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ARTICLE

Memantine effects on auditory discrimination and training in schizophrenia patients

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The uncompetitive low-affinity NMDA receptor antagonist, memantine, acutely increases electrophysiological measures of auditory information processing in both healthy subjects (HS) and patients with schizophrenia. Memantine effects on functional measures of auditory discrimination performance and learning are not known; conceivably, beneficial effects on these measures might suggest a role for memantine in augmenting the cognitive and functional impact of auditory targeted cognitive training (TCT). Here, carefully characterized HS ($n = 20$) and schizophrenia patients ($n = 22$) were tested in measures of auditory discrimination performance (words-in-noise (WIN), quick speech-in-noise (QuickSIN), gaps-in-noise) and auditory frequency modulation learning (a component of TCT) on 2 days about a week apart, after ingesting either placebo or 20 mg memantine po, in a double-blind, within-subject cross-over random order design. Memantine modestly enhanced functional measures of auditory discrimination in both schizophrenia patients (WIN) and HS (WIN and QuickSIN), as well as auditory frequency modulation learning in schizophrenia patients. These findings converge with a growing literature showing that memantine can enhance a range of metrics of auditory function. These properties could contribute to the apparent benefits of memantine as an adjunctive treatment in schizophrenia, and suggest that memantine might augment learning and potentially clinical gains from auditory-based TCT.

INTRODUCTION

Memantine is an uncompetitive NMDA receptor modulator which is currently FDA-approved for the treatment of moderate-to-severe Alzheimer's disease, and is often used adjunctively in a variety of neuropsychiatric illnesses, including schizophrenia [1]. Meta-analyses have confirmed that memantine treatment is well-tolerated and modestly effective at reducing negative symptoms and improving mini-mental state exam cognition scores in antipsychotic (AP)-medicated schizophrenia patients. We previously reported that a single 20 mg dose of memantine modestly enhanced laboratory measures of auditory information processing, including prepulse inhibition (PPI), mismatch negativity (MMN) [2] and the auditory steady-state response [3] in both healthy subjects (HS) and AP-medicated schizophrenia patients, and normalized electroencephalographic measures of excitatory/inhibitory balance in patients [4]. The acute effects of memantine on PPI extended our previous findings in HS [5], and our findings of acute effects of memantine on MMN extended those of Korostenskaja et al. [6]. Depending on the study cohort, dose, and other methodological differences, across these reports, effect sizes of memantine on measures of auditory information processing have ranged from small to large (e.g., MMN $d = 0.19$ [2] to 0.87 [6]; PPI $d = 0.56$ [5] to 0.76 [2]). Importantly, deficits in early auditory information processing have been shown to mediate cognition and function in schizophrenia patients; theoretically, even small gains in these measures in schizophrenia patients should result in medium-to-large effect size gains in psychosocial functioning and

cognition [7]. Thus, an intervention that enhances early auditory information processing might engage mechanisms that ultimately have therapeutic value [8, 9].

Given these effects on pre-attentive neurophysiologic measures of auditory information processing, the present study tested the hypothesis that memantine (20 mg po) will enhance performance of "functional" measures of auditory processing in healthy adults and schizophrenia patients. To detect such functional gains, we employed measures of auditory discrimination (the ability to correctly identify degraded auditory information), auditory temporal resolution (noise gaps separation), and auditory learning (a component of auditory targeted cognitive training (TCT)) in HS and schizophrenia patients. Gains in such basic functions might conceivably contribute to the mechanism(s) by which early auditory information processing mediates cognition and function in schizophrenia patients. Measures of auditory discrimination were studied because performance on these measures is reported to be deficient in schizophrenia patients, and because memantine-induced gains in auditory discrimination would provide a plausible explanation for both its associated procognitive gains in schizophrenia patients and its associated gains in verbal communication in patients with Alzheimer's disease [10]. Memantine effects on auditory learning were tested for two reasons: (1) evidence that auditory information processing strongly predicts auditory learning performance in schizophrenia patients [11] and hence strong inference that an intervention (memantine) that enhances auditory information processing

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should enhance auditory learning, and (2) to explore the possibility that memantine might be used to augment auditory learning within an auditory TCT program, and thereby accelerate or amplify the clinical gains from TCT among schizophrenia patients [12]. Clearly, memantine might enhance auditory processing in ways that would not necessarily be detected by these specific measures of auditory discrimination, temporal resolution, and learning; thus, this study is to be viewed as a preliminary survey of memantine effects on measures that might connect its known impact on neurophysiological indices of early auditory processing, with its modest procognitive properties in neuropsychiatric patients.

METHODS
This protocol was approved by the UCSD IRB and posted on clinicaltrials.gov. Details of recruitment procedures are found in previous reports from our laboratory (e.g., Ref. [2]). Briefly, AP medicated (stable regimen > 30 days) patients with a primary diagnosis of schizophrenia or schizoaffective disorder (depressed type) as well as HS were phone- or field-screened for medical, psychiatric, and substance history. Consent and diagnostic assessment (M.I.N.I. 6.0; [13]) was conducted; qualifying patients and HS came to the lab for a screening day: a confirmatory diagnostic assessment, physical exam, electrocardiogram, vision and hearing tests (exclusion for detection threshold > 40 dB at 1000 Hz), urine toxicology (exclusion for recreational drug use), and pregnancy test (all subjects "negative"). Full inclusion criteria are seen in Table S1. Eligible patients completed measures of symptoms; all subjects completed baseline measures of single word reading (Wide Range Achievement Test-Reading (WRAT; [14])) and neurocognition (MATRICS Consensus Cognitive Battery (MCCB; [15])). Subjects were randomized to dose order (placebo–memantine vs. memantine–placebo) and then tested two times at 7–10-day intervals (test days); on test days, subjects ingested either placebo or memantine (20 mg po) and were then tested in measures of auditory discrimination and auditory learning.

