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Impact of baseline early auditory processing on response to cognitive remediation for schizophrenia

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Abstract

Background: Early auditory processing (EAP) has increasingly become a focus of efforts to identify biomarkers of treatment response in schizophrenia. EAP deficits lead to poor functional outcome via impaired cognition, and treatments that target EAP may drive downstream cognitive improvements. Assessment of baseline need provides an opportunity for cognitive remediation (CR) programs that give EAP training to personalize treatment and optimize its impact. This initial efficacy study examined the differential benefit of EAP training for those with and without baseline EAP deficits as defined by performance on the Tone Matching Test.

Methods: 103 outpatient adults diagnosed with schizophrenia or schizoaffective disorder were classified as having intact (48.5%) or impaired (51.5%) EAP and randomized to a CR program with restorative exercise plans that either included EAP training (N = 49) or did not (N = 54). Cognitive and functional outcomes were measured post-treatment and 3 months later.

Results: Only in EAP impaired participants was there a significant benefit from EAP training on verbal learning. Treatment condition did not significantly impact global cognitive or functional outcomes for either EAP group. Cognitive gains partially mediated the relationship between gains in EAP and functional capacity.

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Conclusion: These findings support the importance of addressing basic auditory deficits when attempting to remediate higher order auditory impairments such as verbal learning. In addition, they highlight the need for routine assessment of EAP in cognitive remediation participants, as well as the need for more effective programs to reverse these impairments.

Keywords

Cognitive remediation; Neurocognition; Early auditory processing

1. Introduction

Early auditory processing (EAP) has increasingly become a focus of efforts to identify biomarkers of clinical disability and treatment response in schizophrenia. EAP deficits are a type of lower order cognitive dysfunction that are commonly found in all phases of schizophrenia, and have been linked to the widespread disturbances in higher-order cognition and daily functioning (Javitt and Freedman, 2015; Voss et al., 2018). EAP deficits in schizophrenia are manifest in impaired abilities to discriminate length (Davalos et al., 2003), intensity (Holcomb et al., 1995) and pitch (Strous et al., 1995) of non-verbal sounds, as well as in segregating sequences of pitches into the different perceptual categories that form a melodic stream (McLachlan et al., 2013). A large cross-sectional cohort study demonstrated that EAP deficits lead to poor functional outcome via impaired cognition, as measured by deficits in skills like memory, working memory, attention, and executive functioning (Thomas et al., 2017). This suggests that treatments that target EAP may drive downstream cognitive and functional improvements.

Cognitive remediation (CR) is the current treatment of choice to improve cognitive processes (EAP, attention, memory, executive function, social cognition, or metacognition) that impact daily functioning in schizophrenia (Medalia and Erlich, 2017). Nevertheless, results of CR studies that target EAP have been mixed (Adcock et al., 2009; Dale et al., 2016; Fisher et al., 2015; Keefe et al., 2012; Murthy et al., 2012; Rass et al., 2012), possibly because a systematic method of identifying who needs EAP training was not utilized. While EAP impairment is useful in differentiating healthy controls from schizophrenia, it is not universally present in those diagnosed with schizophrenia (Rabinowicz et al., 2000; Thomas et al., 2017). Thus, when everyone in a CR program receives EAP training, regardless of baseline need, results of the interventions may become diluted. Identification of prognostic indicators that predict differential benefit from EAP engagement is one way to personalize treatment and optimize its impact.

EAP deficits in schizophrenia typically remain undetected unless specifically evaluated, yet EAP assessment is rarely performed in clinical settings. Tests that are biased toward measurement of sensory ability are not included in standard neurocognitive assessment batteries for schizophrenia, such as the MATRICS Consensus Cognitive Battery (Nuechterlein et al., 2008), nor are they included in baseline cognitive assessments used in clinical practice of CR (Medalia and Bowie, 2016; Medalia et al., 2017). Mismatch negativity (MMN) is an electrophysiological paradigm used to index function of early auditory regions in cortex, but is impractical for clinic settings where cognitive remediation

is performed. However, pitch discrimination, which is one of the most documented EAP impairments in schizophrenia, can be measured with the Tone Matching Test (TMT), a quick, simple, accurate and reliable way to assess pitch discrimination performance for non-verbal sounds (Petkova et al., 2014; Strous et al., 1995). Severely impaired TMT performance in schizophrenia is independent from psychotic symptoms, present in about half of those diagnosed, correlates significantly with early cortical measures of auditory processing such as MMN deficits, and contributes directly to impairments in higher cognitive functions such as attention and memory (Donde et al., submitted; Donde et al., 2017; Javitt, 2009; Javitt and Sweet, 2015; Lee et al., 2018; Petkova et al., 2014). Further, behavioral improvements on the TMT during auditory training correlate with changes in MMN (Javitt et al., 2000; Kantrowitz et al., 2016). Taken together, these qualities of the TMT make it a good candidate for use as a tailoring variable when assigning clinic-based treatments that involve EAP training.

Many CR programs that use restorative computer-based cognitive exercises deliver cognitive exercises in a hierarchy, starting with attention and progressing to processing speed, working memory, verbal learning and memory, and problem solving. It remains unclear when it is useful to begin the hierarchy at an earlier level of information processing, targeting more basic non-semantic information processing in the auditory domain along with practice on exercises that incorporate working memory, verbal learning and memory. Using the TMT as a tailoring variable allows for study of the differential benefit of EAP training for those with and without EAP deficits. Do people with EAP deficits make greater cognitive improvement when given EAP training? When people without EAP deficits receive EAP training does it impact their CR outcomes?

To answer these questions, this initial efficacy study randomized patients with intact and impaired EAP, as measured by TMT, to two types of restorative CR exercise plans: one which included EAP training and one which did not. Because the emphasis of this study was to inform clinical practice, it was conducted in outpatient treatment (as opposed to research) settings, using exercises drawn from web-based platforms available to practitioners in the community. Cognitive and functional outcomes were measured post-treatment and 3 months later. We hypothesized that: 1) EAP impaired (EAP–) patients would benefit more from CR that included EAP training, while EAP intact (EAP+) patients would not experience greater cognitive and functional advantage with EAP training, 2) EAP– patients who improved most during EAP training would show the largest gains in cognition, and 3) cognitive gains would mediate the relationship between gains in EAP and functional outcome.

2. Methods

2.1. Participants and procedures

This registered clinical trial () was conducted under the guidance of the New York State Psychiatric Institute (NYSPI) Institutional Review Board. Participants were outpatients, 18–65 years old, with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Exclusion criteria were documented auditory disorders or known visual impairment that precluded completing assessment, intellectual disability, presence or history of any neurologic illness that may affect brain physiology, current substance dependence,

participation in cognitive remediation in the 12 months prior to study entry. Participants continued to receive their usual mental health services including stable doses of their psychiatric medications (e.g. typical and atypical antipsychotics). Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV; First et al., 2002) completed at screening by trained MA-level research assistants was used to confirm the diagnostic inclusion/ exclusion criteria. The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) was used to estimate premorbid full scale IQ (FSIQ).

