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Moderators of functional improvement after integrative cognitive remediation in schizophrenia: Toward a personalized treatment approach

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ABSTRACT

Cognitive remediation is an effective intervention for improving functional outcome in schizophrenia. However, the factors that moderate this improvement are still poorly understood. The study aimed to identify moderators of functional outcome improvement after integrative cognitive remediation (REHACOP) in schizophrenia. This was a secondary analysis of data from two randomized controlled trials, which included 182 patients (REHACOP group=94; active control group=88). Hierarchical regression analyses were conducted to identify moderators of functional outcome improvement. Two baseline level groups (low-level and high-level) were created to analyze the moderating role of this baseline level cluster using repeated measures ANCOVA. The REHACOP was effective regardless of participants' baseline level, but regression analyses indicated that the effectiveness on functional outcome was higher among those who were older, had fewer years in education, lower scores in baseline cognition and functional outcome, and more negative symptoms. Repeated measures ANOVA showed that the baseline level cluster influenced the improvement in functional outcome, with the low-level group showing greater improvements. The results reinforced the need to implement cognitive remediation programs more broadly as a treatment for schizophrenia in healthcare services. Furthermore, they provided evidence for the development of personalized cognitive remediation plans to improve benefits in different schizophrenia profiles.

1. Introduction

Schizophrenia is one of the most disabling diseases in the world (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017), with cognitive impairment and clinical symptomatology accounting for much of this disability (Green et al., 2015). In recent decades, cognitive remediation has proved to be an effective intervention in improving not only cognitive impairment, but also functional outcome (Cella et al., 2020, 2017; Fitapelli and Lindenmayer, 2022; Kurtz et al., 2015; Revell et al., 2015). Moreover, some studies have suggested that these improvements could be even greater if cognitive remediation was combined with additional interventions such as training in social and functional skills (Bowie et al., 2012; Cella et al., 2015; Galderisi et al., 2010; Peña et al., 2016; Sampedro et al., 2021; Sánchez et al., 2014).

Despite the effectiveness of this intervention, some questions remain unanswered. Specifically, it is unclear what mechanisms may contribute to cognitive remediation and produce different response patterns (Seccomandi et al., 2021a). Accordingly, in recent years there has been increasing interest in identifying the variables that may moderate improvement after cognitive remediation. A moderator has been classically defined as a variable that affects the direction and/or strength of the relationship between a predictor and an outcome variable (Baron and Kenny, 1986). However, while most studies have analyzed the predictors of cognitive improvement, few have focused on the enhancement of functional outcome (e.g., Bell et al., 2014; Farreny et al., 2016; Lindenmayer et al., 2017; Tan et al., 2020; Twamley et al., 2011; Vita et al., 2013), which is regarded as the ultimate goal of treatments. Particularly, some of the factors that have been associated with functional response to cognitive remediation included different

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patients' characteristics, such as age, education level, baseline cognition, functioning and clinical symptoms (Barlati et al., 2019; Lejeune et al., 2021; Seccomandi et al., 2020; Vita et al., 2021). However, results across studies have been quite diverse. For example, as indicated in different reviews (Barlati et al., 2019; Seccomandi et al., 2020), while some studies have found that a better baseline cognitive, functional and clinical profile predicts greater improvement, others have found the opposite. In two recent meta-analyses, greater improvements in functional outcome and/or cognition were seen among the most clinically compromised (Vita et al., 2021) and the more chronic individuals (Lejeune et al., 2021). Moreover, in the recent systematic review carried out by Seccomandi et al. (2020), no high-quality replicated evidence was found of any reliable moderator predicting improvement after cognitive remediation. These authors (Seccomandi et al., 2020) suggested that one of the main reasons could be the lack of statistical power to conduct moderation analysis, coupled with the poor methodological quality of some studies, which could produce biased results. In fact, few studies (Bell et al., 2014; Seccomandi et al., 2021b; Tan et al., 2020) have examined which variables moderate the effect of treatment (experimental vs. control group) on functional outcome using a statistical interaction. In addition, only a limited number of studies have looked at moderators of functional improvement after using an integrative cognitive remediation approach that combined cognitive training with social or functional skill training (Bell et al., 2014; Tan et al., 2020).

