Effects of Memantine on Event-Related Potential, Oscillations, and Complexity in Individuals With and Without Family Histories of Alcoholism

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ABSTRACT. Objective: Enhanced N-methyl-D-aspartate (NMDA) receptor function associated with a positive family history of alcoholism (FHP) has been hypothesized to contribute to the heritable risk for alcoholism. The objective of this study was to evaluate the relationship of alcoholism family history, NMDA receptor function, and cortical information processing by testing acute effects of the NMDA receptor antagonist memantine on event-related potential (ERP). **Method:** Twenty-two healthy FHP and 20 healthy family history-negative (FHN; no alcoholic relatives) subjects were administered placebo or 40 mg of memantine under double-blind counterbalanced conditions on two separate occasions. Electroencephalogram data were collected from eight channels with eyes open during an auditory oddball discrimination task. We evaluated P3b amplitude, total theta, alpha activity, and fractal dimension from ERP trials. **Results:** FHP and FHN subjects did not differ

in P3b amplitude. A significant Group $\times$ Drug interaction was observed in theta, alpha activity, and fractal dimension at the parietal and occipital sites. FHP individuals exhibited significantly higher fractal dimension and lower theta and alpha activity after placebo relative to FHN subjects. Following memantine administration, theta activity decreased in both groups but more markedly for FHN individuals. Alpha activity decreased for FHN subjects and increased for FHP individuals, whereas the fractal dimension decreased for FHP subjects and increased for FHN subjects after memantine. **Conclusions:** A plausible interpretation of these results is that FHP individuals may have altered NMDA receptor function compared with FHN individuals. These findings provide additional evidence of differences in the regulation of NMDA receptor function between FHP and FHN individuals. (*J. Stud. Alcohol Drugs*, 74, 245–257, 2013)

A MAJOR RISK FACTOR FOR ALCOHOL ABUSE/dependence is a family history of alcoholism in close relatives (Cloninger et al., 1981; Goodwin et al., 1973). Family history-positive (FHP) individuals possess increased impulsivity levels (Gough, 1994) and exhibit neural disinhibitory characteristics. It is hypothesized that FHP individuals exhibit reduced dysphoric and cognitive effects as a result of ethanol intoxication relative to family history-negative (FHN) subjects, reflecting a lack of an alcohol-induced “braking” signal to stop drinking (Krystal et al., 2003a).

Scalp-recorded electroencephalogram (EEG) activity represents highly heritable brain oscillations controlled by genetic factors that have previously been linked to a family history of alcoholism. Event-related potential (ERP) is the brain response embedded in the EEG to the occurrence of

discrete events in the form of sensory stimulus or psychological reaction to a stimulus. The P300 component of the ERP waveform is a positive peak around 300 ms after the stimulus. The P300 reflects attention allocation, cognitive information processing, context updating, and termination of mental processes (Polich, 2007). The amplitude of P300 signifies inhibition of responses to standard or non-important stimuli that needs to be neglected while effectively responding to important or target stimuli (Birbaumer et al., 1990; Desmedt, 1980) in the typical oddball paradigm. Brain processes are involved in neural inhibition of unrelated activity while focusing attention on processing important task-related information. P300 amplitude has been proposed to reflect more general central nervous system inhibition, an underlying hypothesis in the predisposition to alcoholism (Begleiter and Porjesz, 1999). P300 amplitude is significantly lower in alcoholics during visual (Porjesz et al., 1980) and auditory tasks (Cohen et al., 1995) compared with controls. A gender-specific deficit in P300 amplitude was noted in both male (Hada et al., 2000) and female (Suresh et al., 2003) alcoholics. P300 amplitude deficits were reported in both female (Hill and Steinhauer, 1993) and male offspring of alcoholics (Ramachandran et al., 1996). Another EEG analysis ap-

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proach used in alcoholism research involves time–frequency (TF) decompositions of ERP. Such event-related oscillations (EROs) characterize both phase-locked and non-phase-locked oscillations underlying the ERP waveform by quantifying the oscillatory dynamics within a specific time window compared with P300 amplitude, which characterizes a single point in the waveform. EROs reflect neural synchrony and represent neuronal communication that forms the basis for coordinated and integrated brain functions. Low-frequency EROs signify communication between distant brain regions, whereas high-frequency oscillations represent shorter range neuronal communication in closer spaced brain regions. The neurobiology of low-frequency oscillations measured at the scalp is not well understood. Intracortical studies implicate N-methyl-D-aspartate receptors (NMDARs) in some form of theta oscillations (Buzsaki, 2002) and in the relationship between theta and gamma oscillations (Jensen and Lisman, 1996). The NMDA antagonist ketamine attenuates theta and increases gamma activity (Lazarewicz et al., 2010), providing evidence for the role of NMDARs in mediating the balance between theta and gamma oscillations. Abnormal low-frequency amplitudes in visual oddball (Padmanabhapillai et al., 2006; Rangaswamy et al., 2007) and go/no-go paradigms (Kamarajan et al., 2006) are reported in FHP individuals. A comprehensive review of ERO-based studies in alcoholism can be found in Pandey et al. (2012).

