A Multicenter, Rater-Blinded, Randomized Controlled Study of Auditory Processing–Focused Cognitive Remediation Combined With Open-Label Lurasidone in Patients With Schizophrenia and Schizoaffective Disorder

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ABSTRACT

Objective: Small-scale studies of auditory processing cognitive remediation programs have demonstrated efficacy in schizophrenia. We describe a multicenter, rater-blinded, randomized, controlled study of auditory-focused cognitive remediation, conducted from June 24, 2010, to June 14, 2013, and approved by the local institutional review board at all sites.

Method: Prior to randomization, participants with schizophrenia (*DSM-IV-TR*) were stabilized on a standardized antipsychotic regimen (lurasidone [40–160 mg/d]), followed by randomization to adjunctive cognitive remediation: auditory focused (Brain Fitness) versus control (nonspecific video games), administered 1–2 times weekly for 30 sessions. Coprimary outcome measures included MATRICS Consensus Cognitive Battery (MCCB) and the University of California, San Diego, Performance-Based Skills Assessment-Brief scale.

Results: 120 participants were randomized and completed at least 1 auditory-focused cognitive remediation (n = 56) or video game control session (n = 64). 74 participants completed ≥ 25 sessions and postrandomization assessments. At study completion, the change from prestabilization was statistically significant for MCCB composite score ($d = 0.42$, $P < .0001$) across groups. Participants randomized to auditory-focused cognitive remediation had a trend-level higher mean MCCB composite score compared to participants randomized to control cognitive remediation ($P = .08$). After controlling for scores at the time of randomization, there were no significant between-treatment group differences at study completion.

Conclusions: Auditory processing cognitive remediation combined with lurasidone did not lead to differential improvement over nonspecific video games. Across-group improvement from prestabilization baseline to study completion was observed, but since all participants were receiving lurasidone open label, it is difficult to interpret the source of these effects. Future studies comparing both pharmacologic and behavioral cognitive enhancers should consider a 2 × 2 design, using a control for both the medication and the cognitive remediation.

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Schizophrenia is associated with deficits in neurocognitive processes across a wide range of neuropsychological domains that contribute disproportionately to social and occupational dysfunction.[1] Antipsychotic treatment alone has minimal effects on cognitive function,[2,3] and most schizophrenia patients continue to exhibit pronounced impairment even with adequate antipsychotic treatment.[4] An alternative strategy to enhance cognitive function in schizophrenia includes "cognitive remediation," commonly defined as "a behavioral training–based intervention that aims to improve cognitive processes."[5(p472)] Meta-analyses[5,6] of cognitive remediation trials in schizophrenia indicate a moderate effect size for improvement in cognitive performance ($d = 0.45$).

While many cognitive remediation approaches target relatively complex brain processes such as executive function or working memory,[7] patients with schizophrenia also demonstrate severe deficits within sensory domains.[8] For example, deficits in early sensory processing of auditory information[9–12] have been increasingly documented over recent years and correlate with impairments in higher level functional outcomes.[13–17] Multiple studies of "auditory-focused" cognitive remediation have now been performed, using a program targeting both early auditory processing and working memory operations developed by Posit Science.[18,19] In the first study,[19] patients with schizophrenia showed significant, moderate to large ($d = 0.56–0.86$) effect-size improvements in global cognition for auditory-focused cognitive remediation compared to a video game control. A follow-up multicenter study[20] found significant mean MATRICS Consensus Cognitive Battery (MCCB)[21] composite score improvement ($P = .047$) only at study midpoint.

In the present report, we expand on previous reports of auditory-focused cognitive remediation. In an attempt to minimize interparticipant variation, all participants were stabilized on a standardized antipsychotic (lurasidone) for at least 6 weeks prior to randomization to auditory-focused cognitive remediation versus control. Putative procognitive qualities of lurasidone include lack of histamine (H_1) antagonism, resulting in less daytime sedation, lack of acetylcholine (M_1) receptor antagonism,[22] and cognitive-enhancing effects in preliminary clinical studies.[23] As such, it is possible that consistent stabilization of all participants on

Clinical Points

- Specialized cognitive remediation has been shown to be helpful in schizophrenia in controlled studies, but the effect of intersubject variability in antipsychotic medication is unknown.
- Thirty sessions of specialized auditory-focused cognitive remediation did not lead to differential improvement over nonspecific computer games among participants stabilized on and treated with lurasidone.

lurasidone might provide a conducive pharmacologic base for identifying positive effects of cognitive remediation, and we hypothesized that auditory-focused cognitive remediation combined with lurasidone could produce greater improvement than lurasidone plus video games alone.

METHOD

Participants

The study was registered on ClinicalTrials.gov (identifier: NCT01173874). Written informed consent was obtained from all participants, and approval was obtained by the local institutional review board at all sites. Participants were recruited from 19 sites in the United States and participated from June 24, 2010, to June 14, 2013.

Inclusion criteria. We included participants who were aged 18–55 years, with *DSM-IV-TR*[24] diagnosis of schizophrenia/schizoaffective disorder, and currently receiving lurasidone or those with change in antipsychotic medication clinically warranted by suboptimally controlled schizophrenia symptoms, side effects, or participant preference to switch and Wechsler Test of Adult Reading[25] raw score > 12 at screening.

Exclusion criteria. We excluded participants with current treatment with clozapine, history of treatment resistance, learning disability, serious medical or neurologic illness, sensory impairment, substance abuse/dependence, or cognitive remediation during the previous 6 months.

Lurasidone Stabilization and Randomization

Lurasidone was begun at 40 mg/d with food, and study physicians had up to 8 weeks to complete transition to lurasidone (40–160 mg/d) and achieve stability for ≥ 2 weeks prior to randomization. Previous antipsychotic drugs (Table 1), if any, were discontinued over a period of ≤ 4 weeks from screening. Participants already receiving lurasidone were required to be receiving it for ≥ 6 weeks before entering a prospective 2-week stability assessment. Participants who were unable to achieve 2 weeks of stable symptomatology were not eligible for randomization. Clinical stability was defined as (1) ≤ 4 on Positive and Negative Syndrome Scale (PANSS)[26] items of conceptual disorganization, hallucinations, suspiciousness, and unusual thought content items; (2) Simpson-Angus Scale (SAS)[27] total score ≤ 6; and (3) Calgary Depression Scale[28] total score ≤ 10.

