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# Auditory Cortical Plasticity Drives Training-Induced Cognitive Changes in Schizophrenia

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**Schizophrenia is characterized by dysfunction in basic auditory processing, as well as higher-order operations of verbal learning and executive functions. We investigated whether targeted cognitive training of auditory processing improves neural responses to speech stimuli, and how these changes relate to higher-order cognitive functions. Patients with schizophrenia performed an auditory syllable identification task during magnetoencephalography before and after 50 hours of either targeted cognitive training or a computer games control. Healthy comparison subjects were assessed at baseline and after a 10 week no-contact interval. Prior to training, patients ($N$ = 34) showed reduced M100 response in primary auditory cortex relative to healthy participants ($N$ = 13). At reassessment, only the targeted cognitive training patient group ($N$ = 18) exhibited increased M100 responses. Additionally, this group showed increased induced high gamma band activity within left dorsolateral prefrontal cortex immediately after stimulus presentation, and later in bilateral temporal cortices. Training-related changes in neural activity correlated with changes in executive function scores but not verbal learning and memory. These data suggest that computerized cognitive training that targets auditory and verbal learning operations enhances both sensory responses in auditory cortex as well as engagement of prefrontal regions, as indexed during an auditory processing task with low demands on working memory. This neural circuit enhancement is in turn associated with better executive function but not verbal memory.**

## Introduction

Schizophrenia is characterized by a range of cognitive deficits that include both abnormal sensory responses[1,5] and impaired higher-order operations such as verbal memory and executive function ([6,7]; see[8] for review). A growing interest in cognitive training methods has led to randomized controlled trials to promote changes in behavioral and neural activation patterns underlying these deficits,[8,15] but raises questions about neurobehavioral effects of specific training methods. For example, some methods focus on improving higher-order working memory and executive functions associated with prefrontal cortex,[10,11,14] while some target auditory perceptual processes that contribute to prefrontal-sensory interactions.[9,12,15] In the latter focus, the relative contributions of plasticity within sensory and prefrontal regions to cognitive gains remain unknown ([12,15]; see also[13]). Such knowledge is critical to developing optimal training regimens.

We used magnetoencephalography (MEG) to investigate training-induced plasticity in prefrontal and sensory cortical representations during an auditory processing task with low demands on verbal working memory. The task was chosen to assess sensory representational fidelity under conditions requiring attention and response selection with minimal demands on verbal encoding, working memory, and executive function. We hypothesized that targeted cognitive training of auditory processing and auditory working memory would enhance neural responses to phoneme presentation within primary auditory cortex of participants with schizophrenia. We then investigated associations between training-related change in sensory cortical responses, prefrontal activation, and gains in cognitive outcome measures reflecting functions that rely on prefronto-temporal efficiency.[12,15,16]

## Materials and Methods

### *Participants*

Participants in a randomized controlled trial of neuroplasticity-based cognitive training in schizophrenia

(NCT00312962) were invited to participate in imaging sessions for this report. Participants were chronically ill, clinically stable schizophrenia patients, and healthy volunteers, determined by presence or absence of Axis I diagnosis,[17] respectively. Inclusion and matching criteria are summarized in supplementary text 1 and reported in the parent study.[9] Imaging participants had no contraindications to magnetic resonance imaging (MRI), and no hearing loss greater than 20 dB via pure tone audiometry at 1000, 4000, and 8000 Hz. Demographic information for each imaging group is in table 1. The Committee on Human Research at University of California San Francisco, approved all study procedures.

Participants with schizophrenia were randomly assigned to 50 hours of targeted cognitive training ("Active Training" [AT]) or 50 hours of playing commercially available computer games ("Computer Games" [CG]), over 10 weeks. Baseline clinical and neuropsychological assessments were conducted during the 2–3 weeks after informed consent, followed by a battery of tasks in MEG and MRI sessions. Upon completion of the intervention period, participants returned for another MEG and MRI session. Patient participants also underwent a second clinical/neuropsychological assessment, with personnel blinded to group assignment. All patient participants in this report experienced the full intervention duration as a condition of inclusion for the second MEG session.