In addition to traditional measures (e.g., P300 amplitude and EROs), ERPs also can be quantified using chaos theory–derived measures of dimensionality or complexity of the underlying ERP generator. Whereas P300 and EROs measure linear dynamics of ERP waveforms, dimensionality quantifies nonlinear dynamics that characterize the number of degrees of freedom associated with systems generating the ERP waveform. Thus, dimensionality describes the “roughness” or orderly state of those systems. Traditional tools are capable of characterizing spectral properties and peak amplitudes of ERPs; however, they lack the ability to quantify the regularity or orderliness of EEG and ERP systems accurately. Dimensionality is unrelated to ERP power, amplitude, or latency. Thus, nonlinear dynamics might provide complementary information about ERPs not revealed by traditional methods (Fell et al., 1996). The conceptual basis for applying nonlinear dynamics tools to ERP stems from the hypothesis that ERPs represent neuroelectric activity generated by neuronal ensembles firing at different frequency ranges that become synchronous and coherent on stimulus presentation. Stimulus activation thus transforms an unstructured state of oscillations underlying the neuroelectric activity to a structured one. Cognitive functions (e.g., perception, decision making) likely depend on synchronous or synergic neuronal interactions. ERP-related nonlinear dynamics and implications of dimensionality are reviewed in Molnar (1999), Rapp et al. (1989), and Stam (2005).

A primary reason to use dimensionality measures for characterizing ERPs is to study self-similarity of complex, large-scale neuronal systems in the brain with nonlinear dynamic properties. The presence of such nonlinear properties in neural systems in schizophrenia was shown by Breakspear (2006). Numerous studies have applied nonlinear analysis to EEGs for understanding the brain dynamics in both healthy and patient populations during intrinsic states or while performing cognitive tasks and in various psychiatric disorders ranging from Alzheimer’s (Jeong et al., 2001) to schizophrenia (Breakspear et al., 2003; Carlino et al., 2012), dementia, and Parkinson’s disease (Stam et al., 1994). Specifically in alcoholism, prior work using dimensionality measures demonstrated a low correlation dimension (Ehlers et al., 1995) in resting state EEG and high wavelet entropy in ERPs (Jones et al., 2002) in FHP subjects.

Alcoholism is likely associated with impaired neurotransmitter systems. Abnormal dopamine interactions are reported in human (Martinez et al., 2005) and rodent studies (McBride et al., 1993). Alcohol activates dopaminergic neurons by inhibiting GABAergic cells that normally limit dopamine release. NMDAR function is implicated in alcohol dependence and alcoholism risk. NMDARs are sensitive to alcohol in the brain (Krystal et al., 2003a), interact with dopaminergic systems in nucleus accumbens, and are implicated in alcohol-associated behaviors such as withdrawal, craving, and relapse. Acute ethanol administration inhibits NMDAR function, resulting in cognitive and subjective effects associated with ethanol intoxication that further generate the negative feedback signal for ethanol intoxication. NMDAR overregulation is likely responsible for both alcohol tolerance and severe withdrawal-related symptoms seen in alcohol dependence. NMDAR antagonists are used in numerous human and animal studies to model plausible pathophysiological mechanisms underlying neuropsychiatric disorders such as Alzheimer’s disease (Rogawski and Wenk, 2003) and schizophrenia (Lahti et al., 1995). Alcohol-like subjective effects and cognitive impairment occur in healthy subjects in response to subanesthetic doses of ketamine (Dickerson et al., 2010). FHP individuals may exhibit overregulated NMDAR function (Petrakis et al., 2004) similar to alcohol-dependent subjects (Krystal et al., 2003b, 2003c), as reflected by reduced sensitivity to the subjective and behavioral effects of ketamine. Further, FHP individuals show reduced sensitivity to the effects of the low-affinity, uncompetitive NMDAR antagonist memantine on behavior and cortical activation measured with functional magnetic resonance imaging during behavioral inhibition (Jamadar et al., 2012) on go/no-go tasks.

In the present double-blind, placebo-controlled, memantine challenge study in matched FHP and FHN individuals, we analyzed P3b amplitude derived from target stimulus, low-frequency EROs, and ERP-derived dimensional complexity to capitalize on the unique, yet complementary, infor-

mation provided by each EEG analysis approach. Memantine has been shown to reduce alcohol cue-induced cravings in recovering alcohol-dependent patients and to be an effective treatment for symptoms of alcohol withdrawal (Krupitsky et al., 2007). The primary objective of the proposed pilot study was to use memantine as a probe of the NMDA system in FHP individuals. Based on previous reports, we hypothesized that theta, alpha EROs, and P3b amplitude in FHP subjects would be lower in frontal and parietal regions compared with FHN subjects following placebo. Based on the hypothesis that P300 ERP corresponds to the termination of the decision-making processing and likely reflects neuronal inhibition, we predicted a high fractal dimension (FD) in FHP subjects relative to FHN subjects post-placebo. Glutamatergic system abnormalities are implicated in the pathophysiology of addictive disorders that are related to behavioral characteristics such as impulsivity and inhibition. NMDAR antagonists modulate cognitive control, mediating the balance between inhibition and excitation; memantine improves response inhibition in gambling (Grant et al., 2010) by reducing glutamate excitability. Thus, based on the hypothesized relationship between NMDAR and impulsivity, we expected memantine to differentially modulate P3b amplitude, total theta, alpha activity, and FD in ERP between groups such that FHP subjects would show diminished changes in the dependent measures relative to FHN subjects.