Randomization and Masking

Participants were randomized in a 1:1 ratio to receive twice weekly cognitive remediation sessions, for a total of 30 cognitive remediation sessions within a 4- to 6-month timeframe, and at least 5 per month. Randomization lists were generated by the data management group at the Nathan Kline Institute, independent from the study team. Randomization was conducted in blocks of 4, with each block randomized as to order. Separate randomization lists were created for each site. Participants were enrolled at each site by the study team, which remained blind to cognitive remediation assignment. Only dedicated cognitive remediation administrators were aware of group assignments.

Cognitive Remediation

Auditory processing–focused cognitive remediation ("Brain Fitness"), was developed by Posit Science and is fully described elsewhere.[19] Commercially available video games (After Dark Games; Sierra-online) were used as the control cognitive remediation. As in previous studies,[19,20] participants met in small group settings for 75 minutes per session, which included 60 minutes of cognitive remediation and a 15 minute "bridging" component (Neuropsychological Educational Approach to Remediation [NEAR] program[29]) in the auditory-focused condition, or Healthy Behaviors discussion in the control condition.

Outcome Measures

Study outcomes were measured by clinical raters blinded to cognitive remediation assignment. The MCCB was the primary outcome and was assessed 4 times: at prestabilization (screening), randomization (after 6 to 8 weeks of lurasidone stabilization, prior to initial cognitive remediation), midpoint (after 20 cognitive remediation sessions; approximately 2 to 3 months postrandomization), and study completion (final visit, after 30 cognitive remediation sessions, approximately 4–6 months postrandomization). The coprimary outcome was the University of California, San Diego, Performance-Based Skills Assessment-Brief (UPSA-B).[30] The key secondary outcomes were the Cognitive Assessment Interview (CAI),[31] PANSS, the Abnormal Involuntary Movement Scale (AIMS),[32] SAS, and the Barnes Akathisia Scale (BAS).[33] An exploratory analysis assessed the Intrinsic Motivation Inventory (IMI),[34] training intensity, and the impact of prestabilization antipsychotic on outcomes, auditory processing, and memory (Tone Screening Test[35] and Word Serial Position Test[36]).

Adjunctive Medications

Participants were permitted to continue antidepressant, mood-stabilizing, and antianxiety drugs that were at a stable dose for ≥ 1 month prior to screening. Adjunctive benzodiazepines (lorazepam or clonazepam ≤ 2 mg/d up to 5 times per week as needed), benztropine (≤ 2 mg/d), propranolol (≤ 120 mg/d), or zolpidem ≤ 10 mg) were allowed. Participants requiring a second antipsychotic drug

for more than 1 week during the stabilization period were discontinued.

Statistical Analyses

All analyses were carried out in SAS 9.3 software after verifying that data were normally distributed. The primary analysis (study completion MCCB) was conducted in a modified intent to treat (mITT) using all randomized participants who attended at least 1 cognitive remediation session, while PANSS was analyzed in all available participants. Improvement in cognitive outcomes during the stabilization period was tested by 1-sample *t* tests with the null hypothesis $\mu_0 = 0$. Randomization visit differences between treatment groups or between those who dropped out and study completers were assessed using 2-sample *t* tests for continuous variables and χ^2 tests for categorical variables. We conducted linear regression models to test postrandomization group differences in the main cognitive outcomes. Because of significant differences between groups at randomization (see Supplementary eTable 1 at PSYCHIATRIST.COM), the models were run with and without randomization score adjustment. Prestudy lurasidone treatment and training intensity were all considered as predictors of the cognitive outcome measures and as moderators of the effect of treatment on the outcomes. The longitudinal patterns of PANSS scores throughout the study period (stabilization to completion) were modeled using mixed-effects regression, with random intercept and slope of time. Cohen *d* was calculated as mean change divided by prestabilization or randomization baseline SD.

RESULTS

Sample Description

One hundred eighty-seven participants were enrolled (Supplementary eFigure 1A–B) across 19 sites. One hundred thirty-three participants met stabilization criteria and were randomized, although 13 of these participants dropped out prior to their first cognitive remediation session and were grouped with the dropouts for statistical analysis (Table 1). One hundred twenty participants completed at least 1 cognitive remediation session (auditory focused [n = 56] versus control [n = 64]) and were included in the mITT.

Prestabilization period demographics and ratings are presented in Table 1. Randomized participants were similar to those who discontinued during stabilization, with the exception of a significantly smaller percentage of randomized participants who were receiving risperidone or antipsychotic polypharmacy prestudy, and a significantly larger percentage of randomized participants on lurasidone prestudy. Randomized participants were similar between groups for those receiving lurasidone prestudy and adjunctive medications, other than a trend for control cognitive remediation participants to be more likely to be receiving antidepressants (Supplementary eTable 1).

Table 1. Baseline Demographics and Outcome Measures[a]

Variable	Randomized (N = 120)	Pre–Cognitive Remediation Dropouts (n = 67)	Between Group, *P*[b]
Demographics and medication			
Age, y	37.7 ± 10.1	36.3 ± 9.5	.37
Men, %	65	73	.25
WTAR score (total)	31.4 ± 10.6	32.4 ± 10.0	.55
Lurasidone dose at randomization or dropout, mg	66.4 ± 29.4	68.2 ± 25.3	.67
Highest grade completed, y	12.6 ± 2.2	12.0 ± 3.3	.22
Baseline PANSS (score)			
Total	70.3 ± 16.3	71.7 ± 16.0	.47
Positive	17.6 ± 5.1	17.3 ± 5.2	.34
Negative	18.1 ± 6.4	18.9 ± 5.9	.63
General	34.6 ± 8.6	35.5 ± 8.4	.24
Baseline cognition/function (*t* score or total score)			
MCCB			
Composite	29.0 ± 11.3	28.5 ± 10.8	.36
Speed of processing	32.6 ± 10.4	32.0 ± 10.4	.32
Attention and vigilance	36.7 ± 11.9	37.1 ± 13.0	.14
Working memory	37.2 ± 11.6	37.4 ± 11.7	.26
Verbal learning	36.8 ± 7.8	35.7 ± 6.5	.51
Visual learning	36.8 ± 13.3	36.4 ± 13.7	.59
Reasoning and problem solving	38.0 ± 8.8	37.1 ± 8.8	.31
Social cognition	39.9 ± 10.8	39.5 ± 11.5	.83
UPSA-B	72.6 ± 14.6	72.9 ± 14.6	.98
Cognitive Assessment Interview	3.0 ± 1.3	3.0 ± 1.2	.77
Prestudy antipsychotic, n			
Aripiprazole	14	5	NS
Asenapine	1	1	NS
First generation	12	6	NS
Lurasidone			**.0011**
Monotherapy	**22**	**2**	
Antipsychotic polypharmacy	**9**	**3**	
Multiple antipsychotics	20	9	NS
None	6	7	NS
Olanzapine	15	6	NS
Paliperidone	3	2	NS
Quetiapine	6	8	NS
Risperidone	**16**	**19**	**.018**
Ziprasidone	5	2	NS
No. of antipsychotics (prestudy)	**1.6 ± 1.0**	**2.1 ± 1.6**	**.03**

