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Early versus adult onset schizophrenia as a predictor of response to neuroscience-informed cognitive training

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Abstract

Developmental stages characterized by greater neural plasticity might be critical periods where the effects of cognitive training (CT) could theoretically be maximized. However, experiencing a first episode of schizophrenia before 18 years of age (early onset schizophrenia, EOS) may reduce the brain's ability to benefit from CT. This study examined the effects of EOS versus onset at 18+ years of age (adult onset schizophrenia, AOS) as a predictor of response to CT, and the relationship between duration of illness (DI) and cognitive improvements.

METHOD: This is a secondary analysis of data from two randomized trials that examined the cognitive effects of neuroscience-informed auditory training exercises (AT) in 84 outpatients with schizophrenia (26 EOS, 58 AOS, recruited between 2004 and 2014).

RESULTS: There was a significant effect of time in all cognitive domains ($F>10.22$, $p<0.002$). The effect of EOS was significant only for verbal learning and memory ($F=5.79$, $p=0.018$). AOS increased the mean change score by 5.70 points in this domain while EOS showed no change ($t=-2.280$, $p=0.025$). However, the effect of EOS was no longer statistically significant after controlling for multiple comparisons. Shorter DI was associated with greater improvement in problem solving in the AOS group ($r=-0.27$, $p=0.040$).

CONCLUSION: AT is effective in improving cognition in individuals with both EOS and AOS. Treatment effects in all cognitive domains were similar, with the exception of verbal learning and memory. This result requires replication. CT provided earlier in the course of the illness results in greater improvements in executive functions (ClinicalTrials.gov: NCT00312962, NCT00694889).

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Keywords

adolescence; early-onset schizophrenia; cognitive remediation; neuroplasticity

INTRODUCTION

Meta-analyses of cognitive training (CT) in schizophrenia show small to medium effects on cognition,[1,2] however, little is known about potential predictors of a favorable treatment response.[3,4] There is evidence that age or developmental stage of participants could be an important moderator of response to treatment [3,5–8] but meta-analytic results showed no relationship between response to training and age.[2] However, most studies included in this meta-analysis were of individuals with a mean age of 30-40 years. Childhood and adolescence are critical periods wherein specific neural systems are undergoing rapid changes such as decreased synaptic density and axon retraction in the prefrontal cortex, which coincide with an increased ability in complex high-order cognitive tasks.[9] Brain imaging studies have also shown that adolescence is characterized by critical processes in neurodevelopment such as increased white matter density, progressive functional development of cortical networks, and an increase in global connectivity.[10]

Heightened neural plasticity during childhood and adolescence suggests that these may be “sensitive periods” wherein CT could have a robust effect.[8] This may be especially crucial for interventions that are “restorative” in nature, where the main goal is to drive the impaired neural systems in the direction of more typical functioning.[11,12] However, it is also possible that a first-episode of schizophrenia during these neurodevelopmental periods may confer damage that reduces the ability of the brain to benefit from CT. Early-onset schizophrenia (EOS), defined as the manifestation of psychotic symptoms prior to 18 years of age,[13,14] is a less common and phenotypically more severe form of the disorder, and is a marker of poor prognosis.[13–19] There is a great degree of neural pathology in patients with EOS, with delayed and altered maturation processes in both gray and white matter, and disrupted development of the brain’s normal maturational trajectory.[20–22] Neurocognitive impairment in EOS is generalized across several cognitive domains, and although the degree of impairment is comparable to that documented in AOS,[23–25] some cognitive domains such as working and verbal memory are disproportionally impaired.[25,26]

There is currently limited but growing evidence that CT can improve cognition when administered early in the course of schizophrenia.[27–30] A recent meta-analysis of CT in early schizophrenia concluded that the overall pattern of improvement in cognition after CT was similar to that observed in chronic schizophrenia, but with smaller effect sizes.[31] However, these studies included mixed samples of adolescents with EOS and young adults with early and adult-onset, making it difficult to determine the effects of EOS. Very few studies of CT have specifically examined treatment effects in patients with EOS. Wykes et al.[5] showed that a strategy learning CT intervention produced clinically significant and lasting improvements in cognitive flexibility in a sample of young adults and adolescents with EOS. Applying the same CT program to a sample of adolescents with EOS, Puig et al.[32] found significant improvements in verbal memory and executive

function post-treatment, which were maintained at 3-months follow-up. Testing a different CT program, Ueland et al.[33,34] found few and not very durable cognitive changes after CT in a small study of adolescent inpatients with mixed diagnoses within the schizophrenia spectrum as well as other psychotic disorders. Finally, Holzer et al.[35] examined a drill and practice CT computerized program and found improvements in visuospatial abilities after the treatment, and enhanced reasoning and inhibition abilities after a six-month follow-up,[36] but the sample in this study was a mixed group of adolescents at risk of psychosis and patients with established psychotic illness.