Method

Ethics statement

The study was approved by the Hartford Hospital and Yale University Institutional Review Boards and carried out at Hartford Hospital's Institute of Living. All study participants provided written informed consent after the study had been fully explained to them. Subjects were paid for study participation.

Subjects

FHP subjects consisted of 15 right-handed individuals with an alcoholic biological father and at least two other first-degree (sibling) or second-degree alcoholic relatives. FHP status was based on the Family History Assessment Module (FHAM; Compton et al., 2002). To avoid possible fetal alcohol effects, subjects with an alcoholic biological mother were excluded. All subjects eligible for this study were screened, and those individuals with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR; American Psychiatric Association, 2000), Axis I psychiatric diagnoses per the Structured Clinical Interview for DSM-IV (First et al., 1998), other than nicotine dependence, were excluded, as were those with any major central nervous system disorder. All women

were urine screened for pregnancy, and all subjects underwent urine toxicological screening for commonly abused substances on each test day; positive tests resulted in exclusion.

Comparison subjects (FHN) consisted of 15 right-handed, healthy individuals with no FHAM-measured history of alcohol in any first- or second-degree relatives. Additionally 13 subjects (7 FHP, 6 FHN) recruited for a related study using identical inclusion and exclusion criteria participated in the memantine portion of the study but received no placebo before recording baseline data on an initial no-drug day. The objective in including the extra subjects was to increase the sample size without altering the balance between groups, and no specific hypotheses were framed regarding these additional participants. Of the resulting 43 total subjects, 1 had no usable ERP data for one session. The two groups (FHP and FHN) did not differ in age, $t(40) = -0.734$, $p = .467$, or sex, $\chi^2(1) = 0.087$, $p = .768$, as shown in Table 1, which also shows alcohol consumption in the last 30 days and 12 months for each group. The number of standard drinks consumed in the last 30 days was significantly different, $t(27) = -2.02$, $p = .05$, between the FHN and FHP individuals.

TABLE 1. Demographic information for 42 subjects and clinical information for 29 subjects

Variable	FHP ($n = 22$)		FHN ($n = 20$)	
Age, in years ^a				
M (SD)	23.5 (2.98)		22.9 (3.1)	
Range	18–30		18–30	
No. of standard drinks				
in last 30 days, M (SD) ^b	17.27 (22.39)		4.64 (6.5)	
Lifetime smokers, n^c	7		2	
Current smokers, n^c	2		0	
	Male n	Female n	Male n	Female n
Sex ^a	12	10	10	10
Ever consumed alcohol (lifetime)? ^c	8	6	7	7
How often consumed (last 12 months) ^c				
3–4 times/week	1	0	0	1
2 times/week	1	2	2	0
1 time/week	1	1	3	2
1 time/month	2	1	0	2
2–3 times/month	2	0	2	1
1–2 times/year	1	0	0	1
None	0	2	0	0
How many drinks consumed in a typical day (last 12 months) ^c				
1	1	0	2	2
2–4	4	4	3	5
4–8	3	1	1	0
>8	0	0	1	0
None	0	1	0	0

Notes: FHP = family history positive; FHN = family history negative.

^aGroups did not differ in age, $t(40) = -0.734$, $p = .467$, or sex, $\chi^2(1) = 0.087$, $p = .768$; ^bgroups differed in number of drinks consumed in last 30 days, $t(27) = -2.02$, $p = .05$; ^cdrinking and smoking data were not available for 13 subjects.

TABLE 2. Number of artifact-free trials for P3b amplitude, EROs, and FD

Variable	FHN		FHP	
	Placebo <i>M (SD)</i>	Memantine <i>M (SD)</i>	Placebo <i>M (SD)</i>	Memantine <i>M (SD)</i>
P3b amplitude and FD	81.45 (16.28)	85.95 (8.56)	84.68 (11.13)	84.04 (11.61)
ERO	64.9 (19.4)	71.8 (14.4)	66.5 (13.8)	60 (22.8)

Notes: ERO = event-related oscillation; FD = fractal dimension.

Experimental design

Subjects were seated comfortably in a soundproof, electrically shielded experimental booth for two sessions on 2 separate days. At each session, subjects were administered either a 40 mg dose of memantine orally or an identical-appearing placebo (in the case of the additional 13 subjects, memantine or no capsule). The number of days separating the placebo and drug administration ranged between 5 and 30. Dose administration for the 30 placebo-controlled subjects was randomized in a double-blind, counterbalanced design; drug was always given second in the 13 additional subjects. Three hours after drug administration, participants underwent EEG examination while performing the auditory oddball task. Heart rate and blood pressure were checked hourly.

