results derived from computer-aided cognitive training techniques encouraged the development of a new approach to mental pathologies. A recent study by Reeder and colleagues (2016)<sup>12</sup> showed both a good tolerance and acceptance of computer-aided treatment by patients, and an actual improvement in perception in terms of memory, attention, concentration, reasoning and problem-solving. A further significant point is the awareness with which most patients adapted the strategies learned during treatment to everyday life, especially as regards the memorizing techniques. A study by Bernoit and colleagues (2016) investigated whether cognitive functioning insight, evaluated before and after a computer-aided cognitive training, could represent an improvement predictor.<sup>15</sup> This would enable us to identify

patients who benefit the most by applying it to the skills acquired for and applied to everyday life.

The review of a recent meta-analysis by Wykes (2011)<sup>16</sup> and Mc Gurk (2007)<sup>17</sup> shows that CRT is more effective when the consequences of cognitive dysfunctions on social life are considered and it is accompanied by specific programs of psychiatric rehabilitation.<sup>18</sup> Therefore, a proper integration of CRT and other psychiatric interventions provides an effective strengthening and/or rehabilitation of cognitive abilities and functional resources.<sup>11</sup> Over the last 30 years, the development of neuroimaging techniques has shown a considerable reduction of cortical connectivity in subjects suffering from schizophrenia, and the normal adolescent exacerbation of neuronal pruning could be responsible.<sup>19</sup> In January 2016, an important study described the cause of pruning and identified the genetic factors involved: it seems that a genetic variation speeds up this process in subjects with schizophrenia. The research team led by Steven Mc Carroll found that four common variants of the C4 gene are located in the MHC locus, capable of producing two different proteins: C4-A and C4-B.

By analyzing over 64,000 subjects' genome, hyperactive forms of C4-A were observed in subjects with schizophrenia. An anomalous production of this protein could be responsible for excessive synaptic pruning, and could explain both the thinning of connections and reduction in the prefrontal layer and the early onset in adolescence or early adulthood. Isaac and Januel,<sup>20</sup> observed that in 271 patients with CRT it was possible to find a significant increase in the activity of different areas of the brain (particularly frontal, prefrontal, occipital and the anterior cingulate) during the execution of specific tasks for working memory and executive functions.

In a study by Eack and colleagues,<sup>21</sup> it was highlighted that in patients with schizophrenia undergoing two years of CRT showed considerable reduction in the volumetric loss of grey matter at the level of the parahippocampal gyrus and fusiform as well as a contextual increase of the same at the level of the left amygdala. Similar results indicate the benefit of this rehabilitative practice as a neurobiological protection factor, with favorable impacts on global cognitive functioning and cognitive outcome in the long term. The work we present gives the results obtained following the ideation and practical implementation of a randomized, controlled, monocentric, single-blind trial. We consider the comparison between two different rehabilitation programs adopted for the restoration and

recovery of neuropsychological functioning of residential patients with schizophrenia.

## Participants

For the present study, a sample of 110 patients at the Rehabilitative Psychiatry and Research Villa Chiara clinic in Mascalucia (CT) were involved. These subjects were aged between 18 and 65 years with a DSM-V diagnosis of schizophrenia.<sup>22</sup>

As main criteria for inclusion, in addition to a DSM-V diagnosis of schizophrenia: i) Pharmacological treatment unchanged for at least six months and in clinical stable conditions; ii) Willingness to take part in the study for one hour a day, three times a week for at least three months.

Patients presenting with the following were excluded: i) Psychopathological, neurological comorbidity and epilepsy; ii) QI <70.

## Goals of the research work

The 110 patients were randomly assigned to two groups with a 1:1 ratio. During the experimental period, of three months, the study group followed the experimental treatment with sets of *domain-specific* exercises taken from the Cogpack® software (SRT+CRT), while a second control group was treated with sets of *non-domain specific* exercises (SRT+PBO). The results produced by one or the other treatment were then compared, so as to verify the achievement of the primary and secondary goals.

The primary goal was represented by improving the psychological functioning (BACS, Kefee *et al.*, 2004; CPT-AX, Stratta *et al.*, 2000),<sup>23-25</sup>

Secondary goals are: i) improvement of the general psychopathological functioning (PANSS, Kay *et al.*, 1987);<sup>26</sup> ii) improvement of the adaptive functioning (*Mini-ICF-APP*, Linden *et al.*, 2005; Molodynski *et al.*, 2013).<sup>27,28</sup>

## Assessment

During the assessment, we collected basic data including the personal, family and pathologic history of each patient. At baseline (T0) the following profiles were evaluated: psychopathological via PANSS,<sup>27</sup> neuropsychological through BACS and CPT in AX version,<sup>23,24</sup> as well as adaptive functioning through the ladder Mini-ICF-APP.<sup>27,28</sup> The assessment of cognitive performances represented a step of fundamental relevance in order to be able to obtain a useful profile aimed at the "con-

struction" of the exercises in the context of individualized treatment and targeted at specific deficits found, so as to modulate the training about the real capacity of each patient. The software used in training allows sets of exercises to be created on the basis of the cognitive disruptions observed in assessment. The results were then compared with those obtained after a new administration of the same tests at the end of the three months of experimental treatment (SRT+CRT) or placebo (SRT+PBO) (T1), so as to evaluate the effect of the experimental treatment and monitor outcomes obtained among patients.