[a]Data are mean ± SD unless otherwise specified.
[b]Bold indicates $P < .05$.
Abbreviations: MCCB = MATRICS Consensus Cognitive Battery; NS = nonsignificant; PANSS = Positive and Negative Syndrome Scale; UPSA-B = University of California, San Diego, Performance-Based Skills Assessment-Brief; WTAR = Wechsler Test of Adult Reading.

Eighty-nine participants completed at least 1 post-randomization ratings assessment, while 74 participants completed the study, defined as completing ≥ 25 cognitive remediation sessions, and assessments at midpoint and study completion. There was no significant between-group difference in the percentage of completers (auditory-focused = 59%, control = 64%; $P = .58$).

Cognition and Function

Stabilization period. Prestabilization MCCB scores were > 2 SDs below normative levels ($t = 50$), suggesting clinically significant cognitive deficits at baseline (Table 1). Among randomized participants (Table 2), significant, but small, effect size improvements were seen across the stabilization period in the MCCB composite score ($P < .0001$, $d = 0.20$),

Table 2. Study Outcomes

Variable	Across Group Total Scores,[a] Mean ± SD (*P*, Cohen *d*)[b]		Between-Group Mean Difference After Cognitive Remediation[c] (*P*, Cohen *d*)[b]	
	At Randomization (poststabilization)	Study Completion (post–cognitive remediation)	Midpoint	Study Completion
PANSS score				
Total	**59.1 ± 16.0 (<.0001, −0.68)**	**60.1 ± 16.1 (<.0001, −0.55)**	−4.5 (.099, 0.4)	0.9 (.78, −0.07)
Positive	**14.0 ± 4.6 (<.0001, −0.70)**	**14.4 ± 5.0 (<.0001, −0.56)**	−1 (.24, 0.28)	0.1 (.96, −0.01)
Negative	**15.5 ± 5.1 (<.0001, −0.40)**	**16.1 ± 5.7 (.0095, −0.26)**	−1.5 (.12, 0.37)	0.7 (.51, −0.16)
General	**29.6 ± 9.0 (<.0001, −0.59)**	**29.6 ± 8.5 (<.0001, −0.52)**	−2 (.16, 0.33)	0.2 (.93, −0.02)
Cognition/function				
MCCB score (*t* score or total score)				
Composite	**32.3 ± 11.3 (<.0001, 0.20)**	**33.8 ± 12.6 (<.0001, 0.42)**	2.1 (.24, 0.29)	0 (.99, 0)
Speed of processing	**34.7 ± 10.5 (<.0001, 0.21)**	**37.0 ± 11.0 (<.0001, 0.41)**	*2.7 (.09, 0.42)*	−0.8 (.68, −0.1)
Attention and vigilance	37.5 ± 12.9 (.22, 0.08)	**38.0 ± 14.5 (.03, 0.17)**	0.7 (.71, 0.09)	−0.6 (.77, −0.07)
Working memory	38.4 ± 12.0 (.19, 0.07)	**39.5 ± 12.7 (<.0001, 0.28)**	*3.5 (.06, 0.46)*	1.3 (.38, 0.21)
Verbal learning	38.0 ± 9.1 (.17, 0.12)	**39.3 ± 11.0 (.01, 0.32)**	1.7 (.39, 0.21)	1.2 (.55, 0.14)
Visual learning	38.4 ± 14.5 (.11, 0.11)	**40.5 ± 13.8 (.009, 0.23)**	3 (.19, 0.32)	2.8 (.17, 0.34)
Reasoning and problem solving	**40.6 ± 9.1 (.0002, 0.29)**	**41.1 ± 9.8 (.0003, 0.46)**	−0.6 (.69, −0.1)	−1.5 (.35, −0.23)
Social cognition	41.5 ± 12.1 (.12, 0.13)	**41.1 ± 12.4 (.013, 0.26)**	2.1 (.41, 0.2)	1.6 (.48, 0.17)
UPSA-B	**76.3 ± 13.9 (.0001, 0.24)**	**77.7 ± 14.3 (.001, 0.32)**	1.9 (.46, 0.18)	2.1 (.41, 0.2)
Cognitive Assessment Interview	**2.8 ± 1.3 (.03, −0.15)**	*2.8 ± 1.4 (.07, −0.20)*	0 (.74, 0.08)	0.1 (.73, 0.08)

[a]Across groups final score after the lurasidone stabilization and after completing cognitive remediation. Statistics represent across group change from baseline.
[b]Bold indicates $P < .05$; italics $P < .1$.
[c]Between-group differences are covaried for scores at randomization, with positive effect sizes favoring active cognitive remediation.
Abbreviations: MCCB = MATRICS Consensus Cognitive Battery; PANSS = Positive and Negative Syndrome Scale; UPSA-B = University of California, San Diego, Performance-Based Skills Assessment-Brief.

