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Memantine effects on EEG measures of putative excitatory/inhibitory balance in schizophrenia

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Abstract

BACKGROUND—Abnormalities in cortical excitation and inhibition (E/I) balance are thought to underlie sensory and information processing deficits in schizophrenia (SZ). Deficits in early auditory information processing (EAIP) mediate both neurocognitive and functional impairment, and appear to be normalized by acute treatment with the NMDA antagonist, memantine (MEM).

METHODS—Thirty-six subjects with a diagnosis of schizophrenia and 31 control subjects (NCS) underwent EEG recordings. Subjects ingested either placebo or MEM (10 or 20 mg) in a double-blind, within-subject cross-over randomized design. The aperiodic, 1/f-like scaling property of the neural power spectra, which is thought to index relative E/I balance, was estimated using a robust linear regression algorithm.

RESULTS—SZ patients had greater aperiodic components compared to NCS ($p<.01$, $d=.64$), which was normalized after 20 mg MEM. Analysis revealed a significant dose x diagnosis interaction ($p<.0001$, $d=.82$). Further, the "MEM effect" (change in aperiodic component in MEM vs. placebo conditions) was associated with baseline attention and vigilance ($r=.54$, $p<.05$) and MEM-induced enhancements in gamma power ($r=-.60$, $p<.01$).

CONCLUSIONS—Findings confirmed E/I balance abnormalities in SZ that were normalized with acute MEM administration and suggest that neurocognitive profiles may predict treatment response based on E/I sensitivity. These data provide "proof-of-concept" evidence for the utility of E/I balance indices as metrics of acute pharmacologic sensitivity for central nervous system therapeutics.

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Keywords

excitation/inhibition balance; electroencephalography; early auditory information processing; memantine; cognition; schizophrenia

Introduction

Neurocognitive deficits are core pathophysiologic dimensions of chronic psychotic disorders (1,2). While psychotic symptoms fluctuate over the disease course, cognitive symptoms are pervasive and are refractory to conventional treatment modalities. Moreover, cognitive symptoms mediate the degree of functional impairment, disability, and clinical course in chronic psychotic disorders (3–5). Despite the pervasiveness of cognitive impairments, the biology underlying these cognitive deficits remains unclear and there are no reliable biomarkers that can be used to predict response to novel therapeutics.

Converging evidence from preclinical and translational studies suggest that disruptions in cortical NMDA receptor signaling in schizophrenia (SZ) affect the large scale spatial and temporal organization of excitation and inhibition (E/I) in neural networks that mediate cognition and behavior (6,7). In addition to the distributed effects of cortical NMDA hypofunctioning, GABA-ergic interneuron signaling also appears to be profoundly affected in SZ. Postmortem studies in SZ have consistently demonstrated an abnormal pattern of expression of GABA signaling molecules in interneuron populations across cortical structures (8–10). These disruptions in both excitatory and inhibitory signaling are thought to underlie the pathological cognitive and perceptual states associated with SZ and other neuropsychiatric disorders (11–14).

The merging of computational models of E/I balance with experimental approaches has provided novel insights into the hierarchical organization of neural networks (15–18). Yet, the study of E/I balance as it relates to human cortical physiology and neural network dynamics is in its relative infancy. Traditional measures of E/I balance often require invasive methods, such as single-unit or voltage-clamp recordings in rodents and/or non-human primates (19–21), which have precluded their application to *in vivo* human studies. Recent findings suggest that the aperiodic, *1/f*-like component of the neural power spectra may index tonic E/I balance and can be studied non-invasively using electroencephalographic (EEG) recordings. Interestingly, this aperiodic component is dynamically modulated by conscious and perceptual states (22–25), and preliminary findings suggest that it may be also be altered in SZ (26).

One way to explicate the biology underlying the E/I balance and its potential abnormalities in SZ is to assess changes in E/I balance in response to pharmacologic probes. Previous studies from our group demonstrated that the NMDA receptor antagonist, memantine

(MEM), “normalized” EEG measures of early auditory information processing (EAIP) (27,28), which have been shown to mediate neurocognition in schizophrenia (3). Preclinical studies suggest that MEM can also “normalize” pathological E/I tone (29,30). We hypothesized: 1) that the aperiodic, 1/f-like scaling properties of the EEG power spectrum would be disrupted in patients with SZ, consistent with an aberrant E/I balance; and 2) that aberrant E/I balance in SZ would also be “normalized” by acute exposure to MEM. The present study was designed to test this hypothesis, by applying a novel signal processing algorithm to EEG recordings acquired during EAIP testing described in previous reports (27).