Overall, the few studies of CT in EOS suggest that CT induces smaller cognitive effects than what have been found in adult onset samples. To our knowledge, no previous study has directly examined the potential role of EOS versus AOS as a predictor of treatment response in terms of cognitive improvements. The aim of this study was to test whether early versus adult onset had a moderating effect on response to CT in schizophrenia. We also analyzed the relationship of the duration of illness (DI) with cognitive response in both early and adult-onset schizophrenia. We hypothesized that both patient groups would show cognitive gains, and that EOS patients would show smaller improvements relative to AOS patients. We also hypothesized that DI would be correlated with cognitive improvements.

METHOD

This is a secondary analysis of two previously completed studies carried out by the same research group to test the effects of a neuroscience-informed auditory training program in schizophrenia (ClinicalTrials.gov identifiers: NCT00312962 and NCT00694889).[11,30,37] Both trials received human subjects research approval from the IRB at the University of California, San Francisco, and the University of California, Davis.

Participants

The sample included 84 subjects pooled from the two studies. All participants included in the current analysis were (1) clinically stable outpatients with schizophrenia spectrum disorders recruited from mental health treatment settings, (2) randomized to the auditory training (AT) arm of the parent study and completed the treatment protocol, and (3) had sufficient data to categorize them into the EOS or AOS groups.

Thirty-seven (44%) participants were from the sample of the first study, which included chronically ill volunteer adult participants with schizophrenia or schizoaffective disorder (chronic schizophrenia study). The other forty-seven (56%) participants were from a study of recent-onset schizophrenia, which included participants aged 14-30 years, with recent-onset schizophrenia spectrum disorders (diagnosis of schizophrenia, schizophreniform or schizoaffective disorder, with onset within the previous 5 years). In both studies all participants were fluent in English, were on a stable dose of psychiatric medications, had an IQ ≥ 70, did not have a known neurological disorder, and did not have substance dependence in the past year. Participants aged 18 and older gave written informed consent, while those younger than age 18 provided assent, with written parental/legal guardian consent.

For the current analysis, participants were classified as EOS patients provided they were aged 18 or younger at the baseline assessment or they had had their first psychiatric hospitalization at 18 years or younger (EOS n=26, AOS n=58). Twelve subjects (12.5%) were excluded since data about their first psychiatric hospitalization was unknown. DI was computed as current age minus age of first psychotic symptoms reported by participants.

Procedures

In both studies, subjects were randomly assigned to either the AT condition or a control condition of commercial computer games. In the chronic schizophrenia study, participants in the AT condition were asked to engage in the intervention for 50 hours (1 hour/day, 5 days/week, for 10 weeks). Most of the participants in this study performed the exercises in the laboratory and the few that performed at home were monitored by weekly calls. In the recent-onset schizophrenia study, subjects were loaned laptop computers and most of them participated in the intervention at home. Subjects were asked to participate for 40 hours (1hour/day, 5 days/week, for 8 weeks) and were contacted 1-2 times/week by telephone. The computer games condition was designed to control for the effects of computer exposure, contact with research personnel, and monetary payments. This “placebo” was also selected to control for the nonspecific engagement of attentional systems, executive functions, and motivation. In both studies, the control subjects rotated through a series of 16 different enjoyable commercially available games (e.g., visuospatial puzzle games, clue-gathering mystery games, pinball-style games) for the same number of hours as the subjects who received the training program. They played four or five games on any given day and were monitored by staff in the same manner as the subjects in the training condition. In both studies participants received monetary compensation for their participation.

Auditory Cognitive Training Exercises

The cognitive training program was provided by Posit Science Corporation and has been described previously.[11] It consists of computerized exercises designed to improve speed and accuracy of auditory information processing while engaging auditory and verbal working memory. This training approach is based on evidence that schizophrenia is characterized by widespread disturbances in frontotemporal neural systems sub-serving auditory processing and verbal memory.[38,39] The rationale is that, in order to understand and remember verbal information, the brain must first generate precise and reliable neurological responses that represent the frequency, the timing, and the complex sequential relationships between speech sounds. The exercises contain stimulus sets spanning the acoustic organization of speech. During the initial stages of training in all exercises, auditory stimuli are processed to exaggerate the rapid temporal transitions within the sound stimuli by increasing their amplitude and stretching them in time. The goal of the processing is to increase the effectiveness with which these stimuli engage and drive plastic changes in brain auditory systems. This exaggeration is gradually removed so that by the end of training, all auditory stimuli have temporal characteristics representative of real-world rapid speech. These exercises continuously adjust the difficulty level to user performance to maintain an approximately 85% rate of correct responses. Trials with correct responses are rewarded with points and animations. Compliance was monitored by electronic data upload.

