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Mechanisms of functional improvement through cognitive rehabilitation in schizophrenia

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ABSTRACT

Whereas the efficacy of cognitive rehabilitation in schizophrenia is widely known, studies examining mechanisms for functional improvement are still scarce. The aim of the study was to examine the mediational mechanisms through which cognitive rehabilitation improves functioning in schizophrenia. One hundred and eleven schizophrenia patients were randomly assigned to either a 4-month cognitive rehabilitation group or an active control group. Patients underwent a neurocognitive battery (including processing speed, verbal memory, working memory and executive functioning) and social cognition assessment (emotion perception, theory of mind and social perception). Functioning was assessed by the combined use of a performance-based instrument, the UCSD Performance-based Skills Assessment (UPSA) and an observer-rated instrument, the Global Assessment of Functioning (GAF). The trial was registered in clinicaltrials.gov (NCT02796417). Multiple mediational analyses revealed that the effect of cognitive rehabilitation on functional improvement was partially mediated by changes in processing speed and verbal memory, but not by the domains of social cognition and negative symptoms. More specifically, verbal memory partially mediated the treatment's effect on performance-based functioning (UPSA), whereas processing speed acted as a partial mediator for observer-rated functioning (GAF). The effect of rehabilitation on functioning did not take place through all the domains that showed significant improvement. Verbal memory and processing speed emerged as the most crucial factors. However, these complex interactions need further research.

1. Introduction

Cognitive rehabilitation in schizophrenia has recently received increasing attention, as its benefits on functioning have become more evident in various meta-analyses (Kurtz et al., 2016; Wykes et al., 2011). Additionally, since social cognition has also been established as a crucial predictor of functional outcomes (Fett et al., 2011), several social cognitive treatment programs have been proposed. In a recent meta-analysis, Grant et al. (2017) showed that social cognitive intervention improves functional outcomes, mainly social functioning and engagement.

A number of approaches have combined social cognitive treatment and cognitive remediation in order to develop enhanced interventions (Bechi et al., 2015; Lindenmayer et al., 2013; Mueller et al., 2015; Peña et al., 2016). As expected, these approaches have shown better results than single approaches in several domains, including functioning (Bowie et al., 2012; Lindenmayer et al., 2013; Mueller et al., 2015; Roder et al., 2011), social cognition (Lindenmayer et al., 2013; Mueller et al., 2015; Peña et al., 2016) and negative symptoms (Peña et al., 2016; Schmidt et al., 2011).

Given these promising results, the next step should include identifying the mechanisms through which rehabilitation improves functioning. If these factors were determined, treatment efforts would be optimized by reducing time and cost. This could be attained by selecting the most relevant variables for treatment. A highly significant study carried out recently (Reeder et al., 2014) demonstrated that change in cognition after cognitive remediation is associated with the cost of care among patients with schizophrenia. These findings

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strengthen the additional financial gain that could be achieved through this line of research.

Several studies have been published so far. For example, Rispaud et al. (2016) examined 96 patients with schizophrenia that attended either computer skills training or drill-and-practice cognitive remediation. They found that improved working memory and processing speed predicted improvement in UCSD Performance-based Skills Assessment (UPSA). However, the lack of a control group did not guarantee that the improvement found in the experimental group was not due to many different factors other than the specific ones included in the treatment, such as practice effect or provision of care from skilled clinicians (Eack et al., 2011).

Several randomized controlled trials have analyzed if changes in neurocognitive domains after rehabilitation are associated with changes in functioning. For example, Fiszdon et al. (2008) compared patients who received work therapy with patients who received work therapy plus cognitive remediation. They found that improvement in memory was associated with a better quality of life, whereas improvement in executive functioning was associated with a worse quality of life. In another RCT study, Penadés et al. (2003) showed that changes in executive functioning were associated with changes in personal autonomy and general functioning after receiving cognitive remediation. Wykes et al. (2012) found that planning improvement was associated with improved work quality. Hogarty et al. (2006) proved that changes in processing speed partially mediated the effect of cognitive enhancement therapy on social adjustment.