### *Assessment and Cognitive Training*

Neuropsychological tests recommended by the Measurement and Treatment Research to Improve Cognition in Schizophrenia Committee,[18] were administered pre- and postintervention. Raw score transformations for these measures and symptom assessments are reported elsewhere.[9] The current report examined *z*-score-normalized post- minus preintervention changes for the primary outcome measure of the parent trial, verbal learning and memory (VLM). Given the analytic focus on prefrontal cortex, a secondary outcome measure of executive function was assessed (Tower of London [ToL], c.f. 19).

The AT intervention utilized computerized targeted cognitive training of auditory and verbal learning processes via a suite of increasingly complex and individually adaptive auditory working memory and verbal learning exercises (Posit Science). This program was identical to Popov and colleagues[12,15] but involved more training (50 hours) over a longer period (10 weeks). Patients assigned to the CG group rotated through 16 computer games for the same duration (eg, visuospatial puzzles, clue-gathering, and pinball). AT and CG interventions were previously reported[9] as equally enjoyable on the 7-item subscale of interest/enjoyment of the Intrinsic Motivation Inventory.[20] All participants received nominal payment, contingent on attendance. Healthy participants were imaged before and after a 10 week interval, with no intervening contact.

Sixteen healthy and 40 patient (22 AT, 18 CG) participants completed at least 1 MRI and both MEG sessions. Poor imaging data quality reduced analyses to 13 healthy and 34 patient participants (18 AT, 16 CG). Missing VLM measures further reduced VLM analyses to 15 AT and 15 CG participants.

### *Data Acquisition and Processing*

MEG was recorded within a magnetically-shielded room from a 275 sensor array, sampled at 1200 Hz under 0.001–300 Hz online filtering (VSM MedTech, Ltd.; [21]). Twenty-nine reference sensors corrected distant magnetic field disturbance by calculating a synthetic third order gradiometer.[22] Head location within the array was measured at task start and end using 3 magnetic coils attached to fiducial landmarks,[21] with inclusion contingent on <6 mm translations in head movement.

An auditory discrimination task localized cortical responses to phonetic stimuli. Two successive syllables were binaurally presented on each trial ("/ba/ /pa/" or "/pa/ /ba/"; 61.8 dB SPL, Etymotic E-A-RTONE), with second syllable deterministic at first syllable presentation

**Table 1.** Demographic and Clinical Characteristics of Participant Groups

| Subject Characteristics (mean, *SD*) | Healthy Comparison Subjects (*N* = 16) | SZ Active Training Group (*N* = 22) | SZ Computer Games Control Group (*N* = 18) |
|---|---|---|---|
| Average subject age | 42.31 (12.10) | 37.18 (12.13) | 41.22 (10.11) |
| Gender (female/male) | 4/12 | 4/18 | 5/13 |
| Average years education | 14.19 (1.72) | 13.14 (2.40) | 13.56 (1.92) |
| Mean IQ | 112.73 (11.62) | 100.38 (16.44) | 103.67 (13.59) |
| Smoker (current/ever) | 3/9 | 12/15 | 7/12 |
| Average PANNS score at baseline | | 2.43 (0.58) | 2.35 (0.52) |
| Global assessment of functioning | | 44.06 (11.40) | 45.27 (13.66) |
| Chlorpromazine equivalents | | 445.24 (464.73) | 435.29 (468.96) |

*Notes*: PANSS, Positive and Negative Syndrome Scale. All values reported as mean (*SD*) or numeric counts per category, as appropriate.

(Syllable 1: 0–400 msec; Syllable 2: 500–900 msec, supplementary figure 1). A dominant hand response on 1 of 2 buttons identified the sequence, with trials starting 350 or 450 msec postresponse. At least 80 trials were acquired per session. MEG epochs consisted of data −500 to 1000 msec relative to first syllable onset, and rejected if they contained artifact or lacked a response within 3 sec. Artifacts were defined as magnetic flux exceeding 2.5 pT at any sensor under a temporarily applied 1–50 Hz filter. If more than 20 epochs included artifact, problematic sensors were removed and data reexamined. An individual's data were excluded if more than 5 sensors were removed, or less than 50 trials remained in either session. A previous report included Session One data on an alternate version of this task.[4]

Anatomical images were acquired on a 3 Tesla General Electric Signa LX 15 scanner, utilizing 3D magnetization prepared rapid gradient echo MRI (160 1-mm slices; field of view = 260 mm, matrix = 256 × 256, echo time = 6 msec, repetition time = 35 msec, flip angle = 30°). T1-weighted images were co-registered with MEG data via fiducial landmarks, and spatially normalized to the Montreal Neurological Institute template ([MNI], via SPM2: fil.ion.co.uk/spm2,[23]). A multiple spheres head model was calculated for each sensor relative to the volume. Coordinates corresponding to the centroid of Brodmann Area 41 (BA41) were identified in each individual (Left: [−47, −27, 10]; Right: [47, −27, 10]).