## Materials

Among the various softwares on the market used in cognitive remediation therapy (CRT), the program Cogpack® (Marker, 1987-2007) was used for the purposes of our research work. Cogpack® is a software constituted by 64 exercises classifiable as *domain-specific* exercises and *non-domain-specific* exercises. The former act on individual skills such as *verbal memory*, *verbal fluency*, *motor coordination*, *sustained attention*, *selective attention*, *working memory*, and *executive functions*. The *non-domain-specific* exercises do not focus on one specific cognitive domain in particular but require the use and simultaneous involvement of aspects such as language, culture, and basic logical and mathematical skills. The exercises may be administered randomly and have their difficulty level adjusted by the computer on the basis of the performance in the course of sessions, so as to prevent the patient carrying out exercises that are too simple or excessively difficult. The program records the results obtained by each patient for every session, thereby allowing us to monitor single sessions and entire treatments. This gives the therapist an opportunity to draw a clear profile on the progress of each individual patient. At the end of each exercise, feedback is provided on the progress of current performance, which is compared with the preceding one and the best value obtained in each exercise. For each exercise the sessions of the initial test are presented so as to increase patients' confidence with computer practice and they can also receive some online assistance. In 2005, Sartory and colleagues documented the beneficial effects of a program of computerized cognitive remediation on *verbal learning*, *processing speed* and *verbal fluency*, with positive effect on the *executive functioning* and *global neurocognitive functioning* of subjects with schizophrenia.<sup>29</sup>

In Italy, studies such as those of Cavallaro *et al.*<sup>30</sup> have confirmed the effec-

tiveness of Cogpack® on clinical measures, neuropsychological tests and overall functioning in subjects with schizophrenia submitted to three months of intensive ambulatory treatment. Moreover, the impact that the use of Cogpack® is able to make on the improvement of the neurocognitive functioning in people with high susceptibility to schizophrenia, the *ultra-high-risk* (UHR) individuals, has recently been studied.<sup>31</sup> It was shown that the inclusion of subjects at high risk within rehabilitation programs that include strategies for cognitive remediation has a delaying effect on the onset of the condition of outright psychosis.<sup>32</sup>

## Procedures

Patients involved in our research work were assigned to two groups of separate treatment - three months a CRT rehabilitation program or placebo in addition to the standard rehabilitation (SRT) they had under gone inside the Rehabilitation and Research Villa Chiara psychiatry clinic. The patients were randomly assigned to each group, and the neurocognitive, psychopathological and adaptive performances of interest were evaluated and compared at *baseline* (T0) and after three months (T1). During training, psychologists who had not carried out assessments supervised and assisted the members of both groups, to whom the only information that was given to patients regarded the integration of more or less specific exercises aimed at strengthening cognitive functions, in relation to the treatment they had received up to that point. Once the assessment phase had been completed, the experimental and placebo conditions were entered within the scope of usual rehabilitative care

Thanks to the computer-generated random number tables any statistically significant differences between the two groups at *baseline* were excluded. The exercises were explained to patients with the initial tests and a code was assigned by which they could have access to individual profiles in successive sessions. In accordance with the profile of the trend in the performance. Operators supplied the necessary aid to the resolution of specific tasks if patients experienced particular difficulties. Most interventional approaches in cognitive functioning today are of a *drill and practice* or *drill and strategy* type, or are the result of a balanced combination of the two. The first assumes a learning through *trial and error*, encouraging the explicit component of learning, which is thought to be most compromised in schizophrenia, while the second teaches a resolution strategy suitable for specific tasks, assuming a learning that

is both implicit and explicit.<sup>33</sup> Therefore, in the context of individualized computer treatment, the operators, recognizing the difficulties related to explicit memory, attention and self-monitoring reported by patients, have monitored the execution of exercises by trying to understand the reasons for failure of each patient. They encouraged them to improve by using principles of motivational interviewing, but still taking into account their learning times and limits. The experimental condition (55 SRT+CRT) consisted of three weekly sessions of 1 hour for a total duration of 12 weeks, devoted to the completion of the *domain-specific* exercises in the software Cogpack®,

The specific exercises were added for each area that had deteriorated worst, while other *non-domain-specific* tasks were integrated on the basis of relatively undamaged or preserved cognitive aspects; then the patients were subjected to four sets of specific exercises organized in accordance with the standard procedure. During the first three weeks *set 1* was administered, which was made of more easily adaptable exercises, so that the patient was able to acquire greater confidence with the use of the computer. Sets *a*, *b* and *c*, administered over the remaining weeks, were developed in such a way as to act always on the same deficit areas, but using different types of exercise presented alternately and in a *bottom-up* approach.

To patients belonging to the placebo group (55 SRT+PBO), the same generic exercises that had been used in the cases of the experimental group were assigned, varying only in terms of the difficulties on the basis of individual skills. These exercises were administered in weekly sessions of 1 hour, for a total of 36 hours over 12 weeks.

## Results

For the statistical analysis of the data, and for the management of the same, the software *Microsoft Excel* was used, while the IBM software *SPSS 19* was used for analysis of variance, with the objective of assessing over time variations of the results obtained through the administration of the rating scales used a *baseline* (T0) and after 3months (T1). To ensure the similarity in the characteristics of the two samples in statistical terms at *baseline*, these were compared using analysis of variance and a t-test for independent samples; no statistically significant difference between the two samples was found with the alpha level of significance defined at 5% ( $P < 0.05$ ).

In order to assess the impact of the two treatments (SRT+CRT and SRT+PBO), an analysis of variance (ANOVA) mixed with repeated measures (*Split-Plot* type) was performed. In this analysis of variance (ANOVA) mixed with repeated measures (*Split-Plot* type), the two types of treatment (SRT+CRT and SRT+PBO) were applied as factors *between subjects* and the two temporal observations (T0 and T1) were applied as factors *within subject*, also by analyzing the “interaction time X treatment”. Due to the structure of the study (2 factors *between subjects* and 2 factors *within subjects*), post-hoc tests were not deemed necessary, but *Bonferroni* correction was applied. All the patients completed the study.

The 110 subjects included in the sample were 48 males and 62 females (Table 1), with a mean age of 36.7 years, specifically 38.2 for the experimental group and 35.7 for the control group (Table 2).

