HHS Public Access

Author manuscript

*Schizophr Res*. Author manuscript; available in PMC 2022 July 07.

Published in final edited form as:

*Schizophr Res*. 2021 October ; 236: 135–141. doi:10.1016/j.schres.2021.07.033.

# Central auditory processing deficits in schizophrenia: effects of auditory-based cognitive training

**Juan L. Molina**[1,6], **Yash B. Joshi**[1,6], **John A. Nungaray**[1], **Michael L. Thomas**[2], **Joyce Sprock**[1], **Peter Clayson**[3], **Victoria A. Sanchez**[4], **Mouna Attarha**[5], **Bruno Biagianti**[5], **Neal R. Swerdlow**[1], **Gregory A. Light**[1,6]

[1]Department of Psychiatry, University of California, San Diego, San Diego, CA, USA

[2]Department of Psychology, Colorado State University, Fort Collins, CO, USA

[3]Department of Psychology, University of South Florida, Tampa, Fl, USA

[4]Department of Otolaryngology - Head & Neck Surgery, University of South Florida, Tampa, Fl, USA

[5]Department of R&D, Posit Science Corporation, San Francisco, CA, USA

[6]VA Desert Pacific Mental Illness Research, Education and Clinical Center (MIRECC), VA San Diego Healthcare System, San Diego, CA, USA

## Abstract

**Background—**Sensory processing abnormalities are common in schizophrenia (SZ) and impact everyday functions, such as speech perception in noisy environments. Auditory-based targeted cognitive training (TCT) is a “bottom up” cognitive remediation intervention designed to enhance the speed and accuracy of low-level auditory information processing. However, the effects of TCT on behavioral measures of central auditory processing (CAP) and the role of CAP function on verbal learning outcomes in SZ are unknown.

**Methods—**SZ (n=42) and healthy subjects (CTL; n=18) underwent comprehensive clinical, neurocognitive, and auditory assessments, including tests of hearing sensitivity and speech recognition (Words-in-Noise (WIN), Quick Speech-in-Noise (SIN)). SZ patients were randomized to receive either treatment-as-usual (TAU); or 30-h of TCT + TAU using a stratified, parallel design. SZ patients repeated assessments ~10–12 weeks later.

**Results—**Patients exhibited CAP deficits in WIN ($p$<0.05, $d$=0.50) and SIN ($p$<0.01, $d$=0.63). A *treatment x time* interaction on WIN ($p$<0.05, $d$=0.74), but not SIN discriminability, was seen in the TCT group relative to TAU. Specific enhancements in the 4-dB over background range drove gains in WIN performance. Baseline CAP deficits were associated with gains in verbal learning after 30-h of TCT ($p$<0.01, $d$=1.28).

**Conclusion—**Findings demonstrate that intensive auditory training enhances the fidelity of auditory processing and perception, such that specific CAP deficits were ‘normalized’. Moreover,

**Corresponding Author:** Gregory A. Light, Ph.D. Department of Psychiatry, University of California San Diego, 9500 Gilman Drive, La Jolla, CA, USA 92093-0804, Tel.: (619) 543-2496, glight@health.ucsd.edu.

CAP deficits were robustly associated with verbal learning gains. It is conceivable that patients with deficiencies in CAP measures may benefit most from TCT and other interventions targeting auditory dysfunction in SZ.

**Keywords**

Schizophrenia; cognitive training; central auditory processing; speech perception; speech-in-noise; neurocognition

## 1. INTRODUCTION

Sensory and perceptual processing deficits in schizophrenia (SZ) are fundamental contributors to the disabling clinical, cognitive and psychosocial features of the illness (Javitt, 2009; Javitt and Freedman, 2015; Uhlhaas and Mishara, 2007). The most compelling evidence of sensory dysfunction in SZ comes from neurophysiologic studies of the central auditory system (Javitt, 2009; Light et al., 2015, 2007; Light and Braff, 2005), where deficits in early information processing are linked to aberrant neurodevelopmental processes, psychosis risk, and worse cognitive and psychosocial outcomes (Braeutigam et al., 2018; Bruggemann et al., 2013; Koshiyama et al., 2020b; Oades et al., 2006; Thomas et al., 2017). Hence, dysfunction of the central auditory system is increasingly viewed as a viable target for the development of novel therapeutics for SZ and other neuropsychiatric disorders.

SZ patients demonstrate a broad range of central auditory processing (CAP) deficits, including impairment in auditory discrimination (e.g., speech perception and recognition), sound localization and lateralization, and auditory temporal processing (Iliadou et al., 2013; Martin et al., 2018; Perrin et al., 2010; Wexler et al., 1998). This constellation of abnormalities in behavioral and electrophysiological tests of auditory function has led clinical investigators to suspect the presence of a comorbid Central Auditory Processing Disorder in certain SZ patients (Iliadou et al., 2013; McKay et al., 2000). Indeed, impairment in auditory attention, working memory and processing speed are commonly experienced and contribute to functional impairment in both disorders. A cardinal feature of central auditory processing disorders is impaired speech-in-noise perception. In both conditions, difficulty discriminating spoken language in noisy backgrounds arises despite ‘normal’ hearing sensitivity to pure-tone stimuli (Pienkowski, 2017; Viertiö et al., 2014).

Understanding speech in noisy backgrounds requires that intact CAP systems extract meaningful ‘signals’ while filtering out unwanted ‘noise’. Interestingly, reduced cortical signal-to-noise ratio has been implicated as a mechanism for multimodal sensory and cognitive dysfunction in SZ (Molina et al., 2020b; Rolls et al., 2008). Not surprisingly, deficits in speech-in-noise perception contribute to impairment in everyday functioning (e.g., school, work, interpersonal communication and relationships) and negatively impact quality of life (Brown and Kuperberg, 2015; Griffin et al., 2019; Vannson et al., 2015).

Enhancing central auditory processing with auditory-based targeted cognitive training (TCT) is a promising approach to cognitive remediation in SZ. TCT is a “bottom-up” cognitive remediation intervention that is designed to enhance the speed and accuracy of low-level sensory and perceptual processing of auditory information (e.g., cortical mechanisms that

support higher-order cognition)(Mahncke et al., 2006). The efficacy of TCT and other cognitive remediation interventions on cognitive, clinical and functional outcomes have been confirmed by individual studies and meta-analyses (Cella et al., 2017; Fisher et al., 2009; Prikken et al., 2019; Smith et al., 2009; Wykes et al., 2011). Similar forms of auditory training produce “bottom-up” gains in neurocognition and clinical outcomes in disorders with central auditory nervous system involvement (Anderson et al., 2013; Ferguson and Henshaw, 2015; Weihing et al., 2015). Moreover, measurements of CAP deficiencies may help identify SZ patients who are likely to respond to specific interventions, such as auditory training (Weihing et al., 2015). For example, Medalia et al. reported that central auditory function as measured by performance on a tone matching task was predictive of improvement in verbal learning in response to auditory training.