Identifying the factors that moderate improvement after cognitive remediation could be important in order to improve its efficacy by personalizing and tailoring treatment to different patient profiles. In fact, an increasing number of authors have emphasized the development of personalized treatment plans as a future goal of mental health research (Medalia et al., 2018; Seccomandi et al., 2021b; Wykes and Spaulding, 2011). The aim of this study was therefore to identify which baseline characteristics moderate functional improvement after integrative cognitive remediation in people with schizophrenia. Based on evidence from a recent meta-analysis (Vita et al., 2021), it was hypothesized that patients with a lower baseline level (characterized by lower baseline education level, cognitive and functional outcome, and greater clinical symptoms) would benefit the most from cognitive remediation.

2. Method

2.1. Participants

The study's sample consisted of 182 patients diagnosed with schizophrenia who were recruited from the Psychiatric Hospital of Álava and the Mental Health Network in Álava (Spain). This sample was obtained from two previously published clinical trials (Peña et al., 2016; Sampedro et al., 2021). All patients had been diagnosed with schizophrenia based on the criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (American Psychiatric Association, 2000). The specific exclusion criteria for each clinical trial have been published elsewhere (Peña et al., 2016; Sampedro et al., 2021).

2.2. Procedure

A parallel-group randomized trial design was used. The patients' psychiatrists offered them the opportunity to participate in the study. All participating patients gave written informed consent and took part on a voluntary basis. After being briefed about the characteristics of the study, the participants were randomly assigned to either a cognitive remediation group or to an active control group, using an online computer-generated randomization system. All participants underwent a neuropsychological and a psychiatric assessment at baseline and at the 5-month follow-up. Post-treatment assessment was performed within three weeks after completing the intervention. All raters were blind to the experimental treatment condition and had no other role in the study that could undermine the trial's blinding. The study protocol of both clinical trials had the approval of the Clinical Research Ethics Committees of the Autonomous Region of the Basque Country, Spain. Both research projects were registered with clinicaltrials.gov (NCT03509597 and NCT02796417). Patients did not receive financial reward for their participation.

2.3. Intervention

REHACOP is a group-based integrative cognitive remediation program that combines training in neurocognition, social cognition, social skills, and functional skills (Ojeda and Peña, 2012). The program was implemented in groups of between 4 and 8 patients each at several centers in the Mental Health Network in Álava, Spain. The members of the clinical team who conducted the intervention were trained in REHACOP administration and used the same materials and instructions for all the groups. The sessions lasted 60–90 min and were held 3 days per week, for a total of 20 weeks. The REHACOP program included training in a number of areas, each of which was a separate unit: attention; learning and memory; language; executive functions; social cognition; social skills; and functional skills. Processing speed was also trained throughout the first four units. The active control group carried out occupational group activities with the same duration and frequency as the cognitive remediation group. A more detailed description of the interventions has been provided elsewhere (Sampedro et al., 2021).

2.4. Measures

2.4.1. Neurocognition

Neurocognition was measured through a series of tests, which assessed processing speed, inhibition, working memory, and verbal memory. These included Word, Color, and Word-Color values from the Stroop Color and Word Test (Golden, 2010); the Backward Digit Span subtest from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997); the three learning trials and the delayed recall trial from the Hopkins Verbal Learning Test (Brandt and Benedict, 2001); and the Symbol-Coding subtest from the WAIS-III (Wechsler, 1997). All these scores were converted into Z-scores based on the study's sample and a composite neurocognition score was calculated using these Z-scores (Cronbach's alpha = 0.85).

2.4.2. Social cognition

Social cognition was measured by means of Happé's Strange Stories Test (Happé, 1994) which assesses theory of mind.

