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When Top-Down Meets Bottom-Up: Auditory Training Enhances Verbal Memory in Schizophrenia

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A critical research priority for our field is to develop treatments that enhance cognitive functioning in schizophrenia and thereby attenuate the functional losses associated with the illness. In this article, we describe such a treatment method that is grounded in emerging research on the widespread sensory processing impairments of schizophrenia, as described elsewhere in this special issue. We first present the rationale for this treatment approach, which consists of cognitive training exercises that make use of principles derived from the past 2 decades of basic science research in learning-induced neuroplasticity; these exercises explicitly target not only the higher order or "top-down" processes of cognition but also the content building blocks of accurate and efficient sensory representations to simultaneously achieve "bottom-up" remediation. We then summarize our experience to date and briefly review our behavioral and serum biomarker findings from a randomized controlled trial of this method in outpatients with long-term symptoms of schizophrenia. Finally, we present promising early psychophysiological evidence that supports the hypothesis that this cognitive training method induces changes in aspects of impaired bottom-up sensory processing in schizophrenia. We conclude with the observation that neuroplasticity-based cognitive training brings patients closer to physiological patterns seen in healthy participants, suggesting that it changes the brain in an adaptive manner in schizophrenia.

Key words: schizophrenia/cognition/cognitive training/psychophysiology

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Introduction

Schizophrenia is profoundly disabling; the symptoms and cognitive impairments first described by Kraepelin over 100 years ago translate to functional losses that are costly both to the individual and to society at large. Despite Kraepelin's focus on cognition in his first descriptions of schizophrenia, for many decades positive symptoms were the key targets for treatment, and their reduction remains the primary benefit of nearly all antipsychotic medications. But, by successfully treating positive symptoms and thus decoupling them from cognitive impairment, the use of antipsychotic medications has revealed that stable deficits in both cognition and function persist across fluctuations in positive symptom burden[1] and that cognition and function are strongly correlated.[2–5] Thus, it is now abundantly clear that a critical research priority for our field is to identify treatment methods that specifically enhance cognition and thereby attenuate the functional losses associated with schizophrenia.

In this article, we will describe such a treatment method that is grounded in emerging research on the widespread sensory processing impairments of schizophrenia, as described elsewhere in this special issue. We will first describe the rationale for this treatment approach, which consists of cognitive training exercises that make use of principles derived from the past 2 decades of basic science research in learning-induced neuroplasticity and that explicitly target both "bottom-up" sensory representations as well as "top-down" attention and working memory functions. We will then summarize our experience to date and briefly review our behavioral and serum biomarker findings from a randomized controlled trial (RCT) of this method in outpatients with long-term symptoms of schizophrenia. Finally, we will present promising early psychophysiological evidence that supports the hypothesis that this cognitive training method normalizes aspects of impaired sensory processing in the illness.

What Is the Rationale for Targeting Sensory Processing in the Treatment of Schizophrenia?

Schizophrenia Is Characterized by Impaired Sensory Processing

As early as Bleuler, authors have argued that the sensory disturbances common among schizophrenia patients

arise from demonstrable dysfunction in "higher order" cognitive processes,[6–8] but Bleuler's famous assertion that "sensory response to external stimulus is quite normal" has now been conclusively disproven (as demonstrated, eg, by the research presented in this special issue). In the context of designing cognitive interventions, as in basic cognitive neuroscience, it may be counterproductive to attempt to localize a primary deficit in schizophrenia either to faculties like attention, working memory, and executive function, which have historically often been described as top-down processes associated with higher order (frontal or parietal) association cortex, or to bottom-up sensory processing historically associated with posterior cortical regions. There is now abundant experimental evidence that the top-down behavioral phenomena of "attention" and "active maintenance" involve the integration of multiple brain systems that manifest as early in processing as primary sensory cortex[9–13] and that have on impact perception via enhanced cortical representations of the external world (and of memory). Conversely, degraded or ambiguous neural representations of sensory information—eg, representations of objectively noisy or ambiguous information—take a toll on performance not only by transmitting unreliable information but also by taxing working memory and attentional systems. Importantly, any putative primary pathophysiological insult in schizophrenia that impairs the ability to actively maintain an accurate representation in working memory or attentional focus of an action-outcome goal or of a behavioral context (as has been proposed by multiple authors[14–17]) would be expected to have an impact on the fidelity and efficiency of cortical representations that are fundamentally sensory.