During each session, EEG data were collected during a 15-minute duration auditory oddball task, consisting of two stimulus types. The first stimulus was defined by frequent, standard tones (1,000 Hz, 80 dB SPL, 50 ms duration) occurring in 80% of trials (567 stimuli). The second stimulus type consisted of deviant, target tones (1,400 Hz, 80 dB SPL, 50 ms duration) occurring in 20% of trials (100 stimuli). Target stimuli were pseudo-randomly embedded within standard stimuli. The interstimulus interval was 1.5 seconds. Subjects were instructed to gaze at a fixation cross on a monitor while listening to the tones and responding to target events by pressing a button with their left hand, giving equal emphasis to speed and accuracy.

Data acquisition

EEG recordings were collected using a Neuroscan (Compumedics, Charlotte, NC) system equipped with a 64-channel cap and Ag/Ag/Cl-sintered electrodes. We recorded from the eight midline scalp locations where ERP activity measured was expected to be maximal (i.e., channels Fpz, Fz, Fcz, Cz, Cpz, Pz, Poz, and Oz), arrayed according to the 10–20 system, with the nose as reference. Horizontal and vertical electrooculograms (EOGs) were used for monitoring eye movements. For all signal recordings, a ground electrode was attached to the middle of the forehead. Impedance was kept below 5 k Ω . The sampling rate was set to 1,000 Hz and signals were filtered on-line at 100 Hz during data acquisition.

Event-related potential processing

ERP recordings were processed using EEGLAB (Delorme and Makeig, 2004) and custom scripts in Matlab (MathWorks, Natick, MA). Raw EEG data were resampled to 250 Hz. ERP data were filtered between 0.5 and 35 Hz for processing P3b amplitude and FD. For EROs the data were filtered between 0.5 and 50 Hz. Faulty electrode recordings were identified by visual inspection and corrected using spherical spline interpolation. Vertical and horizontal eye movement artifacts were corrected by identifying source components obtained by independent component analysis that correlated well with the reference HEOG and VEOG electrodes. ERP trials were generated by segmenting from 200 ms prestimulus to 1 second post-stimulus. Individual trials were eliminated if the absolute amplitude exceeded 75 μ V. Additional rejection criteria—including improbable distribution, kurtotic behavior from the EEGLAB toolbox (Delorme and Makeig, 2004), and careful visual inspection—were used to exclude epochs containing residual artifacts and abnormal noncerebral activity. Mean artifact-free trials for the various measures during placebo and memantine conditions for the FHP and FHN groups are listed in Table 2.

P300 event-related potential

Before extracting ERP data, trials were baseline corrected by subtracting mean prestimulus amplitude from poststimulus activity. Mean waveforms of trials obtained from target stimuli with button press responses were reconstructed to obtain ERPs. Automatic peak detection was used to extract P3b amplitude from ERPs, which was selected as the largest amplitude peak within a time window of 250–500 ms.

Event-related oscillations

S-transform was used to derive TF energy distribution for each epoch. S-transform (Stockwell et al., 1996) is an efficient method for extracting estimates of localized power of nonstationary evoked potentials and has been extensively used in prior alcoholism studies (Kamarajan et al., 2006; Padmanabhapillai et al., 2006; Rangaswamy et al., 2007). S-transform is a generalization of the short-time Fourier transform with a variable-length Gaussian window function

sliding across time at different frequency scales. S-transform provides frequency-dependent resolution (Gaussian window length is inversely proportional to the examined frequency) in estimating the TF distribution. The amplitude of the TF distribution averaged over individual trials yielded the total TF distribution. Finally, mean total amplitude was computed by integrating the TF distribution along the time and frequency domains. We used a time window of 300–700 ms for the theta (4–8 Hz) and alpha (8.15–12 Hz) bands. TF distributions were baseline adjusted (Kamarajan et al., 2006; Padmanabhapillai et al., 2006) by subtracting the mean pre-stimulus amplitude from the poststimulus values within the time window of interest.

Higuchi fractal dimension (HFD)

The complexity of individual ERP trials was measured by HFD because of its simplicity and reliability in characterizing short-segment time series (Accardo et al., 1997);

like other linear methods, it assumes stationarity of the time series. Similar to the approach undertaken by Georgiev et al. (2009), we simulated the Weistrass fractal curve with a predefined FD of 1.5. Using this curve as a reference, varying lengths of sliding windows were used to estimate the FD. From the calibration experiment, we selected a window length of 100 ms, which well approximated the true FD. The HFD was estimated at each time point of the trial based on neighboring points, and a new FD time series was constructed. The mean FD curve was obtained by averaging the FD time series over the trials. Finally, we computed the area under the FD curve within the P300 range of 250–500 ms for the target condition.

