Available online at www.sciencedirect.com
SCIENCE DIRECT
Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 936 – 943
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

N400 as an index of semantic expectancies: Differential effects of alcohol and cocaine dependence

Natalie A. Ceballos[a,*], Rebecca J. Houston[b], Natosha D. Smith[d], Lance O. Bauer[c], Robert E. Taylor[d]

[a]*Department of Behavioral Sciences, 1035 University Drive, 236 Medical School Building, University of Minnesota School of Medicine, Duluth, MN 55812-3031, United States*
[b]*Research Institute on Addictions, State University of New York at Buffalo, Buffalo, NY 14203, United States*
[c]*Alcohol Research Center, Department of Psychiatry, University of Connecticut School of Medicine, 263 Farmington Avenue, MC-2103, Farmington, CT 06030-2103, United States*
[d]*Collaborative Alcohol Research Center, Department of Pharmacology, Howard University, College of Medicine, Washington, DC 20059, United States*

Accepted 18 April 2005
Available online 20 June 2005

Abstract

Background: Chronic substance abuse has been associated with decrements in the processing and expression of language. The present study utilized the N400 event-related electroencephalographic potential to index semantic processing in 133 adults with ($n=49$) or without ($n=84$) a history of alcohol and/or cocaine dependence. The contributions of age, gender, and comorbid marijuana and nicotine dependence, and antisocial symptomology to N400 decrements were either covaried or controlled.
Methods: A continuous series of 300 stimuli was presented for 150 ms each (interstimulus interval=1475 ms) on a computer screen. The series was arranged such that a word (approximately 17% of stimuli) immediately preceded presentations of its antonym (primed condition; approximately 17% of stimuli), or a semantically unrelated word (unprimed condition; approximately 17% of stimuli). The remaining 50% of stimuli consisted of unpronounceable letter combinations (non-word condition). EEG responses to the antonyms, unrelated words, and letter jumbles were retained for analysis. Throughout the task, the subject pressed response keys to discriminate words from non-words.
Results: Analyses revealed a detrimental effect of alcohol dependence on N400 amplitude and no significant main or interactive effects of cocaine dependence.
Conclusion: The present findings suggest that alcohol-dependent individuals may exhibit verbal processing decrements. These findings also challenge hypotheses suggesting that the combined use of cocaine and alcohol is more deleterious to brain function than alcohol use alone.

Keywords: Alcohol; Cocaine; Evoked potentials; N400

1. Introduction

Language comprehension can be studied via the N400 component of the event-related electroencephalographic potential. In the classic study of N400 by Kutas and Hillyard (1980), sentences were presented visually word-by-word. For half of the sentences, the concluding word of the sentence was congruous with its context. For other sentences, the concluding word was incongruous or odd, and did not logically complete the sentence. Incongruous sentence endings evoked a large scalp negativity

Abbreviations: ALC−/COC−, Alcohol and Cocaine Dependence Negative; ALC+/COC−, Alcohol Dependence Positive and Cocaine Dependence Negative; ALC−/COC+, Alcohol Dependence Negative and Cocaine Dependence Positive; ALC+/COC+, Alcohol and Cocaine Dependence Positive; ERP, Event-Related Potential; COGA, Collaborative Study on the Genetics of Alcoholism; PCA, Principal Components Analysis; SSAGA, Semi-Structured Assessment for the Genetics of Alcoholism.

* Corresponding author. Tel.: +1 218 726 8425; fax: +1 218 726 7559.
E-mail address: nceballo@d.umn.edu (N.A. Ceballos).

0278-5846/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2005.04.036

approximately 400 ms after the onset of the incongruous word.

Since that classic study, the N400 Event-Related Potential (ERP) has been studied in a number of contexts (Bentin, 1989; Ganis et al., 1996; Hamberger et al., 1995). It has, for example, been utilized to study language processing in patients afflicted with Alzheimer's Disease (Auchterlonie et al., 2002), Parkinson's Disease (Minamoto et al., 2001) and schizophrenia (Hokama et al., 2003). N400 decrements have also been reported in patients with psychoactive substance use disorders. Ji et al. (1999) used a match-to-sample task and found that alcoholics failed to differentiate between semantically matching and mismatching word categories. N400 has also been studied by investigators directing the Collaborative Study on the Genetics of Alcoholism (COGA). In the COGA study, alcohol-dependent patients were found to exhibit N400 responses which did not differentiate between words that were semantically primed or not (Porjesz et al., 2002). In another study of alcoholic patients, Nixon et al. (2002) used Kutas and Hillyard's sentence completion task and demonstrated a similar finding.

It is noteworthy that previous N400 studies have largely overlooked the effects of other major drugs of abuse or combinations thereof. Co-abuse of cocaine and alcohol is frequent and may result in the formation of a pharmacologically active by-product, cocaethylene (Bunney et al., 2001; Brookoff et al., 1996; Grant and Harford, 1990). Combined exposure to these substances has been associated with increased toxicity in cellular preparations, animal models and human patients (Boyer and Petersen, 1990; Etkind et al., 1998; Foltin and Fischman, 1988; Henning and Wilson, 1996; Odeleye et al., 1993; Oztezcan et al., 2000; Ponsoda et al., 1999; Schechter and Meehan, 1995; Vanek et al., 1996). Although cognitive studies in human patients initially linked simultaneous cocaine and alcohol dependence to greater neurophysiological deficits than cocaine or alcohol dependence alone (Bolla et al., 2000; Horner, 1997), the literature remains inconsistent with regard to this issue. Other investigations have failed to detect either additivity or synergism (Di Sclafani et al., 1998; Easton and Bauer, 1997; Lawton-Craddock et al., 2003; Robinson et al., 1999).

