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Transdermal Nicotine Administration and the Electroencephalographic Activity of Substance Abusers in Treatment

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Abstract

Objectives—It is widely recognized that individuals with alcohol or illicit substance abuse disorders often smoke cigarettes. However, few studies have examined the direct effects of nicotine among substance abuse subgroups. The current study examined patterns of electroencephalographic (EEG) activity in alcohol-dependent (AD), stimulant-dependent (StimD), alcohol- and stimulant-dependent (ASD) participants, as well as community controls (CC). All participants were regular smokers.

Methods—After overnight nicotine abstinence, subjects were administered either a high (14 or 21 mg) or low (7mg) dose transdermal nicotine patch. EEG data were collected during a 2 minute eyes open and 5 minute eyes closed baseline recording session, which occurred as part of a larger study of brain electrophysiology.

Results—The most interesting finding was a differential pattern of nicotine dose effects by group. EEGs of Controls and ASD participants did not distinguish between high and low nicotine doses; whereas, nicotine administration in the AD and StimD groups resulted in opposite findings across a range of spectral bands.

Conclusions—Although further research is warranted, these results may have implications for the study of smoking cessation and attentional functioning among substance abusers in treatment. These data suggest that nicotine-related changes in neurophysiology may be associated with specific brain areas and/or specific drug histories and reinforce the need for caution in generalizing among such groups.

Keywords

Nicotine; Alcohol; Cocaine; Methamphetamine; Electroencephalogram

Introduction

Cigarette smoking is highly prevalent among alcohol dependent and other substance abusing groups [1]. Some studies have estimated smoking rates in alcohol dependent populations to be as high as 90% [2]. Our own data indicate smoking rates of approximately 73-90% in a large

sample of males and females seeking treatment for substance abuse disorders [3,4]. Given the opposing effects of acute nicotine administration, which is often presumed to be cognitively enhancing [5,6,7], and the chronic effects of other drugs of abuse, which are typically negative [8,9,10,11,12], the co-morbidity of nicotine and other substance dependence may be of direct relevance to the investigation of the long-term neurocognitive effects of chronic substance abuse. Consistent with this hypothesis are recent data from our own work, in which acute nicotine administration altered the typical performance patterns of alcohol [13] and stimulant dependent [14,15] participants on tasks assessing attentional functioning. Specifically, alcohol- and stimulant-dependent individuals often exhibit deficits of attentional functioning [16]; which were not observed in our study when nicotine levels were stabilized throughout the testing session.

Although research regarding the combined effects of nicotine and other substance abuse has increased, there remains a dearth of information regarding the potentially compensatory and/or interactive effects of acute nicotine administration on a variety of neurocognitive functions in chronic substance abusers. Of particular interest to the current study were the potential effects of drug combinations (e.g., chronic and acute) on quantitative electroencephalographic activity (EEG). In this technique, brain electrical activity is recorded in the relaxed state with eyes open or eyes closed, resulting in absolute power (μV^2) values corresponded to the EEG frequency bands of alpha, beta, delta and theta. Alpha activity is indicative of a relaxed, alert state; whereas, beta activity is indicative of cortical arousal [17,18,19,20]. As opposed to recordings produced during sleep, clinically significant increases delta and theta activity during the awake but resting state may be characteristic of generalized brain dysfunction [21].

Alcohol and stimulant dependent individuals have demonstrated differences in the EEG relative to controls. For example increased beta power has been found in the resting EEG of abstinent alcohol dependent and stimulant dependent participants when compared to controls [22,23,24]. Another common finding is low voltage alpha (LVA) in the EEGs of alcohol dependent individuals. As mentioned previously, increased alpha activity is indicative of a relaxed, alert state; whereas, alpha activity decreases and beta activity increases during a state of arousal [17,18,19,20]. Thus, the resting EEG of alcoholics with LVA more closely resembles an aroused state as seen in control participants without a history of alcohol dependence [17]. Among alcohol dependent individuals, this trait appears to be more common in patients with co-morbid anxiety disorders than among those without [25]; thus, it is possible that enhanced arousal during rest might induce alcohol dependent individuals to self-medicate with alcohol in order to reduce arousal/anxiety to “normal” levels.

Given the high prevalence of smoking among alcohol and substance dependent individuals, it is also of interest to note that acute nicotine administration has been associated with changes (e.g., indicative of cortical arousal/activation) in the power of various components of the quantitative EEG in a number of studies [26,27,28,29,30,31,32,33].

Most relevant to the current proposal, Knott and colleagues [34] found absolute power decreases in delta (1-3.5 Hz) and theta (4-7.5 Hz) power with increases in α_2 (11-13.5 Hz) power in response to transdermal nicotine administration. On measures of relative power, Knott et al. report theta (4-7.5 Hz) power decreased; whereas, increases in power were noted for α_2 (11-13.5 Hz) and β_2 (22-29.5 Hz). Similarly, the work of Lindgren and colleagues [35] also indicated decreases in absolute power of delta (0.5-4.0 Hz) and theta (4.1-8.0 Hz) power with corresponding increases in α_2 (10.6-13.0 Hz). Absolute beta (13.1-26.5 Hz) power also increased, but only in response to high nicotine concentrations (intravenous nicotine administration of 28 $\mu g/kg$ body weight).

To extend this work to a population of substance dependent regular smokers and community controls, the current study was designed to examine potential differences in EEG power estimates in terms of frequency and topography in four groups: 1) alcohol dependent cigarette smokers (AD), 2) alcohol + stimulant (cocaine and/or methamphetamine) dependent cigarette smokers (ASD), 3) stimulant dependent cigarette smokers (StimD), and 4) cigarette smokers without a history of alcohol or drug abuse/dependence (CTRL). Importantly, throughout the testing session, nicotine withdrawal symptoms were controlled by the double-blind administration of a low (7mg) or high (14 or 21mg) dose transdermal nicotine patch.

Based on the current literature, as well as our own findings, we predicted that under the influence of nicotine administration, these four groups would exhibit differential EEG power estimates. As a result of our theoretical interest in attention and the current literature regarding beta power and to a lesser extent alpha power, we hypothesized that the greatest differences between groups would be observed in the beta and alpha spectral bands.

Our previous studies using primarily behavioral methods [14,15] suggested that detoxified alcoholics performed more efficiently (vs. recovering stimulant abusers) under the influence of nicotine administration. No dose effects of nicotine administration were noted. However, we anticipated that the failure to observe dose differences might have been due to the specific dependent variables and that a more subtle indicator, such as brain electrophysiology, would reveal stimulant-related nicotine responses.

Methods

Participants

Data were collected at the University of Oklahoma Health Sciences Center. Alcohol-dependent (AD, $n=26$; 19 male), stimulant-dependent (StimD, $n=20$; 11 male), and alcohol- and stimulant-dependent (ASD, $n=14$; 8 male) individuals and community controls ($n=22$; 16 male) participated in the study. Both male and female participants were recruited. Informed consent was obtained from all participants prior to participation in each phase of the study, and the study protocol was approved by the University of Oklahoma Health Sciences Center Institutional Review Board. Participants were between ages 21 and 54 and smoked a minimum of 10 cigarettes per day throughout the previous year (Mean Cigarettes/Day across groups ≥ 14.6 , most ≥ 20.0 ; See Table 2). Substance abusing participants (AD, StimD, and ASD) were recruited from the treatment setting; whereas, community control participants learned of the study through newspaper ads, flyers or word-of-mouth.