Statistical analysis

P3b amplitude. We conducted a two-way repeated-measures analysis of variance (RMANOVA) on the P3b amplitude for targets at each channel with drug (placebo/me-

FIGURE 1. Grand averaged event-related potential (ERP) waveforms for placebo and memantine conditions in family history-positive (FHP) and family history-negative (FHN) groups

FIGURE 2. Mean P3b amplitude in family history–positive (FHP) and family history–negative (FHN) groups for placebo and memantine conditions

mantine) as the within-subjects factor and group (FHP/FHN) and sex (male/female) as the between-subject factors. The primary interest was the effect of memantine on the FHP and FHN groups. In the instance where the Group $\times$ Drug interaction was significant, a post hoc test using univariate analysis of variance (ANOVA) was conducted to examine for group differences under each drug condition separately.

Event-related oscillations. ERO measures were tested for normality using the Shapiro–Wilks test; because normality was preserved, no transformation was applied to the data. We were interested in the Group $\times$ Drug interaction effect on theta and alpha bands; hence, for each frequency band, two-way RMANOVAs were carried out at each channel location with drug as the within-subjects factor and group and sex as between-subject factors. Significant or close to significant interaction effects were followed up with post hoc tests, including univariate ANOVA for both placebo and memantine conditions to provide a meaningful interpretation of the effects of drug and group.

HFD. Statistical analysis using RMANOVA was carried out in a similar fashion to P3b amplitude.

Results

P300 event-related potential

Grand-averaged ERP waveforms for leads Fz, Cz, and Pz for the FHP and FHN groups under placebo and memantine conditions are shown in Figure 1. The FHP group showed a lower amplitude envelope compared with the FHN group after both placebo and memantine. Primary P3b amplitude analysis for target stimuli revealed no significant group main effect or Group $\times$ Drug interaction effect at all channels (Table 3). Figure 2 shows the peak amplitude of the P3b component of the ERP waveform for all channels. The main effect of the drug was significant (Table 3), with reduced P3b amplitude in the frontal and parietal channels after meman-

TABLE 3. Repeated measures analysis of variance on P3b amplitude at individual channels

Channel	Group (1, 38 df)		Sex (1, 38 df)		Drug (1, 38 df)		Group $\times$ Drug (1, 38 df)	
	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Fpz	1.31	.25	0.26	.6	1.6	.2	0.77	.38
Fz	0.56	.45	0.25	.61	28.7	.000004**	0.85	.36
Fcz	0.7	.4	0.9	.34	30.9	.000002**	0.85	.36
Cz	1.09	.3	1.56	.21	20.9	.000049**	0.45	.5
Cpz	1.5	.22	2.44	.12	15.8	.00029**	0.58	.45
Pz	1.79	.18	3.2	.07	18.7	.0001**	0.14	.7
Poz	2.22	.14	2.65	.11	5.4	.02*	2.17	.14
Oz	1.65	.2	2.64	.11	1.5	.22	1.93	.17

p* < .05; *p* < .01.

TABLE 4. Results of repeated measures analysis on total theta activity

Channel	Group (1, 38 df)		Sex (1, 38 df)		Drug (1, 38 df)		Group $\times$ Drug (1, 38 df)	
	F	p	F	p	F	p	F	p
Fpz	1.33	.25	3.93	.05*	0.06	.8	2.6	.11
Fz	1.21	.27	0.85	.36	7.33	.01*	1.96	.16
Fcz	1.57	.21	0.02	.86	14.07	.001*	1.7	.19
Cz	1.96	.17	0.04	.84	15.09	.003**	3.85	.05*
Cpz	3.46	.07 [†]	0.07	.79	9.49	.004**	3.03	.08 [†]
Pz	2.15	.15	0.02	.88	6.02	.02*	2.93	.09 [†]
Poz	3.02	.09 [†]	0.02	.88	1.12	.29	1.92	.17
Oz	3.13	.08 [†]	0.01	.91	0.09	.76	2.07	.15

[†] $p < .1$; * $p < .05$; ** $p < .01$.

TABLE 5. Results of repeated measures analysis on total alpha activity

Channel	Group (1, 38 df)		Sex (1, 38 df)		Drug (1, 38 df)		Group $\times$ Drug (1, 38 df)	
	F	p	F	p	F	p	F	p
Fpz	2.53	.11	3.43	.08 [†]	0.62	.43	2.27	.13
Fz	3.85	.05*	0.68	.41	0.24	.55	0.87	.35
Fcz	4.69	.03*	0.11	.73	0.91	.34	0.33	.56
Cz	4.45	.04*	0.26	.60	1.84	.18	0.59	.44
Cpz	5.24	.02*	0.24	.62	1.69	.2	0.98	.32
Pz	3.1	.08 [†]	0.76	.38	0.21	.64	0.00005	.99
Poz	3.73	.06 [†]	0.33	.56	0.00009	.99	0.2	.65
Oz	3.99	.05*	0.005	.94	0.12	.72	3.3	.07 [†]

[†] $p < .1$; * $p < .05$; ** $p < .01$.

time, as seen in Figure 2. The main effect of sex and other interaction effects were nonsignificant.

