Improvement in negative symptoms and functional outcome after a new generation cognitive remediation program: A randomized controlled trial

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<td>Sanchez, Pedro; Hospital Psiquiátrico de Alava, Refractory Psychosis Unit; CIBERSAM, Centro de Investigación Biomédica en Red de Salud Mental; University of the Basque Country, Department of Neuroscience Peña, Javier; University of Deusto, Bengoetxea, Eneritz; University of Deusto, Department Department of Foundations and Methods of Psychology Ojeda, Natalia; University of Deusto, Department Department of Foundations and Methods of Psychology Elizagarate, Edorta; Hospital Psiquiátrico de Alava, Refractory Psychosis Unit; CIBERSAM, Centro de Investigación Biomédica en Red de Salud Mental; University of the Basque Country, Department of Neuroscience Ezcurrea, Jesus; Hospital Psiquiátrico de Alava, Refractory Psychosis Unit Gutierrez, Miguel; Hospital Universitario Alava- Sede Santiago, Department of Psychiatry; University of the Basque Country, Department of Neuroscience; CIBERSAM, Centro de Investigación Biomédica en Red de Salud Mental,</td>
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<tr>
<td>Keywords:</td>
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Improvement in negative symptoms and functional outcome after a new generation cognitive remediation program: A randomized controlled trial

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Abstract

Cognitive remediation improves cognition in schizophrenia, but its effectiveness on other relevant factors such as negative symptoms and functional outcome has not been studied to the same degree.

Eighty-four inpatients with schizophrenia were recruited from Alava Hospital (Spain). All subjects underwent a baseline and a 3 months assessment including neurocognition, clinical symptoms, insight, functional outcome (Global Assessment of Functioning (GAF) and Disability Assessment Schedule (DAS-WHO). Patients were randomly assigned to either neuropsychological rehabilitation (REHACOP) or control group for 3 months in addition to treatment as usual. REHACOP is an integrative Spanish program that taps all basic cognitive functions. It included experts’ last suggestions about positive feedback and activities of daily living in patients’ environment.

REHACOP group showed significantly greater improvements at 3 months in neurocognition, negative symptoms, disorganization and emotional distress measures compared to the control group (Cohen’s effect size for these changes ranged from $d = .47$ for emotional distress to $d = .58$ for disorganization symptoms). REHACOP group also improved significantly in both GAF ($d = .61$) and DAS-WHO total score ($d = .57$). More specifically, they showed significant improvement in vocational outcome ($d = .47$), family contact ($d = .50$) and social competence ($d = .56$).

In conclusion, neuropsychological rehabilitation may be useful for the reduction of negative symptoms and functional disability in schizophrenia. These findings support the feasibility of integrating neuropsychological rehabilitation into
treatment as usual programs for patients with schizophrenia. Reasons for the efficacy of this program are discussed.

Key Words: schizophrenia; negative symptoms; functional outcome; cognitive rehabilitation; REHACOP.
Introduction

Negative symptoms and cognitive impairment are two of the most common dimensions in schizophrenia. More than 50% of patients with schizophrenia suffer from either negative and/or cognitive symptoms in the prodromal phase, during psychosis and even after the remission of positive symptoms. In addition, negative and cognitive symptoms are supposed to be strong predictors of transition to psychosis in ultra high-risk samples and of poorer prognosis and functional outcome. More specifically, it has been suggested that the presence of negative symptoms in early stages is associated with a more adverse course, more psychotic episodes and greater impairment in adaptative life skills.

The NIMH-MATRICS consensus statement on negative symptoms suggested that persistent and clinically significant negative symptoms are a distinct and important therapeutic target. Unfortunately, although proven as an important factor in schizophrenia, negative symptoms have received less attention in the literature than positive symptoms. Moreover, first and second antipsychotic drugs have demonstrated limited efficacy on the improvement of negative symptoms, although new promising glutamatergic agents are being explored to target negative symptoms. Therefore, as a result new treatments efforts should be placed on negative symptoms.

