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REPYFLEC cognitive remediation group training in schizophrenia Looking for an integrative approach

Aida Farreny *, Jaume Aguado, Susana Ochoa, Elena Huerta-Ramos, Ferran Marsà, Raquel López-Carrilero, Vanessa Carral, Josep Maria Haro, Judith Usall

Parc Sanitari Sant Joan de Déu, Fundació Sant Joan de Déu, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Sant Boi de LLobregat, Barcelona, Spain

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ABSTRACT

Background: Overall results from Cognitive Remediation (CR) indicate robust and long-lasting effects with medium effect size on global cognition and functioning, and a small ES on symptoms present at post-treatment but not at follow-up. However, results are not the same in all CR therapies and in some cases no efficacy results are achieved.
Aims: To develop an integrative intervention taking into account previous efficacious therapies. To evaluate the efficacy of our cognitive remediation group training: Problem Solving and Cognitive Flexibility training (REPYFLEC), with the aim of improving cognition and functioning in schizophrenia patients.
Method: Participants with a diagnosis of schizophrenia or schizoaffective disorder (n = 62) were randomized to 32 group sessions of REPYFLEC CR, or to 32 group sessions of activities without specific objectives and focused on leisure. In both groups the sessions were conducted twice a week. Functioning and psychiatric symptoms were measured at baseline (week 0) and thereafter at 8, 16 and 40 weeks. Cognition was measured at weeks 0, 16 and 40. Mixed Models were used to estimate statistical differences.
Results: Patients in the cognitive remediation group demonstrated significant improvements in executive function, negative symptoms and functioning at post-treatment compared with patients in the control group. At 6-month follow-up, significant improvements in executive function and functioning remained.
Conclusion: These results apparently show that REPYFLEC works as cognitive remediation training, improving executive thinking and functioning outcomes compared with a control group.

1. Background

Cognitive impairment has been shown to have a prognostic value regarding whether a person with schizophrenia will be able to meet functional goals (Green et al., 2004; Medalia and Choi, 2009). To date, voluminous evidence has accumulated to support the potential to affect cognitive impairment in schizophrenia through cognitive remediation interventions. As defined by the Experts Committee in 2010, Cognitive Remediation (CR) consists of "behavioral training-based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization" (Wykes et al., 2011). According to Kurtz et al. (2007) we know that CR effects are durable up to at least 6 months after the therapies are withdrawn, particularly in terms of executive ability, and working and verbal memory and that these neurocognitive gains can be translated to improvements in social behavior and symptoms, real-world problem-solving ability and occupational outcome. Overall results from CR metanalyses indicate robust and long-lasting effects with medium effect size (ES) on cognition and functioning, and a small ES on symptoms at post-treatment but not at follow-up (McGurk et al., 2007; Wykes et al., 2011). However, successful results are not equally achieved in all CR therapies. For instance, two current randomized, controlled trials on CR were effective in improving performance on computer exercises but did not generalize to broader neuropsychological or functional outcome measures (Dickinson et al., 2010; d'Amato et al., 2011). In a recent meta-analysis of computer-assisted CR, the results revealed a significant overall effect with small effect size only on cognitive measures (Grynszpan et al., 2011). This may seem paradoxical if we do not bear in mind that CR therapies differ in name, mode of operation, treatment times, the presence of a therapist, and whether they are provided to individuals, groups, or both. Some programs build practice on a specific skill set, whereas others build practice around different tasks where the strategies might be the same but are generalized across tasks with different formats (Wykes and Spaulding, 2011). Another issue that could affect training effects involves the directional approach to the training curriculum: "Bottom-up" and/or "Top-down" interventions (Roder et al., 1996; Medalia and Richardson, 2005). But these differences between CR treatments did not seem to have an impact in the meta-analysis by

* Corresponding author at: Dr. Antoni Pujadas, 42, Sant Boi de Llobregat, 08830 Barcelona, Spain.
E-mail address: afarreny@pssjd.org (A. Farreny).

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McGurk et al. (2007), providing no evidence of a lack of homogeneity of effects in global cognition between separate studies; so suggesting that most were equivalent. And the recent meta-analysis by Wykes et al. (2011) did find some heterogeneity in global cognition that allowed the investigation of therapy differences but found no therapy characteristics that explained the variation in cognitive outcome.

This leads us to ask why CR interventions with distinct methodologies achieve both cognitive and functional aims and others do not. What are the ingredients for developing successful CR treatments? What elements are less appropriate?