Event-related oscillations

Theta and alpha band activation is visible in the total TF distribution on channel Cz, shown in Figure 3. Total theta and alpha activity was lower after placebo for the FHP group relative to FHN. The main effects of group, drug, and sex and the interaction of Group $\times$ Drug and Group $\times$ Sex associated with total theta and alpha activity are summarized in Tables 4 and 5, respectively. The main effect of group on alpha activity was significant at the frontal (Fz, Fcz), central (Cz, Cpz), and occipital (Oz) channels. Sex main effect at channel Fpz was significant in the theta band, whereas a trend was noted in the alpha band. The Group $\times$ Sex interaction was nonsignificant at all channels. Total theta activity but not alpha activity significantly differed between placebo and memantine conditions at the Fz, Fcz, Cz, Cpz, and Pz sites (Table 4). Memantine reduced theta activity for both groups, but a smaller reduction was noted in the FHP group compared with the FHN group (Figure 4a).

A significant Group $\times$ Drug interaction was observed in theta activity at channel Cz, whereas a trend was noted at the Cpz and Pz (Table 4) sites. Post hoc univariate ANOVA revealed a significant group effect during placebo at channel Cpz, $F(1, 39) = 4.2$, $p < .04$, and a trend at Cz, $F(1, 39) = 3.38$, $p < .07$, Pz, $F(1, 39) = 3.29$, $p < .07$, with increased ac-

tivity in the FHN group compared with the FHP group. After memantine, the group main effect was not significant at the Cz, $F(1, 39) = 0.18$, $p < .67$, Cpz, $F(1, 39) = 0.35$, $p < .55$, and Pz, $F(1, 39) = 0.33$, $p < .56$, sites with decreased theta activity in both groups, but a greater margin of reduction was observed in the FHN group compared with a nonsignificant change in the FHP group (Figure 4a). In the alpha band, the Group $\times$ Drug interaction was close to significance at channel Oz (Table 5). Univariate ANOVA showed a significant group effect, $F(1, 39) = 5.07$, $p < .03$, during placebo, with increased activity in the FHN group compared with the FHP group (Figure 4b). After memantine, the group effect was not significant, $F(1, 39) = 2.2$, $p < .14$, but alpha activity decreased for the FHN group and increased for the FHP group. The Group $\times$ Drug significance values for both theta and alpha activity were not significant after adjusting for $p = .05 / 8$ to account for multiple comparisons at eight leads. Results from RMANOVA on the subset ($n = 29$) of subjects who had both placebo and memantine (supplementary results are not presented here but may be obtained from the authors) confirmed that the data pattern was similar except for the significance levels. Thus, the extra subjects ($n = 13$) were included to gain statistical power.

Fractal dimension

For target stimuli, the main effect of group displayed a trend at parietal sites Pz and Poz (Table 6). The main ef-

FIGURE 3. Total event-related activity distribution in the time–frequency plane for family history–positive (FHP) and family history–negative (FHN) groups in placebo and memantine conditions at lead Cz. S = second.

fect of sex was significant at the frontal sites (Fpz and Fz), whereas a trend was observed at frontal site Fcz, the two central sites, and at parietal site Poz. The main effect of drug and the Group $\times$ Sex interaction effect were not significant. Group $\times$ Drug interaction was significant at parietal site Pz and occipital site Oz (Table 6). Figure 5 shows the mean FD for the FHP and FHN groups during both placebo and memantine conditions. The FD was lower for the FHN group than the FHP group for placebo at all sites. After memantine, the FD increased for the FHN group but decreased for the FHP group, thereby equalizing values between groups. Post hoc univariate test revealed a significant group difference during placebo at Pz, $F(1, 39) = 7.86, p < .008$, and Oz, $F(1, 39) = 0.08, p < .77$. After memantine, the group difference was not significant at both sites. Supplementary results for the subset of data, after excluding 13 subjects without placebo, can be obtained from the authors.

Discussion

We investigated the effects of acute memantine challenge on the P3b amplitude, low-frequency EROs, and FD of ERP

derived from an auditory oddball task in individuals with and without family histories of alcoholism. We expected FHP subjects to manifest diminished P3b amplitude, theta activity, and alpha ERO activity and higher FD relative to FHN subjects following placebo. We hypothesized that memantine administration would differentially alter P3b amplitude, total theta, alpha activity, and FD in the two groups.