Thus, the present study utilized the N400 ERP to disentangle the effects of single versus dual dependence on alcohol and cocaine on semantic processing. It was hypothesized that the presence of alcohol dependence versus its absence would be associated with a different N400 ERP response to words that were semantically primed. Based on foregoing investigations (Easton and Bauer, 1997), we did not expect to observe greater deficits associated with combined dependence upon alcohol and cocaine. Importantly, co-morbid factors that may confound comparisons between substance-dependent and control groups were either statistically controlled or specifically examined. These variables included age (Gunter et al., 1998), antisocial symptomatology (Ceballos et al., 2003; Kiehl et al., 1999), depression (Abdullaev et al., 2002; Fossati et al., 2003) and use of marijuana (Belmore and Miller, 1980) and nicotine (Warburton et al., 2001).

2. Methods

2.1. Participants

A total of 133 participants (63 males) were recruited from the Washington, DC metropolitan area. Informed consent was obtained prior to participation. The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994; Hesselbrock et al., 1999) was used to screen for psychiatric diagnoses. Individuals with psychiatric conditions (i.e., mania, psychosis) expected to significantly interfere with cognitive function were excluded from further study. Likewise, other medical conditions that affect cognitive function were also exclusionary. These conditions were ascertained via self-report and included history of severe head trauma, history of neurosurgery, liver disease, Multiple Sclerosis, stroke, Korsakoff's Syndrome, Alzheimer's Disease, Pick's Disease, Huntington's Disease, dementia, HIV/AIDS, Tuberculosis, Hepatitis, and/or life-threatening illness.

Participants included in the current analysis were 18 to 56 years of age. Groups were defined by the absence versus presence of a lifetime diagnosis of DSM-IV (American Psychiatric Association, 1994) alcohol and/or cocaine dependence. Diagnoses were determined using the SSAGA. Of the total of 133 participants, 84 were negative for both diagnoses (ALC−/COC−), 14 were positive for alcohol dependence only (ALC+/COC−), 14 were positive for cocaine dependence only (ALC−/COC+), and 21 were positive for both diagnoses (ALC+/COC+).

2.2. Experimental procedure

All sessions were conducted at the Howard University Collaborative Alcohol Research Center, Washington, DC. Prior to the session, a breath sample was obtained to verify recent abstinence from alcohol. Cigarette smoking and caffeine intake were not restricted on the day of testing. ERP recordings were obtained with the participant seated in an acoustically shielded booth, and stimuli were presented on a computer monitor. Electroencephalographic activity was collected from 61 electrodes, distributed within an electrode cap (Electro-cap International, Eaton, OH). An electrode attached to the tip of the nose served as a reference. Both vertical and horizontal eye movements were monitored. To ensure adequate electrode attachment, impedance was maintained at or below 5 kΩ.

Amplifier gain was set at 10,000× with a high pass filter cutoff of 0.30 Hz and low pass filter cutoff of 70 Hz. Data were collected in continuous acquisition mode at a sampling rate of 256 Hz. In offline analyses, data were processed further using a 30 Hz low pass, digital filter and epochs spanning a window of −200 ms to 800 ms relative to stimulus onset were extracted. Epochs on which amplitude of eye movement channels exceeded ±75 μV were excluded from analyses. An automatic peak detection program was used to identify the N400 waveform, defined as the largest negative peak between 300 ms and 600 ms.

2.3. Activation task

Previous work has demonstrated the usefulness of this task in eliciting the N400 component (Almasy et al., 2001; Kuperman et al., 1995; Porjesz and Begleiter, 1996). Words and letter jumbles were presented for 150 ms each (interstimulus interval=1475 ms) on a computer screen in a continuous series of 300 stimuli. An example of task stimuli is presented in Fig 1. The series was arranged such that a word (approximately 17% of stimuli) immediately preceded presentations of its antonym (primed condition; approximately 17% of stimuli), or a semantically unrelated word (unprimed condition; approximately 17% of stimuli). The remaining 50% of stimuli consisted of unpronounceable letter combinations (non-word condition). EEG responses to the antonyms, unrelated words, and letter jumbles were retained for analysis. Participants were instructed to press response keys throughout the task to discriminate words from non-words. Responses occurring within a window of 11 ms to 1000 ms were used for calculating response accuracy and reaction time.

It is important to note that the present task differs from the sentence completion tasks often employed in N400 studies. Accordingly, an explanation of the predicted effects of task condition on N400 amplitude is needed. As in the classic sentence completion paradigm, the present paradigm compares a condition in which there is a semantic relationship, albeit an opposite one, between adjacent words (i.e., the prime condition) to conditions (unprimed and non-word) in which there is no relationship between adjacent words. The latter conditions are therefore expected to evoke a more negative N400 Event-Related Potential than the former. As noted, this response pattern has been previously demonstrated using this task (Kuperman et al., 1995).