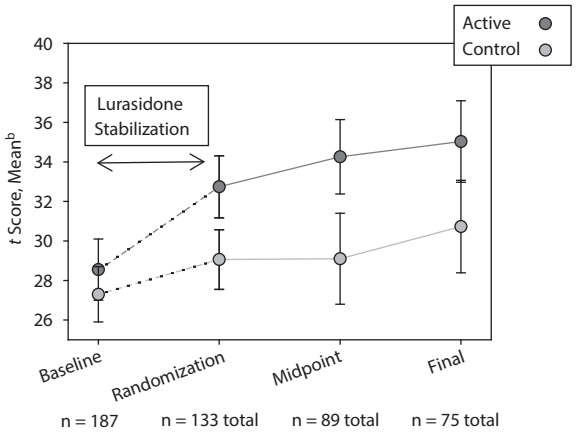
speed of processing ($P < .0001$, $d = 0.21$), and reason and problem solving ($P = .0002$, $d = 0.29$). Thirty-one percent of participants showed meaningful (≥5 *t* score points on the MCCB composite) improvement during the stabilization period. Sixty-three percent showed no change (−4 to 4 *t* score points), and 6% worsened (≥−5 *t* score points). Significant, but small, effect size improvements were also seen in the UPSA-B and CAI composite (Table 2). No significant effects were seen for other cognitive measures across the stabilization period.

Cognitive remediation period. Across treatment groups, a moderate effect size improvement from the prestabilization baseline to the end of the study was seen in the MCCB composite score ($P < .0001$, $d = 0.42$, Table 2) among study completers.

There were significant differences between groups at randomization, with the auditory-focused cognitive remediation group having significantly higher MCCB domain scores, including visual learning ($P = .03$) and reasoning and problem solving ($P = .02$), along with a trend toward statistical significance for higher MCCB composite ($P = .08$, Supplementary eTable 1). Similar between-group differences were seen at randomization among study completers. These between-group differences were not retrospectively present at the prestabilization visit and resulted from differential improvement prior to randomization (Figure 1).

Without adjusting for between-group differences at randomization, participants in the auditory-focused group had a significantly higher visual learning domain score ($P = .026$, $d = 0.53$) at study completion. After controlling for scores at the randomization visit (Table 2), there were no significant between-group differences at midpoint or final

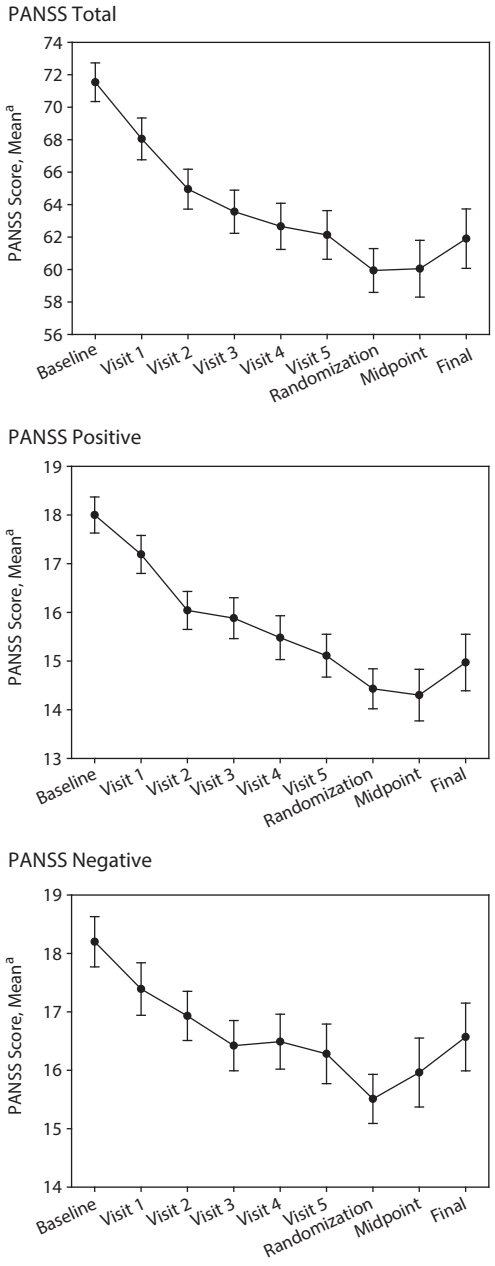
Figure 1. Mean MATRICS Consensus Cognitive Battery (MCCB) Composite *t* Score at Baseline (prestabilization), Randomization (poststabilization), Midpoint (after 20 sessions of cognitive remediation), and Study Completion[a]



[a]Active (auditory) is in dark gray and control (video games) is in light gray. Dashed line indicates retrospective separation of the active and control groups prior to randomization.
[b]Error bars represent standard error of the mean.

assessments (Supplementary eFigure 2). Small to moderate effect sizes were seen in favor of the auditory-focused group for the speed of processing ($P = .09$, $d = 0.42$), the visual learning domain ($P = .17$, $d = 0.34$) and the working memory domain ($P = .06$, $d = 0.46$) at midpoint, but not at study completion. There were no significant differences between completers and postrandomization dropouts in randomization assessment MCCB. Across groups, change between prestabilization and randomization in the MCCB composite was negatively correlated with change during

Figure 2. Mean Positive and Negative Syndrome Scale (PANSS) Total, Positive, and Negative Scores of Participants Across Group



[a]Error bars represent standard error of the mean.

cognitive remediation ($r = -0.43$, $P < .001$). Similar results were seen for other domains.

PANSS

Stabilization period. Prestabilization period PANSS scores reflected mild to moderate illness severity (Table 1). There was a significant effect of time among all enrolled participants on PANSS total in the stabilization period ($P < .0001$, Figure 2 and Table 2). Similar results were seen when the analysis was restricted to the randomized population ($P < .0001$, $d = 0.73$). Of the randomized participants, 42.5% had a ≥20% reduction in symptoms between prestabilization and randomization.

Cognitive remediation period. Across treatment groups, a continued effect of time was seen at study completion for PANSS total (Table 2: 16% reduction from baseline, $P < .0001$). Among individual PANSS subscales, small to moderate effect size improvements were seen for positive (21% reduction, $P < .0001$) and negative (15% reduction, $P < .001$) symptoms at randomization compared to those at prestabilization (Table 2). Randomized noncompleters had significantly higher total ($P < .05$) and negative scale ($P = .006$) PANSS at randomization.