Measures of auditory processing fidelity
Auditory discrimination was tested using words-in-noise (WIN; NIH Toolbox [16]) and quick speech-in-noise (QuickSIN; Etymotic Research, Elk Grove, IL; [17]) tests with modifications to allow for binaural presentation; auditory temporal resolution was tested via gaps-in-noise (GIN; [18]). Critical appraisal of these measures is found in Bellis and Bellis [19] and Sharma et al. [20]. Both WIN and QuickSIN assess the ability to recognize speech over background noise, akin to deciphering conversation in a noisy environment, and are deficient in schizophrenia patients [21]. Speech stimuli are presented in varying intensities of background conversation noise (four-talker babble); WIN uses one-word stimuli, whereas QuickSIN utilizes sentence stimuli. Subjects repeat the words or sentences aloud, and their responses are scored based on repetition accuracy of the word (WIN) or five "key" words (QuickSIN). Primary measure for both is the # correct scores at each background dB level, with a maximum score of 5. Since these tests are widely used in audiologic assessments, ceiling effects in normal hearing subjects are expected when stimuli are greater than 10 dB above background noise. Similarly, floor effects are expected when the words are presented 0 dB above background. Auditory temporal resolution was measured by GIN, a nonverbal test that determines the smallest detectable silent interval. GIN is sensitive to central auditory deficits in schizophrenia [18, 22, 23]; subjects identify 2–20 ms gaps imposed on 6 s noise trials, with 6 repetitions/gap (60 total gaps; ITI = 5 s). The key dependent measure is the # correct scores at each gap duration, which is also used to calculate a gap detection threshold.

Measure of auditory frequency learning
"Sound Sweeps" TCT (PositScience; brainhq.com) is an auditory learning task based on frequency discrimination time-order judgment. Participants are presented with pairs of frequency-modulated sound "sweeps" and indicate whether they perceived each sweep as becoming higher or lower in pitch. The training is continuously adaptive—sweep duration, frequency range, and interstimulus interval become shorter after correct responses, but longer after incorrect responses. Baseline and best auditory processing speed (APS) scores are automatically calculated, with possible scores ranging from 16 to 1000 ms and lower scores indicating better APS. On screen and test days, subjects completed 1 h of TCT, as described in Swerdlow et al. [24]. A research assistant monitored each session. Analytic software yielded the key dependent measure for this study, "Delta (ms)," which is the difference between the baseline (first) APS and the best of the subsequent trials, and which serves as the operational measure of "APS learning." Sound Sweeps training progresses through multiple "stages," each of which was divided into three blocks; because many subjects completed only one stage during the 1 h session, analyses of "learning" included only that first stage. The present study utilized a Sound Sweeps paradigm that was modified somewhat from our previously published reports [11, 24–26], based on a migration from "Flash" to "HTML5" platforms, making the current platform comparable to the commercial version. Two schizophrenia subjects exhibited "ceiling" (1000 ms) latency scores both pre- and post-Sound Sweeps training, for both placebo and memantine conditions, and key "memantine-enhanced learning" metrics are reported both with and without those subjects included.

Autonomic function (heart rate and blood pressure) and self-assessed levels of "happy," "drowsy," "queasy," "dizzy," "focus attention," and "anxious" (100 mm visual analog Symptom Rating Scales (SRS)) were recorded at eight different time points throughout the test days. Relative to pill administration ($t = 0$), key measures were administered at 265 min (TCT) and 430 min (WIN, QuickSIN, and GIN, in that sequence).

Our *a priori* hypothesis was that memantine would produce functional gains in auditory processing; the selected measures were used to detect memantine effects on auditory fidelity, temporal processing, and learning. Because these measures are not typically used to assess drug effects, and because memantine-induced gains in MMN, ASSR, and PPI do not implicate a specific feature of auditory function, there was no clear basis for predicting which one or more specific measures would be most sensitive to memantine effects. There is some evidence, from memantine effects on PPI [2], and from drug-induced gains in auditory discrimination [27], that memantine effects would be most easily detected within the dynamic range of these measures, i.e., at non-floor or non-ceiling levels, when performance had "room to move" [28].

Primary dependent measures (# correct responses in WIN, QuickSIN, GIN, and learning (ms) change in APS) were analyzed by ANOVA with diagnosis as the between factor and memantine dose (placebo vs. 20 mg) as a within-subject factor. Additionally, models included either dB salience (WIN, QuickSIN) or gap duration (GIN) as within-subject factors. Simple main effects are reported first, followed by relevant interactions and post hoc comparisons; alpha was set to 0.05. WIN and QuickSIN analyses were conducted both with and without scores from "0 dB" conditions (equal intensity background and words). QuickSIN measures include three separate speech "lists"; for this study, "List 1" speech was used as a primary measure. Based on the limited range of scores (1–5 (WIN, QuickSIN) or 1–6 (GIN)), nonparametric analyses were used to confirm significant effects detected by ANOVA, and to assess inter-measure correlations. Based on published findings, planned analyses assessed effects of baseline (Screen) levels of neurocognition (specifically the MCCB attention/vigilance T-score) on the primary dependent measures; these

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analyses were pursued by dividing groups (patient and HS) into the lowest vs. highest 50% (i.e., a "median split" analysis). Exploratory analyses based on previous findings of regulatory effects on one or more primary measures assessed effects of age, baseline hearing threshold, smoking, medication, and drug order.