Taking into account this background, we developed a mixed approach, joining differentiated theoretical features from previous successful CR therapies in a single intervention with the goal of achieving better understanding and performance in CR. Firstly, we chose two differentiated Models from CR to understand our training basis: Model of vicious circles by Brenner et al. (Brenner et al., 1992), adapted by Penadés et al. (Penadés et al., 2003); and the Model of Cognitive Remediation Therapy by Wykes and Reeder (2005). Next, we created a Problem Solving and Cognitive Flexibility group treatment called REPYFLEC *(Resolución de Problemas y Flexibilidad Cognitiva)*. Its contents and the training context have been mainly adapted from three efficacious therapies: Integrated Psychological Therapy (IPT; Brenner et al., 1992; Roder et al., 1996), Cognitive Remediation Therapy (CRT; Delahunty et al., 2002; Wykes and Reeder, 2005) and Neuropsychological Educational Approach to Cognitive Remediation (NEAR; Medalia and Richardson, 2005; Medalia and Freilich, 2008). For instance, elements used in REPYFLEC adopt a top-down focus to intervention in Problem Solving as proposed in IPT or NEAR, and more bottom-up tasks in Cognitive Flexibility training as proposed in CRT *(See Therapy for further details)*.

Subsequently, with the development of REPYFLEC CR, our aim was to assess its efficacy conducting a single-blind, randomized and controlled trial. The primary outcomes were executive function and memory that could be directly improved by REPYFLEC. Functioning and psychiatric symptoms would be assessed as secondary outcomes so we expected improvements through treating executive function and metacognition.

2. Method

2.1. Design

A single-blind, randomized, controlled clinical trial was developed in which the psychologists carrying out the assessment were blinded to the treatment until the conclusion of the study. The experimental group took part in 32 group sessions of REPYFLEC cognitive training and the control group received 32 group sessions dedicated to leisure and socialization. The participants were assigned to the experimental and control groups through a randomization procedure once the baseline assessments had been performed. This clinical trial is registered at *ClinicalTrials.gov*: NCT01279070 and was approved by the Parc Sanitari Sant Joan de Déu Ethics Committee.

2.2. Participants

Participating in the study were 62 outpatients from the Barcelona metropolitan area, who were known to the Parc Sanitari Sant Joan de Déu Mental Health Services, with a diagnosis of schizophrenia or schizoaffective disorder (American Psychiatric Association, 2002). Patients were included if: 1) they had a diagnosis of schizophrenia or schizoaffective disorder and more than 2 years' illness duration; 2) they had finished primary studies or they were able to successfully complete a reading comprehension task used for 13-year-old students; and 3) if they had a Mini Mental State Examination score of 24 or more and a Global Assessment of Functioning score between 40 and 70. Patients were excluded if: 1) they were suffering acute illness exacerbation; 2) they had intellectual disability or any neurological disorder; 3) they were participating in social skills training, cognitive remediation or any other psychological intervention differing from usual care; 3) they had had a switch of antipsychotic drug the month before the trial or during the 40 week study period; 4) and/or a diagnosis of alcohol or drug dependence within 6 months prior to inclusion.

To confirm the stability of the diagnosis we checked the medical history to corroborate that the DSM-IV criteria required were appropriately described inside. We found two unconfirmed cases so we used the Structured Clinical Interview for DSM-IV (SCID; First et al., 1996) to verify the diagnoses. In one of these cases, Schizophrenia diagnosis was changed to Bipolar Disorder and this patient was excluded. In the other case the diagnosis was maintained.

2.3. Therapy

REPYFLEC CR is a strategy-based training that targets executive function and metacognition. It is carried out using paper and pencil and a blackboard (required to develop some of the tasks, explanations, examples, etc.); in a group format (4–6 participants), over 4 months twice a week and consisting of 32 sessions lasting 1 h. We developed a Spanish manual where training is described session by session; incorporating the materials for developing sessions, some theoretical points and bibliography for therapists. Working contents are divided into two main areas: Problem Solving (PS) and Cognitive Flexibility (CF).

In the PS module (16 sessions), training in executive function, thinking processes and self-monitoring was emphasized. The PS aims were: (1) to provide a structured mechanism for dealing with everyday problematic situations, (2) to train executive function and metacognition, (3) to train participants to recognize problems, find appropriate solutions and choose their best solutions for each situation, (4) to promote active coping through tasks, practicing and training techniques and, (5) to encourage both transfer and generalization to everyday life. On the whole, sessions combine the training for a reflexive understanding about problematic situations with strategy-teaching on how to achieve better monitoring of these situations; training in cognitive–emotional processes which could be involved; and repeated practice in several hypothetical problems that are expressly designed for REPYFLEC CR.