Indeed, an accumulation of convergent behavioral and physiological data has explicated and specified the historical observations of sensory disturbances in patients. For instance, behavioral demonstrations of early auditory processing impairments in schizophrenia subjects include deficits in tone matching[18–20] and speech perception, particularly in noise.[21–23] Evidence from event-related potentials in electroencephalography and magnetoencephalography (MEG), which allow the fine-grained decomposition of neurophysiological correlates of auditory processing, further suggests impairments in initial sensory registration,[24–26] prediction and temporal integration in paired speech stimulus in noise paradigms (C.L. Dale, A.M. Findlay, and R.A. Adcock, unpublished data, 2009), expectancy violation in mismatch negativity paradigms,[27–31] and early obligatory responses to auditory stimuli in N1/P1 paradigms.[30,32–34] Such early auditory deficits correlate not only with current functional status and outcome[35] but also with the likelihood to develop schizophrenia among at-risk youth.[36]

The etiology and pathophysiology of sensory deficits have important implications for our understanding of schizophrenia, as is described elsewhere in this special issue. The critical points for the current discussion are that sensory processing deficits in schizophrenia patients: (*a*) unequivocally exist, (*b*) impair higher order cognition, as outlined below, and thus (c) may limit a patient's ability to make cognitive improvements unless specifically remedied.

Sensory Representation Impacts Higher Order Cognition

The proposition that the quality of elemental sensory representations is important to processes that operate on those representations is hardly surprising. Although cognitive operations are not strictly serial in nature but rather integrative and parallel, deficiencies in cortical representations of sensory information—eg, of pitch or the resolution of temporal information—would be expected not only to impair speech comprehension[32] and verbal memory[37] but also prosody[38] and emotion detection, cognitive functions correlated with effective social interactions and functional outcome.[39]

However, the requirement to disambiguate degraded bottom-up sensory representations, as occurs in low signal-to-noise sensory inputs,[40] also appears to increase attentional load,[41,42] thus decreasing performance indirectly via competition for top-down resources. Such reallocation of attentional resources to shore up perceptions at the cost of "higher order" functions like processing speed and working memory encoding has been demonstrated in multiple populations from healthy controls under noisy conditions,[41,43] to schizophrenia patients,[44] to healthy older adults.[45]

Improvements in Sensory Representations Should Thus Benefit Higher Order Cognitive Processing

If the fidelity, precision, and signal-to-noise ratio of sensory representations are important determinants of overall cognitive performance, as argued above, poor quality sensory representations could prove to be rate-limiting factors in any cognitive remediation paradigm regardless of the explicit content of the training exercises. From this premise, together with the substantial evidence for sensory impairments in schizophrenia, it follows that optimum cognitive training programs for remediation of cognitive deficits in schizophrenia should include training exercises that target not only top-down functions like attention, working memory, and executive function but also specifically remedy the precision of sensory representations that facilitate cognitive function from the bottom-up.

It Is Possible to Develop Cognitive Training Exercises for Schizophrenia That Simultaneously Target Bottom-Up and Top-Down Processing

The cognitive training exercises we have been investigating are explicitly designed to improve early perceptual processing along with working memory capacity. Psychophysical training that places implicit, increasing

demands on auditory perception and accurate aural speech reception is embedded within increasingly complex auditory working memory and verbal learning exercises. The exercises implement the findings from basic neuroscience research delineating the behavioral and biological determinants of significant neurophysiological change mediated via alterations in synaptic connection and neuronal network functioning (hereafter termed "neural plasticity") in adult brains. Such plastic changes are epitomized by the refinement or remapping of cortical receptive fields but span a wide range of physiologically demonstrable alterations in function. A rich literature (eg, Mercado et al[46] and Bao et al[47]) has shown that neural plasticity in adults requires intensive practice occurring in the context of heightened neuromodulatory neurotransmission (ie, release of neurotransmitters like dopamine, acetylcholine, and norepinephrine that are implicated in top-down functions like attention, executive function, and working memory, in response to behaviorally relevant stimuli). The exercises we have investigated are thus (1) intensive, with thousands of trials per exercise, 2) attentionally engaging, with self-paced initiation of each learning trial and closely regulated task difficulty, (3) adaptive, with the critical content of each exercise adjusting trial by trial to user performance, and (4) rewarding, with entertaining embellishments to reinforce correct responses, which occur frequently due to the adaptive structure of the exercise. This approach capitalizes on the fact that the neural responses to repetitive practice appear to be intact in schizophrenia.[48]

What Results Have Been Obtained to Date Using an Auditory Training Approach?

