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# Single-Dose Memantine Improves Cortical Oscillatory Response Dynamics in Patients with Schizophrenia

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Aberrant gamma-band (30–80 Hz) oscillations may underlie cognitive deficits in schizophrenia (SZ). Gamma oscillations and their regulation by NMDA receptors can be studied via their evoked power ( $\gamma$ EP) and phase locking ( $\gamma$ PL) in response to auditory steady-state stimulation; these auditory steady-state responses (ASSRs) may be biomarkers for target engagement and early therapeutic effects. We previously reported that memantine, an NMDA receptor antagonist, enhanced two biomarkers of early auditory information processing: prepulse inhibition and mismatch negativity (MMN) in SZ patients and healthy subjects (HS). Here, we describe memantine effects on  $\gamma$ EP and  $\gamma$ PL in those subjects. SZ patients ( $n = 18$ ) and HS ( $n = 14$ ) received memantine 20 mg (p.o.) and placebo over 2 test days in a double-blind, randomized, counterbalanced, cross-over design. The ASSR paradigm (1 ms, 85 dB clicks in 250–0.5 s trains at a frequency of 40 Hz; 0.5 s inter-train interval) was used to assess  $\gamma$ EP and  $\gamma$ PL. SZ patients had reduced  $\gamma$ EP and  $\gamma$ PL; memantine enhanced  $\gamma$ EP and  $\gamma$ PL ( $p < 0.025$  and  $0.002$ , respectively) in both SZ and HS. In patients, significant correlations between age and memantine effects were detected for  $\gamma$ EP and  $\gamma$ PL: greater memantine sensitivity on  $\gamma$ EP and  $\gamma$ PL were present in younger SZ patients, similar to our reported findings with MMN. Memantine acutely normalized cortical oscillatory dynamics associated with NMDA receptor dysfunction in SZ patients. Ongoing studies will clarify whether these acute changes predict beneficial clinical, neurocognitive and functional outcomes. These data support the use of gamma-band ASSR as a translational end point in pro-cognitive drug discovery and early-phase clinical trials. *Neuropsychopharmacology* (2017) **42**, 2633–2639; doi:10.1038/npp.2017.81; published online 31 May 2017

## INTRODUCTION

Patients with schizophrenia (SZ) have deficits in many domains, ranging from early sensory processing to executive function, which contribute to impairments in cognitive and psychosocial functioning (Thomas *et al*, 2017). Neural oscillations in the 30–50 Hz range (centered near 40 Hz and referred to as the ‘gamma band’) appear to reflect a fundamental CNS resonance frequency that is critical for communication across multiple brain regions (Traub *et al*, 1996). Gamma-band oscillations are transiently generated during a wide range of cognitive operations such as sensory discrimination, learning, and memory—all domains in which many SZ patients have deficits (for reviews, see Ford and Mathalon, 2008; McNally and McCarley, 2016; Salisbury *et al*, 2017; Spencer *et al*, 2004).

In recent years, the response to auditory steady-state stimulation measured in the electroencephalogram (EEG) has emerged as a leading candidate biomarker of disease process, therapeutic effect, and the capacity of neural circuits to support gamma-band oscillations under ‘optimized’

(ie, stimulus-driven) conditions (O'Donnell *et al*, 2013; Sun *et al*, 2011; Light *et al*, 2006; Kirihara *et al*, 2012). In this auditory steady-state response (ASSR) paradigm, clicks or amplitude-modulated tones are presented at a rate of 40 Hz; the resulting stimulus-driven gamma power and phase synchronization in the EEG is thought to reflect the capacity of the auditory system to generate oscillations in synchrony with the stimuli. As described in Thuné *et al* (2016), 20 studies have assessed ASSR dynamics in SZ patients using a variety of stimulation and analytic procedures; 17 of these studies identified impairment in both evoked power and phase synchronization. Notably, many of these studies also identified significant correlations between ASSR oscillatory dynamics and clinical symptoms (eg, auditory hallucinations: Hirano *et al*, 2015) and cognitive test performances (eg, working memory: Light *et al*, 2006; verbal learning: Kirihara *et al*, 2012).