Assessment Procedures

All assessment staff were blind to treatment assignment. Cognitive assessment staff were trained and monitored on manualized assessment procedures by the same senior researcher (M.F.). Clinical assessment staff were trained and observed by the same senior researchers (R.L., J.D.R., T.N). Eligibility diagnoses were determined using the Structured Clinical Interview for DSM-IV.[40] Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS).[41] An abbreviated battery of MATRICS recommended measures was administered.[42] A tower test was used in place of the NAB Mazes subtest (described below). Raw scores were transformed to *T* scores using age-appropriate normative data. All cognitive outcome measures were distinct and independent from tasks practiced during the training: global cognition (average *T* score across all measures); speed of processing (Trail Making Test Part A; category fluency animal naming); working memory (letter-number span; WMS-III spatial span); verbal learning and memory - VLM- (HVLT-R immediate and delayed recall); visual learning and memory (BVMT-R immediate and delayed recall); problem solving (Tower of London, from the Brief Assessment of Cognition in Schizophrenia in the chronic schizophrenia study, and the Tower Test from the Delis-Kaplan Executive Function System in the recent-onset schizophrenia study). Alternate forms of HVLT-R and BVMT-R, and Tower of London in the chronic schizophrenia study, were administered and counterbalanced at baseline and post-training. All neurocognitive tests were rescored by a second staff member blind to the first scoring.

Statistical analyses

Chi-square tests and one-way analysis of variance (ANOVA) were used for baseline comparisons, with nonparametric tests being applied when required. General linear models (GLM) for repeated measures were used as the main statistical analysis method. Pre-post differences between groups in outcome variables (cognitive domains) were examined using GLM for repeated measures, with group condition as the independent variable and post-treatment scores as the dependent variable. Baseline cognitive scores were also included in all models as covariates to control for effects of regression to the mean. Further GLM models were run including other potential confounds as covariates (i.e. baseline clinical differences between groups, and total hours of training). False discovery rate (FDR) method was used for correcting for multiple comparisons. Secondarily, regression models were computed as complementary analyses to examine the amount of change induced by treatment in cognitive scores in each group (AOS versus EOS), using the mean change scores (post-training minus baseline). Finally, we conducted exploratory Pearson correlations to examine potential relationships between mean change scores and DI. All tests were two-tailed. All analyses were conducted using IBM SPSS Statistics for Windows (version 18).

RESULTS

Baseline sociodemographic, clinical and cognitive characteristics

Table 1 shows demographic, clinical, and cognitive characteristics of the groups. As expected, the EOS group was younger, had fewer years of education and had a younger age at first hospitalization. There were no other significant differences between groups

in demographic variables or symptoms. The proportion of patients from the chronic schizophrenia study and from the recent-onset schizophrenia study was similar in both groups (X^2=1.36, p=0.244). All group differences in baseline cognitive performance were non-significant. Overall, both groups had means approximately one standard deviation below the normative mean across cognitive domains, with the exception of verbal learning and memory (VLM) in which both groups showed greater deficits, the magnitude of which were well-matched between groups.

EOS versus AOS group differences in cognitive response to AT treatment

GLM analysis showed a significant effect of time (pre-post training scores) for all cognitive domains (Table 2). The effect of group was significant only for the VLM domain. Mean scores at baseline and post-training showed improved performance in VLM in the AOS group, and no change in performance in the EOS group. This difference remained significant when controlling for years of education (F=4.66, p=0.034) and for total hours of training (F=4.53, p=0.036). However, the difference was no longer statistically significant when controlling for multiple comparisons (p_{FDR}>0.005). A regression model was conducted to predict mean change scores in the VLM domain, with baseline differences in years of education entered in the first block and early versus adult-onset in the second block. The model was statistically significant and showed that AOS increased the mean change score by 5.70 in this domain while EOS showed no change (95% CI 0.73-10.68) in response to training (t=−2.280, p=0.025). The group effect was not significant in any of the other cognitive domains, in which both groups improved to a similar degree.