Analyzing the entire sample (SRT+CRT, SRT+PBO) at *baseline* (T0) and examining the mean of the results obtained in the test batteries used in the assessment step, the mean of the overall

**Table 1. Composition of the sample: sex.**

|                 | Males | Females | Total |
|-----------------|-------|---------|-------|
| SRT + CRT Group | 24    | 31      | 55    |
| SRT + PBO Group | 24    | 31      | 55    |

Tables 1 and 2 show the characteristic anagraphical data of the two groups of patients subjected to the study. The experimental group was administered SRT+CRT treatment, and the control group SRT+PBO treatment.

**Table 2. Composition of the sample: age.**

|                 | Mean | Std. Dev. | Min  | Max  |
|-----------------|------|-----------|------|------|
| SRT + CRT Group | 38.2 | 9.2       | 20.0 | 64.0 |
| SRT + PBO Group | 35.7 | 9.6       | 22.0 | 54.0 |

Tables 1 and 2 show the characteristic anagraphical data of the two groups of patients subjected to the study. The experimental group was administered SRT+CRT treatment, and the control group SRT+PBO treatment.



scores for the BACS results is 2.6 (std. dev.1.9), and it is 28.7 (std. dev. 25.1) for CPT-AX, with regard to neurocognitive functioning. Then, observing the scores for the PANSS (total), used for the psychopathological assessment, the mean is 120.4 (std. dev. 40.5), while the MINI-ICF-app – test battery for adaptive functioning – result is 32.5 (std. dev. 9.7). Tables 3 and 4 show the scores obtained by the two groups compared at *baseline* (T0); they denote the absence of statistically relevant differences between the two samples of all variables investigated except of *verbal memory* (F=6.30 and P=0.01).

Table 5 shows a comparison of the BACS subcategories scores recorded after three months (T1) between the two groups.

A first means-comparison indicated that, in all subcategories, the experimental group (SRT+CRT) obtained an improvement (increased score) compared to the control group (SRT+PBO). If we compare the means of total BACS score of the two groups at T1 the SRT+CRT group has a

mean of 12.2 (2.6 at T0) against a mean of 3.1 for the SRT+PBO group (1.9 at T0) (Table 6).

The variables investigated are represented by the overall scores obtained at BACS, CPT-AX, PANSS (total) and Mini-ICF-APP. It also seems advisable to remember that:

- i) An increase in the total BACS score means an improvement of the global cognitive functioning and, subsequently, an increased score in each specific subcategory relates to an improvement of the *target* cognitive domain;
- ii) A decrease in the score of the CPT-AX means an improvement in sustained attention;
- iii) A decrease of the total PANSS score, represents a general psychopathological improvement;
- iv) A decrease of the Mini-ICF-APP score, means an improvement in adaptive functioning.

The results reported in Table 6 allow us to observe a significant improvement in the

neurocognitive functioning in the experimental group (SRT+CRT), because the score for the BACS increases “dramatically”. Looking specifically at the subcategories of the BACS for the experimental group (SRT+CRT) at T1 showed in Table 5, (Table 5), the most encouraging results are the improvement reported in the following *target* items: *verbal memory*, *working memory* and *selective attention*. Specifically, the mean value obtained for the subcategory *verbal memory* at T0 is 0.7 compared to 2.3 at T1, for *working memory* it goes from 0.3 at T0 to 2.5 at T1, and for *selective attention* from 0.2 at T0 to 1.9 after three months of treatment. This evidence tests the effectiveness of the *domain-specific* training in terms of the number of correct answers provided by patients.

No statistically relevant evidence was found between the two groups for the CPT-AX as the means are 21.6 (SRT+CRT) and 21.7 (SRT+PBO) respectively. However, despite this no statistically relevant evidence, it was possible observe a consider-

**Table 3. Characteristics of the SRT+CRT and SRT+PBO groups at T0.**

|              | SRT+CRT (n=55) |           | SRT+PBO (n=55) |           | Analysis of Variance |      |
|--------------|----------------|-----------|----------------|-----------|----------------------|------|
|              | Mean           | Std. Dev. | Mean           | Std. Dev. | F                    | P    |
| Age          | 38.2           | (9.2)     | 35.7           | (9.6)     | 1.89                 | 0.17 |
| Total PANSS  | 122.0          | (45.4)    | 118.8          | (35.3)    | 0.16                 | 0.69 |
| CPT-AX       | 32.9           | (26.7)    | 24.5           | (22.8)    | 3.17                 | 0.08 |
| MINI-ICF-APP | 32.7           | (10.3)    | 32.3           | (9.1)     | 0.04                 | 0.84 |
| Total BACS   | 2.6            | (1.9)     | 1.9            | (1.8)     | 3.87                 | 0.05 |

**Table 4. Scores reported by SRT+CRT and SRT+PBO groups for BACS subcategories at T0.**

|  | SRT+CRT (n=55) |           | SRT+PBO (n=55) |           | Analysis of Variance |      |
|--|----------------|-----------|----------------|-----------|----------------------|------|
|  | Mean           | Std. Dev. | Mean           | Std. Dev. | F                    | P    |
| Verbal Memory ( <i>5-trial mean</i> )            | 0.7            | (0.7)     | 0.4            | (0.6)     | 6.30                 | 0.01 |
| Verbal Fluency ( <i>n words produced</i> )       | 0.5            | (0.5)     | 0.4            | (0.5)     | 2.34                 | 0.13 |
| Working Memory ( <i>n correct answers</i> )      | 0.3            | (0.5)     | 0.2            | (0.5)     | 2.02                 | 0.16 |
| Executive Functions ( <i>n correct answers</i> ) | 0.5            | (0.6)     | 0.5            | (0.5)     | 0.25                 | 0.62 |
| Psychomotor Coordination ( <i>n coins</i> )      | 0.4            | (0.6)     | 0.3            | (0.5)     | 0.52                 | 0.47 |
| Selective Attention ( <i>n correct items</i> )   | 0.2            | (0.4)     | 0.1            | (0.3)     | 0.93                 | 0.34 |