While the neural mechanisms of ASSR remain unclear, the involvement of parvalbumin-positive GABAergic basket interneurons and the pyramidal cells of the upper layers of sensory cortex is well documented (review Featherstone *et al*, 2015; Sivarao *et al*, 2016). Within the circuitry, *N*-methyl-D-aspartic acid (NMDA) receptor function appears to be critical for EEG synchronization in the gamma frequency range. NMDA hypofunction is implicated in the pathophysiology of SZ (Javitt, 2012), and NMDA antagonists have been shown to modulate ASSR in a dose-dependent manner

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in preclinical studies (Hiyoshi *et al*, 2014). NMDA antagonists also augment the 40 Hz ASSR response in rodents expressing a SZ-linked phenotype (Phillips *et al*, 2012). While animal models of SZ suggest the feasibility of pharmacologically regulating ASSR in patients with SZ via drugs acting at NMDA receptors, few studies have addressed the effect of NMDA alterations on ASSR in human subjects, none involving patients with SZ.

Memantine (MEM) is an uncompetitive NMDA receptor antagonist, with low affinity but rapid blocking and unblocking ability; its minimal impact on basal NMDA transmission distinguishes it mechanistically from other NMDA antagonists (Lipton, 2006). Its main clinical indication is Alzheimer's disease, however, it has positive activity in 'cognitive' measures in both healthy animals and a range of animal models, including those for dementia, depression, ischemia, and neuroinflammation (cf. Ma *et al*, 2015). While its mechanism of therapeutic action remains unclear, MEM enhances hippocampal long-term potentiation (LTP), and reverses the loss of LTP under various experimental conditions; it also alters excitation/inhibition (E/I) dynamics in frontal circuitry implicated in models of SZ neuropathology (Povysheva and Johnson, 2016).

We previously demonstrated that MEM enhanced sensorimotor gating—as measured by prepulse inhibition (PPI) of startle—and mismatch negativity (MMN) in patients with SZ and healthy comparison subjects (HS) (Swerdlow *et al*, 2016). These two measures index pre-attentive information processing and are each positively associated with both neurocognition and daily life functioning (Giakoumaki *et al*, 2006; Light *et al*, 2007; Swerdlow *et al*, 2006; Thomas *et al*, 2017; Rissling *et al*, 2014). Here we report findings of ASSR measures in these subjects, after acute administration of MEM (20 mg, p.o.) or placebo in a double-blind, within-subject cross-over design.

## MATERIALS AND METHODS

All procedures were approved by the UCSD Human Subject Institutional Review Board. Participants were 18–50-year-old adult HS and patients with a clinically stable chronic psychotic disorder (SZ,  $n=17$ ; schizoaffective disorder, depressed,  $n=1$ ) who met the inclusion criteria for this study (Table 1).

Subjects who passed a phone checklist were invited for an in-person screening session that included an urine toxicology test, hearing test (Saico Audiometer, Assens Denmark), a startle reflex test to confirm adequate reflex magnitude, and questionnaires related to demographic and clinical information (Table 2). Diagnoses in CPD patients were confirmed by the MINI International Neuropsychiatric Interview (6.0) (Sheehan *et al*, 1998), and symptom severity was assessed with the positive and negative syndrome scale (Kay *et al*, 1987). Participants who met the study inclusion criteria returned for testing after 6–10 days, and for a second test 7 days later. Testing followed a double-blind, placebo-controlled, pseudo-randomized balanced drug order design. CPD subjects maintained their medication doses during the study. Subjects arrived at ~0830 on the test day, ate a standardized breakfast, and completed urine toxicology and hearing tests. At 0900, MEM HCl (20 mg) or placebo was

