Early- Versus Adult-Onset Schizophrenia as a Predictor of Response to Neuroscience-Informed Cognitive Training

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ABSTRACT

Background: Developmental stages characterized by greater neural plasticity might be critical periods during which the effects of cognitive training (CT) could theoretically be maximized. However, experiencing a first episode of schizophrenia during childhood or adolescence (ie, 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 (ie, adult-onset schizophrenia [AOS]) as a predictor of response to CT and the relationship between duration of illness and cognitive improvements.

Methods: This study is a secondary analysis of data from 2 randomized trials that examined the cognitive effects of neuroscience-informed auditory training (AT) exercises 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 ($F > 10.22$, $P < .002$). The effect of EOS was significant only for verbal learning and memory ($F = 5.79$, $P = .018$). AOS increased the mean change score by 5.70 points in this domain, whereas EOS showed no change ($t = -2.280$, $P = .025$). However, the difference between AOS and EOS was no longer statistically significant after control for multiple comparisons. Shorter duration of illness was associated with greater improvement in problem solving in the AOS group ($r = -0.27$, $P = .040$).

Conclusions: Auditory training is effective in improving cognition in both EOS and AOS. Treatment effects in all cognitive domains were similar, with the exception of verbal learning and memory. This result requires replication. Cognitive training provided earlier in the course of the illness results in greater improvements in executive functions.

Trial Registration: ClinicalTrials.gov identifiers: NCT00312962, NCT00694889

J Clin Psychiatry 2020;81(2):18m12369

To cite: Puig O, Fisher M, Loewy R, et al. Early- versus adult-onset schizophrenia as a predictor of response to neuroscience-informed cognitive training. *J Clin Psychiatry*. 2020;81(2):18m12369.

To share: https://doi.org/10.4088/JCP.18m12369

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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[2] showed no relationship between response to training and age. However, most studies included in that 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] The existence of such periods may be especially crucial for interventions that are restorative in nature, for which 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 adult-onset schizophrenia (AOS),[23–25] some cognitive domains such as working and verbal memory are disproportionately 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[31] concluded that the overall pattern of improvement in cognition after CT was similar to that observed in chronic schizophrenia, but with smaller effect sizes. However, these studies included mixed samples of

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 both early-onset schizophrenia (EOS) and adult-onset schizophrenia (AOS).
- Relative to those with AOS, patients with EOS showed a reduced response to cognitive training in the verbal learning and memory domain; however, this finding requires replication.

adolescents with EOS and young adults with early- and adult-onset schizophrenia, 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 posttreatment, which were maintained at 3-month follow-up. Testing a different CT program, Ueland and Rund[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 6-month follow-up,[36] but the sample in that 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 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 duration of illness would be correlated with cognitive improvements.

METHODS

This is a secondary analysis of 2 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 institutional review board at the University of California, San Francisco, and the University of California, Davis.

Participants

The sample included 84 subjects pooled from the 2 studies. Subjects were recruited between 2004 and 2014. All participants included in the current analysis (1) were clinically stable outpatients with schizophrenia spectrum disorders recruited from mental health treatment settings, (2) were 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 participants (44%) were from the sample of the first study,[11] which included chronically ill volunteer adult participants with schizophrenia or schizoaffective disorder (chronic schizophrenia study). The other 47 participants (56%) were from a study of recent-onset schizophrenia,[30] 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 neurologic disorder, and did not have substance dependence in the past year. Participants aged 18 years and older gave written informed consent, while those younger than age 18 years provided assent, with written parental/legal guardian consent.

For the current analysis, participants were classified as EOS patients provided they were aged 18 years 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 were unknown. Duration of illness was computed as current age minus age at 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 per day, 5 days per 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 (1 hour per day, 5 days per week, for 8 weeks) and were contacted 1 or 2 times per 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 (eg, 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 4 or 5 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 subserving auditory processing and verbal memory.[38,39] The rationale is that, to understand and remember verbal information, the brain must first generate precise and reliable neurologic 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 measures recommended by the National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative was administered.[42] A tower test (described later in this paragraph) was used in place of the Neuropsychological Assessment Battery Mazes subtest. 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 (mean *T* score across all measures); speed of processing (Trail Making Test part A; category fluency animal naming); working memory (letter-number span; Wechsler Memory Scale Third Edition spatial span); verbal learning and memory (VLM; Hopkins Verbal LEARNING Test–Revised [HVLT-R] immediate and delayed recall); visual learning and memory (Brief Visuospatial Memory Test–Revised [BVMT-R] immediate and delayed recall); problem solving (Tower of London test 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 the HVLT-R and BVMT-R, and the Tower of London test in the chronic schizophrenia study, were administered and counterbalanced at baseline and posttraining. All neurocognitive tests were rescored by a second staff member blind to the first scoring.