Methods and Materials

Participants, assessments, and experimental design

All procedures were approved by the UCSD Human Subject Institutional Review Board. Detailed descriptions of the recruitment and ascertainment methods were reported previously (27). Briefly, sixty-seven adults (with a diagnosis of a chronic psychotic disorder (SZ, n=36) or normal comparison subject (NCS, n=31) participated in the study. All subjects underwent baseline screening with demographic and clinical questionnaires, hearing tests, and urine toxicology. Neurocognitive functioning was assessed with the MATRICS Consensus Cognitive Battery. Diagnosis of SZ was confirmed with the MINI International Neuropsychiatric Interview and symptom severity was assessed with the positive and negative syndrome scale. Participants who met inclusion criteria were tested on two days separated a week apart in a double-blind, placebo-controlled, pseudo-randomized balanced drug order design where MEM HCl (10 or 20 mg) or placebo (PBO) was administered (p.o.). Testing of experimental measures was timed to coincide with peak blood levels of MEM in healthy subjects (31); sensorimotor gating (prepulse inhibition, “PPI”) was tested 210 min after pill administration and EEG measures were recorded about 345 min post-pill. Detailed methods of these measures were previously described (27,28).

EEG data acquisition and processing

A passive auditory oddball paradigm comprised of standard (50-ms, 1000-Hz) and deviant stimuli that differed from the standard in duration (125-ms, 1000-Hz), pitch (50-ms, 1100-Hz), or both pitch and duration (125-ms, 1100-Hz). Stimuli were presented in a pseudo-randomized sequence as per previous reports (27). EEG data were continuously recorded from 64 channels using a BioSemi ActiveTwo system at a sampling rate of 2048-Hz, which was downsampled offline to 512-Hz. Data processing was performed offline using MATLAB, EEGLAB, and BrainVision Analyzer and as per established protocols (27,28,32,33). Briefly, vertical and horizontal eye movement artifacts were corrected using independent component analysis (34). Continuous data were segmented at 500 ms epochs relative to the stimulus onset and each epoch was baseline-corrected relative to the 100 ms pre-stimulus interval. Epochs containing ± 70 μV were automatically rejected. All artefact-free epochs from all stimulus types were included in our analyses of aperiodic slopes and spectral parameters. Mismatch negativity (MMN) was calculated as the mean amplitude from the 135–205 ms range on the difference waveform between deviant and standard tones at electrode FZ and was averaged across all deviant types as previously reported (27).

Analysis of aperiodic and periodic spectral features

EEG signals were decomposed into their frequency-domain components via power spectral density (PSD) estimation using Welch's method. PSDs from the 4–50 Hz range were used to characterize the aperiodic "background" or 1/f-like signal and oscillatory components using a robust linear regression algorithm (35). Additional measures of oscillatory power were derived to better characterize the drivers of the aperiodic signal and putative shifts in E/I balance. The algorithm treated PSDs as the linear sum of the aperiodic component in log-log space and modeled the superimposed oscillatory peaks (i.e., regions of the power spectrum rising above the aperiodic background signal) as Gaussian functions. The peak oscillatory amplitudes (the distance between the peak of the Gaussian and the aperiodic fit) represent the oscillatory power of the EEG signal at that given frequency band. The oscillatory peaks were then iteratively modeled and removed from the signal, providing a robust approximation of the aperiodic, *1/f*-like slope. The aperiodic, *1/f*-like slope, and oscillatory components of the EEG power spectra were calculated from trial-by-trial PSDs, generating spectral estimates for all stimulus types (standard and deviants), which were then averaged across all electrodes.