Despite the widespread recognition that auditory dysfunction is a core mechanism underlying important aspects of the social-cognitive impairment in SZ (Javitt, 2009; Javitt and Freedman, 2015), behavioral measures of CAP function remain underutilized in clinical and translational SZ research. Speech-in-noise perception tasks have been described as ‘stress tests’ of auditory function (Wilson and McArdle, 2007), as the signal-to-noise ratio can be dynamically adjusted to determine individual speech recognition thresholds and index the degree of perceptual improvement in response to specific auditory interventions, like TCT (MacPherson and Akeroyd, 2014).

We previously demonstrated that CAP indices of words- and sentences-in-noise were dynamically modulated by acute pharmacologic challenges in SZ patients and healthy controls (Swerdlow et al., 2020, 2017). These studies suggest that plasticity of the central auditory system exists within a ‘dynamic range’, where task demands exceed the capacity of the underlying CAP system. However, the effects of TCT on plasticity of the CAP system remain incompletely understood (Dale et al., 2020; Koshiyama et al., 2020a; Molina et al., 2020a). We previously reported that TCT improved verbal learning in a cohort of treatment-refractory SZ patients; moreover, neurophysiologic biomarkers collected at the outset of treatment predicted the magnitude of clinical and cognitive gain (Hochberger et al., 2019; Molina et al., 2020a; Thomas et al., 2018). As part of these recent studies of auditory-based TCT, measures of auditory discrimination and speech perception were also used to characterize the extent of CAP deficits in SZ patients compared to healthy subjects and to determine whether TCT led to improvement in behavioral measures of CAP. We also aimed to explore whether baseline CAP performance was associated with the observed gains in verbal learning in refractory SZ patients after a therapeutic course of TCT.

## 2. MATERIALS AND METHODS

### 2.1 Participants and study design

Sixty participants, including subjects with treatment-refractory psychotic disorders (n=42) and nonpsychiatric comparison subjects (n=18) were recruited from the greater San Diego community. Details of the recruitment and ascertainment procedures for this clinical trial were previously described (Hochberger et al., 2019; Molina et al., 2020a; Thomas et al., 2018). Briefly, patients with SZ or schizoaffective disorder were recruited from a community-based inpatient treatment program following an acute care hospitalization.

Healthy nonpsychiatric comparison subjects were recruited via online advertisements. Diagnosis was confirmed using an abbreviated version of the Structured Clinical Interview for DSM-IV-TR (First et al., 2002). Exclusion criteria included premorbid intellectual disability (e.g., Wide Range Achievement Test (WRAT) reading subtest below 70), inability to provide informed consent, limited English proficiency, history of neurological illness or head injury, severe systemic illness, or diagnosed hearing loss. Hearing was screened, in both ears independently, to ensure participants could detect 40-dB HL (decibel Hearing Level) pure tones from 1–8 kHz frequencies using standardized headphones and a manual audiometer (AM 232; Welch Allyn, Inc., Skaneateles Falls, NY) in a quiet room. Nonpsychiatric comparison subjects were additionally excluded if they had any significant history of mental illness or screened positive on urine toxicology.

After initial screening, all participants underwent comprehensive auditory (e.g., audiograms, CAP testing), clinical, and neurocognitive (e.g., MATRICS Consensus Battery (Nuechterlein et al., 2008)) assessments. SZ patients were randomized to receive standard of care treatment or “treatment-as-usual” (TAU, n=21), including medication management, individual and group therapy, and participation in structured social activities; or 30-h of auditory-based targeted cognitive training (TCT, n=21) in addition to TAU using a parallel design with stratified random assignment by age, sex, and ethnicity. Structured auditory, clinical and cognitive assessments were repeated at the end of the study (approximately 10–12 weeks later) in SZ patients. The Institutional Review Board of University of California, San Diego approved all experimental procedures (IRB#130874).

### 2.2 Central Auditory Processing Assessments

Auditory discrimination was tested using Words-In-Noise (WIN; NIH Toolbox (Zecker et al., 2013)) and Quick Speech-In-Noise (SIN; Etymotic Research, Elk Grove, IL (Killion et al., 2004)) tests with modifications to allow for binaural presentation. Both WIN and SIN assess the ability to recognize speech over background noise, similar to deciphering conversation in a noisy environment (e.g., a “cocktail party”); e.g., functions that are deficient in SZ (Abdul Wahab et al., 2017; McKay et al., 2000; Viertiö et al., 2014). Speech stimuli are presented at varying signal-to-noise ratios (SNR), such that the intensity of the ‘signal’ (e.g., speech) varies over a background conversation ‘noise’ (e.g., four-talker babble). Specifically, WIN is presented at 7 SNRs calibrated in 4-dB decrements from 24-dB to 0-dB and SIN is presented at 6 SNRs in 5-dB decrements from 25-dB to 0-dB. WIN uses single monosyllabic words to assess recognition performance, whereas SIN utilizes sentence-level stimuli with limited contextual cues. Subjects repeat the words or sentences aloud, and their responses are scored based on repetition accuracy of the word (WIN) or five “key” words (SIN). The primary measure for both tests is the sum of the # correct at each dB over background level. As these tests are widely used in the audiologic assessment of hearing-impaired populations, ceiling effects in our normal hearing subjects are expected when stimuli are presented at levels greater than 10-dB above background noise. Similarly, floor effects are expected when the words are presented at 0-dB above background. In addition to overall performance (total # correct), complimentary measures of the 50% point (e.g., the SNR needed to obtain 50% correct recognition) were calculated using the Spearman-Kärber equation to quantify SNR loss in decibels (Wilson et al., 2007)

and are shown in Table 1. WIN performance data (e.g., analyses of pre- and post- total score data) in SZ patients were previously reported (Thomas et al., 2018).

### 2.3 Targeted Cognitive Training

TCT was administered on individual laptop computers with headphones. Details of the cognitive training exercises delivered to this cohort as part of the TCT training suite were previously reported (Hochberger et al., 2019; Joshi et al., 2019; Molina et al., 2020a; Thomas et al., 2018). Briefly, the TCT program consisted of six training exercises provided by BrainHQ (Posit Science Corporation; San Francisco, CA). Training exercises were designed to engage neuroplasticity mechanisms in auditory networks of auditory perception and processing speed (Sound Sweeps, Fine Tuning) and auditory memory (Syllable Stacks, Memory Grid, To-Do List Training, Rhythm Recall). Exercises applied an n-up/m-down algorithm to participant responses to estimate thresholds, ensuring that participants were engaging in the exercises and were continuously challenged at an appropriate level (~80% accuracy) as their abilities improved.

### 2.4 Statistical analyses

Group differences in WIN and SIN performance were evaluated with independent sample t-tests. Next, linear mixed effects models were used to evaluate whether auditory-based TCT led to improvements in CAP measures of speech discrimination in SZ patients. WIN and SIN total scores were regressed onto contrast-coded treatment (TAU, TCT), time (before (*pre*) and after 30-h of TCT (*post*)), and interaction terms modeled as fixed effects and random intercepts included for individual subjects. Lastly, post hoc analyses of CAP performance in SZ patients were conducted to explore whether SZ patient with relatively higher vs. lower performance on WIN and SIN performance (based on median splits) were more likely to show improvement in verbal learning. Subject-level psychometric functions were fit to speech discrimination data to estimate the 'slope' of the function (i.e., the rate of perceptual benefit gained from small changes in SNR) using a maximum likelihood logistic function as implemented in the "*psignfit*" package (Fründ et al., 2011) in Python. Statistical analysis were implemented in R using the "*lme4*"(Bates et al., 2015) and '*EMAtools*" packages and built-in functions.