Statistical Analyses

Chi-square tests and 1-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 posttreatment 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 were run including other potential confounds as covariates (ie, baseline clinical differences between groups and total hours of training). The 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 vs EOS) using the mean change scores (posttraining minus baseline). Finally, we conducted exploratory Pearson correlations to examine potential relationships between mean change scores and duration of illness. All tests were 2-tailed. All analyses were conducted using IBM SPSS Statistics for Windows (version 18; SPSS, Inc; Chicago, Illinois).

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 psychotic symptoms and first hospitalization. There were no other significant differences between groups in demographic variables or symptoms. The proportions of patients from the chronic schizophrenia study and from

Table 1. Baseline Demographic, Clinical, and Cognitive Characteristics of EOS and AOS Participants

Characteristic	AOS (n = 58)[a]	EOS (n = 26)[a]	Statistic[b]	*P*
Male/female, n	43/13	15/11	3.45[c]	.062
Age, y	33.62 (12.72)	24.08 (10.33)	11.28	.001
Education, y	13.38 (2.02)	12.35 (1.83)	4.96	.029
WASI IQ	101.52 (13.70)	103.04 (10.98)	0.21	.649
Clinical variables				
Duration of illness, y	12.55 (13.54)	7.81 (10.88)	1.68[d]	.099
Age at first psychotic symptoms, y	21.27 (5.99)	16.47 (2.29)	15.07[d]	< .001
Age at first hospitalization, y[e]	23.81 (5.75)	17.13 (0.99)	31.75	< .001
No. of hospitilizations	4.26 (5.66)	3.67 (3.64)	0.226	.636
PANSS score				
Total	64.62 (19.47)	63.04 (14.87)	0.14	.713
Positive symptoms	14.83 (6.30)	14.19 (4.97)	0.21	.651
Negative symptoms	16.91 (5.89)	16.73 (7.37)	0.02	.904
General symptoms	32.88 (10.23)	32.12 (7.17)	0.12	.731
Cognitive variables[f]				
Global cognition	39.50 (7.45)	39.34 (7.72)	0.01	.928
Speed of processing	42.93 (7.86)	42.11 (8.09)	0.19	.661
Working memory	43.18 (8.45)	44.46 (8.03)	0.43	.515
Verbal learning and memory	29.50 (13.07)	30.30 (14.62)	0.06	.803
Visual learning and memory	37.89 (14.72)	35.37 (17.90)	0.46	.500
Problem solving	46.51 (9.64)	48.70 (7.11)	1.07	.303
Treatment variable				
Hours of AT	40.83 (11.14)	36.15 (8.44)	3.63	.60

[a]Values are mean (SD) unless otherwise noted.
[b]Statistic values are *F* values unless otherwise noted.
[c]χ^2 result.
[d]*t* result; AOS n = 57, EOS n = 25.
[e]AOS n = 58, EOS n = 24.
[f]Raw scores on cognitive measures were converted to *T* scores using age-appropriate normative data. See the Methods section for the measures used for each variable.
Abbreviations: AOS = adult-onset schizophrenia, AT = auditory training, EOS = early-onset schizophrenia, IQ = intelligence quotient, PANSS = Positive and Negative Syndrome Scale, WASI = Wechsler Abbreviated Scale of Intelligence.

the recent-onset schizophrenia study were similar in both groups ($\chi^2 = 1.36$, $P = .244$). All group differences in baseline cognitive performance were nonsignificant. Overall, both groups had means approximately 1 standard deviation below the normative mean across cognitive domains, with the exception of VLM, for 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 posttraining showed improved performance in VLM in the AOS group and no change in performance in the EOS group. This difference remained significant after control for years of education ($F = 4.66$, $P = .034$) and for total hours of training ($F = 4.53$, $P = .036$). However, the difference was no longer statistically significant after control for multiple comparisons ($P_{FDR} > .005$). 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 ($t = -2.280$, $P = .025$). The group effect was not significant in any of the other cognitive domains, in which both groups improved to a similar degree.

Association Between Duration of Illness and Change in Cognition

Although differences between groups in duration of illness were not statistically significant, we conducted post hoc correlation analyses to examine potential relationships between duration of illness 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 duration of illness 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 study is the first to investigate the potential role of early- versus adult-onset illness as a

Table 2. General Linear Models for Repeated-Measures Results[a,b]

Outcome Measure	AOS (n = 58) Baseline, Mean (SD)	AOS (n = 58) Posttraining, Mean (SD)	EOS (n = 26) Baseline, Mean (SD)	EOS (n = 26) Posttraining, Mean (SD)	Time Effect *F*	Time Effect *P*	Group Effect *F*	Group Effect *P*
Global cognition	39.50 (7.45)	42.88 (7.76)	39.34 (7.72)	42.04 (7.95)	10.95	.001	0.46	.500
Speed of processing	42.93 (7.86)	44.94 (7.38)	42.11 (8.09)	46.78 (9.73)	23.68	< .001	2.35	.129
Working memory	43.18 (8.45)	46.04 (9.41)	44.46 (8.03)	46.92 (9.12)	10.22	.002	0.00	.950
Verbal learning and memory	29.50 (13.07)	34.79 (12.58)	30.30 (14.62)	29.88 (13.81)	24.71	< .001	5.79	.018*,[c]
Visual learning and memory	37.89 (14.72)	41.43 (14.94)	35.37 (17.90)	38.64 (15.74)	27.48	< .001	0.20	.658
Problem solving	46.51 (9.64)	50.26 (8.74)	48.70 (7.11)	52.26 (69.24)	51.91	< .001	0.39	.536