A comprehensive screening packet was administered to obtain general demographic information. The packet also included measures of depressive symptomatology (Beck Depression Inventory, BDI-II) [36], state anxiety (Spielberger State Anxiety Inventory, SSAI) [37], verbal and abstracting skills (Shipley Institute of Living Scale-Vocabulary, SILS-V; Shipley Institute of Living Scale-Abstracting, SILS-A) [38], as well as a detailed history of alcohol, illicit drug and nicotine use. The alcohol use questionnaire also included assessment of participants' quantity frequency indices (QFI) [39], or ounces of absolute ethanol consumed per day over the six month period prior to testing. Drug use variables included chronicity, frequency, and typical use patterns. A preliminary carbon monoxide (CO) reading was obtained during the screening phase of the study to provide a baseline of typical CO levels per participant.

Further information regarding general medical health was obtained in a separate interview. In addition, exclusionary criteria included neurological, psychiatric and/or medical disorders that could interfere with cognitive function and/or brain electrophysiology. To screen for such disorders, all participants underwent medical and diagnostic interviews including the Diagnostic Interview Schedule, Version IV (DIS-IV) [40]. In addition, individuals who

endorsed conditions that would prohibit the use of the transdermal nicotine patch, such as chronic skin conditions or hypertension, were also excluded from the study.

Nicotine dependence level was measured by two methods. Participants self-reported symptoms of nicotine dependence in a questionnaire format by completing the Fagerstrom Test for Nicotine Dependence, an instrument that emphasizes morning smoking and overall “heaviness” of smoking [41]. In addition, the DIS-IV interview also measured the DSM-IV symptoms and diagnoses pertaining to nicotine dependence; this method emphasizes adverse consequences, desire to cut down and mood changes during withdrawal [41].

Participants who reported occasional use of marijuana were accepted in the current study; however, they were questioned with regard to their marijuana use at each phase of the study and required to abstain from using marijuana in the 48 hours prior to neurocognitive testing. These marijuana-related criteria are supported by previous studies in which no THC-related neurophysiological differences were noted in medically and psychiatrically normal marijuana users vs. controls [42,43; however, see also 44]. As an additional measure of control, participants’ symptoms of marijuana dependence were recorded and retained for use as a possible covariate in analyses of electroencephalographic activity.

Participants reported recent use for all substances at three time points: initial screening, diagnostic interview, and day of laboratory testing. Individuals who failed to meet inclusionary criteria were excluded from the day of laboratory testing, and EEG data were not recorded for these individuals. Based on participants’ medical history as obtained in the interview phase, a physician approved all participants prior to study participation. A summary of the requirements for inclusion in individual participant groups are detailed below and shown in Table 1.

Community Comparison Group

Participants within the control group reported a QFI (e.g., quantity/frequency of alcohol use over the last 6 months) [39] of less than 1.0. This drinking level is approximately equivalent to less than 2 alcoholic drinks per day. In addition, participants reported no significant history of alcohol abuse or illicit drug use.

Substance Abusing Subgroups

Individuals were assigned to their drug group on the basis of self-reported QFI and primary drug of choice, as well as Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) [45] classification, as derived from the diagnostic interview screening described above. In addition, the minimum drinking levels for alcohol-dependent women were adapted to enhance the recruitment of female participants [See 46 for review]. Women within both alcohol dependent (AD) and alcohol / stimulant dependent (ASD) groups reported a minimum QFI of 2, which is approximately equivalent to 4 drinks per day over the previous six months prior to treatment. Participants attained a minimum of 21 days of sobriety/abstinence prior to participating in the laboratory portion of the study (range 21-75 days).

The alcohol dependent (AD) group was comprised of individuals who identified alcohol as their primary drug of choice and who met DSM-IV criteria for alcohol dependence with a minimum QFI of 5 (~10 drinks per day). The stimulant dependent (StimD) group included individuals who met DSM-IV criteria for stimulant abuse and/or dependence and/or who reported regular use of cocaine and/or methamphetamine over the last year. This group reported drinking less than or equal to 2 standard drinks per day with no chronic periods of problem drinking over the last year. The alcohol and stimulant dependent (ASD) group met DSM-IV criteria for stimulant abuse and/or dependence and a minimum drinking level of 8 standard drinks per day.

Laboratory Testing

Participants were asked to refrain from smoking overnight prior to testing. Carbon monoxide (CO) readings were obtained on the morning of testing and compared to screening values. Compliance was evidenced by a maximum CO reading of 12ppm or less or 50% of baseline CO [13,14,15]. Participants were presented with a standard breakfast, and a single caffeinated beverage was made available for individuals who regularly consumed caffeine in the morning. Prior to the application of the transdermal nicotine patch, blood pressure, breath alcohol content and urine analyses for pregnancy and drugs of abuse were conducted.

Two doses of transdermal nicotine (low or high nicotine dose) were randomized in order to detect potential dose responses across substance dependent groups, particularly with regard to potential stimulant cross-tolerance effects among cocaine/methamphetamine users.

Participants were randomly assigned to receive a low (7mg) or high (14mg for women, 21mg for men) dose of nicotine via a Nicoderm CQ transdermal nicotine patch placed on the upper left scapula. Nicotine administration was double-blind. Female participants received a 14mg high dose of nicotine based on previous work in our laboratory, which indicated that the 21mg patch was poorly tolerated by this group [14].

Gender distribution across groups for individuals receiving the low dose nicotine administration was as follows: Controls (n=12; 8 male), AD (n=13; 10 male); ASD (n=7; 4 male) and StimD (n=8; 6 male). For the high dose nicotine group, gender distribution across groups included 10 Controls (8 male), 13 AD (9 male), 7 ASD (4 male) and 12 StimD (6 male). Thus, analyses based on gender differences were beyond the scope of the current study due to the low availability of female participants across groups.

Data Collection

A number of instruments were administered prior to nicotine uptake, including the BDI-II, the SSAI and the Withdrawal Symptoms Checklist (WSC) [45,47]. The WSC was included in the study as a control measure to determine whether or not participants experienced the same degree of withdrawal (or lack thereof) prior to nicotine uptake.

Electrophysiology

Quantitative EEG data were collected approximately one hour following the application of the transdermal nicotine patch, in accordance with the methods of Levin et al. [48]. Data were acquired from a 64-channel electrode cap. Additionally, four tin electrodes were placed on the face as follows: A single electrode was placed on the nose for reference and ocular movement was monitored via linked electrodes above and below the right eye (2cm above the eyebrow; 2cm below the eye; both in line with the pupil). The fourth electrode was placed on the forehead as a ground. Impedance measurements at or below 5 kOhms were required prior to testing, and the activity of each electrode was monitored throughout testing.

After electrode application, participants were escorted to an electrically and acoustically shielded, G-series Panel Audiometric Examination Booth (Eckel Industries, Morrisburg, Ontario, Canada) and allowed to acclimate to this environment. Approximately one hour after nicotine administration, EEG data were acquired. Participants were seated behind a table and fitted with a chin rest to minimize head movement. EEG data with the participant's eyes open were recorded for a period of 2 minutes; whereas, eyes closed data were recorded for a period of 5 minutes. EEG data were amplified using a Sensorium EPA-4 Electrophysiology Amplifier (Sensorium, Inc., Charlotte, VT) with an overall gain of 10,000. Online filtering was set at 0.02Hz high pass and 50Hz low pass. Data were sampled at an analog to digital conversion rate of 500Hz.