As far as the authors are aware, none of the previous studies that included only social cognitive interventions have analyzed the mechanisms of improvement in functioning. One study was conducted that included social cognition as a possible mediating mechanism along with neurocognition in a randomized controlled trial. In this study, Eack et al. (2011) selected 58 patients in the early course of schizophrenia who received either cognitive enhancement therapy or enriched supportive therapy. Emotion management and neurocognition were considered as possible mediators of the effect of treatment on functioning (assessed with observer-rated instruments). It was found that improvement in both neurocognition (mostly executive functioning) and emotion perception mediated the effect of treatment on functioning.

Although not as numerous as neurocognition studies, RCT studies have also demonstrated that patients with schizophrenia improve negative symptomatology after cognitive rehabilitation (Bellucci et al., 2003; Eack et al., 2009; Roder et al., 2011; Sánchez et al., 2014). Given the robust relationship between negative symptoms and functioning (Fervaha et al., 2014; Galderisi et al., 2014; Greenwood et al., 2005), the improvement in functioning after cognitive rehabilitation could be partially due to an improvement in negative symptoms, as Eack et al. (2011) suggested. However, no studies have been found that have assessed if the improvement of negative symptoms partially explains the improvement in functioning.

1.1. Aims of the study

This study investigated whether the effect of cognitive rehabilitation on functioning occurs through the changes caused by the treatment to neurocognition, social cognition and negative symptoms. More specifically, we aimed to evaluate if the domains that previously showed improvement after cognitive rehabilitation (processing speed, verbal memory, working memory, executive functioning, emotion perception, theory of mind, social perception and negative symptoms) (Peña et al., 2016) mediated the relationship between treatment and two different measures of functioning (a performance-based instrument to assess functional capacity and an observer-rated measure of functioning).

2. Methods

2.1. Participants

The participants enrolled in the study had taken part in a randomized, previously published, controlled trial (Peña et al., 2016). The sample consisted of 111 patients diagnosed with schizophrenia. They were recruited from the Osakidetza Public Mental Health Services in Bizkaia (Spain). All the patients met the criteria for a diagnosis of schizophrenia, according to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (APA, 2000). Exclusion criteria were (i) evidence of alcohol or drug abuse within the past 30 days; (ii) history of significant loss of consciousness; (iii) mental retardation and; (iv) relevant neurological or medical conditions. The Ethics Committee at the Health Department of the Basque Mental Health System in Spain approved the study protocol. All patients were volunteers and provided written informed consent to participate in the study. The trial was registered in clinicaltrials.gov (NCT02796417).

2.2. Measures

2.2.1. Neurocognition

The evaluation of neurocognitive functioning included tests for processing speed (PS), working memory (WM), verbal memory (VM) and executive functioning (EF). All neurocognitive scores were converted into Z-scores based on the pooled schizophrenia group. Scores were adjusted so that higher scores indicated better cognitive performance. PS was derived from the Stroop Color subtest (Golden, 2001), Trail Making Test-A (Reitan and Wolfson, 1985) and Symbol Digit from Wechsler General Intelligence Scale; WAIS-III (Wechsler, 1997) (Cronbach's $\alpha = 0.78$). The VM domain included learning and long-term recall from the Hopkins Verbal Learning Test (Brandt and Benedict, 2001) (Cronbach's $\alpha = 0.78$). The WM scores were obtained by administering Digit Forward and Digit Backward subtests from WAIS-III (D Wechsler, 1997) (Cronbach's $\alpha = 0.74$). Finally, EF was measured by word-color and interference subtests from the Stroop test (Golden, 2001) (Cronbach's $\alpha = 0.85$).

2.2.2. Social cognition

Theory of Mind (ToM) was assessed by the Happé test (Happé, 1994) using four different stories. Higher scores indicated better ToM performance. Emotion perception (EP) was assessed using the Perceiving Emotions branch from the Mayer-Salovery-Caruso Emotional Intelligence Test, version 2.0 (MSCEIT) (Extremera et al., 2006). Higher scores indicated better performance in emotion perception. Social perception (SP) was assessed by the Situational Feature Recognition Test (SFRT) (Corrigan, 1996). The SFRT is a paper-and-pencil measure that requires participants to identify features from a list of descriptors that describe nine situations (e.g., taking a test, reading in a library, building an igloo, performing surgery). Participants were presented with a list of features, corresponding to actions and goals. Higher scores indicated better performance in social perception.

2.2.3. Clinical symptoms

Psychopathology was assessed through the Positive and Negative Syndrome Scale; PANSS (Peralta Martín and Cuesta Zorita, 1994). Positive, negative and general psychopathology scores were analyzed.