[a]Group condition (AOS vs EOS) was the independent variable and posttraining score was the dependent variable, with control for baseline cognitive scores.
[b]Raw scores on cognitive measures were converted to *T* scores using age-appropriate normative data. See the Methods section for the measures used for each variable.
[c]*df* = 1, partial eta squared = 0.067.
*P_{FDR} > .005.
Abbreviations: AOS = adult-onset schizophrenia, EOS = early-onset schizophrenia, FDR = false discovery rate.

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 after control 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 cognitive profile similar to that of the AOS group in all cognitive domains, including a selective deficit in VLM. This finding 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, such as duration of illness, could be related to a reduced response of VLM to CT in EOS, 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 frontotemporal cortical volume reductions and asymmetry have also been found to be related to an earlier age at 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. These results are 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 to boost treatment benefits for EOS. For example, coaching and

Table 3. Association Between Duration of Illness and Change in Cognition From Baseline to Posttraining[a]

Cognitive Domain	Duration of Illness: Overall Sample (n = 82) *r*	Overall Sample (n = 82) *P*	AOS Group (n = 57) *r*	AOS Group (n = 57) *P*	EOS Group (n = 25) *r*	EOS Group (n = 25) *P*
Global cognition	−0.06	.600	−0.03	.840	−0.18	.388
Speed of processing	−0.10	.373	−0.04	.770	−0.15	.472
Working memory	0.03	.821	−0.03	.830	0.18	.383
Verbal learning and memory	0.14	.218	0.23	.080	−0.32	.117
Visual learning and memory	−0.04	.703	−0.05	.720	−0.04	.585
Problem solving	−0.21	.056	−0.27	.040*	−0.07	.743

[a]Duration of illness data were available for a subset of participants: AOS, n = 57; EOS, n = 25.
*P < .05, indicating statistical significance.
Abbreviations: AOS = adult-onset schizophrenia, EOS = early-onset schizophrenia.

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 that focuses on "bottom-up" processes. Strategy-based approaches are mainly "compensatory" and focus on "top-down" processes 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 found no significant association between duration of illness and cognitive change in EOS, lower duration of illness in AOS was associated with greater gains in executive function. This finding 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 of limitations to this study. First, we used a pooled sample from 2 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 included only 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 response to AT similar to that of 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.

Submitted: May 21, 2018; accepted September 9, 2019.

Published online: March 3, 2020.

Potential conflicts of interest: **Dr Vinogradov** is a site investigator on an SBIR (Small Business Innovation Research) 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. Dr Vinogradov is on the advisory board for Mindstrong Inc and Alkermes. **Dr Carter** has served on advisory boards for Merck, Lilly, Pfizer, Roche, and Servier and has received research funding from GlaxoSmithKline. **Dr Loewy** has received honoraria as a faculty member of the Lundbeck International Neuroscience Foundation. **Drs Puig**, **Fisher**, **Ramsay**, **Ragland**, and **Niendam** and **Ms Miley** report no competing interests.

Funding/support: Study NCT00694889 was supported by Stanley Medical Research Institute grant 06TAF-972, the Laszlo N. Family Tauber Foundation, National Institute of Mental Health (NIMH) grant 5R01MH081051, and the San Francisco Department of Veterans Affairs (DVA) Medical Center. Study NCT00312962 was supported by NIMH grant MH-068725, MH-68725-02, NIMH Small Business Technology Transfer grant R42 MH-073358, and the San Francisco DVA Medical Center. The cognitive training software used in these studies was supplied free of charge by Posit Science Inc.

Role of the sponsor: The study sponsors did not contribute to authorship, including design, acquisition of data, analysis and interpretation of data, or writing of the article.

Acknowledgments: The authors gratefully acknowledge participants and their families; the support of M. Merzenich, PhD; H. Mahncke, PhD; S. Chan, PhD; P. Delahunt, PhD; and D. Tinker, PhD, of Posit Science, Inc, who provided the cognitive training software and technical support free of charge; and the assistance of G. Poelke, F. Amirfathi, S. Yohannes, C. Holland, A. Genevsky, C. Garrett, P. Alexander, V. Powell, and R. So from the University of California, San Francisco, who assisted with recruitment, assessments, and data entry. Dr Puig also acknowledges Fundación Alicia Koplowitz, who supported Dr Puig with a traveling grant. These individuals have no potential conflicts of interest relevant to the subject of this article.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.