## 3. RESULTS

### 3.1 Demographics and clinical features

Demographic and clinical characteristics of the sample are summarized in Table 1. As expected, SZ patients completed fewer years of formal education ($t$=4.7, $p$<0.001) and had lower WRAT scores ($t$=4.9, $p$<0.001) relative to nonpsychiatric comparison subjects. There were no significant differences in age or sex between SZ patients and healthy comparison subjects. No demographic or clinical variables were significantly different between the TCT and TAU groups (all $d$'s<0.4).

### 3.2 Central Auditory Processing deficits in Schizophrenia

Discriminability for single-words- (WIN; $t$=2.1, $p$=0.042, $d$=0.50; Figure 1a) as well as sentences- (SIN; $t$=2.8, $p$=0.007, $d$=0.63; Figure 1b) in-noise were significantly impaired in

SZ patients relative to nonpsychiatric comparison subjects. Auditory discrimination scores between WIN and SIN performance were highly correlated in all subjects (Pearson's $r$=0.59, $p$<0.0001; Figure 1c).

### 3.3 Effects of Cognitive Training on Central Auditory Processing

Linear mixed effects models revealed a significant *treatment x time* interaction on single-words- (WIN; $\beta$=1.7, $SE$=0.8, $p$=0.041, $d$=0.74; Figure 2a), but not sentences- (SIN; $\beta$=−0.1, $SE$=0.9, $p$>0.5, $d$=−0.05) in-noise discriminability.

Analyses of WIN revealed a significant *treatment x time x dB* interaction, where TCT enhanced WIN performance at the most linear potion of the psychometric function, the 4-dB over background range, (Figure 2c; $\beta$=1.1, $SE$=0.5, $p$=0.018, $d$=0.21). Of note, the *treatment x time x dB* interaction remained statistically significant after adjustment for age, chlorpromazine equivalents, and anticholinergic burden.

Supplemental Figure 1a shows the psychometric function curves of the mean WIN performance before and after 30-h of TCT, revealing a 'normalization' of specific speech perception deficits in SZ relative to healthy comparison subjects. Moreover, TCT-induced gains (i.e., post *minus* pre difference score) in WIN performance at the 4-dB level were significantly correlated with the magnitude of change (i.e., post *minus* pre difference score) in slope (Supp. Fig. 1b; $r$=0.75, $p$<0.001) and threshold (Supp. Fig. 1c; $r$=0.65, $p$=0.002) estimates derived from subject-level psychometric functions at the 50% point.

### 3.4 Central Auditory Processing deficits are associated with Verbal Learning Outcome

In an exploratory set of analyses, SZ patients who underwent TCT were classified as 'CAP-deficit' or 'CAP-nondeficit' based on the median split of baseline WIN and SIN performance. There were no statistically significant differences in age, chlorpromazine equivalents or anticholinergic burden between 'CAP-deficit' vs. 'CAP-nondeficit' groups. Interestingly, SZ subjects who were most impaired in sentence-in-noise processing (SIN; $t$=2.9, $p$=0.008, $d$=1.28) showed robust improvement in verbal learning outcome. WIN-impaired subjects also showed large effects size gains in verbal learning (WIN; $t$=1.9, $p$=0.08, $d$=0.86).

## 4. DISCUSSION

Listening has been referred to as "where hearing meets the brain". The processing of speech in noisy environments requires higher-order cortical functions to separate relevant signals from backgrounds with varying degrees of sensory and perceptual 'noise'. Therefore, it is unsurprising that the speed and accuracy of auditory processing in real-world, noisy settings is critical for everyday functioning, and why SZ patients with impairment in auditory processing experience poor functional outcomes. Indeed, SZ patients had worse performance on auditory processing tasks relative to controls, with a 1.2 and 2.2 dB SNR loss for single-words (e.g., WIN) and sentences-in-noise performance (e.g., SIN), respectively (Table 1). These finding suggest that SZ patients require an additional 1–2 dB SNR (i.e., greater listening and/or cognitive effort) to understand 50% of speech spoken in noise as compared to healthy subjects without CAP deficits. Specific CAP deficits were normalized by – and

were predictive of – cognitive gains after an intensive 30-h course of auditory-based TCT in SZ.

These findings are consistent with previous studies showing that TCT-induced enhancement in sensory processing (e.g., auditory processing speed) drive gains in verbal learning (Biagianti et al., 2016) and modulate the activity and connectivity of distributed corticothalamic circuits (Dale et al., 2016; Koshiyama et al., 2020a; Subramaniam et al., 2014). Further, the generalization of TCT-induced gains in *downstream* sensory processing onto *upstream* central processing suggest an intermediate step (e.g., CAP gains) in the 'bottom up' cascade of events linking improved sensory processing to the salutary effects of TCT on neurocognition. In other words, SZ patients who underwent intensive auditory training aimed at improving the low-level perceptual processing of specific acoustic features (e.g., frequency, intensity, duration) experienced gains in higher-order speech-in-noise perception, which support enhanced plasticity in cortical structures involved in language, cognition and behavior. Importantly, this distal 'transfer' of learning involved training that was unrelated to task demands (e.g., quiet vs noise background) and stimulus type (e.g., tones/phonemes vs. speech). Similar improvement in speech-in-noise perception have been reported for individuals with audiological impairment as well as those with normal hearing after intensive auditory discrimination training (Ferguson and Henshaw, 2015; Gao et al., 2020; Weihing et al., 2015).

Notably, the improvement in auditory processing in this study was most pronounced within the most linear portion of the psychometric function (Supp Fig. 1a), the 4-dB over background range for single-words in noise, which appeared to drive the changes in discrimination thresholds (Supp. Fig. 1c). Indeed, 4-dB performance was correlated with the degree of 'normalization' of speech discrimination thresholds and perceptual gains for single-word in noise in SZ patients. We previously reported that speech-in-noise perception is dynamically enhanced in the 4–5 dB range by acute pharmacologic manipulations with pro-attentional and pro-cognitive drugs, like amphetamine and memantine (Swerdlow et al., 2020, 2017). Taken together, these studies suggest that pro-cognitive interventions like TCT and drugs that enhance early sensory processing, may enhance the figure-ground resolution of auditory 'signals' embedded in backgrounds of noise. Speculatively, this improvement in CAP may generalize to enhanced everyday communication skills in SZ patients and may have beneficial consequences on interpersonal functioning and other quality of life domains (Leroi et al., 2020). Future studies are needed to better clarify the functional and psychosocial consequences of improved speech-in-noise discrimination in SZ.