At the time of data collection, EEG data were initially screened in real time via visual examination by trained research assistants for the presence of issues such as drowsiness, which could influence subsequent analyses. Data from participants with at least 2 minutes of artifact-free eyes open EEG and at least 5 minutes of artifact-free eyes closed data, were stored for subsequent spectral analysis.

Spectral Analyses

Data were subjected to spectral analysis using the Neuroscan SCAN EDIT software (Neuroscan Labs, Charlotte, NC). Cosine tapering techniques (Hanning Window) were employed, in accordance with published guidelines [49]. Manual eye-blink rejection was used to eliminate participants with EEG values of + or – 50 μ V at the ocular movement electrode. Resulting absolute power (μ V²) values corresponded to the frequency bands alpha1 (8.5-10.5 Hz), alpha2 (10.6-13.5 Hz), beta1 (13.5-19.5 Hz) and beta2 (19.5-26 Hz) [19].

Of the original 92 research participants, data from 82 participants remained following removal of individuals with significant drowsiness, eye-blink or other electrophysiological artifacts, and/or technical problems.

Analysis of quantitative EEG data focused primarily on inter-hemispheric averages of absolute power values (μ V²), as suggested in Pivik et al. [49]. Previous studies suggest that hemispheric analyses are an appropriate choice for quantitative EEG data collected under conditions of rest, as opposed to cognitive demand [50,51]. In addition, electrical activity of anterior and posterior brain regions were analyzed as well as potentially differential activity in left anterior, left posterior, right anterior and right posterior quadrants.

These averaging techniques serve to decrease the overall probability of Type I error by reducing the number of independent analyses performed on interrelated data [52], presenting a more stable overview of brain activity within a particular hemisphere vs. the examination of 64 individual electrode sites.

Results were then log transformed in accordance with recommendations from Pivik and colleagues to provide a more Gaussian distribution prior to parametric analyses. Each functionally distinct brain region defined above was then analyzed separately for eyes open and eyes closed conditions.

Data Analysis

Background characteristics, including demographic, mental health and substance use variables, were analyzed via separate ANOVAs with drug group and nicotine dose as grouping variables. Distribution of gender, race/ethnicity and tobacco dependence diagnosis (DSM-IV) were analyzed using Chi-Square statistics. For each EEG condition (e.g., eyes open, eyes closed), the individual frequency bands were analyzed via separate repeated measures ANOVAs using drug group and nicotine dose as grouping variables with hemisphere (left or right) as the within-subjects factor.

In repeated measures analyses, Greenhouse-Geisser corrections were employed where applicable to protect against violations of the assumption of sphericity. Significant within-subjects effects of cerebral hemisphere groupings were followed by ANOVA. Significant between-subject effects were followed with pair-wise comparisons with Bonferroni adjustments where applicable.

Results

Background Variables

Demographic information, measures of depression and anxiety, as well as alcohol use levels are listed as background variables in Table 2. The distribution of male and female participants across groups did not differ significantly by drug group or by nicotine dose ($ps > .60$); likewise the distribution of race/ethnicity (in order to increase statistical power, this variable was represented as percent Caucasian participants) did not differ between groups or nicotine doses ($ps > .10$). Age and years of education did not differ significantly by drug group or nicotine dose group or their interaction ($ps > .34$). No statistically significant differences in verbal performance were noted by drug group, nicotine dose group or their interaction ($ps > .08$). Although levels of depression were not clinically significant, statistical differences were noted between groups for depression on the day of testing ($F(3,71)=6.39$; $p=.001$). Control participants endorsed significantly fewer symptoms of depression on the day of testing compared to all substance abusing groups ($ps < .02$), which did not differ from one another on this measure. Similarly, group differences were noted for symptoms of anxiety on the day of testing ($F(3,72)=2.87$; $p=.04$). The AD group was statistically more anxious than the control group ($p=.005$). No other significant differences were noted. As previously indicated, despite statistical differences in anxiety levels on the day of testing, all values were below the level of clinical significance (see Table 2 for means).

As expected, ounces of absolute ethanol consumed per day over the 6 months prior to testing (QFI; Cahalan et al., 1969) differed between groups ($F(3,72)=34.69$; $p<.001$). Controls and StimD groups reported drinking less than 1 ounce of absolute ethanol per day and differed from all other groups ($ps < .001$). The ASD group reported approximately 7.5 ounces per day and differed from all other groups ($ps < .02$), and the AD group differed significantly from all groups and reported the highest level of drinking, approximately 11 ounces of absolute ethanol per day ($ps < .02$).

Although marijuana symptoms in the overall sample were quite low, a significant group difference was also noted for symptoms of marijuana dependence ($F(3,73)=4.44$; $p=.006$). Subsequent Bonferroni-corrected pair-wise comparisons revealed a similar number of marijuana dependence symptoms (range of symptoms = 0 to 6) for Controls as well as AD and ASD groups; however, the StimD group reported a greater number of marijuana dependence symptoms compared to the Controls and AD groups ($ps < .004$); See Table 2.

To assess the potential influence of marijuana dependence symptoms on the dependent measures of interest for both eyes open and eyes closed conditions, zero-order correlations were performed. Results indicated no significant correlations between the number of self-reported marijuana dependence symptoms and the log transformed absolute power values of the spectral bands (Eyes Open = $ps > .10$, most greater than .33; Eyes Closed = $ps > .15$, most greater than .26). Due to the lack of significant correlations, marijuana symptoms were not included in any subsequent analyses of EEG variables.

Nicotine Consumption Characteristics

Significant group differences were noted for the average number of cigarettes smoked per day ($F(3,71)=4.44$; $p=.006$). The AD group smoked significantly fewer cigarettes compared to all other groups ($ps < .04$). Other groups did not differ significantly from one another on this variable ($ps > .12$). No significant differences were noted for the age at which participants began smoking regularly ($ps > .13$). Participants did not differ significantly with regard to their levels of self-reported nicotine withdrawal prior to nicotine administration ($ps > .18$).

A significant group difference in nicotine dependence (FTND score) was noted ($F(3,66)=6.03$; $p=.001$; (FTND range = 0 to 10). The AD group reported the highest number of FTND symptoms compared to all groups, with the exception of StimDs ($ps<.04$). The StimD group differed significantly from the ASD group only ($p=.01$). The ASD group was statistically similar to controls. However, despite differences in self-reported FTND symptoms, no significant differences in DSM-IV nicotine dependence (as determined by the DIS-IV) were noted when these data were analyzed by group and by nicotine dose assignment ($ps>.07$). Further, no group or nicotine dose differences, or interactions, were noted for smoking expectancies as measured by the Smoking Consequences Questionnaire ($ps > .63$). Means for all measures are presented in Table 3.