### *Analysis of Cortical Response*

Induced oscillatory activity was examined using adaptive spatial filtering techniques (c.f. 24, 25, supplementary text 2). Broadband activity estimated from BA41 at each time point in a trial was averaged across trials, root-mean-square transformed, and z-normalized using the 500 msec prestimulus period. Average amplitude from 50–150 msec post-syllable-onset assessed M100 responses[26] (supplementary text 2). Repeated-measures ANOVA (SPSS statistics IBM Corp.) tested hypotheses in the *a priori* region with factors of Syllable (First, Second), Hemisphere (Left, Right), and Diagnosis (Healthy, Patient) during Session One. Training factors included Session (One, Two), Syllable (First, Second), Hemisphere (Left, Right) and Group (AT, CG, HC). Tests of significant interactions obtained within full-factor ANOVA further characterized effects. Pearson's *r* assessed relationships between measures.

An exploratory analysis of neural sources across the cortex examined regions affected by the intervention, and assessed relationships with *a priori* physiological and neuropsychological measures. Cortical activity within 4 frequency bands (4–12 Hz, theta/alpha; 12–30 Hz, beta; 30–55 Hz, low gamma; 63–117 Hz, high gamma) was estimated via adaptive spatial filtering methods, and spatially normalized to the MNI template[23–25] (http://nutmeg.berkeley.edu,fil.ion.co.uk/spm2, supplementary text 2). Pseudo-*t* statistics obtained via permutation tests derived significance levels[25] (supplementary text 2), and relationships between measures were examined using Pearson's *r*. A spatial threshold of 20 contiguous 5 mm voxels having 2-tailed *t*- or *r*-values corresponding to $P < .05$ reduced spurious activation. Reported onset and offset latencies were derived at $P < .005$. Substandard MRI prevented this analysis in one AT participant (HC = 13, AT = 17, and CG = 16).

## Results

Auditory task performance during MEG recording showed no significant difference between groups or sessions in accuracy or reaction time (Overall Accuracy = .790 [*SD* = .016], Group: $F[2,44] = 0.317$, $P = .73$, Session: $F[1,44] = 1.084$, $P = .304$, Group x Session: $F[2,44] = 0.33$, $P = .721$. Overall response time = 1.508 msec [*SD* = .034], Group: $F[2,44] = 0.497$ $P = .61$, Session: $F[1,44] = 1.385$, $P = .246$, Group x Session: [2,44] = 0.045, $P = .956$).

### *Baseline M100 Response in Auditory Cortex*

Activity within auditory cortex during Session One reveals reduced M100 amplitude in patients relative to healthy participants (figure 1: Diagnosis: $F[1,45] = 6.24$, $P = .016$), primarily during Syllable 1 (Syllable x Diagnosis: $F[1,45] = 6.92$, $P = .012$). The M100 response of AT and CG patient groups did not differ prior to intervention (Group: $F[1,32] = 1.995$, $P = .167$). These findings are consistent with weaker M100/N100 responses in patients with schizophrenia (eg, 4, 27). Exploratory analyses of low frequency activity confirmed Session One reductions at 100 msec within 1.5 cm of *a priori* locations (Left [−55, −25, 10] at 100–125 msec: $t[45] = 3.187$, $P = .003$; Right [50, −35, 20] at 100–125 msec: $t[45] = 2.604$, $P = .007$; peak at 25–50 msec: $t[45] = 2.722$, $P = .004$ in figure 1 insets, supplementary figure 2**).** Relationships were not found between M100 and VLM ($r[32] = -0.024$, $P = .896$) or ToL ($r[33] = -0.263$, $P = .139$) in the patient group during Session One.

