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Computerized cognitive remediation therapy, REHACOM, in first episode of schizophrenia: A randomized controlled trial

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A B S T R A C T

Patients with schizophrenia show cognitive impairments that have been linked to poor social functioning. Computerized cognitive remediation therapy has shown to be effective in improving both cognition and functioning in chronic schizophrenia, but relatively little is known about how these approaches improve cognition and functioning when applied to early stages of psychosis. Eighty-six participants with a first episode of psychosis, undergoing a specific program for early stages of schizophrenia, undertook either the REHACOM computerized cognitive remediation intervention (n = 36), or an active control condition (n = 50) consisting in 24 one-hour sessions addressed twice a week. Clinical features, cognition and functioning were assessed at baseline, post-treatment and six months after finishing the intervention. A significant progressive improvement in neurocognition and functioning was globally shown with no differences observed between the experimental and control group at post training or follow up. All cognitive domains but Social Cognition improved between 0.5 and 1 S.D. through the study period. The computerized cognitive remediation therapy REHACOM has not proved to be effective on improving cognition nor functioning compared to controls in outpatients with a first episode of schizophrenia.

1. Introduction

The presence of cognitive deficit in patients with schizophrenia has been well documented, and has led to considering neurocognition a core feature in psychosis (Green et al., 2000). Neurocognitive impairment is known to affect almost all patients with schizophrenia with global cognitive deficit averages between 1 and 2 standard deviation (SD) below the mean of healthy subjects (Green et al., 2004). Cognitive deficits are detectable not only at the onset of the illness, but also at prodromal stages and even in populations at genetic risk (Seidman et al., 2010; Sheffield and Barcha, 2016).

Cognitive impairment in psychosis ranges from moderate to severe, remains stable throughout the course of the illness (Shmukler et al., 2015) and is strongly linked to functional disability (Keefe et al., 2012), which places cognition as a crucial treatment target. Although second generation antipsychotics have improved tolerability and quality of life (Lecardeur, 2015), drugs seem to do little to ameliorate cognitive difficulties (Davidson et al., 2009), hence, interventions targeting cognition have become a key tool to prevent disability in schizophrenia (Kane et al., 2015; McGurk et al., 2007).

The Cognitive Remediation Experts Workshop defines cognitive remediation (CR) as a "behavioral training based intervention that aims to improve cognitive processes with the goal of durability and generalization" (Wykes et al., 2011). Data support the efficacy of CR showing moderate effect on cognition at post treatment and follow-up (Grynszpan et al., 2011; McGurck et al., 2007; Wykes et al., 2011).

Prospective and double-blind randomized controlled trials with patients with schizophrenia undergoing cognitive remediation (Bosia et al., 2017; Cassetta and Goghari, 2016; Nuechterlein et al., 2011) have also shown strong evidence for a predictive relationship between cognition and functional outcome, that has even been supported by genetic analyses (Kuo et al., 2018). Meta-analysis including randomized, controlled trials of cognitive remediation in schizophrenia have documented beneficial effects of CR on cognitive performance,

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symptoms and functional capacity (McGurck et al., 2007) with stronger predictive power for cognition over positive or negative symptoms in determining functional domains (Østergaard et al., 2014) such as work performance and independent living (Kurtz, 2006).

Recent interest in early intervention in schizophrenia includes CR as one of the strategies to develop (Kim et al., 2018), despite it´s not included in clinical practice international guidelines (Young and Geyer, 2015). While randomized controlled studies involving cognitive training in old persons with severe mental illness (McGurk and Mueser, 2008) and individuals at high risk (Piskulic et al., 2018) have shown poor treatment response, prospective studies in earlier stages seem to be associated with greater cognitive and functional gains (Bowie et al., 2014).

Neurocognitive remediation techniques are well accepted among patients (Wykes et al., 2011), have proved to be durable up to six months after the withdrawal of the therapy (d´Amato et al., 2011) and may also facilitate the ability to benefit from different psychosocial interventions (Breitborde et al., 2011). Meta-analytic data suggest that neurocognitive improvement is not affected by the trial methodology applied showing comparable results regardless of the type of intervention used (McGurck et al., 2007; Wykes et al., 2011) and concludes that psychosocial functioning is most likely to be targeted when practice is provided in an integrated and comprehensive rehabilitation context and is reinforced by real-world settings synergies, promoting transfer and generalization to real world situations (Bryce et al., 2018).

To date, several models of CR can be assessed (Best and Bowie, 2017; Bon and Franck, 2018; Fan et al., 2017). From all different methodologies, computer-assisted cognitive remediation approaches propose an interactive, dynamic and flexible way of improving cognitive domains. In addition, computers allow adjusting the task automatically depending on the level of difficulty reached by the patient (Sartory et al., 2005), offer the possibility of designing exercises with unlimited repetitions and with numerous types of reinforcements, facilitate the individualization of the learning activities and the immediate feedback (Sartory et al., 2005) and the reduction in costs and number of therapists. They are also considered motivation enhancers (Raffard et al., 2009), with the positive effect of avoiding the sensation of observation or criticism over the patient.

REHACOM, is a computer-assisted remediation therapy for cognitive functions whose efficiency has been shown in studies based in a pre and post treatment design involving patients with brain injury (Fernández et al., 2012) and in randomized controlled trials in remitted schizophrenia (d´Amato et al., 2011). As far as we know, no trial has been published on patients with a first episode of schizophrenia (FEP) using REHACOM, so the main goal of the present study is to assess the effect of a 12-week computerized assisted cognitive remediation therapy (CRT), on neurocognition and functioning at post training and follow up, as part of an early intervention program. We hypothesize that training cognitive domains will benefit cognition, and that cognitive improvement obtained will result in a better functional performance which will ultimately translate into an improvement in real world social functioning.

2. Method

2.1. Clinical trial design

We designed a randomized, prospective and controlled trial to evaluate the effect of REHACOM on cognition and functioning in FEP. Patients were randomized to either the computer assisted cognition intervention (CRT) or to a specifically designed computerized active control group (CC). A control task involving computers was chosen, in order to eliminate the possible restorative effect of computer use and to ensure results could be attributed more specifically to REHACOM therapy. Both computerized activities were added to the usual treatment followed in the FEP Unit.