**Table 1** Demographic and Clinical Characteristics of Participants

	Healthy subjects	Schizophrenia patients
Age (mean, range)	26.64 (19–36)	37.22 (21–48) <sup>a</sup>
M:F	10:4	11:7
Smoke: non-smoker	0:14	7:11 <sup>b</sup>
WRAT reading (mean, SEM)	103.89 (3.99)	93.78 (2.52) <sup>b</sup>
GAF (mean, SEM)	—	56.89 (1.10)
Illness duration (mean, range)	—	21.18 (6–34)
Chlorpromazine equiv (mean, SEM)	—	586.73 (122.43)
Anticholinergic equiv (mean, SEM)	—	8.28 (1.78)
PANSS		
Positive		17.56 (1.10)
Negative		17.39 (1.85)
General		31.00 (2.45)

<sup>a</sup>Significant group differences ( $p < 0.01$ , two-tailed).

<sup>b</sup>Significant group differences ( $p < 0.05$ , two-tailed).

administered (p.o.) in either healthy controls or SZ patients. An initial group of patients and HS were tested with a lower MEM dose (20 mg); however, as previously reported (Swerdlow *et al*, 2016), this lower dose produced no measurable changes in subjective ratings, autonomic measures, PPI, or MMN, and this inactivity was confirmed for ASSR measures (no significant MEM main or interaction effects in the 10 mg group were detected with any ASSR parameters). Since the 10 mg dose appears to be inert in all of our laboratory measures, only data from the 20 mg dose group are presented here. At 1130, subjects received a standardized lunch.

Neurophysiological measures were timed to coincide with peak blood levels of MEM after a single oral dose of 20 mg (Sonkusare *et al*, 2005). Startle testing began 210 min after pill administration, and 345 min post-pill, MMN testing commenced; findings from both PPI and MMN measures were reported previously (Swerdlow *et al*, 2016). ASSR measures followed immediately after MMN testing, beginning about 385 min post-pill.

The ASSR paradigm utilized 1 ms, 85 dB clicks presented in 500 ms trains at a frequency of 40 Hz. A total number of 250 click trains were played with an inter-train interval of 0.5 s. The auditory stimuli were delivered through insert earphones. Participants were instructed to ignore auditory stimuli while staring at a fixation cross at the center of the screen. The ASSR recording lasted approximately for 4 min (Supplementary Figure 1).

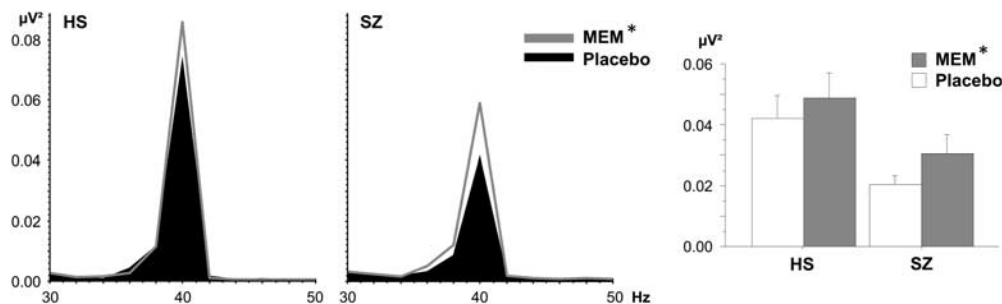
Electroencephalographic (EEG) data were continuously recorded with a 64-channel BioSemi ActiveTwo system at a sampling rate of 2048 Hz. Data processing was performed offline using Matlab, EEGLab, and BrainVision Analyzer and as per established methods (Kirihaara *et al*, 2012; Light *et al*, 2006). Briefly, an averaged reference was applied to the EEG recordings; vertical and horizontal eye movement artifacts were corrected using the independent component analysis. Continuous data were then segmented relative to the onset of