### *Training Effects on Activity in Temporal and Prefrontal Cortices*

The M100 response in BA41 changed differentially in each group across session (figure 2, top: Group x Session: $F[2,44] = 4.34$, $P = .019$). Across syllable, the AT group showed increased M100 (Session: ($F[1,17] = 8.881$, $P = .008$), while CG and healthy participants did not (CG: $F[1,15] = 1.76$, $P = .20$; HC: $F[1,12] = .003$, $P = .96$). Additionally, changes in M100 were not correlated across hemispheres in the AT group ($r[17] = .176$, $P = .49$). Exploratory analyses support training-related increases in M100, revealing elevated high gamma activity during Session Two, within 1 cm of *a priori*

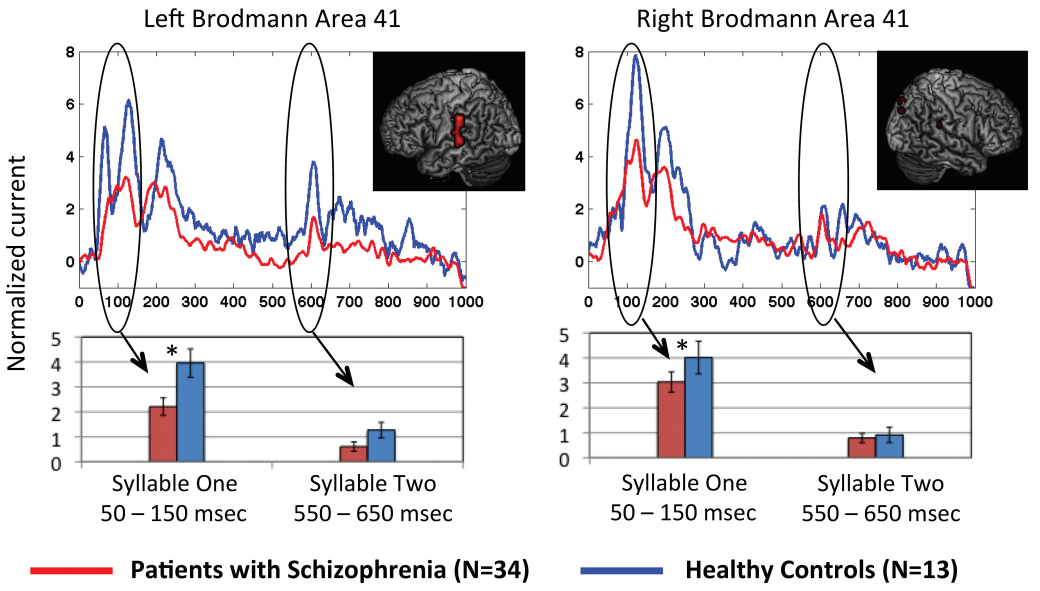


**Fig. 1.** Session One activity in schizophrenia and healthy participants. Activity estimated from left [−47, −27, 10] and right [47, −27, 10] Brodmann Area 41 shows reduced sensory response in patients with schizophrenia (red) relative to healthy participants (blue) prior to intervention. Cortical reconstruction difference between patients and controls in low frequency activity at left ([−55, −25, 10], 100–125 ms shown) and right ([50, −35, 20], 25–50 ms shown) sensory cortex are presented in each panel (threshold at $P < .05$).