After controlling for randomization scores, there were no between-group differences at midpoint or study completion (Table 2). A trend toward a significantly larger improvement in PANSS total at midpoint favoring the auditory-focused cognitive remediation group ($P < .1$, $d = 0.4$) was seen at midpoint, along with nonsignificant, small to moderate effect size differences in PANSS subscales. Within the auditory-focused group, improvements on PANSS total significantly correlated with improvement on the speed-of-processing domain at midpoint ($r = -0.41$, $P = .02$), while within the control group, significant or trend-level correlations were seen in the attention/vigilance ($r = -0.33$, $P = .04$), working memory ($r = -0.38$, $P = .01$), and composite ($r = -0.28$, $P = .08$).

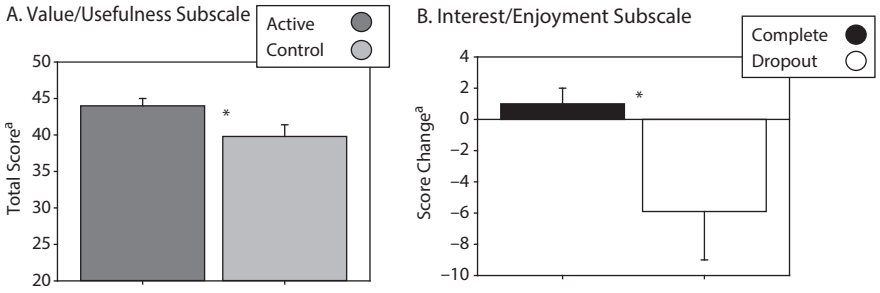
Impact of Prior Lurasidone Treatment

Of 120 randomized participants, 31 (26%) were receiving lurasidone either as monotherapy or as part of antipsychotic polypharmacy prior to beginning the stabilization period (Table 1). Across treatment groups at randomization, participants already receiving lurasidone prestudy had lower PANSS total (between-group difference = −6.6, $P = .01$), higher UPSA-B (5.5, $P = .004$), and a trend toward higher MCCB composite (2.1, $P = .07$) scores after controlling for prestabilization values. These differences remained at study completion after control for prestabilization values (PANSS [−9.2, $P < .01$], UPSA-B [6.5, $P = .03$] and MCCB composite [5.0, $P = .003$] scores), but not after control for randomization values (PANSS [−4.0, $P = .27$], UPSA-B [2.7, $P = .34$] and MCCB composite [1.9, $P = .22$] scores). There were no statistically significant between–cognitive remediation group differences in the percentage of participants taking lurasidone prestabilization at randomization, or study completion, and there were no statistically significant between-group differences in outcome.

Intrinsic Motivation, Training Intensity, and Ancillary Measures

An exploratory analysis examined the impact of intrinsic motivation (IMI) and ancillary auditory measures. There was an effect of cognitive remediation treatment on the IMI value/usefulness subscale, with participants assigned to auditory-focused cognitive remediation showing higher scores at study completion ($P = .03$, $d = 0.51$, Figure 3A). Intrinsic motivation was also related to the ability to

Figure 3. Intrinsic Motivation Inventory (A) Value/Usefulness Subscale at Study Completion and (B) Interest/Enjoyment Subscale Among Group Completers (black: completed 30 sessions) Versus Noncompleters (white)



*$P < .05$.
[a]Error bars represent standard error of the mean.

complete the study, as study-end interest/enjoyment was larger in those participants who completed 30 sessions across group ($P = .015$, $d = 0.80$, Figure 3B). No between-group differences were seen on the total IMI or on other subscales. Among study completers, there appeared to be no between–cognitive remediation group differences in training intensity at midpoint (both groups: mean ± SD = 1.8 ± 0.3 sessions per week) or at study completion (1.7 ± 3 vs 1.7 ± 4), and no correlations with any outcomes. There were no between-group differences in auditory processing/memory from randomization to study completion.

Safety

Minimal levels of extrapyramidal symptoms, as measured by the AIMS, BAS, and SAS were seen at prestabilization, with no significant changes during the study.

DISCUSSION

To our knowledge, this is the first randomized study to date to assess the potential benefit of auditory processing–focused cognitive remediation in combination with a uniform antipsychotic (lurasidone) in comparison to lurasidone + nonspecific video games. Moderate effect size improvements were seen across group for cognitive and symptom outcomes, although no statistically significant between-group differences were seen at study completion after controlling for randomization scores. Trends favoring auditory-focused cognitive remediation at study midpoint were seen for several MCCB domains (Table 2).

Between-Group Differences at Randomization

Analysis of the study was complicated by statistically significant and trend-level differences among participants assigned to auditory-focused and control cognitive remediation, with the participants assigned to the auditory-focused cognitive remediation having uniformly higher overall scores, including a 3.7 *t* score trend-level difference on the MCCB composite ($P = .08$). This resulted from differential improvement during the stabilization period. Although participants in the auditory-focused group had consistently higher scores at study completion, after covarying for the differential in randomization visit scores, there were no significant differences. While we feel that the choice to covary for randomization scores was correct, it remains possible that the significant differences at the randomization visit may have obscured the ability to detect between-group differences. A highly significant negative correlation between change during the stabilization period and change during the cognitive remediation period was seen, suggesting that there may have been some regression to the mean postrandomization by the large stabilization-period improvers in the active group.

Comparison to Prior Studies and Limitations

In the present report, participants were asked to complete 30 sessions over a 4–6 month period, and we defined completers as ≥ 25 cognitive remediation sessions. Compared with prior studies using similar methods and a similarly impaired population,[19,20] the present project used a smaller "dose" of cognitive remediation (30 vs > 40 sessions), over a longer time period (> 4 months vs < 3 months). This decision was made to reduce the overall burden on participants and increase practicality for clinical settings by not requiring daily treatment. However, it is possible that we underdosed the amount or rate of sessions and note that our mean number of sessions per week (approximately 1.7) was low compared to previous studies. Moreover, given our comparably high attrition rate (approximately 40%), the reduced dose may have reduced the ability for participants to engage and may have resulted in reduced power to detect differences. We also note that similar to one prior study,[20] we found a larger effect at study midpoint, which seemingly argues for a reduced dose.