**Table 5. Scores reported by SRT+CRT and SRT+PBO groups for BACS subcategories at T1.**

|  | SRT+CRT (n=55) |           |     |      | SRT+PBO (n=55) |           |     |     |
|--|----------------|-----------|-----|------|----------------|-----------|-----|-----|
|  | Mean           | Std. Dev. | Min | Max  | Mean           | Std. Dev. | Min | Max |
| Verbal Memory ( <i>5-trial mean</i> )            | 2.3            | (1.0)     | 1.0 | 4.0  | 0.6            | (0.7)     | 0.0 | 2.0 |
| Verbal Fluency ( <i>n words produced</i> )       | 1.9            | (0.9)     | 1.0 | 4.0  | 0.5            | (0.5)     | 0.0 | 1.0 |
| Working Memory ( <i>n correct answers</i> )      | 2.5            | (1.0)     | 1.0 | 4.0  | 0.2            | (0.5)     | 0.0 | 2.0 |
| Executive Functions ( <i>n correct answers</i> ) | 1.9            | (0.7)     | 1.0 | 4.0  | 0.7            | (0.5)     | 0.0 | 2.0 |
| Psychomotor Coordination ( <i>n coins</i> )      | 1.7            | (0.9)     | 0.0 | 3.0  | 0.7            | (0.4)     | 0.0 | 1.0 |
| Selective Attention ( <i>n correct items</i> )   | 1.9            | (0.8)     | 0.0 | 3.0  | 0.5            | (0.5)     | 0.0 | 2.0 |
| Total BACS                                       | 12.2           | (3.2)     | 6.0 | 19.0 | 3.1            | (1.6)     | 0.0 | 9.0 |



able improvement in the group treated by SRT+CRT (mean 32.9 at T0) and considering these results, we could consider the potential positive effect of the experimental treatment on the *sustained attention* (in term of decreased score from *baseline*). Moreover, in the experimental group (SRT+CRT) a significant decrease in the PANSS score was also observed, meaning a modest psychopathological improvement; the total PANSS mean at T0 is 122.0 (95.4 at T1). A slight improvement was also reported by the control group (SRT+PBO).

The latter result can support the effects that cognitive remediation therapy (CRT) would bring regarding the extent of various dimensions of schizophrenia phenomenology, using both *domain-specific* and *non-*

*domain-specific* exercises. Even more encouraging is the decrease in the Mini-ICF-APP score (more significant for the SRT+CRT group). Table 7 shows the *effect size* for each parameter analyzed.

In Table 8 the effects on the scores (between T0 and T1) of the variables “treatment” and “time” and of the interaction “time X treatment” are analyzed. In particular, for the total BACS, the *main effect* of the *between-factors* variable “treatment” is statistically significant (F=201.562 P=0.000), as well as the effect of the *within-factors* variable “time”(F=496.68 P=0.000). The interaction of these two factors is also statistically significant (F=299.594 P=0.000).

A relevant result is the statistical signif-

icance of “time X treatment” for all the tests administered. In the light of the above, it is possible to provide the following considerations about the benefits and limitations arising from rehabilitative practice:

- i) The addition of cognitive remediation therapy (CRT) to a standard treatment of metacognitive training (MCT) resulted in a significant improvement in global neurocognitive functioning;
- ii) The use of *domain-specific* exercises by *computer-aided* training has reported positive effects with regard to the strengthening of *verbal* and *working memory*, *selective* and *sustained attention*;
- iii) The improvement in neurocognitive functioning (total BACS score and

**Table 6. Comparison of the scores given by the SRT+CRT and SRT+PBO groups at T1.**

|              | SRT+CRT (n=55) |           |      |       | SRT+PBO (n=55) |           |      |       |
|--------------|----------------|-----------|------|-------|----------------|-----------|------|-------|
|              | Mean           | Std. Dev. | Min  | Max   | Mean           | Std. Dev. | Min  | Max   |
| Total PANSS  | 95.4           | (35.3)    | 44.0 | 187.0 | 108.9          | (28.2)    | 55.0 | 170.0 |
| CPT-AX       | 21.6           | (20.5)    | 2.0  | 100.0 | 21.7           | (16.7)    | 8.0  | 82.0  |
| Total BACS   | 12.2           | (3.2)     | 6.0  | 19.0  | 3.1            | (1.6)     | 0.0  | 9.0   |
| MINI-ICF-APP | 27.7           | (9.3)     | 12.0 | 47.0  | 30.7           | (8.2)     | 10.0 | 44.0  |

**Table 7. Effect size.**

|                          | SRT+CRT* |           | SRT+PBO* |           | Time X treatment effect** |       |
|--------------------------|----------|-----------|----------|-----------|---------------------------|-------|
|                          | Mean     | Std. Dev. | Mean     | Std. Dev. | F                         | P     |
| PANSS                    | -0.65    | 0.83      | -0.25    | 0.31      | 11.595                    | 0.001 |
| MINI-ICF-APP             | -0.52    | 0.71      | -0.17    | 0.28      | 11.649                    | 0.001 |
| CPT-AX                   | -0.45    | 0.41      | -0.11    | 0.32      | 23.899                    | 0.000 |
| BACS                     | 5.11     | 1.75      | 0.64     | 0.77      | 299.594                   | 0.000 |
| Verbal memory            | 2.36     | 1.27      | 0.29     | 0.58      | 122.640                   | 0.000 |
| Verbal fluency           | 2.68     | 1.64      | 0.15     | 0.65      | 114.150                   | 0.000 |
| Working memory           | 4.47     | 2.07      | 0.04     | 0.76      | 222.615                   | 0.000 |
| Executive functions      | 2.45     | 1.10      | 0.22     | 1.01      | 122.387                   | 0.000 |
| Psychomotor coordination | 2.45     | 1.45      | 0.86     | 0.95      | 46.186                    | 0.000 |
| Selective attention      | 4.41     | 2.24      | 0.83     | 1.29      | 105.639                   | 0.000 |

\*The Effect Size: (PostTest Score - PreTest Score)/(Std. Dev. Total Sample PreTest). \*\*Exact Statistic.