2.2.4. Functioning

Functional competence was evaluated by means of the University of California, San Diego UCSD Performance-based Skills Assessment (UPSA) (Patterson et al., 2001). UPSA involves role-play tasks to assess skills in tasks of daily living, including transportation, household chores, finance, communication and planning recreational activities.

Global functioning was based on the clinician's (observer's) ratings

of the Global Assessment of Functioning (GAF) (Frances et al., 1994).

2.3. Procedure

The study design was a parallel-group randomized trial with equal randomization. The assignment was based on computer-generated randomization. Recruitment and enrollment was carried out between March 2012 and April 2014. Post-treatment assessment was performed within the first week after completing the intervention.

2.4. Intervention

REHACOP is an integrative program that combines neurocognitive remediation, social cognitive intervention, and functional skills training. It includes top-down and bottom-up strategies. Two psychologists received the same training on REHACOP and led the REHACOP group at the hospitals. Patients attended 90-min sessions, 3 days per week. The REHACOP group consisted of Attention (4 weeks), Memory (3 weeks), Language (3 weeks), Executive functions (2 weeks) and Social cognition (1 week), focused on ToM, social reasoning, and moral dilemmas. The training was based on paper-and-pencil tasks, role playing and active group discussions.

The control group took part in occupational group activities with the same frequency and timing as the experimental group. The activities included gardening, drawing, reading the daily news, and building objects from different materials (such as paper or wood).

2.5. Statistical analyses

SPSS v.23 (IBM, 2012) was used to perform the statistical analyses. The $\chi 2$ test was used to analyze differences in gender between both groups. Change scores (post-treatment - baseline) were compared between the REHACOP and control groups on each of the neurocognitive, social cognitive, clinical and functioning variables with a multivariate analysis of variance (MANOVA). Partial eta squared (η_p^2) was obtained as an indicator of effect size and it was interpreted as small, medium, and large based on values of 0.01, 0.06, and 0.14, respectively.

To assess how changes in neurocognition (PS, VM, WM and EF), social cognition (EP, ToM and SP) and negative symptoms mediated the relationship between receiving cognitive rehabilitation (vs control group) and functioning (GAF and UPSA), the PROCESS (Hayes, 2013) macro for SPSS was used. PROCESS is based on a regression-based path-analytic framework and estimates the indirect effect and bias-corrected confidence intervals (CIs). An indirect effect is considered significant when the CIs do not include zero (Field, 2013). Within the macro, model 4 and 5000 bias-corrected bootstrap samples were selected. A 95% confidence level was chosen to apply a p-value of 0.05. Using these settings, two analyses were performed. The first one was used to test multiple mediational pathways on UPSA change scores, whereas the second one was used for the GAF score as a measure of functioning. In both multiple mediational analyses, group (cognitive rehabilitation vs occupational activities) was selected as an independent variable. Fig. 1 displays the path diagrams of the multiple mediational analyses.

3. Results

3.1. Baseline characteristics and change scores differences between the REHACOP and control groups

There were no significant differences between the groups in any of the variables analyzed at baseline (See Table 1). These included age, years of education, gender, number of hospitalizations and chlorpromazine equivalent doses. Differences in change scores indicated that patients receiving REHACOP improved when compared to the control group in PS, VM, WM, EF, EP, ToM, SP and negative symptoms (See Table 2).

3.2. Mediational analyses for performance-based functioning (UPSA)

Table 3 shows the results of the analysis done with PROCESS. The direct effect of group on UPSA was significantly different from zero ($p = 0.001$). Therefore, receiving cognitive rehabilitation (vs control group) had an impact on UPSA. The 95% confidence interval of the bootstrap results revealed that the indirect effect of cognitive rehabilitation on UPSA through the change in VM was different from zero (lower level: 0.172; upper level: 3.413), indicating that the change in VM partially mediated the relationship between cognitive rehabilitation and UPSA. These results supported the partial mediational hypothesis, since cognitive rehabilitation was still a significant predictor of change in UPSA in the presence of possible mediators (lower level: 0.177; upper level: 9.228).

The significant mediational path between group and change in UPSA through the change in VM remained even after controlling for age, medication dosage (chlorpromazine equivalent doses - mg/day) and age at onset.