Association between DI and change in cognition

Although differences between groups in DI were not statistically significant, we conducted post-hoc correlation analyses to examine potential relationships between DI and cognitive gains (Table 3). No significant associations were found when analyzing the sample as a whole, with the exception of a negative association at trend level significance between DI and improvements in problem solving (r=−0.21, p=.056). In the samples separately, a shorter duration of illness in AOS, but not in EOS, was associated with greater improvements in problem solving (r=−0.27, p=.040).

DISCUSSION

In this study we conducted secondary analyses to examine the role of early versus adult onset schizophrenia as a predictor of treatment response to a neuroscience-informed auditory training program in schizophrenia. To our knowledge, this is the first study to investigate the potential role of early versus adult onset illness as a predictor of treatment response to CT. Our main finding was that patients with EOS had a similar response to AT compared to patients with AOS. The unique exception was that patients with EOS did not show improvement in VLM after the treatment, but this difference was no longer statistically significant when controlling for multiple comparisons. Nonetheless, this result might be important as verbal memory is a significant predictor of long-term functioning in EOS patients, who are at major risk of poor functional outcomes.[43–45]

At baseline, the EOS group had a similar cognitive profile compared to the AOS group in all cognitive domains, including a selective deficit in VLM. This is in line with previous meta-analyses and reviews showing a similar degree of cognitive impairment in EOS compared to AOS.[23–25] However, there is also evidence suggesting that verbal memory is especially impaired in EOS.[24,46–49] In our sample, while the baseline cognitive profile was similar between groups, the response to the treatment differed in the VLM domain. In line with previous findings supporting a selective verbal memory deficit in EOS, these findings suggest that impairment in this cognitive domain was less malleable in patients with EOS relative to AOS patients, even when using a drill and practice approach, which has been identified as a predictor of better response to CT in the verbal memory domain[1]. However, additional research is needed given the limited and conflicting evidence of VLM response to CT in EOS. For example, Wykes et al.[5] also found that young adults and adolescents with EOS did not improve their memory abilities after administering a CT program that used strategy coaching. However, Puig et al.[32] found significant improvements in verbal memory using the same CT program in a sample composed uniquely of adolescents with EOS.

AT is a cognitive intervention designed to harness sensory inputs that feed forward to higher-order cognitive operations thereby restoring and enhancing early perceptual and working memory processes. Previous research has shown that subjects who showed the largest training induced gains after AT in psychophysical performance showed the most improvement in verbal working memory.[11] Our current results show that patients with EOS improved working memory performance to a similar degree to that of patients with AOS. Our findings, if replicated, also suggest that this improvement might not be enough to generalize to higher-order processes such as long-term memory in EOS. Although other factors could be related to a reduced response in VLM to CT in EOS, such as duration of illness, we speculate that neurobiological factors could also play a role. It has recently been reported that CT efficacy is moderated by baseline cortical thickness in frontal and temporal areas[50] which are known to be critical areas for memory function. Greater fronto-temporal cortical volume reductions and asymmetry have also been found to be related to an earlier age of onset.[51] Additional neuroimaging studies in EOS samples are warranted to elucidate the potential role of underlying neural mechanisms in the response to CT in this population.

Results thus far support the efficacy of the AT intervention for improving cognitive functioning in both early and adult onset schizophrenia. This is consistent with previous meta-analytic results.[2] If future studies confirm that there is a reduction in VLM response to AT, some adaptations could be considered in order to boost treatment benefits for EOS. For example, coaching and a strategy-learning approaches may need to be combined for optimal results. In particular, training on relational encoding strategies[32,52] may be combined with the “restorative” approach which focuses on “bottom-up” processes. Strategy-based approaches are mainly “compensatory” and focus on “top-down” processes, in order to reinforce strategies for improving impaired cognitive processes. Individuals with EOS may need direct reinforcement of these strategies in order to enhance the generalization of early perceptual and working memory improvements to higher-order cognitive processes such as verbal memory.

Finally, while we did not find any significant association between DI and cognitive change in EOS, lower duration of illness in AOS was associated with greater gains in executive function. This is consistent with previous results of improved efficacy of CT programs when administered earlier in the course of the illness,[31,53] and findings suggesting that chronicity of illness is a rate-limiting factor of treatment effects in AOS.[6] However, our exploratory results should be interpreted with caution since we did not correct for multiple comparisons.

There are a number limitations to this study. First, we used a pooled sample from two different trials of cognitive training. While the groups were highly comparable, further investigation with a unique sample composed of prospectively recruited patients is warranted. Second, the sample only included patients aged 14 years and older, thus it will be important for future studies to include younger adolescents with EOS. Third, the results are limited only to cognitive response to CT. We acknowledge that functional improvements are one of the main targets for CT programs. Future studies are warranted to specifically examine the effects of EOS versus AOS in terms of functional gains. Fourth, the current results are based on the response to AT, and we cannot be sure that using a different CT program would yield similar results.