P300 event-related potential

P3b amplitude failed to differentiate between FHP and FHN subjects following memantine challenge. Our findings during placebo were inconsistent with prior reports (Ramachandran et al., 1996; Suresh et al., 2003). The current study used a heterogeneous sample (both male and female) compared with prior studies, where males (Ramachandran et al., 1996) and females (Suresh et al., 2003) were examined separately. The lack of family history effect may be attributed to the modest sample size. Following memantine challenge, the P3b amplitude decreased in both groups versus placebo, consistent with prior ketamine studies (Gunduz-Bruce et al., 2012; Watson et al., 2009). The reduction was

FIGURE 4. Total event-related activity for family history–positive (FHP)/family history–negative (FHN) groups during placebo and memantine in (a) theta and (b) alpha band

TABLE 6. Repeated measures analysis showing main effects of group, drug, and sex and Group $\times$ Drug and Group $\times$ Sex interaction effects on fractal dimension

Channel	Group (1, 38 df)		Sex (1, 38 df)		Drug (1, 38 df)		Group $\times$ Drug (1, 38 df)	
	F	p	F	p	F	p	F	p
Fpz	0.29	.58	9.4	.004**	1.39	.24	2.39	.13
Fz	1.5	.22	4.35	.04*	0.007	.93	2.69	.1
Fcz	1.93	.17	3.18	.08†	0.9	.34	0.69	.4
Cz	2.02	.16	3.08	.08†	0.21	.64	2.5	.12
Cpz	1.49	.22	3.12	.08†	0.06	.79	0.96	.33
Pz	2.69	.1†	3.3	.07†	0.16	.69	5.01	.03*
Poz	2.91	.09†	2.5	.12	0.14	.7	2.83	.1
Oz	2.63	.11	2.25	.14	0.01	.92	5.99	.01**

† $p < .1$; * $p < .05$; ** $p < .01$.

FIGURE 5. Mean fractal dimension (FD) for family history–positive (FHP)/family history–negative (FHN) groups during placebo and memantine

mainly confined to frontal and parietal channels, likely as a result of reduced glutamatergic activity following NMDAR blockade.

Total event-related theta activity

Effect following placebo. As expected, central and parietal theta activity for FHP subjects was lower during placebo, consistent with prior studies reporting decreased theta power in a visual P300 task (Rangaswamy et al., 2007), and during the no-go condition (Kamarajan et al., 2006) of go/no-go tasks. Low theta activity may be a marker of circuit dysfunction associated with impaired learning, memory, and selective attention (Klimesch et al., 2001; Yordanova and Kolev, 1998). The number of standard drinks differed between the FHP and FHN groups, and its influence on the spectral profile was nonsignificant because it was uncorrelated with theta activity for the subset of subjects ($n = 29 / 42$) for which this measure was available. We were unable to account for the effects of drinking behavior because the drinking data were available for only a subset of the subjects. For the same reason, we could not control for the effects of smoking on P3b amplitude. Moreover, the current sample had only two current smokers (Table 1) in the FHP group; hence, current smoking is unlikely to influence our results.

Effect following memantine. After memantine administration, total theta activity decreased in both groups (more markedly for the FHN group) compared with a diminished

reduction in the FHP group. The insignificant change in theta activity after memantine in FHP individuals was as predicted. The underlying neurobiology of these changes is not yet well understood. However, it is well known that NMDAR antagonists impair cortical functional connectivity while inducing a relative increase in high-frequency (gamma) oscillations (Hakami et al., 2009). The current data are consistent with preclinical evidence that increased gamma oscillations are accompanied by reductions in slower (theta) oscillations (Lazarewicz et al., 2010). Although we focused on low-frequency theta oscillations in this study, based on prior evidence that evoked gamma activity is disrupted in FHP individuals (Padmanabhapillai et al., 2006), we also examined evoked gamma activity for which results are not presented here but found no differences between FHP and FHN subjects. The neurobiology of underlying cortical oscillations is quite complex, involving the kinetics of voltage and ligand-gated ion channels, such as NMDARs, as well as the synchronizing inhibitory input of subpopulations of GABAergic neurons (Buzsaki, 2002; Tukker et al., 2007). FHP subjects showed reduced sensitivity to the theta-reducing effects of memantine compared with FHN subjects, consistent with the hypothesis that FHP subjects have an upregulation in NMDAR function. However, FHP subjects showed a deficit in theta relative to FHN subjects during placebo that might seem to be inconsistent with their upregulation of NMDAR function. We caution against this overly simplistic interpretation of the complex neurobiology of resting corti-

cal oscillations. Presumably, there are many ways that FHP subjects and FHN subjects differ neurobiologically, and the cause of the difference between FHP subjects and FHN subjects in cortical oscillations is not yet known.

Total event-related alpha activity

Effect following placebo. As hypothesized, we observed significantly lower parietal and occipital total alpha activity in FHP individuals relative to FHN individuals after placebo. Our finding is consistent with reports of decreased slow alpha during a visual no-go (Kamarajan et al., 2006) condition in the go/no-go paradigm. EEG studies suggest that alpha oscillations are correlates of active inhibition (Pfurtscheller et al., 2000). Diminished alpha power reflects poor inhibition (Kamarajan et al., 2006) that may be associated with alcoholism. Specifically, inhibitory GABA activity arising from cortical sensory processing regions manifests as increased alpha power (Mathewson et al., 2011). Alpha oscillations reflect attentional allocation (Spencer and Polich, 1999) in stimulus-driven tasks. The diminished activity in FHP subjects suggests that these individuals may possess attentional deficits.