Marked training related changes were observed for WIN performance, a task of *single-word* perception in noisy backgrounds, but not SIN performance—a task of *sentence* discrimination in noisy backgrounds. This dissociation between WIN vs. SIN, could be attributable to task-related differences in the phonological and semantic complexity of presented stimuli and the additional cognitive resources required to accurately recall a list of 5- vs 1- words embedded in a noisy background. Importantly, no differences in attentional performance were observed between TCT and TAU groups at baseline or follow-up 10–12 weeks later. In other words, neither attention nor the more attentionally demanding speech-in-noise task "moved" following TCT in this study.

It is worth noting that we have observed similar dissociations between single-word vs. sentence-in-noise discriminability in at least two independent experimental medicine studies conducted in our laboratory. Whereas acute exposure to the pro-attentional drug amphetamine, improved sentence- but not word-in-noise discriminability, the sensory-enhancing drug memantine acutely improved single-word (Swerdlow et al., 2020, 2016, 2009) but not sentence-in-noise discriminability, supporting the general notion that the immediate recall of complex sentences in noisy backgrounds involves greater attentional and working memory demands than single-words.

Given prior behavioral and neurophysiologic studies suggesting that CAP deficits could help identify individuals who benefit from TCT (Biagianti et al., 2016; Hochberger et al., 2019; Medalia et al., 2019; Molina et al., 2020a), we created indices of 'CAP-deficit' status, reflecting poor performance on WIN and SIN. Importantly, 'CAP-deficit' status, particularly on SIN performance, was associated with improved verbal learning outcomes in response to TCT, which could have implications for patient stratification strategies in future pro-cognitive clinical trials. While these post hoc analyses should be interpreted with caution and require prospective replication in larger clinical cohorts; these findings are in agreement with previous studies demonstrating that individual differences in baseline CAP performance were predictive of clinical benefit in SZ patients and nonpsychiatric clinical populations undergoing auditory training (Medalia et al., 2019; Smith et al., 2016). Similarly, these intriguing results suggest that the most impaired patients on specific CAP tasks may have the most "room to move" and therefore might benefit most from intensive auditory training (Swerdlow et al., 2018).

Findings from the current study should be considered in the context of several important limitations. First, the sample size of this study was modest and powered to detect moderate to large effect sizes (Thomas et al., 2018), that said, the statistical interactions between TCT, WIN performance and the 4-dB range are consistent with our prior experimental medicine studies revealing a 'dynamic range' where the fidelity of speech-in-noise perception benefits both from acute doses of sensory-enhancing drugs and from intensive auditory sensory and perceptual training. Second, medication status was not experimentally controlled in our design. While we cannot rule out the possibility that medications impacted training-induced gains in speech discrimination and perception, chlorpromazine equivalents and anticholinergic burden were not statistically different in any of our comparison groups, and present findings were not significantly affected by covarying for medication status. Third, speech stimuli in our study were presented binaurally. Previous studies suggest that speech-in-noise performance is benefitted up to 1-dB by binaural vs monoaural presentation (Wilson, 2003). Therefore, it is unclear whether the severity of speech-in-noise deficits in SZ patients in the present study were underestimated due to the binaural presentation of auditory stimuli. Fourth, this study was conducted in treatment refractory SZ patients with well-established illness, therefore these findings may not generalize to at-risk, early-illness, or non-refractory clinical populations.

## 5. CONCLUSIONS

These findings add to the growing body of evidence linking auditory processing deficits in SZ to impairment in everyday functional tasks, such as speech-in-noise perception. Moreover, these findings demonstrate that intensive auditory training enhances the fidelity of auditory processing and perception, such that specific deficits in CAP moved closer to the levels of healthy, nonpsychiatric comparison subjects. Conceivably, patients identified to have deficiencies in behavioral measures of CAP may benefit most from TCT and other treatments targeting auditory dysfunction in SZ. These findings call for a more nuanced psychophysical and behavioral characterization of CAP function, complemented by well-validated neurophysiological biomarkers (Light et al., 2020; Light and Swerdlow, 2020, 2015; Molina et al., 2020a; Molina et al., 2016), in the evaluation of central auditory dysfunction and pro-cognitive therapeutic development in SZ.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## REFERENCES

Abdul Wahab NA, Zakaria Mohd.N., Abdul Rahman AH, Sidek D, Wahab S, 2017. Listening to Sentences in Noise: Revealing Binaural Hearing Challenges in Patients with Schizophrenia. Psychiatry Investig. 14, 786–794. 10.4306/pi.2017.14.6.786

Anderson S, White-Schwoch T, Parbery-Clark A, Kraus N, 2013. A dynamic auditory-cognitive system supports speech-in-noise perception in older adults. Hear. Res 300, 18–32. 10.1016/j.heares.2013.03.006 [PubMed: 23541911]

Bates D, Mächler M, Bolker B, Walker S, 2015. Fitting Linear Mixed-Effects Models Using lme4. J. Stat. Softw 67, 1–48. 10.18637/jss.v067.i01

Biagianti B, Fisher M, Neilands TB, Loewy R, Vinogradov S, 2016. Engagement with the auditory processing system during targeted auditory cognitive training mediates changes in cognitive outcomes in individuals with schizophrenia. Neuropsychology 30, 998–1008. 10.1037/neu0000311 [PubMed: 27617637]

Braeutigam S, Dima D, Frangou S, James A, 2018. Dissociable auditory mismatch response and connectivity patterns in adolescents with schizophrenia and adolescents with bipolar disorder with psychosis: A magnetoencephalography study. Schizophr. Res 193, 313–318. 10.1016/j.schres.2017.07.048 [PubMed: 28760539]

Brown M, Kuperberg GR, 2015. A Hierarchical Generative Framework of Language Processing: Linking Language Perception, Interpretation, and Production Abnormalities in Schizophrenia. Front. Hum. Neurosci 9. 10.3389/fnhum.2015.00643

Bruggemann JM, Stockill HV, Lenroot RK, Laurens KR, 2013. Mismatch negativity (MMN) and sensory auditory processing in children aged 9–12 years presenting with putative antecedents of schizophrenia. Int. J. Psychophysiol 89, 374–380. 10.1016/j.ijpsycho.2013.05.008 [PubMed: 23707338]

Cella M, Preti A, Edwards C, Dow T, Wykes T, 2017. Cognitive remediation for negative symptoms of schizophrenia: A network meta-analysis. Clin. Psychol. Rev 52, 43–51. 10.1016/j.cpr.2016.11.009 [PubMed: 27930934]

Dale CL, Brown EG, Fisher M, Herman AB, Dowling AF, Hinkley LB, Subramaniam K, Nagarajan SS, Vinogradov S, 2016. Auditory Cortical Plasticity Drives Training-Induced Cognitive Changes in Schizophrenia. Schizophr. Bull 42, 220–228. 10.1093/schbul/sbv087 [PubMed: 26152668]

Dale CL, Brown EG, Herman AB, Hinkley LBN, Subramaniam K, Fisher M, Vinogradov S, Nagarajan SS, 2020. Intervention-specific patterns of cortical function plasticity during auditory encoding in

people with schizophrenia. Schizophr. Res 215, 241–249. 10.1016/j.schres.2019.10.022 [PubMed: 31648842]

Ferguson MA, Henshaw H, 2015. Auditory training can improve working memory, attention, and communication in adverse conditions for adults with hearing loss. Front. Psychol 6. 10.3389/fpsyg.2015.00556

First M, Spitzer R, Gibbon M, Williams J, 2002. Structured clinical interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition, in: (SCID-I/P).