RESULTS

Subjects

Subject demographics and medications are seen in Table 1. Patients were chronically ill, moderately-to-severely impaired, and taking multiple medications. Compared to HS, patients were generally older, heavier, less educated, less likely to have been married, more likely to smoke, and had lower WRAT scores. Patients had modestly elevated hearing thresholds for 1000 Hz tones ($F = 5.58$, df: 1.40, $p < 0.025$) and 6000 Hz tones ($F = 4.98$, df: 1.40, $p < 0.035$), but not for 500 Hz tones ($F < 1$). MCCB scores for patients and HS are seen in Table 2 and revealed the expected pattern of significant deficits across all MCCB domains (p's < 0.03–0.0001) with the exception of reasoning and problem solving, which did not differ based on diagnosis.

Memantine subjective effects

Subjective ratings and autonomic measures are seen in Supplementary Fig. S1 and document the relative inactivity of 20 mg memantine in these measures, consistent with our previous reports [2, 5]. SRS data generally yielded no meaningful main or interaction effects, with the exception of "Focus Attention" (Fig. S1). In this scale, HS tended to decline across the test session more so than patients (diagnosis × time: $F = 2.35$, df: 6.240, $p < 0.035$), and this effect was opposed by memantine (drug × time: $F = 2.60$, df: 6.240, $p < 0.02$) with no significant differential drug effect across diagnoses (diagnosis × drug × time: $F < 1$). In secondary analyses, this effect did not appear to be moderated by age, smoking, or MCCB A/V scale score (all interactions ns). Consistent with the modest drug effects on SRS data, subjects correctly identified the active dose of memantine at near-chance levels (58.3%). As in our past reports [2, 5], analyses of autonomic measures revealed no significant main or interaction effects of diagnosis and drug on change in heart rate, systolic or diastolic blood pressure.

Task performance

Words-in-noise (WIN; Fig. 1). ANOVA (Table 3) detected no significant main effect of diagnosis or drug. Both patients and HS exhibited the expected performance curves showing degradation with decreasing signal-over-noise level (significant main effect of "dB": $F = 462.8$, df: 4.240, $p < 0.0001$). There was a significant dB × drug interaction ($F = 3.15$, df: 6.240, $p < 0.006$); comparable results were detected without the "0 dB" condition (dB × drug interaction: $F = 3.57$, df: 5.200, $p < 0.005$). A "threshold" for maximal performance loss was evident when word noise level dropped from 8 to 0 dB over background (Fig. 1a). At the midpoint of this decline (4-dB level), ANOVA confirmed a significant main effect of drug ($F = 5.98$, df: 1.40, $p < 0.019$); memantine significantly enhanced performance in patients ($F = 5.54$, df: 1.21, $p < 0.03$; $d = 0.56$) but not in HS ($F = 1.51$, df: 1.19, ns; Fig. 1b) including an HS subgroup age matched to patients ($F < 1$).

Order effects and confirmatory analyses: These memantine effects did not interact with drug order ($F < 1$). Findings were confirmed via nonparametric analyses (Wilcoxon signed-rank test in patients ($z = -2.18$, $p < 0.03$) vs. HS ($z = -1.12$, ns)). The normalizing effects of memantine were most evident among patients with low vs. high baseline MCCB A/V scores ($d = 0.89$ vs. 0.23; Fig. 1c), consistent with our *a priori* hypothesis. The magnitude of this memantine effect in patients (memantine minus PBO) was not significantly associated with age ($r = 0.23$, ns), baseline hearing threshold ($r = 0.09$, ns), chlorpromazine equivalents ($r = 0.20$, ns), or smoking status ($F < 1$). In this "threshold" portion of the WIN performance function, the mean memantine-induced gain in performance in schizophrenia patients (0.68 words) corresponds to a 1.74 dB gain in signal intensity; in effect, performance sensitivity in patients was "normalized" by 1.74 dB.

Quick speech-in-noise (QuickSIN; Fig. 2 and Table 3). QuickSIN performance did not differ significantly between HS and schizophrenia groups ($F < 1$). As with WIN, QuickSIN performance in both patients and HS exhibited the expected performance degradation with decreasing signal-over-noise level (main effect of dB: $F = 262.54$, df: 5.200, $p < 0.0001$) but also a small but generalized enhancement of performance by memantine across all speech intensities (main effect of drug: $F = 4.48$, df: 1.40, $p < 0.05$; $d = 0.25$), with no significant dB × drug interaction ($F < 1$).