In the CF module (16 sessions), all the tasks require practice of cognitive flexibility combined with other executive abilities such as planning or self-monitoring. The CF aims were: (1) to train cognitive flexibility, (2) to exercise reasoning and imagination, (3) to affect more automatic cognition including working and verbal memory, attention and processing speed and (5) to train empathy. Tasks in the CF module mainly focus the strategy-training on the ability to produce an increasing amount of responses with growing variety between them. Exercises aim to generalize from more basic tasks (e.g. shift cognitive sets; train flexible categorization straightening an office up; plan several routes to walk from one place to another; count elements in a picture using different strategies to count them; finish a story with variety of endings; etc.) to upper cognitive components related to social knowledge (such as reporting as many advantages and disadvantages as possible from the same situation: being a child, living in a shared flat with no-relatives, having lot of siblings, etc.; or to be able to make the case for both sides in a debate).

As mentioned above, REPYFLEC is mainly composed of elements from IPT (Roder et al., 1996), NEAR (Medalia and Freilich, 2008) and CRT (Wykes and Reeder, 2005), despite the materials and contents are particular to our training. REPYFLEC shares integrating skills training to stimulate cognitive tasks in real life with IPT and NEAR as well as problem solving contents and an approach that aims at both "top-down" and "bottom-up" intervention. From this perspective, cognitive deficits are not seen simply as a manifestation of

neuropsychological dysfunction, but as a social - cognitive dysfunction. This view achieves an interactive approach in learning processes, taking into account cognitive, emotional and social needs in people with schizophrenia using the group format (Medalia and Freilich, 2008). Regarding CRT, REPYFLEC shares the interest in cognitive flexibility and planning training, as well as the learning context proposed by Wykes and Reeder (2005), which develop specific strategies and techniques to improve cognitive performance (self-monitoring, scaffolding, errorless learning, etc.) in the context of CR.

Parallel to the experimental group, a leisure control group was established which participated in 32 stimulating and socializing activities (e.g., card games, board games, "coffee & talk", etc.).

2.4. Outcome measures

2.4.1. Cognition

Behavioral Assessment of the Dysexecutive Syndrome (BADS) (Wilson et al., 1996). This scale evaluates cognitive flexibility, inhibition of impulsive responses, planning and organization, working memory and time-estimation capacity. All subscales (Rule shift cards, Action Program, Key search, Temporal judgement, Zoo map and Six elements) were administered. We used subscales raw scores which run from 0 to 4 and standardized score for total score (min. 12–max. 129). A higher score indicates better performance. *The Trail Making Test (TMT)* (Reitan, 1958; Fernández et al., 2002) evaluates attention, processing speed and cognitive flexibility. Raw scoring measured in seconds was used. Some *Wechsler Memory Scale-III (WMS-III)* (Wechsler, 2004) subscales were selected with the aim of assessing verbal and visual memory (*Texts I* and *II*, and *Scenes I* and *II)*. Raw scores were used.

2.4.2. Functioning

The Spanish validation of the *Life Skills Profile (LSP)* (Rosen et al., 1989; Fernández de Larrinoa et al., 1992) was used. This scale measures functionality in daily life activities such as self-care, social behavior and autonomy. Raw scoring was used for the various subscales and for the total (min. 39–max. 156) with a higher score indicating a better result. The 5 subscales are: Self-care, Non-turbulence, Social contact, Communication and Responsibility. We used the Spanish validation (Torres and Olivares, 2005) of the *Social Functioning Scale (SFS)* (Birchwood et al., 1990) for measuring social behavior and relationships, autonomy, employment-occupation and leisure. Raw scoring was used for each subscale and for total score (min. 0–max. 223) with a higher score indicating a better result. All 7 subscales were administered: social engagement/withdrawal, interpersonal behavior, independence-competence, independence-performance, pro-social activities, recreation and employment/occupation.

2.4.3. Psychiatric symptoms

The Spanish validation (Peralta and Cuesta, 1994) of the *Positive and Negative Syndrome Scale (PANSS)* (Kay et al., 1987) was used for measuring positive, negative and general symptomatology. Raw scoring was considered (min. 0–max. 210) with a score of 0 representing an absence of psychiatric symptoms.

2.5. Procedure

The procedure for sample collection began with the recruitment of outpatients from our mental health services. Users who met inclusion criteria attended a first interview where they signed an informed consent form, underwent the screening tests and were administered a demographic questionnaire. If it was considered that the individual met study criteria, two further interviews were arranged to perform the rest of the assessment. Once the baseline evaluation had been completed, an independent researcher carried out randomization using a random number list. Subsequently, both activity groups (REPYFLEC CR and control group) began at the same time. Participants in both groups were assessed at baseline, at 8 weeks of treatment (with the exception of the neuropsychological tests which were not administered at this time to avoid learning effects); at 16 weeks (post treatment) and at 40 weeks (follow-up).