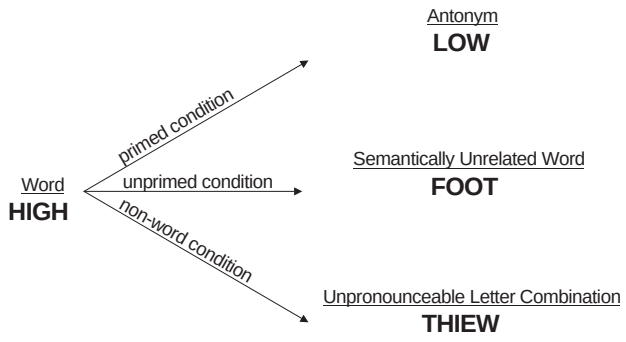

Fig. 1. N400 activation task. A continuous series of 300 stimuli was presented, in which a word immediately preceded presentation of either its antonym (primed condition), a semantically related word (unprimed condition) or an unpronounceable letter combination (non-word condition). Participants pressed response keys to discriminate words from non-words.

2.4. Statistical analysis

Data were analyzed using SPSS version 11.0 for Windows. Demographic data were analyzed via 2 (lifetime alcohol dependence: ALC+ or ALC−) × 2 (lifetime cocaine dependence: COC+ or COC−) ANOVAs.

For behavioral data, the response accuracy was calculated as percentage of correct responses for each task condition and normalized via arcsin transformation (Cohen, 1988). The reaction times were normally distributed and did not require a transformation. Response accuracy and reaction times were analyzed via separate 2 (lifetime alcohol dependence: ALC+ or ALC−) × 2 (cocaine dependence: COC+ or COC−) repeated measures ANCOVAs with semantic condition (primed, unprimed and non-word) serving as the within-subjects variable. Variables used as covariates were derived from the SSAGA. For entry as a covariate, antisocial symptomology was indexed as the number of reported symptoms of childhood conduct disorder plus symptoms associated with antisocial behavior in adulthood. Other covariates included age, depression symptoms, and marijuana dependence symptoms.

To reduce the number of ERP variables and the attendant risk of Type 1 error, the correlation matrix of N400 amplitudes measured at the 61 scalp locations was submitted to a principle components analysis (PCA). Separate PCAs were performed for each task condition. Via this method, scalp regions containing inter-correlated activity were identified and separated into coherent units by orthogonal rotation. The PCAs yielded two orthogonal factors. Thirty-five electrodes, posterior or adjacent to the central sulcus (P_5, PO_2, PO_Z, O_Z, PO_1, P_3, O_1, O_2, P_4, P_6, PO_8, P_7, P_2, P_1, PO_7, P_8, CP_5, P_Z, CP_3, TP_7, CP_4, CP_6, CP_1, CP_2, CP_Z, TP_8, C_5, C_3, T_7, C_4, C_2, C_1, C_Z, C_6, T_8), loaded highest on the first factor. Twenty-six electrodes, primarily located over the frontal lobes (AF_Z, AF_2, AF_1, F_2, F_4, F_Z, F_6, F_3, FP_1, F_1, AF_7, AF_8, FP_Z, FP_2, F_5, F_8, FC_6, F_7, FC_4, FC_Z, FC_1, FC_3, FC_2, FC_5, FT_8, FT_7), loaded highest on the second factor. Amplitudes were averaged within anterior and posterior electrode groupings. To separately examine potential hemispheric differences associated with language, data from a subset of temporal electrodes were averaged to form left (FT_7, T_7 and TP_7) and right (FT_8, T_8 and TP_8) hemisphere groupings.

Averaged N400 amplitudes were then analyzed via 2 (alcohol dependence: ALC− or ALC+) × 2 (cocaine dependence: COC− or COC+) repeated measures ANCOVAs with

semantic condition (primed, unprimed and non-word) and scalp region (anterior vs. posterior or left hemisphere vs. right hemisphere) serving as the within-subjects variables. Anterior vs. posterior and left vs. right hemispheric analyses were conducted separately. Age, as well as antisocial symptomology, depression and marijuana dependence symptoms were entered as covariates in each analysis.

Because experimental groups had unequal *n*'s in both behavioral and electrophysiological analyses, Levene's Test of Equality of Error Variance was applied to detect violations of the homogeneity of variance assumption. Unless otherwise indicated, results were non-significant. In all repeated measures analyses, Greenhouse–Geisser corrections were applied to guard against violations of the sphericity assumption. In both behavioral and electrophysiological analyses, Bonferroni corrections were applied to pair-wise comparisons of semantic condition. Unless otherwise noted, mean values presented in text are covariate adjusted.

A set of secondary analyses examined the potential effects of nicotine dependence on semantic priming. Because of sample size limitations, it was not possible to examine this as a grouping factor, along with alcohol and cocaine dependence, in the primary analyses. Further, nicotine symptoms correlated significantly with age, antisocial symptomology, depression and marijuana use (ps$<.001$). Thus, it also was not appropriate to include this factor as a covariate. The potential effects of nicotine on semantic priming were addressed in a separate set of secondary analyses, which involved computing zero order correlations between the number of nicotine dependence symptoms and the dependent variables of interest. Sixty-nine participants reported one or more symptoms of nicotine dependence (SSAGA symptom range = 1–6). Dependent variables of interest included behavioral measures, as well as N400 amplitudes for each electrode grouping and task condition.

3. Results

3.1. Demographics

Ninety-six percent of participants were African-American. Racial composition was equivalently distributed among all experimental groups. As shown in Table 1, gender representation differed slightly but significantly across the groups ($X^2(3)=24.08$; $p<.001$): the ALC− and COC− groups included a higher percentage of females than the ALC+ and COC+ groups. Education level was generally lower in participants with histories of either alcohol ($F(1, 129)=7.68$; $p=.006$) or cocaine ($F(1,129)=4.82$; $p=.03$) dependence. Cocaine-dependent patients were older than their COC-counterparts ($F(1,129)=15.47$; $p<.001$). No other age differences were significant.