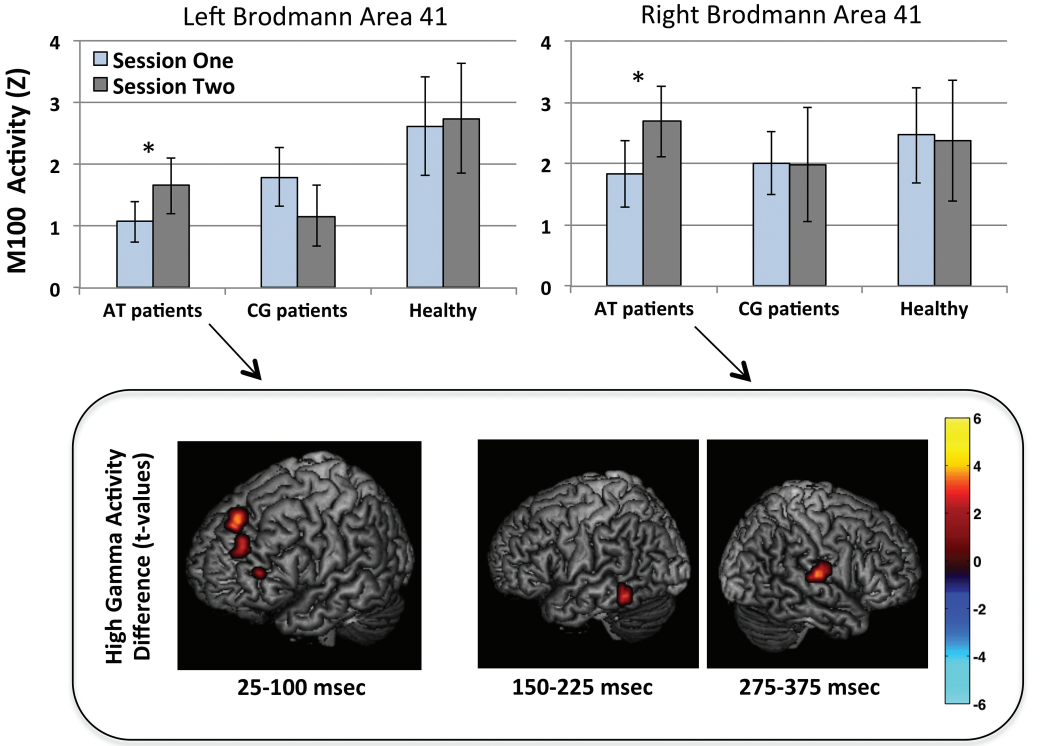


**Fig. 2.** Training-related changes between Sessions One and Two. Top panel: Broadband M100 response within *a priori* locations is increased in the AT patient group. Both healthy participants and the CG patient group showed no effect of Session on M100 response. Bottom panel: Changes in high gamma activity occurred in the AT group. Amplitude difference between sessions (Two–One) occurred from 25 to 100 ms (50–75 ms shown) in both left Dorsolateral Prefrontal Cortex (peak difference: [−25, 50, 35] at 50–75 ms) and IFG (peak difference: [−55, 50, 15] at 25–50 ms), followed by increased activity in temporal regions (Left, 150–225 ms: [−50, −35, 0], 200–225 ms shown; Right, 225–375 ms: [60, −20, 15], 275–300 ms shown).

coordinates during this time period (Left [−50, −30, 10]: peak $t[16] = 2.095$ at 100–125 msec, $P = .03$; Right [55, −30, 5]: peak $t[16] = 1.923$ at 100–125 msec, $P = .04$, supplementary figure 3). Additionally, a low frequency increase was observed near Right BA41 ([50, −35, 20]: peak $t[16] = 3.015$ at 100–125 msec, $P = .003$).

Training-related increases in high gamma activity occurred early in the trial at Left Dorsolateral Prefrontal Cortex (DLPFC; [−25, 50, 35]: 25–100 msec, peak $t[16] = 2.97$ at 50–75 msec, $P = .001$) and Inferior Frontal Gyrus (IFG, [−55, 50, 15]: 25–100 msec, peak, $t[16] = 2.843$ at 25–50 msec, $P = .003$, figure 2, bottom, supplementary figure 4). These changes preceded those in bilateral temporal cortex (Left [−50, −35, 0]: 150–250 msec, peak $t[16] = 2.384$ at 200–225 msec, $P = .003$; Right [65, −25, 15]: 225–375 msec, peak $t[16] = 2.98$ at 275–300 msec, $P = .003$, supplementary figure 5). In contrast, the CG group showed no difference in neural activity across the cortex between Sessions One and Two.

### *Relationship Between Changes in Neurophysiology and Cognitive Measures*

Training-related change in VLM scores indicate improvement in verbal memory associated with the AT intervention (Session x Group: $F[1,28] = 5.057$, $P = .033$, partial eta = .153; change: AT = .594, CG = −.383), consistent with results from the larger cohort.[9] However, associations between change in VLM and change in M100 were not found (AT: $r[14] = .014$, $P = .96$; CG: $r[14] = .42$, $P = .120$), nor were relationships between changes in VLM and high gamma activity across the cortex.

