



What variables predict cognitive remediation associated improvement in individuals with psychosis?



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ARTICLE INFO

Keywords:

Psychosis
Schizophrenia
Cognitive remediation
Moderators
Treatment outcome

ABSTRACT

On average, cognitive remediation (CR) is effective in improving cognitive function in individuals with psychosis, though there is considerable variability in treatment response. No consensus has emerged to date about the potential influence of patient and illness characteristics on CR efficacy. In the current analyses, we examined baseline demographic, cognitive, clinical, and functional ability variables as potential moderators of cognitive improvements during a randomized, controlled trial of a hybrid drill-and-practice plus strategy training CR intervention.

In an attempt to disentangle non-specific vs. CR specific treatment effects, we separately examined potential predictors of cognitive improvement in individuals who received CR versus those in the control condition. Cognitive gains were predicted by a large array of demographic, symptom and cognitive variables, however this was true both in the CR and the control condition. CR-specific cognitive improvement was associated with more severe course of illness as indexed by higher number of hospitalizations, with poorer baseline cognition, and with less severe baseline negative symptoms.

1. Introduction

A large body of research supports the efficacy of cognitive remediation (CR) for individuals with psychosis. The impact of CR has been examined on a wide range of outcomes, including symptoms, cognition, and functioning. Cognitive outcomes have likely been the most widely studied, and have generally been associated with small to moderate range improvements (Wykes et al., 2011; McGurk et al., 2007; Prikken et al., in press). Recently, there has been increased interest in understanding variables that predict response to this intervention. Better understanding who, and under what conditions, is most likely to benefit from CR is particularly important given the time- and labor-intensive nature of this intervention, and the considerable heterogeneity in response, with some individuals normalizing their performance to healthy control levels, while others show no benefit (Fiszdon et al., 2005; Vita et al., 2013; Bosia et al., 2017). Better understanding individual variables that predict treatment response may help professionals match individuals to treatments most likely to be beneficial to them, as well as help identify variables which may need to be targeted before commencing cognitive remediation.

To date, the literature on moderators of CR effects has been limited, and no consensus has emerged regarding the potential influence of individual characteristics like demographics, baseline cognition, and symptoms on treatment response. While some studies indicate that CR may be more effective in improving cognition in younger individuals (Thomas et al., 2017; Wykes et al., 2009; Kontis et al., 2013; Corbera et al., 2017; McGurk and Mueser, 2008), others suggest it may be more effective in older individuals (Twamley et al., 2011), and others yet find no age differences in response to the intervention (Wykes et al., 2011; Medalia and Richardson, 2005; Fiszdon et al., 2005; Prikken et al., in press). Similarly mixed are results of studies that evaluate the impact of baseline cognitive function, with some suggesting that cognitive remediation may be more effective for individuals with poorer baseline cognition (Rodewald et al., 2014; Twamley et al., 2011), others finding better outcomes in those with better baseline cognition (Fiszdon et al., 2005; Vita et al., 2013), and several reports of no impact of neurocognitive abilities on treatment outcomes (Medalia and Richardson, 2005; Scheu et al., 2013). The two studies that examined current IQ both found that it does not impact cognitive remediation outcomes (Fiszdon et al., 2005; Twamley et al., 2011), while there is mixed data

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<https://doi.org/10.1016/j.scog.2019.100148>

Received 10 November 2018; Received in revised form 20 February 2019; Accepted 17 April 2019

Available online 01 May 2019

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on the efficacy of CR for those with lower premorbid IQ estimates (Fiszdon et al., 2006; Kontis et al., 2013). With regard to baseline symptoms, there are also mixed reports, with some reporting better outcomes in those with more symptoms (Twamley et al., 2011), some reporting better outcomes in those with less symptoms (Fiszdon et al., 2005; Vita et al., 2013; Wykes et al., 2011), and several reporting that symptoms do not moderate treatment effects (Medalia and Richardson, 2005; Scheu et al., 2013). Data regarding illness chronicity is also inconclusive, with some reporting no evidence that illness duration impacts outcomes (Fiszdon et al., 2005; Twamley et al., 2011; Wykes et al., 2011), while others suggest that longer illness duration may adversely impact some cognitive outcomes (Bowie et al., 2014; Prikken et al., in press).