A recent meta-analysis carried out by Wykes et al. reported data of the effectiveness of cognitive remediation on clinical symptoms in general, but not on negative symptoms in particular. A closer inspection at studies included in this meta-analysis and studies published after it, offers inconsistent results. In
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spite of using different modalities of cognitive remediation, some authors have found positive significant effects on negative symptoms\textsuperscript{11-13}. However, there are also other studies published that have not found evidence of cognitive remediation efficacy on negative symptoms\textsuperscript{14-20}. Most of the programs used in these clinical trials were not specifically designed to target improvement in negative symptoms but focused on the amelioration of cognitive deficits and their impact in daily living.

On the other hand, most authors agree that the ultimate goal of any treatment is to improve the functional capacity and quality of life of patients\textsuperscript{10}. According to the meta-analysis previously mentioned\textsuperscript{10}, cognitive remediation is effective for improving functioning, although effect sizes obtained were small to medium. As previously stated with negative symptoms, functioning was included as a single construct in this meta-analysis. Therefore, we cannot conclude if cognitive remediation is equally effective for different functional outcome domains, such as social functioning, vocational outcome, or self-care management. A closer review of the literature including also recent studies published in this topic indicates that the most studied functioning domains were vocational and occupational outcome. Data showed mainly positive improvement regarding occupational outcome\textsuperscript{13,16,19,21}. These results suggest that cognitive remediation can be an effective tool for improving work or vocational outcome in psychosis.

Social functioning has also been analysed, but studies have shown more inconsistent results. Some studies reported that cognitive remediation improved social functioning\textsuperscript{12,13,22} whereas others have not\textsuperscript{18,23}. Less attention has been
paid to other outcome domains, such as self-care management or family contact. To the best of our knowledge, there is only one study that directly addressed self-care management and has not informed of significant improvements$^{17}$.

According to McGurk et al.'s meta-analysis and Roder's research update $^{12,24}$, authors suggest that the use of a strategy learning method and transfer techniques may increase the beneficial effect of the treatment. In addition, they suggest that a combination of cognitive remediation with psychiatric rehabilitation and social skills training might provide stronger effects, rather than cognitive remediation programs alone. Spanish REHACOP is a new generation multidimensional remediation program which includes these proposals with specific emphasis on the implementation of learned skills into activities of daily living. Besides the combination of strategy learning, drill and practice, the patients are required to transfer obtained knowledge to a set of concrete activities relevant in their lives. In order to achieve this goal, patients combine practice of activities of daily living in group, (during the rehabilitation program) and homework activities at their real environment.

In the current study we aimed to evaluate the efficacy of cognitive remediation with the REHACOP in schizophrenia. The primary targets of this study were negative symptoms and functional outcome, including specific domains such as self-care management, vocational outcome, family contact and social competence.
Methods

Participants

Eighty-four inpatients with schizophrenia were recruited from the Alava Hospital. In order to be included in the study patients had to meet diagnostic criteria for Schizophrenia according to American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)\(^2\). In addition, they had to show no evidence of alcohol or drug abuse in the last 30 days, previous history of significant lack of consciousness, mental retardation, and relevant neurological or medical condition.

Ten days after admission, clinical, cognitive and functional evaluation was carried out. Afterwards, they were randomly allocated to either the REHACOP Group or the Control Group (see Figure 1). Assignment to the program was conducted on the basis of a computer-generated randomization list. Both groups received treatment as usual, consisted of individual case management and medical review. All patients were voluntary and gave written informed consent to participate in the study. The study protocol was approved by the Ethics Committee at the Health Department of the Basque Mental Health System in Spain.

Measures
Clinical symptoms, neurocognitive performance and functional outcome were assessed before and after treatment. Baseline assessments were carried out when patients were stable in psychopathology and medication after intake on the hospital. Post-treatment assessment was carried out within the first week after completing the intervention. All raters were blind to treatment condition and had no other role in the project that would undermine the blinding.