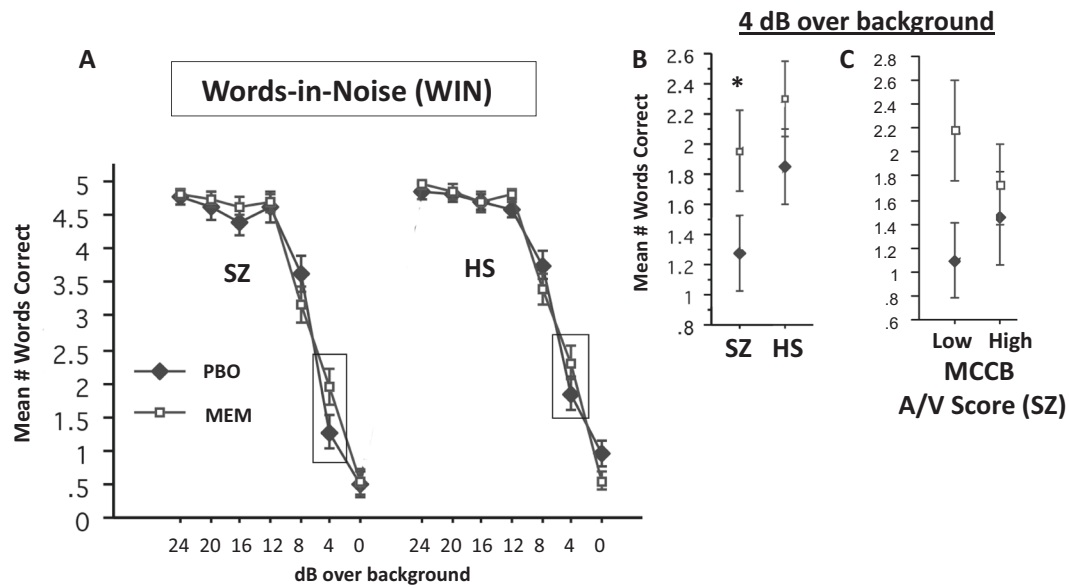| Table 1. Subject characteristics.			
Diagnoses (n)	SZ (22)	HS (20)	p
Age in years (mean (SD))	40.6 (8.1)	29.5 (10.0)	<0.0001
Weight in lbs (mean (SD))	216.6 (47.8)	159.0 (51.3)	<0.0001
Sex (M:F)	11:11	12:8	NS
Smoker:nonsmoker	12:10	0:20	<0.0001
Race (% white)	36.8%	35.0%	NS
Daily caffeine (mg)	256.1 (243.1)	245.0 (364.1)	NS
Wide Range Achievement Test (WRAT)	90.0 (8.4)	107.9 (9.4)	<0.0001
Education (years; SD)	12.3 (1.4)	15.6 (2.3)	<0.0001
Hearing threshold (dB)			
500 Hz	25.6 (1.9)	24.0 (1.1)	NS
1000 Hz	20.8 (2.1)	15.0 (1.0)	<0.002
6000 Hz	28.9 (3.4)	19.1 (2.6)	<0.007
Duration illness (years; SD)	21.2 (8.7)		
Age of onset (years; SD)	19.4 (3.7)		
GAF (mean (SD))	57.4 (10.7)		
SANS total score (mean (SD))	24.6 (17.5)		
SAPS total score (mean (SD))	25.9 (20.9)		
Chlorpromazine equivalents (mg (SD))	848.1 (1034.8)		

Table 2. MCCB T-scores (SEM).							
	SP	A/V	WM	VL	VisL	RPS	SC
HS	50.4 (2.4)	46.7 (1.9)	49.9 (2.0)	43.6 (2.1)	49.4 (2.2)	48.6 (1.9)	50.7 (2.5)
SZ	34.4*** (2.9)	37.3* (3.5)	34.3*** (2.7)	32.5*** (1.7)	31.9*** (3.0)	46.8 (2.4)	38.6** (3.2)

HS > SZ: *$p < 0.03$; **$p < 0.006$; ***$p < 0.0001$.

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Fig. 1 Words-in-noise (WIN) performance in schizophrenia (SZ) patients and HS, after PBO or memantine (MEM: 20 mg po). a Mean # words correct under conditions of 24–0 dB relative salience over background. Analyses yielded a significant drug × intensity interaction; post hoc comparisons at 4 dB (enclosed in rectangles) are seen in (**b**). **b** Analyses confirmed significant memantine-enhanced performance in SZ patients (*); these gains correspond to a 1.74 dB gain in signal intensity. **c** Impact of memantine on performance in SZ patients with low vs. high levels of baseline A/V scores on the MCCB. In those patients with poor attention (lowest 50% of A/V scores), effect of memantine was large ($d = 0.89$); in those with good attention (highest 50% of A/V scores), effect of memantine was small ($d = 0.23$).

Order effects and confirmatory analyses: This main effect of memantine did not interact with drug order ($F < 1$). Comparable results were detected without the "0 dB" condition (main effect of drug: $F = 3.99$, df: 1.40, $p = 0.053$; $d = 0.14$). As with WIN, nonparametric analyses supported the ANOVA results (Wilcoxon signed-rank test (memantine vs. PBO): $z = -2.08$, $p < 0.04$)); averaged across dB and diagnoses, performance with memantine exceeded that with placebo with a frequency significantly greater than chance (memantine > placebo, $n = 25$; placebo > memantine, $n = 11$; placebo = memantine, $n = 6$; $p < 0.03$, one-sample sign test). Unlike WIN, QuickSIN performance did not exhibit a clear "threshold," but instead declined sharply from 5 dB to 0 dB levels. With 5 dB speech levels, ANOVA confirmed superior performance among patients with high vs. low baseline MCCB A/V scores ($p < 0.003$), but no interaction of drug × MCCB scores (F's < 1; Fig. 2).