Description of the Auditory Training Intervention

We briefly review here the results we have obtained in our ongoing RCT of computerized "neuroplasticity based" auditory training vs a commercial computer games (CGs) control condition in clinically stable adult outpatients with long-term schizophrenia, registered at ClinicalTrials.gov NCT00312962 (as reported previously[49–52]). Volunteer participants are stratified by age, gender, education, and symptom severity and randomly assigned to either 50 hours of auditory training (AT) or 50 hours of a CGs control condition (1 h/d, 5 d/wk). Before and after the intervention, they receive symptom, quality-of-life, and cognitive assessments (based on Measurement and Treatment Research to Improve Cognition in Schizophrenia [MATRICS][53] recommendations) by personnel blind to group assignment. Healthy controls are assessed at repeated time points but do not undergo cognitive training. The goal of this study is to test the hypothesis that by improving the speed and fidelity of information processing in the auditory system—while simultaneously training working memory functions—participants will improve their "downstream" verbal memory performance.

Auditory training exercises, developed by PositScience Corporation, are presented in a continuously adaptive manner in that they first establish the precise parameters within each stimulus set required for an individual subject to maintain approximately 85% correct performance; once that threshold is determined, task difficulty increases systematically and parametrically as performance improves. In all exercises, correct performance is heavily rewarded in a game-like fashion through novel and amusing visual and auditory embellishments as well as the accumulation of points. (See Fisher et al[49] for more details).

The CGs condition is designed to control for the effects of computer exposure, contact with research personnel, and monetary payments for participation. CG subjects rotate through 16 different enjoyable commercially available games (eg, visuospatial puzzle games, clue-gathering mystery games, pinball-style games), playing 4–5 games on any given day, and are monitored by staff in the same manner as the AT subjects.

Cognitive Improvement After auditory Training

At baseline, there were no significant differences between the AT group ($N = 29$) and CG control group ($N = 26$) on measures of symptom ratings or on cognitive performance measures.[49,50] After training, repeated-measures analysis of variance (ANOVA) revealed a significant group-by-time interaction (table 1) with the AT group showing improvement in the cognitive outcome variables of verbal working memory (letter-number span), verbal learning (Hopkins Verbal Learning Test, immediate recall), verbal memory (Hopkins Verbal Learning Test, delayed recall), and global cognition (composite score of all MATRICS[53]-recommended measures). There were no group-by-time interactions on change scores in speed of processing (symbol coding, category fluency-animals, Trail Making Test Part A), nonverbal working memory (Wechsler Memory Scale-III, spatial span), visual learning (Brief Visuospatial Memory Test-Revised, immediate recall), visual memory (Brief Visuospatial Memory Test-Revised, delayed recall), or social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test) or on symptom change or quality-of-life change.

An examination of the effect sizes computed for each outcome measure revealed very strong positive effects on verbal cognition measures for the AT condition but with no differential effect between conditions on visual cognition measures (figure 1). We also examined the relationship between training-induced psychophysical gains in the most basic auditory exercise (time-order discrimination of frequency modulation sweeps) and cognitive improvement. We found that auditory psychophysical gains, as assessed by the amount of the exercise content completed by each participant, showed a significant

Table 1. Between-Group Comparison of Change in Cognition in 29 Schizophrenia Subjects Undergoing 50 h Neuroplasticity-Based computerized AT Vs 26 Matched Schizophrenia Subjects Undergoing 50 h of a CGs Control Condition