In sum, efforts to date have not identified any variables that have been consistently associated with a positive response to CR. However, this literature is still in its infancy, and more work is needed. In the current secondary analyses, we examine baseline demographic, cognitive, clinical, and functional ability variables as potential moderators of improvements in cognition. As the existing literature on CR moderators is limited and lacks consistency, we did not have directional hypotheses. We chose cognition as the primary outcome, as this variable is most consistently assessed and reported in CR trials. In an attempt to disentangle non-specific vs. specific CR treatment effects, we separately examine the predictive value of these variables in individuals who received CR versus those randomized to the control condition.

2. Methods

2.1. Participants

Participants were individuals with structured clinical interview for DSM-IV (SCID, First et al., 1996) confirmed psychotic spectrum illness, aged 18 to 65. All met the following criteria: English as primary language, no evidence of substance abuse or dependence in the past 30 days, and psychiatric stability as evidenced by no hospitalizations nor changes in medications or housing in the past 30 days. The study had been approved by the local Institutional Review Board, and all participants provided written informed consent.

2.2. Study design

For details of the original study, please refer to Fiszdon et al. (2016). Briefly, participants were randomized (2:1 ratio) to two months of either cognitive remediation (CR), or treatment as usual (TAU) condition. CR consisted of four weeks (five 1-h sessions per week) of computerized drill-and-practice attention and memory training using PSS CogReHab (Bracy, 1995), and four weeks (five, 1-h sessions per week) of manualized, strategy-focused training (Delahunty et al., 1993). For computerized training, participants were administered 5–7 tasks per session, with task difficulty titrated based on prior performance. For strategy-focused training, participants were administered paper-and-pencil memory tasks, and worked with a trainer to identify and practice strategies (e.g. verbal mediation, chunking, etc.) to enhance their task performance. The order of computerized drill-and-practice versus strategy-focused training was counterbalanced. TAU entailed continuation of whatever standard outpatient psychiatric and psychological treatment participants were receiving prior to enrollment in the study, which most often consisted of medication management, case management and/or group or individual therapy. Comprehensive assessments were conducted at study intake and end of the 2-month active phase.

2.3. Measures

The following demographic information was obtained at study intake: age, education, number of prior hospitalizations, age at first

hospitalization, age at illness onset, premorbid IQ estimate (based on Wide Range Achievement Test reading, Jastak and Wilkinson, 1993) and current IQ estimate (based on 2-subtest Wechsler Abbreviated Scale of Intelligence, Wechsler, 1999). Additional measures were collected at both intake and end of the 2-month active phase. Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987, Bell et al., 1994). Self-report task motivation and self-esteem were assessed using the Intrinsic Motivation Inventory for Schizophrenia Research (IMI, Choi et al., 2010) and the Rosenberg Self-Esteem Scale (RSES, Rosenberg, 1965), respectively. Visuospatial memory was assessed using the Rey-Osterreith Complex Figure (Osterreith, 1944). Set shifting was assessed using the percent perseverative errors and percent conceptual level scores from the Wisconsin Card Sorting Test (Heaton, 1981). Vigilance was assessed using the Continuous Performance Test, x/a (Loong, 1991). Processing speed/attention and speeded set-shifting were assessed using Trail Making Test Part A and B, respectively (TMT, Lezak, 1983). List learning was assessed using the California Verbal Learning Test-II, Trials 1–5 total (Delis et al., 2000). Immediate and delayed story memory was assessed using the Wechsler Memory Scale revised, Logical Memory I and II (Wechsler, 1987). Simple attention and working memory were assessed using the digits forward and digits backward subtests from the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III, Wechsler, 1997). Emotion recognition was assessed using the Bell-Lysaker Emotion Recognition Task (BLERT, Bell and Lysaker, 1994). Functional ability was assessed using the UCSD Performance-Based Skills Assessment (UPSA, Patterson et al., 2001a), Social Skills Performance Assessment (SSPA, Patterson et al., 2001b), and the Medication Management Ability Assessment (MMAA, Patterson et al., 2002).