Statistical analysis

Linear mixed effects models were used to analyze the relationships between aperiodic slope, oscillatory power, and MEM in our sample. Dependent variables were regressed onto contrast-coded diagnosis, dose (0, 10, 20), and stimulus types, as well as interaction terms modeled as fixed effects. All models included centered fixed effects and random intercepts for subjects. Additionally, we provide complementary estimates of effects size (Cohen's d) to help clarify effects of diagnosis and interactions (calculated using MEM minus PBO difference scores, henceforward referred to as the "MEM effect"). Note: aperiodic slope and oscillatory power responses to standard vs. deviant stimuli did not interact significantly with diagnosis or dose in linear mixed models; hence, spectral features were averaged across stimulus type and electrodes in "MEM effect" analyses. To further characterize the clinical and physiologic implications of the "MEM effect" on EEG spectral features, we assessed their relationships to: 1) MEM effects on traditional measures of EAIP (MMN and PPI); and 2) demographic, clinical, and cognitive measures in SZ patients. Statistical analysis were implemented using the "*lme4*" package in R (36) and the "*statsmodels"* package in Python (37).

Results

Demographic, clinical and neurocognitive assessments

Demographic and clinical characteristics of the sample were previously reported (27) and are summarized in Table 1. NCS participants were significantly younger compared to SZ patients (t=4.28, p<.001), although age was not significantly different between SZ dose groups (10 vs. 20 mg: t=.50, p>.5). Age did not significantly contribute to any statistical model in *post hoc* analyses; therefore, it was not included in the linear mixed effects analyses reported below.

Despite careful randomization for key demographic variables, there was a modest cohort effect on baseline measures of PANSS Positive (t=2.9, p<.01), PANSS General Psychopathology (t=2.6, p<.05), and PANSS Total Symptoms (t=2.7, p<.05) in the 10 vs. 20 mg dosage groups (Table 1). The effects of these phenomenological differences were analyzed *post hoc;* none contributed significantly to the analyses of the primary dependent measures when treated as covariates in linear mixed effects models. No other demographic or clinical variables were found to be significantly different between patients, control, or dosage groups.

Relationships between diagnosis, MEM, and the aperiodic signal

SZ patients had greater aperiodic slopes compared to HCS during the PBO condition (Figure 1b; t=2.60, p=.011, d=.64). Figure 1a shows how diagnostic differences in aperiodic slopes manifest on PSDs during the PBO condition. MEM 20 mg "normalized" aperiodic slope differences in SZ relative to NCS and abolished the effect of diagnosis (Figure 1b; t=.25, p=.801, d=.09). Analysis revealed a significant dose x diagnosis interaction (b=0.12, SE=.02, t=−4.92, p<.0001, d=.82) among individuals receiving 20 mg MEM vs PBO. Consistent with previous EAIP studies (26, 27), MEM 10 mg appeared to be inert as contrasts that included MEM 10 mg did not yield significant main effects or interactions. Exploratory analyses did not detect significant associations between aperiodic slope and clinical variables in these SZ patients (Supplemental Table 1). See Supplemental Material for PSD plots during drug conditions and scalp topographies.

Relationships between diagnosis, MEM, and oscillatory power

Since differences in oscillatory power may contribute to E/I balance abnormalities in SZ, we assessed the effects of MEM in canonical frequency bands. Analyses of power bands during the PBO condition revealed diagnostic differences; SZ patients had significantly greater power in theta (t=2.81, p=.006, d=.69) and alpha (t=2.99, p=.004, d=.73) frequency bands and lower gamma power (t=−2.42, p=.018, d=.59) relative to NCS. Among individuals receiving PBO vs. 20 mg MEM, there was a significant dose x diagnosis interaction (Figure 1c) for alpha (b=−.09, SE=.02, t=−3.45, p<.001, d=.51) and gamma (b=.18, SE=.04, t=3.87, p<.001, d=.88) frequency bands.

MEM effects, EAIP measures, and cognition

The parameterization of EEG spectral features is a novel method for extracting meaningful signals from neural power spectra (35). Given our prior reports of the relationships between MEM effects on MMN and PPI (27), we sought to assess the relationships between these EAIP measures and MEM effects on EEG spectral features during the 20 mg condition (which had a significant effect on E/I balance) (Table 2). Interestingly, there was no significant relationship between MEM effect on aperiodic slopes vs. MEM effects on either MMN or PPI. MEM effects on aperiodic slope did correlate significantly with the magnitude of MEM-enhanced spectral gamma power (r=−.60, p=.008), but not with MEM-induced changes in any other frequency band. Further, MEM effects on gamma power were associated with both MMN (r=−.65, p=.005) and PPI (r=.55, p=.043). It is important to note that these correlations do not survive Bonferroni correction for multiple comparisons (α<.002).