	AT (N = 29)		CG (N = 26)			
Outcome Measures	Baseline, Mean (SD)	After, Mean (SD)	Baseline, Mean (SD)	After, Mean (SD)	F (P)	AT Effect Size
Global cognition	−1.08 (0.62)	−0.72 (0.69)	−0.92 (0.63)	−0.93 (0.68)	12.82 (<.01)	0.86
Verbal working memory	−1.33 (1.22)	−0.86 (1.39)	−0.93 (1.35)	−1.05 (1.40)	4.46 (.04)	0.58
Verbal learning	−2.22 (1.07)	−1.73 (1.10)	−2.00 (0.80)	−2.34 (0.98)	9.97 (<.01)	0.86
Verbal memory	−2.10 (1.06)	−1.43 (1.40)	−1.97 (1.25)	−2.27 (1.23)	8.60 (<.01)	0.89
Nonverbal working memory	−0.57 (0.80)	−0.34 (0.89)	−0.40 (0.90)	−0.21 (1.08)	0.04 (.85)	0.05
Visual learning	−1.34 (1.21)	−0.70 (1.32)	−0.98 (1.24)	−0.80 (1.45)	1.64 (.21)	0.35
Visual memory	−0.95 (1.40)	−0.59 (1.40)	−0.65 (1.60)	−0.47 (1.62)	0.28 (.60)	0.15

Note: Baseline and posttraining age-adjusted z scores are presented, with results of repeated-measures analysis of variance and effect sizes. AT, auditory training; CG, computer game.

positive correlation with the z-score change in verbal working memory and in global cognition (Pearson r = .46, 2-tailed $P < .03$, and r = 0.39, $P < .04$, respectively; see figure 2 for relationship with global cognition). This finding indicates that those subjects who were able to make the most progress through basic psychophysical auditory training also showed the most improvement in higher order cognitive outcome measures.

Taken together, these data indicate that neuroplasticity-based auditory training that focuses heavily on psychophysical efficiency and auditory/verbal working memory induces robust improvements in verbal and general cognition. These results also provide discriminant validity for the specificity of the effects, suggesting that this training is, as predicted by the underlying neuroscience rationale, specifically enhancing functioning in the neural systems that subserve verbal cognition.

We have also examined the durability of the cognitive improvements after a 6-month no-contact follow-up period in 10 control subjects and 22 cognitive training subjects, some of whom received additional training in visual and cognitive control exercises as well as the auditory exercises. We found significant group-by-time interactions, from baseline to posttraining to the 6-month follow-up; the cognitive training subjects showed significantly greater improvement in verbal learning and memory measures (F = 4.49, P = .03) from baseline to the 6-month follow-up, indicating the durability of the cognitive training effects beyond the immediate posttraining period. Although sampling bias cannot be entirely ruled out in these early data, we note that all subjects were randomly assigned to the different treatment groups. More importantly, significant correlations were observed between change in cognition and improvement in quality-of-life measures 6 months after the intervention in the 22 cognitive training subjects. The association between improvements in functional status at 6 months and cognitive gains are important to note in light of the specificity of training effects to the auditory/verbal modality.

Serum Biomarker Findings After Auditory Training

We examined serum brain-derived neurotrophic factor (BDNF) and serum D-serine in a subgroup of our study subjects, hypothesizing that these compounds may potentially serve as peripheral biomarkers for training-

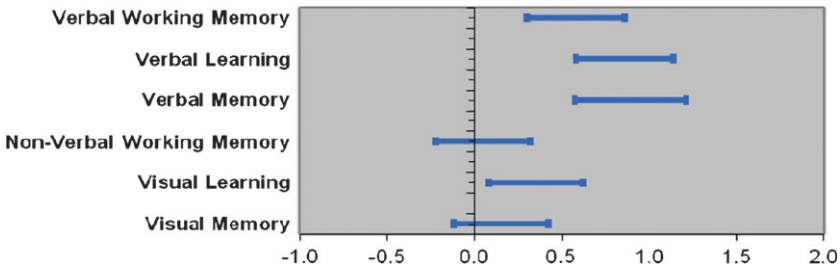

Fig. 1. Effect Sizes (With SE) of Computerized Neuroplasticity-Based Auditory Training on Measures of Verbal Vs Visual Cognition in Patients With Schizophrenia, as Compared With Schizophrenia Patients Undergoing a Computer Games Control Condition. The figure illustrates the large effects of intensive auditory training on measures of verbal cognition in schizophrenia and the discriminant validity of the effects of targeted auditory training on verbal/auditory-based domains of cognitive function as compared with visual domains.

