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Cognitive remediation for adults with schizophrenia: Does age matter?

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ABSTRACT

Cognitive remediation (CR), a novel behavioral intervention designed to improve cognitive deficits through repeated task practice and/or strategy acquisition has gained increasing empirical support in people with schizophrenia, but substantial individual differences in treatment response remain (Wykes et al., 2011). The role of age on response to CR in schizophrenia remains understudied. We evaluated the role of three age ranges in treatment response to CR relative to a closely-matched computer skills control intervention in a blinded, randomized control trial (RCT) with 112 adults with schizophrenia divided into three groups: an early-stage group (ES; 25 years or younger, mean=3.4 years of illness; n=45), an early-chronic group (EC; 26–39, mean=7.6 years of illness; n=31) and a late-chronic group (LC; 40 and over, mean=18.2 years of illness; n=36). With respect to cognitive outcomes, early-stage and early-chronic individuals with schizophrenia showed greater improvement in response to CR on a working memory measure at a trend level, relative to late-chronic clients. These findings were confirmed in analyses of a subsample of clients who received an adequate dose of treatment. These findings emphasize the need for adaptations of currently-existing CR programs to more effectively address the needs of older client populations.

1. Introduction

Cognitive impairment is a core feature of schizophrenia that persists even with optimal pharmacotherapy (Heaton et al., 2001), and predicts functional impairment (Bowie et al., 2008; Green et al., 2000). Deficits are evident in individual with familial high risk and at clinical ultra-high risk of psychosis as well as in first-episode psychosis (Bora, 2014; Bora and Murray, 2014; Mesholam-Gately et al., 2009). These deficits remain chronic during the remaining middle-aged stages of the illness (Kurtz, 2005) and in geriatric schizophrenia (Irani et al., 2011) and contribute to the large economic cost for society of the illness (Reeder et al., 2014).

Cognitive remediation (CR) is a behavioral intervention consisting of task practice and/or strategy acquisition, with a goal of producing durable improvements in cognitive and psychosocial function. There is a growing body of research showing efficacy of cognitive remediation treatment (CR) in treating these deficits and a number of meta-analyses have shown small-to-moderate effects on global cognition (d=0.45) and specific cognitive domains such as verbal working memory (d=0.35) and on functional outcomes (d=0.42), but only when CR is offered along with other rehabilitation services (Wykes et al., 2011). Effects of CR on functioning were in the moderate range (d=0.59) when CR was paired with other rehabilitation interventions, but in the small range (d=0.28) and not statistically significant when CR was offered as a stand-alone intervention; (McGurk et al., 2007; Wykes et al., 2011). Sustained auditory attention and working memory, motivation, and work style, are all factors that have been linked to CR response (Fiszdon et al., 2005; Kurtz et al., 2009; Medalia and Richardson, 2005; Twamley et al., 2011). For example, Choi and Medalia (2005), found that patients with higher treatment motivation as measured by their voluntary attendance benefited more from CR than those that took longer to complete their training. Participant age is another variable that would be presumed to play a crucial factor in CR treatment response in schizophrenia given volumetric changes in key brain regions associated with illness duration (Mathalon et al., 2001), the increased time spent in the hospital associated with longer term illness, long-term exposure to neuroleptic medication, and the accumulative stress associated with living with a chronic psychiatric illness, among other features. To date results from studies of the role of age in CR treatment response have been inconsistent (Wykes and

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Spaulding, 2011).