Recent findings from our laboratory suggest that MEM-induced gains in specific neurocognitive and sensory measures may be greatest among individuals with low attentional functioning (38). Therefore, we assessed the relationship between attention and MEM effects on aperiodic slopes in this 20 mg patient dose group. MEM effects on aperiodic slope were positively associated with attention and vigilance (Figure 2; r=.54, p=.021); this reflected the fact that MEM had greater "normalizing" effects (slope reduction) in individuals with lower vs. higher baseline attention. The effect of MEM on the spectral parameter did not correlate significantly with other clinical measures, including age of illness onset, symptom severity, chlorpromazine equivalents, or cognitive measures.

Discussion

Despite major advances in psychiatric neuroscience, the pathophysiology of SZ and its associated cognitive impairment remain elusive. This lack of progress is underscored by the dearth of effective therapies for the disabling cognitive symptoms of SZ. While several neuromodulatory systems have been implicated in this disorder, converging lines of evidence point to a fundamental role of cortical glutamatergic dysfunction and a disruption in the dynamic balance of excitation and inhibition in the pathogenesis of SZ (39–41). Yet, the investigations of E/I balance in SZ and its applications to CNS therapeutics have been limited by the invasiveness of electrophysiological measures of E/I and the lack of reliable biomarkers. To this end, the *1/f*-like, aperiodic scaling property of the EEG power spectrum has emerged as a candidate biomarker of cortical E/I balance.

The present findings demonstrate E/I balance abnormalities in SZ patients during auditory information processing as measured by non-invasive electrophysiologic recordings. Specifically, "steeper" aperiodic slopes were detected in patients with SZ relative to NCS during PBO conditions, similar to findings in an independent sample of chronic SZ patients (26). Further, SZ patients had greater power in theta and alpha frequency bands and less power in gamma frequencies relative to NCS, suggesting a possible framework for understanding how deficits in oscillatory dynamics may contribute to E/I balance disturbances.

As hypothesized, MEM had "normalizing" effects on aperiodic slopes in SZ patients. MEM's neurochemical properties are distinct from other NMDA receptor antagonists: it appears to spare physiologic NMDA receptor functioning and its therapeutic effects may involve both glutamatergic and non-glutamatergic targets (42–47). Interestingly, scalp topographies reveal that the 'MEM effect' extends beyond the fronto-central electrodes in both groups, reflecting a bi-frontal aperiodic slope enhancement in NCS and a more distributed slope reduction in SZ (Supplemental Figure 2). These differences in drug effects may be partially explained by MEM's actions on pathological vs. normal functioning brain states. While it is highly speculative, the MEM-induced shift towards higher frequency spectra in SZ patients - particularly those with low baseline attention - may result in greater neurophysiological resources to extract signal from noise, and thereby to more effectively process attentionally-demanding information.

Theoretical and experimental models of SZ posit that NMDA hypofunction at parvalbumin-expressing interneurons leads to disinhibited pyramidal firing and excess cortical excitatory tone or “increased” E/I ratio within local microcircuits. These microcircuit abnormalities exist in the setting of widespread deficits to both “E” and “I”, which likely contribute to variations in E/I balance across different circuits and contexts. In contrast, the present findings of increased aperiodic slopes relative to NCS suggest a “decreased” E/I ratio in SZ patients (48) during passive auditory information processing. These findings should be interpreted from the perspective that aperiodic slopes are a reflection of the autocorrelation structure of PSDs (49) and do not preclude the possibility of regional E/I variations during other task-related paradigms. A “steeper” slope in SZ patients vs. NCS implies tighter temporal correlations, particularly within lower frequencies. Greater aperiodic slopes are also seen in other states where slow waves and greater inhibitory tone (i.e. reduced E/I ratio) predominate, such as sleep and altered states of consciousness where GABAergic tone is explicitly manipulated (50,51). These findings are largely consistent with neural circuit models of cortical dysfunction in SZ (52–55), where disruptions in cortical E/I balance may lead to a state of pathological “overcoupling” (15,56,57). This rigidity in the temporal structure of ongoing neural activity may represent an inability to properly tune responses and discern signal from noise in environmental stimuli (53,54,57,58).