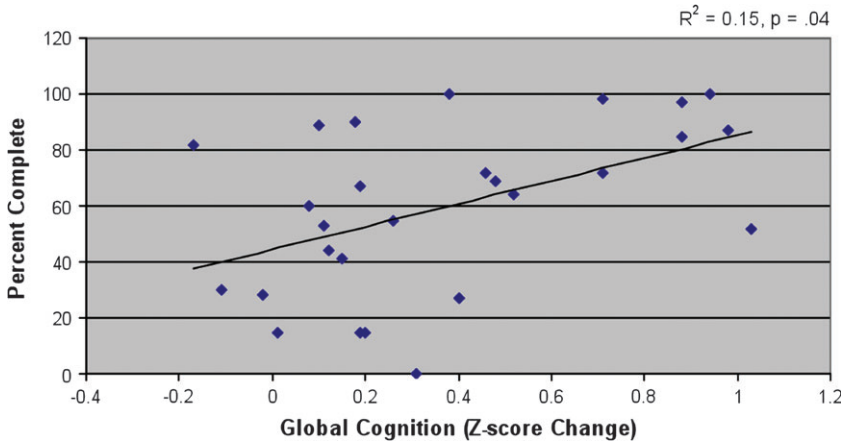

Fig. 2. Association Between Psychophysical Improvement on the Auditory Training Exercise for Time-Order Discrimination of Frequency Modulation Sweeps (Percent of Exercise content Completed) and Improvement in Global Cognition Composite Score (Pearson $r = 0.39$, 2-tailed $P = .04$, $N = 25$).

induced physiological changes (R. Panizzutti, M. Fisher, C. Holland, and S. Vinogradov, unpublished data, 2009).[51] This prediction was based on 2 notions: (1) decreases in apoptosis and increases in BDNF signaling are observed in response to cognitive stimulation[54,55] and (2) the cognitive pathophysiology of schizophrenia may be associated with impairments in *N*-methyl-D-aspartic acid (NMDA) receptor activity—a critical component of learning and memory processes[56]; if these processes are partially restored, this may in turn increase levels of D-serine, a key NMDA receptor coagonist.

At baseline, schizophrenia subjects ($N = 56$) had a significantly lower mean BDNF level of 25.27 ng/ml (SD = 10.34), compared with a mean of 31.30 (SD = 8.95) in healthy comparison subjects ($N = 16$) ($t = 2.11$, $P < .04$), consistent with prior reports (eg, Buckley et al[57] and Rizos et al[58]). There were no differences between patients assigned to AT (mean = 25.03 ng/ml, SD = 11.21) vs CG (mean = 25.54 ng/ml, SD = 9.44). Repeated-measures ANOVA revealed a significant difference between the AT and CG schizophrenia subgroups in BDNF change from baseline, to week 2, to posttraining (wk 10), $F_{2,53} = 3.47$, $P = .04$. Post hoc contrasts revealed that the AT and CG subgroups differed significantly in BDNF serum level from baseline to week 2, $F_{1,54} = 4.97$, $P = .03$, and from baseline to week 10, $F_{1,54} = 6.10$, $P = .02$. After training, the AT group's serum BDNF level was comparable to that of the healthy subjects (mean = 32.23 ng/ml, SD = 15.10), while the CG group's BDNF levels did not change significantly (mean = 23.97 ng/ml, SD = 11.21). The increase in serum BDNF in the AT group was significantly correlated with an increase in quality-of-life scores (Pearson $r = 0.44$, 2-tailed $P = .01$). These data indicate that the neuroplasticity-based cognitive exercises, but not the CGs, induce a biological response involving neurotrophins over the 10 weeks of treatment and that this response is associated with aspects of improved quality of life in schizophrenia patients. Several lines of evidence suggest that there is a relationship between BDNF measured in the periphery and neurotrophic responses in the brain, but at present our understanding of these processes is speculative.[59–62]

At baseline, the ratio of D-serine/total serine, covarying for age, was significantly lower in the schizophrenia subjects (0.80 ± 0.11%, $N = 42$) as compared with healthy subjects (1.31 ± 0.20%, $N = 15$) ($F_{1,54} = 5.12$, $P < .03$). Although there are open questions about how closely serum and cerebrospinal fluid (CSF) D-serine reflect the levels in neural tissue, there is strong evidence for decreased D-serine levels or decreased D/L serine ratio in CSF[63,64] in schizophrenia patients, and similar findings have been reported for serum levels.[63–66] Our baseline findings are consistent with these prior reports. While there was no significant group-by-time interaction in mean D-serine/total serine baseline to posttraining ratio, cognitive gains in the AT group were significantly correlated with increases in D-serine/total serine ratio. In the AT group, D-serine/total serine increases were correlated with improvements in speed of processing (Pearson $r = 0.73$, 2-tailed $P < .001$), verbal learning and memory ($r = 0.53$, $P < .01$), and global cognition ($r = 0.49$, $P < .02$). Although the relationship between serum D-serine and neural plasticity is incompletely understood, these results parallel relationships between D-serine and symptom burden[67] and raise the possibility that changes in serum D-serine reflect the brain's ability to generate training-induced cognitive improvements.