**Table 8. Output SPSS.**

|                          | Treatment effect |       | Time effect |       | Time X treatment effect |       |
|--------------------------|------------------|-------|-------------|-------|-------------------------|-------|
|                          | F*               | P     | F*          | P     | F*                      | P     |
| PANSS                    | 0.617            | 0.434 | 56.277      | 0.000 | 11.595                  | 0.001 |
| MINI-ICF-APP             | 0.625            | 0.431 | 45.359      | 0.000 | 11.649                  | 0.001 |
| CPT-AX                   | 1.034            | 0.311 | 66.274      | 0.000 | 23.899                  | 0.000 |
| BACS                     | 201.562          | 0.000 | 496.680     | 0.000 | 299.594                 | 0.000 |
| Verbal memory            | 63.020           | 0.000 | 199.367     | 0.000 | 122.640                 | 0.000 |
| Verbal fluency           | 59.699           | 0.000 | 141.733     | 0.000 | 114.150                 | 0.000 |
| Working memory           | 140.321          | 0.000 | 230.426     | 0.000 | 222.615                 | 0.000 |
| Executive functions      | 33.341           | 0.000 | 176.237     | 0.000 | 122.387                 | 0.000 |
| Psychomotor coordination | 23.679           | 0.000 | 201.158     | 0.000 | 46.186                  | 0.000 |
| Selective attention      | 84.223           | 0.000 | 225.654     | 0.000 | 105.639                 | 0.000 |

CPT-AX) obtained in the experimental SRT+CRT group was accompanied simultaneously by improvements in both psychopathological (total PANSS score) and adaptive functioning (Mini-ICF-APP score);

- iv) The use of *domain-specific cognitive training* amplifies the effects of SRT, in line with primary and secondary goals of this research. Therefore, the integration of these two types of rehabilitation training is recommended

However:

- i) A longer period of treatment would help to identify the more incisive effects of the rehabilitative strategy employed (SRT+CRT);
- ii) More time periods, rather than just two periods (T0 and T1), would allow us to observe more stable and generalized results on neuropsychological, psychopathological and adaptive measures;
- iii) The analysis of several more time periods, would relate the contextual trend of the tested performances with greater accuracy;
- iv) A longer treatment period would underline what aspects of the CRT are more complementary, amplifying the standard intervention by metacognitive training (MCT);
- v) A larger sample size would lead to more significant results.

## Discussion

The present study investigated how the integration between CRT and MCT led to improvements in the neuropsychological, psychopathological and adaptive functioning. The sample consisted of residential patients with a diagnosis of schizophrenia. The place where the treatment was administered (Villa Chiara) is conceived to harmonize therapeutic-rehabilitation with socio-rehabilitative practices, which allows patients to regain their interpersonal relationships by supporting the achievement of the main clinical goals.

In 2005, McGurk and colleagues developed and implemented a program,<sup>34</sup> “Thinking Skills for Work”, that foresaw a combination of Cogpack® and a supported employment (SE) program. The 2-3-year follow-ups demonstrated how in the control group the use of SE program only, led to a lower impact on professional outcome measures, highlighting the benefits of integrated computerized training.<sup>34</sup> The first Japanese study conducted by Sato and colleagues (2014)<sup>35</sup> on the effectiveness of CR on professional outcome measures, demonstrated how the integration of CR-Cogpack® with Supported Employment

(SE) had positive effects on cognition, psychiatric symptoms and social functioning. When combined with the emotion perception remediation program, the Cogpack® was able to produce significant improvements in the recognition and discrimination of emotions as well as in social and neurocognitive functioning.<sup>36</sup>

In the present study, the CRT has been integrated with the standard treatment, or the Moritz’s metacognitive training (MCT); the latter focuses on significant gaps in the perception and evaluation of metacognition and social cognition.<sup>37,38</sup> Preliminary data shows how the individually administered MCT is able to effectively intervene on psychotic symptoms, cognitive bias and individual patient insight.<sup>39</sup> This is possible, by identifying the positive symptoms as the focus of intervention, and applying a strategy initially focused on those cognitive processes related to delirious and hallucination themes. Therefore, the metacognitive training (MCT) is particularly suitable for patients who present higher difficulties in the removal of delirious themes and distortions that affect their self-esteem,<sup>40,41</sup> preparing them for the correction of their deficit and avoiding the struc-

turing and maintenance of pathological beliefs. It is evident how cognitive depletion has a substantial effect not only on the actual functioning, but also on patients’ abilities to benefit from interventions aimed at improving the psychosocial functioning level.<sup>42</sup> In 1997, Brekke *et al.*<sup>43</sup> underlined a strong correlation between the residential autonomy level and better neuropsychological performances, particularly in the visual-motor abilities and verbal processing. The combination of MCT and CRT techniques, inside the active group of the present study, was designed in order to provide the patients with greater awareness of their cognitive limits and therefore give them the opportunity to review their entire system of beliefs, decisions and expectations, so as to become more adapted to the physical and relational reality that is around them.

The Cogpack® used for the present study, records the results obtained by individual patients providing them both instant feedback on their single-session performance and on the entire treatment. Therefore, the therapist can draw a clear patient profile.