In sum, we found that patients with EOS had a similar response to AT compared to patients with and adult onset of the illness, with the unique exception of a reduced degree of response in verbal learning and memory. However, this result did not survive correction for multiple comparisons and requires replication.

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Conflict of interests:

The cognitive training software used in these studies was supplied free of charge by Posit Science Inc. Dr. Vinogradov is a site investigator on an SBIR grant to Posit Science Inc., a company with a commercial interest in the cognitive training software used in this study. None of the other authors have any financial interest in Posit Science Inc. Drs. Puig, Fisher, Loewy, Ramsay, Carter, Ragland, Niendam, and Vinogradov, and Ms. Miley report no competing interests. Dr. Vinogradov is on the advisory board for Mindstrong Inc. and Alkermes. Dr. Carter has served on the advisory board of Merck, Lilly, Pfizer, Roche, and Servier, and has received research funding from Glaxo Smith Kline. Dr. Loewy has received honoraria as a faculty member of the Lundbeck International Neuroscience Foundation.

References

1. McGurk SR, Twamley EW, Sitzer DI, et al. Meta-Analysis of Cognitive Remediation in Schizophrenia. Am J Psychiatry. 2007;164(12):1791–1802. [PubMed: 18056233]
2. Wykes T, Huddy V, Cellard C, et al. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am J Psychiatry. 2011;168(5):472–485. [PubMed: 21406461]
3. Kurtz MM, Seltzer JC, Fujimoto M, et al. Predictors of change in life skills in schizophrenia after cognitive remediation. Schizophr Res. 2009;107(2-3):267–274. [PubMed: 19006657]
4. Wykes T, Spaulding WD. Thinking About the Future Cognitive Remediation Therapy—What Works and Could We Do Better? Schizophr Bull. 2011;37(Suppl 2):S80–S90. [PubMed: 21860051]
5. Wykes T, Newton E, Landau S, et al. Cognitive remediation therapy (CRT) for young early onset patients with schizophrenia: an exploratory randomized controlled trial. Schizophr Res. 2007;94(1-3):221–230. [PubMed: 17524620]
6. Kontis D, Huddy V, Reeder C, et al. Effects of age and cognitive reserve on cognitive remediation therapy outcome in patients with schizophrenia. Am J Geriatr Psychiatry. 2013;21(3):218–230. [PubMed: 23395189]
7. Vita A, Deste G, De Peri L, et al. Predictors of cognitive and functional improvement and normalization after cognitive remediation in patients with schizophrenia. Schizophr Res. 2013;150(1):51–57.. [PubMed: 23998953]
8. Keshavan MS, Vinogradov S, Rumsey J, et al. Cognitive training in mental disorders: update and future directions. Am J Psychiatry. 2014;171(5):510–522. [PubMed: 24700194]
9. Vyas NS, Kumra S, Puri BK. What insights can we gain from studying early-onset schizophrenia? The neurodevelopmental pathway and beyond. Expert Rev Neurother. 2010;10(8):1243–1247. [PubMed: 20662747]
10. Rubia K Functional brain imaging across development. Eur Child Adolesc Psychiatry. 2013;22(12):719–731. [PubMed: 22729957]
11. Fisher M, Holland C, Merzenich MM, et al. Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. Am J Psychiatry. 2009;166(7):805–811. [PubMed: 19448187]
12. Vinogradov S, Fisher M, de Villers-Sidani E. Cognitive training for impaired neural systems in neuropsychiatric illness. Neuropsychopharmacology. 2012;37(1):43–76. [PubMed: 22048465]
13. McClellan J, Stock S, American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. J Am Acad Child Adolesc Psychiatry. 2013;52(9):976–990. [PubMed: 23972700]
14. Vyas NS, Patel NH, Puri BK. Neurobiology and phenotypic expression in early onset schizophrenia. Early Interv Psychiatry. 2011;5(1):3–14. [PubMed: 21272270]
15. Hollis C. Adult outcomes of child- and adolescent-onset schizophrenia: diagnostic stability and predictive validity. Am J Psychiatry. 2000;157(10):1652–1659. [PubMed: 11007720]
16. Lay B, Blanz B, Hartmann M, et al. The Psychosocial Outcome of Adolescent-Onset Schizophrenia: A 12-Year Followup. Schizophr Bull. 2000;26(4):801–816. [PubMed: 11087013]
17. Fleischhaker C, Schulz E, Tepper K, et al. , Long-Term Course of Adolescent Schizophrenia. Schizophr Bull. 2005;31(3):769–780. [PubMed: 16123530]
18. Vyas NS, Gogtay N. Treatment of Early Onset Schizophrenia: Recent Trends, Challenges and Future Considerations. Front Psychiatry. 2012;3:29. [PubMed: 22485097]
19. Kendall T, Hollis C, Stafford M, et al. Recognition and management of psychosis and schizophrenia in children and young people: summary of NICE guidance. BMJ. 2013;346:f150. [PubMed: 23344308]
20. Arango C, Rapado-Castro M, Reig S, et al. Progressive Brain Changes in Children and Adolescents With First-Episode Psychosis. Arch Gen Psychiatry. 2012;69(1):16–26. [PubMed: 22213785]