Further support for the notion that this form of cognitive training relies on the engagement of key neuromodulatory systems in the brain comes indirectly from the observation that medication-related serum anticholinergic activity, as measured via radioimmunoassay, was negatively correlated with improvement in global cognition (Pearson $r = -0.46$, 2-tailed $P < .02$, $N = 25$); squared semipartial correlations indicated that serum

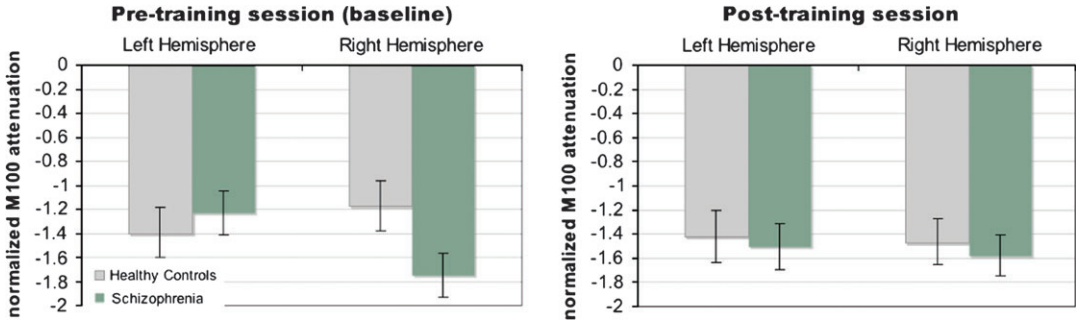

Fig. 3. M100 Attenuation for Second Relative to First Syllable During Discrimination of Rapidly Presented Successive Syllables in Quiet. At baseline, schizophrenia patients ($n = 18$) showed significant hemispheric asymmetry of attenuation, relative to healthy comparison subjects ($n = 14$). After auditory training exercises, this asymmetry was reduced and resembled normal patterns.

anticholinergic activity uniquely accounted for 20% of the variance in global cognition change in the AT subjects. Consistent with demonstrations in animal models of the critical role of cholinergic projections in learning-induced plasticity,[46] these results indicate that cholinergic blockade from psychotropic medications reduces the brain's ability to adapt in response to the cognitive training.

What Are the Preliminary Data on Psychophysiological Effects of Auditory Training?

We report here highly preliminary data from an ongoing study of measures of early neural response dynamics to rapidly presented auditory stimuli obtained before and after auditory training in our RCT participants. We are using MEG to reveal the time course of stimulus-locked activity over bilateral auditory cortices during discrimination of syllable pairs that differ either in voice-onset time (VOT, ie, requiring integration of rapidly changing temporal features of stimuli) or place of articulation (ie, requiring discrimination of spectral features of stimuli) (C.L. Dale, A.M. Findlay, and R.A. Adcock [unpublished data, 2009], give a detailed description of rationale, experimental tasks, and data acquisition methods).

In the MEG analysis reported here, we focus on the M100 response arising from auditory cortex during the discrimination of 2 syllables differing in VOT (eg, "Ba-Pa"), presented in quiet, the first syllable occurring at trial start (0–400 ms) and the second syllable 500 milliseconds later (500–900 ms). Schizophrenia subjects underwent this MEG task at baseline and again in a second session after 50 hours (approximately 10 wk) of auditory training exercises; healthy comparison subjects underwent MEG at baseline and in a second session after 10 weeks but did not engage in cognitive training. (Data from computer games control subjects are in final stages of acquisition and processing and are not reported here). To assess the efficiency with which subjects process the successive VOT stimuli, the amplitude of the M100 response to the first syllable was subtracted from the M100 response to the second syllable, resulting in an overall measure of "attenuation" that represents the normal suppression of neural activity associated with second syllable presentation due to ongoing first syllable processing. At baseline, schizophrenia subjects ($N = 18$) showed a hemispheric asymmetry in their attenuation of the M100 response to the second syllable (hemisphere: $F_{1,17} = 9.139$, $P = .008$), while healthy comparison subjects ($N = 14$) did not (hemisphere: $F_{1,13} = 0.438$, $P = .52$), an effect that produced a significant baseline group difference, as seen in figure 3 (group × hemisphere: $F_{1,30} = 4.379$, $P = .045$). This finding indicates that individuals with schizophrenia show hemispheric asymmetry abnormalities in early neural response dynamics during the rapid temporal integration of auditory stimuli.