The study used a repeated-measures, stratified randomized trial design. Following completion of all baseline assessments, participants were randomized to receive one of two treatment conditions: “Brain Basics” or “Brain Training” with randomization stratified by EAP status. “Brain Basics” trained auditory psychophysical efficiency (Fisher et al., 2009) in addition to working memory, verbal learning and memory, attention and processing speed. “Brain Training” trained attention, processing speed, working memory, verbal learning and memory, abstract reasoning and problem solving. The difference in the conditions was that only participants in Brain Basics trained auditory psychophysical efficiency and only participants in Brain Training trained abstract reasoning and problem solving. Both conditions entailed 30 separate 75-min group sessions, allotting 60 min for computer exercises, and 15-min for a group “bridging” discussion consistent with the CR treatment model used throughout mental health clinics in New York Office of Mental Health (see Medalia et al., 2018 for a description of the treatment model and treatment fidelity monitors). Cognitive exercise curricula and bridging group content were informed by a preliminary 10-session open trial and focus group feedback which included 12 outpatients and CR clinicians from one psychiatric rehabilitation program in New York City. At each of the 7 separate outpatient behavioral health facilities, 30 sessions of CR were administered 3 times weekly in a group format. All sessions were led by a MA-level research clinician, blinded to baseline assessment results, who provided coaching and support. Treatment fidelity was monitored weekly.

2.2. Assessment

Participants were tested on the following measures at baseline, within 1-week following end of treatment, and at 3-month follow-up by an MA-level evaluator who was blind to treatment condition and independent from those involved in the cognitive remediation. Compensation was provided for completion of assessments.

EAP was assessed with the Tone Matching Test (TMT), consisting of 5 sets of 26 pairs of 100-ms tones in series, with 500-ms inter-tone interval. Within each set, tones (50% each) are either identical or differ in frequency by a specified amount in each block (2.5%, 5%, 10%, 20%, or 50%). Subjects indicate whether the pitch is the same or different. Three base frequencies (500, 1000, and 2000 Hz) are used within each block to avoid learning effects. The TMT has demonstrated good test-retest reliability in both schizophrenia (ICC = 0.83) and healthy control (ICC = 0.821) samples (Petkova et al., 2014). The mean (SD) total percent correct in 10 studies ranges from 65.5% (9.9) to 73.3% (2.2) for 371 schizophrenia patients and 73.8 (2.3) to 92.3 (9.9) for 342 healthy controls, with a large effect size (1.17) difference (Donde et al., 2017). Within schizophrenia samples two clusters are consistently

identified, with about half of the individuals having total correct scores that are significantly lower than those of healthy controls (Donde et al., submitted manuscript; Donde et al., 2017; Lee et al., 2018; Petkova et al., 2014). A cut-off score of 70% correct, based on the distribution of performance deficits, was used to classify participants in this study as EAP impaired (<70% correct; EAP–) or intact (≥70% correct; EAP+) (Donde et al., submitted manuscript; Petkova et al., 2014).

The NIMH MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008) assessed neurocognitive functioning with measures of: a) working memory; b) attention/ vigilance; c) verbal learning; d) visual learning; e) processing speed; and f) reasoning and problem solving. The MCCB neurocognitive composite T-score was the primary outcome measure.

The functional outcome measure was the Brief UCSD Performance-Based Skills Assessment (UPSA-B; Mausbach et al., 2007), an assessment of functional capacity that requires participants to complete a series of role-play tasks that assess everyday life skills. The UPSA-B total score was the outcome variable.

The Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS; Kay et al., 1992) was used to assess symptoms of psychotic disorders including positive, negative and general psychopathology.

2.3. Statistical analysis

We first checked the balance of participant baseline characteristics between treatment conditions using 2 sample t-tests for continuous variables, and Chi-squared tests for categorical variables. The same approach was used to identify baseline characteristics that affect EAP status.

To characterize overall response to CR, improvements on the MCCB neurocognitive composite and UPSA-B were assessed using Cohen’s d effect size, and tested using paired-sample t-tests, which for the MCCB compared change to practice effect, i.e., >2 T score points (Keefe et al., 2011). Number Needed to Treat (NNT) was calculated by defining clinically significant improvement as a gain of 9 points on the MCCB at follow-up (Harvey and Keefe, 2016), and transition from <60 on the UPSA-B to 60 or higher at follow-up (Mausbach et al., 2007).

Wilcoxon’s rank-sum test, a non-parametric test which is more robust to potential outliers and error variance assumptions as compared to t-test in relatively small samples, examined the main effect of treatment condition, and the main effect of EAP status on improvement in MCCB and UPSA-B from baseline to post-treatment and from baseline to follow-up. Cohen’s d effect size was also computed. The same approach was used to quantify the treatment effect within each EAP subgroup to address hypothesis 1. In addition, the treatment by EAP subgroup interaction was tested using ANOVA F-test. Post-hoc, we examined the treatment effect on verbal learning using the same approach.

To further examine the role of auditory processing in CR response, percentage improvement in Auditory Processing Speed (APS) was quantified for all Brain Basics participants, an

index of target engagement during auditory training (Biagianti et al., 2016; Tarasenko et al., 2016). To test hypothesis 2, Pearson's correlation examined the association between APS and MCCB improvement. In addition, we classified Brain Basics participants as auditory learners or non-learners using a median split of APS improvement. Auditory learners and non-learners were compared on average MCCB improvement using Wilcoxon's rank-sum test, and percentage of participants with MCCB gain of 9 or more (Harvey and Keefe, 2016) using Fisher's exact test. To further address hypothesis 2, these analyses were conducted separately for EAP– and EAP+ subgroups. The interaction effect between learner status and baseline EAP status on MCCB was tested using two-way ANOVA.

To address hypothesis 3, Sobel's method of mediation analysis was used to examine neurocognition (MCCB) as a mechanism through which EAP (TMT) impacted functioning (UPSA-B) at baseline, as well as improvement at follow-up. All analyses were carried out in SAS 9.4 software.

3. Results

A total of 103 participants met inclusion criteria, provided informed consent, completed the baseline assessments, and were randomized to Brain Basics, which included EAP training (N = 49) or Brain Training (N = 54), which did not. For the study's CONSORT diagram, see Fig. 1. Participant characteristics by treatment conditions are summarized in Table 1. Treatment groups did not differ on demographic, diagnostic, cognitive, functional capacity, or psychiatric symptom measures at baseline. EAP– participants were significantly ($p = 0.006$) older (mean ± SD: 46 ± 11) than EAP+ participants (39 ± 13) and had significantly ($p = 0.001$) lower FSIQ (mean ± SD: 83 ± 8 vs 90 ± 11).

3.1. Feasibility assessment

Of the 103 subjects who completed baseline assessment 50 (48.5%) were EAP+ and 53 (51.5%) were EAP–. It is thus feasible to stratify by baseline EAP as measured by TMT. Of those randomized, 98 participants initiated the intervention to which they were allocated. Treatment completion was defined by 30 sessions. Of the 68 treatment completers, average time to completion was 12.65 weeks, or 2.5 sessions per week, with no significant differences in treatment intensity between completers in Brain Basics (n = 33) and Brain Training (n = 35). There were no effects of site on treatment intensity or structure. Post-treatment data were collected in 67 participants, and 3-month follow-up data were collected in 61 participants.