Electrophysiological Analyses

Eyes Closed

Hemispheric analyses (Left vs. Right): Log transformed data were used for all analyses. For delta power, no significant group, dose or hemispheric differences were noted ($ps \geq .23$). A significant effect of cerebral hemisphere was noted for theta power ($F(1,72)=7.11$; $p=.009$). Absolute theta power was greater in left vs. right hemispheres. Further, an interaction of hemisphere $\times$ drug group $\times$ nicotine dose was also observed ($F(3,72)=3.22$; $p=.03$). However, subsequent analyses by hemisphere revealed no significant group or dose differences or interactions for theta power ($ps \geq .17$). A strong within-subjects hemispheric difference was noted for α_1 ($F(1,72)=20.68$; $p<.001$), in which absolute power of α_1 was greater in the left versus right hemisphere. An additional between-subjects effect of drug group was also observed ($F(3,72)=3.28$; $p=.03$). Follow-up analyses indicated greater α_1 power in the ASD and StimD groups compared to the control and AD groups. No other significant differences were noted for α_1 .

Among other effects, significant within-subject interactions of hemisphere $\times$ drug group $\times$ nicotine dose were noted for α_2 ($F(3,72)=5.42$; $p=.002$) and β_1 ($F(3,72)=3.53$; $p=.02$), in analyses of data collected in the eyes closed condition. Thus, prior to interpretation of other within- and between-subject effects, subsequent analyses were conducted in which spectral bands were analyzed using separate ANOVAs within each hemisphere. Results for analysis of α_2 power in the left hemisphere revealed a significant effect of drug group ($F(3, 72)=4.30$; $p=.008$), in which the stimulant abusers exhibited higher absolute power values compared to the alcohol dependent participants ($p=.003$) and controls ($p=.005$). Analysis of α_2 power in the right hemisphere indicated a significant group $\times$ patch interaction ($F(3, 72) = 5.32$; $p=.002$), as well as a main effect of drug group ($F(3,72)=3.59$; $p=.018$). Subsequent comparisons revealed a differential pattern of nicotine dose effects across groups. Although no significant dose differences were noted for controls and the ASD group, low dose nicotine administration in the AD group resulted in higher α_2 power, compared to the effects of the high dose transdermal patch ($F(1,24; 6.20; p=.02)$). However, the opposite effect was noted in the StimD group ($F(1, 17) = 8.52$; $p=.01$), in which the high dose transdermal patch resulted in higher α_2 power compared with the effects of the low dose patch.

A similar interaction of drug group $\times$ nicotine dose was observed for β_1 in the analysis of neuroelectric activity within the left hemisphere ($F(3, 72)=2.89$; $p=.04$). Subsequent comparisons revealed a differential pattern of nicotine dose effects across groups. Controls ($p=.21$), ASD ($p=.85$) and StimD ($p=.13$) groups did not exhibit differential reactions to high and low nicotine doses. However, ADs demonstrated greater β_1 power in response to the low dose vs. the high dose of nicotine ($F(1,24)=8.17$; $p=.009$). Again, the opposite effect was observed for the StimD group, in that a higher absolute power of β_1 was observed in response to the high dose vs. low dose transdermal nicotine patch, although this effect failed to reach statistical significance ($p=.13$). In the right hemisphere, an additional group $\times$ nicotine dose

interaction was observed for absolute power of β_1 ($F(3,72)=4.35$; $p=.007$). Follow-up analyses indicated the same pattern of findings mentioned previously; that is, no significant differences in response to nicotine dose for Controls and the ASD group and opposite effects for the AD and StimD groups. Once again, ADs exhibited a higher level of β_1 power in response to the low dose vs. high dose patch ($F(1,24)=12.42$; $p=.002$). In contrast, the StimDs exhibited higher levels of β_1 in response to the high dose vs. low dose patch, although this finding failed to reach statistical significance ($p=.07$). Interactive effects for β_1 and α_2 are shown in Figures 1, 2 and 3.

Finally, other than a significant hemispheric effect ($F(1,72)=5.65$; $p=.02$) in which β_2 power was greater in the left vs. right hemisphere across participants, no other significant effects were noted for β_2 .

Regional Analysis (Anterior vs. Posterior): For delta power, a significant effect of brain region was noted ($F(1,74)=41.463$; $p<.001$), in which the anterior region exhibited increased spectral power relative to the posterior region. A region $\times$ group interaction was also observed ($F(3,74)=4.718$; $p=.005$), and this effect was further dissected by a series of regional comparisons by group. For controls ($F(1,21)=31.95$; $p<.001$), ADs ($F(1,25)=27.45$; $p<.001$) and StimDs ($F(1,19)=7.193$; $p=.015$), a significant region effect was noted. The anterior region exhibited increased spectral power relative to the posterior region ($p<.015$). For the ASD's no significant regional effects occurred ($p=.745$).

In the theta spectral band, analyses revealed a significant effect of brain region ($F(1,74)=88.91$; $p<.001$). Anterior electrode sites exhibited decreased spectral power relative to posterior sites. In addition, a region $\times$ group interaction was also noted ($F(3,74)=2.986$; $p=.037$). No other significant effects were observed ($p>.14$). Additional analyses were conducted to dissect the interaction effect, as described previously. Within the control group ($F(1,20)=14.28$; $p=.001$), the anterior region exhibited greater spectral power vs. the posterior group. However, within the ADs ($F(1,24)=10.39$; $p=.004$), the ASDs ($F(1,12)=27.39$; $p<.001$), and the StimDs ($F(1,18)=55.084$; $p<.001$), this pattern was reversed, indicating a differences among substance dependent individuals vs. the community control group.

For α_1 , a significant within subjects effect of brain region was noted ($F(1,74)=342.969$; $p<.001$), in which the anterior region exhibited increased spectral power relative to the posterior region. In addition, a significant between-subjects group effect was also observed ($F(3,74)=3.623$; $p=.017$). The control group was equivalent to the AD and StimD groups, but exhibited decreased spectral power relative to the ASD group ($p=.046$). No other significant effects were noted.

A significant within-subjects effect of region was noted for the α_2 spectral band ($F(1,74)=1929.257$; $p<.001$) in which anterior electrode sites exhibited reduced spectral power relative to posterior electrode sites. An interaction of region $\times$ dose $\times$ group was also observed ($F(3,74)=4.16$; $p=.009$), along with an overall between-subjects effects of group ($F(3,74)=3.957$; $p=.011$) and a between-subjects group $\times$ dose interaction ($F(3,74)=3.249$; $p=.027$). Interaction effects were disentangled using separate region $\times$ dose comparisons for each group. Significant region effects were noted for the controls ($F(1,20)=477.801$; $p<.001$), the ADs ($F(1,24)=800.401$; $p<.001$), the ASDs ($F(1,12)=251.113$; $p<.001$) and the StimDs ($F(1,18)=584.485$; $p<.001$). Across groups, a pattern emerged in which the anterior region exhibited increased spectral power relative to the posterior region, suggesting that the interaction effect was ordinal. However, the StimD group was unique. Within this group, an additional interaction effect of region $\times$ dose was observed ($F(1,18)=16.39$; $p=.001$), along with a between-subjects dose-related difference ($F(1,18)=5.14$; $p=.036$), in which the low dose was associated with decreased spectral power relative to the high dose. To disentangle the StimD interactive effect, separate

regional analyses were conducted within each dose group. Results indicated significant effects for both the low dose group ($F(1,7)=281.176$; $p<.001$) and the high dose group ($F(1,11)=286.059$; $p<.001$), in which the anterior region exhibited decreased spectral power relative to the posterior region.