Fisher M, Holland C, Merzenich MM, Vinogradov S, 2009. Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. Am. J. Psychiatry 166, 805–811. 10.1176/appi.ajp.2009.08050757 [PubMed: 19448187]

Fründ I, Haenel NV, Wichmann FA, 2011. Inference for psychometric functions in the presence of nonstationary behavior. J. Vis 11. 10.1167/11.6.16

Gao X, Yan T, Huang T, Li X, Zhang Y-X, 2020. Speech in noise perception improved by training fine auditory discrimination: far and applicable transfer of perceptual learning. Sci. Rep 10, 19320. 10.1038/s41598-020-76295-9 [PubMed: 33168921]

Griffin AM, Poissant SF, Freyman RL, 2019. Speech-in-Noise and Quality-of-Life Measures in School-Aged Children with Normal Hearing and with Unilateral Hearing Loss. Ear Hear. 40, 887–904. 10.1097/AUD.0000000000000667 [PubMed: 30418282]

Hochberger WC, Joshi YB, Thomas ML, Zhang W, Bismark AW, Treichler EBH, Tarasenko M, Nungaray J, Sprock J, Cardoso L, Swerdlow N, Light GA, 2019. Neurophysiologic measures of target engagement predict response to auditory-based cognitive training in treatment refractory schizophrenia. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol 44, 606–612. 10.1038/s41386-018-0256-9

Iliadou VV, Apalla K, Kaprinis S, Nimatoudis I, Kaprinis G, Iacovides A, 2013. Is central auditory processing disorder present in psychosis? Am. J. Audiol 22, 201–208. 10.1044/1059-0889(2013/12–0073) [PubMed: 23824433]

Javitt DC, 2009. Sensory Processing in Schizophrenia: Neither Simple nor Intact. Schizophr. Bull 35, 1059–1064. 10.1093/schbul/sbp110 [PubMed: 19833806]

Javitt DC, Freedman R, 2015. Sensory processing dysfunction in the personal experience and neuronal machinery of schizophrenia. Am. J. Psychiatry 172, 17–31. 10.1176/appi.ajp.2014.13121691 [PubMed: 25553496]

Joshi YB, Thomas ML, Hochberger WC, Bismark AW, Treichler EBH, Molina J, Nungaray J, Cardoso L, Sprock J, Swerdlow NR, Light GA, 2019. Verbal learning deficits associated with increased anticholinergic burden are attenuated with targeted cognitive training in treatment refractory schizophrenia patients. Schizophr. Res 208, 384–389. [PubMed: 30738698]

Killion MC, Niquette PA, Gudmundsen GI, Revit LJ, Banerjee S, 2004. Development of a quick speech-in-noise test for measuring signal-to-noise ratio loss in normal-hearing and hearing-impaired listeners. J. Acoust. Soc. Am 116, 2395–2405. 10.1121/1.1784440 [PubMed: 15532670]

Koshiyama D, Miyakoshi M, Thomas ML, Joshi YB, Molina JL, Tanaka-Koshiyama K, Nungaray JA, Sprock J, Braff DL, Swerdlow NR, Light GA, 2020a. Auditory-Based Cognitive Training Drives Short- and Long-Term Plasticity in Cortical Networks in Schizophrenia. Schizophr. Bull. Open 1. 10.1093/schizbullopen/sgaa065

Koshiyama D, Thomas ML, Miyakoshi M, Joshi YB, Molina JL, Tanaka-Koshiyama K, Sprock J, Braff DL, Swerdlow NR, Light GA, 2020b. Hierarchical Pathways from Sensory Processing to Cognitive, Clinical, and Functional Impairments in Schizophrenia. Schizophr. Bull 10.1093/schbul/sbaa116

Leroi I, Simkin Z, Hooper E, Wolski L, Abrams H, Armitage CJ, Camacho E, Charalambous AP, Collin F, Constantinidou F, Dawes P, Elliott R, Falkingham S, Frison E, Hann M, Helmer C, Himmelsbach I, Hussain H, Marié S, Montecelo S, Thodi C, Yeung WK, 2020. Impact of an intervention to support hearing and vision in dementia: The SENSE-Cog Field Trial. Int. J. Geriatr. Psychiatry 35, 348–357. 10.1002/gps.5231 [PubMed: 31713262]

Light GA, Braff DL, 2005. Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. Arch. Gen. Psychiatry 62, 127–136. 10.1001/archpsyc.62.2.127 [PubMed: 15699289]

Light GA, Joshi YB, Molina JL, Bhakta SG, Nungaray JA, Cardoso L, Kotz JE, Thomas ML, Swerdlow NR, 2020. Neurophysiological biomarkers for schizophrenia therapeutics. Biomark. Neuropsychiatry 2. 10.1016/j.bionps.2020.100012

Light GA, Swerdlow NR, 2020. Selection criteria for neurophysiologic biomarkers to accelerate the pace of CNS therapeutic development. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol 45, 237–238. 10.1038/s41386-019-0519-0

Light GA, Swerdlow NR, 2015. Future clinical uses of neurophysiological biomarkers to predict and monitor treatment response for schizophrenia. Ann. N. Y. Acad. Sci 1344, 105–119. 10.1111/nyas.12730 [PubMed: 25752648]

Light GA, Swerdlow NR, Braff DL, 2007. Preattentive sensory processing as indexed by the MMN and P3a brain responses is associated with cognitive and psychosocial functioning in healthy adults. J. Cogn. Neurosci 19, 1624–1632. 10.1162/jocn.2007.19.10.1624 [PubMed: 18271737]

Light GA, Swerdlow NR, Thomas ML, Calkins ME, Green MF, Greenwood TA, Gur RE, Gur RC, Lazzeroni LC, Nuechterlein KH, Pela M, Radant AD, Seidman LJ, Sharp RF, Siever LJ, Silverman JM, Sprock J, Stone WS, Sugar CA, Tsuang DW, Tsuang MT, Braff DL, Turetsky BI, 2015. Validation of mismatch negativity and P3a for use in multi-site studies of schizophrenia: characterization of demographic, clinical, cognitive, and functional correlates in COGS-2. Schizophr. Res 163, 63–72. 10.1016/j.schres.2014.09.042 [PubMed: 25449710]

MacPherson A, Akeroyd MA, 2014. Variations in the Slope of the Psychometric Functions for Speech Intelligibility: A Systematic Survey. Trends Hear. 18. 10.1177/2331216514537722

Mahncke HW, Bronstone A, Merzenich MM, 2006. Brain plasticity and functional losses in the aged: scientific bases for a novel intervention. Prog. Brain Res 157, 81–109. 10.1016/S0079-6123(06)57006-2 [PubMed: 17046669]