While the majority of studies to date have focused on chronic samples, CR has proven to be feasible and efficacious amongst clinical high-risk and recent-onset patients with schizophrenia (Eack et al., 2009; Hooker et al., 2014; Mendella et al., 2015; Wykes et al., 2011, 2007). In separate studies using the same restorative program of CR, recent-onset patients showed a similar improvement profile as chronic older adults (verbal learning, memory and global cognition) although the authors did not compare different aged participants directly in these studies (Fisher et al., 2009, 2015). Similar results have been reported using strategy-based CR (e.g., Mendella et al., 2015). To our knowledge, only four trials have directly compared response to CR in younger vs. older individuals with schizophrenia to date. Wykes et al. (2009) compared effects of a strategy-based form of CR called CRT (of approximately 30 h) with treatment-as-usual (TAU) in patients under and over 40 years old (n=85). Both groups improved their memory scores after CRT but the younger group benefited more from CRT showing increases in flexibility at follow-up and in planning at post-treatment. Additionally, negative symptoms only improved in the younger group receiving CRT. Kontis et al. (2013) placed adult patients who had received at least 20 sessions of CR in the experimental group (n=85) and those who received less than 20 sessions or received TAU in the control group (n=49), and then divided them into those under and over 40 years old. Improvement in working memory was only evident in the younger group treated with an adequate dose of CR. McGurk and Mueser (2008) found effects of a drill-and-practice form of CR paired with supported employment across a range of cognitive functions in younger (under 45 years old) but not older clients (age 45 years old or over) with severe mental illness. Finally, Bowie et al. (2014) investigated the effects of CR in a small sample of patients in the early course of the illness (n=12; mean age of 28.1 years old and within 5 years of first episode) vs older patients (n=27; mean age of 45.4 years old and with more than 15 years of illness) and found significant improvements in both groups but larger improvements in early course patients in some cognitive domains (processing speed and executive functioning), in adaptive competence and real-world work skills. In contrast, the two major meta-analyses in the literature have either shown older age to be associated with better treatment outcomes (McGurk et al., 2007) or for age to have no impact on outcome; (Wykes et al., 2011). Thus, while the area remains understudied, work to date suggests conflicting results. Limitations of extant work are that in three studies the younger sample groups consisted of a mix of early-stage and chronic illness (Kontis et al., 2013; McGurk and Mueser, 2008; Wykes et al., 2009), while the absence of a control group and small sample in the one study that investigated CR-response in early-stage patients (Bowie et al., 2014) makes it difficult to evaluate CR-specific age-related differences in cognition and functional outcome.

We investigated the differential effects of three age ranges on cognitive, symptom and adaptive functioning improvement in 112 patients in a secondary data analysis from two, blinded randomized, controlled trials (RCTs; Kurtz et al., 2007, 2015) in which adults with schizophrenia were randomized to either CR or a closely matched computer-skills training control condition (CS). This active control condition ensured that all participants had the same time of exposure to computer work and to clinician interaction without exposure to the specific drill-and-practice cognitive exercises in the active condition. To evaluate the effects of age on benefit from CR, we compared three age ranges and illness chronicities: early-stage group (ES; n=45; 25 years old or younger), early-chronic group (EC; n=31; 26–39 years old) and late-chronic group (LC; n=36; 40 years old or older). Age 40 was selected as an older cut-off to be consistent with two major previous studies in this research area (Kontis et al., 2013; Wykes et al., 2009), while selecting age 25 as a younger cut-off created a group that was comparable in age and chronicity to other published studies of drill-and-practice CR in early-stage schizophrenia (e.g., Bowie et al., 2014; Eack et al., 2009). When compared to CS training in our previous studies, our CR program produced greatest gains in verbal working memory (Kurtz et al., 2007, 2009). Thus, in order to evaluate possible effects of age on outcome in this study, we selected verbal working memory as the primary outcome, and symptoms and adaptive functioning as secondary exploratory outcomes. A secondary analysis included only those participants who received a minimum of 40 h of CR treatment to assess whether any observed effects of age in the overall sample would be compensated by sustained exposure to CR in this subsample. Some studies have suggested that a minimum of 40–50 h of CR treatment is necessary to produce significant and sustained effects of CR on cognition (e.g., Fisher et al., 2010). We hypothesized that cognitive outcomes in response to CR would be stronger in the early-stage group, as compared to early and late chronic samples. We also hypothesized that these age-related treatment effects would generalize to a measure of adaptive function. Based on reported studies to date (Wykes et al., 2011), we hypothesized that CR would have modest effects on psychiatric symptoms, and thus we expected that these three age ranges would have little effect on changes in symptoms in response to CR.

2. Material and methods

Relevant institutional review boards approved all study procedures and all participants provided written, informed consent. Data were derived from two previously-reported, blinded RCTs in which participants were assigned to one of the two computerized treatment groups (CR; cognitive remediation vs CS; computer skills training) (Kurtz et al., 2007, 2015).