**Table 2** Significant Relationships were Detected between MEM Effects on Gamma Evoked Power and Phase Locking and Age in Schizophrenia Patients (Supplementary Figures 2); by Including Data Previously Reported from Measures of Mismatch Negativity and Prepulse Inhibition (Swerdlow et al, 2016), Significant Relationships were also Evident between MEM Effects on  $\gamma$ EP and MMN and Between  $\gamma$ PL and PPI

	Age	MEM effect on $\gamma$ EP	MEM effect on $\gamma$ PL	MEM effect on MMN
MEM effect on $\gamma$ EP	-0.71 <sup>a</sup>			
MEM effect on $\gamma$ PL	-0.63 <sup>a</sup>	0.74 <sup>a</sup>		
MEM effect on MMN	-0.56 <sup>b</sup>	0.54 <sup>b</sup>	0.26	
MEM effect on PPI	0.54 <sup>b</sup>	-0.51	-0.59 <sup>b</sup>	-0.70 <sup>a</sup>

<sup>a</sup>Significant correlation ( $p < 0.01$ , two-tailed). Memantine effects on  $\gamma$ EP and  $\gamma$ PL were greater among younger patients (Supplementary Figures 2 and 3); pattern was previously reported for MMN, while the opposite pattern (greater memantine effects among older patients) was reported for PPI (Swerdlow et al, 2016).

<sup>b</sup>Significant correlation ( $p < 0.05$ , two-tailed).



**Figure 1** Gamma evoked power (EP) in healthy subjects (left) and schizophrenia patients (right) in placebo (black) and 20 mg MEM (red) conditions. In the placebo condition, schizophrenia patients show significant reductions in EP relative to healthy subjects, consistent with previous reports. \*MEM significantly increases EP in both groups; in schizophrenia patients, MEM increased EP to levels that did not differ statistically from healthy subjects after placebo ( $F = 1.54$ ,  $df 1,30$ , NS). A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

the stimuli (-100 ms to 500 ms), and each epoch was baseline-corrected relative to the 100 ms pre-stimulus interval. Epochs containing  $\pm 70 \mu\text{V}$  were automatically rejected.

Gamma evoked power ( $\gamma$ EP) and phase locking ( $\gamma$ PL) were assessed based on the first 100 artifact-free epochs at Fz. For  $\gamma$ EP analyses, the averaged epochs across the click trains were transformed into power spectrum by means of fast Fourier transform (FFT) using a bin width of 2 Hz. The 40 Hz power spectrum was averaged across 4 Hz band from 38 to 42 Hz.

$\gamma$ PL was calculated on wavelet coefficients obtained from Morlet wavelet transformation of the segmented data (frequencies represented from 5 to 95 Hz, with a total number of 45 frequency layers);  $\gamma$ PL was estimated by extracting and averaging across the 30–50 Hz frequency layer.  $\gamma$ PL quantifies consistency of oscillatory phase across individual trials, ranging from 0 (purely non-phase-locked activity) to 1 (fully phase-locked activity). For statistical analyses, mean values were obtained for each of the six 100 ms windows from -100 to 500 ms relative to stimulus onset.

Symptom rating scales (SRS) were assessed before, and 30, 90, 150, 200, and 230 min after pill consumption, as previously described (eg, Swerdlow et al, 2009; see Supplementary Methods for details).

Data were analyzed by RM-ANOVA, with diagnosis as a between-subject factor, and drug condition (placebo vs active) as a within-subject factor for measures of  $\gamma$ EP and  $\gamma$ PL. Initial analyses revealed robust and time bin-independent effects of diagnosis and drug across the 200–500 ms stimulation window, and thus this interval was