Gaps-in-noise (GIN; Fig. 3 and Table 3). GIN performance was deficient in schizophrenia vs. HS groups (main effect of diagnosis: $F = 11.58$, df: 1.40, $p < 0.002$; $d = 0.39$), but unlike WIN and QuickSIN, GIN performance did not appear to be memantine sensitive (no significant main effect of memantine ($F < 1$)). The significant main effect of group was not evident among age-matched subgroups, suggesting that age differences contributed to this group effect. There was a significant main effect of gap length (ms) ($F = 216.95$, df: 9.360, $p < 0.0001$) and an interaction of ms × diagnosis ($F = 3.17$, df: 9.360, $p < 0.002$), but no significant interaction effects of memantine (drug × diagnosis: $F < 1$; drug × ms: $F = 1.78$, df: 9.360, ns). Performance declined abruptly at the 5 ms "threshold"; at this level, performance was impacted by diagnosis ($F = 9.24$, df: 1.40, $p < 0.002$; $d = 0.78$) but not drug or A/V level (both F's < 1) (Fig. 3).

Frequency modulation task (Sound Sweeps; Fig. 4 and Table 3)
Screen day: ANOVA of Sound Sweeps baseline performance on the screening day revealed slower APS values in patients vs. HS ($F = 8.92$, df: 1.40, $p < 0.005$) (Fig. 4a). This group difference ($d = 0.96$) remained robust when HS and patient groups were matched for age ($d = 0.86$). On average, screen day APS learning tended to be greater among subjects with higher vs. lower A/V scores, but these

differences did not reach statistical significance in either patients ($d = 0.52$) or HS ($d = 0.22$).

Test days: On test days, APS during stage 1 (when learning was assessed) was slower in patients than in HS (Fig. 4b). ANOVA of stage 1 APS revealed a significant main effect of diagnosis ($F = 10.73$, df: 1.40, $p < 0.003$), no significant effect of memantine ($F = 1.07$, df: 1.40, ns) or block ($F < 1$), and no significant two- or three-way interactions (Table 3). This APS slowing in the full sample ($d = 0.95$) was equally robust among age-matched subgroups of patients vs. HS ($d = 1.03$).

Analysis of APS "learning" (ms) on test days (Fig. 4c) detected no significant main effects of either diagnosis ($F = 3.38$, df: 1.40, ns), drug ($F = 2.74$, df: 1.40, ns), or block ($F < 1$). There was a significant interaction of diagnosis × drug ($F = 4.25$, df: 1.40, $p < 0.05$) but no other significant two- or three-way interactions (Table 3). Memantine significantly enhanced APS "learning" among schizophrenia patients ($F = 4.30$, df: 1.21, $p = 0.05$; $d = 0.40$) but not HS ($F < 1$). The lack of memantine-enhanced learning among HS was evident in an older subgroup, age matched to patients ($F < 1$). Omission of two "ceiling level" subjects (see "Methods") yielded comparable learning results, with no significant effect of diagnosis ($F = 2.41$, df: 1.38, ns) or drug ($F = 3.03$, df: 1.38, ns) but a significant interaction of diagnosis × drug ($F = 4.67$, df: 1.38, $p < 0.04$); memantine enhanced APS learning in these schizophrenia patients ($F = 4.41$, df: 1.19, $p < 0.05$; $d = 0.40$).

The magnitude of memantine-induced APS slowing in stage 1 in patients was roughly comparable to the amount of memantine-enhanced learning (mean (SEM) = 33.70 (24.54) ms vs. 46.59 (22.47) ms, respectively; see Fig. 4b, c). A temporal dissociation between these memantine effects in patients was evident across the three test blocks in stage 1: memantine-induced APS slowing was maximal at the end of the stage (means for blocks 1–3 were 26, 23, and 52 ms, respectively), while memantine-enhanced learning was maximal early in the stage (means for blocks 1–3 were 59, 46, and 35 ms, respectively) (Supplementary Fig. S2). Thus, while both processes presumably reflect the impact of memantine on brain activity, their temporal dissociation suggests that they are not otherwise mechanistically linked.

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Table 3. ANOVA outcomes for main analyses for primary dependent measures.

	F	df	p
WIN (all dB)			
Diagnosis (Dx)	2.19	1.40	ns
Drug	<1		
Drug × Dx	<1		
dB	462.83	6.240	<0.0001
dB × Dx	<1		
dB × drug	3.15	6.240	<0.006
dB × Dx × drug	<1		
WIN (4 dB)			
Dx	2.74	1.40	ns
Drug	5.98	1.40	<0.02
Dx × drug	<1		
QuickSIN (all dB)			
Dx	<1		
Drug	4.48	1.40	<0.05
Drug × Dx	<1		
dB	262.54	5.200	<0.0001
dB × Dx	<1		
dB × drug	<1		
dB × Dx × drug	<1		
GIN (all ms)			
Dx	11.58	1.40	<0.002
Drug	<1		
Drug × Dx	<1		
ms	216.95	9.360	<0.0001
ms × Dx	3.17	9.360	<0.002
ms × drug	1.78	9.360	<0.08
ms × Dx × drug	<1		
APS (stage 1)			
Dx	10.73	1.40	<0.0025
Drug	1.07	1.40	ns
Block	<1		
Dx × drug	2.12	1.40	ns
Dx × block	<1		
Drug × block	<1		
Drug × block × Dx	<1		
APS learning			
Dx	3.38	1.40	<0.075
Drug	2.74	1.40	ns
Block	<1		
Dx × drug	4.25	1.40	<0.05
Dx × block	1.62	2.80	ns
Drug × block	<1		
Drug × block × Dx	<1		