All patients were evaluated at two time points after the baseline assessment. The first one after the cognitive or control intervention (post-training); and the second one at the end of the study, six months after the intervention had finished.

2.2. Participants

A total of 113 patients were enrolled, all of them outpatients from the FEP Unit in Alicante (Spain), a 3 year integrated and intensive multi professional approach. Recruitment for the trial began in November 2011 and concluded in December 2014. Patients were included if (1) they met the DSM-IV-TR (American Psychiatric Association, 2000) criteria for schizophreniform disorder or schizophrenia based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1995), (2) they had received the diagnosis in the last year, (3)they were clinically stabilized, which has been understood as no changes in pharmacological treatment or hospitalizations in the last 3 months. Exclusion criteria were (1) neurological disorders, (2) active substance dependence (excluding caffeine and nicotine), (3) intellectual disability (IQ below 70), (4) autism, and (5) not willing or being able to complete psychometric measures at baseline were excluded.

All subjects gave written informed consent and the study was approved by a local ethical committee.

Over the 113, 110 patients met inclusion criteria and were finally included. Fifty-four patients were randomized to CRT, from which 18 (33.3%) dropped out during the intervention. On CC, 6 patients out of 56 (10.7%) did not complete the minimum number of sessions required and were considered drop outs (Fig. 1).

2.3. Instruments

Sociodemographic information on age, gender, ethnicity, occupation and educational level measured as the maximum degree of studies reached was collected at baseline through a semi-structured interview specifically designed for this purpose. Premorbid adjustment, antipsychotic drug dose (mg/day) and substance use was obtained in the same interview from patient (and additionally, if it was necessary, from family members or electronic medical data).

2.3.1. Clinical assessment

Diagnoses meeting DSM-IV-TR criteria (APA, 2000) were assessed using the SCID-I (First et al., 1995). Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Duration of untreated psychosis (DUP), (Norman and Malla, 2001), was estimated using information related to the development of symptomatology collected directly from the individual and the family members.

2.3.2. Premorbid adjustment

Premorbid adjustment was assessed with the Premorbid Assessment of Functioning (PAS) (Cannon-Spoor et al., 1982). This measure obtains ratings of functioning in particular domains across the developmental periods of childhood, early adolescence, late adolescence, and adulthood. Five-factor subscale scores were also calculated for social, academic, sexuality, employment and independence.

2.3.3. Neurocognitive assessment

Cognitive performance was assessed using The MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008) that includes tasks assessing seven domains of cognition including Speed of processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning and Problem Solving, and Social Cognition. The ten MCCB tests were administered in the order established by Kern (Kern et al., 2008) using the Spanish normative and standardized data obtained by our group (Rodriguez-Jimenez et al., 2012).

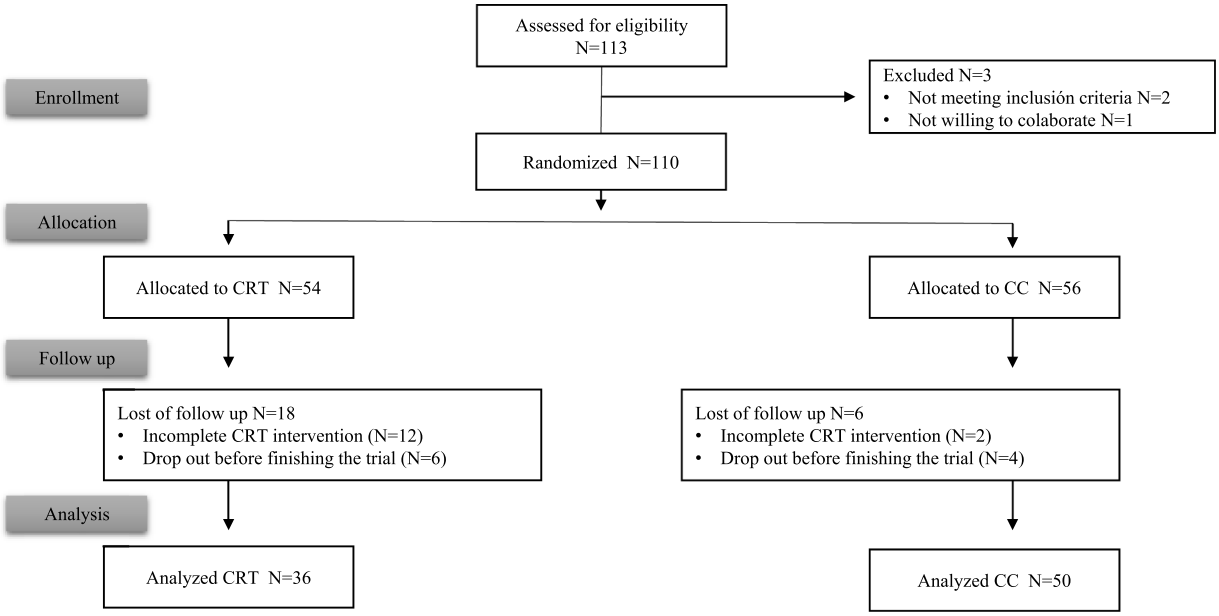

Fig. 1. Flow diagram of the trial.

2.3.4. Social functioning

We have measured two different domains of functionality to be able to evaluate both capacity and real world competence. Functional capacity was assessed using the UCSD Performance-based Skills Assessment (UPSA) (Patterson et al., 2001), which involves role-play tests administered as simulations of events in the areas of general organization, finance, social/communications, transportation, and household chores. Global functioning was assessed using the Global Assessment of functioning (GAF-f) subscale (Endicott et al., 1976) whose validity has been stablished (Pedersen and Karterud, 2012). It is a quick measure that assigns a numerical judgment to the individual's overall functioning level.

All scales were administered at three points during the trial: at baseline, once the intervention had finished (between weeks 13 and 15), and six months later (between weeks 38 and 42). Tests were administered by a trained team, blinded from the remediation treatment personnel.