Executive function performance (ToL) showed trend level changes between session (Group: $F[1,32] = .002$, $P = .97$, partial eta = .00; Session: $F[1,32] = 3.637$, $P = .066$, partial eta = .102; Session x Group: $F[1,32] = 3.22$, $P = .082$, partial eta = .091), similar to training-induced changes previously reported in an independent patient sample.[28] Changes in ToL were positively associated with M100 changes in the AT group (figure 3; $r[17] = .818$, $P = .001$), persisting after removal of a participant with large decreases in left hemisphere activity ($r[16] = .708$, $P = .001$). Early-trial changes in left frontal regions were not significantly related to those of ToL (DLPFC: $r[16] = 0.220$, $P = .40$; IFG: $r[16] = −0.188$, $P = .47$), nor was there a relationship between changes in VLM and ToL (AT: $r[14] = .132$, $P = .60$; CG: $r[14] = .271$, $P = .31$), consistent with prior reports.[9]

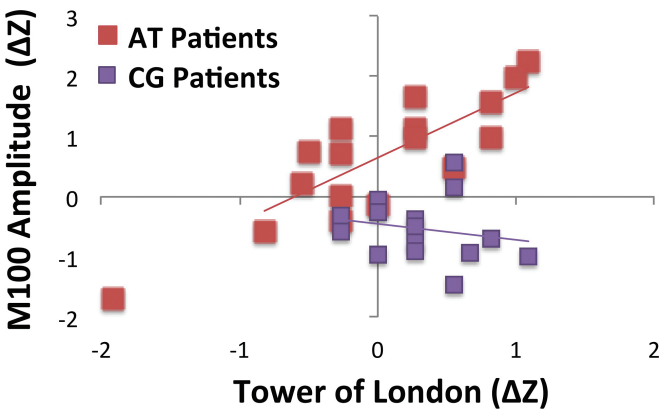


**Fig. 3. Relationship between change in M100 and executive function.** The M100 change positively correlated with improvement in Tower of London performance in the AT group ($r[17] = .818$, $P = .001$). Patients in the CG group did not show this relationship ($r[14] = −.202$, $P = .47$).

### *Role of Enhanced M100 in Cortical and Cognitive Changes*

Training-related changes in M100 response did not correlate with early prefrontal activity changes (Left DLPFC: left M100, $r[16] = −0.043$, $P = .87$, and right M100 $r[16] = 0.429$, $P = .086$; Left IFG: left M100, $r[16] = −0.038$, $P = .89$, and right M100, $r[16] = .020$, $P = .94$). However, changes in Left M100 amplitude positively correlated with gains in *later* high gamma activity in left DLPFC (250–275 msec, $r[16] = .712$, $P = .002$), while right M100 changes correlated with those of right medial PFC (175–200 msec, $r[16] = .795$, $P = .0002$, see figure 4, top). These relationships persisted after removing the outlier participant ($r[15] = .585$, $P = .017$). Training-related changes at this time period and within these prefrontal regions were also related to increases in ToL (figure 4, bottom; $r[16] = .613$, $P = .009$), perhaps driven by the outlier ($r[15] = .404$, $P = .12$). These later prefrontal changes were not significant when probed independently of M100 or ToL. Partial correlation analyses reveal changes in M100 positively correlate with those of later DLPFC activity, independent of gains in ToL ($r[13] = .650$, $P = .009$), while increased M100 relates to gains in ToL, independent of enhanced DLPFC activity ($r[13] = .740$, $P = .002$). Changes in ToL did not significantly correlate with those of DLPFC when controlling for M100.

## Discussion

### *Summary of Findings*

Individuals with schizophrenia showed normal task performance but exhibited abnormal sensory representations in auditory cortex (via reduced M100 response) during a low-demand syllable identification task that required auditory attention but posed no significant memory, or executive function load. Fifty hours (10 weeks) of computerized targeted cognitive training of auditory processing and auditory/verbal learning increased M100 and prefrontal cortical responses. Participants performing the computer games control showed no such increase. Because patients performed the task equally well before and after training, we posit that these neural changes reflect changes in the efficiency of brain networks operating during the task.