2.4.3. Functional outcome

Functional outcome was measured using the Spanish Version of the University of California, San Diego, Performance-Based Skills Assessment (UPSA; Garcia-Portilla et al., 2013) which assesses functional competence in everyday activities.

2.4.4. Clinical symptoms

Positive and negative symptoms were assessed by means of the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and following the consensus 5-factor model proposed by Wallwork et al. (2012). Only the positive and negative factors were considered for the purposes of this study.

2.5. Data analyses

This is a secondary analysis of data obtained from two previously published randomized controlled trials. Data from both studies was merged by selecting only those variables that had been obtained in the same way in both clinical trials, that is, using the same assessment instrument. Only patients who had completed the post-treatment assessment were selected, 101 patients from one clinical trial (Peña et al., 2016) and 81 from the other (Sampedro et al., 2021). IBM SPSS version 28.0 (SPSS Inc., Chicago, USA) was used for statistical analyses. The Kolmogorov-Smirnov test was employed to test data for normality. The expectation maximization algorithm was used to impute missing values.

The differences between the experimental group and the active control group on sociodemographic, cognitive, functional outcome, and clinical data at baseline were assessed using either a two-tailed independent *t*-test or a Mann-Whitney *U test*. Differences between groups in categorical data were analyzed using the chi-square (X^2) test.

Moderated hierarchical regression analyses were conducted to analyze whether the improvement in functional outcome was moderated by baseline characteristics. The dependent variable was functional outcome at post-treatment; the independent variable was the intervention; and the included covariates were the "study variable" and baseline functional outcome. The moderators included in the analyses were age, years in education, premorbid IQ, baseline positive and negative symptoms, baseline neurocognition and social cognition, and baseline functional outcome. A separate regression analysis model was used for each moderator, so a total of eight independent regression models were performed. Continuous variables were transformed into z-scores and the intervention variable was coded as a dummy variable, either 0 (active control group) or 1 (REHACOP group). In the first step, the "study variable" (0 = study 1; 1 = study 2) and baseline functional outcome was entered as a predictor of functional outcome at post-treatment, in order to control its possible influence. In the second step, the intervention variable and the moderator were entered as predictors. Finally, in the third step, a two-way interaction term was entered: intervention × moderator variable. The two-way interactions were plotted and the statistical significance of slope differences was tested (Aiken and West, 1991; Dawson, 2014).

After obtaining significant results with several moderators, a K-means clustering analysis was conducted in order to unify previous results and analyze whether there was a patient profile that moderated the improvement after the intervention. The number of clusters selected was two and the iterate (max. 10) and classify method was selected to update cluster centers iteratively. Only the z-transformed variables that had been significant moderators (age, years spent in education, baseline negative symptoms, baseline neurocognition and social cognition, and baseline functional outcome) were entered to create two baseline level clusters (a low-level group with a lower baseline performance and a high-level group with a higher baseline performance).

The differences between the two clusters in these variables were analyzed by using an analysis of variance (ANOVA). A chi-square (X^2) test was used to analyze statistical differences in the distribution of patients from the two clusters to the intervention groups (REHACOP group and active control group).

In order to assess the role of the baseline level cluster as a moderator variable of the functional improvement after the intervention, a repeated measures of covariance (ANCOVA) analysis was performed instead of a regression analysis, as both the cluster and the intervention variables were dichotomous variables. The between-subjects factors were "intervention" (REHACOP group or active control group) and "baseline level" (low-level group or high-level group), and the within-subjects factor was "time" (pre-treatment and post-treatment). In addition, the "study variable" was entered as covariate in order to control for the influence of data being included from two different clinical trials. No study effect was observed. Additional post-hoc analyses were carried out to determine whether the REHACOP group improved significantly, regardless of the cluster moderator.

3. Results

Baseline differences between the REHACOP and the active control group were only found in negative symptoms and premorbid IQ, with the REHACOP group obtaining higher premorbid IQ and lower negative symptoms (see Table 1).