2.1. Treatments

The standardized CR intervention consisted of a sequence of computerized cognitive exercises designed to improve attention, working memory, verbal and non-verbal memory, executive function and language processing through repeated drill-and-practice (Bell et al., 2001; Bracy, 1995, 1998; Kurtz et al., 2007; Seltzer et al., 1997). Exercises and goals were started at a level of difficulty at which all patients were successful and goals were modified as performance improved. The CS intervention was a course of computerized tutorials in general computer literacy and specific skills using Microsoft Office and related programs. Participants in this group received similar duration of treatment and equivalent interaction with clinicians but they did not receive practice on exercises expressly designed to strengthen basic neurocognitive skills. Both conditions offered a potential maximum of 100 h of training. A more detailed description of the conditions and procedure has been previously reported (Kurtz et al., 2007). Inclusion criteria were slightly different in the two parent studies from which the current analyses are derived. In one of the parent studies (Kurtz et al., 2007) only patients receiving at least 15 h of computer training (CR or CS) were included in analyses. In the second parent study (Kurtz et al., 2015), outcome data from all patients randomly assigned to a condition were included, regardless of degree of participation.

2.2. Participants

Participants were 112 adult outpatients meeting DSM-IV (APA, 1994) criteria for schizophrenia or schizoaffective disorder as assessed by the Structured Clinical Interview for DSM-IV (First et al., 1995) by a research assistant supervised by a doctoral-level licensed psychologist. Detailed exclusion criteria and recruitment description can be found in previous reports (Kurtz et al., 2007, 2015). Exclusion criteria for patients included uncorrected auditory or visual impairment, mental retardation as evidenced by a documented history of services, traumatic brain injury with a sustained loss of consciousness, presence or history of any neurologic illness other than schizophrenia, lack of

Table 1
Participant characteristics and group differences at baseline.

	All Subjects (*n*=112)	Early Stage (*n*=45)	Early Chronic (*n*=31)	Late Chronic (*n*=36)	F/ChiSquare	*p*	Bonferroni Post hoc comparisons[e]
	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**			
Gender							
Male	79(70.5)	34(30.4)	23(20.5)	22(19.6)			
Female	33(29.5)	11(9.8)	8(7.1)	14(12.5)	2.28	0.32	Ns
Ethnicity/Race							
Caucasian	79(70.5)	25(22.3)	23(20.5)	31(27.7)	17.95	0.02	LC > ES; ES > EC
African American	17(15.2)	8(7.1)	7(6.3)	2(1.8)			ES > LC; EC > LC
Hispanic	10(8.9)	8(7.1)	0(0.0)	2(1.8)			ES > EC; ES > LC
Asian American	3(2.7)	1(0.9)	1(0.9)	1(0.9)			Ns
Other	3(2.7)	3(2.7)	0(0.0)	0(0.0)			ES > EC; ES > LC
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**			
Age (years)	32.96(11.57)	22.22(2.12)	31.58(4.28)	47.58(5.77)	368.60	< 0.001	LC > EC > ES
Duration of Illness	9.34(9.44)	3.44(2.84)	7.65(5.61)	18.17(10.87)	44..79	< 0.001	LC > EC > ES
Lifetime # of Hospitalizations[a]	3.96(3.03)	3.27(3.24)	3.45(2.46)	5.33(3.68)	4.422	0.014	LC > ES
Education (years)	12.82(2.40)	12.22(1.89)	12.77(3.19)	13.61(2.00)	3.491	0.034	LC > ES
Paternal Education (years)[b]	13.96(2.69)	14.90(2.14)	13.85(2.21)	12.83(3.31)	4.225	0.019	ES > LC
Computer Hours[c]	48.61(30.79)	42.08(29.98)	56.59(32.26)	49.25(29.57)	1.611	Ns	Ns
PANSS (5 factors)[d]							
Positive	17.23(5.37)	16.76 (5.99)	16.62(4.61)	18.35(5.12)	2.225	Ns	Ns
Negative	19.94(5.84)	21.14 (5.57)	19.55(6.98)	18.79(4.95)	0.742	Ns	Ns
Cognitive	17.36(4.48)	16.95(3.56)	17.00(5.00)	18.17(5.02)	0.829	Ns	Ns
Hostility	6.54(2.68)	5.73(1.91)	6.58(2.70)	7.50(3.20)	4.294	0.016	LC > ES
Emotional Disc	11.02(2.94)	10.52(2.56)	10.58(3.22)	12.02(2.95)	3.024	Ns	Ns

Note: ES: Early-stage; EC: Early-Chronic; LC: Late-Chronic. The following items were obtained by client self-report: Education Self and Paternal years. **Measures**: PANSS: Positive and Negative Symptom Scale. [a] Mean differences are significant at the 0.05 level.