2.4. Procedure

Computer-assisted remediation therapy (REHACOM modules) consisted in 24 individual 1-h sessions addressed twice a week, over a 12-week period. These sessions provided supportive, graduated training and practice in selecting, executing, and monitoring cognitive operations. CRT was conducted on a computer with a special input panel using REHACOM software package.

Trying to cover the most affected cognitive domains in schizophrenia, six procedures have been chosen which are detailed at the REHACOM website at http://www.hasomed.de : Vigilance, Divided Attention, Attention and Concentration, Logical Reasoning, Topological Memory and Shopping. Each training session was divided in modules selected by the therapist in which different cognitive domains and levels of difficulty were established. CRT intervention was considered complete when patients attended at least 20 out of the 24 treatment sessions scheduled. Any participant who had trained 19 sessions or less has been considered a drop out.

Patients on control condition were exposed and encouraged by the same therapist to develop free computer activities available in Internet. Control activities consisted in viewing music videos, answering the email, reading the local newspaper or looking for information related to leisure activities or employment in the area, and are listed in supplementary material,appendix 1, in detail. Control condition sessions were paired to the CRT intervention group in number, duration and frequencyand consisted in 24 individual one-hour sessions addressed twice a week, over a 12-week period. Therapist feedback was given at the end of each training session.

CRT and CC were carried out during the first year that follows the diagnosis in parallel to the individual multidisciplinary approach designed to achieve clinical remission, reduce medication doses and treat associated comorbidity and family impact, and simultaneously to the group psychoeducational intervention carried out weekly for 16 consecutive weeks.

2.5. Data analysis

Basic characteristics of the sample including socio-demographics and clinical information were described using frequencies, percentages, mean and standard deviations (SD). Comparison of demographic and clinical characteristics between groups based on the intervention received were made using univariate analysis (χ^2, Fisher's test, Student's *T*-test, *U*-Mann–Whitney). Normality of all variables was assessed performing Shapiro–Wilk normality test. In the same way, changes in the outcome variables (cognition and functioning) have been described throughout the follow-up.

Multivariate analysis models were built to predict differences in time between the three study visits in the outcomes:cognitionand functioning.We have carried out a linear regression model that allow us to know changes that occur in test scores in each visit taking into account the intrinsic variability of each individual and adjusting forpotential covariates, age, gender, educational leveland premorbid adjustment. Effect sizes were calculated for all the statistical tests using Cohen's d for *t*-test and Cramer's V (Φc) for χ^2. When Mann–Whitney test is used, effect sizes from *z* values were calculated.

All analyses were conducted in the statistical package R version 3.2.1 for Windows, defining statistical significance at $p = 0.05$.

3. Results

3.1. Patient demographic and clinical characteristics at baseline

Information of the baseline sample is shown in Table 1. The mean age at baseline was 25.5 years (SD 7.5); 97.7% ($n = 84$) were of white

Table 1
Comparison of baseline demographic and clinical characteristics of the groups.

Variable	CRT	CC	p^*
N	36 (39.2%)	50 (58.1%)	
Age(years) M (SD)	24 (6.7)	26.6 (7.9)	0.080
Gender			
Males	28 (77.8%)	31 (62.0%)	0.124
Females	8 (22.2%)	19 (38.0%)	
Universitary degree	1 (2.8%)	6 (12.0%)	0.188
Years of education M (SD)	13.5 (3.4)	13.3(3.6)	0.794
Family education (years)			
Father	12.4 (4.1)	11.7 (4.9)	0.332
Mother	12.1 (3.5)	11.4 (4.7)	0.232
Unemployed	13 (36.1%)	27 (54.0%)	0.287
Psychiatric family history	21 (58.3%)	30 (60.0%)	0.636
DUP (months) M (SD)	6.3 (10.3)	5.5 (6.6)	0.601
PANSS M (SD)			
Positive	28.4 (6.9)	29.3 (6.1)	0.565
Negative	27.6 (6.0)	25.6 (6.5)	0.296
Total	107.6 (13.3)	109.6 (15.1)	0.399
CPZE mg/day M (SD)	1210.5 (599.2)	964.7 (489.6)	0.104
PAS total M (SD)	0.31 (0.2)	0.22 (0.1)	0.028

CRT: Cognitive Remediation Therapy; CC: Computerized Control; DUP: duration of untreated psychosis; PANSS: Scale for positive and negative symptoms; CPZE: Chlorpromazine equivalent doses (Woods, 2003); PAS: premorbid adjustment scale. M: mean; SD: standard deviation.
p^* The Wilcoxon and Chi squared tests have been applied for the comparison of quantitative and categorical variables respectively between groups.

ethnicity, 68.6%(59) were male and 59.3% ($n = 51$) had family story of mental disorders. Only 8.1% ($n = 7$) had obtained a university degree and 46.5% ($n = 40$) were unemployed.

Only PAS score showed differences between CRT and CC at baseline showing the CC group better degree of adjustment prior to the onset of the disease (Table 1). No other significant differences were found between patient groups in clinical features, mean drug dosage (mean chlorpromazine equivalent dose) (Table 1), cognitive performance (MCCB) and functioning (UPSA and GAF-f) at baseline (Table 2). Likewise, no significant differences were either found in these same variables at baseline between participants and drop outs (supplementary material, appendix 2).

3.2. Cognitive outcome

A progressive improvement on neuropsychological performance assessed by the MCCB from baseline to the end of the trial was globally shown. Nonetheless, no statistically differences between CRT and CC were observed at post-training and follow-up (Table 2, supplementary material,appendix 3).

The improvement shown during the training period is maintained in a statistically significant way ($p < 0.001$) six months after the ending of the intervention, and is observed in both study groups, without significant differences between them; and without being able to infer a deferred effect of the experimental therapy on any cognitive domain at the end of the trial.