2.4. Data analysis

All variables were inspected for normality and, as needed to adjust for skew, a log 10 transformation or a reflect and log 10 transformation was applied (Schinka et al., 2003). Baseline demographic group differences were explored using *t*-tests and chi-squared tests. CR outcome measures selected as dependent variables for the current analyses were cognitive variables which we had previously reported improved significantly more for those in the CR vs. TAU condition at the end of active phase. These variables indexed visuospatial memory (Rey-Osterreith immediate recall), list learning (CVLT-II trials 1–5 total), and working memory (WAIS-III Digits backward.) For each of these three measures, post- scores were regressed on pre- scores in order to generate residualized change scores reflecting amount of change during the two-month active phase. These scores were then multiplied by -1 , so that positive values reflected greater cognitive improvement from pre to post. Next, Pearson correlations were used to examine the degree of relationship between baseline demographic, self-report, symptom, cognitive, and functional ability measures and the residualized change scores for the CR condition. As these were exploratory analyses, we retained a $p < 0.05$ as the significance level in spite of multiple comparisons.

Next, in order to determine whether significant correlations found in the CR condition were unique to that sample and thereby more likely to reflect CR-specific factors, we re-ran Pearson correlations between baseline variables and residualized change scores in the TAU condition. For baseline variables that were significantly correlated with cognitive improvement in the CR condition, we then conducted Fisher r to z transformations to compare correlation coefficients between the two conditions. Lack of significant differences in correlation strength between the two conditions was interpreted as indicating that the predictor variable indexed non-specific cognitive improvement, meaning it was associated with change in cognition over time, but not necessarily as a result of CR.

Table 1
Sample demographics.

Variable	Full sample	CR condition	TAU condition
	n = 63	n = 40	n = 23
Age	48.81 (8.84)	48.03 (8.87)	50.17 (8.81)
Age at onset	20.85 (6.81)	20.03 (6.27)	22.25 (7.61)
Number hosp	13.59 (20.85)	10.53 (11.29)	19.10 (31.21)
Age at 1st hosp	24.98 (9.13)	25.83 (9.81)	23.52 (7.85)
Education	12.30 (2.01)	12.50 (1.99)	11.96 (2.23)
PANSS grand total	52.44 (11.38)	52.08 (11.81)	53.09 (10.83)
Gender (male)		70%	70%
Race (Caucasian)	49%	50%	48%
Marital status (never married)	62%	60%	65%

3. Results

Of the 50 individuals randomized to CR and 25 to the TAU condition, 63 completed assessments conducted at the end of the 2-month active phase (CR = 40; TAU = 23). Demographic information for this completer sample as a whole and for each condition is presented in [Table 1](#). There were no group differences in the examined baseline characteristics. On average, participants were in their late 40's, with 12 years of education. Nearly three quarters of the sample were male, with a little more than half never married and half Caucasian. Age at onset was early 20's with first hospitalization in the mid-twenties. Current psychiatric symptoms were mild. Participants in the CR condition completed an average of 33.48 (SD = 10.45) training sessions [14.39 (7.42) for computerized drill and practice and 15.59 (6.80) for strategy-based sessions].

3.1. Visuospatial memory improvement

Please refer to [Table 2](#) for details of moderator analyses. In the CR condition, significant correlations were observed between greater improvement in visuospatial memory (Rey-Osterreith) and poorer baseline visuospatial memory performance, poorer baseline delayed story memory (Logical Memory II), and more hospitalizations. When the strength of these correlations was compared to those observed in the TAU condition, the only condition difference was for number of hospitalizations, suggesting that this variable may uniquely predict visuospatial improvement that occurs in response to CR, while the other two variables may predict non-specific cognitive change.