3.1. Moderators explaining improvement after cognitive remediation

Regression analyses indicated that years of education ($\beta = -0.213$, $t = -3.497$, $p = .001$), age ($\beta = 0.155$, $t = 2.608$, $p = .010$), baseline neurocognition ($\beta = -0.169$, $t = -2.598$, $p = .010$), baseline social cognition ($\beta = -0.189$, $t = -3.134$, $p = .002$), baseline functional outcome ($\beta = -0.211$, $t = -3.503$, $p = .001$), and baseline negative symptoms ($\beta = 0.142$, $t = 2.275$, $p = .024$) played a moderating role in the improvement of functional outcome after integrative cognitive remediation. Specifically, analyses indicated that the effect of the REHACOP program on functional outcome was stronger among those participants who were older, had spent fewer years in education, had lower scores in baseline cognition and functional outcome, and experienced more negative symptoms. Slopes between the REHACOP and the active control groups were significant for both low- and high-level groups, indicating that the REHACOP program was effective regardless of the baseline profile. No significant interaction results were found with baseline positive symptoms ($\beta = 0.037$, $t = 0.581$, $p = .562$) or premorbid IQ ($\beta = -0.110$, $t = -1.715$, $p = .088$)

3.2. Effects of baseline level cluster on improvement after cognitive remediation

A cluster analysis was performed which identified the following two clusters: a low baseline level cluster ($n = 92$) and a high baseline level cluster ($n = 90$). Statistically significant differences between the two clusters were found in all variables (Supplementary Table S1). Specifically, patients from the low baseline level cluster were older, had a lower level of education, obtained lower scores for baseline cognition and functional outcome, and experienced more negative symptoms. No statistical differences were found ($X^2 = 0.557$, $p = .455$) in the distribution of patients from the two clusters to the intervention groups (REHACOP group and active control group). The sample size from each of the four subgroups was the following: REHACOP group – low baseline level ($n = 45$), REHACOP group – high baseline level ($n = 49$), active control group – low baseline level ($n = 47$), and active control group - high baseline level ($n = 41$). Baseline mean scores of each subgroup can be seen in Table 2. Heatmaps for baseline scores in each subgroup are shown in Fig. 1.

A repeated measures ANCOVA showed a significant interaction between time x intervention ($F = 34.519$, $p < .001$, $\eta_p^2 = 0.166$) as well as a significant interaction between time x intervention x baseline cluster group ($F = 10.765$, $p = .001$, $\eta_p^2 = 0.058$), indicating that the baseline level cluster variable influenced the improvement of functional outcome at post-interventions. As can be seen in Fig. 2, longitudinal differences between the REHACOP and the active control groups were greater in the low-level cluster.

Post-hoc analyses indicated significant longitudinal changes in functional outcome in the REHACOP group – low ($p = <0.001$) and REHACOP group – high ($p = <0.001$) and no significant changes in the active control group – low ($p = .540$) and active control group – high ($p = .059$) separately. In addition, separate subsequent analyses of each of the two clusters (low and high) indicated significant longitudinal differences between the REHACOP and the active control groups both in the low-level cluster ($F = 330.90$, $p = <0.001$, $\eta_p^2 = 0.274$) and the high-level cluster ($F = 4.366$, $p = .040$, $\eta_p^2 = 0.047$). It is worth noting that, the effect sizes were higher in the low-level cluster ($\eta_p^2 = 0.274$) than in the high-level one ($\eta_p^2 = 0.047$).

Table 1
Socio-demographic, cognitive, functional, and clinical data at baseline.