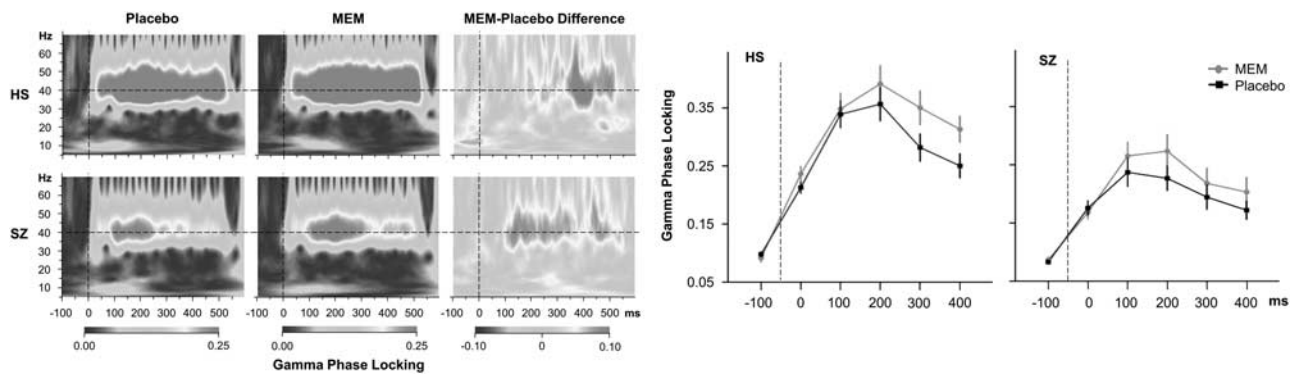
the focus of all subsequent analyses, including correlations with clinical and experimental variables. SRS and autonomic measures were continuous variables and analyzed by ANOVA as ‘change scores’ (difference from pre-pill baseline). These change score calculations of MEM effects on MMN were scaled so that positive values indicate greater MEM effect, consistent with  $\gamma$ EP,  $\gamma$ PL, and PPI.

Study recruitment did not balance groups for sex, age, or medication status, but where possible, these variables were examined *post hoc* to determine their potential impact on MEM effects. Age-matched subgroups of patients and HS were formed using the 10 youngest patients and the 10 oldest HS. Drug order (placebo test 1 vs active test 1) was also assessed as a potential moderator of drug effects. For all statistical comparisons, alpha was 0.05 for two-tailed contrasts and 0.10 for one-tailed contrasts.

## RESULTS

Demographic and clinical characteristics of the final cohort are shown in Table 1. Most (16/18) patients were taking atypical antipsychotics (APs), one was taking only typical APs and one was unmedicated at the time of testing. On average, patients were significantly older than HS ( $p < 0.0001$ ).

Analyses of autonomic measures revealed no significant main or interaction effects of diagnosis or MEM dose on change in heart rate, diastolic or systolic blood pressure. SRS data generally yielded no meaningful main or interaction effects. Thus, consistent with our past experience, MEM



**Figure 2** Gamma phase locking (PL): time-frequency plots in healthy subjects (top row) and schizophrenia patients (bottom row) during placebo (left panel), 20 mg MEM (middle panel), and MEM-placebo difference (right panel). The x axis indicates time in ms and the y axis indicates frequency. Color indicates phase locking factors. The right panel shows mean gamma PL in healthy subjects (left) and schizophrenia patients (right) during placebo (black) and 20 mg MEM (red) across 100 ms time bins from  $-100$  to  $500$  ms. In the placebo condition, schizophrenia patients show significant reductions in PL relative to healthy subjects, consistent with previous reports. MEM significantly increases PL in both groups; in schizophrenia patients, MEM increased PL to levels that did not differ statistically from healthy subjects after placebo ( $F = 3.21$ ,  $df$  1.30, NS). A full color version of this figure is available at the *Neuropsychopharmacology* journal online.

(20 mg p.o.) had minimal effects on autonomic and subjective measures (Swerdlow *et al*, 2016; Bhakta *et al*, 2016).