All MCCB domains except Social Cognition reached an improvement between 0.5 and 1 SD. This cognitive gain achieved is global and generalized, reaching benefits in domains not specifically trained with a moderate effect size (ES) for Speed of at post training Processing (ES 0.34 95% confident interval (CI) −4.68 to 5.28) and at follow up (ES 0.54 95% CI −4.46 to 5.54) and small for the rest of domains without significant differences between both groups (Table 3). Verbal and Visual Learning and Memory are the domains that have improved the most during the study.

3.3. Functional outcome

There was a significant improvement in overall functioning from baseline to endpoint. Functional performance of both groups improved significantly at post-training and follow up ($p < 0.05$).

Comparison of functional competence (UPSA) and global functioning (GAF) between groups at three time points (baseline, post training and follow up) is presented in Table 4.No differences between groups have been described in none of the study visits. In the intergroup time comparison, we found functional improvement with a large effect sizes on both functional competence UPSA (−1.477, 95% CI −1.73 to −1.22, $p < 0.05$) and global functioning GAF (4.26, 95% CI 3.85 to 4.97, $p = 0.05$) along the study period. However, no differences between groups were detected.

At the end of the study a moderate correlation has been found between improvement in global cognition and social functioning in the CRT (REHACOM) group (r 0.511, p 0.011). No other correlation has been found between cognitive and functional gains (supplementary material, appendix 4).

4. Discussion

In the present study we point out several results of interest and clinical application. The main result found is that although both groups significantly improve after the intervention and six months later, no significant differences are obtained between cognitive remediation and control intervention, so REHACOM has not shown to be effective compared to an active control on improving cognition in patients with a FEP of schizophrenia or schizophreniform disorder. Moreover, neither functional competence nor global functioning have improved in a significant way in the CRT group compared with the CC.

This results do not go on line with those supporting evidence of the positive effect of CRT on neurocognition (Grynszpan et al., 2011;

Table 2
MCCB score at baseline, post-treatment and end of trial of the groups.

MCCB M (SD)	Baseline			Post-Training			End of trial			P^*
	CRT	CC	*P*	CRT	CC	*p*	CRT	CC	*p*	
Speed of processing	34.08 (10.19)	35.77 (10.03)	0.348	36.03 (7.74)	39.33 (8.61)	0.119	39.72 (8.85)	41.95 (8.52)	0.417	0.224
Attention/Vigilance	34.08(9.97)	36.50(12.20)	0.348	37.94 (9.43)	40.43 (10.73)	0.397	39.14 (7.97)	40.87 (12.31)	0.421	0.602
Working memory	40.94 (10.84)	40.88 (14.37)	0.927	43.24 (10.28)	45.02 (11.96)	0.467	45.66 (8.64)	45.50 (10.58)	0.799	0.751
Verbal learning	36.92 (12.28)	37.84 (14.85)	0.546	43.15 (11.10)	44.43 (11.56)	0.557	48.21 (11.07)	47.66 (12.55)	0.756	0.438
Visual learning	34.81 (14.78)	37.84 (14.70)	0.298	38.88 (13.46)	41.69 (12.46)	0.335	43.21 (10.24)	42.95 (12.52)	0.723	0.638
Reasoning and problem-solving	40.08 (11.61)	40.98 (10.61)	0.683	42.27 (9.67)	45.02 (9.76)	0.148	45.34 (10.39)	45.79 (9.56)	0.969	0.595
Social Cognition	41.31 (14.31)	42.82 (12.66)	0.674	43.91 (11.42)	42.76 (13.08)	0.694	39.97 (16.03)	42.74 (12.15)	0.742	0.437
Neurocognition	32.11 (11.21)	34.07 (13.35)	0.381	36.88 (9.19)	40.04 (10.78)	0.173	41.34 (9.42)	42.03 (11.52)	0.969	0.429
MCCB Overall Composite	31.72 (11.7)	33.96 (13.43)	0.315	36.64 (8.97)	39.29 (10.93)	0.199	39.89 (10.63)	41.11 (11.33)	0.904	0.369

MCCB: MATRICS Consensus Cognitive Battery; M: mean; SD: standard deviation. Average score in the 7 cognitive domains evaluated with the MCCB at baseline, after the training intervention and at the end of study visit. The significance values of the differences between CRT and CC groups are provided.
p Differences between the study groups in the three study visits: at baseline, post-training and end of the trail.
P^* Differences over time between performance and group in the three study visits are calculated by a mixed linear regression model.

Table 3
Cognitive benefit obtained at post-training and end of trial.

MCCB	From baseline to post training				From post training to final visit				From baseline to final visit			
	CRT	CC	CI	Effect size	CRT	CC	CI	Effect size	CRT	CC	CI	Effect size
Speed of processing	1.95	3.56	−4.68 to 5.28	0.30	3.96	2.62	−4.74 to 5.22	0.24	5.64	6.18	−4.46 to 5.54	0.54
Atention/Vigilance	3.86	3.93	−4.67 to 4.75	0.04	1.22	0.44	−5.09 to 4.33	−0.37	5.06	4.37	−5.07 to 4.39	−0.34
Working memory	2.31	4.14	−5.24 to 5.48	0.11	4.42	0.48	−5.32 to 5.4	0.04	4.72	4.62	−5.22 to 5.54	0.16
Verbal memory	6.23	6.59	−6.22 to 6.94	0.36	5.06	3.23	−6.67 to 6.51	−0.08	11.29	9.82	−6.33 to 6.89	0.28
Visual memory	4.07	3.85	−6.35 to 6.93	0.29	4.33	1.26	−6.78 to 6.51	−0.13	8.41	5.11	−6.52 to 6.84	0.16
Reasoning and problem-solving	2.19	4.08	−4.68 to 5.28	0.29	3.07	0.77	−4.81 to 5.15	0.17	5.26	4.62	−4.55 to 5.47	0.46
Social Cognition	2.60	−0.06	−8.49 to 9.61	0.56	−3.94	−0.02	−9.27 to 8.83	−0.22	−1.34	−0.08	−8.76 to 9.44	0.34
Neurocognition	4.77	5.97	−4.75 to 5.39	0.32	4.46	1.99	−5.11 to 5.03	−0.04	9.23	6.96	−4.82 to 5.38	0.28
MCCB Overall Composite	4.92	5.33	−5.17 to 6.02	0.42	3.25	1.82	−5.68 to 5.52	−0.07	8.17	7.15	−5.29 to 5.96	0.34

Cognitive benefits (improvement in MCCB *T*-score). CRT: Cognitive Remediation Therapy; CC: Computerized Control; CI: confidence interval. The effect size has been calculated by Cohen's D.