		REHACOP group (n = 94)		Active control group (n = 88)			
		Mean n (%)	SD	Mean n (%)	SD	$t/U/X^2$	p
Age (years)		40.77	9.76	40.64	10.50	0.086	.931
Education (years)		10.23	2.92	9.99	2.99	3874.00	.457
Gender	Male	72 (76.6 %)		67 (76.1 %)		0.005	.942
	Female	22 (23.4 %)		21 (23.9 %)			
Age of onset (years)		24.11	6.56	22.68	6.67	3524.50	.084
Hospitalization status	Outpatients	41 (43.6 %)		36 (40.9 %)		0.137	.712
	Inpatients	53 (56.4 %)		52 (59.1 %)			
Medication dosage		520.40	276.24	507.50	268.91	3996.00	.693
Premorbid IQ		97.02	9.65	94.32	9.57	3402.500	.039
Neurocognition		0.05	0.75	−0.05	0.69	0.885	.377
Social cognition		3.88	2.29	3.58	2.35	3814.50	.361
Functional outcome		66.43	14.25	64.56	14.70	0.871	.385
Negative symptoms		17.56	7.08	19.66	7.08	−1.997	.047
Positive symptoms		10.59	4.68	9.99	4.67	3803.50	.348

SD = Standard Deviation; t=t-test; U = Mann-Whitney U; X^2 = Chi-square; Medication dosage refers to chlorpromazine equivalent doses (mg/day).

Table 2
Baseline mean scores in each subgroup.

	REHACOP group				Active control group			
	Low baseline level (n = 45)		High baseline level (n = 49)		Low baseline level (n = 47)		High baseline level (n = 41)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	0.39	0.93	−0.35	0.86	0.35	0.99	−0.42	0.95
Education (years)	−0.25	0.91	0.31	0.99	−0.36	0.95	0.32	0.98
Neurocognition	−0.68	0.75	0.74	0.77	−0.67	0.69	0.63	0.71
Social cognition	−0.60	0.70	0.67	0.81	−0.60	0.83	0.55	0.85
Functional outcome	−0.54	0.89	0.61	0.71	−0.70	0.88	0.66	0.59
Negative symptoms	0.19	0.96	−0.44	0.93	0.55	0.86	−0.31	0.94

SD = Standard Deviation. Means are represented in Z-scores.