**Clinical assessment**

After admission, patients completed a psychiatric interview and evaluation with the Spanish version \(^{26}\) of Positive and Negative Syndrome Scale (PANSS) \(^{27}\), which was scored using a 5-factor model. The five components were positive, negative, disorganization, excitement and emotional distress (See \(^{28}\) for details). The Premorbid Adjustment Scale (PAS) was administered to obtain a measure of clinical premorbid adjustment. Insight was evaluated with Schedule for the Assessment of Insight (SAI) \(^{29}\). After the training period, inter-rater reliability coefficients were obtained for the clinical scales (they ranged from .83 for CGI to .91 for PANSS).

**Cognitive Evaluation**

Measures of cognitive functioning included tests to assess attention, working memory, verbal learning and memory, verbal fluency, processing speed and executive functioning. Our evaluation protocol consisted of the
following tests: Digit Span, Symbol Search and Digit Symbol from the Wechsler General Intelligence Scale (WAIS-III), Trail Making Test A and B, The Hopkins Verbal Learning Test (form 2 & 4), The Stroop Word and Color Test, and Verbal Fluency Subtest from Test Barcelona. We made a composite score with the tests described above. All cognitive measures were converted into Z-scores and the sign of some measures were adjusted so that higher scores indicated better neurocognitive performance. The internal consistency of these composite neurocognitive score was high (Cronbach’s alpha = .81). On the other hand, the Accentuation Reading Test (TAP), which is the Spanish version of the National Adult Reading Test (NART), was also administered to obtain an estimation of each patient’s premorbid abilities.

Functional Outcome

Functional disability was assessed with the Global Assessment of Functioning (GAF), The Clinical General Impression Scale (CGI), and Disability Assessment Schedule (DAS-WHO) scales. The four functional disability characteristic indicators offered by DAS-WHO were analyzed with the aim of having a better understanding of functional disability and its improvement: Self-Care Management, Social Competence, Vocational Outcome and Family Contact.

Intervention
Developed by Ojeda and Peña in 2007, the REHACOP program is the first Spanish cognitive remediation program specifically designed for psychosis and schizophrenia. REHACOP is a structured program based on paper-pencil tasks, using the principles of restoration, compensation, and optimization with a number of training procedures which gradually increased the level of cognitive effort and demand. REHACOP trains patients in traditionally impaired cognitive domains such as attention, memory, processing speed, language, and executive functioning. Additionally, the program includes three units related to functional outcome treatment: social skills training, activities of daily living and psychoeducation. Patients’ relatives also take part in psychoeducation groups, which provide them all with a better knowledge about the illness, ways to cope with symptoms, early identifications of signs and relapse, and clinical and social resources availability.

The REHACOP includes up to 150 different tasks (30 tasks per domain) hierarchically organized in three levels of difficulty and subtypes of abilities to be trained. Once a basic cognitive strategy has been trained and well acquired, the therapist moves on to the next level. This characteristic enables patient’s progression as performance feedback is provided in each session after tasks are completed and the patient has access to the information about their level of difficulty of the task. Each task includes fixed instructions for the therapist to be read to the patients, verbal and visual materials, and the patient’s response sheet for the answers. It also provides the therapist with a solution sheet for tasks with non open responses to facilitate a fast correction and interpretation. It also offers a graph representation about the patient’s progression that can be
shown to the patient depending on the therapist’s criteria. In addition, patients
are required to put into practice obtained benefits with homework activities. The
format of the program allows both, the individual and the group administration
(between 5 and 8 patients per group), although for the purpose of this study, the
group administration was chosen.

In the present study, REHACOP’s group attended 90-minutes-long
sessions taking place at least three days per week. During three months,
patients are supposed to integrate the learning experience, to practice in real
life context and to bring to the sessions feedback about possible new difficulties
that must be faced. In this study, REHACOP groups were conducted by a
trained neuropsychologist, although the highly structured design, instructions
and materials could allow its administration by other trained professionals.

The Control Group consisted of treatment as usual along with group
activities including drawing, reading daily news, creating constructions using
different materials (such as paper or wood). These activities were accomplished
in group format and with the same frequency as the implementation of Rehacop
in the experimental group.