McGurk et al., 2007; Morin and Franck, 2017; Wykes et al., 2011) and transfer of these cognitive benefits to functioning that has been reported in chronic patients (Wykes et al., 2011) and early stages of psychosis (Revell et al., 2015). Furthermore, it has also been identified a lower effect size in computerized programs (0.38, CI 0.20–0.55, $p < 0.05$) when compared with classical interventions (Grynszpan et al., 2011), showing medium range effect size (McGurk et al., 2007; Wykes et al., 2011), which is probably attributable to the lack of one to one interaction (Fisher et al., 2015; Østergaard et al., 2014). And additionally, metaanalysis applied in early stages warns of the smaller effect CRT shows (0.19, CI 0.00–0.38, $p < 0.05$) (Revell et al., 2015) compared with chronic schizophrenia (0.45, CI 0.31–0.59, $p < 0.05$) (Wykes et al., 2011).

Despite this, there are also rigorous studies that do not support this efficacy (Dickinson et al., 2010; Gomar et al., 2015; Urben et al., 2012) and others noting that the cognitive improvements achieved after CRT do not always generalized to functioning (d´Amato et al., 2011; Fisher et al., 2015; Fiszdon et al., 2016).

The lack of apparent efficacy of CRT can be due first, to the environment of intensive treatment enriched with interventions of proven efficacy in FEP, that have already proved to benefit outcome themselves (Peña et al., 2016). The fact that CRT in our study was performed within an intensive FEP intervention program may have contributed to blurring the role the therapy. This explanation can also lay behind the disparity found in different clinical settings (Eack et al., 2011; Lee et al., 2013) and is supported by the benefits that literature attributes to early intervention programs, based on intensive, integrated and patient-adapted interventions aimed to restore functionality (Correll et al., 2018). Moreover, both CRT and CC improve cognition and functioning, in fact, they show an overall progressive improvement even when the intervention has finished, and present better scores at follow up than at post training, supporting the benefit of the early intervention program in which it has been developed.

Second, due to REHACOM specific characteristics. Aspects such as duration and intensity may have had a partial role, despite our intervention length was on average of the rest of studies published with CRT in FEP (Eack et al., 2011; Holzer et al., 2014; Lee et al., 2013; Mendella et al., 2015; Urben et al., 2012), it may have not been sufficient to generate a global cognitive change higher than that expected throughout the first year that follows diagnosis and usual treatment. And perhaps, the REHACOM selected modules although have been effective in chronic schizophrenia (d´Amato et al., 2011) may not be the suitable ones for FEP.

Third, to the lower cognitive deficit of the population, in which Working Memory, Problem Solving and Social Cognition are only slightly altered in relation to patients with longer evolution (Eack et al., 2011). This might be explained by the so-called “ceiling effect” in the rehabilitation process, that postulates marginal cognitive deficit is no longer modifiable (Bowie et al., 2014).

Other factors to be taken into account that might have influence why REHACOM is not superior to CC are the fact that premorbid adjustment in the control group at baseline, one of the factors most related to prognosis, was better in CC participants, and the higher drop-out rate observed in CRT patients, that although is similar to that reported in studies with FEP undergoing CR (Østergaard et al., 2014), can have contributed to the final result obtained. Finally, the possible restorative effect that has been attributed to interventions within control groups (Radhakrishnan et al., 2016) could somehow explain the lack of differences between CRT and controls. Nonetheless, we should remain cautious of attributing this lack of difference to the potential effect of our control intervention.

This trial presents strengths and limitations. It has entailed the incorporation of a novel intervention into the usual clinical context of the Spanish National Health System, its integration within a specific FEP program, the parallel development of a research line focused on cognition in clinical practice and its early application in patients with a debut of the disease. In addition, it supports the need to communicate negative results in order to optimize interventions. But some limitations have to be considered. First, our small sample size; secondly, the non multicentric design,third, the absence of a direct comparison between early and late psychosis and finally, our findings do only apply to REHACOM and hence, may not be extended to other computerized cognitive remediation interventions. Regarding to statistics, a completer analysis has been chosen rather than an intention-to-treat as the trial does not reflect a real world situation but an experimental treatment, so it did matter if participants left the CRT or CC intervention.

Table 4
Functional profile in CRT and CC groups.

Function M (SD)	Baseline			Post Training			End of trial			*P**
	CRT	CC	*p*	CRT	CC	*p*	CRT	CC	*p*	
UPSA	0.82 (0.11)	0.84 (0.1)	0.332	0.88 (0.07)	0.90 (0.07)	0.096	0.91 (0.09)	0.93 (0.06)	0.530	0.301
GAF- Functioning	43.55 (12.32)	45.52 (11.39)	0.443	68.38 (11.09)	69.38 (14.62)	0.784	73.75 (13.21)	80.33 (13.34)	0.113	0.803

CRT: Cognitive Remediation Therapy; CC: Computerized Control; UPSA: University of California San Diego Performance-Based Skills Assessment; GAF: Global Assessment of Functioning; M: mean; SD: standard deviation.
p Differences between the study groups at baseline, post-training and end of the trail.
*P** Differences over time between performance and group in the three study visits are calculated by a mixed linear regression model.

In conclusion, the REHACOM computerized therapy has not proved to be effective on improving cognition nor functioning. Although, as mentioned, this lack of efficacy may have been masked by the benefit of the program itself, so results recommend caution to clinicians when including this type of remediation therapy in FEP programs, and to researchers to carry out more studies that confirm or reject the results obtained here.

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Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112563.

References

d'Amato, T., Bation, R., Cochet, A., Jalenques, I., Galland, F., Giraud-Baro, E., Pacaud-Troncin, M., Augier-Astolfi, F., Llorca, P.M., Saoud, M., Brunelin, J., 2011. A randomized, controlled trial of computer-assisted cognitive remediation for schizophrenia. Schizophr. Res. 125 (2–3), 284–290. https://doi.org/10.1016/j.schres.2010.10.023.