For the β_1 spectral band, A significant within-subjects effect of region was noted ($F(1,74)=1175.042$; $p<.001$), in which the anterior region exhibited increased beta power relative to the posterior region. In addition, a between-subjects interaction of group $\times$ dose was also observed ($F(3,74)=35.58$; $p=.018$). No other significant effects were found ($ps \geq .72$). The interaction was further examined using separate region $\times$ dose analyses per group. For controls ($F(1,20)=388.603$; $p<.001$) and ASDs ($F(1,12)=202.381$; $p<.001$), a significant within-subjects effect of region was noted, in which the anterior region exhibited decreased spectral power relative to the posterior region. No other significant effects were noted for controls. A similar regional pattern was noted within the AD group ($F(1,24)=805.478$; $p<.001$) and the StimD group ($F(1,18)=139.745$; $p<.001$). However, in addition to regional differences, a between-subjects dose effect was observed for the AD group ($F(1,24)=11.145$; $p=.003$) and the StimD group ($F(1,18)=4.910$; $p=.04$). For the AD group, the low dose was associated with increased spectral power relative to the high dose. Conversely, for the StimD group, the high dose of nicotine was associated with increased spectral power relative to the low dose. This could reflect a cross-tolerance effect, among chronic abusers of illicit stimulants vs. those participants who primarily abused alcohol (see Discussion section).

Finally, within the β_2 spectral band, a significant within-subjects effect was observed ($F(1,74)=1462.960$; $p<.001$), in which the anterior region exhibited decreased beta power as compared to the posterior region. No other significant effects were noted ($ps>.14$).

Quadrant Analyses (Left Anterior, Right Anterior, Left Posterior, Right Posterior):

Given reports of frontal brain dysfunction among substances abusers [53], this section focuses primarily on differences between frontal quadrants relative to other brain regions.

In the delta spectral band, a significant quad $\times$ group interaction was noted ($F(9,222)=3.32$; $p=.005$), along with an overall effect of quadrant ($F(3,222)=28.06$; $p<.001$). In the overall sample, spectral power differences were segregated by region with anterior regions exhibiting greater spectral power vs. posterior regions. For instance, the spectral power observed in the LA quadrant was equal to that observed in the RA quadrant and greater than that observed in the right and left posterior quadrants ($ps<.001$). Subsequent analyses further dissected the interaction effect by comparing the spectral power within each quadrant for each group separately. Results for the control ($F(3,63)=21.11$; $p<.001$), AD ($F(3,75)=17.43$; $p<.001$), and StimD groups ($F(3, 57)=5.50$; $p=.012$), indicated within-subject effects of quadrant. For Controls and ADs, the anterior quadrants exhibited higher spectral power compared to the posterior quadrants. For the StimD group, Bonferroni adjustment rendered these effects non-significant ($ps>.09$). Further, no significant effects were noted for the ASD group ($ps>.51$).

Analyses of the theta spectral band revealed a significant quadrant $\times$ group interaction ($F(9,222)=2.68$; $p=.019$), along with an overall within-subjects effect of quadrant ($F(3,222)=61.02$; $p<.001$). No other significant within- or between-subjects effects were noted. To summarize the overall pattern of quadrant effects across groups, the anterior quadrants were similar to the posterior quadrants with respect to spectral power values. The anterior quadrants exhibited reduced spectral power relative to the posterior quadrants ($ps<.001$). Subsequent analyses examined quadrant effects for each group separately, and results indicated significant effects of quadrant for Controls ($F(3,75)=8.77$; $p=.002$), ADs ($F(3,75)=8.77$; $p=.002$), ASDs ($F(3,39)=17.45$; $p<.001$) and StimDs ($F(3,57)=30.51$; $p<.001$). Within the control group, the spectral power of the left anterior quadrant was similar to that of the right anterior and posterior

quadrants, but exhibited less spectral power relative to the left posterior quadrant ($p=.048$). A similar pattern was noted within the AD group ($p=.007$). Within the ASD group, the left anterior quadrant was similar to the right anterior quadrant, but exhibited less spectral power compared to both anterior- and posterior- quadrants ($p=.035$). A similar pattern of findings was noted for the StimD group ($ps<.001$).

A significant quadrant $\times$ group $\times$ dose interaction was noted within the α_1 spectral band ($F(9,222)=2.78$; $p=.024$), along with an overall quadrant effect ($F(3,222)=1051.10$; $p=.024$). All other effects were non-significant ($ps \geq .06$). In the overall sample, the left anterior quadrant exhibited reduced spectral power compared to the left and right posterior quadrants; however, increased spectral power was observed relative to the right anterior quadrant ($p=.001$). Follow-up analyses focused on separate dose $\times$ quadrant comparisons within each group, and significant within-subject effects of quadrant were noted for controls ($F(3,60)=281.72$; $p<.001$), ADs ($F(3,72)=364.287$; $p<.001$), ASDs ($F(3,36)=149.22$; $p<.001$), and StimDs ($F(3,54)=315.358$; $p<.001$). For Controls, ADs and ASDs, a pattern emerged in which the left anterior quadrant was similar to the right anterior quadrant and exhibited less spectral power in comparison to both left and right posterior quadrants ($ps<.001$). However, in the StimD group, there was an additional interaction between dose and quadrant ($F(3,54)=11.61$; $p<.001$). Subsequent analyses a pattern within both the low dose ($F(3,21)=156.403$; $p<.001$) and high dose ($F(3,33)=147.26$; $p<.001$) nicotine assignments, in which the left anterior quadrant was similar to the right anterior quadrants and exhibited less spectral power compared to the left and right posterior quadrants ($ps<.001$), suggesting that the interaction was ordinal in nature.

For the α_2 spectral band, a significant within-subjects effect of quadrant was noted ($F(3,222)=921.19$; $p<.001$) in which the left anterior quadrant exhibited greater spectral power compared to the right anterior quadrant ($p=.008$) and less spectral power in comparison to the left and right posterior quadrants ($ps<.001$). In addition, a quadrant $\times$ dose $\times$ group interaction effect was observed, along with between-subjects effects of group ($F(3,74)=3.77$; $p=.014$) and an interaction of group $\times$ dose ($F(3,74)=4.18$; $p=.009$). Subsequent analyses dissected the within-subject interaction effects of quadrant $\times$ dose $\times$ group via separate group analyses of quadrant $\times$ dose. Results for the Controls ($F(3,60)=260.02$; $p<.001$), the ADs ($F(3,72)=454.138$; $p<.001$), the ASDs ($F(3,36)=147.035$; $p<.001$) and the StimDs ($F(3,54)=167.45$; $p<.001$) indicated a within-subjects effect of quadrant in which the left anterior quadrant was equal to the right anterior quadrant, but exhibited significantly lower spectral power compared to the left and right posterior quadrants ($ps<.001$). Within the StimD group, an additional interaction of quadrant $\times$ dose was also observed and examined via separate quadrant analyses for each dose. Results indicated significant effects within the low dose group ($F(3,21)=59.91$; $p<.001$) as well as the high dose group ($F(3,33)=123.15$; $p<.001$) in which the left anterior quadrant was similar to the right anterior quadrant but exhibited significantly less spectral power compared to the right and left posterior quadrants, suggesting that this interaction was ordinal in nature.