2.6. Statistical analysis

A comparison of sociodemographic and clinical variables was made between the treatment groups at baseline using the Fisher's Exact Test in the case of categorical variables, and the Student's *t*-test or the Mann–Whitney U-test for continuous variables. To evaluate intervention efficacy, linear mixed-effects models were fitted using Restricted Maximum Likelihood (REML). An unstructured correlation matrix was used to account for correlation among several observations for each subject. The dependent variable comprised the measures at 2, 4 and 10 months while the baseline value of the response variable, intervention group (treatment *vs* control), time and the interaction term (time × treatment) were included as covariates. When the interaction was significant in the model, the effect of treatment was considered to vary during the course of the study. When this interaction term was not significant, the model was fitted again without this variable and a significant intervention group effect was interpreted as a result of treatment consistent over the course of the study. In all the models, adjusted mean difference between the two intervention groups, standardized treatment effect (ES) and confidence intervals were calculated. The ES is normally categorized as small (0.2), medium (0.5) or large (0.8) (Roder et al., 2006). The cross-sectional treatment effect at 40 weeks was specifically assessed with estimates derived from the linear mixed-effect models. All the estimates obtained with these models remain unbiased under the missing at random (MAR) assumption; that is missingness of observations can be predicted by group membership and earlier values of the outcome variable without introducing bias.

The statistical analyses were carried out using SPSS 17.0 and SAS 9.1.3. Statistical significance was set at 0.05 in all tests.

3. Results

Sixty-two participants were recruited for this trial, of which 34 were randomized to REPYFLEC cognitive training and 28 to the control group (Fig. 1). As can be seen, there is a greater number of subjects in the experimental group and this is due to the fact that the participants included at first recruitment (N = 17) were not sufficient to form 2 experimental and 2 control groups. The result was 2 experimental groups and 1 control group. The participants were distributed through the same procedure of random numbers to the 3 groups.

Two thirds of the participants were male (68%); 84% were single; 80% lived with their family of origin and 80% had completed at least 8 years of formal education. Some 89% of participants had a diagnosis of schizophrenia (n = 54), principally paranoid-type (n = 35); and the remaining 11% (n = 7) of schizoaffective disorder. The average age was 40.6 years (SD: 7.6) and average illness duration was 17.5 years (SD: 8.9). During the year prior to the study, 80% of the participants had not engaged in any type of work, occupational or academic activity, and did not have responsibility for any household chores. Nevertheless, 63% of the sample attended a rehabilitation centre almost daily.

No statistical differences were found between groups at baseline in sociodemographic, clinical, symptomatological or cognitive variables (Table 1); and nor were significant differences found between those experimental and control subjects who abandoned the study. The baseline difference between groups regarding whether they were taking typical antipsychotics, atypical or combined therapy was not statistically significant ($\chi^2 = 1.99$; $df = 2$; $p = 0.37$); and nor were significant differences found between the average doses of