3.2. Response to CR

Across both treatment conditions overall improvements were significantly >2, the practice effect on the MCCB, from baseline to post-treatment, $t(66) = 4.37$, $p < 0.001$, and from baseline to follow-up, $t(60) = 4.71$, $p < 0.001$. Effect sizes for gains on the MCCB at post-treatment ($d = 0.95$) and at follow-up ($d = 0.94$) were large. NNT was 3.2 for cognitive gain.

Likewise, across both treatment conditions there were significant improvements in UPSA-B from baseline to post-treatment, $t(66) = 6.14$, $p < 0.001$, and from baseline to follow-up, $t(60)$

= 6.14, $p < 0.001$. Effect sizes for gains on the UPSA-B at post-treatment (d =0.75) and at follow-up (d = 0.79) were in the moderate to large range. NNT was 1.6 for functional gain.

Across the full sample, change in MCCB was significantly correlated with change in UPSA-B measured from baseline to follow-up (r =0.55, p b 0.001). Change in TMT performance (Fig. 2) was significantly correlated with change in MCCB (r = 0.53, p b 0.001) and change in UPSA-B (r = 0.51, $p < 0.001$) from baseline to follow-up. Outcomes did not significantly differ by site.

Results for effects of treatment condition and EAP status on MCCB and UPSA-B change scores, as well as treatment effects stratified by EAP status, are summarized in Table 2. There was no significant main effect of treatment condition on MCCB gain at post-treatment (p = 0.291) or follow-up (p = 0.496), but a trend level main effect of treatment condition on UPSA-B gain favoring Brain Basics at post-treatment (p =0.095) and at follow-up (p = 0.073). The main effect of EAP status was not significant for MCCB gain at post-treatment (p = 0.267) or follow-up (p = 0.304), or for UPSA-B gain at post-treatment (p =0.477). The improvement in UPSA-B measured at follow-up was greater among EAP– participants than those classified as EAP+ (p = 0.003).

To test hypothesis 1, we used Cohen's d to ascertain the impact of treatment on response within EAP subgroups. Within the EAP– subgroup, there was a moderate effect of treatment condition on MCCB gain (d = 0.46) at post-treatment and at follow-up favoring Brain Basics over Brain Training. In contrast, within the EAP+ subgroup, there was minimal difference observed between the treatment conditions at both post-treatment (d = 0.04) and follow-up (d = 0.17). On the UPSA-B, there was a moderate post-treatment effect of treatment condition within the EAP– subgroup (d = 0.45), and a small effect within the EAP+ subgroup (d = 0.28). These findings were somewhat reversed at follow-up, with a small effect (d = 0.20) in the EAP– and moderate effect (d = 0.42) in the EAP+ subgroups. All p-values were >0.05 (see Table 2).

Since the MCCB neurocognitive composite score reflects performance on many non-auditory tasks, we examined whether auditory deficits specifically limit improvement on verbal learning, the MCCB domain most dependent on auditory processing. Post-hoc, we examined the effect of treatment condition within the EAP subgroups on change in verbal learning. Results are reported within Table 2 and Fig. 4. Only in the EAP– subgroup at post-treatment was there a significant difference (p = 0.04), which favored Brain Basics over Brain Training. The effect size was d = 0.73.

3.3. Auditory processing and CR response

Brain Basics participants were dichotomized as APS leaners (n = 17) or non-learners (N = 16) based on a median percent improvement(47.46%) on auditory exercises. There was a significant interaction at follow-up (Eta squared = 0.12, p = 0.048) between EAP status and APS learner group; only in the EAP– subgroup, APS learners improved significantly more on neurocognition than APS non-learners (d = 1.7, p = 0.004), supporting hypothesis 2. In addition, 7 out of 11 APS learners in the EAP– subgroup gained ≥9 on the MCCB neurocognitive composite at follow-up, whereas none of APS non-learners made such a gain

(Cohen's h = 1.85, p = 0.035). Change in APS was positively correlated with change in neurocognition in the EAP− subgroup at post-treatment (r = 0.35, p = 0.146) which was statistically significant at follow-up (r = 0.80, p = 0.0001), whereas these relationships were minimal and in the negative direction in the EAP+ subgroup (r =−0.18, p = 0.530; r = −0.08, p = 0.795).

Improvement in EAP, as measured by gain on the TMT, was associated with neurocognitive gain at follow-up for both EAP− (r = 0.48, p = 0.005) and EAP+ subgroups (r = 0.55, p = 0.002). Using the same criteria as stated above, the NNT in the Brain Basics condition was 3.2 for cognition as measured by MCCB and 1.4 for functional outcome as measured by UPSA-B. Whereas both EAP− and EAP+ subgroups showed similar NNT for functional outcome (1.3 and 1.5 respectively) the NNT for cognitive gain on the MCCB was less than half for the EAP− (2.4) compared to the EAP+ (6.0).

3.4. Mechanism of CR impact

Mediation analyses tested the hypothesis that gain in cognition is the mechanism through which gain in EAP impacts functional outcome. Due to baseline differences between EAP subgroups in age and FSIQ, both unadjusted and adjusted models were tested. Since the results did not ultimately differ, Fig. 3 shows only the unadjusted models.

At baseline, EAP measured by the TMT correlated significantly with both functional capacity (β = 0.680, p < 0.001) and cognition (β =0.456, p < 0.001). In the multiple regression model, accounting for the significant effect of cognition (β = 0.727, p = 0.001) reduced the effect of EAP on functional capacity (β = 0.348, p = 0.002); the indirect effect of EAP was significant (β = 0.332, p b 0.001).

At follow-up, change in EAP had a significant effect on change in functional outcome (β = 0.878, p < 0.001) and change in cognition (β =0.381, p = 0.001). In the multiple regression model, change in cognition had an effect on change in functional outcome (β = 0.910, p = 0.003), and the association between change in EAP and change in functional outcome was reduced, but still significant (β = 0.532, p = 0.015). As a result, change in EAP had a significant indirect effect (β = 0.347 p =0.009) on functional outcome change, indicating that change in cognition partially mediated the effect of change in EAP on change in functional outcome.

4. Discussion

While EAP deficits reliably differentiate people in all phases of schizophrenia from healthy controls, and are associated with impaired cognition and poor functional outcome, they are not present in all diagnosed patients (Javitt and Freedman, 2015; Voss et al., 2018). Cognitive treatments that target auditory system dysfunction have the potential to drive downstream cognitive and functional improvements (Dale et al., 2016; Thomas et al., 2017), but may not be necessary for those patients without EAP impairment. To our knowledge, this is the first study to test use of pre-training EAP as a tailoring variable to personalize the treatment plan used in cognitive remediation. The need for clear guide posts for clinicians to make treatment decisions and the properties of the Tone Matching Test together informed

the decision to dichotomize EAP performance. Study data supported the feasibility of stratification based on Tone Matching performance. We then compared the efficacy of two types of restorative CR exercise plans: one which included auditory processing training and one which did not. The hypotheses were that (1) people with baseline EAP impairment would benefit from restorative training exercises that target auditory processing, while those without impairment would not, (2) EAP− participants who engage best with auditory training exercises would show the largest treatment gain, and (3) cognitive gains would mediate the relationship between gains in EAP and functional outcome. Results provided partial support for our first hypothesis and full support for the second and third.