Data analysis

Normality of data was tested with Kolmogorov-Smirnov Test. All
variables resembled the normal distribution, with the exception of CGI which
was log-transformed for further analyses. Raw scores are presented for all
variables. χ2 test was used to analyse any differences between the two groups
on gender, and ANOVA tests on sociodemographic and clinical variables at baseline.

Repeated measures of multiple analysis of variance (MANOVA) was performed for clinical, cognitive and functional variables with Group (REHACOP vs Control Group) as the between subject factor and Time (pre-treatment and post-treatment) as the within group factor. Main effects of Time (longitudinal dimension), Group (cross-sectional dimension) and Time X Group (interaction effect) were examined. Regression analyses were performed in order to analyse predictors of functional changes. Significance level was set at .05. All tests were two-tailed.

Results

Sociodemographic characteristics of the groups

The sociodemographic characteristics of the REHACOP group and Control group are depicted in the Table 1. Differences between the groups were analysed in order to control for the success of the randomization. There were no significant differences between the groups in any of the sociodemographic characteristics studied. Both groups were equivalent in term of age, gender distribution, marital status, occupation, education, premorbid adjustment and premorbid IQ. There were no significant differences in other clinical characteristics such as age at onset, number of previous hospitalizations,
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schizophrenia diagnosis, alcohol and tobacco consumption or dose of antipsychotic medication (mg/day chlorpromazine equivalents).

Clinical changes in REHACOP and Control groups after intervention.

As seen in table 2, both groups showed a similar pattern of clinical symptom severity at baseline, as well as a general improvement in clinical measures. However, REHACOP group improved significantly more than control group, according to significant Group X Time interactions for negative symptoms, disorganization symptoms and emotional distress, as well as PANSS total score. Effect size of these changes fell mostly in the medium range (negative symptoms $d = .48$, disorganization $d = .58$, emotional distress $d = .47$ and PANSS total score $d = .50$). Group X Time interactions for CGI scores, on the other hand, were not significant. Finally, although not significant, there was a trend toward significance in insight.

As previously mentioned, we reported data for negative symptoms factor according to Van der Gaag et al.’s meta-analysis. However, in order to make our results easier to compare to other studies that used the conventional PANSS scores (positive, negative and general psychopathology) and possible future meta-analyses, we decided to provide also results regarding this negative symptoms scale (items N1 to N7). REHACOP group reduced negative symptoms from 26.08 (SD=12.37) at baseline to 20.94 (SD=10.56) after treatment, whereas control group reduced negative symptoms from 23.74
(SD=9.57) to 21.63 (SD=10.24). Interaction effect was significant ($F = 5.30, p < .05$), with Cohen’s effect size falling in the medium range ($d = .51$).

Functional outcome changes in REHACOP and Control groups after intervention

As seen in table 3, both groups showed a similar pattern of functional outcome at baseline, with a general pattern of improvement over the treatment period. Repeated Measures of MANOVA revealed significant Group X Time interactions in GAF and DAS-WHO, suggesting that REHACOP group showed a significantly larger pre-post improvement than the control group. For example, REHACOP group’s improvement in GAF was twice as much as the improvement obtained by control group. The effect size for GAF was $d = .61$ and for DAS-WHO total score was $d = .57$.

A closer inspection at DAS-WHO’s specific domains showed significant Group X Time interactions in vocational outcome ($d = .47$), family contact ($d = .50$) and social competence ($d = .56$). On the other hand, self-care management did not reach statistical significance.

Predictors of change in functional outcome

Changes in negative symptoms ($B = -.58, p < .001$) and cognition ($B = -.36, p < .05$) predicted changes in GAF scores in REHACOP group, whereas different predictors emerged from patients that received occupational therapy.
Only changes in negative symptoms ($B = -.45, p < .001$) predicted changes in GAF scores among patients in control group. Changes in negative symptoms ($B = .62, p < .001$) predicted changes in CGI among patients in control group, whereas changes in negative symptoms ($B = .67, p < .001$) and cognition ($B = .39, p < .01$) predicted changes in CGI scores in REHACOP group.