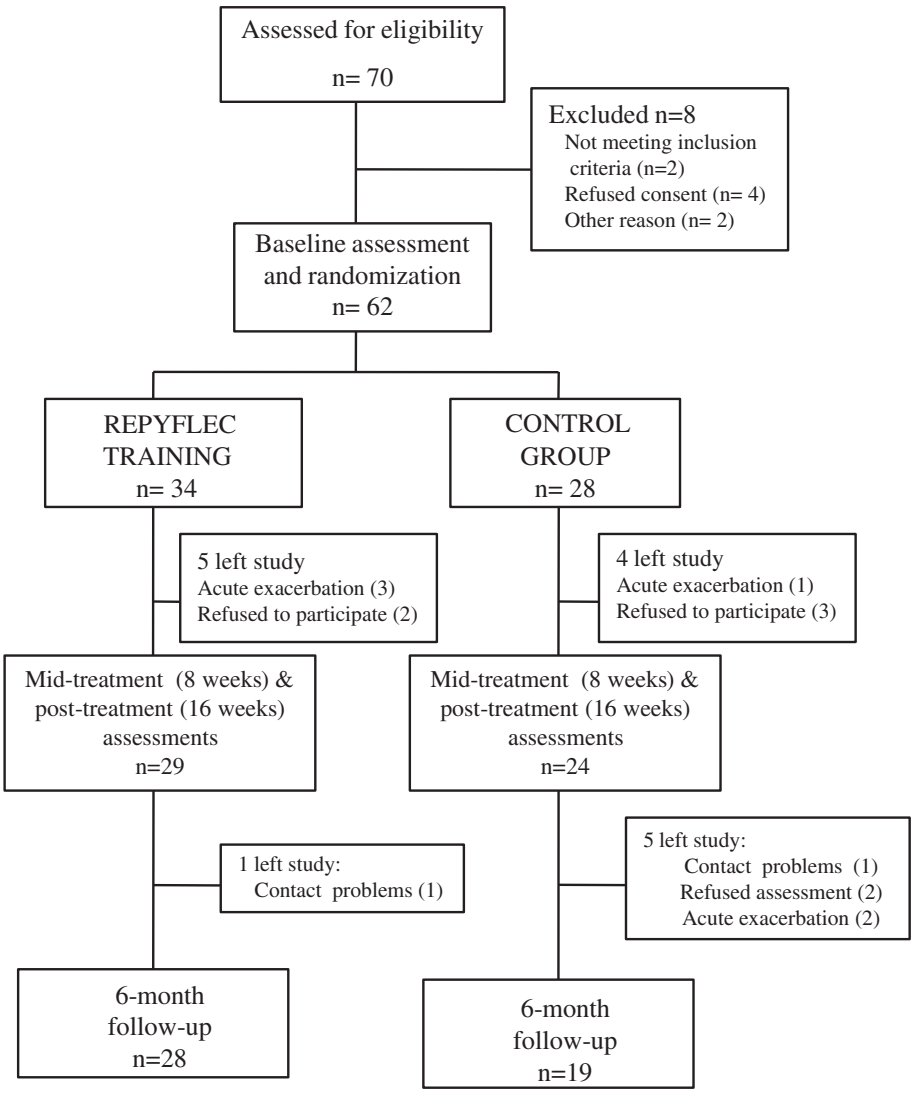

Fig. 1. Study flow diagram.

antipsychotic ($t = 0.17$; $df = 59$; $p = 0.86$) that were expressed in terms of risperidone equivalence (Andreasen et al., 2010); or between the control and experimental groups in benzodiazepines and/or antidepressive medication which they received as complementary treatment ($\chi^2 = 1.96$; $df = 3$; $p = 0.79$).

3.1. Outcomes of therapy: efficacy study

As would be expected after random treatment allocation, there were no differences between the two groups at baseline in any of the outcome measures. Cognition, functioning and psychiatric symptoms scores at each assessment point are described in Table 2.

Variables in which a superior and statistically significant change was produced favored the experimental group in every case. Table 3 shows the results of 2 differentiated analyses: the first part shows the results of the longitudinal model at post-treatment. The second part includes the follow-up evaluation in the longitudinal models and the specific assessment of the cross-sectional effect at 40 weeks. Comparison of both types of analysis allows identification of which variables maintain a more consistent effect at follow-up.

In the assessment at 8 weeks (mid-treatment), no significant differences were found between groups in any of the variables studied (results available upon request). Regarding post-treatment cognition, a group effect was found in the executive function total score (BADS), especially in planning and monitoring (Key search test), as with cognitive flexibility in TMT B. At follow-up, the improvements in the BADS were maintained with a medium ES. Regarding memory tasks, no differences were found between experimental and control groups, but both showed better raw scores after treatment and at follow-up than at baseline.

In functioning outcomes at post-treatment, a group effect was found in the LSP and SFS total scores with a small to medium effect size, as was the case in the self-care, social contact and occupation subscales. At follow-up, according to the results obtained in the longitudinal mixed models, the group effect was maintained with a small to medium effect size in the self-care, social contact and occupation variables and in the total score of two social scales. However, in the transversal analysis which compared the groups at follow-up, the social engagement subscale and the SFS total score ($p = 0.07$) lost significance. The significant improvements which remained were found in the LSP total score with a small to medium effect size, mainly in the LSP self-care and social contact subscales; as well as in the SFS employment-occupation subscale with a medium ES.

With respect to psychiatric symptoms, a significative interaction effect was obtained at post-treatment in negative symptoms with a small to medium ES. At follow-up, no significant differences were obtained in psychiatric symptoms between groups in the PANSS total score or on any of its three subscales scores.

Table 1
Sociodemographic and clinical characteristics by treatment group.

Baseline sociodemographic variables	Experimental n = 34 n (%)	Control n = 28 n (%)
Gender		
Male	23 (67.6%)	19 (67.9%)
Female	11 (32,4%)	9 (32.1%)
Civil status		
Single	27 (79.4%)	25 (89.3%)
In a relationship	6 (17.6%)	1 (3.6%)
Divorced, widow	1 (2.9%)	2 (7.2)
Education		
Primary	22 (64.7%)	16 (57.2%)
Secondary	9 (26.4%)	6 (21.5%)
Higher	3 (8.8%)	6 (21.5%)
Housing		
Alone/own family	6 (17.7%)	4 (13.7%)
Family of origin	27 (79.4)	23 (75%)
Goverment services	1 (2.9)	1 (3.6)
Hospitalizations (total)		
0	7 (20.6%)	9 (32.1%)
1	6 (17.6%)	10 (35.7%)
2	11 (32.4%)	4 (14.3%)
3 or more	10 (29.4%)	5 (17.9 %)
Occupation (last year)		
Unemployed (on the dole)	2 (5.9%)	2 (7.1%)
Student	1 (2.9%)	0 (0%)
Daily-living tasks	1 (2.9%)	2 (7.1%)
Supervised work	3 (8.8%)	1 (3.6%)
No occupation	27 (79.4%)	23 (82.1%)
Clinical variables:		
Baseline antipsichotic doses (risperidone mg.)		
Mean (SD)	9.37 (6.99)	9.66 (5.93)
Group sessions attended		
Median (min.-max.)	27 (min.: 21–max.:32)	29 (min.: 20–max.:32)