3.2. List learning improvement

In the CR condition, significant correlations were observed between greater improvement in list learning (CVLT-II) and poorer baseline list learning, immediate and delayed story memory (Logical Memory), working memory (WAIS digits backward), set shifting (WCST), functional ability (UPSA performance), and with less severe baseline PANSS hostility. The strength of these correlations was not significantly different than that observed in the TAU condition, suggesting these variables index non-specific change.

3.3. Working memory improvement

In the CR condition, significant correlations were observed between greater improvement in working memory (WAIS digits backward) and poorer baseline working memory, speeded set-shifting (Trail Making Test B), list learning (CVLT), set-shifting (WCST), immediate and delayed story memory (Logical Memory), functional ability (MMAA), and with less severe baseline PANSS hostility and negative symptoms. PANSS negative symptoms, Trail Making Test B, and immediate story

memory emerged as the only variables where the strength of association was significantly greater in the CR than in the TAU condition, suggesting these variables may index CR-specific effects. As a post-hoc analysis, these three variables were entered into a stepwise regression. Immediate story memory entered first, accounting for 26.4% of the variance, with PANSS negative factor entering second, accounting for an additional 10.4% of variance. Trail Making Test B was not retained in the final model, which accounted for 36.9% of variance.

4. Discussion

This study is among the first to investigate the relationship between, and specificity of, clinical, demographic, cognitive and functional ability variables at study entry to the degree of cognitive improvement during a CR intervention consisting of both drill-and-practice and strategy-based training. Results indicated that in the CR condition, a large array of demographic, symptom, and cognitive variables predicted improvement in the three cognitive domains which showed improvement in the original clinical trial.

Only a few of these were CR specific however, showing a stronger relationship with cognitive change in the CR than in the TAU condition. Namely, greater visuospatial memory improvement was more strongly predicted in the CR than in the TAU condition by greater number of hospitalizations, while greater working memory improvement was more strongly predicted in the CR than in the TAU condition by less severe baseline negative symptoms, poorer baseline speeded set-shifting, and poorer baseline immediate story memory. Taken together, these findings suggest that a better response to CR, when indexed by cognitive outcomes, is predicted by a more severe course of illness (as measured by number of hospitalizations), by less severe levels of social withdrawal, blunted affect and other negative symptoms, and by poorer baseline speeded set-shifting and immediate story memory.

In terms of variables associated with working memory improvement, the relationship between negative symptoms and working memory is well established (Carter et al., 1996; Menon et al., 2001). Negative symptoms are known to limit cognitive performance, CR adherence, and even overall psychosocial rehabilitation outcomes (Cella et al., 2017; Evans et al., 2004; Milev et al., 2005). Also, given that working memory dysfunction and negative symptoms are similarly tied to disturbances in the dorsolateral prefrontal cortex (Menon et al., 2001; Perlstein et al., 2001), fewer negative symptoms may allow the person to benefit more from a cognitive intervention, particularly one that requires motivation to engage in a time- and labor-intensive therapy. At least one study has reported larger improvements in cognitive outcomes in response to a strategy-based program of CR in clients with poorer baseline cognitive function (Twamley et al., 2011). The authors of this study surmised that clients with greater cognitive impairment at baseline likely had greater room to improve on cognitive measures. In contrast to our study, the study by Twamley and colleagues found that greater negative symptoms predicted a better response to CR. Discrepancies between these findings and the current study may reflect the hybrid approach of strategy and drill-and-practice CR training used in the current study as compared to the group-based strategy-training selected in the 2011 study.

Finding that factors associated with greater illness burden (i.e. more hospitalizations, poorer baseline cognition) as well as factors associated with lesser illness burden (i.e. less severe negative symptoms) both predict improvement in CR was unexpected and somewhat counter-intuitive. At the same time, it highlights our limited understanding of the complex interrelationships between predictor variables. As noted above, negative symptoms may be unique in that if present at high levels, they may limit actual exposure to the intervention. The predictive value of variables associated with higher illness burden, on the other hand, may stem from them indexing individuals who have the greatest room to improve.