Order and "carry forward" effects: Drug order (memantine weeks 1 vs. 2) did not impact memantine-induced gains in learning. Pretraining APS on test day 2 for patients who received memantine on test day 1 was on average 132.4 ms faster than pretraining APS on test day 1. In other words, patients "carried forward" 132.4 ms of gains in APS, 1 week after taking memantine. In comparison, patients who received PBO on test day 1 "carried forward" to test day 2 only 1.46 ms of APS gains ($d = 0.51$). While

this medium effect failed to reach conventional levels of statistical significance, it does suggest that memantine's effects on APS learning are not "state dependent," i.e., were evident 1 week after memantine, prior to that week's training session. A similar pattern of arithmetically greater "carry forward" of APS gains after memantine vs. PBO was evident in HS ($d = 0.56$).

There was no difference in the magnitude of the "memantine effect" on learning (memantine minus PBO) among patients with low vs. high A/V scores, nor was the memantine effect significantly associated with age ($r = -0.38$), hearing threshold ($r = -0.02$), chlorpromazine equivalents ($r = 0.29$), or smoking status ($F = 1.71$, df: 1.20, ns), though relationships with both age (negative) and chlorpromazine equivalents (positive) might be viewed as "trends."

Inter-measure correlations: Across the four primary measures of auditory function, there was a surprising lack of statistically significant correlations. This was true even among structurally similar measures for PBO tests (e.g., average word score in patients, WIN vs. QuickSIN, $r_s = 0.29$, ns), and for memantine sensitivity (i.e., memantine minus PBO scores: WIN vs. QuickSIN, $r_s = 0.14$, ns). Conceivably, some of these analyses might have yielded statistically significant correlations in larger samples. Categorical comparisons (e.g., "Low" vs. "High" memantine sensitivity based on median splits) identified some modest inter-measure relationships; for example, patients with "High" memantine sensitivity on APS learning exhibited significant memantine-induced gains in WIN performance (and vice versa), using either parametric (ANOVA: $F = 5.38$, df: 1.10, $p < 0.045$; $d = 0.89$) or nonparametric comparisons (Wilcoxon signed-rank test; $z = -2.03$, $p < 0.045$), while patients with "Low" memantine sensitivity did not (ns for either comparison). But overall, analyses in this modest sample size suggested that performance on one measure of auditory discrimination and learning did not strongly predict performance on another measure.

DISCUSSION

This study provides evidence that memantine enhances auditory information processing in a manner that produces functional gains in auditory discrimination and learning. These effects were modest in magnitude and were detected within a "threshold" word intensity range in WIN, across speech intensity levels in QuickSIN and with frequency modulation learning in the Sound Sweeps task. These results build on previous findings of modest memantine-induced gains in EEG-based measures of early auditory information processing in both schizophrenia patients and HS [2, 3].

These findings also converge with a growing literature suggesting that memantine can have positive effects on auditory function. Protective effects of memantine have been detected in animal models, in which memantine reduced both noise- and salicylate-induced hearing deficits [29–32]. Memantine's effects on auditory function are detected at multiple levels of auditory circuitry; it appears to impact both nicotinic and glutamatergic neurotransmission very early in auditory processing (e.g., outer and inner hair cells, respectively [33, 34]), but also enhances "higher" auditory measures of consonant-vowel-induced activation of middle temporal gyrus, superior frontal gyrus, and middle frontal gyrus in healthy humans [35]. Perhaps most importantly, memantine has been shown to enhance verbal communication in patients with Alzheimer's disease, as assessed by the American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults, the Functional Communication Language Inventory and related measures [10, 36–38]. Thus, there is evidence for salutary effects of memantine from the "bottom" levels of auditory processing, up to the "top" levels of cortical function, with noted gains in communication and language skills.

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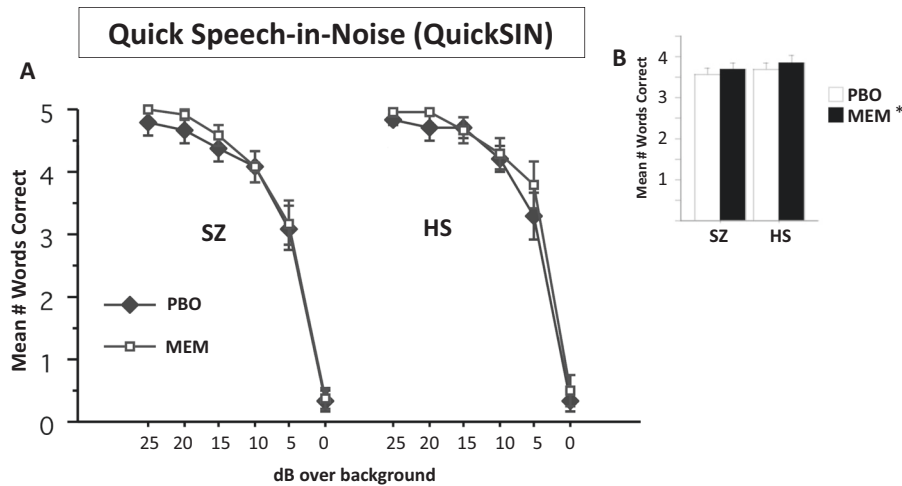
Fig. 2 Quick speech-in-noise (QuickSIN) performance in schizophrenia (SZ) patients and HS, after PBO or memantine (MEM: 20 mg po).
a Mean # words correct under conditions of 25–0 dB relative salience over background. Analyses revealed small but significant performance-enhancing effects of memantine, independent of diagnosis, with no interaction of word salience over background. **b** Data collapsed across salience levels.