Impact of Lurasidone

Unlike previous trials of cognitive remediation, all participants in this study were stabilized on a standardized antipsychotic: flexibly dosed lurasidone. Although antipsychotics have questionable differential cognitive benefits,[2] lurasidone has theoretical procognitive benefits, including low daytime sedation[37] and minimal anticholinergic properties.

Across groups, significant improvement was seen across time, larger than one would expect from practice effects ($d = 0.25$), suggesting potential benefits. In contrast, as opposed to continuing on lurasidone, switching antipsychotics was associated with a higher rate of discontinuation prior to randomization and worse cognitive performance and higher levels of symptoms throughout. Thus, it is possible that participants switching may not have been as stable as those already receiving lurasidone, and that this potential lack of stability may have contributed to the lack of differential improvement.[5] No significant between-group interactions existed between outcome and receiving lurasidone prestudy, but since all participants were receiving lurasidone open label, any independent or interaction effect of lurasidone on cognition is difficult to interpret. Nevertheless, while the decision to use a uniform antipsychotic was intended to reduce interparticipant variability, trend-level between–cognitive remediation group differences were noted at randomization.

Secondary Outcomes

Participants with schizophrenia appear to have relatively normal ability to experience pleasure,[38] but reduced ability to work for a delayed reward.[39,40] In the present study, participants with higher interest and enjoyment were more likely to complete the study, a finding consistent with prior studies suggesting that this subscale is a core construct of intrinsic motivation.[41] Although we did not directly measure anhedonia, auditory-focused cognitive remediation was rated to be more valuable and useful in an exploratory analysis, which may be an important indicator of efficacy and improvement in anhedonia. Finally, we note that participants with higher levels of negative symptoms at randomization were less likely to complete the study, suggesting that these symptoms may be rate limiting for cognitive remediation. In contrast, changes in total PANSS score were relatively independent of changes in cognition in the active group.

In conclusion, auditory processing cognitive remediation did not lead to differential improvement over nonspecific computer games among participants stabilized on and treated with lurasidone. Future studies comparing both pharmacologic and behavioral cognitive enhancers should consider a 2×2 design, eg, using a control for both the medication and the cognitive remediation, and most likely should use more sessions over a shorter time window.

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Drug names: aripiprazole (Abilify and others), asenapine (Saphris), clonazepam (Klonopin and others), clozapine (Clozaril, FazaClo, and others), lorazepam (Ativan and others), lurasidone (Latuda), olanzapine (Zyprexa and others), paliperidone (Invega and others), propranolol (Inderal, Innopran, and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others), zolpidem (Ambien, Edluar, and others).

Potential conflicts of interest: **Dr Kantrowitz** reports having received consulting payments within the last 12 months from Vindico Medical Education, Annenberg Center for Health Sciences at Eisenhower, Health Advances, Havas Life, Strategic Edge Communications, and Cowen and Company; has conducted clinical research supported by the National Institute of Mental Health, Stanley Foundation, Roche-Genentech, Forum, Sunovion, Lilly, and GlaxoSmithKline; and owns a small number of shares of common stock in GlaxoSmithKline. **Dr Sharif** has received grant support from Sunovion. **Dr Medalia** has received a royalty from Oxford University Press, has served as a consultant to Dainippon Sumitomo Pharma, and has served on speaker/advisory boards for Takeda and Forum. **Dr Keefe** has received consulting payments within the last 12 months from Abbvie, Akebia, Amgen, Asubio, AviNeuro/ChemRar, Biogen Idec, Biomarin, Boehringer-Ingelheim, FORUM, GW Pharmaceuticals, Lundbeck, Merck, Minerva Neurosciences, Mitsubishi, Novartis, New York State Office of Mental Health, Otsuka, Pfizer, Reviva, Roche, Sanofi-Aventis, Sunovion, Takeda, and the University of Texas Southwest Medical Center; has conducted clinical research supported by the US Department of Veterans Affairs, the National Institute of Mental Health, and the Singapore Medical Research Council; owns shares in NeuroCog Trials and Sengenix; and has received royalties from the Brief Assessment of Cognition (BAC) and the MATRICS Battery (BACS Symbol Coding). **Dr Harvey** has served as a consultant to Boehringer-Ingelheim, Forum Pharma, Genentech, Lundbeck, Otsuka America Pharmaceuticals, Roche-Genentech, Sanofi, Sunovion, and Takeda; and has conducted contracted research for Genentech. **Dr Barch** has served as a consultant to Pfizer, Takeda, Roche, and Amgen. **Dr Lieberman** serves on the advisory board of Intracellular Therapies and does not receive direct financial compensation or salary support for his participation; serves on the advisory board of Pierre-Fabre; receives grant support from Alkermes, Biomarin, Lilly, Psychogenics, EnVivo/Forum, Genentech, Novartis/Novation, and Sunovion; is a member of the advisory board of and holds financial interest in Clintara and Pear Therapeutics; and holds a patent from Repligen. **Drs Bruder**, **Choo**, and **Lee** have no conflicts to disclose.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: A Multicenter, Rater-Blinded, Randomized Controlled Study of Auditory Processing–Focused Cognitive Remediation Combined With Open-Label Lurasidone in Patients With Schizophrenia and Schizoaffective Disorder

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List of Supplementary Material for the article