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders (4th ed., text rev.). https://doi.org/10.1176/appi.books.9780890423349.

Best, M.W., Bowie, C.R., 2017. A review of cognitive remediation approaches for schizophrenia: from top-down to bottom-up, brain training to psychotherapy. Expert Rev. Neurother. 17 (7), 713–723. https://doi.org/10.1080/14737175.2017.

Bon, L., Franck, N., 2018. The impact of cognitive remediation on cerebral activity in schizophrenia: systematic review of the literature. Brain Behav. 8 (3), e00908. https://doi.org/10.1002/brb3.908.

Bosia, M., Buonocore, M., Bechi, M., Spangaro, M., Pigoni, A., Croci, M., Cocchi, F., Guglielmino, C., Bianchi, L., Smeraldi, E., Cavallaro, R., 2017. Cognitive remediation and functional improvement in schizophrenia: is it a matter of size? Eur. Psychiatry 40, 26–32. https://doi.org/10.1016/j.eurpsy.2016.06.007.

Bowie, C.R., Grossman, M., Gupta, M., Oyewumi, L.K., Harvey, P.D., 2014. Cognitive remediation in schizophrenia: efficacy and effectiveness in patients with early versus long-term course of illness. Early Interv. Psychiatry 8 (1), 32–38. https://doi.org/10.1111/eip.12029.

Breitborde, N.J., Moreno, F.A., Mai-Dixon, N., Peterson, R., Durst, L., Bernstein, B., Byreddy, S., McFarlane, W.R., 2011. Multifamily group psychoeducation and cognitive remediation for first-episode psychosis: a randomized controlled trial. BMC Psychiatry 11, 9. https://doi.org/10.1186/1471-244X-11-9.

Bryce, S.D., Rossell, S.L., Lee, S.J., Lawrence, R.J., Tan, E.J., Carruthers, S.P., Ponsford, J.L., 2018. Neurocognitive and self-efficacy benefits of cognitive remediation in schizophrenia: a randomized controlled trial. J. Int. Neuropsychol. Soc. 24 (6), 549–562. https://doi.org/10.1017/S1355617717001369.

Cannon-Spoor, H.E., Potkin, S.G.., Wyatt, R.J., 1982. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr. Bull. 8 (3), 470–484. https://doi.org/10.1093/schbul/8.3.470.

Cassetta, B.D., Goghari, V.M., 2016. Working memory and processing speed training in schizophrenia: study protocol for a randomized controlled trial. Trials 17, 49. https://doi.org/10.1186/s13063-016-1188-5.

Correll, C.U., Galling, B., Pawar, A., Krivko, A., Bonetto, C., Ruggeri, M., Craig, T.J., Nordentoft, M., Srihari, V.H., Guloksuz, S., Hui, C.L.M., Chen, E.Y.H., Valencia, M., Juarez, F., Robinson, D.G., Schooler, N.R., Brunette, M.F., Mueser, K.T., Rosenheck, R.A., Marcy, P., Addington, J., Estroff, S.E., Robinson, J., Penn, D., Severe, J.B., Kane, J.M., 2018. Comparison of early intervention services vs treatment as usual for early-phase psychosis: a systematic review, meta-analysis, and meta-regression. JAMA Psychiatry 75 (6), 555–565. https://doi.org/10.1001/jamapsychiatry.2018.0623. 1.

Davidson, M., Galderisi, S., Weiser, M., Werbeloff, N., Fleischhacker, W.W., Keefe, R.S., Boter, H., Keet, I.P., Prelipceanu, D., Rybakowski, J.K., Libiger, J., Hummer, M., Dollfus, S., López-Ibor, J.J., Hranov, L.G., Gaebel, W., Peuskens, J., Lindefors, N., Riecher-Rössler, A., Kahn, R.S., 2009. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). Am. J. Psychiatry 166 (6), 675–682. https://doi.org/10.1176/appi.ajp.2008.08060806.

Dickinson, D., Tenhula, W., Morris, S., Brown, C., Peer, J., Spencer, K., Li, L., Gold, J.M., Bellack, A.S., 2010. A randomized, controlled trial of computer-assisted cognitive remediation for schizophrenia. Am. J. Psychiatry 167 (2), 170–180. https://doi.org/10.1176/appi.ajp.2009.09020264.

Eack, S.M., Pogue-Geile, M.F., Greenwald, D.P., Hogarty, S.S., Keshavan, M.S., 2011. Mechanisms of functional improvement in a 2-year trial of cognitive enhancement therapy for early schizophrenia. Psychol. Med. 41 (6), 1253–1261. https://doi.org/10.1017/S0033291710001765.

Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J., 1976. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. Arch. Gen. Psychiatry 33 (6), 766–771. https://doi.org/10.1001/archpsyc.1976.01770060086012.

Fan, F., Zou, Y., Tan, Y., Hong, E., Tan, S., 2017. Computerized cognitive remediation therapy effects on resting state brain activity and cognition in schizophrenia. Sci. Rep. 7, 4758. https://doi.org/10.1038/s41598-017-04829-9.

Fernández, E., Bringas, M.L., Salazar, S., Rodríguez, D., García, M.E., Torres, M., 2012. Clinical impact of rehacom software for cognitive rehabilitation of patients with acquired brain injury. MEDICC Rev. 14 (4).

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.W., 1995. Structured clinical interview for DSM-IV axis I disorders patient edition. Biometrics Research Department, New York State Psychiatric Institute, New York. NY (SCID-I/P, Version 2.0.).

Fisher, M., Loewy, R., Carter, C., Lee, A., Ragland, J.D., Niendam, T., Schlosser, D., Pham, L., Miskovich, T., Vinogradov, S., 2015. Neuroplasticity-based auditory training via laptop computer improves cognition in young individuals with recent onset schizophrenia. Schizophr. Bull. 41 (1), 250–258. https://doi.org/10.1093/schbul/sbt232.