The goal of personalizing cognitive treatment is best conducted in the context of an efficacious CR approach. In this study, both conditions were structured like the CR programs used in outpatient clinics in the NY State Office of Mental Health system of care (Medalia et al., 2017). We found that the CR approach was efficacious. Across both conditions cognitive change significantly exceeded practice effects, and the effect sizes were large post-treatment and three months later. The NNT of3.21 indicated that about 3 people had to be treated with CR for one to make a clinically significant cognitive gain that was unlikely to have occurred by chance. Functional change was also significant across treatment conditions, with moderately large effect sizes at both endpoints. The NNT of 1.625 indicated that <2 people needed to be treated for one to make clinically significant functional gain. Even in the absence of a non-cognitive control condition, these data indicate that the treatment approach provided an excellent foundation for this study of using EAP status to personalize CR.

Results provided some support for using baseline EAP as a tailoring variable to personalize CR. Only in the EAP− subgroup did the auditory-dependent domain of verbal learning respond significantly better to CR that included EAP training. Global neurocognition was not significantly more improved when EAP− participants received EAP training, but moderate treatment effect sizes for cognitive outcomes favored provision of EAP training for the EAP− subgroup. As predicted, the EAP+ subgroup showed no advantage with EAP training and treatment effect sizes comparing impact of the CR approaches for cognitive outcomes were negligible. Effect sizes for comparative impact of the two types of CR on functional outcome were small to moderate for both EAP+ and EAP− subgroups.

Training data also supported tailoring treatment by baseline EAP status. Only in the EAP impaired group was improvement on the task that targets Auditory Processing Speed (APS) significantly associated with cognitive gain. Further, the NNT analysis speaks to a difference in how baseline EAP status impacts response to CR with auditory training. Whereas only 1 in 6 EAP+ patients exposed to EAP training made clinically significant improvement in cognition (9+ T points), 1 in 2.43 EAP− patients exposed to EAP training had clinically significant improvement in cognition. Interestingly, the NNT of 2.43 for cognition in EAP− patients compares favorably to the predicted NNT of 2.36 provided in the Thomas et al. (2017) study which was based on cross-sectional data from 1415 patients who underwent EAP, cognition and functional assessments.

Several factors may have influenced why there were not significantly better global cognition and functional outcomes for the EAP−subgroup exposed to EAP training. The benefit of

auditory processing training may only be evident on auditory-based cognitive domains, as we found. Also, small subgroup sample sizes and the EAP training approach used may require adjustment. Tone Matching performance did selectively improve with use of the commercially available EAP training program, but the change was not large relative to the magnitude of the background deficit. EAP− patients in particular, may need to spend more time on EAP exercises, or the exercises may need to better target earlier phases of auditory processing. The data suggests that all these possibilities are worthy of further investigation.

Consistent with prior research (Best and Bowie, 2017), we found that the mechanism of functional change in cognitive remediation is linked to cognitive change. Across the full sample, improvement in MCCB was significantly correlated with improvement in UPSA-B measured from baseline to follow-up. Furthermore, mediation analyses at baseline supported prior research reported by Thomas et al. (2017); in this study, cognition partially mediated the effect of baseline EAP on functioning. This present study is, however, relatively unique in its approach to understanding the role of EAP in change in functional outcome following CR. Across treatment conditions for the full sample, improvement in our measure of EAP had a significant effect on change in functional outcome, where change in cognition partially mediated this relationship. These data highlight the role of EAP in driving cognitive and functional change and underscore the role of cognitive gain in improving functional outcome.

It is important that feasibility guides research on methods to implement personalized CR. Unlike the Thomas et al. (2017) study which used neurophysiological measures including MMN, P3a, and reorienting negativity to measure EAP, our measure of EAP was the Tone Matching Test, chosen both for its merits as a measure of EAP and its ease of use in clinic settings. It is unlikely that clinic-based CR programs would have access to electrophysiological measures, thus it is important that we found similar results using a simple behavioral EAP assessment tool. Future research using all these EAP measures will have value in confirming the results of our study, keeping in mind the necessity for measures that are feasible to implement.

In conclusion, the present findings support the role of EAP in developing assessment and treatment approaches for schizophrenia.

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References

Adcock RA, Dale C, Fisher M, Aldebot S, Genevsky A, Simpson GV, Nagarajan S, Vinogradov S, 2009 When top-down meets bottom-up: auditory training enhances verbal memory in schizophrenia. Schizophr. Bull 35 (6), 1132–1141. [PubMed: 19745022]

Best MW, Bowie CR, 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. [PubMed: 28511562]

Biagianti B, Fisher M, Neilands TB, Loewy R, Vinogradov S, 2016 Engagement with the auditory processing system during targeted auditory cognitive training mediates changes in cognitive outcomes in individuals with schizophrenia. Neuropsychology 30 (8), 998–1008. [PubMed: 27617637]

Dale CL, Brown EG, Fisher M, Herman AB, Dowling AF, Hinkley LB, Subramaniam K, Nagarajan SS, Vinogradov S, 2016 Auditory cortical plasticity drives training-induced cognitive changes in schizophrenia. Schizophr. Bull 42 (1), 220–228. [PubMed: 26152668]

Davalos DB, Kisley MA, Ross RG, 2003 Effects of interval duration on temporal processing in schizophrenia. Brain Cogn. 52 (3), 295–301. [PubMed: 12907174]

Donde C, Luck D, Grot S, Leitman DI, Brunelin J, Haesebaert F, 2017 Tone-matching ability in patients with schizophrenia: A systematic review and meta-analysis. Schizophr. Res 181, 94–99. [PubMed: 27742161]

Donde C, Martinez A, Kantrowitz JT, Silipo G, Dias E, Corcoran C, Medalia A, Saperstein A, Vail B, Javitt DC, 2019 Bimodal Distribution of Tone-matching Deficits Indicates Discrete Pathophysiological Entities Within the Syndrome of Schizophrenia (submitted).

First MB, Spitzer RL, Gibbon M, Williams JBW, 2002 Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P) Biometrics Research, New York State Psychiatric Institute, New York.

Fisher M, Holland C, Merzenich MM, Vinogradov S, 2009 Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. Am. J. Psychiatry 166, 805–811. [PubMed: 19448187]

Fisher M, Loewy R, Carter C, Lee A, Ragland JD, 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. [PubMed: 24444862]

Harvey PD, Keefe RSE, 2016 Assessment as it relates to functional goals In: Medalia A, Bowie CR (Eds.), Cognitive Remediation to Improve Functional Outcomes. Oxford University Press, New York, pp. 24–46.