3.3. Mediational analyses for observer-rated functioning (GAF)

Similarly to UPSA scores, only one mediator emerged as a partial mediator (see Table 4). The direct effect of group on GAF was significantly different from zero ($p = 0.002$). Therefore, receiving cognitive rehabilitation (vs control group) had an impact on GAF. The 95% confidence interval of the bootstrap results revealed that the indirect effect of cognitive rehabilitation on GAF through the change in PS was different from zero (lower level: 0.218; upper level: 4.330), indicating that the change in PS partially mediated the relationship between cognitive rehabilitation and GAF. Again, these results supported the partial mediational hypothesis. Cognitive rehabilitation was still a significant predictor of GAF in the presence of possible mediators (lower level: 0.349; upper level: 12.043).

The significant mediational path between group and change in GAF through the change in PS remained even after controlling for age, medication dosage (chlorpromazine equivalent doses - mg/day) and age at onset.

4. Discussion

This is the first study that has analyzed the mechanism through which an integrative program that combines neurocognitive remediation, social cognitive intervention, and functional skills improves both performance-based functional capacity (UPSA) and observer-rated functioning score (GAF).

Among all the domains that significantly improved after cognitive rehabilitation compared to the control group, only VM emerged as a partial mediator of the effect of treatment on functional competence improvement. The mediating effect of VM was found even in the presence of improvement in other neurocognitive domains (PS, WM and EF), negative symptoms and social cognitive domains (ToM, EP and SP). Moreover, PS acted as a partial mediator when the analysis took into account an observer-rated instrument (GAF). These mediation results for UPSA and GAF remained even after controlling for age, medication dosage (chlorpromazine equivalent doses - mg/day) and age at onset. Contrary to expectations, none of social cognitive domains acted as a mediator between treatment and improvement in any of the functioning measures included in the study. Our results indicate that not all changes in neurocognitive domains are equally related to improvement in functioning after cognitive rehabilitation.

These results are consistent with previous literature to some extent. For example, in the study carried out by Fiszdon et al. (2008), improvement in VM was associated with a better quality of life. Rispaud et al. (2016) discovered that changes in PS and WM were associated