RM-ANOVA revealed that patients with SZ had significantly reduced  $\gamma$ EP (Figure 1) and  $\gamma$ PL (Figure 2), consistent with previous reports (main effect of diagnosis— $\gamma$ EP:  $F = 5.89$ ,  $df$  1.30,  $p < 0.025$ ;  $\gamma$ PL:  $F = 11.83$ ,  $df$  1.30,  $p < 0.002$ ). This effect on phase locking was independent of time bins (diagnosis  $\times$  bin interaction:  $F = 1.62$ ,  $df$  2.60, NS; Figure 2), and was evident with subgroups of age-matched HS and patients ( $p < 0.025$ ). MEM significantly enhanced  $\gamma$ EP and  $\gamma$ PL in both SZ patients and HS (main effects of drug— $\gamma$ EP:  $F = 6.40$ ,  $df$  1.30,  $p < 0.02$ ;  $\gamma$ PL:  $F = 10.42$ ,  $df$  1.30,  $p < 0.004$ ). There was no significant interaction of diagnosis  $\times$  drug for either  $\gamma$ EP or  $\gamma$ PL (both  $F$ 's  $< 1$ ), suggesting that MEM effects on these measures were not specific for diagnosis.

MEM effects on both  $\gamma$ EP and  $\gamma$ PL were independent of test order (both drug  $\times$  test order interactions NS) and were also significant when groups were matched for age as above (main effects of drug:  $p$ 's  $< 0.007$  and  $0.003$ , respectively). While group differences in MEM-associated enhancement of  $\gamma$ EP and  $\gamma$ PL were evident when groups were age-matched, the magnitudes of MEM effects on both of these measures (difference score: MEM minus placebo) were significantly and negatively correlated with age in SZ patients ( $r$ 's =  $-0.71$  and  $-0.63$ ;  $p$ 's  $< 0.0015$  and  $0.005$ , respectively). Greater MEM sensitivity in younger patients reproduces the pattern previously detected for MMN, while the opposite pattern (greater MEM sensitivity in older patients) was previously reported for PPI (Table 2, Supplementary Figures 2); (Swerdlow *et al*, 2016). This MEM effect difference score in patients did not correlate significantly with other clinical measures, including age of illness onset, symptom severity, chlorpromazine equivalents, or estimated level of anticholinergic activity.

## DISCUSSION

In this study, a single 20 mg dose of MEM significantly increased gamma evoked power and phase synchronization in patients with SZ and HS. Preclinical studies have shown that MEM enhances spontaneous gamma power in rodents via a linear, positive dose-response effect; by contrast, other NMDA antagonists—PCP, ketamine, and MK801—exhibit inverted-U dose-response functions with respect to spontaneous gamma power in rodents, and also adversely impact other frequency bands (Hiyoshi *et al*, 2014).

Several studies have linked higher levels of early auditory information processing (EAIP), including gamma power and phase locking, with better clinical and functional outcomes in SZ patients (Light *et al*, 2006; Kirihara *et al*, 2012; Thomas *et al*, 2017). On the basis of these reports, the simplest interpretation of the present findings—and those of MEM-enhanced PPI and MMN previously published by our group (Swerdlow *et al*, 2016)—might suggest that MEM should have clinical and functional benefits in SZ patients. Studies of MEM effects on neurocognition and symptoms in SZ, however, have yielded conflicting results.

One large study (Lieberman *et al*, 2009) reported 'negative' effects of MEM in SZ patients: an 8-week double-blind, randomized clinical trial (RCT) of MEM (20 mg/d;  $n = 70$ ) vs placebo ( $n = 68$ ) added to atypical APs found no change in positive or negative symptoms or brief assessment of cognition in SZ scores. Unfortunately, this early 'negative' study has shaped much of the field's view of MEM as a non-efficacious adjunct to antipsychotics in SZ. At least six placebo-controlled studies and several large open-label reports, however, have demonstrated benefits of MEM in SZ. A 12-week double-blind RCT of MEM vs placebo added to existing antipsychotics ( $n = 64$ ) (Omranifard *et al*, 2015) found enhanced function and life quality in both groups, with significantly greater gains in the MEM group ( $p$ 's  $< 0.001$ ). Another placebo-controlled double-blind 12-week cross-over study of MEM effects in clozapine-refractory SZ patients ( $n = 52$ ) found significant gains in cognition and symptoms, with further symptom improvement by 26 and 52 weeks (Veerman *et al*, 2016a,b). A PBO-