Martin AMS, Bartolomeo L, Howell J, Hetrick WP, Bolbecker AR, Breier A, Kidd G, O'Donnell BF, 2018. Auditory feature perception and auditory hallucinatory experiences in schizophrenia spectrum disorder. Eur. Arch. Psychiatry Clin. Neurosci 268, 653–661. 10.1007/s00406-017-0839-1 [PubMed: 28936548]

McKay CM, Headlam DM, Copolov DL, 2000. Central auditory processing in patients with auditory hallucinations. Am. J. Psychiatry 157, 759–766. 10.1176/appi.ajp.157.5.759 [PubMed: 10784469]

Medalia A, Saperstein AM, Qian M, Javitt DC, 2019. Impact of baseline early auditory processing on response to cognitive remediation for schizophrenia. Schizophr. Res 208, 397–405. 10.1016/j.schres.2019.01.012 [PubMed: 30665714]

Molina JL, González Alemán G, Florenzano N, Padilla E, Calvó M, Guerrero G, Kamis D, Stratton L, Toranzo J, Molina Rangeon B, Hernández Cuervo H, Bourdieu M, Sedó M, Strejilevich S, Cloninger CR, Escobar JI, de Erausquin GA, 2016. Prediction of Neurocognitive Deficits by Parkinsonian Motor Impairment in Schizophrenia: A Study in Neuroleptic-Naïve Subjects, Unaffected First-Degree Relatives and Healthy Controls From an Indigenous Population. Schizophr. Bull 42, 1486–1495. 10.1093/schbul/sbw023 [PubMed: 26994395]

Molina Juan L., Thomas ML, Joshi YB, Hochberger WC, Koshiyama D, Nungaray JA, Cardoso L, Sprock J, Braff DL, Swerdlow NR, Light GA, 2020a. Gamma oscillations predict pro-cognitive and clinical response to auditory-based cognitive training in schizophrenia. Transl. Psychiatry 10, 405. 10.1038/s41398-020-01089-6 [PubMed: 33230190]

Molina Juan L., Voytek B, Thomas ML, Joshi YB, Bhakta SG, Talledo JA, Swerdlow NR, Light GA, 2020b. Memantine Effects on Electroencephalographic Measures of Putative Excitatory/Inhibitory Balance in Schizophrenia. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 5, 562–568. 10.1016/j.bpsc.2020.02.004 [PubMed: 32340927]

Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD, Essock S, Fenton WS, Frese FJ, Gold JM, Goldberg T, Heaton RK, Keefe RSE, Kraemer H, Mesholam-Gately R, Seidman LJ, Stover E, Weinberger DR, Young AS, Zalcman S, Marder SR, 2008. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry 165, 203–213. 10.1176/appi.ajp.2007.07010042 [PubMed: 18172019]

Oades RD, Wild-Wall N, Juran SA, Sachsse J, Oknina LB, Röpcke B, 2006. Auditory change detection in schizophrenia: sources of activity, related neuropsychological function and symptoms in patients with a first episode in adolescence, and patients 14 years after an adolescent illness-onset. BMC Psychiatry 6, 7. 10.1186/1471-244X-6-7 [PubMed: 16466573]

Perrin MA, Butler PD, DiCostanzo J, Forchelli G, Silipo G, Javitt DC, 2010. Spatial localization deficits and auditory cortical dysfunction in schizophrenia. Schizophr. Res 124, 161–168. 10.1016/j.schres.2010.06.004 [PubMed: 20619608]

Pienkowski M, 2017. On the Etiology of Listening Difficulties in Noise Despite Clinically Normal Audiograms. Ear Hear. 38, 135–148. 10.1097/AUD.0000000000000388 [PubMed: 28002080]

Prikken M, Konings MJ, Lei WU, Begemann MJH, Sommer IEC, 2019. The efficacy of computerized cognitive drill and practice training for patients with a schizophrenia-spectrum disorder: A meta-analysis. Schizophr. Res 204, 368–374. 10.1016/j.schres.2018.07.034 [PubMed: 30097278]

Rolls ET, Loh M, Deco G, Winterer G, 2008. Computational models of schizophrenia and dopamine modulation in the prefrontal cortex. Nat. Rev. Neurosci 9, 696–709. 10.1038/nrn2462 [PubMed: 18714326]

Smith GE, Housen P, Yaffe K, Ruff R, Kennison RF, Mahncke HW, Zelinski EM, 2009. A Cognitive Training Program Based on Principles of Brain Plasticity: Results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) Study. J. Am. Geriatr. Soc 57, 594–603. 10.1111/j.1532-5415.2008.02167.x [PubMed: 19220558]

Smith SL, Saunders GH, Chisolm TH, Frederick M, Bailey BA, 2016. Examination of Individual Differences in Outcomes From a Randomized Controlled Clinical Trial Comparing Formal and Informal Individual Auditory Training Programs. J. Speech Lang. Hear. Res. JSLHR 59, 876–886. 10.1044/2016_JSLHR-H-15-0162 [PubMed: 27567017]

Subramaniam K, Luks TL, Garrett C, Chung C, Fisher M, Nagarajan S, Vinogradov S, 2014. Intensive cognitive training in schizophrenia enhances working memory and associated prefrontal cortical efficiency in a manner that drives long-term functional gains. NeuroImage 99, 281–292. 10.1016/j.neuroimage.2014.05.057 [PubMed: 24867353]

Swerdlow NR, Bhakta S, Chou H-H, Talledo JA, Balvaneda B, Light GA, 2016. Memantine Effects On Sensorimotor Gating and Mismatch Negativity in Patients with Chronic Psychosis. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol 41, 419–430.

Swerdlow NR, Bhakta SG, Light GA, 2018. Room to move: Plasticity in early auditory information processing and auditory learning in schizophrenia revealed by acute pharmacological challenge. Schizophr. Res 199, 285–291. 10.1016/j.schres.2018.03.037 [PubMed: 29627173]

Swerdlow NR, Bhakta SG, Talledo J, Kotz J, Roberts BZ, Clifford RE, Thomas ML, Joshi YB, Molina JL, Light GA, 2020. Memantine effects on auditory discrimination and training in schizophrenia patients. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol 45, 2180–2188. 10.1038/s41386-020-00865-8

Swerdlow NR, Tarasenko M, Bhakta SG, Talledo J, Alvarez AI, Hughes EL, Rana B, Vinogradov S, Light GA, 2017. Amphetamine Enhances Gains in Auditory Discrimination Training in Adult Schizophrenia Patients. Schizophr. Bull 43, 872–880. 10.1093/schbul/sbw148 [PubMed: 27798224]

Swerdlow NR, van Bergeijk DP, Bergsma F, Weber E, Talledo J, 2009. The effects of memantine on prepulse inhibition. Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol 34, 1854–1864. 10.1038/npp.2009.7

Thomas ML, Bismark AW, Joshi YB, Tarasenko M, Treichler EBH, Hochberger WC, Zhang W, Nungaray J, Sprock J, Cardoso L, Tiernan K, Attarha M, Braff DL, Vinogradov S, Swerdlow N, Light GA, 2018. Targeted cognitive training improves auditory and verbal outcomes among treatment refractory schizophrenia patients mandated to residential care. Schizophr. Res 202, 378–384. 10.1016/j.schres.2018.07.025 [PubMed: 30055883]