Following this approach, our research goal was to detect how computer-aided cog-

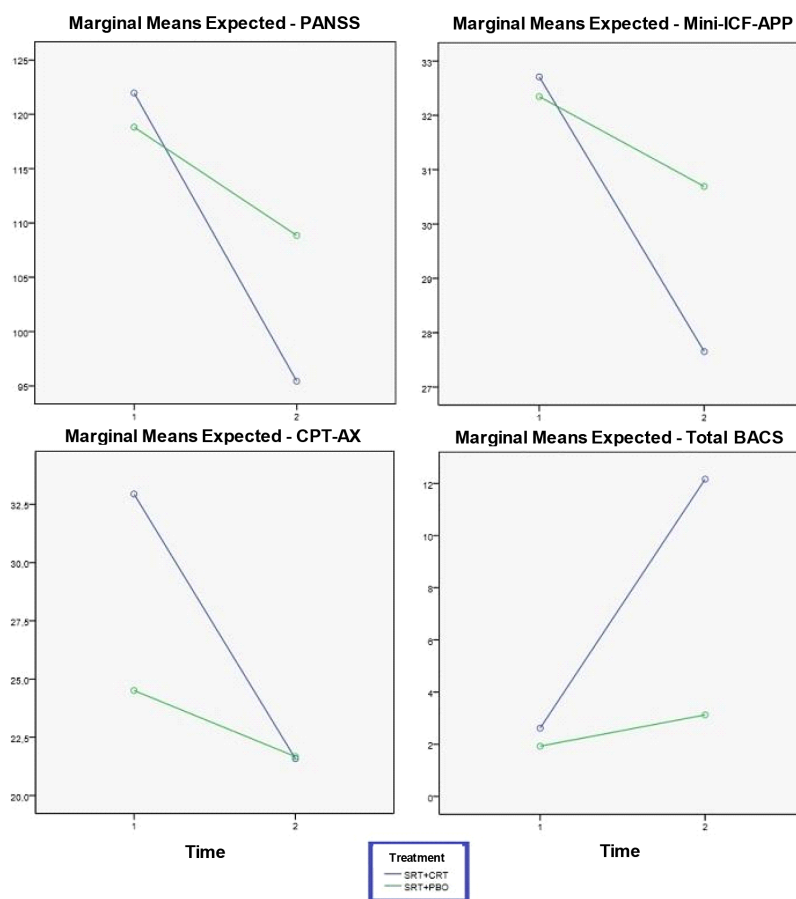


Figure 1. Comparison scores: PANSS, MINI-ICF-APP, CPT-AX and BACS.

nitive approach might affect neuropsychological, psychopathological and adaptive functioning, together with the metacognitive standard training,<sup>44</sup> employed in the treatment of residential patients afflicted by schizophrenia.

The whole sample was randomly divided in two groups of equal size. The experimental group (55 SRT+CRT) participated to a treatment organized over 12 weeks, with 3 weekly sessions of 1 hour, devoted to the completion of the Cogpack® *domain-specific* exercises, for a total of 36 hours. Specific exercises for each of the most deteriorated areas were then added, while other *non-domain-specific* tasks were integrated on the basis of relatively undamaged or preserved cognitive aspects, in line with the neuropsychological assessment at *baseline* (T0). The control group (55 SRT+PBO) under took the same generic exercises as the experimental group (varying solely in terms of difficulty levels on the basis of individual skills) in weekly sessions of 1 hour, for a total of 36 hours over 12 weeks. At T1, patients were again evaluated using the same tests administered at *baseline*. As can be seen from graphs 1 and 2, the addition of *cognitive remediation therapy* (CRT) to the standard intervention of metacognitive training (MCT) resulted in a significant improvement in global neurocognitive functioning, with an increase in total BACS score and a decrease in CPT-AX score for the experimental group. In particular, the use of *domain-specific* exercises contributed to the strengthening of individual cognitive domains including *sustained attention* (Figure 1), *verbal and working memory*, and *selective attention* (Figure 2) as the increase in the individual BACS subcategories scores shows.

Alongside the improvement in neurocognitive functioning obtained in the experimental group, an improvement in the psychopathological (reduction in total PANSS score) and adaptive functioning (reduction in Mini-ICF-APP score) was simultaneously recorded. This highlights how treatment of cognitive can influence psychopathological adaptive dimensions.

The reduction of Mini-ICF-APP score is of particular importance given the residential context of patients; the integrity of basic neuropsychological functions constitutes an essential prerequisite for the development of an adequate social cognition. Therefore, it appears to be of great utility a cognitive training that intervenes on the most deteriorated areas, by adapting it to the patients' psychopathological profile.<sup>45</sup> In this sense, the analysis of several time periods would allow us to observe more stable and generalized results relative to the neu-

rocognitive, psychopathological and adaptive functioning and to analyze with greater accuracy the contextual trend of these profiles. In our opinion, it would be of utmost interest to analyze the impact that a combined treatment of CRT plus a standard rehabilitation treatment would produce on the insight of a single patient and his/her reporting, self-sufficiency abilities within a context such as the residential one. In fact, the residential context could be considered

as the social dimension that everybody experiences daily and that is precluded to those patients.

Further researches on this topic may be necessary in order to deepen and validate the results produced by the use of contextual cognitive remediation therapy (CRT) plus other standard rehabilitation treatments. This study can lead researchers to derive the best rehabilitative approaches by creating a wider autonomy and recovery.