4. Discussion

The main finding of this study is that REPYFLEC seems to give good results as CR training, producing a positive change in executive function and daily living competences in outpatients with schizophrenia and schizoaffective disorder in comparison with an active control group. These improvements are largely maintained six months after completion of the intervention. In addition, REPYFLEC could apparently be influencing the improvement in symptomatological variables such as negative symptoms.

Cognitive outcomes showed an improvement in executive function which is maintained at follow-up. This aspect is interesting due to the probable relationship between the improvement in executive function and that in functioning (Reeder et al., 2006; Üçok et al., 2006; Penadés et al., 2010; Wykes et al., 2012). However, we observe that differential gains do not exist in other areas such as verbal memory where we could expect a non-specific effect, for instance, from strategy training (Kurtz et al., 2001).

With respect to functioning, the group effects indicate a positive change in favor of the experimental group in the scores of the two scales, which tested life skills and psychosocial functioning. The majority of the improvements observed at post-treatment were maintained at follow-up, particularly in the areas of self-care, social behavior and employment-occupation.

Concerning psychiatric symptoms, the differential effect in favor of REPYFLEC in the negative symptoms subscale is an especially interesting result. Negative symptoms are the most difficult to treat both pharmacologically and through psychological therapies while, at the same time, these symptoms may be interfering to the greatest extent in functioning. It has been reported that only those inpatients who received problem-solving remediation significantly improved on the PANSS measures (Bark et al., 2003). At follow-up, the main results in negative symptoms were not maintained and we could not draw conclusions regarding the effect of REPYFLEC in this dimension. It was observed that the effects of cognitive remediation on symptoms are small and are mainly found as long as the interventions last (Twamley et al., 2003; McGurk et al., 2007; Wykes et al., 2011). We contemplate that more research would be necessary to reach a better understanding of the role of negative symptoms in CR interventions.

Based on these results and our treatment characteristics, we would consider that these achievements are associated with four main aspects:

Firstly, to the training of executive function and metacognition. Other authors have underlined the benefits of PS in the treatment of schizophrenia (e.g. Brenner et al., 1992; Medalia et al., 2002; Medalia and Freilich, 2008) as well as in the relevance of CF, which has been related to the transfer of knowledge to different situations, and with the generalization of new cognitive schemas (Green et al., 2004; Reeder et al., 2006; Üçok et al., 2006; Wykes et al., 2007).

Secondly, to the group and learning context, as we were able to observe that strategy-based tasks and training techniques to improve

Table 2
Scores on outcome variables.

Outcome measures	Experimental				Control			
	Baseline	8 weeks mid-treatment score	16 weeks post-treatment score	40 weeks follow-up	Baseline	8 weeks mid-treatment score	16 weeks post-treatment score	40 weeks follow-up
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
BADS standard total	83.7 (20.4)	NA	99.5 (14.5)	101.8 (10.1)	88.5 (16)	NA	95.7 (13.5)	94.5 (14.7)
BADS key search	2.2 (1.4)	NA	2.7 (1.2)	3 (1.1)	1.9 (1.4)	NA	1.7 (1.3)	1.7 (1.4)
TMT trail B (sec.)	145.3 (83.3)	NA	105.7 (48.9)	95.9 (33)	122.9 (74)	NA	119.2 (77.6)	91 (38)
WMS ST verbal	23.6 (11.6)	NA	25 (12.7)	27.2 (12.2)	26.5 (10.5)	NA	29.3 (11.6)	33.8 (10.9)
WMS LT verbal	12.3 (7.5)	NA	14.1 (9.3)	16.3 (9.8)	15.3 (7.7)	NA	16.6 (8.8)	21.1 (7.9)
LSP total score	126.7 (15.5)	133 (9)	137.4 (6.9)	135.7 (7.7)	131.8 (11.3)	132 (10.6)	133.6 (11.4)	132.9 (12)
LSP Social behavior	35.8 (4.1)	36.9 (2.6)	38.3 (2)	37.8 (1.8)	36.6 (3)	36.4 (2.6)	37 (2.5)	36.5 (3.2)
LSP Self care	34.8 (4.9)	36.2 (3)	37.6 (2.1)	36.8 (2.3)	35.8 (3.6)	35.1 (3.4)	35.8 (4)	35.2 (4.7)
SFS total score	104.1 (19.9)	108.3 (17)	108.8 (17.6)	107 (16.5)	109.4 (18.3)	106.2 (20)	105.9 (19.3)	107.2 (14.8)
SFS Occupation	2.5 (2)	2.8 (2.7)	3.4 (2.5)	3.9 (2.8)	3.2 (2.8)	2.4 (2.6)	2.8 (2.2)	2.5 (2.1)
SFS Social withdrawal	10.2 (2.2)	11 (2.1)	11.6 (2.3)	11.1 (2)	11.5 (2.3)	11.2 (2.1)	11.4 (2.2)	11.6 (1.5)
Negative PANSS	19.2 (4.1)	17.1 (3.8)	16.6 (4.1)	17.6 (3.7)	18.1 (5.4)	16.4 (4.7)	17.5 (5.2)	16.9 (3.8)
PANSS total score	65.6 (9.4)	59.9 (10)	55.6 (10.6)	61.4 (9.5)	64.2 (13)	61.1 (13.4)	60.4 (12.3)	61.8 (10.5)