Specifically, training increased early high gamma activity (25–100 msec post-stimulus onset) within left DLPFC and left IFG, followed by enhanced bilateral broadband responses in primary auditory cortex around 100

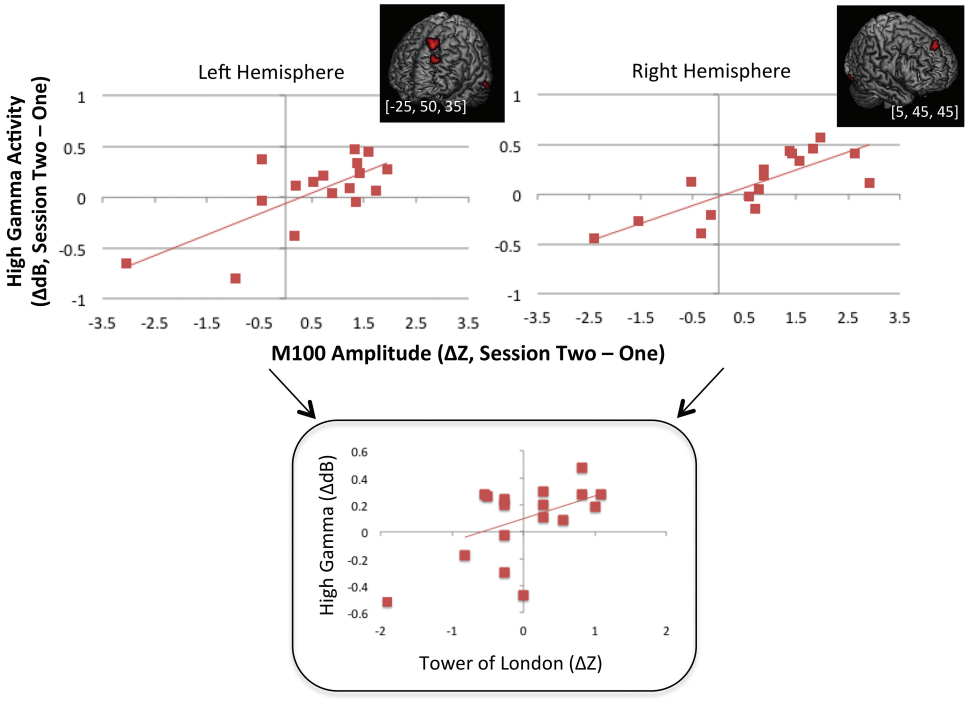


**Fig. 4.** Relationships among changes in M100 amplitude, late prefrontal high gamma activity, and executive function. Changes in M100 amplitude were significantly related to subsequent changes in the activity of corresponding left ([−25, 50, 35], 250–275 ms) and right ([5, 45, 45], 175–200 ms) hemisphere regions of prefrontal cortex. Late prefrontal changes were also correlated with changes in performance on the untrained Tower of London task.

msec poststimulus onset (M100). This enhanced sensory response was then related to later (175–275 msec) enhancement of high gamma activity within bilateral prefrontal cortex, including the region of left DLPFC that exhibited an earlier training-related increase. High gamma band activity was also increased in secondary auditory cortex later in stimulus presentation (150–375 msec). Enhancement of the M100 cortical response was associated with improved executive function, but not with gains in verbal learning and memory. While M100 was enhanced bilaterally, it showed no interhemispheric correlation. This may reflect a differential response to training within each hemisphere and/or baseline hemispheric response asymmetry in patients (due to heterogeneity in pathophysiology, handedness, etc.). Additional study is required to elucidate potential hemispheric differences in training response.

### *Enhanced M100 Correlates With Better Executive Functioning, Not Verbal Memory*

Why do neural enhancements during the auditory task correlate with improvements on an untrained executive function measure but, surprisingly, not with verbal learning and memory, the primary focus of this training? We propose that this is due to the nature of the task, which did not probe auditory working memory and verbal learning (the target of training exercises and the hypothesized mechanism by which verbal memory is improved after training). Instead, in this experiment, we used a task probing sensory-prefrontal integrity during simple syllable identification—requiring only the ability to attend to, register, and identify 2 rapidly-presented syllables. We show that patients perform the task well, but demonstrate reduced (inefficient) neural activity patterns. When we repeat this task after auditory training, we see that sensory and prefrontal representations have been enhanced, showing significant relationships, and that this heightened prefrontal-sensory "integrity" is associated with behavioral evidence of better executive functioning in an untrained ToL measure.