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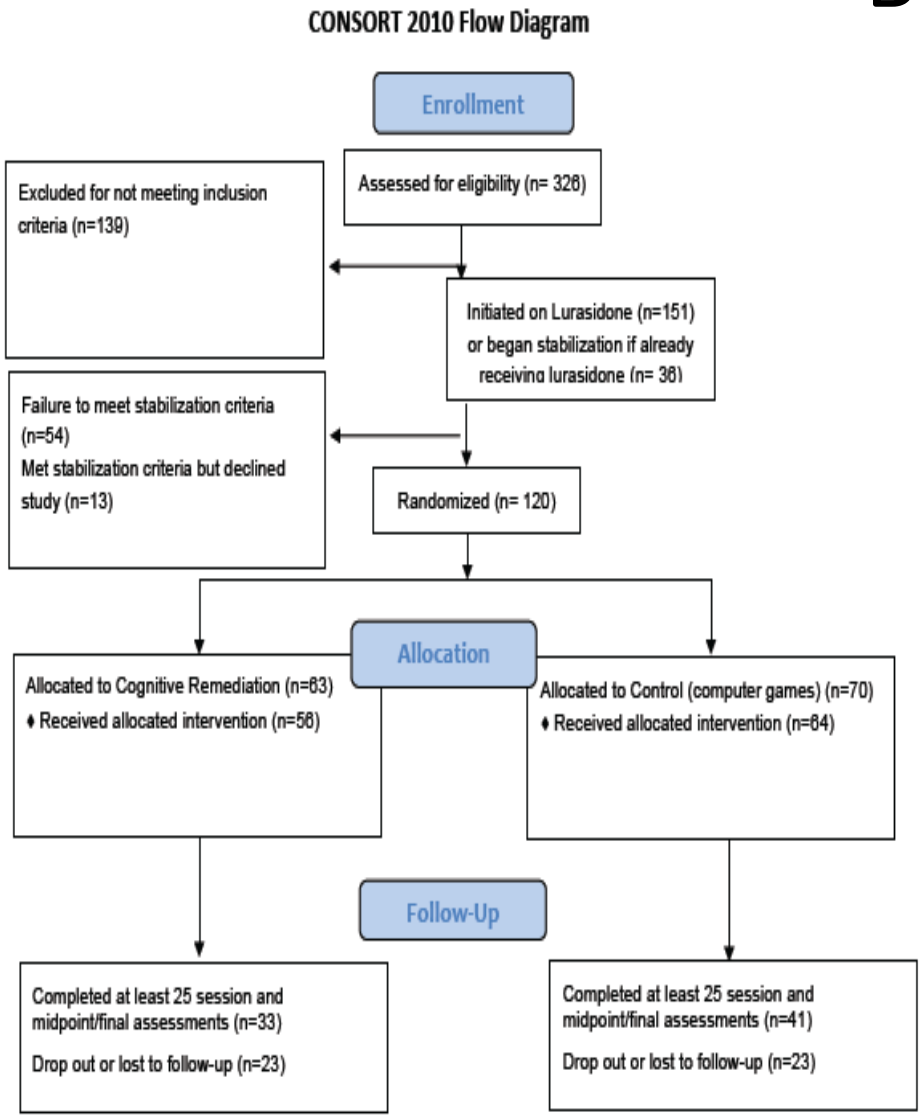
A



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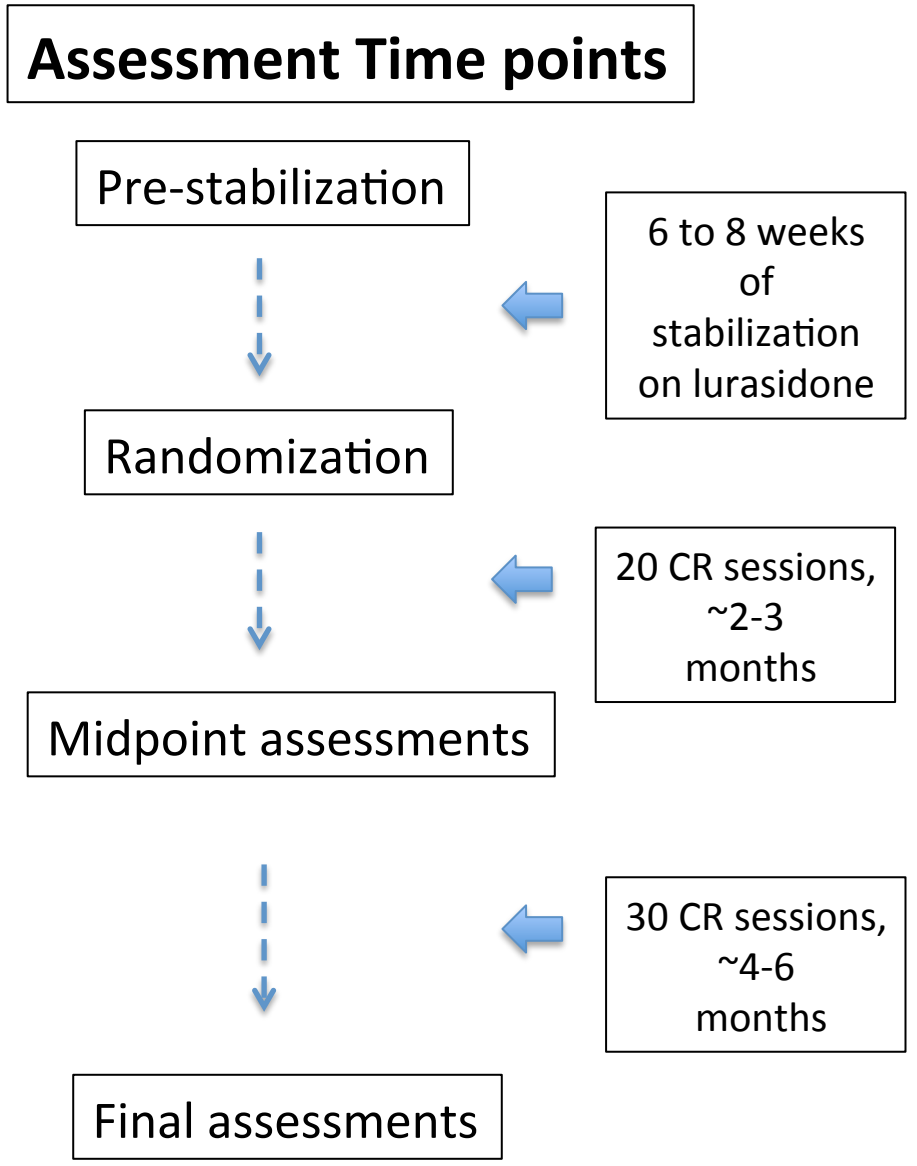
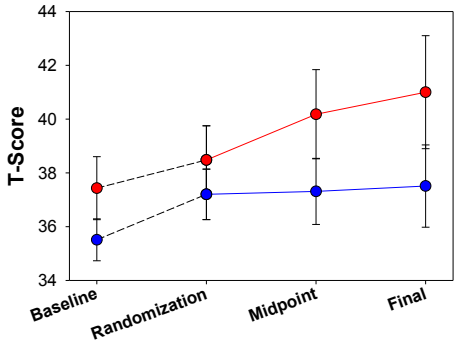