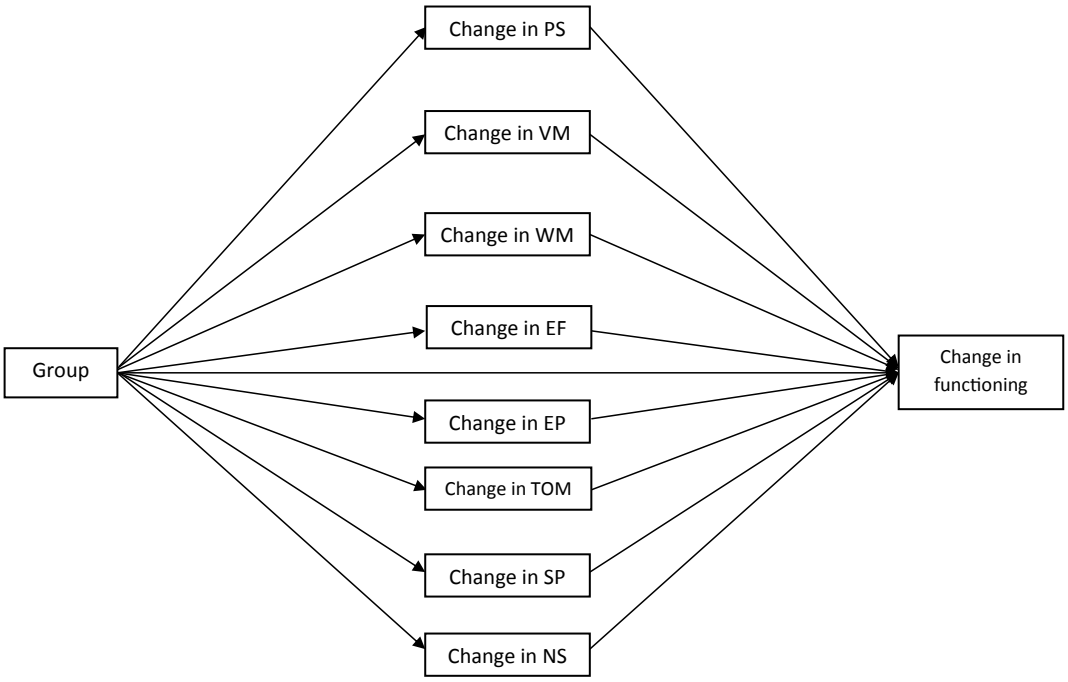

Fig. 1. Indirect effect of treatment group (0 = control group, 1 = REHACOP) on Functioning change (UPSA and GAF) through change in neurocognition, social cognition and negative symptoms.
UPSA = University of California, San Diego, UCSD Performance-Based Skills Assessment; GAF = Global Assessment of Functioning; PS = Processing Speed; VM = Verbal Memory; WM = Working Memory; EF = Executive Functioning; EP = Emotion Perception; TOM = Theory of Mind; SP = Social Perception; NS = Negative Symptoms.

Table 1
Participant characteristics at baseline.

	REHACOP Group (n = 52)		Control Group (n = 49)		*P*
	Mean (95% CI)	SD	Mean (95% CI)	SD	
Age (years)	39.87 (37.23–42.50)	9.5	38.13 (36.54–42.36)	10.1	0.831
Years of education (years)	10.55 (9.26–11.09)	3.29	10.25 (8.99–10.73)	3.0	0.618
Age at onset (years)	24.13 (22.16–26.11)	7.1	22.29 (20.52–24.07)	6.1	0.169
Number of hospitalizations	8.10 (6.00–10.20)	7.5	7.08 (4.58–9.59)	8.7	0.532
Gender: n (%)					
Males	36 (75.5%)		37 (69.2%)		0.481
Females	16 (24.5%)		12 (30.8%)		
DSM-IV-TR: n (%)					
Paranoid	35 (67.3%)		33 (67.4%)		0.411
Disorganized	4 (7.7%)		8 (16.3%)		
Residual	5 (9.6%)		2 (4.1%)		
Non-specified	8 (15.4%)		6 (12.2%)		
Chlorpromazine equivalent doses (mg/day)	497.65 (435.9–559.4)	227.7	479.66 (402.7–556.7)	275.7	0.755

Abbreviations: CI = Confidence Interval; SD = Standard Deviation; DSM-IV-TR = The Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revised.

with improvement in the brief version of UPSA. Additional evidence of the mediating effect of change in PS was provided in Hogarty et al.´s study (2006). Many previous studies have also found a relationship between changes in EF and functioning (Eack et al., 2011; Penadés et al., 2003; Reeder et al., 2004; Wykes et al., 2012). One possible reason for not finding that EF acted as a mediator may be the measure used in the current study. The Stroop test (interference and color-word scores) was used as an EF measure, and it may not be as sensitive to changes as other EF measures.

Regarding social cognitive results, there is only one previous study that included both social cognitive and neurocognitive change scores in mediation analyses (Eack et al., 2011). It reported that changes in verbal memory, EF and EP acted as mediators between the effect of cognitive enhancement therapy and functional improvement. There are some relevant differences between the study by Eack et al. (2011) and the current study which explain some of the discrepancies in the results obtained. Whereas Eack et al. (2011) included early-course schizophrenia participants, our patients' profile was multiepisodic. This is relevant because processing speed was preserved in their patients with early course schizophrenia. Therefore, they did not include change in PS as a potential mediator, which was the significant mediator we found for GAF. Social cognitive measures did not emerge as significant mediators in the present study.

We found that the significant improvement in negative symptoms after cognitive rehabilitation did not mediate the improvement in any of the functioning measures included. As far as the authors are aware, none of the previous studies analyzed this possible mediational analysis. Despite the non-significant results, we recommend not discarding its role in future research. This is mainly due to the large amount of literature that links negative symptoms to functional outcomes in schizophrenia (Fett et al., 2011; Green et al., 2015). In this study we used the Positive and Negative Syndrome Scale (PANSS) was used. Some studies (Daniel, 2013) have suggested that this instrument has some limitations and therefore we suggest including more reliable measures for negative symptoms in future studies.

Both significant mediators (VM and PS) were partial mediators. These results make perfect sense when considering that the intervention included in the study also used functional skills training. This characteristic of the REHACOP program could explain the direct effect of treatment on both functioning measures (GAF and UPSA), along with its effect through the improvement of neurocognition.