A significant alcohol × cocaine dependence interaction was noted for number of antisocial symptoms ($F(1,129)=17.44$; $p<.001$). An analysis of simple effects revealed that, within the alcohol negative group, participants who were positive for cocaine dependence reported a greater number of antisocial symptoms compared to those were negative for cocaine dependence ($F(1,96)=23.97$; $p<.001$). No significant difference was noted within the alcohol positive group. Alcohol, but not cocaine, dependence was associated with increased depression ($F(1, 129)=27.21$; $p<.001$).

Group differences in estimated days since last alcohol consumption were not statistically significant. The expected main effect of alcohol dependence was observed for the average number of drinks consumed per week in the 6 months prior to testing ($F(1,118)=10.39$; $p=.002$). The alcohol dependent groups reported a greater number of standard drinks per week compared to non-alcohol dependent participants, but did not differ from one another.

Table 1
Demographic characteristics of study participants: estimated marginal means (S.E.)

	ALC+/COC+ ($n=21$)	ALC+/COC− ($n=14$)	ALC−/COC+ ($n=14$)	ALC−/COC− ($n=84$)
% Female[a]	19.05	14.29	64.29	65.48
Years of education[b,c]	11.00 (.48)	11.71 (.59)	12.00 (.59)	13.46 (.24)
Age[b]	39.76 (1.87)	32.21 (2.29)	38.86 (2.29)	31.27 (.93)
ASP symptoms[d]	6.43 (.54)	7.71 (.66)	6.21 (.66)	2.87 (.27)
Depression symptoms[c]	5.33 (.70)	5.64 (.85)	1.71 (.85)	1.77 (.35)
Days since last alcohol consumption	459.78 (196.94)	239.07 (223.31)	433.50 (241.20)	247.16 (96.48)
Drinks consumed per week (last 6 months)[c]	57.53 (10.11)	48.31 (11.56)	31.75 (12.04)	9.43 (4.66)
Maximum frequency of cocaine use (days/month)	22.00 (1.95)	–	24.17 (2.45)	–
% Marijuana dependent[a]	47.62	71.43	35.71	2.38
Marijuana dependence symptoms[d]	2.81 (.41)	3.50 (.50)	2.21 (.50)	0.61 (.20)
% Nicotine dependent[a]	71.43	50.00	35.71	9.52
Nicotine dependence symptoms[d]	3.67 (.38)	3.43 (.46)	2.93 (.46)	1.00 (.19)

Depression, ASP, marijuana and nicotine dependence measures reflect DSM-IV symptom counts derived from the SSAGA interview.

[a] Denotes unequal distribution across groups, $p<.05$.

[b] Denotes main effect of cocaine dependence, $p<.05$.

[c] Denotes main effect of alcohol dependence, $p<.05$.

[d] Denotes interaction of cocaine × alcohol dependence, $p<.05$. Among ALC− participants, COC+s reported significantly more symptoms of ASP, marijuana dependence and nicotine dependence relative to their COC− counterparts (ps$<.001$). No significant differences were noted for ALC+ participants.

Likewise, cocaine-dependent participants with and without co-morbid alcohol dependence reported similar frequencies of cocaine use during periods of heavy use. The small number of non-cocaine dependent participants who reported at least one period of regular cocaine use prohibited inclusion of these groups in statistical analyses.

Approximately 20% of participants met criteria for marijuana dependence (lifetime). This diagnosis was unequally distributed across groups ($X^2(3)=51.03$; $p<.001$). With respect to symptoms of marijuana dependence, a significant interaction of alcohol and cocaine dependence was noted ($F(1,129)=7.56$; $p<.007$). An analysis of simple effects revealed that, within the ALC− group, COC+ individuals reported significantly more symptoms compared to COC− participants ($F(1,96)=13.14$; $p<.001$). COC+ and COC− groups within the ALC+ group did not differ in marijuana symptoms. Given the existence of these group differences, it is appropriate that age, antisocial symptomology, depression, and marijuana use were entered as covariates.

Rates of lifetime diagnosis with abuse or dependence upon other illicit substances were quite low and ranged from 1% (stimulant abuse, stimulant dependence, sedative abuse) to 5% (opiate dependence). In contrast, approximately 26% of participants met lifetime criteria for nicotine dependence, which was unequally distributed across groups ($X^2(3)=38.94$; $p<.001$) As shown in Table 1, a significant interaction of alcohol and cocaine dependence was noted for symptoms of nicotine dependence ($F(1,129)=4.68$; $p<.03$). Within the ALC− group, COC+ individuals reported significantly more symptoms ($F(1,96)=15.47$; $p<.001$) compared to COC− participants. COC+ and COC− groups within the ALC+ group did not differ in nicotine symptoms.