Results of the present study should be considered in light of potential limitations. First, most of our current understanding of E/I balance reflects studies conducted at the level of cellular electrophysiology. By contrast, the current study applies novel signal processing methods to estimate E/I balance based on non-invasive EEG recordings. Scalp electrodes detect the aggregate activity of both excitatory and inhibitory populations from local and distant circuitries; the aperiodic slope does not dissociate the individual contributions of “E” or “I”, rather it represents a theoretical measurement of presumed E/I tone. Future computational and experimental studies are needed to clarify the precise contributions of “E” and “I” to aperiodic slopes.

Second, data were collected while subjects were exposed to passive auditory stimuli. Therefore, the parameterization of aperiodic (background slope) and periodic (oscillatory) spectral features likely reflects both task-evoked and non-task or “resting” features. While linear mixed effect analysis did not detect any differences as a function of stimulus type, future studies are needed to clarify the extent to which task (EAIP-evoked) and non-task (resting state) responses affect the neural power spectrum.

Third, it is possible that group (NCS vs. SZ) differences in E/I balance reflect the impact of antipsychotic medications. All SZ patients in this study were treated with antipsychotics, but no significant relationships were detected between E/I measures and antipsychotic load (chlorpromazine equivalents). Fourth, the present study included clinically stable outpatients with longstanding illness, and thus its findings may not generalize to other patient populations. Fifth, MEM effects on the key dependent measures of E/I balance were evident in the 20 mg dose group, but not the 10 mg dose group, similar to previous findings with MMN, PPI or gamma power and coherence (27,28); conceivably this apparent dose difference may have reflected a cohort effect (i.e. the use of clinically or demographically distinct patients in the 10 vs 20 mg groups). Importantly, none of the group differences in

clinical or demographic variables (Table 1) accounted for the observed differences on MEM effects on E/I balance.

In summary, this study confirms the presence of cortical E/I balance deficits in antipsychotic-treated SZ patients and highlights a novel biomarker of an important construct in psychiatric neuroscience (i.e., “E/I balance”). The findings demonstrate that E/I balance can be transiently normalized in SZ patients with a single dose of MEM. These data provide “proof-of-concept” evidence for the utility of indices of E/I balance as metrics of pharmacologic sensitivity in drug discovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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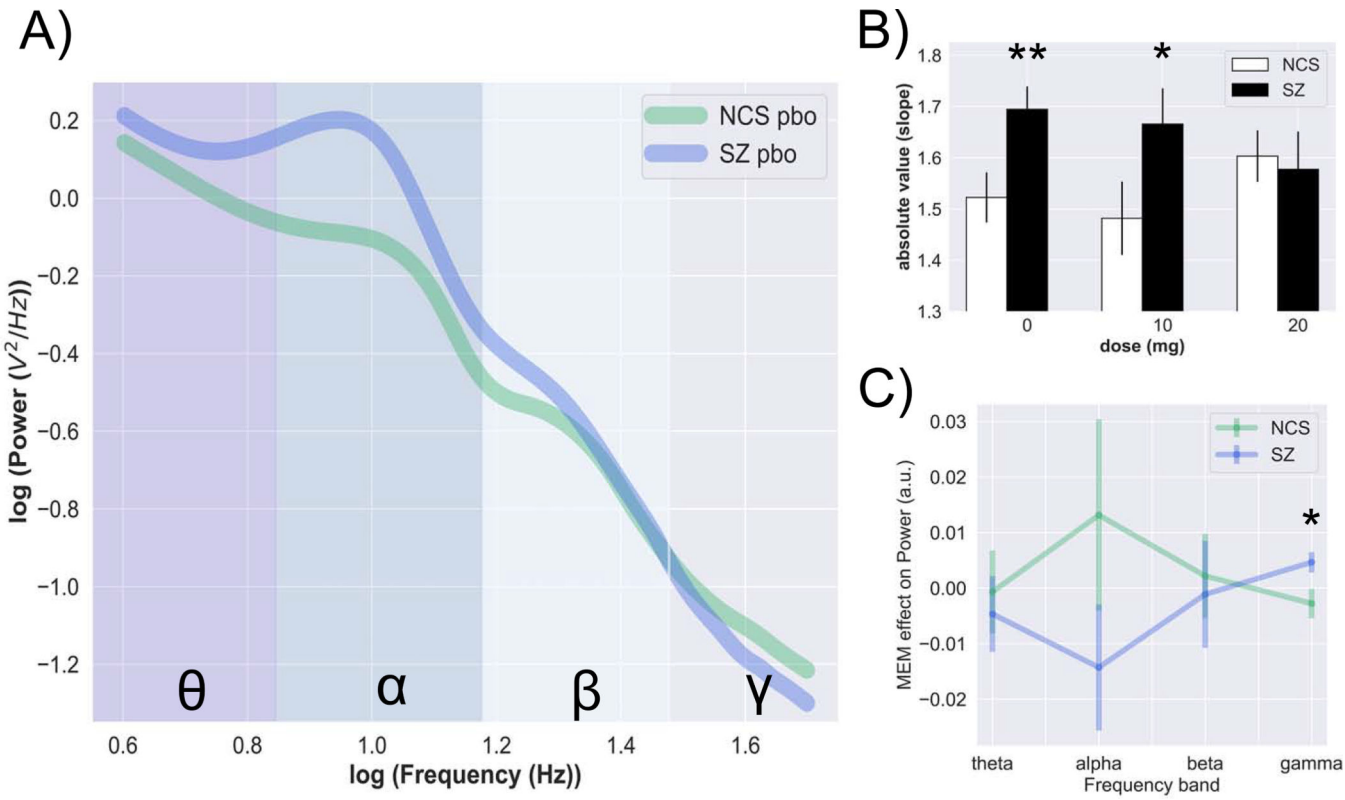