Holcomb HH, Ritzl EK, Medoff DR, Nevitt J, Gordon B, Tamminga CA, 1995 Tone discrimination performance in schizophrenic patients and normal volunteers: impact of stimulus presentation levels and frequency differences. Psychiatry Res. 57 (1), 75–82. [PubMed: 7568562]

Javitt DC, 2009 When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. Annu. Rev. Clin. Psychol 5, 249–275. [PubMed: 19327031]

Javitt DC, Freedman R, 2015 Sensory processing dysfunction in the personal experience and neuronal machinery of schizophrenia. Am. J. Psychiatry 172 (1), 17–31. [PubMed: 25553496]

Javitt DC, Sweet RA, 2015 Auditory dysfunction in schizophrenia: integrating clinical and basic features. Nat. Rev. Neurosci 16 (9), 535–550. [PubMed: 26289573]

Javitt DC, Shelley A, Ritter W, 2000 Associated deficits in mismatch negativity generation and tone matching in schizophrenia. Clin. Neurophysiol 111 (10), 1733–1737. [PubMed: 11018486]

Kantrowitz JT, Epstein ML, Beggel O, Rohrig S, Lehrfeld JM, Revheim N, Lehrfeld NP, Reep J, Parker E, Silipo G, Ahissar M, Javitt DC, 2016 Neurophysiological mechanisms of cortical plasticity impairments in schizophrenia and modulation by the N-methyl-D-aspartate type glutamate receptor agonist D-serine. Brain 139 (Pt12), 3281–3295. [PubMed: 27913408]

Kay S, Opler LA, Fiszbein A, 1992 The Structured Clinical Interview for the Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. Multi-Health Systems, New York.

Keefe RS, Fox KH, Harvey PD, Cucchiaro J, Siu C, Loebel A, 2011 Characteristics of the MATRICS Consensus Cognitive Battery in a 29-site antipsychotic schizophrenia clinical trial. Schizophr. Res 125 (2–3), 161–168. [PubMed: 21075600]

Keefe RS, Vinogradov S, Medalia A, Buckley PF, Caroff SN, D'Souza DC, Harvey PD, Graham KA, Hamer RM, Marder SM, Miller DD, Olson SJ, Patel JK, Velligan D, Walker TM, Haim AJ, Stroup ST, 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. [PubMed: 22687548]

Lee M, Dehatpour P, Dias EC, Silipo G, Kantrowitz JT, Martinez AM, Javitt DC, 2018 A tale of two sites: differential impairment of frequency and duration mismatch negativity across a primarily inpatient versus a primarily outpatient site in schizophrenia. Schizophr. Res 191, 10–17. [PubMed: 28779851]

Mausbach BT, Harvey PD, Goldman SR, Jeste DV, Patterson TL, 2007 Development of a brief scale of everyday functioning in persons with serious mental illness. Schizophr. Bull 33, 1364–1372. [PubMed: 17341468]

McLachlan NM, Phillips DS, Rossell SL, Wilson SJ, 2013 Auditory processing and hallucinations in schizophrenia. Schizophr. Res 150 (2–3), 380–385. [PubMed: 24054462]

Medalia A, Bowie CR, 2016 Cognitive Remediation to Improve Functional Outcomes.Oxford University Press, New York.

Medalia A, Erlich M, 2017 Why cognitive health matters. Am. J. Public Health 107 (1),45–47. [PubMed: 27925815]

Medalia A, Erlich MD, Soumet-Leman C, Saperstein AM, 2017 Translating cognitive behavioral interventions from bench to bedside: the feasibility and acceptability of cognitive remediation in research as compared to clinical settings. Schizophr. Res 203, 49–54 (Jul 30. pii: S0920–9964(17)30455–3). [PubMed: 28768601]

Medalia A, Saperstein AM, Erlich MD, Sederer LI, 2018 Cognitive remediation in large systems of psychiatric care. CNS Spectr. 2, 1–11.

Murthy NV, Mahncke H, Wexler BE, Maruff P, Inamdar A, Zucchetto M, Lund J,Shabbir S, Shergill S, Keshavan M, Kapur S, Laruelle M, Alexander R, 2012 Computerized cognitive remediation training for schizophrenia: an open label, multi-site, multinational methodology study. Schizophr. Res 139 (1–3), 87–91. [PubMed: 22342330]

Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Essock S,Fenton WS, Frese FJ 3rd, Gold JM, Goldberg T, Heaton RK, Keefe RS, Kraemer H, Mesholam-Gately R, Seidman LJ, Stover E, Weinberger DR, Young AS, Zalcman S, Marder SR, 2008 The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry 165 (2), 203–213. [PubMed: 18172019]

Petkova E, Lu F, Kantrowitz J, Sanchez JL, Lehrfeld J, Scaramello N, Silipo G,DiCostanza J, Ross M, Su Z, Javitt DC, Butler PD, 2014 Auditory tasks for assessment of sensory function and affective prosody in schizophrenia. Compr. Psychiatry 55 (8), 1862–1874. [PubMed: 25214372]

Rabinowicz EF, Silipo G, Goldman R, Javitt DC, 2000 Auditory sensory dysfunction in schizophrenia: imprecision or distractibility? Arch. Gen. Psychiatry 57 (12), 1149–1155. [PubMed: 11115328]

Rass O, Forsyth JK, Bolbecker AR, Hetrick WP, Breier A, Lysaker PH, O'Donnell BF, 2012 Computer-assisted cognitive remediation for schizophrenia: a randomized single-blind pilot study. Schizophr. Res 139 (1–3), 92–98. [PubMed: 22682988]

Strous RD, Cowan N, Ritter W, Javitt DC, 1995 Auditory sensory ("echoic") memory dysfunction in schizophrenia. Am. J. Psychiatry 152 (10), 1517–1519. [PubMed: 7573594]

Tarasenko M, Perez VB, Pianka ST, Vinogradov S, Braff DL, Swerdlow NR, Light GA, 2016 Measuring the capacity for auditory system plasticity: an examination of performance gains during initial exposure to auditory-targeted cognitive training in schizophrenia. Schizophr. Res 172 (1–3), 123–130. [PubMed: 26851143]

Thomas ML, Green MF, Hellemann G, Sugar CA, Tarasenko M, Calkins ME, Greenwood TA, Gur RE, Gur RC, Lazzeroni LC, Nuechterlein KH, Radant AD, Seidman LJ, Shiluk AL, Siever LJ, Silverman JM, Sprock J, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff

DL, Light GA, 2017 Modeling deficits from early auditory information processing to psychosocial functioning in schizophrenia. JAMA Psychiat. 74 (1), 37–46.

Voss P, Thomas ME, Guercio GD, de Villers-Sidani E, 2018 Dysregulation of auditory neuroplasticity in schizophrenia. Schizophr. Res 10.1016/j.schres.2018.04.025 (Apr 24. pii: S0920–9964(18)30238-X).

Wechsler D, 2001 Wechsler Test of Adult Reading: WTAR. The Psychological Corporation, San Antonio.