[a] Lifetime # Hospitalizations for ES group *n*=44; EC group *n*=29; LC *n*=33.
[b] Paternal Education for ES group *n*=30; EC group *n*=20; LC *n*=23.
[c] Computer Hours for ES group *n*=33; EC group *n*=25; LC *n*=25.
[d] PANSS for ES group *n*=42; EC group *n*=29; LC *n*=34.
[e] Bonferroni Post hoc comparison = Pair-wise comparisons.

proficiency in English, and/or criteria met for concurrent substance abuse or dependence. Recruitment was continuous over a period of twelve years (2001–2013) and occurred at two sites. The majority of patients in the study (n=108) were enrolled from an intensive outpatient program for patients with schizophrenia at The Institute of Living, Hartford Corporate Hospital's Mental Health Network (IOL) in Hartford, Connecticut (CT), that included goal-setting groups, psychoeducation, vocational counseling, exercise groups, case management and medication consultation on a three-day per week basis; four additional participants were recruited from Midstate Medical Center in Meriden, CT. Table 1 provides a summary of demographic and baseline clinical characteristics. Patients were divided into three groups based on age: Early-stage group (ES; n=45; 25 years old or younger); early-chronic group (EC; n=31; 26–39 years old); and late-chronic group (LC; n=36; 40 years old or older).

2.3. Outcome measures

For these analyses two measures of working memory, symptoms and adaptive functioning assessed at baseline and at termination of the computer interventions were selected from a broader assessment battery. Randomization occurred after baseline assessments by a member of the unit clinical team who was not involved in pre- or post-training assessment, scoring or data analysis. This team member was instructed not to disclose group assignments to members of the research assessment team. The success of the blinding procedures was evaluated by asking research assistants to guess the condition of participants at the time of their follow-up in a subset of the participants in one of the two parent studies study (n=28). Accurate assessment of group membership was at exact chance levels (50%) for these participants. Assessments were conducted by clinical doctoral students who underwent supervised training before collecting data for the study. All training and study data collection was under the supervision of a licensed psychologist (M.M.K.).

2.3.1. Working memory

Digit-Span (DS) and Letter-Number-Sequencing (LNS) subtests from the Wechsler Adult Intelligence Scale-III & IV (Scaled Scores; WAIS-III & IV; Wechsler, 1997, 2008)were selected to assess working memory.. Age-corrected scaled scores were selected for analysis.

2.3.2. Clinical assessment

Information pertaining to the participant's psychiatric history (i.e., medication, duration of illness, year first hospitalized, number of lifetime hospitalizations) was provided by the patient and confirmed by clinician's report and chart when available. The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used to assess current symptom levels using 5 component scores: Positive, Negative, Cognitive, Hostility, and Emotional Discomfort (Bell et al., 1994). Symptom raters for the study maintained interrater reliability through periodic rater training sessions, and all raters were trained to a criterion reliability of 0.7 intraclass correlation coefficient (ICC).

2.3.3. Adaptive functioning

UCSD Performance-Based Skills Assessment (UPSA-BRIEF; Patterson et al., 2001; Mausbach et al., 2007). This standardized, performance-based instrument of everyday function provides information regarding the patient's ability to count out and provide change using actual domestic currency and write checks (Finance Domain) and

ask for information and reschedule a doctors' appointment via telephone (Communication Domain). We selected the total scores of each subdomain for analysis.

2.4. Statistical analysis

Data were analyzed using IBM SPSS Statistical Package (version 19.0.0, 2010). Homogeneity of variance in all measures was confirmed using Levene's test (Levene, 1960) or the Hartley's FMax test when applicable. Analyses then were conducted in 3 phases: (1) Baseline characteristics were compared using Chi-square tests for the categorical demographic measures and one-way ANOVAs for baseline neurocognitive, functional and symptom variables with Bonferroni corrected post hoc comparisons. (2) All outcome measures were analyzed with repeated measures analyses of covariances (ANCOVAs). Age group (ES vs EC vs LC), time (pre vs. post-treatment testing) and condition (CR vs CS) were considered as fixed factors; the posttest scores as the dependent variable, and the baseline scores of the specific variable as covariates. In RCTs in which subjects are assigned to each condition randomly, the ANCOVA approach has shown to be the most powerful for detecting treatment (Vickers and Altman, 2001) effect. Additionally, we conducted post-hoc comparisons with Bonferroni corrections to compare the three groups when applicable and pairwise contrasts with the interactions. (3) We conducted an additional exploratory ANCOVA using the same factors as above but just including participants who had received 40 or more hours of computer training (ES n=12; EC n=14; LC n =14). All statistical tests were two-tailed and alpha was set at 0.05.