Figure 1.

Aperiodic and periodic features – effects of acute MEM. SZ is characterized by steeper aperiodic slopes relative to NCS, indicative of greater power at lower frequencies. PSD are presented in log-log space; color-coded region represent canonical frequency bands as follows: theta (dark grey, 4–8 Hz), alpha (blue, 8–12 Hz), beta (light blue, 12–30 Hz), gamma (light grey, 30–50 Hz) (a). Acute dose of MEM 20 mg had a "normalizing" effect on aperiodic slopes (b). The "memantine effect" was more pronounced at gamma frequencies (c). Data are presented as mean ± SEM. Note: $^{**}p < .01$, $^{*}p < .05$.

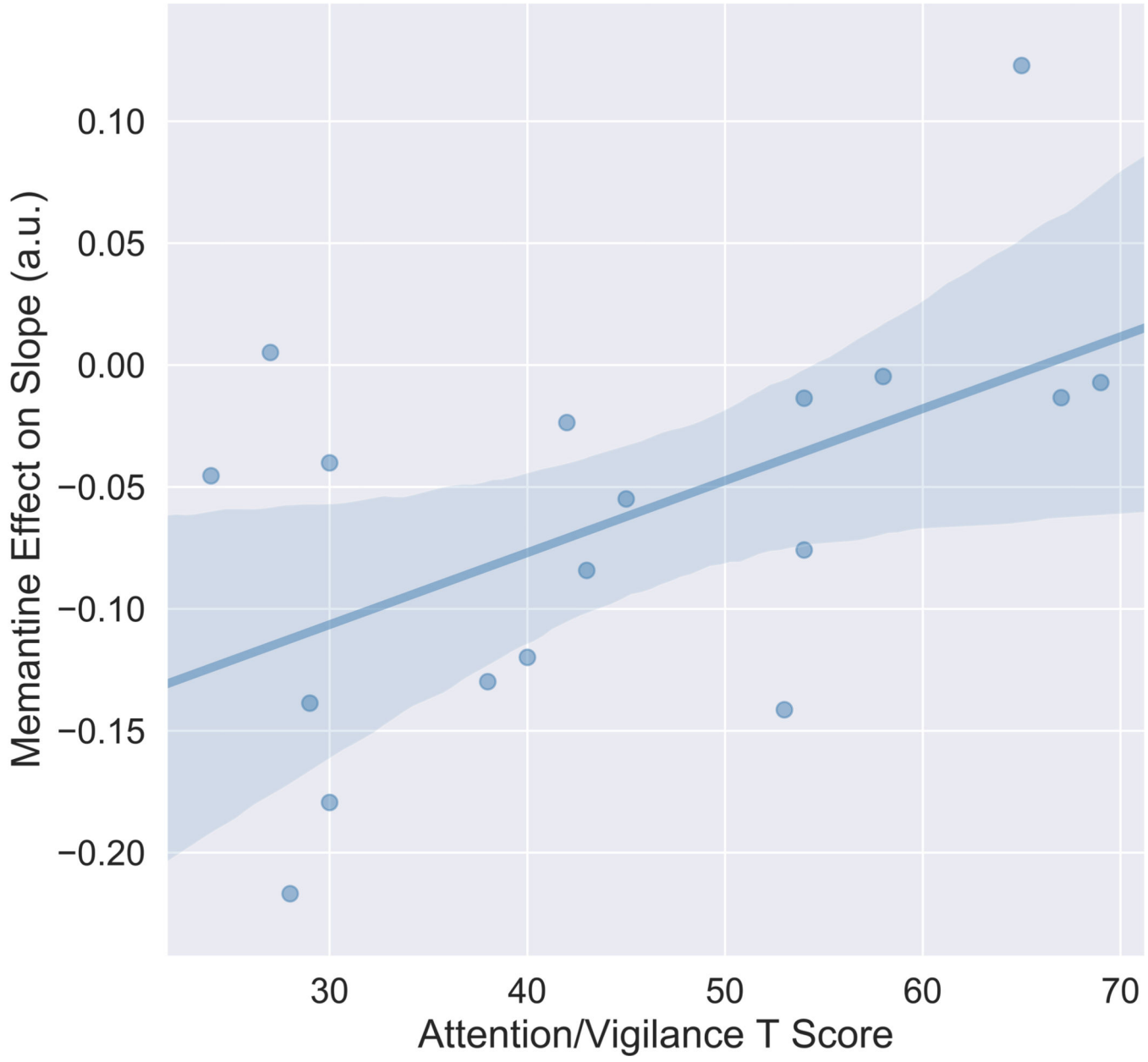

Figure 2.
Baseline Attention and Vigilance predicts MEM effect of aperiodic slopes. MEM had greater "normalizing" effects (slope reduction) in individuals with lower vs. higher baseline attention (r= .54; p< .05).

Table 1

Demographics and Clinical Characteristics (Mean (SEM))