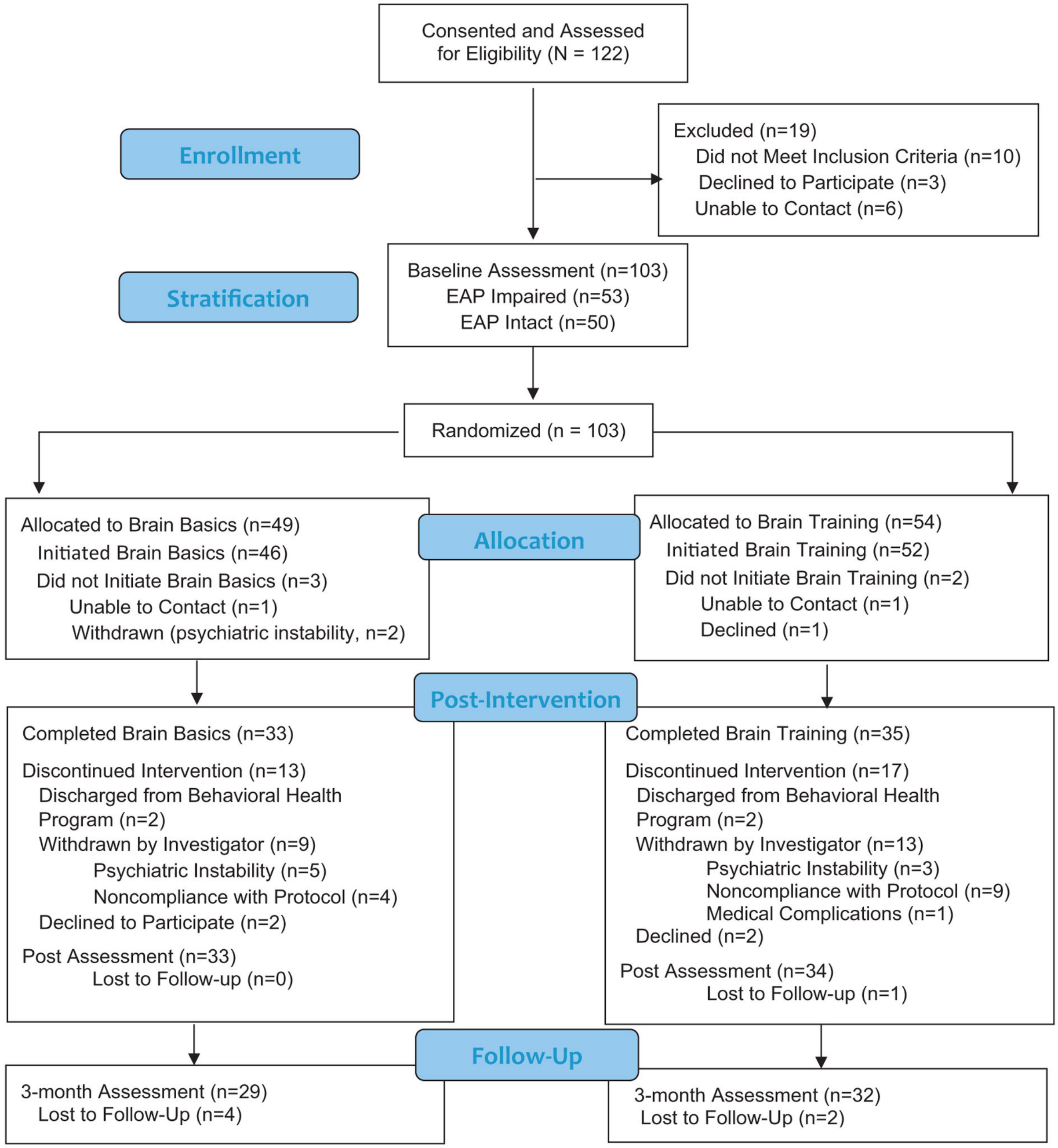


Fig. 1.
CONSORT flow diagram.

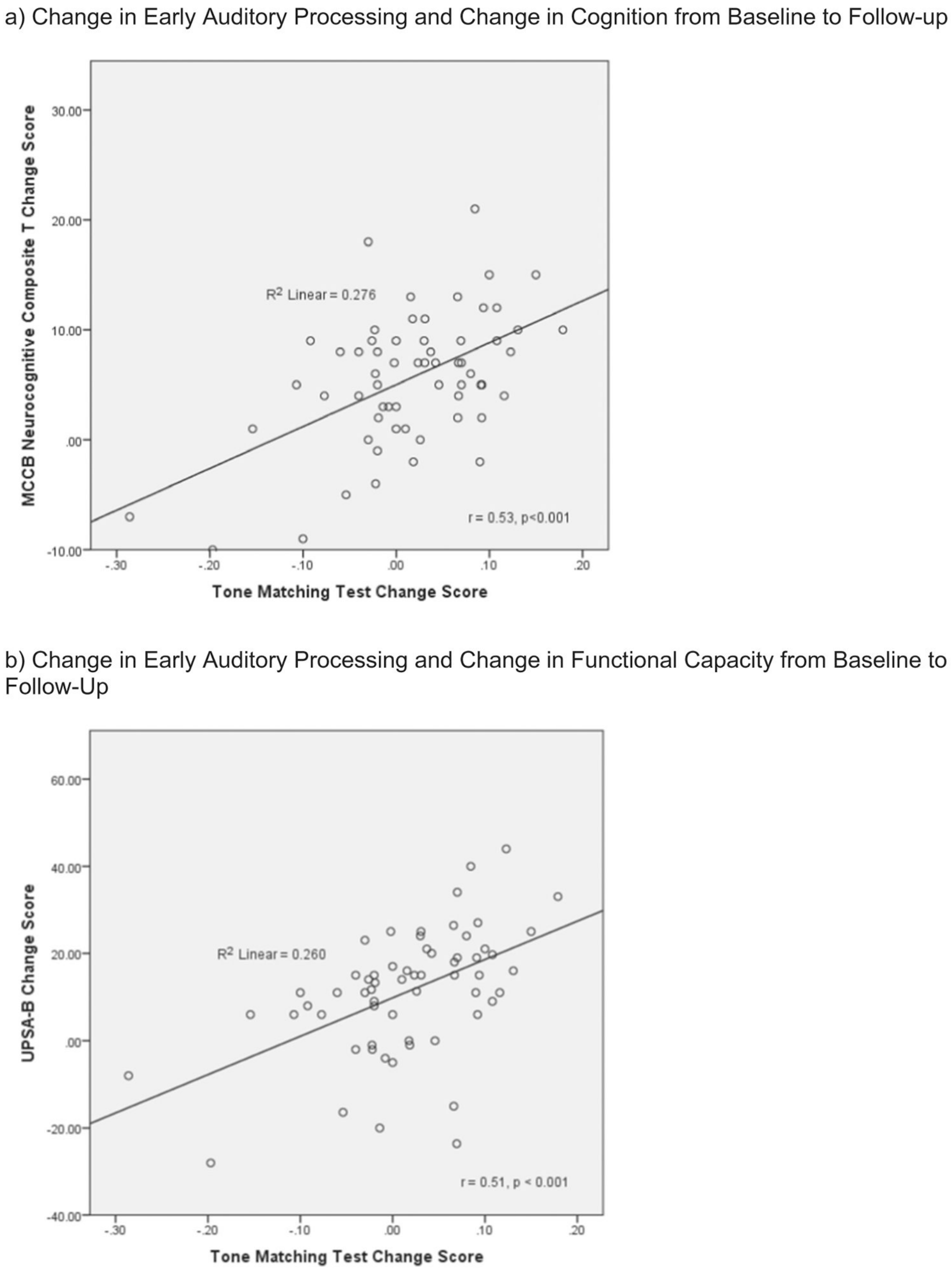


Fig. 2.

a) Change in early auditory processing and change in cognition from baseline to follow-up. b) Change in early auditory processing and change in functional capacity from baseline to follow-up.