Another result to take into account is that this study shows that the exact mechanisms of improvement may differ depending on the functioning instrument used. As Rispaud et al. (2016) suggested, UPSA is a proximal measure of functioning based on observed task performance. According to these authors (Rispaud et al., 2016), “it poses advantages

Table 2
Differences in change scores between REHACOP group and Control group.

	REHACOP Group		Control Group		ANOVA for change scores		
	Mean Change Score (95% CI)	SD	Mean Change Score (95% CI)	SD	F	P	η_p^2
PS	0.09 (−0.03 to 0.20)	0.41	−0.09 (−0.20 to 0.01)	0.37	5.30	0.023	0.051
VM	0.20 (−0.01 to 0.40)	0.72	−0.21 (-0.42 to 0.00)	0.73	7.65	0.007	0.072
WM	0.12 (−0.06 to 0.30)	0.64	−0.13 (-0.29 to 0.03)	0.56	4.42	0.038	0.043
EF	0.14 (0.00–0.28)	0.51	−0.15 (-0.30 to 0.00)	0.53	7.89	0.006	0.074
TOM	1.47 (1.03–1.92)	2.13	0.15 (−0.30 to 0.61)	1.31	17.03	< 0.001	0.148
SP	2.70 (−0.79 to 6.20)	8.78	−4.71 (−8.35 to −1.07)	15.82	7.50	0.004	0.082
EP	−1.80 (−3.63 to 0.03)	3.91	−0.54 (-1.78 to 0.69)	2.78	1.45	0.236	0.071
NS	−5.43 (−7.08 to −3.79)	6.64	−2.84 (−4.49 to −1.20)	4.33	4.90	0.029	0.082
GAF	13.27 (10.25–16.28)	15.61	6.95 (3.84–10.05)	8.85	8.36	0.005	0.081
UPSA	8.24 (5.63–10.85)	9.16	0.94 (−1.64 to 3.52)	9.06	15.61	< 0.001	0.154

Abbreviations: CI = Confidence Interval; SD = Standard deviation; = partial eta squared; PS = Processing Speed; VM = Verbal Memory; VSM = Visual Memory; EF = Executive Functioning; TOM = Theory of Mind; SP = Social Perception; EP = Emotion Perception; NS = Negative symptoms from PANSS; GAF = Global Assessment of Functioning; UPSA = University of California, San Diego, UCSD Performance-Based Skills Assessment.

Table 3
Results of multiple mediation analysis investigating change in cognition, social cognition and negative symptoms as mediators between treatment group and functional competence (UPSA).

	Coefficient	SE	t	p
Direct effect of group on UPSA	6.134	1.854	3.309	0.001
Effect of group on PS	0.183	0.079	2.300	0.023
Effect of PS on UPSA	−1.017	2.516	−0.404	0.686
Effect of group on VM	0.402	0.146	2.765	0.006
Effect of VM on UPSA	3.056	1.419	2.153	0.034
Effect of group on WM	0.253	0.121	2.102	0.038
Effect of WM on UPSA	−0.161	1.619	−0.100	0.921
Effect of group on EF	0.292	0.104	2.809	0.006
Effect of EF on UPSA	−0.734	1.941	−0.378	0.706
Effect of group on EP	9.884	3.337	2.962	0.003
Effect of EP on UPSA	0.012	0.059	0.196	0.845
Effect of group on TOM	1.338	0.355	3.767	< 0.001
Effect of TOM on UPSA	0.199	0.560	0.357	0.722
Effect of group on SP	7.039	2.485	2.833	0.005
Effect of SP on UPSA	0.099	0.083	1.199	0.234
Effect of group on NS	−2.266	1.015	−2.232	0.027
Effect of NS on UPSA	−0.300	0.191	−1.571	0.119

Bootstrap results for indirect effects	Bootstrap estimate		95% CI	
	Estimate	SE	Lower	Upper
Total indirect effect of group on UPSA	4.702	2.277	0.177	9.228
Indirect effect through change in PS	−0.186	0.496	−1.534	0.593
Indirect effect through change in VM	1.229	0.789	0.172	3.413
Indirect effect through change in WM	−0.041	0.393	−0.979	0.661
Indirect effect through change in EF	−0.214	0.505	−1.375	0.678
Indirect effect through change in EP	0.114	0.577	−0.940	1.393
Indirect effect through change in TOM	0.268	0.825	−1.358	2.004
Indirect effect through change in SP	0.697	0.713	−0.565	2.271
Indirect effect through change in NS	0.680	0.571	−0.005	2.093

Abbreviations: SE = Standard Error; CI = Confidence Interval; UPSA = University of California, San Diego, UCSD Performance-Based Skills Assessment; PS = Processing Speed; VM = Verbal Memory; WM = Working Memory; EF = Executive Functioning; EP = Emotion Perception; TOM = Theory of Mind; SP = Social Perception; NS = Negative Symptoms.

for studying the relationship between cognitive and functional change because proxy measures are likely to be most sensitive to changes in cognition in the context of brief treatment trials".