For the β_1 spectral band, a significant within-subjects effect of quadrant was noted ($F(3,222)=924.12$; $p<.001$) in which the left anterior quadrant was equal to the right anterior quadrant, but exhibited significantly reduced spectral power relative to the left and right posterior quadrants ($ps<.001$). In addition, a between-subjects interaction of group $\times$ dose was also observed ($F(3,74)=3.58$; $p=.02$) and was further disentangled using separate group analyses of dose-related differences. Results indicated no significant dose differences within the control and ASD groups ($ps>.51$); however, significant dose-related differences were noted within the AD ($F(1,24)=11.26$; $p=.003$) and StimD ($F(1,18)=4.95$; $p=.039$) groups. Within the AD group, the low dose of nicotine was associated with increased spectral power vs. the high dose administration. Once again, the StimD group was unique and exhibited an opposite pattern in

which the high dose of nicotine was associated with higher spectral power vs. the low dose of nicotine. All other comparisons were non-significant ($ps > .11$).

Finally, results from analyses of the β_2 spectral band revealed a significant within-subject effect of quadrant was noted ($F(3,222)=1137.17$; $p < .001$) in which the left anterior quadrant exhibited greater spectral power relative to the right anterior quadrant ($p = .012$) and less spectral power relative to the left- and right- posterior quadrants ($ps < .001$). All other effects were non-significant ($ps \geq .14$).

Eyes Open

Hemispheric Analyses (Left vs. Right): A significant effect of cerebral hemisphere was observed for measures of log transformed absolute power of delta ($F(1,72)=9.144$; $p = .003$), in which greater delta power was found in the left vs. right hemisphere. Similar effects were noted for theta ($F(1,72)=17.19$; $p < .001$), α_1 ($F(1,72)=12.66$; $p = .001$) and α_2 ($F(1,72)=12.69$; $p = .001$). Greater spectral power was consistently observed in the left vs. right hemisphere. No other statistically significant within- or between-subject effects were noted for these spectral bands. No significant within- or between-subject effects were noted for β_1 ($ps > .06$) or β_2 ($ps > .12$).

Regional Analyses (Anterior vs. Posterior): Within the delta spectral band, no significant within-subjects effects were noted ($ps \geq .15$). Between-subject group differences were non-significant ($p \geq .38$). A significant group $\times$ dose interaction was observed ($F(1,74)=5.21$; $p = .025$), and a significant main effect of dose was also revealed ($F(3,74)=3.94$; $p = .012$). Subsequent analyses focused on separate dose $\times$ region effects in each group. Result indicated no significant within-subject differences in region across groups ($ps \geq .23$). Further, no between-subject differences were noted for controls, ASDs and StimDs. For the AD group, a significant effect of dose was observed ($F(1,24)=11.42$; $p = .002$), in which the low dose was associated with a lower spectral power compared to spectral power among those individuals who received a high dose of nicotine.

For the theta spectral band, a significant within-subject effect of region was noted ($F(1,74)=39.84$; $p < .001$) in which the anterior region exhibited lower spectral power compared to the posterior region. All other within-subject comparisons yielded non-significant results ($ps \geq .61$). All between-subject comparisons were non-significant ($ps \geq .24$).

A significant within-subject interaction of region $\times$ dose $\times$ group was noted within the α_1 spectral band ($F(1,74)=1081.83$; $p < .001$), as well as a significant overall effect of region ($F(3,74)=3.03$; $p = .034$). Follow-up analyses of region $\times$ dose comparisons were conducted for each group. For controls, a significant effect of region was observed ($F(1,20)=190.746$; $p < .001$), in which the anterior region exhibited reduced spectral power compared to the posterior region. All other effects for controls were non-significant ($ps \geq .21$). For the AD group, a significant within-subjects effect of region was revealed ($F(1,24)=567.37$; $p < .001$), in which the anterior region exhibited reduced spectral power compared to the posterior region. No other significant effects were observed for the AD group ($ps > .31$). For the ASD group, a significant region effect was noted ($F(1,12)=288.54$; $p < .001$) in which the anterior region exhibited reduced spectral power compared to the posterior region. No other significant effects were noted ($ps \geq .19$). Finally, for the StimD group, a significant within-subject interaction of dose $\times$ region was observed ($F(1,18)=6.36$; $p = .021$), along with an overall effect of region ($F(1,18)=268.49$; $p \leq .001$), in which the anterior region exhibited reduced spectral power as compared to the posterior region. Follow-up analyses focused on comparisons of region with each dose (low or high); results indicated significant effects within the low dose group ($F(1,7)=83.64$; $p < .001$) as well as the high dose group ($F(1,11)=238.77$; $p < .001$). In both cases, the anterior

region exhibited reduced spectral power compared to the anterior grouping, suggesting an ordinal interaction.

Results for the α_2 spectral band revealed a significant within-subject interaction of region $\times$ group $\times$ dose ($F(3,74)=4.604$; $p=.005$), along with an overall effect of brain region ($F(1,74)=1328.78$; $p<.001$), in which the anterior region exhibited reduced spectral power compared to the posterior region. In addition, a between-subjects interaction of group $\times$ patch was also noted ($F(3,74)=2.96$; $p=.038$). Follow-up analyses focused on separate dose $\times$ region comparisons for each group. For controls, a significant within-subjects effect of region was noted ($F(1,20)=333.11$; $p<.001$) with the aforementioned pattern of reduced anterior power relative to posterior power. All other effects were non-significant ($ps \geq .06$). Similar patterns were noted for the AD group [$F(1,24)=461.86$; $p<.001$] and the ASD group [$F(1,12)=207.77$; $p<.001$]. However, the StimD group was once again unique in that a region $\times$ dose interaction was observed ($F(1,18)=12.77$; $p=.002$), along with an overall within-subjects effect of region ($F(1,18)=438.78$; $p<.001$) and a between subjects effect of dose ($F(1,18)=8.65$; $p=.009$). Subsequent analyses focused on region effects within each dose (low vs. high). Results indicated similar effects within each dose group, suggesting an ordinal interaction [low dose ($F(1,7)=212.30$; $p<.001$); anterior < posterior]; high dose ($F(1,11)=213.059$; $p<.001$); anterior < posterior.

A significant within-subjects effect of region was noted for the β_1 spectral band ($F(1,74)=1010.86$; $p<.001$), in which the anterior brain region exhibited reduced spectral power relative to the posterior brain region. All other effects were non-significant ($ps \geq .10$).

Finally, within the β_2 spectral band, a significant within-subjects effect of region was noted ($F(1,74)=1398.369$; $p<.001$), in which the anterior brain region exhibited reduced spectral power relative to the posterior brain region. All other effects were non-significant ($ps \geq .31$).

Quadrant Analysis (Left Anterior, Right Anterior, Left Posterior, Right Posterior).

No within quadrant differences or interactions were noted for the delta spectral band ($ps > .17$). However, a significant between-subjects interaction of group $\times$ dose ($F(3,74)=3.91$; $p=.012$) was noted, along with an overall effect of dose ($F(1,74)=5.36$; $p=.023$). In the AD ($p=.002$) and StimD ($p=.046$) groups, log transformed delta power values were higher in participants receiving the high dose of nicotine vs. those who received the low dose of nicotine. Among controls and the ASD group, no significant nicotine dose-related differences were noted. No other significant effects were noted.