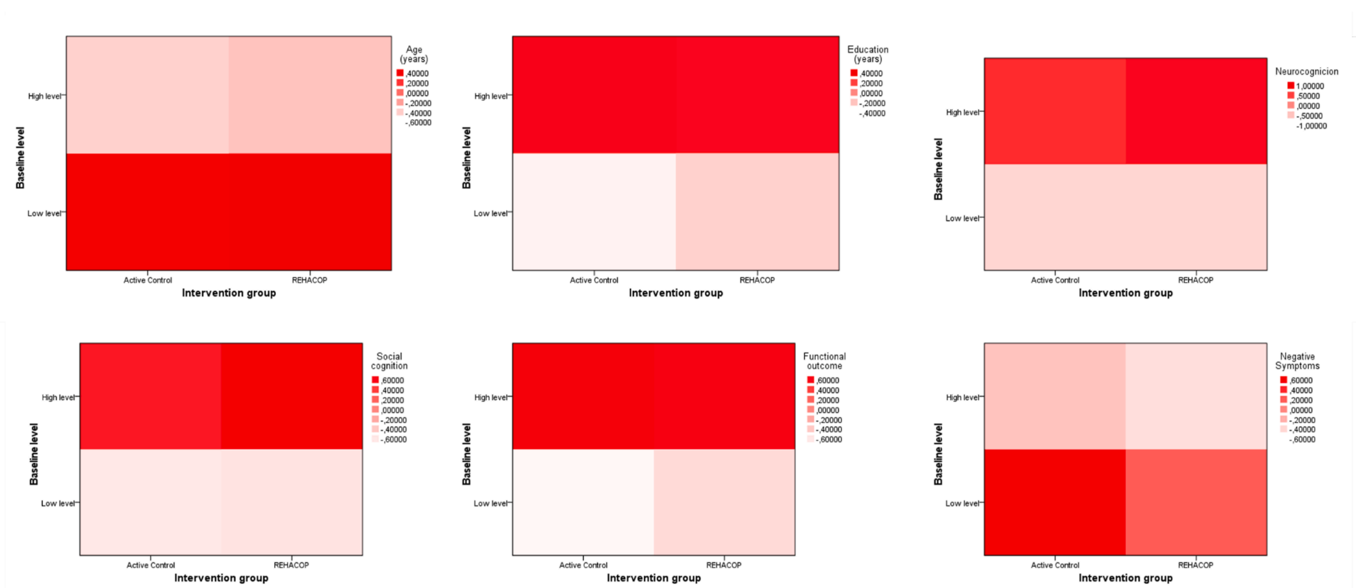

Fig. 1. Heatmap representing baseline mean scores in each subgroup.
This heatmap shows baseline means in each of the four subgroups formed by the two intervention groups (REHACOP group and active control group) and the two cluster groups (baseline low-level group or high-level group). Baseline means are represented in Z-scores.

4. Discussion

The present study aimed to examine the role of multiple baseline characteristics as moderators of the improvement in functional outcome after integrative cognitive remediation in schizophrenia. As far as the authors are aware, few studies (Bell et al., 2014; Tan et al., 2020) have

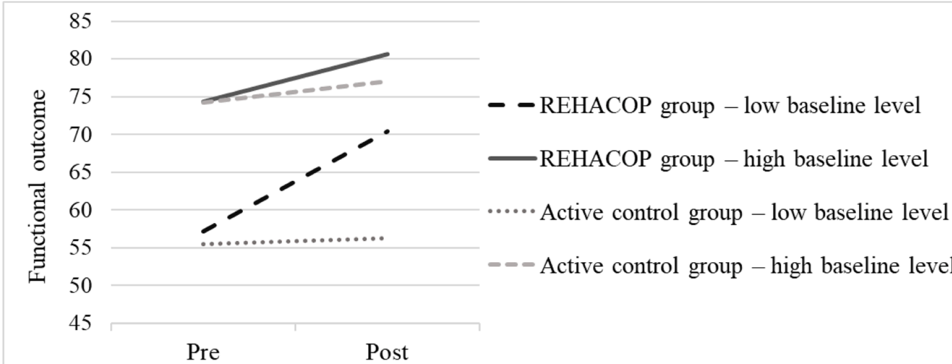

Fig. 2. Effects of baseline level in the improvement of functional outcome after the intervention.
This figure shows longitudinal changes in functional outcome in the four subgroups formed by the two intervention groups (REHACOP group and active control group) and the two cluster groups (baseline low-level group or high-level group).

analyzed which factors moderate improvement in functional outcome after implementing an integrative cognitive remediation program; specifically, one that combines cognitive training with training in other skills (e.g., functional or social skills) in patients with schizophrenia using a statistical interaction including both an experimental and a control group.

The results from this study indicate that multiple factors significantly moderate functional improvement after integrative cognitive remediation. Specifically, the REHACOP program had a stronger effect on functional outcome among those participants who were older, spent fewer years in education, had lower scores in baseline cognition and functional outcome, and experienced more negative symptoms. Moreover, the baseline level cluster variable played a moderating role in the improvement of functional outcome after the interventions, showing that the low-level group obtained greater improvements from the cognitive remediation program than the high-level group. These findings were in line with the results from a recent meta-analysis (Vita et al., 2021) in which more compromised patients were found to show greater improvements after cognitive remediation. In addition, the meta-analysis by Lejeune et al. (2021) found that the chronicity of the disease moderated improvement in functional outcome, with the more chronically ill individuals experiencing greater improvement. Although in this meta-analysis no other variables moderated functional improvement, some variables such as education level and estimated IQ did moderate cognitive improvement, with those who had lower educational attainment and IQ level showing greater cognitive improvements (Lejeune et al., 2021). The trend toward greater functional improvement in this patient profile has been observed in studies with different psychiatric populations, including schizophrenia, schizoaffective disorder and bipolar disorder (Bell et al., 2014; Rodewald et al., 2014; Tsapekos et al., 2022; Twamley et al., 2011). However, these results differ from other studies in which younger patients or participants with a higher baseline cognitive and functional levels have been associated with greater improvements (Lindenmayer et al., 2017; Seccomandi et al., 2021b). These differences between studies may be partly due to methodological differences, including the lack of a control group, the type of intervention (e.g., only cognitive training vs. integrative programs including social and functional skills training), or the assessment instrument used (performance-based skill assessment vs. questionnaire for assessing functional outcome), which precludes a direct comparison of results. With respect to other studies using integrative cognitive remediation programs, Bell et al. (2014) also found that patients with a worse baseline functioning showed a greater improvement in functional outcome. In contrast, Tan et al. (2020) obtained no significant results in functional outcome improvement, probably partly due to the kind of intervention of the active control group as well as the lack of a long-term follow up, as suggested by the authors. Nevertheless, in the same direction as these results, Tan et al. (2020) did find that a worse baseline cognition explained greater cognitive improvement.