21. Reig S, Parellada M, Castro-Fornieles J, et al. Multicenter Study of Brain Volume Abnormalities in Children and Adolescent-Onset Psychosis. Schizophr Bull. 2011;37(6):1270–1280. [PubMed: 20478821]
22. Douaud G, Mackay C, Andersson J, et al. Schizophrenia delays and alters maturation of the brain in adolescence. Brain. 2009;132(9):2437–2448. [PubMed: 19477963]
23. Nieto RG, Castellanos FX. A meta-analysis of neuropsychological functioning in patients with early onset schizophrenia and pediatric bipolar disorder. J Clin Child Adolesc Psychol. 2011;40(2):266–280. [PubMed: 21391023]
24. Rajji TK, Ismail Z, Mulsant BH. Age at onset and cognition in schizophrenia: meta-analysis. Br J Psychiatry. 2009;195(4):286–293. [PubMed: 19794194]
25. Frangou S. Cognitive Function in Early Onset Schizophrenia: A Selective Review. Front Hum Neurosci. 2010;3:79. [PubMed: 20140271]
26. Tuulio-Henriksson A, Partonen T, Suvisaari J, et al. Age at onset and cognitive functioning in schizophrenia. Br J Psychiatry. 2004;185:215–219. [PubMed: 15339825]
27. Barlati S, De Peri L, Deste G, et al. A. Cognitive Remediation in the Early Course of Schizophrenia: A Critical Review. Curr Pharm Des. 2012:18(4):534–541. [PubMed: 22239585]
28. Eack SM, Hogarty GE, Cho RY, et al. Neuroprotective effects of cognitive enhancement therapy against gray matter loss in early schizophrenia: results from a 2-year randomized controlled trial. Arch Gen Psychiatry. 2010;67(7):674–682. [PubMed: 20439824]
29. Lee RS, Redoblado-Hodge MA, Naismith SL, et al. Cognitive remediation improves memory and psychosocial functioning in first-episode psychiatric outpatients. Psychol Med. 2013;43(6):1161–1173. [PubMed: 23237010]
30. Fisher M, Loewy R, Carter C, et al. Neuroplasticity-Based Auditory Training Via Laptop Computer Improves Cognition in Young Individuals With Recent Onset Schizophrenia. Schizophr Bull. 2015;41(1):250–258. [PubMed: 24444862]
31. Revell ER, Neill JC, Harte M, et al. A systematic review and meta-analysis of cognitive remediation in early schizophrenia. Schizophr Res. 2015;168(1-2):213–222. [PubMed: 26305063]
32. Puig O, Penadés R, Baeza I, et al. Cognitive Remediation Therapy in Adolescents With Early-Onset Schizophrenia: A Randomized Controlled Trial. J Am Acad Child Adolesc Psychiatry. 2014;53(8):859–868. [PubMed: 25062593]
33. Ueland T, Rund BR. A controlled randomized treatment study: the effects of a cognitive remediation program on adolescents with early onset psychosis. Acta Psychiatr Scand. 2004;109(1):70–74. [PubMed: 14674961]
34. Ueland T, Rund BR. Cognitive remediation for adolescents with early onset psychosis: a 1-year follow-up study. Acta Psychiatr Scand. 2005;111(3):193–201. [PubMed: 15701103]
35. Holzer L, Urben S, Passini CM, et al. A Randomized Controlled Trial of the Effectiveness of Computer-Assisted Cognitive Remediation (CACR) in Adolescents with Psychosis or at High Risk of Psychosis. Behav Cogn Psychother. 2014;42(4):421–434. [PubMed: 23631951]
36. Urben S, Pihet S, Jaugey L, et al. Computer-assisted cognitive remediation in adolescents with psychosis or at risk for psychosis: a 6-month follow-up. Acta Neuropsychiatr. 2012;24(6):328–335. [PubMed: 25287174]
37. Fisher M, Mellon SH, Wolkowitz O, et al. Neuroscience-informed Auditory Training in Schizophrenia: A Final Report of the Effects on Cognition and Serum Brain-Derived Neurotrophic Factor. Schizophr Res Cogn. 2016;3:1–7. [PubMed: 26705516]
38. Ragland JD, Gur RC, Raz J, et al. Effect of schizophrenia on frontotemporal activity during word encoding and recognition: a PET cerebral blood flow study. Am J Psychiatry. 2001;158(7):1114–1125. [PubMed: 11431234]
39. Kasai K, Nakagome K, Ithoh K, et al. Impaired cortical network for preattentive detection of change in speech sounds in schizophrenia: a high-resolution event-related potential study. Am J Psychiatry. 2002;159(4):546–553. [PubMed: 11925291]
40. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-Axis I Disorders, Clinician Version (SCID-CV). Washington, DC: American Psychiatric Press, Inc.; 1996.
41. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261–76. [PubMed: 3616518]