The failure to find a link between participant age and degree of

Table 2
Predictors of cognitive improvement, by condition.

Variable	Visuospatial memory Rey-Osterreith improvement			List learning CVLT-II improvement			Working memory Digits back improvement		
	CR (r)	Control (r)	Difference (p)	CR (r)	Control (r)	Difference (p)	CR (r)	Control (r)	Difference (p)
Demographics									
Age	0.031	0.221		-0.085	0.069		0.299 [†]	-0.164	
Education	-0.170	-0.113		-0.231	-0.210		-0.224	-0.177	
No. hospitalizations	0.353 [*]	-0.267	0.0316	0.312 [†]	0.055		0.026	-0.068	
Age at 1st hosp	-0.265	-0.135		-0.154	-0.069		-0.070	0.322	
Age onset	-0.037	0.042		-0.052	0.062		-0.099	0.066	
WRAT	-0.130	-0.354		-0.042	0.193		-0.246	-0.058	
WASI IQ	-0.263	0.187		-0.265	-0.142		-0.085	-0.087	
Symptoms									
PANSS positive	0.053	-0.188		0.010	0.478 [*]		-0.114	0.002	
PANSS negative	-0.039	-0.087		-0.075	0.345		-0.399 ^{**}	0.188	0.0264
PANSS cognitive	0.050	-0.069		-0.077	0.313		-0.274 [†]	0.299	
PANSS emotional	-0.100	-0.206		-0.060	-0.077		-0.224	-0.125	
PANSS hostility	-0.092	-0.280		-0.322 [*]	-0.017	0.2543	-0.398 ^{**}	-0.117	0.2713
Self report									
IMI interest	0.093	-0.060		-0.007	-0.102		0.028	0.134	
IMI effort	0.152	0.198		0.111	-0.125		0.153	0.235	
IMI competence	-0.124	0.028		-0.128	0.017		-0.026	0.147	
Rosenberg SES	0.182	-0.301		0.169	0.048		0.287	-0.110	
Cognition									
Rey-O immediate	-0.642 ^{***}	-0.576 ^{***}	0.7039	-0.284 [†]	-0.113		-0.201	0.072	
Rey-O 30-min delay	-0.585 ^{***}	-0.546 ^{**}	0.8337	-0.288	-0.256		-0.162	0.002	
WCST % CL	-0.157	-0.446 [*]		-0.342 [*]	-0.178	0.5287	-0.330 [*]	-0.011	0.2301
WCST % PE Log	0.151	0.370		0.357 [†]	0.242	0.6527	0.294	-0.108	
CPT RefLog	0.187	0.033		0.075	0.075		0.204	0.210	
BLERT	-0.203	-0.020		-0.274 [†]	-0.136		-0.124	-0.120	
Trails A Log	0.033	0.355		0.011	-0.018		0.293	-0.050	
Trails B Log	0.112	-0.086		0.057	0.357 [†]		0.443 ^{***}	-0.078	0.0444
CVLT Trials 1–5 Tot	-0.071	-0.033		-0.747 ^{****}	-0.789 ^{****}	0.7114	-0.356 [*]	0.097	0.0891
Logical Memory I	-0.291 [†]	0.013		-0.350 [*]	-0.448 [*]	0.6745	-0.514 ^{***}	0.034	0.0293
Logical Memory II	-0.415 ^{**}	-0.146	0.2891	-0.407 [*]	-0.334	0.7642	-0.486 ^{***}	-0.168	0.1902
WAIS Digits forward	0.032	0.286		-0.097	0.192		-0.132	-0.546 ^{**}	
WAIS Digits back	-0.229	0.012		-0.352 [*]	0.058	0.126	-0.718 ^{***}	-0.830 ^{***}	0.303
Functional ability									
UPSA	-0.197	-0.318		-0.335 [*]	-0.222	0.6599	-0.294 [†]	-0.115	
SSPA	0.002	-0.054		-0.152	-0.402 [†]		-0.031	0.045	
MMAA RefLog	0.272	0.238		0.195	0.362		0.368 [*]	0.137	0.3843