Analyses of theta and α_1 spectral bands revealed only significant within-subject quadrant differences [theta: $F(3,222)=31.42$; $p<.001$]; α_1 : ($F(3,222)=714.18$; $ps<.001$)]. The overall pattern was similar in that the left anterior quadrant exhibited lower spectral power as compared to left and right posterior sites (theta: $ps<.01$; α_1 : $ps<.001$) with higher spectral power as compared to the right anterior site (theta: $p=.057$; α_1 : $p=.004$). The left posterior quadrant exhibited higher spectral power compared to all other quadrants (theta: $ps \leq .01$; α_1 : $ps \geq .02$). The right anterior quadrant exhibited less spectral power than all other groups (theta: $ps \leq .057$, most $<.001$; α_1 : $ps \leq .004$). The left posterior quadrant exhibited less spectral power as compared to the left posterior quadrant (theta: $p=.01$; α_1 : $p=.02$).

The most complex results of this section were found within the α_2 spectral band. A significant interaction of quadrant $\times$ dose $\times$ group was noted ($F(9,222)=3.60$; $p=.005$, as well as a significant overall within-subjects effect of quadrant ($F(3,222)=1005.80$; $p<.001$). A between-subjects interaction of dose $\times$ group was also revealed ($F(3,74)=2.96$; $p=.04$). No other significant within- or between-subject differences or interactions were observed ($ps \geq .14$). Subsequent quadrant $\times$ dose comparisons were conducted individually by group. For controls,

ADs, and ASDs, significant within-subject effects of quadrant were noted [controls: ($F(3,60)=268.99$; $p<.001$); AD: ($F(3,72)=349.11$; $p<.001$); ASD: ($F(3,36)=172.96$; $p<.001$)]; however, the interaction of quadrant $\times$ nicotine dose was non-significant for these group ($ps \geq .074$). Within the StimD group, both a dose $\times$ quadrant interaction ($F(3,54)=8.31$; $p=.001$) and an overall within-subjects quadrant effect ($F(3,54)=272.67$; $p<.001$) were noted. Additional comparisons revealed this interaction to be ordinal in nature, with a similar pattern of alpha₂ power across quadrants for each dose. To summarize, left anterior exhibited less spectral power as compared to the left and right posterior quadrants ($ps<.001$), but was not significantly different than the right anterior quadrant. A similar pattern of findings was noted for individuals who received the high dose of nicotine.

A significant within-subjects effect of quadrant was noted for beta₁ ($F(3,222)=796.63$; $p<.001$) and beta₂ ($F(3,222)=1045.69$; $p<.001$). The results of all other comparisons were non-significant (beta₁: $ps \geq .09$; beta₂: $ps \geq .19$). To summarize, the left anterior quadrant exhibited less spectral power compared to the left posterior and right posterior quadrants (beta₁: $ps<.001$; beta₂: $ps<.001$), and exhibited greater or equal spectral power compared to the right anterior quadrant (beta₁: $p=.03$; beta₂: n.s.).

Discussion

The current study is unique in that it is one of the first to examine the direct effects of transdermal nicotine on quantitative electroencephalographic activity of substance abusing subgroups and community controls. Interestingly, results indicated a differential pattern of nicotine dose effects by group, particularly within the hemispheric analyses, which were the focus of the current study. Specifically, the EEGs of Controls and ASD participants did not distinguish between high and low nicotine doses; whereas, nicotine administration in the AD and StimD groups resulted in opposite findings across a range of spectral bands. It is important to note that although group differences in nicotine dependence were noted with regard to FTND symptoms, no significant differences were noted on DSM-IV diagnosis of nicotine dependence (See Table 3). Further, AD, ASD, StimD and Control groups did not differ with regard to nicotine withdrawal symptoms (e.g., WSC scores) prior to nicotine administration (See Table 3). Although additional research is warranted, these data suggest that nicotine-related changes in neurophysiology may be associated with specific brain areas and/or specific drug histories and reinforce the need for caution in generalizing among substance abuse subgroups.

Traditionally, transdermal nicotine administration has been shown to result in a psycho-stimulant arousal pattern of voltage suppression in slow wave frequency bands such as delta, theta and alpha₁, with voltage augmentation in fast wave frequency bands such as beta₁ and beta₂ [26,27,28,29,30,31]. The current findings are interesting in that opposing effects were noted in hemispheric analyses of the Alcohol Dependent (AD) group as compared with the Stimulant Dependent (StimD) group. To summarize, under *low* dose nicotine administration conditions, alpha₂ power was higher for the AD group; whereas this pattern was not noted in the Control, ASD or StimD groups. EEG recordings following *high* dose nicotine administration resulted in a different pattern of findings, with decreased alpha₂ power within the AD group and a differential pattern of findings for the Control, ASD and StimD groups. Such findings were also noted for beta₁ power.

Findings in the AD group could be related to the underlying neuroelectric profiles of these participants, which have been found to differ from those of community controls. Specifically, the resting EEGs of alcoholics (not under the influence of nicotine, *per se*) often more closely resemble an aroused state as seen in control participants without a history of alcohol dependence [17]. This phenomenon may explain, in part, the appearance of higher absolute values of beta power among AD participants vs. Controls; this issue is most apparent in Figure

2. However, interpretation of the current findings requires additional research into the potential mechanisms underlying differences between nicotine-related quantitative EEG responses of one substance abusing subgroup, that is, the AD group, versus another (i.e., the StimD group).

Our findings across a range of different analysis strategies (e.g., hemispheric comparisons, regional comparisons and comparisons by quadrant) are complex and frequently differ from the classical profile of psycho-stimulant arousal in response to nicotine administration within non-substance abusing community control groups. There are a number of possible explanations for this difference. First, due to cross-tolerance effects, the administration of low dose nicotine may have little effect on central nervous system arousal within the stimulant dependent group. Individuals within the StimD group reported long-term abuse and/or dependence on cocaine and/or methamphetamine, illicit drugs which are many times more potent than legal stimulants such as nicotine. Thus, the relatively minor pharmacological impact of low dose nicotine may not have had a significant effect on the central nervous systems of these participants. It appears that a higher dose of nicotine was required to elicit an arousal effect on the baseline EEG.

Additional Issues of Interest

The percentage of participants testing positive for DSM-IV nicotine dependence ranged from 48% (Controls) to 80% (ASD and StimD), despite participants' steady smoking pattern of approximately 14 to 20+ cigarettes per day. Interestingly, these percentages of nicotine dependence are significantly higher than those reported by Donny & Dierker [54], who suggest that approximately 39.4% of daily smokers never qualify for full diagnosis of lifetime nicotine dependence. In fact, their study reports that a substantial portion of individuals (37.7%) who reported smoking ≥ 10 cigarettes per day for ≥ 10 years never met criteria for nicotine dependence.

Finally, given the attentional focus of the current study, a series of post-hoc analyses were conducted to examine the potential relationship between regional (anterior vs. posterior) responses across spectral bands and behavioral measures of attention collected in another component of the study (e.g., Stroop task, as reported previously, 55). The Stroop task is a neuropsychological instrument often employed to evaluate frontal lobe deficits due to its sensitivity in assessing attentional processes and cognitive flexibility [56]. Results indicated no significant pattern of correlations between quantitative EEG measures (e.g., anterior vs. posterior regional groupings) and performance on the Stroop task. However, it is important to note that the current EEG data were collected under resting conditions; and thus, such data are less likely to reveal functional differences in brain activity within the frontal lobe.