Finally, negative symptoms ($B = -.60, p < .001$) and cognition ($B = -.36, p < .01$) predicted changes in DAS-WHO scores in REHACOP group. Only changes in negative symptoms ($B = -.45, p < .001$) predicted changes in DAS-WHO among patients in control group.

**Discussion**

The aim of the present study was to analyse the efficacy of a cognitive remediation program which emphasizes the implementation of acquired skills into activities of daily living, compared to other treatment options, in negative symptoms and functional outcome.

In our study, patients attending cognitive remediation did not only improve neurocognition, but also clinical symptoms and functional outcome. Moreover, improvements in cognition and negative symptoms predicted the changes in functional outcome in REHACOP group, but not in the Control group. This general improvement cannot be justified by receiving more professional attention, differences in medication, or by other sample characteristics. The improvement can be neither attributed to the effect of the number of hours of exposure to treatment, since both groups received
equivalent ones, nor to group vs individual interventions as both formats were alike.

Regarding clinical symptomatology mayor finding of this study is that REHACOP significantly reduced patients’ negative symptoms. Those results support previous studies that indicated improvements in negative symptoms but not all. It is difficult to find a clear reason for these inconsistent results since cognitive remediation has been administrated in the same heterogeneous way through studies that found significant improvements in negative symptoms and those who have not. Moreover, the specific assessment tools used across these studies were similar too. McGurk et al. indicated that only cognitive remediation programs that provide positive learning experiences that bolster self-esteem and perceived self-efficacy have beneficial effects on symptom improvement. Grant supported this idea by showing that cognitive impairment imposes discouraging life experiences in patients. Those experiences may lead them to perceive negative expectancies and develop defeatist believes, especially among patients with schizophrenia.

Consequently, it is possible to suggest that the way cognitive rehabilitation is provided has an important role in the improvement of negative symptoms. The implementation of the REHACOP training in this study emphasized the relevance of these variables.

This cognitive remediation program has several characteristics that can provide patients with positive learning experiences. These characteristics include exercises hierarchically organized depending on their difficulty. Based on patients’ performance and degree of impairment, the therapist starts

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providing exercises and strategies that can be achieved in an adequate way by patients. Once that level is reinforced, the patient is challenged with new tasks with progressively higher levels of difficulty. Therefore, activities’ difficulty only increases once they are able to use learned strategies properly. Owing to gradual learning, positive feedback, and the transfer of learned strategies to their daily life activities (with homework), patients may feel themselves more capable of overcoming daily problems caused by cognitive impairments. As a result, they may be more encouraged to take part in activities that they tended to avoid before.

Unexpectedly, the intervention with the REHACOP turned out to be an effective tool for improving other clinical symptoms, namely emotional distress and disorganization symptoms. Very few studies have previously found significant improvement in disorganization symptoms\textsuperscript{16,19,42}. On the other hand, opposite to previous studies that reported data on emotional distress\textsuperscript{16,17}, we found significant improvement in emotional distress symptoms. Group support, positive feedback, involvement of family members in patient’s treatment and the improvement on other areas (such as neurocognitive performance and negative symptoms) may have accounted for these positive results in emotional distress.

However, REHACOP did not produce significant improvements on positive symptoms, excitement or insight. These results are consistent with most similar studies\textsuperscript{14-16,19,20,45}. Therefore, it might be worth examining potential variables relevant to these clinical symptoms to aim additional benefits in future trials and overcome limitations of this intervention. For example, a future goal
could include analyzing the benefit of adding specific relaxation training
techniques and determine its possible relation to excitement symptoms.