Effect following memantine. Following memantine challenge, total alpha activity decreased in FHN subjects as predicted but increased in FHP subjects unexpectedly, thereby equalizing baseline alpha values between groups. We were unable to verify the diminished change in alpha activity in FHP individuals as hypothesized in this study. The neurobiology of the human cortical oscillations measured in this study is not well understood. The current findings suggest a nonlinear (inverted U) relationship between NMDAR function and alpha oscillations. The reduction in alpha following memantine in FHN subjects is consistent with NMDAR contributions in generating alpha, similar to the sedative and attention-impairing effects of NMDAR antagonists (Oranje et al., 2000; Petrakis et al., 2004). However, depression of alpha in FHP individuals and normalization following memantine would suggest that upregulation of NMDAR function depressed alpha, an effect that is mitigated by a low degree of NMDAR antagonism.

Fractal dimension

We propose that ERP-derived FD is a novel potential biomarker characterizing the orderly state of brain oscillations in FHP versus FHN individuals. The proposed FD measure captures differences between FHP and FHN subjects in the placebo condition. Low FD was noted for target stimuli compared with prestimulus baseline, perhaps explained by temporary relaxation (interruption of search task) likely attributable to increased synchrony or communication between subsystems associated with target response. Our results confirm prior P300 ERP complexity analysis reports. Significant

Group $\times$ Drug interactions were observed at parietal and occipital sites on FD derived from P300 responses elicited by target stimulus.

Effect following placebo. During targets after placebo, FHN subjects had lower FD compared with FHP subjects. As predicted, FHP individuals displayed a greater randomness in ERP waveforms associated with the target stimuli compared with FHN individuals. Our current findings agree with a prior study reporting increased spatial complexity in FHP subjects (Jones et al., 2002). Parietal and occipital sites differed significantly between groups during placebo. After placebo, FHP individuals exhibit unsynchronized neuronal interaction or disturbed cooperation between subsystems resulting in a disorderly state of neural oscillations underlying the P300 response. The neurobiological basis for high FD in FHP subjects is unclear.

Effect following memantine. FD decreased for FHP subjects but increased for FHN subjects after memantine versus placebo. After memantine, parietal and occipital sites displayed no group differences, producing an equalizing effect between family history groups. Our results indicate differential effects in FHP individuals versus FHN individuals in the auditory oddball task, although this is inconsistent with our proposed hypothesis. Higher FD after memantine in FHN subjects indicates that inhibiting NMDAR increases FD relative to placebo; however, FHP subjects displayed a higher FD at baseline and reduced FD after memantine, suggesting a nonlinear (U) shaped relationship between NMDAR function and FD. We were unable to confirm increased sensitivity in the FD in FHN subjects relative to FHP subjects because the FD may not be capturing cognitive characteristics that are generally expected to be sensitive to NMDAR antagonism. To confirm whether the FD can be used as an alcoholism risk endophenotype, additional studies need to be carried out to verify whether the FD can discriminate alcoholics and controls under similar task conditions and to assess its heritability.

Limitations

A major study limitation was the limited statistical power to investigate frequency bands previously associated with alcoholism risk and for the subgroup analyses. The proposed study examined FHP and FHN group differences, and future work could involve further quantifying alcoholism risk by taking into account the genetic characteristics of each subject. The effects of smoking and drinking variables were not available for all subjects; hence, we could not examine their full influence on ERPs. Further, the current study examined only one memantine dose with spatially limited electrodes that lacked the ability to track lateral brain activity. Another limitation was the lack of behavioral data and cognitive test scores to correlate with FD and oscillatory measures that would facilitate the understanding of behavioral aspects

associated with alcoholism risk. Memantine blood levels, dose-response, and time at which memantine maximally influenced EEG could not be studied because these data were not collected.

Conclusion

This study provides new insights into the differential cortical response of FHP and FHN subjects to the effects of the NMDAR antagonist memantine. Principally, FHP individuals were relatively insensitive, compared with FHN individuals, to the reduction in theta oscillations produced by memantine. In addition, FHP and FHN subjects differed in the impact of memantine on FD, increasing it in FHP subjects and decreasing it in FHN subjects. There are several neurobiological reasons FHP and FHN subjects differ in oscillatory activity, but one possible mechanism the current study suggests is that cortical networks generating slow oscillations under the testing conditions may be relatively sensitive to NMDAR antagonists. Thus, these networks may be sites where the putative upregulation in NMDAR function associated with alcoholism risk is present. Although the neurobiology of FD is not well understood, our findings may suggest that low doses of NMDAR antagonist normalize FD in FHP individuals but impair FD in FHN individuals. As predicted from ketamine studies reviewed earlier, memantine diminished P3b amplitude compared with placebo. In conclusion, P300 and theta amplitude were sensitive to the effects of memantine, whereas theta activity and FD were effective in eliciting Group $\times$ Drug interactions.

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