3. Results

There were no gender differences between groups but the ES group was more ethnically diverse. The LC group had more years of parental education (p=0.015), a greater number of years of achieved education (p=0.029) and more hospitalizations than the ES group (p=0.019). As expected the three groups differed from each other in their duration of the illness, the LC group was the one with the longest illness duration (M=18.17, SD =10.87; LC vs. ES $p < 0.001$; LC vs. EC $p < 0.001$) followed by the EC group (M=7.65, SD =5.61) and the ES group (M=3.44, SD=2.84; ES vs EC p=0.036). The LC group endorsed higher hostility ratings than the ES group (p=0.013) and the ES group scored significantly lower than the EC group in the communication domain from the adaptive functioning scale (p=0.030) at baseline but were similar at baseline on all other clinical and functional measures. Groups did not differ in baseline working memory, or on any other symptom ratings (see Table 1). The sample as a whole received 48.61 mean hours of CR or computer skills treatment (SD=30.79); the early-stage group received 42.08 h of treatment (SD: 29.98), the early-chronic group received a mean of 56.59 h of treatment (SD=32.26), while the late-chronic group received 49.25 h of treatment (SD=29.57). These differences in treatment hours were not significantly different.

With respect to the two primary cognitive outcomes (DS and LNS), main effects of time were evident for both measures ($F_{(1, 105)}$ =8.398, p=0.005; $F_{1, 105}$=20.048, $p < 0.001$, respectively), while a time×condition effect ($F_{(1, 105)}$=5.70; p=0.019), revealed significantly greater improvement in the CR condition on one of the two working memory outcome measure (Digit Span) compared to the CS condition. Additionally, the three way interaction between group, time and condition reached a trend level of significance ($F_{(2,105)}$ =2.959; p=0.056) for DS. Further analysis of this effect revealed that the ES group showed improvements in the CR condition that were greater than those in the CS condition ($p < 0.004$), while the EC group showed CR-related improvements in DS that approached significance (p=0.062; (Table 2 and Fig. 1). There were significant main effects of time in the two adaptive functioning subtests from the UPSA measures: Finance ($F_{(1, 90)}$=39.880, $p < 0.001$), and Communication, ($F_{(1, 90)}$=17.583, $p < 0.001$). There were no other main effects or interactions found in this domain.

With respect to symptoms, there were main effects of time on all of the PANSS factors: Positive ($F_{(1, 87)}$=22.71, $p < 0.001$), Negative ($F_{(1, 87)}$=6.997, p=0.010), Cognitive ($F_{(1, 87)}$=32.419, $p < 0.001$), Hostility, ($F_{(1, 87)}$=33.729, $p < 0.001$), and Emotional Discomfort ($F_{(1, 87)}$=14.554, $p < 0.001$) factors. Additionally, our data revealed a two-way time×condition interaction in the hostility subscale ($F_{(1, 87)}$=4.704, p=0.03) and a three way- time×condition×group interaction ($F_{(2, 87)}$=3.625, p=0.031) on the Positive PANSS subscale. The two-way interactions for the Hostility symptom factor showed that participants in the CS condition showed a greater decrease in their Hostility scores relative to the CR condition. In regards to the three-way interaction for the Positive Symptom factor from the PANSS, Positive Symptom Factor improvement was greater in the CS condition as compared to the CR condition for the early-chronic age group (p=0.007 for the EC). See Table 2.

With respect to participants receiving a minimum of 40 h of training and selecting DS and LNS as the outcome, the new ES (n=12; mean age: 22.17 ± 1.467 years old), EC (n=14; mean age: 32.86 ± 4.487 years old) and LC (n=14, mean age: 46 ± 5.823 years old) did not differ in gender or ethnicity. Additionally, they did not differ in number of life time hospitalizations or in baseline working memory and functional measures, although the ES group had more negative symptoms at baseline ($F_{(2,32)}$ =3.48; p=0.043) than the LC group ($\boldsymbol{p}$=0.048). Additionally, the LC group presented with higher hostility symptoms ($F_{(2,32)}$ =3.49; p=0.042) than just the ES group (p=0.038). A time×condition ($F_{(1, 33)}$ =5.94; p=0.020) interaction in DS revealed that all participants receiving CR improved more over time than the ones receiving CS. Additionally, an group×time×condition interaction revealed ($F_{(2,33)}$ =3.97; p=0.028) that only the ES group (p=0.021) and the EC group (p=0.014) improved more if receiving CR as compared to CS.