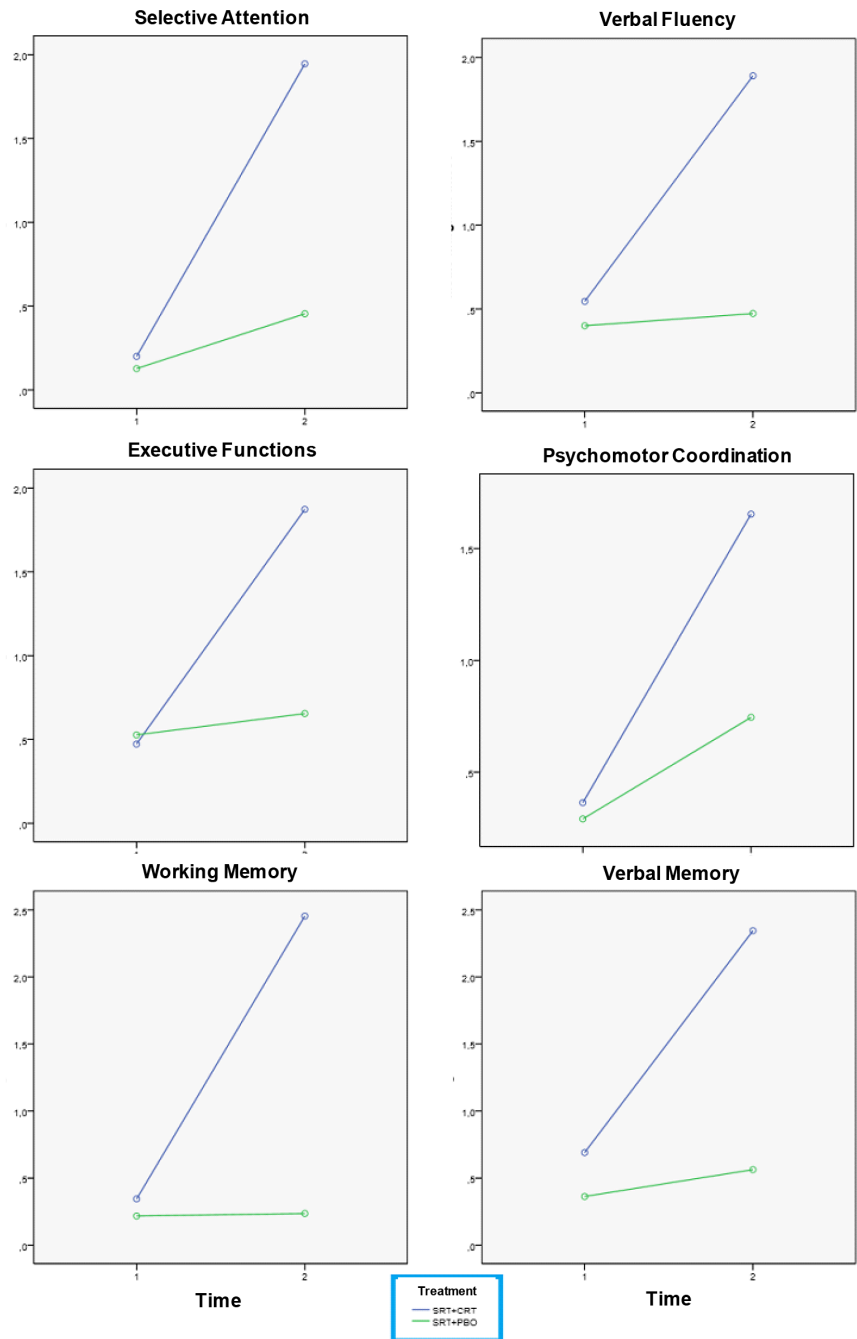


Figure 2. Comparison scores BACS subcategories.