controlled double-blind 12-week trial of MEM ( $n=18$ ) vs placebo ( $n=18$ ) added to antipsychotics found significant benefits of MEM over placebo for negative symptoms ( $p=0.003$ ) and Mini-Mental State Exam (MMSE;  $p<0.001$ ) (Mazinani *et al*, 2017). An 8-week double-blind placebo-controlled study of MEM added to risperidone in 40 SZ patients reported significant MEM-associated improvement in negative symptoms ( $p<0.001$ ) (Rezaei *et al*, 2013). Another double-blind study found large reductions in positive and negative symptoms ( $d=1.38-3.33$ ) and improved MMSE after 12 weeks of MEM (20 mg/d;  $n=10$ ) vs placebo ( $n=11$ ) added to clozapine (de Lucena *et al*, 2009). A smaller, 6-week, open-label study of MEM (5–20 mg/d) in SZ inpatients reported significant improvement in positive and negative symptoms but not cognition (Krivoy *et al*, 2008). A chart-based retrospective case series found improved positive and/or negative symptoms as well as cognitive and/or functional domains in 17 out of 26 SZ patients when MEM was added to an antipsychotic (John *et al*, 2014); in several patients, antipsychotic dose requirements also declined with MEM. Many case reports describe symptom reduction and function gains after MEM (5–20 mg/d) in SZ patients; in some, symptoms returned when MEM was stopped and resolved after MEM was restarted (Zdanys and Tampi, 2008; Matsuda *et al*, 2013; Paraschakis, 2014).

Importantly, none of the above studies utilized this putative pro-cognitive agent in concert with any systematic cognitive intervention, nor were any specific biomarkers employed to predict sensitive subgroups of patients. Both of these factors—the use of a contemporaneous cognitive intervention to engage the MEM-induced information processing gains, and the use of predictive biomarkers to identify patients with a ‘MEM-sensitive’ phenotype—might be important considerations in future therapeutic models with MEM and other putative pro-cognitive therapeutics in SZ, as described in previous reports from our group (Swerdlow, 2011; Light and Swerdlow, 2014; Swerdlow *et al*, 2016; Swerdlow *et al*, in press; Perez *et al*, in press).

In considering the relationship between acute MEM-enhanced EAIP and the potential benefits of MEM in SZ therapeutics, two other issues are quite relevant. First, acute MEM does not enhance neurocognition in SZ patients (Bhakta *et al*, 2016). Thus, there is a dissociation between the immediate EAIP-enhancing effects of MEM and its impact on neurocognition. Certainly, this dissociation could reflect deleterious acute effects of a single 20 mg dose of MEM on neurocognition (NB: not detected in Bhakta *et al*, 2016), which might wane with repeated administration, especially via a gradual titration from lower to higher doses. Alternatively, the mechanisms of MEM-enhanced EAIP may be such that gains in neurocognition would be predicted as a later but not immediate consequence, much like the impact of a hearing aid on speech development in a pre-verbal hearing-impaired child. In other words, we hypothesize that the lack of immediate MEM-enhanced gains in neurocognition reflects the acute nature of this measurement (4–6 h post-MEM) vs the time and experience required in order for enhanced EAIP and subsequent improvements in higher-order auditory processing (eg, speed and fidelity) to produce changes in neurocognition and its underlying forebrain substrates. A second issue, however, is that we

cannot assume that EAIP-enhancing effects of MEM—evident after a single dose—would be sustained with long-term daily MEM dosing. To address this issue, we are currently pursuing measures of EAIP during sustained MEM administration in SZ patients.