4. Discussion

This is the first study, to our knowledge, to specifically examine the predictive value of age in treatment response to a restorative, drill-and-practice CR treatment intervention vs. an active control condition in people with schizophrenia across three different ages and stages of illness: early-stage (25 years or younger) vs. early-chronic 26–39 years old) vs. late-chronic stages (40 years old or older). Three significant outcomes emerged: First, providing partial support for our hypotheses, our results revealed that the early-stage and the early chronic participants showed differential improvements in one of our primary cognitive outcomes, attention and verbal working memory (Digit Span), relative to the computer skills control condition at a trend level. These results were replicated in a subsample of participants who had all completed an adequate dose of at least 40 h of CR training. These latter findings are of particular note as sample sizes were considerably smaller for these secondary analyses. Our results add to previous studies showing superior benefits of CR on cognitive outcomes in younger patients with shorter durations of illness (Bowie et al., 2014; Kontis et al., 2013; Wykes et al., 2009), and expands these conclusions by showing the specificity of these age effects to CR relative to a control condition consisting of extended clinician and computer exposure and cognitive challenge. Our findings also expand the extant literature by providing greater precision regarding the age and illness durations at which these differences emerge. Second, inconsistent with our hypotheses, these age and chronicity-related differences evident in treatment response in cognitive outcomes did not generalize to our measure of adaptive functioning, the UPSA-Brief. Third, and largely consistent with our hypotheses, with the exception of the greater improvement in positive symptoms in the early-chronic group that received CS, there were no effects of age on the improvement in symptoms associated with these interventions.

Table 2
Group differences per age group, time and condition. Pre and post treatment mean and standard deviations of the standardized scores.

	Condition[a]	*n*	Testing Time[b]	Early Stage*n*=45 M(SD)	Early Chronic *n*=31 M(SD)	Late Chronic *n*=36 M(SD)	*F*- Statistic/ *p* values			Bonferroni Pairwise post-hoc Comparisons[c]
							Time	Time×Condition	Condition×Group×Time	
Working Memory										
Digit Span	CR	61	1	8.19(3.03)	8.15(2.72)	8.80(3.64)	8.398	5.70	2.96	Ns
			2	9.95(3.07)	9.50(2.72)	9.50(4.06)	p=0.005	p=0.019	p=0.056	
	CS	51	1	8.75(3.58)	8.36(3.29)	9.25(3.36)				
			2	8.83(4.38)	8.36(2.84)	10.25(3.50)				
LNS	CR	61	1	8.33(3.60)	8.00(2.92)	6.60(3.31)	20.05	Ns	Ns	Ns
			2	8.86(3.15)	8.85(3.81)	7.90(4.70)	$p < 0.001$			
	CS	49	1	8.57(2.92)	8.18(2.79)	8.20(2.30)				
			2	9.04(3.20)	8.09(2.42)	9.20(2.78)				
Adaptive Functioning										
Finance	CR	51	1	7.61(3.15)	8.32(1.86)	8.71(1.90)	39.88	Ns	Ns	Ns
			2	14.28(3.98)	15.32(3.20)	15.00(3.14)	$p < 0.001$			
	CS	46	1	8.22(1.83)	8.50(1.18)	8.77(1.88)				
			2	14.87(3.93)	15.30(1.95)	17.00(1.68)				
Communication	CR	51	1	6.33(1.61)	6.84(1.61)	6.50(1.65)	17.58	Ns	Ns	Ns
			2	15.00(3.27)	15.16(3.86)	15.64(3.67)	$p < 0.001$			
	CS	46	1	6.05(1.46)	7.60(0.97)	6.93(1.21)				
			2	14.68(3.94)	16.60(2.46)	16.21(3.12)				
Clinical Symptoms										
PANSS Positive (5f)	CR	52	1	16.41(6.14)	16.89(4.61)	20.41(4.86)	20.71	Ns	3.625	ES = CR > CS
			2	14.53(4.64)	17.89(4.62)	15.82(4.45)	$p < 0.001$		P=0.031	EC = CS > CR
	CS	42	1	17.27(6.16)	16.29(5.15)	15.54(4.89)				LC = CS > CR
			2	15.86(5.78)	12.86(3.89)	12.92(3.43)				
PANSS Negative (5f)	CR	52	1	21.00(5.64)	18.11(6.38)	18.47(5.47)	6.99	Ns	Ns	Ns
			2	19.17(6.90)	17.11(6.85)	18.53(6.22)	p=0.01			
	CS	42	1	20.54(5.00)	19.43(5.74)	20.69(3.66)				
			2	18.27(8.40)	19.28(8.13)	22.77(4.32)				
PANSS Cognitive (5f)	CR	52	1	16.70(4.52)	17.05(4.72)	18.65(5.25)	32.42	Ns	Ns	Ns
			2	15.23(3.19)	15.28(5.20)	17.88(3.55)	$p < 0.001$			
	CS	42	1	16.90(2.90)	17.00(5.94)	17.31(5.10)				
			2	14.86(4.51)	16.28(5.19)	15.54(3.82)				
PANSS Hostility (5f)	CR	52	1	5.59(2.15)	7.34(3.07)	6.94(2.68)	33.73	4.70	Ns	Ns
			2	6.23(2.16)	5.50(2.28)	7.41(3.61)	$p < 0.001$	p=0.03		
	CS	42	1	5.68(1.73)	5.29(1.11)	7.69(3.92)				
			2	4.77(1.77)	4.28(0.49)	6.23(3.22)				
PANSS Emotional Discomfort (5f)	CR	52	1	11.41(3.18)	11.11(3.01)	11.88(3.33)	14.55	Ns	Ns	Ns
			2	9.59(2.87)	11.78(2.86)	10.94(3.36)	$p < 0.001$			
	CS	42	1	9.59(2.87)	9.71(2.36)	11.54(2.50)				
			2	9.77(4.12)	10.00(3.56)	12.85(4.72)				