Note: BLERT, Bell Lysaker Emotion Recognition Task; CL, conceptual level response; CPT, Continuous Performance Test; CRT, Cognitive remediation; CVLT, California Verbal Learning Test-II; ILSS, Independent Living Skills Survey; IMI, Intrinsic Motivation Inventory for Schizophrenia Research; Log, Log 10 transformation; MMAA, Medication Management Ability Assessment; PANSS, Positive and Negative Syndrome Scale; PE, perseverative errors; QLS, Quality of Life Scale; RefLog, Reflect and log 10 transformation; Rey-Osterreith; Rosenberg SES, Rosenberg Self Esteem Scale; SSPA, Social Skills Performance Assessment; UPSA, UCSD Performance-Based Skills Assessment; WAIS, Wechsler Adult Intelligence Scale, 3rd edition; WASI IQ, Wechsler Abbreviated Scale of Intelligence, estimate based on two-test score for vocabulary and matrix reasoning; WCST, Wisconsin Card Sorting Task; WRAT, Wide Range Achievement Test.

[†] p < 0.10.
^{*} p < 0.05.
^{**} p < 0.01.
^{***} p < 0.005.
^{****} p ≤ 0.001.

improvement was somewhat unexpected in light of several recent reports of stronger responses to CR among younger clients (Corbera et al., 2017; Wykes et al., 2009). For example, Kontis et al. (2013), in a study of 134 people with schizophrenia, investigated the effects of age (younger than 40 vs. older than 40) on improvements in cognition using a CR intervention that was one element of the hybrid intervention reported in the current study. The authors found only very limited effects of CR in the 40 or older group. Differences between this and our study may reflect the much more limited range of ages assessed in the current study (mean age = 48.81; SD = 8.84) reducing sensitivity, along with the inclusion of a drill-and-practice element to the intervention in addition to the strategy training.

Several limitations of the current study should be mentioned. First, sample size was moderate and the power to detect differential predictive relationships between baseline scores and cognitive change

between CR and a TAU control condition was likely limited. Second, the study is correlational and it remains unclear to what degree modifying baseline characteristics (e.g., providing interventions to reduce negative symptoms before entry into sustained and complex programs of CR) would have any effect on cognitive improvements. Third, strategy-training and drill-and-practice CR represent opposite ends of a continuum in approaches to CR treatment. The combination of both approaches in our selected intervention precludes an analysis of the degree to which predictors may be different in one approach versus another, and potentially limits the generalizability of our findings. Fourth, the doses of the drill-and-practice intervention (20 h vs. target of 100 h in other studies, e.g. Bell et al., 2001, Kurtz et al., 2007) and the strategy training component of our intervention (20 h vs. 40 h in other studies, (e.g. Reeder et al., 2006) might have reduced the effect size of positive treatment gains and/or prevented us from seeing

significant improvements in other cognitive domains. Fifth, specific characteristics of our sample could limit the generalizability of our findings. And lastly, there is still no agreement on how much, or to what level, cognition must improve to lead to functional improvements—our results could very well have been different had our outcome been reaching a specific cognitive threshold or had our outcome been change in functioning itself.

In spite of these limitations, this study contributes to the literature on moderators of CR outcome in schizophrenia. Unlike many other studies that more narrowly focus on predictors of improvement in individuals exposed to CR, we identified CR-specific baseline moderators by teasing out the predictive value of these moderators against a treatment as usual group and the associated non-specific effects. The findings highlight the impact that number of hospitalizations, negative symptoms, and verbal memory prior to the start of CR can have on benefiting from this intervention, particularly in the areas of visuospatial and working memory.

Conflict of interest statement

All authors declare that they have no conflicts to disclose.

Funding source

This study was funded by grant from Veterans Administration Rehabilitation Research and Development Service (#F3195V to JMF). The sponsor had no role in the planning or conduct of the study or in the interpretation of study results.

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