The other main purpose of this kind of intervention is usually to improve
patients’ functional outcome. Consistent with previous articles \(^{10}\), the
improvement in the experimental group in functional outcome was significantly
greater than in the control group. Likewise, the intervention with the REHACOP
program enabled our sample to obtain unexpected higher rates in some used
assessment scales. In fact, far from other studies \(^{22}\), participants in this trial
improved twice as much as control group in general functioning (GAF). The
benefit of the cognitive remediation intervention in this study could be reinforced
by the inclusion of strategy learning, transfer techniques and the combination
with treatment as usual. On the other hand, patients learned strategies related
to cognitive functioning. These strategies must be used by the patients again
during the social skills training and homework exercises. Thus, patients
achieved the generalization of acquired knowledge and obtained higher benefits
into their ordinary life activities.

Since functional outcome consists of many different domains, it is useful
to discriminate in greater detail the obtained information about functional
disability. Observed improvements in vocational outcome in our study match up
with most of the previous studies published in this field \(^{13,16,19,21}\). Contrary to the
methodology of our study, however, most other groups have combined
cognitive remediation with various types of vocational rehabilitation in the
experimental group. Despite the absence of vocational rehabilitation,
REHACOP turned out to be effective as well. Only one of the mentioned studies
did not combine cognitive remediation with vocational rehabilitation and showed also positive results. In a similar way to us, Eack et al. \[^13\] trained their patients in various cognitive domains and social skills. In both studies, learned strategies were generalized to patients’ daily living using homeworks and therapists provided them with positive feedback. According to this fact, we may hypothesize that mentioned characteristics can play an important role in the improvement of vocational outcome.

However, the efficacy of cognitive remediation in social competence improvement has been inconsistent. REHACOP improved patients’ social competence as previous studies have done \[^13,22\]. Studies that have not found positive changes in social competence \[^14,17,18,20\] have some features in common, including that most of them were administered individually, and none included social skills or daily life activities. Therefore, the inclusion of social skills training and working with other patients simultaneously with feedback from both, the therapist and colleagues is shown as a key factor for improving social competence.

Consistent with previous findings \[^17\], REHACOP group did not significantly improved self-care management when compared to control group. However, the degree of improvement was reduced and the baseline status of the groups in self-care (good enough) could have introduced a ceiling effect.

Unfortunately, none of the reviewed studies have reported data on family contact, so very little is known about this functional domain. However, the family involvement in rehabilitation process benefits the patients’ recovery and it seems reasonable to think that a good management of the family intervention
can contribute to the general patient’s status. Our cognitive remediation program encourages relatives to take part in some group activities, so that, family members improve their knowledge of the relative’s feelings and improve their management, including fears and worries.

Despite its promising findings, this study has several limitations. Firstly, we did not assess social cognition. At the beginning of the study, REHACOP had not included yet a social cognition training unit. Social cognition unit has just been recently included in REHACOP and we hope to show our results in future studies. Secondly, the study lacks measures of subjective quality of life and it is important to know if REHACOP has a significant influence on patients’ self-esteem or self-efficacy. Finally, a longitudinal follow up must be carried out in order to know if the effects of the treatments are maintained in the long-term.
Conflict of Interest

The Authors declare that there are no conflicts of interest in relation to the subject of this study.

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Table 1. Sociodemographic and Diagnostic Differences of Participants by Treatment Group (REHACOP; Control Group).