Future studies should also include additional outcome measures, such as work outcome, subjective quality of life, self-care, need for professional care, influence on family dynamics, etc. Moreover, studies identifying baseline predictors of improvement would be helpful in designing more customized treatment plans. However, treatment-resistant patients who need further research should not be forgotten.

Although some interesting results were found, this study has some limitations that must be considered. First, there was no patient follow-up after treatment completion. Therefore, it cannot be concluded that the mechanisms for improvement in functioning persist in time, or whether this is an effect that occurred only during the treatment period. Second, the REHACOP program did not include an equal number of treatment sessions for neurocognition, social cognition and functional skills. The lack of significant social cognitive mediation could be partially due to this fact. However, the program demonstrated a significant improvement in EP, ToM and SP individually.

In summary, this study suggests that more intensive programs addressing verbal memory and processing speed may obtain better results regarding functioning in schizophrenia. Nevertheless, the lack of significant mediation throughout social cognitive domains and negative symptoms should not prevent future research from testing these

Table 4
Results of multiple mediation analysis investigating change in cognition, social cognition and negative symptoms as mediators between treatment group and global functioning (GAF).

	Coefficient	SE	*t*	*p*
Direct effect of group on GAF	7.820	2.556	3.060	0.002
Effect of group on PS	0.209	0.079	2.609	0.010
Effect of PS on GAF	7.894	3.270	2.414	0.017
Effect of group on VM	0.424	0.149	2.835	0.005
Effect of VM on GAF	−1.474	−1.841	−0.800	0.426
Effect of group on WM	0.248	0.124	1.999	0.048
Effect of WM on GAF	2.327	2.070	1.124	0.264
Effect of group on EF	0.301	0.107	2.818	0.006
Effect of EF on GAF	1.779	2.504	0.711	0.479
Effect of group on EP	10.413	3.402	3.060	0.003
Effect of EP on GAF	−0.069	0.077	−0.899	0.371
Effect of group on TOM	1.312	0.363	3.609	< 0.001
Effect of TOM on GAF	0.145	0.721	0.201	0.842
Effect of group on SP	1.084	1.197	2.905	0.367
Effect of SP on GAF	−0.538	0.215	−2.509	0.014
Effect of group on NS	−2.369	1.033	−2.293	0.024
Effect of NS on GAF	−0.255	0.253	−1.009	0.316

Bootstrap results for indirect effects	Bootstrap estimate		95% CI	
	Estimate	SE	Lower	Upper
Total indirect effect of group on GAF	6.196	2.942	0.349	12.043
Indirect effect through change in PS	1.646	0.978	0.218	4.330
Indirect effect through change in VM	−0.624	0.789	−2.649	0.670
Indirect effect through change in WM	0.578	0.491	−0.069	2.082
Indirect effect through change in EF	0.535	0.736	−0.545	2.562
Indirect effect through change in EP	−0.722	0.859	−2.932	0.641
Indirect effect through change in TOM	0.189	0.978	−2.033	1.911
Indirect effect through change in SP	−0.583	0.730	−2.355	0.505
Indirect effect through change in NS	0.605	0.707	−0.382	2.530

Abbreviations: SE = Standard Error; GAF = Global Assessment of Functioning; Assessment; PS = Processing Speed; VM = Verbal Memory; WM = Working Memory; EF = Executive Functioning; EP = Emotion Perception; TOM = Theory of Mind; SP = Social Perception; NS = Negative Symptoms.

hypotheses. Additionally, future research should focus on different outcome measures and follow-up studies in order to ascertain whether other mediational mechanisms may have been missed in this study.

Conflicts of interest

NO and JP are co-authors and copyright holders of the REHACOP cognitive remediation program, published by Parima Digital, SL (Bilbao, Spain).

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2018.03.002.

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