After auditory training, the attenuation of the M100 response to second syllable presentation showed a trend toward normalization in schizophrenia subjects, reflected in a reduction of hemispheric asymmetry relative to the pretraining attenuation response (session × hemi × group: $F_{1,30} = 3.853$, $P = .059$). After training, attenuation increased in the schizophrenia subjects in the left hemisphere and decreased in the right hemisphere relative to baseline levels, roughly converging to the mean attenuation levels observed in healthy comparison subjects across hemispheres (figure 3). Post hoc analyses confirm that the between-session difference in asymmetrical response was occurring primarily in the schizophrenia group (session × hemisphere: $F_{1,17} = 9.094$, $P = .008$) but not in the healthy comparison subjects (session × hemisphere: $F_{1,13} = 0.540$, $P = .475$). These findings suggest that the auditory training exercises have had a "normalizing" effect on the temporal integration of rapidly presented successive auditory stimuli as it occurs across hemispheres.

Correlation analyses revealed that the posttraining changes in M100 attenuation during this task seen in the schizophrenia participants were correlated with both task performance and training-related changes in verbal learning. The left hemisphere attenuation response after training correlated with task accuracy such that

better performance in the second session was associated with more overall left hemisphere attenuation during that session, irrespective of baseline attenuation levels ($r = -0.643$, $P = .004$, $n = 18$). Furthermore, changes in left hemisphere attenuation correlated significantly with improved performance after cognitive training on verbal learning ($r = -0.470$, 2-tailed $P = .049$, $n = 18$).

Taken together, these very early but promising findings suggest that the cognitive training exercises, which aim to increase the efficiency with which incoming auditory information is processed, promote physiological changes that are indicative of a ''normalization'' of early linguistic processing across left and right hemispheres in patients with schizophrenia. The changes in physiological activity that we observed in the left hemisphere were associated with both task accuracy and verbal learning gains. Thus, it appears that training-induced normalization of the hemispheric asymmetries in early auditory processing seen at baseline in schizophrenia may induce improvements in higher order verbal cognitive function—as would be predicted by the basic science rationale of this approach. However, we must underscore our relatively small sample size and the highly preliminary nature of these data. Replication of these early neural responses to training and further research with larger subject samples is clearly required before firm conclusions can be drawn.

Discussion

The evidence reviewed here suggests that a program of cognitive training that uses computer-based exercises to accomplish intensive remediation of auditory processing is associated with significant improvements in higher order cognitive performance, as well as detectable physiologic responses suggesting neurobiologic adaptation or restoration of neural system functioning.

Behaviorally, active cognitive training was associated with improvements not only in the trained functions of verbal working memory and immediate verbal learning but also improved verbal memory performance. Notably, improvements did not generalize to the visual modality, suggesting that the training method is anatomically and functionally specific, as expected. Improvements in neurocognitive status following training showed some evidence of durability after a 6-month no-contact follow-up and were significantly correlated with functional outcome as measured by increased quality-of-life ratings,[50] suggesting that the program of training may be of functional benefit or, more likely, can open up a critical window for successful psychosocial rehabilitation.

Physiologically, active cognitive training exercises are associated with increases in peripheral biomarkers thought to be related to neuronal plasticity (BDNF) and to NMDA receptor activity (D-serine/total serine ratio) and may possibly also result in restoration of neural response patterns typical of healthy subjects during early auditory processing of rapidly presented successive stimuli (ie, MEG M100 attenuation to the second syllable). Each of these physiological measures showed significant relationships to cognitive performance and/or function. For BDNF, active training was associated with an increase in serum BDNF levels, which before training were significantly lower in the schizophrenia participants and after training were equivalent to those of healthy subjects; this increase correlated with improved quality of life.[51] For D-serine, the active training group showed correlations between individual in D-serine/total serine and individual cognitive gains in global cognition, processing speed, and verbal learning and memory. Our very preliminary data on M100 measures of early auditory processing indicate that the level of second-syllable attenuation in the left hemisphere achieved after active training was related to better posttraining task accuracy, as well as better verbal learning scores. Overall, the changes observed in these 3 qualitatively different biomarkers suggest the extent of the neurobiological remodeling that must occur to support training effects and that may therefore be presumed to underlie restoration of function in impaired auditory/verbal processing systems.