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<td>Age (years)</td>
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<td>Years of education (years)</td>
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<td>10.24 (2.8)</td>
<td>F = 2.17</td>
<td>0.146</td>
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<td>Males</td>
<td>27 (75.0%)</td>
<td>37 (77.1%)</td>
<td>(\chi^2 = 0.05)</td>
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<td>9 (25.0%)</td>
<td>11 (22.9%)</td>
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<td>Age at onset</td>
<td>22.28 (6.1)</td>
<td>22.04 (6.1)</td>
<td>F = 0.03</td>
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<td>Number of previous hospitalizations</td>
<td>7.11 (6.6)</td>
<td>8.98 (10.3)</td>
<td>F = 0.89</td>
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<td>Accentuation Reading Test (TAP)</td>
<td>18.50 (4.5)</td>
<td>19.56 (6.3)</td>
<td>F = 0.67</td>
<td>0.414</td>
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<td>Premorbid Adjustment (Cannon-Spor)</td>
<td>49.64 (25.5)</td>
<td>46.75 (22.2)</td>
<td>F = 0.30</td>
<td>0.582</td>
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<td>Dose of antipsychotic medication (converted to mg/day chlorpromazine)</td>
<td>695.09 (362.6)</td>
<td>911.88 (922.9)</td>
<td>F = 1.77</td>
<td>0.186</td>
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<td>Paranoid</td>
<td>29 (80.6%)</td>
<td>40 (77.9%)</td>
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<td>Disorganized</td>
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<tr>
<td>Residual</td>
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<td>3 (6.3%)</td>
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<td>Employed</td>
<td>3 (8.3%)</td>
<td>2 (4.2%)</td>
<td>(\chi^2 = 2.35)</td>
<td>0.308</td>
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<td>7 (14.6%)</td>
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<td>Marital Status: n (%)</td>
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<tr>
<td>Single</td>
<td>33 (91.7%)</td>
<td>45 (93.8%)</td>
<td>(\chi^2 = 0.13)</td>
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</tr>
<tr>
<td>Alcohol consumption (g/day)</td>
<td>0.92 (1.5)</td>
<td>0.96 (1.5)</td>
<td>F = 0.06</td>
<td>0.809</td>
</tr>
<tr>
<td>Tobacco Smoking (cigarettes/day)</td>
<td>20.56 (11.2)</td>
<td>18.04 (12.4)</td>
<td>F = 0.90</td>
<td>0.345</td>
</tr>
</tbody>
</table>
Note. DSM-IV-TR = The Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revised.
Table 2. Changes in Clinical Symptoms and Cognitive Functioning from Baseline to Posttreatment by Treatment Group (REHACOP; Control Group)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>REHACOP</th>
<th>Control Group</th>
<th>F</th>
<th>P</th>
<th>F</th>
<th>P</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Symptoms</td>
<td>Pre</td>
<td>18.47 (1.2)</td>
<td>16.47 (1.1)</td>
<td>0.54</td>
<td>0.464</td>
<td>46.15</td>
<td>&lt;0.001</td>
<td>2.10</td>
<td>0.151</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>12.72 (1.1)</td>
<td>12.75 (0.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative Symptoms</td>
<td>Pre</td>
<td>27.23 (1.7)</td>
<td>24.85 (1.5)</td>
<td>0.10</td>
<td>0.749</td>
<td>23.54</td>
<td>&lt;0.001</td>
<td>4.89</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>21.91 (1.6)</td>
<td>22.84 (1.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorganization</td>
<td>Pre</td>
<td>17.03 (1.0)</td>
<td>14.13 (0.9)</td>
<td>1.58</td>
<td>0.212</td>
<td>32.27</td>
<td>&lt;0.001</td>
<td>7.32</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>12.91 (0.9)</td>
<td>12.67 (0.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitement</td>
<td>Pre</td>
<td>12.61 (0.8)</td>
<td>9.56 (0.7)</td>
<td>7.45</td>
<td>0.008</td>
<td>27.72</td>
<td>&lt;0.001</td>
<td>1.64</td>
<td>0.204</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>9.36 (0.6)</td>
<td>7.58 (0.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Distress</td>
<td>Pre</td>
<td>10.97 (0.9)</td>
<td>7.95 (0.8)</td>
<td>5.32</td>
<td>0.024</td>
<td>38.01</td>
<td>&lt;0.001</td>
<td>4.42</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>7.66 (0.6)</td>
<td>6.33 (0.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insight</td>
<td>Pre</td>
<td>6.09 (0.7)</td>
<td>6.31 (0.6)</td>
<td>0.15</td>
<td>0.694</td>
<td>41.81</td>
<td>&lt;0.001</td>
<td>2.98</td>
<td>0.088</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>8.64 (0.6)</td>
<td>7.79 (0.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS-Total</td>
<td>Pre</td>
<td>99.39 (4.9)</td>
<td>84.56 (4.28)</td>
<td>2.77</td>
<td>0.100</td>
<td>48.13</td>
<td>&lt;0.001</td>
<td>4.71</td>
<td>0.033</td>
</tr>
</tbody>
</table>