Another important but unanswered question is whether acute EAIP-enhancing effects of MEM can serve as a biomarker predicting later clinical benefits of MEM. Clearly, if MEM acutely increases gamma power and phase locking in a specific SZ patient, this suggests that MEM is accessing neural mechanisms associated with cortical oscillatory dynamics in a way that ‘normalizes’ these processes. Such evidence of ‘neuroactivity’ suggests that this individual might be more sensitive to the potential salutary effects of MEM, compared, for example, to an individual in whom MEM produces no brain ‘signal’.

The present findings also underscore potential heterogeneity in the MEM ‘brain signal’ in SZ patients, which may be quite relevant to its use as a predictive biomarker. While MEM ‘normalizes’ four different EAIP measures, these effects are not uniform within any individual patient: strong positive correlations are evident among MEM-induced changes in MMN and gamma power, and strong negative correlations are evident between PPI and MMN (Swerdlow *et al*, 2016) and between PPI and gamma phase locking (present study). Furthermore, MEM-enhancement of MMN, gamma power, and phase locking are negatively associated with patient age, while MEM-enhanced PPI is positively associated with patient age. It is thus conceivable that MEM might have differential effects on brain function in SZ patients as a function of age, illness duration, or baseline deficits in different forms of EAIP. Our group also reported preliminary evidence for an association between MEM effects on both PPI and neurocognition, and a single-nucleotide polymorphism in the gene encoding the glutamate ionotropic receptor subtype 3 A (rs1337696; Bhakta *et al*, 2016). Others have reported an association between MEM sensitivity in humans and rodents, and genetic variations in glutamate ionotropic receptor subtypes 2 A and 2D (GRIN2A, GRIN2D) (Lesca *et al*, 2013; Li *et al*, 2016; Pierson *et al*, 2014). Thus, genes regulating glutamate receptor function may also help predict a therapeutic response to MEM in SZ patients.

Results of this study should be considered in the context of several limitations. First, psychotropic medications were not experimentally controlled. As in many studies of SZ, patients were prescribed heterogeneous and complex medication regimens that included medications that could impact biomarker sensitivity to acute MEM effects. Second, sample size was modest. The small number of subjects prevents us from disentangling medications, genes, and demographic factors (eg, age) that may contribute to individual variability in ASSR parameters. Third, only a single active dose of MEM was reported here. In fact, we previously reported that a lower MEM dose (10 mg, p.o.) produced no measurable changes in any measures, including subjective ratings, autonomic measures, PPI, or MMN (Swerdlow *et al*, 2016). Indeed, initial tests of the present gamma-band measures with 10 mg MEM also detected no evidence of bioactivity, and including those subjects in the present analyses yielded results leading to the identical conclusions reported here: that the higher dose of MEM (20 mg) significantly enhanced

gamma-band measures in patients and HS. Fourth, patients were, on average, significantly older than healthy subjects. Despite this fact, patient deficits in gamma-band responses were still detected in subgroups carefully matched for age; with the broader age range among patients, it was possible to detect important age-related MEM effects on gamma-band responses.

Finally, it is worth considering the neural mechanisms that underlie acute MEM-induced increases in gamma power and phase locking. Thus, enhanced gamma power and phase locking might reflect gains in the speed and/or fidelity of auditory processing based on MEM effects at levels ranging from the brain stem (Tarasenko *et al*, 2014) up to thalamo-cortical projections, and many interceding loci. We are beginning to probe the relationship of signal fidelity at these different levels of auditory processing and neurocognitive gains in SZ (Rackelmann *et al*, 2016; Perez *et al*, 2017; Thomas *et al*, 2017). Identifying the mechanisms, or at least the neural locus (loci), of MEM-enhanced EAIP in SZ might have important implications both for our understanding of the role of NMDA function in the pathophysiology of SZ and for the development of future therapeutics (Light and Swerdlow, 2014, 2015a,b).

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