## References

1. Ribeiro-Santos R, Lucio Teixeira A, Vinicius Salgado J. Evidence for an immune role on cognition in schizophrenia: A systematic review. *Curr Neuropharmacol* 2014;12:273-80.
2. Mc Afoose J, Baune BT. Evidence for a cytokine model of cognitive function. *Neurosci Biobehav Rev* 2009;33:355-66.
3. Pfammatter M, Junghan UM, Brenner HD. Efficacy of psychological therapy in schizophrenia: conclusions from meta-analyses. *Schizop Bull* 2006;32:S64-80.
4. Cella M, Wykes T. Understanding processing speed its subcomponents and their relationship to characteristics of people with schizophrenia. *Cogn Neuropsychiatry* 2013;18:437-51
5. Kim H. Neural activity that predicts subsequent memory and forgetting: a meta-analysis of 74 fMRI studies. *Neuro Image* 2011;54:2446-61.
6. Mc Gurk SR, Mueser KT. Cognitive functioning, symptoms, and work in supported employment: a review and heuristic model. *Schizop Res* 2004;70:147-73.
7. Correll CU, Skuban A, Hobart M, et al. Efficacy of brexiprazole in patients with acute schizophrenia: Review of three randomized, double-blind, placebo-controlled studies. *Schizop Res* 2016;174:82-92.
8. Meyer U, Schwarz MJ, Müller N. Inflammatory processes in schizophrenia: a promising neuro immunological target for the treatment of negative/cognitive symptoms and beyond. *Pharmacol Ther* 2011;132:96-110.
9. Green MF, Kern RS, Braff DL, Mintz J. Neurocognitive deficits and functional outcome in schizophrenia: Are we measuring the “right stuff”? *Schizop Bull* 2000;26:119-36 .
10. Tao J, Zeng Q, Liang J, et al. Effects of cognitive rehabilitation training on schizophrenia: 2 years of follow-up. *Int J Clin Exp Med* 2015;8:16089-94.
11. Keefe RS, Haig GM, Marder SR, et al. Report on ISCTM Consensus Meeting on Clinical Assessment of Response to Treatment of Cognitive Impairment in Schizophrenia. *Schizop Bull* 2016;42:19-33.
12. Reeder C, Smedley N, Butt K, et al. Cognitive predictors of social functioning improvements following cognitive remediation for schizophrenia. *Schizop Bull* 2006;32:S123-31.
13. Miles AA, Heinrichs RW, Ammari N, et al. Stability and change in symptoms, cognition, and community outcome in schizophrenia. *Schizop Res* 2014;152:435-9.
14. Vita A, Deste G, Barlati S, et al. Does cognitive remediation modify the use of psychiatric services and the patterns of care of patients with schizophrenia? *Schizop Res* 2016;175:85-9.
15. Bernoit A, Harvey PO, Bherer L, Lepage M. Does the Beck Cognitive Insight Scale Predict Response to Cognitive Remediation in Schizophrenia? *Schizo Res Treat* 2016: 6371856.
16. Wykes T, Huddy V, Cellard C, et al. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry* 2011;168:472-85.
17. Mc Gurk SR, Twamley EW, Sitzer DI, et al. A meta-analysis of cognitive remediation in schizophrenia. *Am J Psychiatry* 2007;164:1791-802.
18. Trapp W, Landgrebe M, Hoels K, et al. Cognitive remediation improves cognition and good cognitive performance increases time to relapse – results of a 5-year catamnestic study in schizophrenia patients. *BMC Psychiatry* 2013;13:184.
19. Mc Glashan TH, Hoffman RE. Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Arch Gen Psychiatry* 2000;57:637-48.
20. Isaac C, Januel D. Neural correlates of cognitive improvements following cognitive remediation in schizophrenia: a systematic review of randomized trials. *Socioaffect Neurosci Psychol* 2016;6:30054.
21. Eack SM, Hogarty GE, Cho RY, et al. Neuroprotective effects of cognitive enhancement therapy against grey matter loss in early schizophrenia. *Arch Gen Psychiatry* 2010;67:674-82.
22. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA: American Psychiatric Publishing; 2013.
23. Kefee RS, Goldberg TE, Harvey PD, et al. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizop Res* 2004;68:283-97.
24. Stratta P, Daneluzzo E, Bustini M, et al. The cognitive bias task (CBT) in healthy controls: A replication study. *Neuropsychiatry Neuropsychol Behav Neurol* 2000;13:279-85.
25. Stratta P, Daneluzzo E, Bustini M, et al. Processing of context information in schizophrenia: Relation to clinical symptoms and WCST performance. *Schizop Res* 2000;44:57-67.
26. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizop Bull* 1987;13:261-76.
27. Linden M, Baron S, Muschalla B. Mini-ICF-Rating fürAktivitäts- und Partizipations störungenbei Psychischen Erkrankungen (Mini-ICF-APP).Verlag Hans Huber: Hogrefe AG, Bern (Italian translation: Linden, M., Baron, S., Muschalla, B. (2012), Mini-ICF-APP. Uno strumento per la valutazione dei deficit di Attività e Partecipazione nei Disturbi Psicici .Eds. Matteo Balestrieri, Elisa Maso. Giunti Editore, Firenze, Italy). 2009.
28. Molodynski A, Linden M, Juckel G, et al. The reliability, validity, and applicability of an English language version of the Mini-ICF-APP. *Soc Psychiatry Psychiatr Epidemiol* 2013;48:1347-54.
29. Sartory G, Zorn C, Groetzing G, Windgassen K. Computerized cognitive remediation improves verbal learning and processing speed in schizophrenia. *Schizop Res* 2005;75:219-23.
30. Cavallaro R, Anselmetti S, Poletti S, et al. Computer-aid edn eurocognitive remediation as an enhancing strategy for schizophrenia rehabilitation. *Psych Res* 2009;169:191-6.
31. Rauchensteiner S, Kawoll W, Krüger-Özgürdal S, Juckel G. Test-performance after cognitive training in persons at risk mental state of schizophrenia and patient with schizophrenia. *Psychiatry Res* 2011;185:334-9.
32. Bechdolf A, Wagner M, Ruhrmann S, et al. Preventing progression to first-episode psychosis in early initial prodromal states. *Br J Psychiatry* 2012;200:22-9.
33. Paquin K, Larouche Wilson A, Cellard C, et al. A systematic review on improving cognition in schizophrenia: which is the more commonly used type of training, practice or strategy learning? *BMC Psychiatry* 2014;14:139.
34. Mc Gurk SR, Schiano D, Mueser KT, et al. Implementation of the thinking skills for work program in a psychosocial club house. *Psychiatr Rehab J* 2010;33:190-9.
35. Sato S, Iwata K, Furukawa SI, et al. The Effects of the Combination of Cognitive Training and Supported Employment on Improving Clinical and Working Outcomes for People with Schizophrenia in Japan. *Clin Pract Epidemiol Ment Health* 2014;10:18-27.
36. Lindenmayer JP, McGurk SR, Khan A, et al. Improving Social Cognition in

- Schizophrenia: A Pilot Intervention Combining Computerized Social Cognition Training With Cognitive Remediation. *Schizop Bull* 2013;39:507-17.
37. Lysaker PH, Di Maggio G, Carcione A, et al. Metacognition and schizophrenia: The capacity for self-reflectivity as a predictor for prospective assessments of work performance over six months. *Schizop Res* 2010;122:124-30.
  38. Lysaker PH, Ringer JM, Buck KD, et al. Metacognitive and social cognition deficits in patients with significant psychiatric and medical adversity: A comparison between participants with schizophrenia and a sample of participants who are HIV-positive. *J Nerv Ment Dis* 2012;2:130-4.
  39. Moritz S, Andreou C, Schneider BC, et al. Sowing the seeds of doubt: a narrative review on metacognitive training in schizophrenia. *Clin Psychol Rev* 2014;34:358-66.
  40. Moritz S, Woodward TS. Metacognitive control over false memories: A key determinant of delusional thinking. *Curr Psychiatry Rep* 2006;8:184-90.
  41. Sundag S. *Vielfeind — vielehr Eine Unter such ungzumZusammenhang von Selbstwertund Paranoia beiSchizophrenie*, The more enemy, the more honor? An investigation into the relationship between self-esteem and paranoia in schizophrenia. Hamburg, Germany: University of Hamburg. 2012.
  42. Auditore R, Caponnetto P, Salerno A, et al. Deficit neurocognitivi e cognitive remediation nei disturbi appartenenti allo spettro schizofrenico. Dalla follia alla cittadinanza. *Esperienze riabilitative in Sicilia*. Seminara G., Testa, F., Bonanno Editore 2013 pp. 129-1422013.
  43. Brekke JS, Raine A, Ansel M, et al. Neuropsychological and psychophysiological correlates of psychosocial functioning in schizophrenia. *Schizophrenia Bull* 1997;23:19-28.
  44. Moritz S, Woodward TS. Metacognitive training in schizophrenia: from basic research to knowledge translation and intervention. *Curr Opin Psychiatry* 2007;20:619-25.
  45. Hogarty G, Flesher S, Ulrich R, et al. Cognitive enhancement therapy for schizophrenia: effects of a 2-year randomized trial on cognition and behavior. *Arch Gen Psychiatry* 2004;61:866-76.