42. Nuechterlein KH. Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am J Psychiatry. 2008;165(2):203–213. [PubMed: 18172019]
43. Milev P, Ho BC, Arndt S, et al. Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am J Psychiatry. 2005;162(3):495–506. [PubMed: 15741466]
44. Cervellione KL, Burdick KE, Cottone JG, et al. Neurocognitive Deficits in Adolescents With Schizophrenia: Longitudinal Stability and Predictive Utility for Short-Term Functional Outcome. J Am Acad Child Adolesc Psychiatry. 2007;46(7):867–878. [PubMed: 17581451]
45. Oie M, Sundet K, et al. Neurocognition and functional outcome in early-onset schizophrenia and attention-deficit/hyperactivity disorder: a 13-year follow-up. Neuropsychology. 2011;25(1):25–35. [PubMed: 21090901]
46. Fitzgerald D, Lucas S, Redobaldo MA, et al. Cognitive functioning in young people with first episode psychosis: relationship to diagnosis and clinical characteristics. Aust N Z J Psychiatry. 2004;38(7):501–510. [PubMed: 15255822]
47. Kravariti E, Morris RG, Rabe-Hesketh S, et al. The Maudsley early onset schizophrenia study: cognitive function in adolescents with recent onset schizophrenia. Schizophr Res. 2003;61(2-3):137–148. [PubMed: 12729865]
48. van der Werf M, Köhler S, Verkaaik M, et al. Cognitive functioning and age at onset in non-affective psychotic disorder. Acta Psychiatr Scand. 2012;126(4):274–281. [PubMed: 22582732]
49. Landrø NI, Ueland T. Verbal memory and verbal fluency in adolescents with schizophrenia spectrum disorders. Psychiatry Clin Neurosci. 2008;62(6):653–661. [PubMed: 19068001]
50. Penadés R, Pujol N, Catalán R, et al. Cortical thickness in regions of frontal and temporal lobes is associated with responsiveness to cognitive remediation therapy in schizophrenia. Schizophr Res. 2016;171(1-3):110–116. [PubMed: 26777884]
51. Maher BA, Manschreck TC, Yurgelun-Todd DA, et al. Hemispheric asymmetry of frontal and temporal gray matter and age of onset in schizophrenia. Biol Psychiatry. 1998;44(6):413–417. [PubMed: 9777170]
52. Ranganath C, Minzenberg MJ, Ragland JD. The cognitive neuroscience of memory function and dysfunction in schizophrenia. Biol Psychiatry. 2008;64(1):18–25. [PubMed: 18495087]
53. Bowie CR, Grossman M, Gupta M, et al. Cognitive remediation in schizophrenia: efficacy and effectiveness in patients with early versus long-term course of illness. Early Interv Psychiatry. 2014; 8(1):32–38. [PubMed: 23343011]

Clinical points:

- Having a first episode of schizophrenia during adolescence may influence patients' response to cognitive training;
- Auditory cognitive training is effective in improving cognition in individuals with both early and adult onset schizophrenia;
- Relative to AOS, patients with EOS showed a reduced response to cognitive training in the verbal learning and memory domain, however this finding requires replication.

Table 1.