	NCS (n=31)	SZ (n=36)
Age (years)[a]	28.0 (0.5)	36.5 (0.4)
Sex (M:F)	24:7	24:12
Smoker (%)	0	53.3
WRAT	103.0 (1.5)	93.4 (0.8)
SZ dose group	***10 mg***	***20 mg***
Age (years)	35.3 (1.9)	37.0 (1.7)
Age of onset (years)	19.9 (0.4)	16.0 (0.6)
GAF	58.7 (0.7)	56.7 (0.4)
PANSS scores		
Positive symptoms[b]	12.4 (0.5)	17.6 (0.4)
Negative symptoms	16.2 (0.4)	17.5 (0.6)
General psychopathology[a]	24.1 (0.6)	31.9 (0.9)
Total[a]	52.8 (1.1)	67.1 (1.5)
Medications		
Aypical: Typical: Both: None	9:1:3:4	13:1:4:1
CPZ equivalents	418.3 (46.7)	501.6 (40.1)

[a] $p<.05$

[b] $p<.01$

Table 2.

MEM effect and relationship to other measures of EAIP

	Aperiodic slope	Theta Power	Alpha Power	Beta Power	Gamma Power	MMN
Theta power	0.07					
Alpha power	0.08	0.67[c]				
Beta power	−0.25	0.63[c]	0.47			
Gamma power	−0.60[c]	0.04	0.04	0.14		
MMN	0.30	−0.51[a]	−0.47	−0.36	−0.65[c]	
PPI	0.09	0.28	0.41	0.23	0.55[a]	−0.70[b]

[a] $p < .05$

[b] $p < .01$

[c] $p < .005$