Fiszdon, J.M., Choi, K.H., Bell, M.D., Choi, J., Silverstein, S.M., 2016. Cognitive remediation for individuals with psychosis: efficacy and mechanisms of treatment effects. Psychol. Med. 46 (16), 3275–3289. https://doi.org/10.1017/S0033291716001951.

Gomar, J.J., Valls, E., Radua, J., Mareca, C., Tristany, J., del Olmo, F., Rebolleda-Gil, C., Jañez-Álvarez, M., de Álvaro, F.J., Ovejero, M.R., Llorente, A., Teixidó, C., Donaire, A.M., García-Laredo, E., Lazcanoiturburu, A., Granell, L., Mozo, P., Pérez-Hernández, M., Moreno-Alcázar, A., Pomarol-Clotet, E., McKenna, P.J., 2015. A multisite, randomized controlled clinical trial of computerized cognitive remediation therapy for schizophrenia. Schizophr. Bull. 41 (6), 1387–1396. https://doi.org/10.1093/schbul/sbv059.

Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr. Bull. 26 (1), 119–136. https://doi.org/10.1093/oxfordjournals.schbul.a033430.

Green, M.F., Kern, R.S., Heaton, R.K., 2004. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. Schizophr. Res. 72 (1), 41–51. https://doi.org/10.1016/j.schres.2004.09.009.

Grynszpan, O., Perbal, S., Pelissolo, A., Fossati, P., Jouvent, R., Dubal, S., Perez-Diaz, F., 2011. Efficacy and specificity of computer-assisted cognitive remediation in schizophrenia: a meta-analytical study. Psychol Med 41 (1), 163–173. https://doi.org/10.1017/S0033291710000607.

Holzer, L., Urben, S., Passini, C.M., Jaugey, L., Herzog, M.H., Halfon, O., Pihet, S., 2014. A randomized controlled trial of the effectiveness of computer-assisted cognitive remediation (CACR) in adolescents with psychosis or at high risk of psychosis. Behav. Cogn. Psychoth. 42 (4), 421–434. https://doi.org/10.1017/S1352465813000313.

Kane, J.M., Schooler, N.R., Marcy, P., Correll, C.U., Brunette, M.F., Mueser, K.T., Rosenheck, R.A., Addington, J., Estroff, S.E., Robinson, J., Penn, D.L., Robinson, D.G., 2015. The RAISE early treatment program for first-episode psychosis: background, rationale, and study design. J. Clin. Psychiatry 76 (3), 240–246. https://doi.org/10.4088/JCP.14m09289.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.

Keefe, R.S., Vinogradov, S., Medalia, A., Buckley, P.F., Caroff, S.N., D'Souza, D.C., Harvey, P.D., Graham, K.A., Hamer, R.M., Marder, S.M., Miller, D.D., Olson, S.J., Patel, J.K., Velligan, D., Walker, T.M., Haim, A.J., Stroup, T.S., 2012. Feasibility and pilot efficacy results from the multisite cognitive remediation in the schizophrenia trials network (CRSTN) randomized controlled trial. J. Clin. Psychiatry 73 (7), 1016–1022. https://doi.org/10.4088/JCP.11m07100.

Kern, R.S., Nuechterlein, K.H., Green, M.F., Baade, L.E., Fenton, W.S., Gold, J.M., Keefe, R.S., Mesholam-Gately, R., Mintz, J., Seidman, L.J., Stover, E., Marder, S.R., 2008. The MATRICS consensus cognitive battery, part 2: co-norming and standardization. Am. J. Psychiatry 165, 214–220. https://doi.org/10.1176/appi.ajp.2007.07010043.

Kim, E.J., Bahk, Y.C., Oh, H., Lee, W.H., Lee, J.S., Choi, K.H., 2018. Current status of cognitive remediation for psychiatric disorders: a review. Front Psychiatry 9, 461. https://doi.org/10.3389/fpsyt.2018.00461.

Kuo, S., Almasy, L., Gur, R.C., Prasad, K., Roalf, D., Gur, R.E., Nimgaonkar, V.L., Pogue-Geile, M.F., 2018. Cognition and community functioning in schizophrenia: the nature of the relationship. J. Abnorm. Psychol. 127 (2), 216–227. https://doi.org/10.1037/abn0000326.

Kurtz, M.M., 2006. Symptoms versus neurocognitive skills as correlates of everyday