Baseline demographic, clinical and cognitive characteristics of EOS and AOS participants

	AOS (n=58)	**EOS (n=26)**		
	Mean (SD)	**Mean (SD)**	***F* value**	***p* value**
Male/Female [a]	45/13	15/11	3.48	0.062
Age	33.62 (12.72)	24.08 (10.33)	11.28	0.001
Education (years)	13.38 (2.02)	12.35 (1.83)	4.96	0.029
WASI IQ	101.52 (13.70)	103.04 (10.98)	0.21	0.649
Clinical variables				
Duration of illness [b]	12.55 (13.54)	7.81 (10.88)	1.68	0.099
Age of first psychotic symptoms [b]	21.27 (5.99)	16.47 (2.29)	15.07	<0.001
Age at first hospitalization [c]	23.81 (5.76)	17.13 (0.99)	31.75	<0.001
Number of hospitalizations	4.26 (5.66)	3.67 (3.64)	0.226	0.636
PANSS Total	64.62 (19.47)	63.04 (14.87)	0.14	0.713
PANSS Positive symptoms	14.83 (6.30)	14.19 (4.97)	0.21	0.651
PANSS Negative symptoms	16.91 (5.89)	16.73 (7.37)	0.02	0.904
PANSS General symptoms	32.88 (10.23)	32.12 (7.17)	0.12	0.731
Cognitive variables				
Global cognition	39.50 (7.45)	39.34 (7.72)	0.01	0.928
Speed of processing	42.93 (7.86)	42.11 (8.09)	0.19	0.661
Working memory	43.18 (8.45)	44.46 (8.03)	0.43	0.515
Verbal learning and memory	29.50 (13.07)	30.30 (14.62)	0.06	0.803
Visual learning and memory	37.89 (14.72)	35.37 (17.90)	0.46	0.500
Problem solving	46.51 (9.64)	48.70 (7.11)	1.07	0.303
Treatment variables				
Hours of AT training	40.83 (11.14)	36.15 (8.44)	3.63	0.060

Abbreviations: EOS = early-onset schizophrenia, AOS = adult-onset schizophrenia, IQ = intelligence quotient, PANSS = Positive and Negative Syndrome Scale, AT = auditory training

[a] Chi-Square results

[b] T-value results, AOS n=57, EOS n=25.

[c] AOS n= 58, EOS n=24.

Table 2.

General linear models (GLM) for repeated measures results, with group condition as independent variable (AOS versus EOS) and post-treatment scores as the dependent variable controlling for baseline cognitive scores

	AOS (n=58)		EOS (n=26)					
Outcome measures	**Baseline**	**Post**	**Baseline**	**Post**	**Time effect**		**Group effect**	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	***F* value**	***p***	**F value**	**p**
Global cognition	39.50 (7.45)	42.88 (7.76)	39.34 (7.72)	42.04 (7.95)	10.95	0.001	0.46	0.500
Speed of processing	42.93 (7.86)	44.94 (7.38)	42.11 (8.09)	46.78 (9.73)	23.68	<0.001	2.35	0.129
Working memory	43.18 (8.45)	46.04 (9.41)	44.46 (8.03)	46.92 (9.12)	10.22	0.002	0.00	0.950
Verbal learning and memory	29.50 (13.07)	34.79 (12.58)	30.30 (14.62)	29.88 (13.81)	24.71	<0.001	5.79	0.018[1*]
Visual learning and memory	37.89 (14.72)	41.43 (14.94)	35.37 (17.90)	38.64 (15.74)	27.48	<0.001	0.20	0.658
Problem solving	46.51 (9.64)	50.26 (8.74)	48.70 (7.11)	52.26 (6.24)	51.91	<0.001	0.39	0.536

Abbreviations: EOS = early-onset schizophrenia, AOS = adult-onset schizophrenia.

[1] df=1, partial eta squared=0.067

[*] pFDR>0.005

Table 3.

Association between duration of illness and change in cognition from baseline to post-training

	Duration of illness					
Cognitive domain	**All sample (n=82)**		**AOS group (n=57)**		**EOS group (n=25)**	
	***r* value**	***p* value**	***r* value**	***p* value**	***r* value**	***p* value**
Global cognition	−0.06	0.600	−0.03	0.840	−0.18	0.388
Speed of processing	−0.10	0.373	−0.04	0.770	−0.15	0.472
Working memory	0.03	0.821	−0.03	0.830	0.18	0.383
Verbal learning and memory	0.14	0.218	0.23	0.080	−0.32	0.117
Visual learning and memory	−0.04	0.703	−0.05	0.720	−0.04	0.858
Problem solving	−0.21	0.056	−0.27	0.040*	−0.07	0.743

Abbreviations: EOS = early-onset schizophrenia, AOS = adult-onset schizophrenia.

* p<0.05