Note: ES: Early-Stage; EC: Early-Chronic; LC: Late-Chronic.
Measures: Working Memory: Wechsler Intelligence Scale III & IV Digit Span, Wechsler Intelligence Scale IV Letter Number Sequencing.
Adaptive Functioning: UCSD Performance- Based Skills Assessment Finance sub score (Finance); UCSD Performance- Based Skills Assessment Communication sub score (Communication); Clinical Symptoms: Positive and Negative Syndrome Scale; 5 factor ratings: Subtotal Score for the five factors, Positive (5f), Negative (5f), Cognitive (5f), Hostility and Emotional Discomfort (5f).
[a] Condition: CR = Cognitive Remediation; CS: Computer Skills.
[b] Testing Time: Pretreatment scores=1; Post-treatment scores=2.
[c] Bonferroni Post hoc comparison=Pair-wise comparisons.

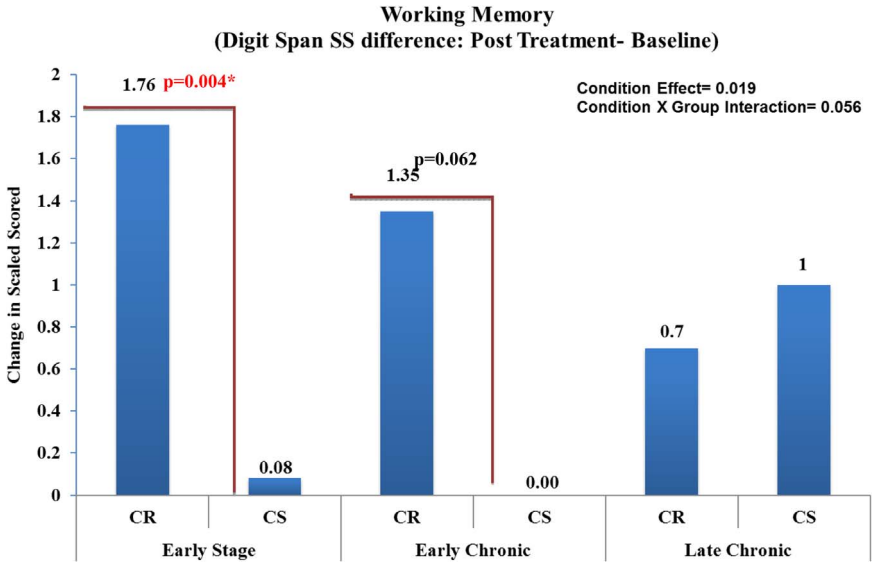

Fig. 1. Improvements in standardized score on a measure of working memory (Digit Span) in three age groups and two experimental treatments. *pair-wise comparisons.