3.2. Behavioral measures

3.2.1. Response accuracy

Overall, participants exhibited mean accuracy values of 96.7% in the primed condition, 94.3% in the unprimed condition and 90.4% in the non-word condition. No significant within- or between-subjects effects were noted for arcsin transformed measures of response accuracy. In this case, the homogeneity of variance assumption was violated for responses to non-word (Levene's $F(3,129)=6.50$;

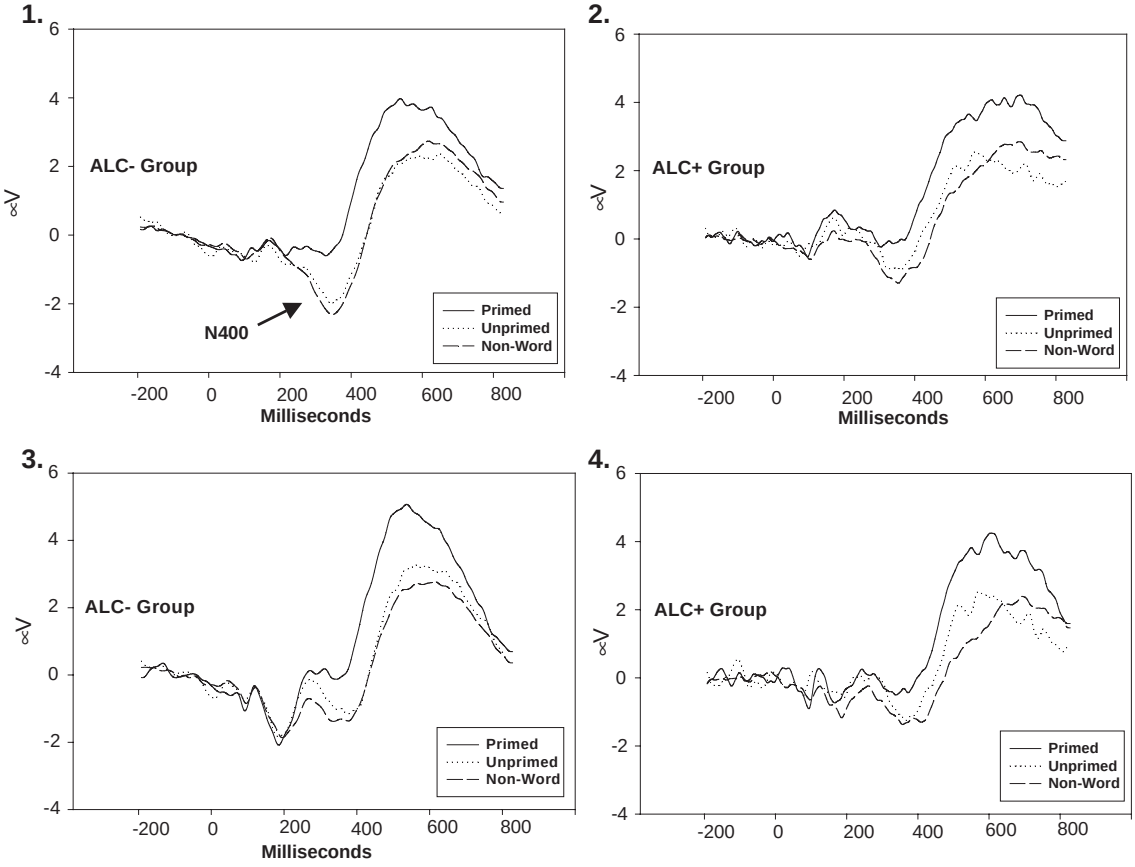

Fig. 2. Group-averaged ERP waveforms for participants without ($n=98$) and with ($n=35$) a history of alcohol dependence. ERPs in panels 1 and 2 are averaged across all anteriorly located electrodes, whereas panels 3 and 4 illustrate posterior averages. Across electrode groupings, an increased N400 is observed in the unprimed and non-word conditions relative to the primed condition. Note that alcohol-dependent participants exhibit smaller N400 amplitudes across all conditions. µV=microvolts.

$p < .001$), but not primed or unprimed, stimuli. Given our null findings, it is unlikely that these results were biased by this violation.

3.2.2. Reaction time

A significant within-subjects effect of semantic condition was noted ($F(1.75,219.11) = 4.17$; $p = .02$). Subsequent analyses revealed that the primed condition elicited the shortest reaction time (Mean = .532 s; S.E. = .01), followed by the unprimed (Mean = .573 s; S.E. = .01) and non-word (Mean = .618 s; S.E. = .01) conditions (values are covariate adjusted, estimated marginal means). All conditions were statistically different from one another ($ps < .001$). Between-subjects differences associated with alcohol dependence, cocaine dependence and their interaction were non-significant.

3.3. Event-Related Potentials

3.3.1. Anterior vs. posterior region

A significant main effect of alcohol dependence was observed ($F(1,125) = 10.29$; $p = .002$), in which alcohol dependent participants exhibited a less negative N400 amplitude relative to non-dependent controls. Cocaine dependence and the interaction with alcohol dependence were non-significant.

Significant within-subjects effects of electrode grouping ($F(1,125) = 35.90$; $p < .001$) and semantic condition ($F(1.95,243.87) = 3.89$; $p = .02$) were also noted. Based on estimated marginal means, the posterior N400 amplitude was slightly, but significantly, more negative than frontal N400 amplitude. For semantic condition, N400 amplitudes in response to primed words were significantly less negative than those elicited by unprimed or non-word stimuli ($ps < .001$). N400s in response to unprimed and non-word stimuli were not statistically different. No within-subjects interactions were noted.

ERP waveforms reflecting these significant effects are shown in Fig. 2.

3.3.2. Left vs. right hemisphere

A significant interaction of electrode group and semantic condition was noted ($F(1.94,242.89) = 3.89$; $p = .02$). Subsequent analyses indicated a more negative N400 amplitude in the left hemisphere grouping relative to the right hemisphere grouping, but this difference was only significant in the non-word condition ($F(1,125) = 6.75$; $p = .01$). The previously noted main effect of alcohol dependence was upheld ($F(1,125) = 5.56$; $p = .02$).