In this study, gains in executive function were independent from gains in verbal learning and memory, consistent with relative independence of these domains in schizophrenia.[30] Thus, 2 dissociable neurobehavioral processes may be altered as a result of training: (1) Encoding of verbal information in working memory, as observed in neuropsychological outcome data but not probed physiologically by this low-demand auditory task; (2) Enhancement of prefrontal-sensory processing integrity, manifested as increased task-related high gamma band activity across prefronto-temporal regions and probed by task-specific attention requirements.

The observation of training-related associations between neural enhancements in the prefronto-temporal network and better executive functioning may, in the absence of a pre-training relationship, appear

counter-intuitive. However, a wealth of evidence suggests that, at baseline, people with schizophrenia have patterns of inefficient and abnormal neural activity during sensory processing, working memory, and executive functions. In a task that was not taxing the memory and executive functions of patients (as evidenced by normative task performance) we would not predict that reduced sensory activation at baseline (via M100) would be reliably coupled with performance on higher-order operations. However, since training actively targets coupling of these functions, such a relationship emerges at the second time point.

### *How Might Training-Related Changes in a Prefrontal-Temporal Network Promote Improved Executive Functioning?*

The sequence and pattern of prefrontal-temporal enhancement and inter-regional correlation we observe suggest that, despite its focus on improved perceptual processing, this training promoted plasticity in a distributed neural system that supports both auditory receptivity and secondary auditory processing, as well as higher-order attentional and cognitive control/executive functioning operations.

First, training-related increases in gamma band activity are seen within left DLPFC and IFG immediately after stimulus presentation; this may reflect improvement in task-directed preparatory attention (DLPFC, c.f. 16) and linguistic processing systems (IFG, reviewed in [31,32]) that then indirectly promotes processing of task-relevant stimuli in primary auditory cortex.[33] Next, the enhanced auditory cortical response correlates with increases in *later* bilateral high gamma activity in DLPFC—a region associated with higher-order functions such as sequencing,[34] task-directed attention,[16] and cognitive control.[16,35] It co-occurs in time with training-related enhancement in temporal cortex associated with higher-order auditory processing.

Thus, in patients with schizophrenia, training appears to increase the choreographed oscillatory activity throughout a cortical network, during a simple task that probes auditory attention: early high-gamma activity in attention and linguistic centers, followed by enhanced representational fidelity of incoming auditory stimulus information, then neural enhancement of prefrontal and secondary auditory sensory high gamma activity. This choreography is reminiscent of auditory working memory operations in healthy individuals[36]; our findings suggest that as integrity of this prefronto-temporal pattern of neural activity during an attention task is enhanced through training, it translates to more efficient prefrontal operations as indexed with an executive function measure. This model is also consistent with findings that enhanced stimulus salience improves performance on the Wisconsin Card-Sorting Task,[37] while impaired sensory processing relates to encoding deficits during cognitive control.[38]

### *Limitations*

The relatively small subject sample may limit the generalizability of our results. While there were no differences between patient groups in terms of their medication regimens, we cannot rule out medication as a potentially confounding factor, as may be other patient features, such as severity and duration of illness, or handedness, and other indicators of hemispheric lateralization.

In contrast to current results, Popov and colleagues[12] failed to find changes in dipole-derived M100 responses in patients with schizophrenia after undergoing similar training, instead reporting improvement in "auditory gating". However, direct comparison of the studies is difficult, as Popov and colleagues[12] utilized a covert attention paradigm and auditory click stimuli at 50 msec interstimulus intervals, in inpatient participants. Because amplitude of the 100 msec response is greater in tasks utilizing longer inter-stimulus intervals,[39] greater demand on attention and/or discrimination processes,[40] and longer, louder or more complex stimuli,[41] the current study is expected to generate more robust M100 responses. A companion study using the same patient population[15] reported training-related increases in gamma activity (60–80 Hz) at centro-parietal scalp locations 100–400 msec post-click-onset, perhaps reflecting enhancement of synchronous bilateral auditory sources similar to the current increase in 63–117 Hz activity within bilateral temporal cortex observed at 100 and 300 msec. Differences in duration of training (50 vs 20 hours) also suggest that observing widespread changes involving prefrontal cortex may be facilitated by longer interventions. To the best of our knowledge, no other studies examine changes to the response of linguistic stimuli under this training regimen.

## Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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