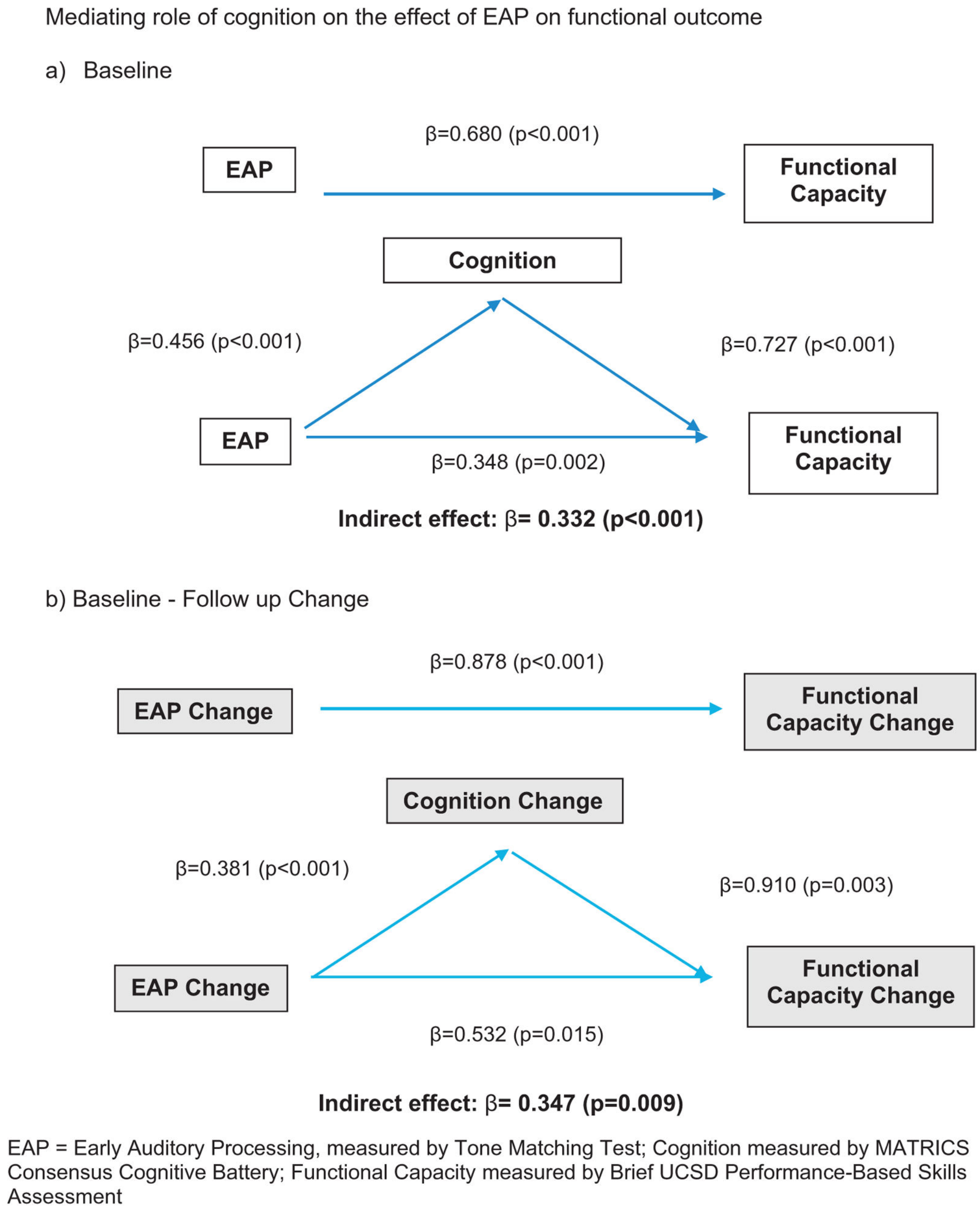
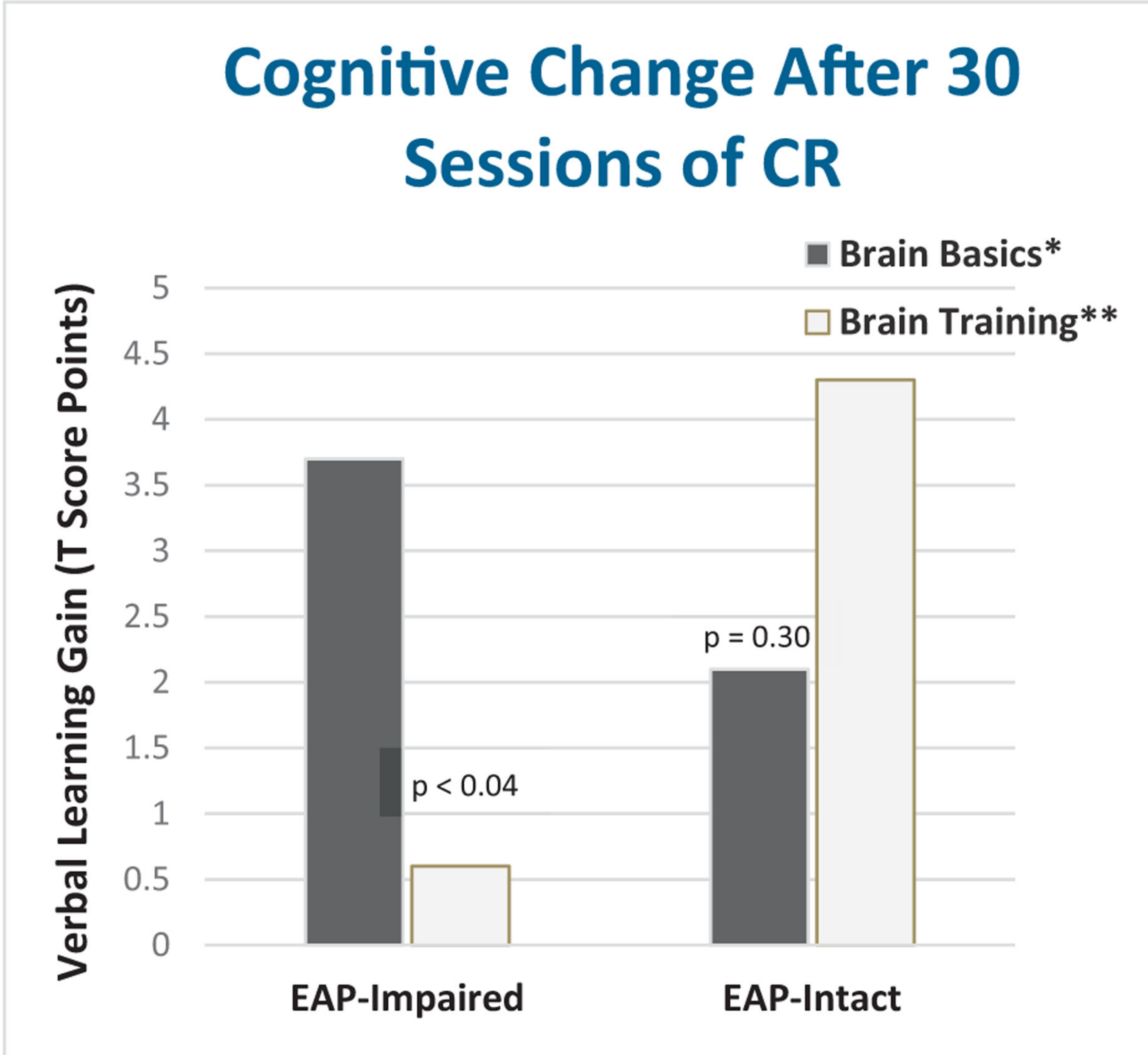