NA: Neuropsychological assessment was not carried out the second month of training to avoid the effects of learning.
SD: Standard desviation; ST: short term LT: Long term.

Table 3
Mixed effects models: efficacy results.

Outcome measures	Treatment phase				Follow-up phase				Cross-sectional effect at 40 weeks ES(95%)
	Interaction	Treatment effect (excluding non-significant interaction)	Estimated advantatge to REPYFLEC[1] (95% CI)	Standardised effect size (95% CI)	Interaction	Treatment effect (excluding non-significant interaction)	Estimated advantatge to REPYFLEC[1] (95% CI)	Standardised effect size (ES) (95% CI)	
Cognition									
BADS standard total	NA	$F_{(1,50)} = 7.75$ p = 0.008	7.8 (2.2–13.3) *	**0.43** (0.1–0.7)	$F_{(1,50)} = 0.00$ p = 0.971	$F_{(1,50)} = 7.75$ p = 0.008	7.5 (2.1–12.8) *	**0.42** (0.1–0.7)	**0.43** (0.03–0.88)
BADS key search	NA	$F_{(1,50)} = 9.13$ p = 0.004	0.8 (0.3–1.3) *	**0.57** (0.2–0.9)	$F_{(1,50)} = 0.26$ p = 0.615	$F_{(1,50)} = 11.79$ p = 0.001	0.8 (0.3–1.3) **	**0.6** (0.2–0.9)	**0.67** (0.23–1.12) *
TMT Trail B (sec.)	NA	$F_{(1,49)} = 5.54$ p = 0.023	34.4 (5–63.7)	**0.47** (0.1–0.9)	$F_{(1,49)} = 1.63$ p = 0.208	$F_{(1,49)} = 1.65$ p = 0.205	**NS**	**NS**	**NS**
WMS ST verbal	NA	$F_{(1,50)} = 0.54$ p = 0.464	**NS**	**NS**	$F_{(1,50)} = 0.05$ p = 0.830	$F_{(1,50)} = 0.60$ p = 0.444	**NS**	**NS**	**NS**
WMS LT verbal	NA	$F_{(1,50)} = 0.08$ p = 0.781	**NS**	**NS**	$F_{(1,50)} = 0.00$ p = 0.955	$F_{(1,50)} = 0.08$ p = 0.777	**NS**	**NS**	**NS**
Functioning									
LSP total score	$F_{(1,50)} = 1.82$ p = 0.183	$F_{(1,50)} = 6.06$ p = 0.017	4.2 (0.8–7.6)	**0.33** (0.06–0.6)	$F_{(2,50)} = 1.01$ p = 0.371	$F_{(1,50)} = 7.22$ p = 0.01	4.4 (1.1–7.7) *	**0.35** (0.09–0.6)	**0.43** (0.07–0.78)
LSP Social behavior	$F_{(1,50)} = 1.58$ p = 0.215	$F_{(1,50)} = 4.79$ p = 0.033	1.1 (0.1–2.1)	**0.32** (0.03–0.6)	$F_{(2,50)} = 0.88$ p = 0.423	$F_{(1,50)} = 6.64$ p = 0.013	1.2 (0.2–2.1)	**0.34** (0.07–0.6)	**0.46** (0.07–0.79) *
LSP Self care	$F_{(1,50)} = 0.60$ p = 0.442	$F_{(1,50)} = 7.47$ p = 0.009	1.5 (0.4–2.6) *	**0.37** (0.1–0.6)	$F_{(2,50)} = 0.35$ p = 0.709	$F_{(1,50)} = 8.55$ p = 0.005	1.5 (0.5–2.6)	**0.4** (0.1–0.6)	**0.43** (0.003–0.86)
SFS total score	$F_{(1,50)} = 0.07$ p = 0.790	$F_{(1,50)} = 5.24$ p = 0.026	6.3 (0.8–11.8)	**0.32** (0.04–0.6)	$F_{(2,50)} = 0.07$ p = 0.937	$F_{(1,50)} = 5.38$ p = 0.025	5.8 (0.8–11)	**0.3** (0.04–0.5)	0.28 (−0.03–0.59) p = 0.07
SFS Occupation	$F_{(1,50)} = 0.39$ p = 0.533	$F_{(1,50)} = 6.77$ p = 0.012	0.9 (0.2–1.6)	**0.35** (0.08–0.6)	$F_{(2,50)} = 1.28$ p = 0.286	$F_{(1,50)} = 6.33$ p = 0.015	0.8 (0.2–1.5)	**0.34** (0.07–0.6)	**0.62** (0.17–1.10) *
SFS Social withdrawal	$F_{(1,50)} = 0.78$ p = 0.382	$F_{(1,50)} = 12.38$ p = 0.001	1.3 (0.5–2) **	**0.57** (0.9–0.2)	$F_{(2,50)} = 0.72$ p = 0.492	$F_{(1,50)} = 10.49$ p = 0.002	0.9 (0.3–1.5) *	**0.42** (0.2–0.7)	**NS**
Psychiatric symptoms									
Negative PANSS	**$F_{(1,50)} = 4.64$ p = 0.036**	NA			$F_{(2,50)} = 2.74$ p = 0.074	$F_{(1,50)} = 0.30$ p = 0.584	**NS**	**NS**	**NS**
8 weeks			0.08 (−1.5–1.7)						
16 weeks			**1.80 (0.06–3.5)**	**0.36** (0.01–0.7)					
PANSS total score	$F_{(1,50)} = 2.51$ p = 0.119	$F_{(1,50)} = 2.78$ p = 0.102	**NS**	**NS**	$F_{(2,50)} = 1.86$ p = 0.166	$F_{(1,50)} = 1.65$ p = 0.204	**NS**	**NS**	**NS**