The absence of corresponding age differences in adaptive function improvement in response to CR was unanticipated given the fact that nearly all clients in the study (n=112) were enrolled in intensive outpatient rehabilitation that would permit exercise of newly enhanced cognitive abilities for improved adaptive skill acquisition. Several explanations for this finding can be offered. First, the study groups may have been underpowered to detect these generalization effects, which are presumed to be much smaller than those on cognitive outcome measures more proximal to the target of the CR intervention. Second, the active control condition, which provides work-related computer skills, and has been shown to improve several domains of cognition relative to baseline in previous studies (Kurtz et al., 2007) may have masked generalization effects of enhanced cognition in the CR groups by improving cognitive factors (other than working memory) for performance of these functional skills in the control group. Third, recent studies have revealed the effects of CR on vocational outcomes only during follow-up periods after cessation of extended CR programs (Bell et al., 2005). These studies suggest that a period of consolidation of newly gained cognitive skills is necessary before these gains translate into measurable functional outcomes. Without a second follow-up assessment in the current study it remains unclear whether differences between groups might have emerged at a later time point.

We note that our findings are different in some respects from those of Bowie et al. (2014) who found a trend towards greater improvement in response to CR in their early-course clients on performance-based skills measures identical to those selected for the current study. The use of an active control group, the focus on a drill-and-practice method of CR, effects of other rehabilitation interventions in which all participants in this study showed some improvement in functioning and differences in sample size may explain these differences in findings.

Our findings suggest that a different type of CR may be needed for older patients for improving cognitive outcomes. While the current program placed a large emphasis on drill-and-practice exercises and a hierarchical approach to neurocognitive training, practice in elementary sensory processing was not an element of the intervention. For example, the Brain Fitness program from Posit Science, used successfully in a number of studies by Vinogradov and colleagues, begins with training fidelity of early sensory encoding and information processing (eg., Fisher et al., 2009). Given age-related decline in early sensory encoding in the general population, and some evidence of accelerated neurobiological aging in people with schizophrenia, perhaps this is a necessary approach with older individuals (Schnack et al., 2016).

Our findings of an advantage of the control CS condition for improving positive symptoms in early chronic patients was unanticipated especially given the fact that all clients enrolled in the study were stabilized outpatients with low levels of positive symptoms at baseline (see Table 1). While it may represent a false positive finding, alternatively, the focus of the control condition on applied office work skills perhaps instilled at least some patients with increased hope and anticipation around the possibility of attaining employment and a corresponding decrease in some psychotic symptoms. This finding will need to be replicated in future studies.

This study has several limitations. As already mentioned, although our overall sample was substantial, our individual group sizes were moderate in size and consequently some of our statistical comparisons may have been underpowered. Second, differences in lifetime medication exposure and non-compliance could be factors influencing our results. Third, cohort effects typically associated with cross-sectional studies could have influenced our findings (i.e., more clinical variability amongst the youngest group with some subjects that eventually remit and some do not and the older groups being comprised of sicker, chronic patients who never are able to get out of treatment). However, the fact that with the exception of Hostility ratings, groups did not differ at baseline in clinical symptoms suggests those effects may be small. Fourth, we note that while age effects were evident on one working memory measure, Digit Span, effects were not evident on a second, more cognitively demanding index of working memory involving mental re-organization of both letters and numbers (LNS). This might suggest a very specific effect for only simpler forms of working memory. Fifth, we note that this report is based on a secondary analysis of data from a randomized, controlled trial, and thus was limited by aspects of the parent study design. Future studies targeted specifically at the effects of age on CR response should include a wider range of ages. Sixth, age and chronicity were largely confounded in this study, and the effects of identical chronicity on response to CR may not be identical to those of age. It also remains unclear to what degree these findings generalize to other forms of CR that are more strategy-based. Lastly, the durability of these age effects remains unknown.

In summary, we demonstrated age- and treatment-specific effects in CR improvement across three different developmental stages of schizophrenia compared to a closely-matched control group. Specifically, the early-stage and early-chronic patients receiving our drill-and-practice CR intervention showed larger improvements in working memory, especially those that received greater treatment duration. Therefore, to the degree that improved cognitive outcomes are viewed as a desirable treatment target, future CR interventions will

need to customize their mechanisms of action to target the cognitive characteristics of clients who are older and have been sick longer more effectively. Additional research on the moderating effects of age on CR response might also provide greater insight on the mechanisms by which CR improves both cognitive, symptom and functional outcomes in schizophrenia.

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