One of the reasons for the disparity between the results across studies is the measure used for the assessment of functional outcome. In this study functional outcome was measured by the UPSA, a performance-based measure of functional competence. This measure was selected, firstly, because it was the measure of functionality that was used in both clinical trials, for which statistically significant differences were found. Secondly, it was chosen because it assesses functional abilities based on performance in the simulation of several real-world tasks (e.g., paying bills or scheduling medical appointments) (Garcia-Portilla et al., 2014). In contrast to other self-reporting or clinical ratings questionnaires, this tool approximates the measurement of real-world functioning by reducing the influence of environmental and social factors, as well as informant bias and low insight (Garcia-Portilla et al., 2014; Heinrichs et al., 2006). Nevertheless, it should not be overlooked that the UPSA measures functional capabilities in an artificial environment and therefore may not be fully equivalent to real-world functioning (Patterson et al., 2001).

The results from the present study suggest that, while patients with lower educational and cognitive levels are particularly vulnerable to difficulties in daily functioning, this profile of patients may also benefit more from cognitive remediation and, therefore, should be an important focus of healthcare services. Moreover, these results may provide evidence in favor of the differential susceptibility model (Belsky et al., 2007), which suggests that those who are more vulnerable to having negative outcomes under adverse environmental conditions may also gain most from interventions or enriched environments. Some people may be more susceptible to environmental factors, both *for better and for worse* (Belsky et al., 2007).

It should be noted that although the effectiveness of integrative cognitive remediation with the REHACOP differed depending on the baseline characteristics of patients, improvements in functional outcome in the REHACOP group compared to the active control group were found in both patients with a low baseline level and a high baseline level. This suggests that cognitive remediation is an effective intervention for most individuals with schizophrenia, regardless of their baseline characteristics (Vita et al., 2021) and it should therefore be included in the treatment plans of healthcare services.

4.1. *Toward personalized treatment plans*

Results from this study have important implications for the development of personalized medicine, and in particular, for personalized cognitive remediation plans for the treatment of schizophrenia. Personalized medicine is the methodical adaptation of medical treatments to tailor healthcare to each individual (Medalia et al., 2018).

Specifically, identifying the baseline factors that explain the greater improvement produced by cognitive remediation could be useful for several purposes: (1) in order to identify the profile of patients who will benefit the most, so that when there is a scarcity of healthcare resources they can be used appropriately; (2) in term of adapting and modifying the design of intervention programs to increase benefits among those who seem to benefit less; and ultimately, (3) to develop and implement personalized cognitive remediation plans for each individual.