The present findings reveal potential functional benefits of memantine on auditory processing, both in the detection of words embedded in a complex noise background, and in the ability to learn to correctly identify sound frequency sweeps. We cannot discern where memantine is acting within auditory and cognitive circuitry to effect these gains; we do know that its actions are evident after acute exposure (rather than sustained dosing) and, in the case of WIN, appear to engage higher cognitive function as suggested by an interaction of memantine-enhanced performance with baseline attention/vigilance scores. We cannot rule out the possibility that the apparent impact of A/V scores on memantine effects reflect the greater response range available in auditory functional measures among low-scoring subjects with relatively poor baseline A/V scores, rather than a true mechanistic interaction, i.e., at a neural circuit level.

This study has many limitations. First, the measures used here to assess changes in auditory processing fidelity are used primarily as clinical tools to screen for hearing loss, rather than to detect acute drug-induced changes in auditory discrimination or temporal resolution abilities. Almost certainly, other measures of auditory function will be more sensitive to detecting acute drug-induced changes. Second, the pattern of drug effects across these measures was inconsistent. Memantine-induced gains in WIN performance, for example, were evident only within the "dynamic range" of the measure, i.e., with a salience level (4 dB) that produced performance within a range between "floor" and "ceiling" levels; interestingly, within individuals, memantine effects on this "threshold-level" WIN performance significantly predicted memantine-enhanced auditory learning. By contrast, memantine effects on QuickSIN performance were small ($d = 0.25$) and seen primarily within higher salience levels (e.g., 15–25 dB), and measures of acoustic temporal resolution (GIN) appeared to be relatively insensitive to memantine. No significant correlations were identified among WIN, QuickSIN, or GIN—either in terms of their baseline levels or sensitivity to memantine—suggesting that these seemingly similar measures do not assess identical processes. A third limitation is that this study was not designed to identify the neural basis for memantine's effects on auditory processing—either in terms of its actions at a specific receptor/cellular level or in terms of the specific neural circuitry that mediate the observed changes in auditory discrimination and learning. While memantine has known activity at NMDA receptors, its distinctive preclinical and clinical profile compared to other NMDA antagonists such as ketamine have raised speculation that its primary mechanisms may involve non-NMDA substrates, or at least non-synaptic NMDA receptors; a recent review of memantine's effectiveness as an adjunctive treatment for schizophrenia [39] concluded that unlike structurally distinct NMDA antagonists like ketamine, phencyclidine, or dizocilpine, memantine acts as a "low-affinity, fast off-rate, voltage-dependent, and uncompetitive antagonist with preferential inhibition of extra-synaptic receptors." Certainly, the present study does not add clarity to this issue. Other limitations to this study include sample size and the use of a single active dose; both n and dose were selected based on findings of memantine effects on measures of early auditory information processing in schizophrenia patients and HS [2–5].

We do not yet know whether the observed memantine-induced gains in auditory processing will translate to clinical benefits in a sensitive population of schizophrenia patients, but such benefits might be predicted based on the relationship between auditory system engagement and gains from auditory-based cognitive training [8, 9, 11, 12, 26]. Large single-site studies as well as meta-analyses confirm that some clinical gains are conferred by sustained dosing of memantine among inclusive samples (i.e., not "biomarker-enriched" subgroups) of schizophrenia patients [1, 40, 41]. Of course, these studies did not incorporate cognitive interventions (e.g., PositScience) that rely on auditory learning or other processes that appear to be targets for memantine, as suggested by the present findings and past reports [12]; nor did they divide cohorts into subgroups based on other potential "biomarkers." In the present study, it was possible to divide patients and HS into subgroups that were least vs. most sensitive to the ability of memantine to enhance APS learning; those most sensitive to these memantine effects were also most sensitive to memantine's ability to enhance auditory discrimination in the WIN task. It would be parsimonious to predict that individuals most sensitive to memantine-enhanced APS learning after a single memantine "challenge" might ultimately benefit most from the addition of memantine to a course of auditory-based TCT. This design is the basis for the "Pharmacologic Augmentation of Cognitive Training" model ("PACT"; [42, 43]) for schizophrenia therapeutics, in which drugs are used to target brain mechanisms (e.g., auditory processing) as a means to enhance the therapeutic impact of cognitive training in biomarker-identified (e.g., "high memantine sensitivity") subgroups of patients.