Thomas ML, Green MF, Hellemann G, Sugar CA, Tarasenko M, Calkins ME, Greenwood TA, Gur RE, Gur RC, Lazzeroni LC, Nuechterlein KH, Radant AD, Seidman LJ, Shiluk AL, Siever LJ, Silverman JM, Sprock J, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff DL, Light GA, 2017. Modeling Deficits From Early Auditory Information Processing to Psychosocial Functioning in Schizophrenia. JAMA Psychiatry 74, 37–46. 10.1001/jamapsychiatry.2016.2980 [PubMed: 27926742]

Uhlhaas PJ, Mishara AL, 2007. Perceptual anomalies in schizophrenia: integrating phenomenology and cognitive neuroscience. Schizophr. Bull 33, 142–156. 10.1093/schbul/sbl047 [PubMed: 17118973]

Vannson N, James C, Fraysse B, Strelnikov K, Barone P, Deguine O, Marx M, 2015. Quality of life and auditory performance in adults with asymmetric hearing loss. Audiol. Neurootol 20 Suppl 1, 38–43. 10.1159/000380746 [PubMed: 25997394]

Viertiö S, Perälä J, Saarni S, Koskinen S, Suvisaari J, 2014. Hearing loss in persons with psychotic disorder--findings from a population-based survey. Schizophr. Res 159, 309–311. 10.1016/j.schres.2014.08.016 [PubMed: 25217365]

Weihing J, Chermak GD, Musiek FE, 2015. Auditory Training for Central Auditory Processing Disorder. Semin. Hear 36, 199–215. 10.1055/s-0035-1564458 [PubMed: 27587909]

Wexler BE, Stevens AA, Bowers AA, Sernyak MJ, Goldman-Rakic PS, 1998. Word and tone working memory deficits in schizophrenia. Arch. Gen. Psychiatry 55, 1093–1096. 10.1001/archpsyc.55.12.1093 [PubMed: 9862552]

Wilson RH, 2003. Development of a speech-in-multitalker-babble paradigm to assess word-recognition performance. J. Am. Acad. Audiol 14, 453–470. [PubMed: 14708835]

Wilson RH, McArdle R, 2007. Intra- and inter-session test, retest reliability of the Words-in-Noise (WIN) test. J. Am. Acad. Audiol 18, 813–825. 10.3766/jaaa.18.10.2 [PubMed: 18496992]

Wilson RH, McArdle RA, Smith SL, 2007. An Evaluation of the BKB-SIN, HINT, QuickSIN, and WIN Materials on Listeners With Normal Hearing and Listeners With Hearing Loss. J. Speech Lang. Hear. Res. JSLHR 50, 844–856. 10.1044/1092-4388(2007/059) [PubMed: 17675590]

Wykes T, Huddy V, Cellard C, McGurk SR, Czobor P, 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am. J. Psychiatry 168, 472–485. 10.1176/appi.ajp.2010.10060855 [PubMed: 21406461]

Zecker SG, Hoffman HJ, Frisina R, Dubno JR, Dhar S, Wallhagen M, Kraus N, Griffith JW, Walton JP, Eddins DA, Newman C, Victorson D, Warrier CM, Wilson RH, 2013. Audition assessment using the NIH Toolbox. Neurology 80, S45–S48. 10.1212/WNL.0b013e3182872dd2

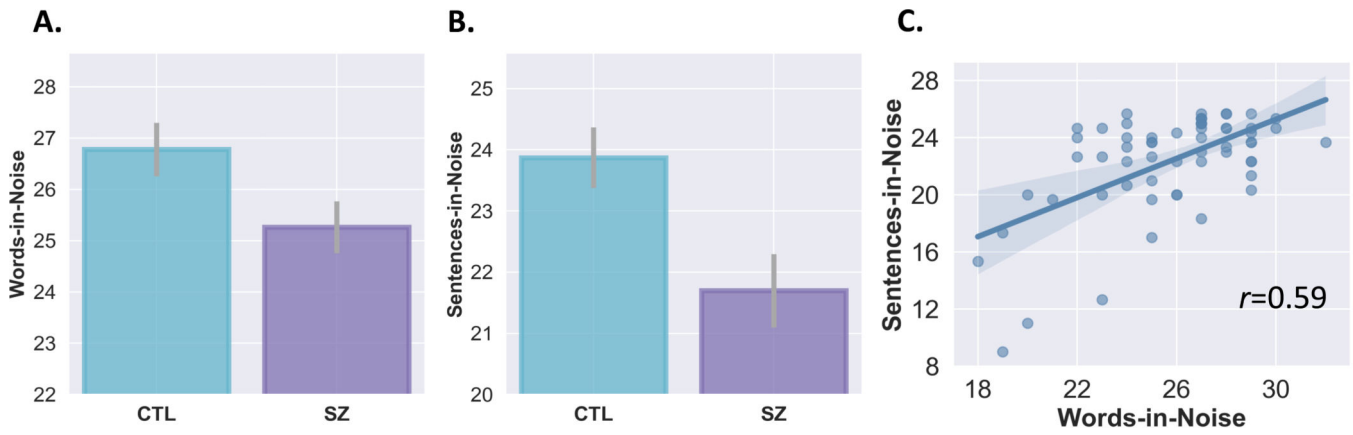


**Figure 1.**

Central auditory processing deficits in schizophrenia. Auditory discrimination deficits were seen for both Words- (A; $d$=0.50, $p$<0.05) and Sentences- (B; $d$=0.63, $p$<0.01) in-Noise tasks relative to nonpsychiatric comparison subjects (CTL). Measures of auditory discrimination were strongly correlated in all subjects (Pearson's $r$=0.58, $p$<0.001).