Supplemental eFigure 1

Verbal Learning



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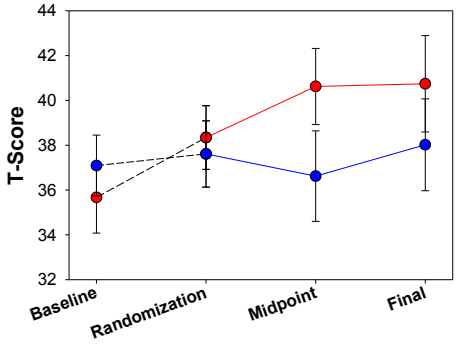

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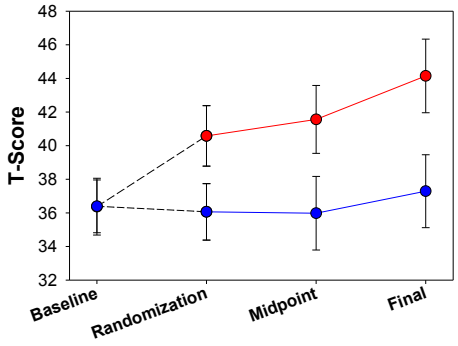

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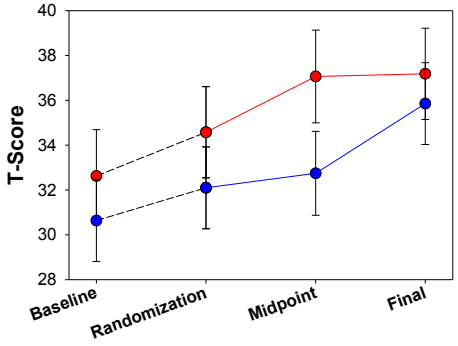

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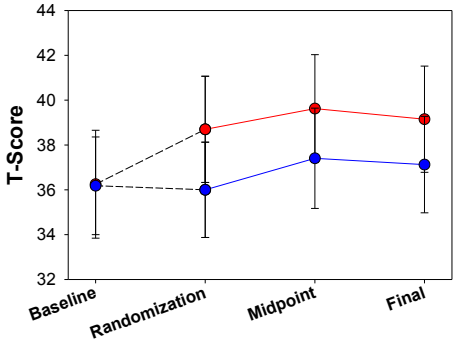
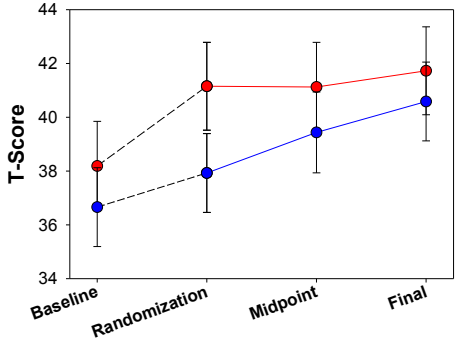


Reason and Problem Solving



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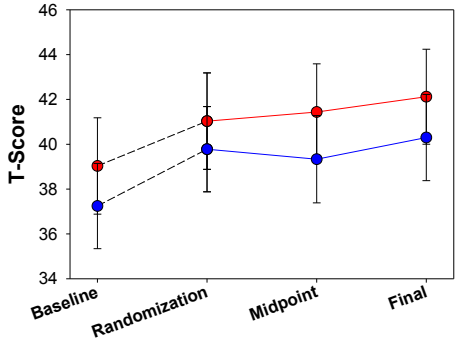

Supplemental eFigure 2

Supplemental eFigure 2 footnote: Line graph showing mean MATRICS consensus cognitive battery (MCCB) by domain T-score at baseline (pre-stabilization), randomization (post-stabilization), midpoint (after 20 session of CR) and at study completion. Active (auditory) is in red and control (Video games) is in blue. Dashed line indicates retrospective separation of the active and control groups prior to randomization. Abbreviations: Speed of Processing (SOP)

Supplemental eTable 1: Demographics and outcome measures at Randomization (post-stabilization)

		Cognitive remediation (n=56)	Computer games (n=64)	Between group (p)
Demographics and medication	Age	37.1±9.9	38.1±10.3	0.58
	Male (%)	61%	69%	0.36
	WTAR	31.6±9.4	31.3±11.6	0.90
	Lurasidone Dose at Randomization or dropout (mean)	63.0±23	69.3±34	0.24
	Receiving lurasidone pre-study	28%	23%	0.54
PANSS (score)	Total	57.8±15.3	60.3±16.8	0.39
	Positive	14.2±4.6	13.9±4.7	0.74
	Negative	14.8±5	16.2±5.1	0.12
	General	28.8±7.9	30.2±9.9	0.4
Cognition/function (T-score or total score)	Composite	*34.2±11.6*	*30.5±10.9*	*0.08*
	Speed of Processing	36.2±9.8	33.5±11.1	0.17
	Attention & Vigilance	38.7±12.5	36.5±13.3	0.36
	Working Memory	39.5±11.3	37.4±12.5	0.35
	Verbal Learning	39±10.4	37.1±7.8	0.27
	Visual Learning	**41.6±14.3**	**35.7±14.2**	**0.03**
	Reasoning & Problem Solving	**42.7±9.3**	**38.8±8.7**	**0.02**
	Social Cognition	42.1±11.6	41.1±12.5	0.66
	UPSA-B	78.1±12.7	74.8±14.8	0.2
	CAI	2.7±1.3	2.8±1.3	0.73

Adjunctive psychotropics (%)[1]	Antidepressants	*18%*	*34%*	*0.06*
	Sedative/hypnotics	30%	31%	0.99
	Mood Stabilizers	5%	8%	0.72
	Anticholinergic	13%	17%	0.61

1. Percent receiving adjunctive psychotropics at any point.

Abbreviations: Cognitive Assessment Interview (CAI), Positive and Negative Symptom Scale (PANSS), University of California Performance-based Skills Assessment-Brief (UPSA-B), Wechsler Test of Adult Reading (WTAR)