Fig. 3.

Mediating role of cognition on the effect of EAP on functional outcome.



*CR conditions differed in that only *Brain Basics trained in EAP and only **Brain Training trained in reasoning.*

Fig. 4.

Change in verbal learning when CR is tailored to EAP status.

Table 1

Demographic, cognitive, and clinical characteristics of the sample.*

	Brain Basics (n = 49)	Brain Training (n = 54)	Total (n = 103)
Age			
Mean (SD)	42.76 (12.79)	42.87 (12.23)	42.82 (12.44)
Sex (male)			
N(%)	39 (79.60)	34 (62.96)	73 (70.87)
Race/ethnicity N (%)			
White/Caucasian	21 (42.86)	27 (50.00)	48 (46.60)
Black/African American	27 (55.10)	26 (48.15)	53 (51.46)
More than One Race	1 (2.04)	1 (1.85)	2 (1.94)
Hispanic/Latinx	16 (32.65)	20 (37.04)	36 (34.95)
Diagnosis N (%)			
Schizophrenia	33 (67.35)	36 (66.67)	69 (67.00)
Schizoaffective	16 (32.65)	18 (33.33)	34 (33.00)
Education (years)			
Mean (SD)	11.23 (2.02)	11.74 (2.07)	11.5 (2.05)
FSIQ estimate[a]			
Mean (SD)	85.06 (9.83)	87.94 (10.64)	86.59 (10.32)
TMI[b] percent correct			
Mean (SD)	71.26 (13.86)	73.20 (14.44)	72.27 (14.13)
MCCB[c] neurocognitive composite (T-score)			
Mean (SD)	19.63 (10.92)	20.76 (12.51)	20.22 (11.74)
UPSA-B[d] (% correct)			
Mean (SD)	51.20 (17.49)	55.59 (17.37)	53.50 (17.48)
PANSS[e] Positive			
Mean (SD)	12.25 (4.75)	13.17 (4.27)	12.74 (4.51)
PANSS Negative			
Mean (SD)	14.35 (5.07)	14.28 (4.99)	14.31 (5.00)
PANSS General			
Mean (SD)	25.42 (6.03)	25.61 (6.33)	25.52 (6.16)

[a]Derived from the Wechsler Test of Adult Reading.

[b]Tone Matching Test.

[c]MATRICS Consensus Cognitive Battery.

[d]Brief UCSD Performance-Based Skills Assessment.

[e]Positive and Negative Syndrome Scale.

*None of the differences between two treatment groups were significant. Continuous variables were compared with the use of *t*-test, and categorical variables were compared with the use of Chi-squared test.

Table 2

Effects of treatment conditions, EAP status, and their interactions on cognitive and functional outcome change scores.

	Main effect of treatment conditions				Main effect of EAP status†				Effect of treatment stratified by EAP status†								Treatment by EAP status† interaction**	
									Intact				Impaired					
Change scores	**Brain Basics Mean (SD)**	**Brain Training Mean (SD)**	**d**	**p***	**Intact Mean (SD)**	**Impaired Mean (SD)**	**d**	**p***	**Brain Basics Mean (SD)**	**Brain Training Mean (SD)**	**d**	**p***	**Brain Basics Mean (SD)**	**Brain Training Mean (SD)**	**d**	**p***	**eta^2**	**P**
Pre/post	**n = 33**	**n = 34**			**n = 31**	**n = 36**			**n = 14**	n = 17			**n = 19**	**n = 17**				
MCCB Composite T score	5.3 (4.6)	3.9 (5.0)	0.28	0.291	4.0 (4.7)	5.1 (4.9)	0.21	0.267	4.1 (5.5)	3.9 (4.2)	0.04	1.000	6.1 (3.8)	3.9 (5.9)	0.46	0.294	0.011	0.400
Verbal learning T score	3.0 (4.4)	2.4 (5.9)	0.11	0.421	3.3 (5.9)	2.2 (4.5)	0.21	0.461	2.1 (5.3)	4.3 (6.4)	0.38	0.450	3.7 (3.6)	0.6 (4.8)	0.73	0.040	0.068	0.037
UPSA-B	11.0 (11.4)	6.6 (11.8)	0.38	0.095	7.9 (11.5)	9.6 (12.0)	0.14	0.477	9.7 (10.4)	6.5 (12.4)	0.28	0.340	12.1 (12.3)	6.8 (11.4)	0.45	0.136	0.002	0.716
Pre/ follow-up	**n = 29**	**n = 32**			**n = 29**	**n = 32**			**n = 12**	**n = 17**			**n = 17**	**n = 15**				
MCCB Composite T score	6.7 (5.1)	4.6 (6.6)	0.35	0.496	4.8 (5.9)	6.3 (6.1)	0.25	0.304	5.4 (4.9)	4.4 (6.7)	0.17	0.773	7.6 (5.3)	4.9 (6.8)	0.46	0.307	0.005	0.570
Verbal learning T score	6.5 (6.3)	5.4 (6.8)	0.16	0.496	7.4 (7.8)	4.6 (4.9)	0.45	0.216	8.0 (8.4)	7.1 (7.5)	0.12	0.790	5.4 (4.1)	3.6 (5.6)	0.37	0.363	0.001	0.796
UPSA-B	14.1 (12.6)	8.6 (15.3)	0.39	0.073	5.7 (16.5)	16.2 (9.6)	0.79	0.003	9.8 (14.7)	2.8 (17.5)	0.42	0.121	17.2 (10.3)	15.2 (9.0)	0.20	0.472	0.008	0.469

MCCB Composite = MATRICS Consensus Cognitive Battery Neurocognitive Composite.

UPSA-B = Brief UCSD Performance-Based Skills Assessment.

* p-Values were calculated using Wilcoxon rank-sum test.

** eta2 is the proportion of variance in the outcome that can be explained by the interaction; p-values were calculated using ANOVA F-test.

† EAP Status defined by TMT % Correct: Intact ≥ 70%; Impaired < 70