3.4. Nicotine dependence

Zero order correlations were examined using data from participants reporting one or more symptoms of nicotine dependence. No significant relationship was found between symptom count and N400 amplitude in any condition or at any electrode grouping. Likewise, nicotine dependence symptoms were not related to response accuracy or reaction time measures.

4. Discussion

4.1. Alcohol dependence

The present study utilized the N400 ERP to assess the neurophysiological processes involved in semantic priming among alcohol- and cocaine-dependent participants. Although the expected semantic priming effect was observed overall, results showed an N400 decrement in the alcohol-dependent group. The result is consistent with previous findings of N400 decrements in alcoholic participants (Ji et al., 1999; Nixon et al., 2002; Porjesz et al., 2002). Furthermore, we demonstrated that the decrement could also not be explained by a number of other factors, which can co-occur with alcohol dependence. More specifically, this effect was present despite covarying for age, antisocial symptomology, marijuana dependence severity and depression severity. Further, nicotine dependence severity was not significantly related to the decrement. One is therefore inclined to hypothesize that N400 decrements reflect neurotoxicity related to a lifetime diagnosis of alcohol dependence. One must, of course, be cautious in inferring causation from a single study. Further tests of the replicability and generalizability of these results across other samples of alcohol dependent patients are required before such a relationship can be established.

Importantly, the N400 decrement in alcohol-dependent participants was consistent across semantic conditions. Therefore, the effects of alcohol dependence are not specifically tied to brain regions involved in decisions about semantic relationships (Glenn and Parsons, 1992; Mann et al., 1999; Nixon et al., 1987). Instead, these effects may involve other areas of language processing or cognition as well. For example, alcohol dependence has been associated with impaired priming in the processing of nonverbal, visuospatial stimuli (Ji et al., 1999).

4.2. Cocaine dependence

Although alcohol-dependent and cocaine-dependent individuals share a number of overlapping neuropsychological and neurophysiological deficits (Nixon and Phillips, 1999; Rogers and Robbins, 2001 for review), including decrements of verbal functioning (Gillen et al., 1998; Nixon et al., 2002; Goldstein et al., 2004), cocaine-dependent participants did not demonstrate the same pattern of deficits observed in the alcohol dependent group. This result is consistent with previous reports (Jasiukaitis and Fein, 1999) that cocaine-dependent patients demonstrate intact semantic priming even

though they may show impairments in other areas. Further, no cocaine × alcohol dependence interactions were observed in the current study. This result challenges hypotheses stating that cocaine and alcohol have a synergistic and negative effect on cognition (Bolla et al., 2000; Horner, 1997). However, the present null findings are supported by a growing literature (Di Sclafani et al., 1998; Easton and Bauer, 1997; Lawton-Craddock et al., 2003; Robinson et al., 1999), which suggests that individuals with concurrent alcohol and cocaine dependence are not a unique group with regard to cognitive decrements.

4.3. Limitations

The current study is limited by gender inequities in alcohol and cocaine dependent groups. The small number of female participants prohibited inclusion of gender as additional grouping factor in statistical analyses. However, to address this concern, analyses were repeated using only male participants. The overall pattern of N400 amplitudes was similar to that observed in the complete sample. Thus, it appears that the N400 amplitude findings noted in the larger analysis were not related to gender differences. This conclusion is substantiated by previous research, which found no gender-related differences in N400 amplitude (Nixon et al., 2002).

Further, a significant number of participants met criteria for nicotine dependence. Thus, post-hoc analyses examined potential correlations between the ERP and behavioral variables of interest and the number of DSM-IV (American Psychiatric Association, 1994) nicotine dependence criteria endorsed on the SSAGA. Nicotine dependence was not correlated with N400 amplitudes or behavioral measures on primed, unprimed or non-word trials. However, the current study was not originally designed as a test of this factor. Future investigations should include a larger percentage of nicotine-dependent participants in alcohol/cocaine dependent and control groups.

The results of the current study are strengthened by the inclusion of participants meeting criteria for the more significant diagnosis of dependence versus the broader and physiologically less significant diagnosis of abuse. Studies which fail to differentiate between dependence and abuse are likely to contain a heterogeneous sample of affected participants and are therefore less likely to reveal neurotoxic effects of alcohol or cocaine.

5. Conclusion

In summary, the current findings support previous reports of semantic processing deficits in alcoholics (Ji et al., 1999; Nixon et al., 2002; Porjesz et al., 2002). Results suggest that this deficit may be mediated by alcohol-related impairment of neuronal activation to verbal stimuli. Interestingly, neither cocaine dependence nor the interaction of cocaine and alcohol dependence was associated with impaired semantic priming. This finding is in contrast to hypotheses that chronic codependence on cocaine and alcohol results in additive, negative effects on cognition. However, a number of recent studies suggest that individuals dependent on both cocaine and alcohol do not comprise a cognitively unique group (Di Sclafani et al., 1998; Easton and Bauer, 1997; Lawton-Craddock et al., 2003; Robinson et al., 1999).

Acknowledgements

This study was supported, in part, by USPHS grants T32AA07290, U10AA08401, U10AA08402, U10AA08403, RO1AA-12553, U24-11898, and M01 RR-10284. The data were collected at the Howard University Collaborative Alcohol Research Center, Washington, DC.