functioning in severe mental illness. Expert Rev. Neurother. 6 (1), 47–56. https://doi.org/10.1586/14737175.6.1.47.
Lecardeur, L., 2015. The quality of life in schizophrenia. Expert Rev. Neurother. 41 (4), 373–378. https://doi.org/10.1016/j.encep.2015.07.001.
Lee, R.S., Redoblado-Hodge, M.A., Naismith, S.L., Hermens, D.F., Porter, M.A., Hickie, I.B., 2013. Cognitive remediation improves memory and psychosocial functioning in first-episode psychiatric out-patients. Psychol. Med. 43 (6), 1161–1173. https://doi.org/10.1017/S0033291712002127.
McGurk, S.R., Twamley, E.W., Sitzer, D.I., McHugo, G.J., Mueser, K.T., 2007. A meta-analysis of cognitive remediation in schizophrenia. Am. J. Psychiatry 164 (12), 1791–1802. https://doi.org/10.1176/appi.ajp.2007.07060906.
McGurk, S.R., Mueser, K., 2008. Response to cognitive rehabilitation in older versus younger persons with severe mental illness. Am. J. Psychiatr. Rehabil. 11 (1), 90–105. https://doi.org/10.1080/15487760701853136.
Mendella, P.D., Burton, C.Z., Tasca, G.A., Roy, P., St Louis, L., Twamley, E.W., 2015. Compensatory cognitive training for people with first-episode schizophrenia: results from a pilot randomized controlled trial. Schizophr. Res. 162 (1–3), 108–111. https://doi.org/10.1016/j.schres.2015.01.016.
Morin, L., Franck, N., 2017. Rehabilitation interventions to promote recovery from schizophrenia: a systematic review. Front Psychiatry 8, 100. https://doi.org/10.3389/fpsyt.2017.00100.
Norman, R.M., Malla, A.K., 2001. Duration of untreated psychosis: a critical examination of the concept and its importance. Psychol Med 31 (3), 381–400. https://doi.org/10.1017/S0033291701003488.
Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese, F.J., Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS consensus cognitive battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry 165 (2), 203–213. https://doi.org/10.1176/appi.ajp.2007.07010042.
Nuechterlein, K.H., Subotnik, K.L., Green, M.F., Ventura, J., Asarnow, R.F., Gitlin, M.J., Yee, C.M., Gretchen-Doorly, D., Mintz, J., 2011. Neurocognitive predictors of work outcome in recent-onset schizophrenia. Schizophr. Bull. 37 (2), 33–40. https://doi.org/10.1093/schbul/sbr084.
Østergaard Christensen, T., Vesterager, L., Krarup, G., Olsen, B.B., Melau, M., Gluud, C., Nordentoft, M., 2014. Cognitive remediation combined with an early intervention service in first episode psychosis. Acta Psychiatr. Scand. 130 (4), 300–310. https://doi.org/10.1111/acps.12287.
Patterson, T.L., Goldman, S., McKibbin, C.L., Hughs, T., Jeste, D.V., 2001. UCSD performance-based skills assessment: development of a new measure of everyday functioning for severely mentally ill adults. Schizophr. Bull. 27 (2), 235–245. https://doi.org/10.1093/oxfordjournals.schbul.a006870.
Pedersen, G., Karterud, S., 2012. The symptom and function dimensions of the global assessment of functioning (GAF) scale. Compr. Psychiatry 53 (3), 292–298. https://doi.org/10.1016/j.comppsych.2011.04.007.
Peña, J., Ibarretxe-Bilbao, N., Sánchez, P., Iriarte, M.B., Elizagarate, E., Garay, M.A., Gutiérrez, M., Iribarren, A., Ojeda, N., 2016. Combining social cognitive treatment, cognitive remediation, and functional skills training in schizophrenia: a randomized controlled trial. NPJ Schizophr. 2, 16037. https://doi.org/10.1038/npjschz.2016.37.
Piskulic, D., Romanowska, S., Addington, J., 2018. Pilot study of cognitive remediation and motivational interviewing in youth at risk of serious mental illness. Early Interv. Psychiatry 12 (6), 1193–1197. https://doi.org/10.1111/eip.12520.
Radhakrishnan, R., Kiluk, B.D., Tsai, J., 2016. A meta-analytic review of non-specific effects in randomized controlled trials of cognitive remediation for schizophrenia. Psychiatr. Q. 87 (1), 57–62. https://doi.org/10.1007/s11126-015-9362-6.
Raffard, S., Gely-Nargeot, M.C., Capdevielle, D., Bayard, S., Boulenger, J.P., 2009. Learning potential and cognitive remediation in schizophrenia. Encephale 35 (4), 353–360. https://doi.org/10.1016/j.encep.2008.06.014.
Revell, E., Neill, J., Harte, M., Khan, Z., Drake, R., 2015. A systematic review and meta-analysis of cognitive remediation in early schizophrenia. Schizophr. Res. 168 (1–2), 213–222. https://doi.org/10.1016/j.schres.2015.08.017.
Rodriguez-Jimenez, R., Bagney, A., Garcia-Navarro, C., Aparicio, A.I., Lopez-Anton, R., Moreno-Ortega, M., Jimenez-Arriero, M.A., Santos, J.L., Lobo, A., Kern, R.S., Green, M.F., Nuechterlein, K.H., Palomo, T., 2012. The MATRICS consensus cognitive battery (MCCB): co-norming and standardization in Spain. Schizophr. Res. 134 (2–3), 279–284. https://doi.org/10.1016/j.schres.2011.11.026.
Sartory, G., Zorn, C., Groetzinger, G., Windgassen, K., 2005. Computerized cognitive remediation improves verbal learning and processing speed in schizophrenia. Schizophr. Res. 75 (2–3), 219–223. https://doi.org/10.1016/j.schres.2004.10.004. 15.
Seidman, L.J., Giuliano, A.J., Meyer, E.C., Addington, J., Cadenhead, K.S., Cannon, T.D., McGlashan, T.H., Perkins, D.O., Tsuang, M.T., Walker, E.F., Woods, S.W., Bearden, C.E., Christensen, B.K., Hawkins, K., Heaton, R., Keefe, R.S., Heinssen, R., Cornblatt, B.A., North American Prodrome Longitudinal Study (NAPLS) Group, 2010. Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. Arch. Gen. Psychiatry 67 (6), 578–588. https://doi.org/10.1001/archgenpsychiatry.2010.66.
Sheffield, J.M., Barcha, D.M., 2016. Cognition and resting-state functional connectivity in schizophrenia. Neurosci. Biobehav. Rev. 61, 108–120. https://doi.org/10.1016/j.neubiorev.2015.12.007.
Shmukler, A.B., Gurovich, I.Y., Agius, M., Zaytseva, M., 2015. Long-term trajectories of cognitive deficits in schizophrenia: a critical overview. Eur. Psychiatry 30 (8), 1002–1010. https://doi.org/10.1016/j.eurpsy.2015.08.005.
Urben, S., Pihet, S., Jaugey, L., Halfon, O., Holzer, L., 2012. Computer-assisted cognitive remediation in adolescents with psychosis or at risk for psychosis: a 6-month follow-up. Acta Neuropsychiatr. 24 (6), 328–335. https://doi.org/10.1111/j.1601-5215.2012.00651.x.
Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J. Clin. Psychiatry 64 (6), 663–667. https://doi.org/10.4088/jcp.v64n0607.
Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am. J. Psychiatry 168 (5), 472–485. https://doi.org/10.1176/appi.ajp.2010.10060855.
Young, J.W., Geyer, M.A., 2015. Developing treatments for cognitive deficits in schizophrenia: the challenge of translation. J. Psychopharmacol. 29 (2), 178–196. https://doi.org/10.1177/0269881114555252.