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Cognitive rehabilitation in schizophrenia: A RCT

<table>
<thead>
<tr>
<th>Neurocognition</th>
<th>Pre</th>
<th>Post</th>
<th>t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.11 (0.59)</td>
<td>0.09 (0.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.13 (0.71)</td>
<td>-0.09 (0.54)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. SD = Standard Deviation; PANSS = Positive and Negative Syndrome Scale; Neurocognition = composite score of previously described neurocognitive tests.
Table 3. Functional outcome from Baseline to Post-treatment by Treatment Group (REHACOP; Control Group).

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Main Effect Group</th>
<th>Main Effect Time</th>
<th>Main Effect Group X Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REHACOP</td>
<td>Control Group</td>
<td>F</td>
<td>P</td>
</tr>
<tr>
<td>GAF Pre</td>
<td>38.88 (2.5)</td>
<td>43.33 (2.2)</td>
<td>0.00</td>
<td>0.983</td>
</tr>
<tr>
<td>Post</td>
<td>58.06 (3.1)</td>
<td>53.75 (2.8)</td>
<td>0.03</td>
<td>0.855</td>
</tr>
<tr>
<td>DAS-WHO Pre</td>
<td>14.50 (0.6)</td>
<td>13.70 (0.6)</td>
<td>0.03</td>
<td>0.855</td>
</tr>
<tr>
<td>Post</td>
<td>10.50 (0.8)</td>
<td>11.63 (0.7)</td>
<td>0.03</td>
<td>0.855</td>
</tr>
<tr>
<td>CGI Pre</td>
<td>5.08 (0.3)</td>
<td>4.64 (0.2)</td>
<td>0.48</td>
<td>0.490</td>
</tr>
<tr>
<td>Post</td>
<td>3.66 (0.2)</td>
<td>3.71 (0.2)</td>
<td>0.04</td>
<td>0.851</td>
</tr>
<tr>
<td>Self-Care Pre</td>
<td>2.70 (0.2)</td>
<td>2.40 (0.2)</td>
<td>0.04</td>
<td>0.851</td>
</tr>
<tr>
<td>Post</td>
<td>2.11 (0.2)</td>
<td>2.07 (0.2)</td>
<td>0.04</td>
<td>0.851</td>
</tr>
<tr>
<td>Social Competence</td>
<td>3.78 (0.2)</td>
<td>3.71 (0.2)</td>
<td>1.99</td>
<td>0.164</td>
</tr>
<tr>
<td>Vocational Outcome</td>
<td>4.00 (0.2)</td>
<td>3.97 (0.2)</td>
<td>2.41</td>
<td>0.127</td>
</tr>
<tr>
<td>Family Contact Pre</td>
<td>3.72 (0.2)</td>
<td>3.46 (0.2)</td>
<td>0.11</td>
<td>0.746</td>
</tr>
<tr>
<td>Post</td>
<td>2.47 (0.2)</td>
<td>2.76 (0.2)</td>
<td>0.11</td>
<td>0.746</td>
</tr>
</tbody>
</table>
Cognitive rehabilitation in schizophrenia: A RCT

Note. SD = Standard Deviation; GAF = Global Assessment of Functioning; DAS-WHO = Disability Assessment Schedule from WHO; CGI = Clinical General Impression Scale.
Figure 1. Recruitment procedure and study profile/Participants’ flow card

N= 92

Baseline assessment
and randomization

N= 38 subjects assigned to the REHACOP Group.

2 patients did not complete treatment (One of them had a diagnosis change and the other suffered from a health

N= 54 subjects assigned to the Control Group.

6 patients did not complete treatment (2 were discharged, 4 declined to collaborate in the time 2

Final N= 36

Final N= 48