The moderating factors identified in this study could provide some indication as to how to tailor interventions to enhance their benefits. According to these results, while most patients benefit from cognitive remediation, those whose functioning is more compromised seem to benefit more. However, it should be mentioned that although the degree of improvement was greater in patients with a low baseline level, this group still achieved lower scores than the high-level group. This will inform treatment planning and how to modify interventions based on each patient's baseline level. Since patients with a lower baseline level have even more room for improvement, this profile of patients could further benefit from longer and more intense interventions (with more exercises). Additionally, by increasing the difficulty of the intervention, greater benefits may be obtained by those patients who start from a higher baseline level. This could be carried out through intervention programs that are flexible in terms of how they are implemented and adapted to the characteristics of the patients. For instance, in the case of the REHACOP program used in this study (Ojeda et al., 2012), the difficulty of the tasks may be increased by having shorter time limits or increasing the level of demand by modifying the instructions in the exercises. Moreover, interventions using the REHACOP program can be extended (e.g., increasing the total number of weeks) by including additional exercises (it contains more than 300 exercises). As indicated in the meta-analysis by Vita et al. (2021), longer treatment duration results in greater functional gain. Similarly, the Cognitive Remediation Expert Working group (Bowie et al., 2020), advised that in cognitive remediation programs that also work on functional skills (such as REHACOP or other specific functional skills training programs) (Patterson et al., 2006), patients could be trained by using more complex functional activities and real-life scenarios. This would promote greater improvement in these abilities and facilitate further generalization and transfer to real world functioning.

In addition to the baseline profile of the patients, another strategy that could be of interest in optimizing interventions would be to design intervention programs taking into account mediators of treatment response. Several studies have identified mediators of functional improvement after cognitive remediation in schizophrenia, such as verbal memory, executive functions or social cognition domains (Eack et al., 2011; Fiszdon et al., 2008; Peña et al., 2018; Sampedro et al., 2021; Sánchez et al., 2014). The results from these studies have provided some useful indications on how to optimize treatment by focusing training on those areas that seem to mediate greater functional improvement.

In line with other authors (Medalia et al., 2018), we suggest that future research on cognitive remediation should consider the heterogeneity of subjects and design clinical trials using a personalized cognitive remediation approach. As indicated by Medalia et al. (2018), a useful tool for this purpose could be a Sequential Multiple Assignment Randomized Trial (SMART), which relies on an adaptive treatment strategy based on both baseline patient characteristics and intermediate evaluations of response to treatment. However, this has rarely been used with psychiatric populations (Nelson et al., 2018). Once the effectiveness of these clinical trial designs based on personalized medicine has been demonstrated, the next step could be to implement personalized plans in healthcare services, offering integrative and holistic treatment plans that consider the person as a whole. There are also other alternative methods that have been proposed to select the optimal subgroup of patients for a specific treatment in different conditions (e.g., when resources are constrained) based on multiple covariates (Vanderweele et al., 2019).

Several limitations to this study should be acknowledged. Data from two different randomized control trials with almost identical study design was used, but there may have been some small differences in the implementation of the clinical trials. This includes the fact that some intervention group ($n = 15$) sessions were conducted during the COVID-19 pandemic. Nevertheless, the "study variable" was entered as a covariate in order to control for its possible influence. Another limitation concerns the study's sample size. Although this was greater than in the majority of the studies about moderators of cognitive remediation in schizophrenia (Seccomandi et al., 2020), it would be more appropriate to use much larger samples in order to conduct a moderation analysis with adequate statistical power. Finally, it would have been interesting to assess moderators of long-term functional improvement, but the present study lacked further follow-up assessment.

Despite these limitations, the results from the present study provide substantial information for the development of strategies aimed at applying the principles of personalized medicine to cognitive remediation; ultimately, this would be intended to offer integrative and personalized cognitive remediation plans to individuals with schizophrenia. In addition, these findings suggest that, while the most severely affected individuals are most at risk of social exclusion and functional dependence, the negative impact can be reduced through interventions such as cognitive remediation. This therefore reinforces the need to include these interventions more widely in the treatment plans of healthcare services, with a view to preventing social exclusion among individuals with schizophrenia.

Data availability

The data that support the findings of this study are available from the corresponding author on reasonable request. The data are not publicly available because they contain information that could compromise research participant privacy or consent.

Role of funding source

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CRediT authorship contribution statement

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Declaration of Competing Interest

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

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Supplementary materials

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