The behavioral and physiological changes we observed beg questions about what specific components of training are critical to these observations. Because training of auditory representations always occurs alongside the training of attention, working memory, and executive function, it remains unclear what specific components of the exercises are the ''active ingredients.'' It is possible that the exercises work by training higher order cognitive processes per se rather than increasing the fidelity of sensory representations. Our preliminary findings of changes in early sensory processing evident in renormalization of hemispheric lateralization in M100 attenuation measures argue against this notion. Further, if training of some higher order cognitive process underlies the benefits observed, improvements in nonauditory functions like nonverbal working memory and visual learning and memory should also be evident, but they are not. The fact that improvement propagates to more complex functions within the trained modality but not to functions in the untrained modality, as well as our finding that training-induced psychophysical improvement is significantly correlated with improved cognition,[49] supports the notion that the specific training of sensory representations is an important determinant of gains in these exercises.

Effect sizes of improvements on MATRICS-based cognitive outcome variables were quite robust compared with those reported across domains in recent meta-analysis of McGurk et al.[68] Auditory training was associated with large effect sizes in the critical domains of -verbal memory (0.89) and general cognition (0.87) compared with those calculated in a recent meta-analysis of RCTs using a range of conventional cognitive remediation methods in schizophrenia (eg, 0.39 and

0.41, respectively [68]). However, these differences cannot be attributed unequivocally and solely to the effects of training sensory representations. The exercises studied here differ from other training strategies in a number of ways: The schedule of training is delivered in a denser schedule than most other programs (5 h/wk); is more intensive, involving thousands of trials for each exercise; and is delivered in an individually adaptive manner so that the learner is always training at threshold with an 85% correct response rate. Thus, there are differences of degree as well as of kind that would be expected to increase the magnitude of gains in the current approach.

Early visual processing deficits are also evident in schizophrenia patients, as detailed elsewhere in this special issue. The training program described here targeted auditory processing rather than visual systems for a number of theoretical reasons related to the critical functional importance of verbal learning and memory deficits in schizophrenia.[49] However, visual system impairments are also importantly related to function in schizophrenia, eg, in the domain of facial affect recognition.[39] We are currently investigating additional cohorts of patients who complete training specifically developed to target visual processing, cognitive control, and social cognition, in addition to the auditory exercises employed here. The results of those training regimes are still accruing and should allow us to determine whether training multiple cognitive modalities provides synergistic or merely additive effects.

The intensive and demanding training schedule used here may call into question the general utility of this approach to cognitive enhancement in schizophrenia. Relative to other therapies, 50 hours of training delivered on a daily schedule of 1 h/d is highly challenging, and it may fairly be questioned whether patients (and clinicians) in real-world treatment settings can dedicate the time and effort necessary to engage in this form of treatment. However, the converse observation is also valid. The period of time required to successfully complete the auditory training program is equivalent to roughly 2 days out of a person's life—a small investment for a treatment that may have highly beneficial effects. Furthermore, it is not at all obvious that robust biological and generalizable neurocognitive gains would be evident after training programs that occupy such a small fraction of an individual's total experience. That such changes in physiology and function may also persist beyond the period of the intervention[50] and are achieved without the risks associated with drug treatments makes this approach especially appropriate for use early in illness or in at-risk populations.

These convergent findings offer both behavioral and physiological evidence of adaptive neuroplasticity in the brains of individuals using cognitive exercises focused on early auditory processing. Clinical outcomes and neuropsychological improvements suggest robust treatment benefits for this method, which includes specific remediation of sensory representation. Further research is needed to determine whether benefits are specifically attributable to the exercises' sensory component; however, early results show not only restoration of general biological markers associated with neuronal plasticity and learning but also imply specific renormalization of dysfunction of early sensory processing. Thus, our observations suggest that bottom-up sensory dysfunction is not only an important determinant of cognitive performance and function for schizophrenia patients but also an appropriate and effective treatment target.

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