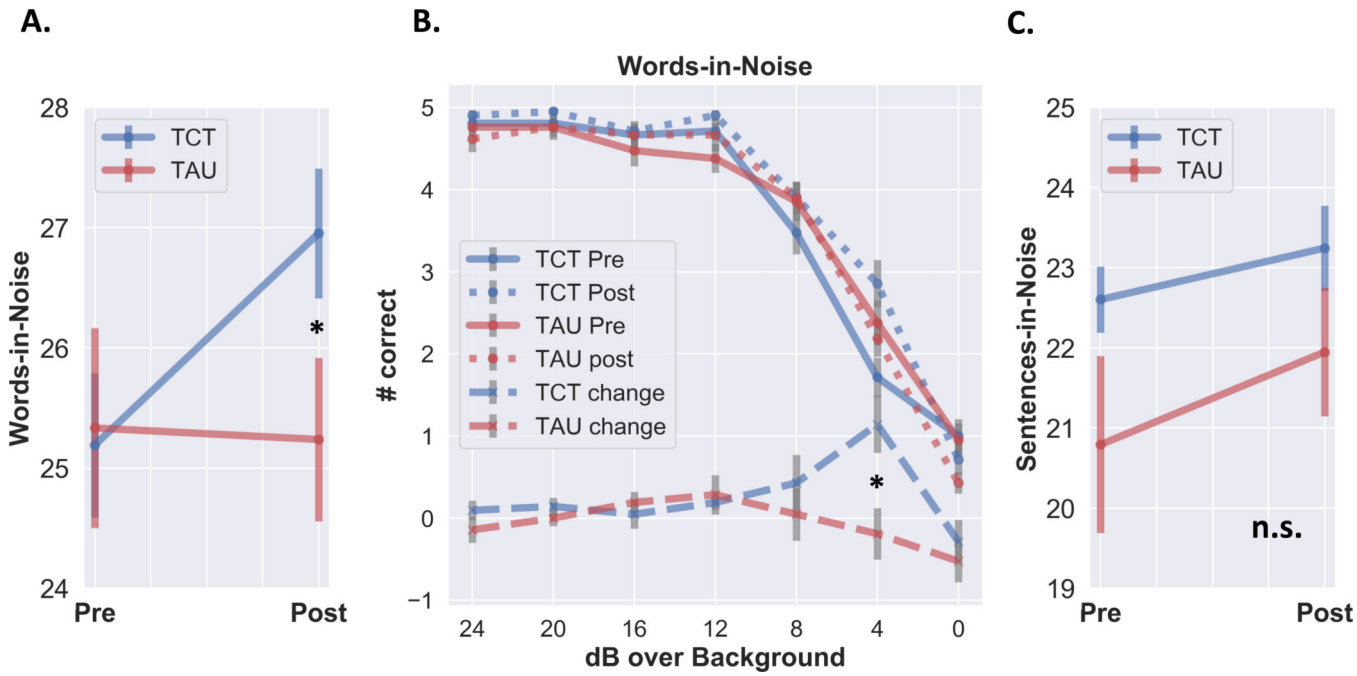


**Figure 2.**

The effects of auditory-based TCT on central auditory processing. 30-h of TCT led to improvement in WIN (A; $d$=0.74, $p$<0.05), but not SIN (C, p>0.5) performance relative to the TAU group. (B) A significant *treatment x time x dB* interaction on WIN performance was observed; TCT specifically enhanced auditory fidelity in the 4-dB over background range ($d$=0.21, $p$<0.05); solid lines represent T1, dotted lines represent T2, dashed lines (lower half of figure) represent the T2-T1 difference scores of WIN performance for TCT (blue) and TAU groups (red).

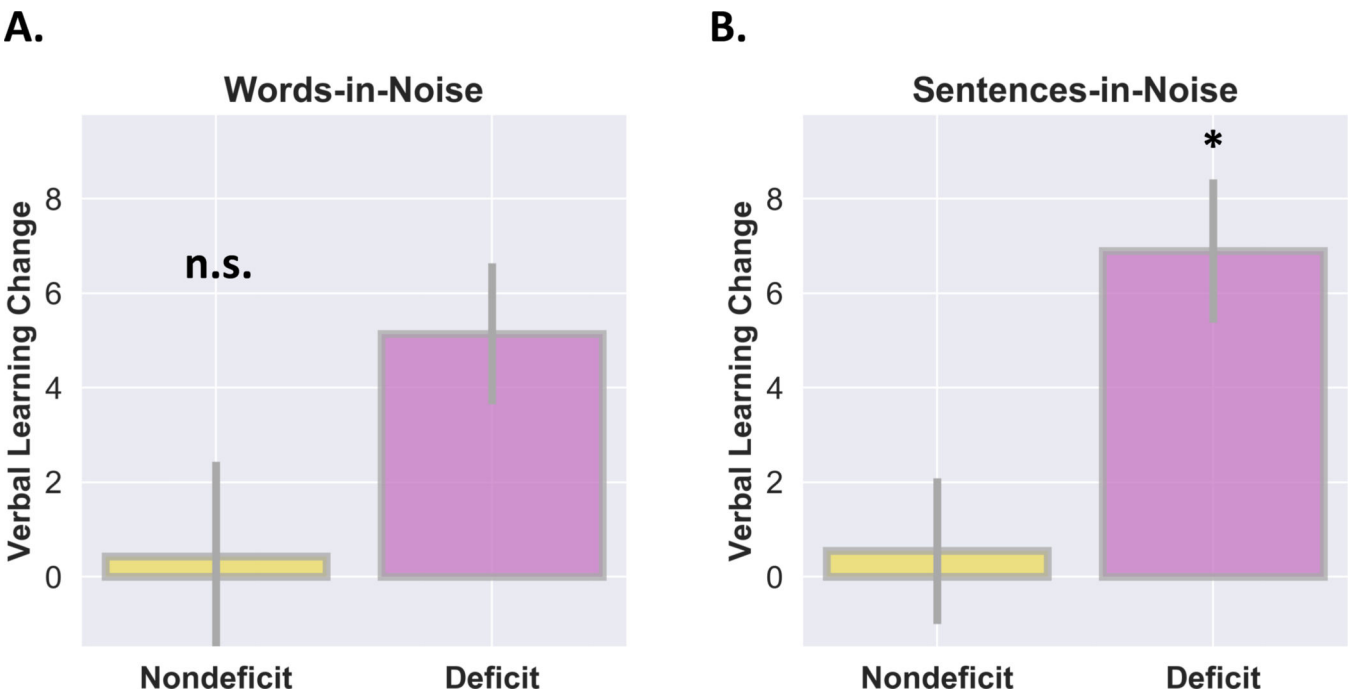


**Figure 3.**

Baseline CAP deficits are associated with Verbal Learning outcomes after 30-h of TCT. Exploratory analyses of central auditory processing (CAP) deficits (based on median split) on verbal learning outcomes in SZ patients who underwent TCT were performed. (A) SZ patients who were most impaired in WIN performance experienced trend level benefits in verbal learning (A; $p$=0.08, $d$=0.86). (B) SIN impaired patients experienced robust gains in verbal learning outcomes ($p$=0.008, $d$=1.28).

**Table 1.**

Demographic and clinical characteristics.

| | CTL (n=18) mean (s.e.m.) | SZ (n=42) mean (s.e.m.) | *p* |
|---|---|---|---|
| **Age** | 39.3 (2.4) | 34.4 (1.8) | n.s. |
| **Duration of Illness** | - | 14.8 (1.9) | - |
| **Sex (F:M)** | 08:10 | 22:20 | n.s. |
| **Education** | 15.2 (0.6) | 12.0 (0.3) | <0.001 |
| **WRAT** | 107.2 (2.4) | 91.9 (2.1) | <0.001 |
| **WIN Total** | 26.8 (0.5) | 25.3 (0.5) | <0.05 |
| **WIN 50% Point** | 4.6 (0.4) | 5.8 (0.4) | - |
| **QSIN Total** | 23.9 (0.5) | 21.7 (0.6) | <0.01 |
| **QSIN 50% Point** | 3.6 (0.5) | 5.8 (0.6) | - |
| **Global Assesssment of Function** | - | 30.8 (0.9) | - |
| **SAPS Composite** | - | 15.0 (2.5) | - |
| **SANS Composite** | - | 19.0 (1.9) | - |
| **Chlorpromazine Eq.** | - | 1041.8 (146.4) | - |
| **Anticholinergic Burden** | - | 5.1 (0.5) | - |