References

Abdullaev, Y., Kennedy, B.L., Tasman, A., 2002. Changes in neural circuitry of language before and after treatment of major depression. Hum. Brain Mapp. 17, 156–167.

Almasy, L., Porjesz, B., Blangero, J., Goate, A., Edenberg, H.J., Chorlian, D.B., Kuperman, S., O'Connor, S.J., Rohrbaugh, J., Bauer, L.O., Foroud, T., Rice, J.P., Reich, T., Begleiter, H., 2001. Genetics of event-related brain potentials in response to a semantic priming paradigm in families with a history of alcoholism. Am. J. Hum. Genet. 68, 128–135.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American Psychiatric Press, Washington, DC.

Auchterlonie, S., Phillips, N.A., Chertkow, H., 2002. Behavioral and electrical brain measures of semantic priming in patients with Alzheimer's disease: implications for access failure versus deterioration hypotheses. Brain Cogn. 48, 264–267.

Belmore, S.M., Miller, L.L., 1980. Levels of processing and acute effects of marijuana on memory. Pharmacol. Biochem. Behav. 13, 199–203.

Bentin, S., 1989. Electrophysiological studies of visual word perception, lexical organization and semantic processing: a tutorial review. Lang. Speech 32, 205–220.

Bolla, K.I., Funderburk, F.R., Cadet, J.L., 2000. Differential effects of cocaine and cocaine+alcohol on neurocognitive performance. Neurology 54, 2285–2292.

Boyer, S.C., Petersen, D.R., 1990. Potentiation of cocaine-mediated hepatotoxicity by acute and chronic ethanol. Alcohol., Clin. Exp. Res. 14, 28–31.

Brookoff, D., Rotondo, M.F., Shaw, L.M., Campbell, E.A., Fields, L., 1996. Coacaethylene levels in patients who test positive for cocaine. Ann. Emerg. Med. 27, 316–320.

Bucholz, K.K., Cadoret, R., Cloninger, C.R., Dinwiddie, S.H., Hesselbrock, V.M., Nurnberger Jr., J., Reich, T., Schmidt, I., Schuckit, M.A., 1994. A new semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. J. Stud. Alcohol 55, 149–158.

Bunney, E.B., Appel, S.B., Brodie, M.S., 2001. Electrophysiological effects of cocaethylene, cocaine, and ethanol on dopaminergic neurons of the ventral tegmental area. J. Pharmacol. Exp. Ther. 297, 696–703.

Ceballos, N.A., Nixon, S.J., Phillips, J.A., Tivis, R., 2003. Semantic processing in alcoholics with and without antisocial symptomatology. J. Stud. Alcohol 64, 286–291.

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, Second edition. Lawrence Erlbaum Associates, Hillsdale, NJ.

Di Sclafani, V., Clark, H., Tolou-Shams, M., Bloomer, C.W., Salas, G.A., Norman, D., Fein, G., 1998. Premorbid brain size is a determinant of functional reserve in abstinent crack-cocaine and crack-cocaine–alcohol-dependent adults. J. Int. Neuropsychol. Soc. 4, 559–565.

Easton, C., Bauer, L.O., 1997. Neuropsychological differences between alcohol-dependent and cocaine-dependent patients with or without problematic drinking. Psychiatry Res. 71, 97–103.

Etkind, S.A., Fantegrossi, W.E., Riley, A.L., 1998. Cocaine and alcohol synergism in taste aversion learning. Pharmacol. Biochem. Behav. 59, 649–655.

Foltin, R.W., Fischman, M.W., 1988. Ethanol and cocaine interactions in humans: cardiovascular consequences. Pharmacol. Biochem. Behav. 31, 877–883.

Fossati, P., Guillaume, L.B., Ergis, A.-M., Allilaire, J.-F., 2003. Qualitative analysis of verbal fluency in depression. Psychiatry Res. 117, 17–24.

Ganis, G., Kutas, M., Sereno, M.I., 1996. The search for "common sense": an electrophysiological study of the comprehension of words and pictures in reading. J. Cogn. Neurosci. 8, 89–106.

Gillen, R.W., Kranzler, H.R., Bauer, L.O., Burleson, J.A., Samarel, D., Morrison, D.J., 1998. Neuropsychologic findings in cocaine-dependent outpatients. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 22, 1061–1076.

Glenn, S.W., Parsons, O.A., 1992. Neuropsychological efficiency measures in male and female alcoholics. J. Stud. Alcohol 53, 546–552.

Goldstein, R.Z., Leskovjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S.S., Wang, G.-J., Fowler, J.S., Volkow, N.D., 2004. Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex. Neuropsychologia 42, 1447–1458.

Grant, B.F., Harford, T.C., 1990. Concurrent and simultaneous use of alcohol with cocaine: results of national survey. Drug Alcohol Depend. 25, 97–104.

Gunter, T.C., Jackson, J., Mulder, G., 1998. Priming and aging: an electrophysiological investigation of N400 and recall. Brain Lang. 65, 333–355.

Hamberger, M.J., Friedman, D., Ritter, W., Rosen, J., 1995. Event-related potential and behavioral correlates of semantic processing in Alzheimer's patients and normal controls. Brain Lang. 48, 33–68.

Henning, R.J., Wilson, L.D., 1996. Cocaethylene is as cardiotoxic as cocaine but is less toxic than cocaine plus ethanol. Life Sci. 59, 615–627.