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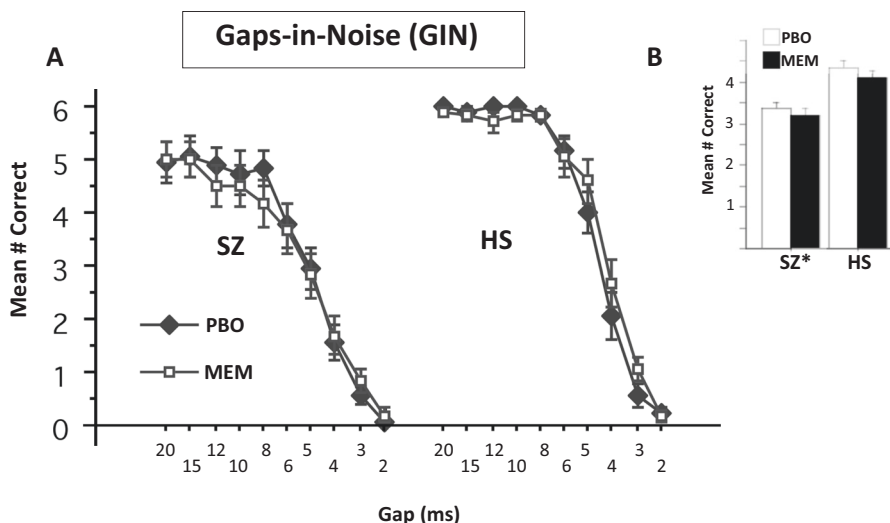
Fig. 3 **Gaps-in-noise (GIN) performance in schizophrenia (SZ) patients and HS, after PBO or memantine (MEM: 20 mg po). a** SZ patients were deficient in this measure compared to HS, but there was no significant main effect of drug, and no particular temporal window that was most sensitive to diagnostic or drug effects. **b** Inset shows data collapsed across gaps, showing lower performance scores in SZ vs. HS subjects (*).
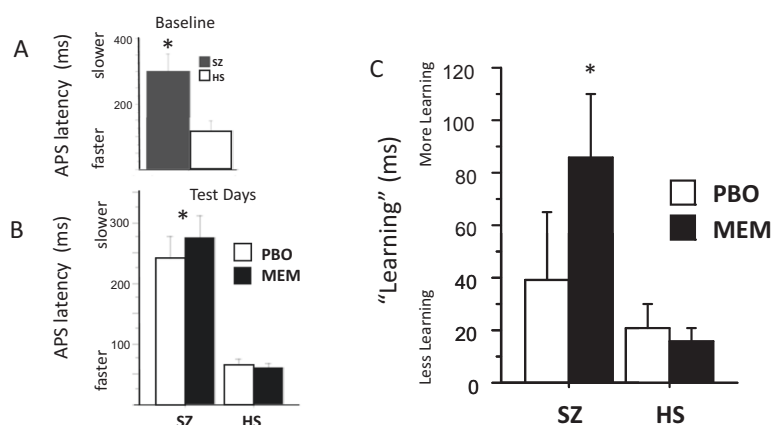
Fig. 4 **Sound Sweeps performance in schizophrenia (SZ) patients and HS, after PBO or memantine (MEM: 20 mg po).** Measures of auditory processing speed on screen day (**a**) and test day (**b**) showed slower processing (more time (ms) required for accurate sweep identification) in SZ vs. HS groups (*). **c** "APS learning" (APS difference from first to best trial of each block in stage 1) is significantly enhanced by memantine in SZ subjects but not HS (*). This learning among subjects tested with memantine in week 1 was largely intact 1 week later, when tested under PBO conditions (see text).

Two other challenges face the use of memantine in this type of "PACT" design. First, the present study as well as past reports demonstrate only the benefits of an acute single-dose challenge of memantine, and not the benefits of sustained daily dosing. Whether similar gains would be detected after sustained dosing is an empirical question. Of note, functional gains in both brain activation and communication/linguistic performance are detected after sustained daily dosing of memantine (10 mg bid), for between 3 and 12 weeks [10, 36, 37, 44]. Indeed, there is a precedent for using daily memantine (10 mg bid) to augment the therapeutic impact of auditory-based therapies in patients with Alzheimer's disease [45]. Second, we have no evidence for the durability of memantine-induced gains in auditory learning, i.e., whether they might fade over time, or be lost once memantine is discontinued. These are also empirical questions; though consistent with previous findings with amphetamine [24], the present findings suggest that clinically significant gains induced by memantine "carry forward" for at least 1 week after a 20 mg dose and that, once established, such learning no longer depends on the presence of memantine in the brain.

In summary, an acute dose of 20 mg memantine enhances functional measures of auditory processing and learning in schizophrenia patients. These findings add to a growing literature of memantine-associated gains in auditory and communication function in healthy and patient populations. A clinical trial pairing memantine with auditory-based TCT could be used to test the utility of such a "PACT" design, using a design like that reported here to identify subgroups predicted to exhibit low vs. high memantine sensitivity.

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AUTHOR CONTRIBUTIONS

Authors made meaningful contributions to this study, including study design (NRS and GAL), measurement development (NRS, GAL, and JT), subject recruitment, screening, testing, and medical coverage (SB, JK, BZR, YJ, and JLM), data acquisition and processing (JT, JK, and BZR), analysis and interpretation of the results (NRS, GAL, JT, REC, and MT), writing (NRS), and critical editing of the report (GAL, JT, JK, BZR, REC, and MT).

ADDITIONAL INFORMATION

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