NA: not applicable NS: not significant.
* p<0.01.
** p<0.001.
[1] Number of points on outcome measure scale.

performance in the context of REPYFLEC (Wykes and Reeder, 2005; Penadés and Gastó, 2010) could have encouraged metacognition and promoted some generalization to functioning. In addition, the group could constitute a sociability context that was useful for our training and which allowed the therapist to act as a model in the social interplay, so promoting satisfactory relationships between group members.

Thirdly, to the duration and intensity of the treatment which, despite demonstrating that approximately 16 sessions were not sufficient to determine differences between groups, did indeed achieve efficacy results in at least 21 of 32 sessions. For instance, similar results were obtained in the IPT metanalyses (Roder et al., 2006; Roder et al., 2011) where they found that patients who maintain improvements at follow-up are those who have completed the entire IPT program. However, these results differ from that found in studies about predictors of change after CR (Kurtz et al., 2009) or in the metanalyses of McGurk et al. (2007) and Wykes et al. (2011) where intervention success was not associated with treatment length.

Finally, to the fact that approximately 60% of the sample participated in a parallel way in other usual-care psychiatric rehabilitation procedures whose effects have probably converged in a synergic way in the results obtained by the experimental group (McGurk et al., 2007; Roder et al., 2011; Wykes et al., 2011).

In conclusion, REPYFLEC is associated with gains at six months after treatment completion in executive performance and psychosocial functioning. This result would support the hypothesis that cognitive remediation allows re-training of cognitive-social processes that were affected by the illness.

5. Study limitations

We consider that it would be very useful to widen the assessment of cognitive flexibility because it would enable us to determine whether we are achieving other specific gains in this area, but we concluded that the assessment time needed would be too long. Metacognition has not been appropriately studied. More research is necessary to assess and understand this dimension in schizophrenia and its connection with executive function, functioning or symptoms. A methodological limitation of the study is the size of the sample which could be insufficient to detect complex effects such as interactions.

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Contributors

Aida Farreny, Susana Ochoa and Judith Usall designed the study and wrote the protocol. Jaume Aguado managed and undertook the statistical analyses with Josep Maria Haro and Aida Farreny. Elena Huerta-Ramos, Ferran Marsà, Raquel López-Carrilero and Vanessa Carral carried out the blinded assessment. Aida Farreny wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

Conflict of interest

None.

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