Hesselbrock, M., Easton, C., Bucholz, K.K., Schuckit, M., Hesselbrock, V., 1999. A validity study of the SSAGA-A comparison with the scan. Addiction 94, 1361–1370.

Hokama, H., Hiramatsu, K.-I., Wang, J., O'Donnell, B.F., Ogura, C., 2003. N400 abnormalities in unmedicated patients with schizophrenia during a lexical decision task. Int. J. Psychophysiol. 48, 1–10.

Horner, M.D., 1997. Cognitive functioning in alcoholic patients with and without cocaine dependence. Arch. Clin. Neuropsychol. 12, 667–676.

Jasiukaitis, P., Fein, G., 1999. Intact visual word priming in cocaine dependent subjects with and without cognitive deficit. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 23, 1019–1036.

Ji, J., Porjesz, B., Begleiter, H., 1999. Event-related potential index of semantic mnemonic dysfunction in abstinent alcoholics. Biol. Psychiatry 45, 494–507.

Kiehl, K.A., Hare, R.D., McDonald, J.J., Brink, J., 1999. Semantic and affective processing in psychopaths: an event-related potential (ERP) study. Psychophysiology 3, 765–774.

Kuperman, S., Porjesz, B., Arndt, S., Bauer, L., Begleiter, H., Cizadlo, T., O'Connor, S., Rohrbaugh, J., 1995. Multi-center N400 ERP consistency using a primed and unprimed word paradigm. Electroencephalogr. Clin. Neurophysiol. 94, 462–470.

Kutas, M., Hillyard, S.A., 1980. Reading senseless sentences: brain potentials reflect semantic incongruity. Science 207, 203–205.

Lawton-Craddock, A., Nixon, S.J., Tivis, R., 2003. Cognitive efficiency in stimulant abusers with and without alcohol dependence. Alcohol., Clin. Exp. Res. 27, 457–464.

Mann, K., Gunther, A., Stetter, F., Ackerman, K., 1999. Rapid recovery from cognitive deficits in abstinent alcoholics: a controlled test–retest study. Alcohol Alcohol. 34, 567–574.

Minamoto, H., Tachibana, H., Sugita, M., Okita, T., 2001. Recognition memory in normal aging and Parkinson's disease behavioral and electrophysiological measures. Brain Res. Cogn. Brain Res. 11, 23–32.

Nixon, S.J., Phillips, J.A., 1999. Neurocognitive deficits and recovery in chronic alcohol abuse. CNS Spectr. 4, 95–108.

Nixon, S.J., Kujawski, A., Parsons, O.A., Yohman, J.R., 1987. Semantic (verbal) and figural memory impairment in alcoholics. J. Clin. Exp. Neuropsychol. 9, 311–322.

Nixon, S.J., Tivis, R., Ceballos, N., Varner, J.L., Rohrbaugh, J., 2002. Neurophysiological efficiency in male and female alcoholics. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 26, 919–927.

Odeleye, O.E., Watson, R.R., Eskelson, C.D., Earnest, D., 1993. Enhancement of cocaine-induced hepatotoxicity by ethanol. Drug Alcohol Depend. 31, 253–263.

Oztezcan, S., Dogru-Abbasoglu, S., Mutlu-Turkoglu, U., Calay, Z., Aykac-Toker, G., Uysal, M., 2000. The role of stimulated lipid peroxidation and impaired calcium sequestration in the enhancement of cocaine induced hepatoxicity by ethanol. Drug Alcohol Depend. 58, 77–83.

Ponsoda, X., Bort, R., Jover, R., Gomez-Lechon, M.J., Castell, J.V., 1999. Increased toxicity of cocaine on human hepatocytes induced by ethanol: role of GSH. Biochem. Pharmacol. 58, 1579–1585.

Porjesz, B., Begleiter, H., 1996. Effects of alcohol on electrophysiological activity of the brain. In: Begleiter, H., Kissen, B. (Eds.), The Pharmacology of Alcohol and Alcohol Dependence, Alcohol and Alcoholism, vol. 2. Oxford University Press, New York, pp. 207–247.

Porjesz, B., Begleiter, H., Wang, K., Almasy, L., Chorlian, D.B., Stimus, A.T., Kuperman, S., O'Connor, S.J., Rohrbaugh, J., Bauer, L.O., Edenberg, H.J., Goate, A., Rice, J.P., Reich, T., 2002. Linkage and linkage disequilibrium mapping of ERP and EEG phenotypes. Biol. Psychol. 61, 229–248.

Robinson, J.E., Heaton, R.K., O'Malley, S.S., 1999. Neuropsychological functioning in cocaine abusers with and without alcohol dependence. J. Int. Neuropsychol. Soc. 5, 10–19.

Rogers, R.D., Robbins, T.W., 2001. Investigating the neurocognitive deficits associated with chronic drug misuse. Curr. Opin. Neurobiol. 11, 250–257.

Schechter, M.D., Meehan, S.M., 1995. The lethal effects of ethanol and cocaine and their combination in mice: implications for cocaethylene formation. Pharmacol. Biochem. Behav. 52, 245–248.

Vanek, V.W., Dikcey-White, H.I., Sighns, S.A., Schechter, M.D., Buss, T., Kulics, A.T., 1996. Concurrent use of cocaine and alcohol by patients treated in the emergency department. Ann. Emerg. Med. 28, 508–514.

Warburton, D.M., Skinner, A., Martin, C.D., 2001. Improved incidental memory with nicotine after semantic processing but not after phonological processing. Psychopharmacology 153, 258–263.