Limitations

A number of limitations remain to be addressed in subsequent work. The design of the current study was tailored to compare EEG power estimates across different alcohol and drug dependent groups under the acute influence of nicotine. The study was not designed to address the acute effects of nicotine, per se, but rather, the authors sought to determine potential differences among alcohol and drug groups under nicotine levels held relatively constant throughout the testing session. For ethical reasons, the study's focus on treatment seeking substance abusers who were only recently abstinent (≥ 21 days) from their drugs of choice precluded the assessment of EEG activity under conditions of overnight nicotine withdrawal; for this reason, the authors did not include a placebo group of smoking substance abusers. It is important to note that collection of a pre-nicotine measure of the EEG immediately following overnight abstinence from nicotine would primarily reflect the effects of nicotine withdrawal rather than a true representation of participants' "baseline" EEG activity. For these reasons, a modified experimental design was employed to provide an acceptable compromise between scientific stringency and clinical sensitivity.

Therefore, the current findings do not address an ongoing question in the nicotine literature; that is, are the potentially facilitative effects of nicotine administration due to the arousing effects of nicotine alone, or are these findings merely do to the alleviation of nicotine withdrawal in a population of regular smokers [See 57,58,59]. However, it is important to note that participant groups did not differ with regard to nicotine withdrawal symptoms prior to nicotine uptake.

In addition, the current study did not monitor nicotine levels (e.g., via cotinine levels of blood or saliva) over the course of the study. The inclusion of this control measure in future studies could be used to further substantiate the stability of nicotine levels over the testing session for both low and high doses of nicotine and across drug groups vs. controls.

Although the current findings demonstrate some specificity with regard to brain activity as recorded at the scalp within cortical hemispheres, regions and quadrants, these data do not reflect true neuroanatomical localization. Thus, it would also be of interest to expand the neurophysiological techniques used to examine these phenomena to include current source density analysis, a technique that derives information regarding neuroanatomical localization based on the EEG [60]. This work is currently underway in our laboratory.

Despite, and in light of, these limitations, additional research is warranted. Previous work in our laboratory has shown that nicotine administration may partially compensate for the deleterious effects of chronic substance abuse on attentional functioning [55]. Across drug groups, individuals receiving a low vs. high nicotine dose exhibited differential levels of quantitative EEG power estimates in some spectral bands (See Figs 1 - 3). Overall, nicotine is known to have an activating/arousing effect on cortical functioning, leading to an increase in the efficiency of attention, a cognitive function that is often compromised among chronic substance abusers. A differential pattern of findings (by nicotine dose) across drug groups suggests that nicotine may affect substance abusing subgroups differently based on their drug use histories (e.g., cross tolerance effects among StimD participants). These findings suggest that at the correct dosage, acute nicotine administration may provide some degree of psycho-stimulant arousal effects, which in turn, might logically be expected to partially compensate for the deleterious effects of chronic substance abuse.

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Eyes Closed Condition

Group X Dose Interaction

Figure 1.

Eyes Closed Condition

Group X Dose Interaction

Figure 2.

Eyes Closed Condition

Group X Dose Interaction

Figure 3.

Table 1**Inclusion and Exclusion Criteria**

<u>Exclusionary Criteria</u> <u>(All Groups)</u>	<u>Inclusionary Criteria</u> <u>(All Groups)</u>	
Psychiatric Disorders* Neurological Disorders Red/Green Colorblindness Diabetes Pregnancy Learning Disabilities Hypertension Skin Disorders Cirrhosis, Hepatitis Unconsciousness > 10hrs Inhalant or PCP Use** Seizures HIV positive Thyroid Problems Heart Problems Stroke Cancer Epilepsy*** FAS/FAE***	24-59 Years of Age 10-16 Years of Education Shipley Verbal $\geq 20/13.1$ BDI-II < 25 Preferred First Language = English No Marijuana Use During Enrollment in Study	
	<u>Inclusionary Criteria</u> <u>(Control Group)</u>	<u>Inclusionary Criteria</u> <u>(ASD Group)</u>
	QFI ≤ 1.0 No Alcohol or Drug Abuse or Dependence.	DSM-IV Stim Dependence Stim Chronicity ≥ 1 Year Days Sober and Abstinent at Testing ≥ 21 QFI ≥ 4 (Men) QFI ≥ 2 (Women)
	<u>Inclusionary Criteria</u> <u>(AD Group)</u>	<u>Inclusionary Criteria</u> <u>(SD Group)</u>
	DSM-IV Alc Dependence Alc Chronicity ≥ 5 Years QFI ≥ 5 (Men) QFI ≥ 2 (Women) No Regular Use/Abuse of Other Drugs Days Sober at Testing ≥ 21	DSM-IV Stim Dependence Stim Chronicity ≥ 1 Year Days Abstinent at Testing ≥ 21 QFI ≤ 1.0 No Alcohol Abuse or Dependence.

* Except for nicotine dependence and/or dependence diagnoses appropriate for drug groups.

** Non-alcohol related.

*** Fetal Alcohol Syndrome/Effects

Table 2
Background Variables: Means (Standard Deviation)

	Controls	AD	ASD	StimD
% Male	71	73	57	58
% Caucasian	73	85	50	80
Age	35.45 (9.98)	38.4 (7.37)	36.43 (6.54)	33.10 (8.49)
Years of Education	13.27 (1.03)	12.31 (1.93)	12.93 (2.13)	12.45 (1.82)
BDI-II ¹ *	3.09 (4.46)	11.35 (9.00)	10.50 (5.54)	8.47 (5.41)
SSAI ² *	42.45 (6.48)	48.96 (9.18)	47.21 (5.81)	46.40 (6.63)
SILS-V ³	17.55 (1.59)	16.70 (1.91)	16.12 (1.31)	16.84 (1.91)
QFI ⁴ *	0.42 (0.53)	10.70 (6.33)	7.49 (4.55)	0.58 (1.45)
Marijuana Dependence Symptoms [*]	0.36 (0.66)	1.0 (1.67)	1.31 (1.84)	2.20 (1.96)

* Significant group differences ($p < .05$).

¹ Beck Depression Inventory II (Beck et al, 1996);

² Spielberger State Anxiety Inventory (Spielberg, 1983);

³ Shipley Institute of Living- Vocabulary Subscale (Zachary, 1986);

⁴ Quantity Frequency Index (Calahan et al., 1969).

Table 3

Nicotine Usage Patterns by Group: Means (SD)

	Controls	AD	ASD	StimD
# of Cigarettes/ daily [*]	20.48 (7.37)	22.0 (8.83)	14.57 (4.78)	24.05 (8.48)
Age of onset (regular smoking pattern)	16.67 (3.83)	17.0 (5.21)	7.71 (4.36)	15.5 (3.44)
SCQ ² Total	49.92 (14.85)	48.11 (10.52)	45.78 (12.69)	51.72 (13.77)
WSC ³	3.18 (2.20)	4.50 (3.25)	3.57 (3.06)	3.85 (2.23)
FTND ⁴ Total [*]	4.00 (2.35)	5.91 (2.35)	3.00 (1.71)	5.63 (2.34)
% Nicotine Dependent ⁵	48	79	80	80

^{*} Significant group differences ($p < .05$).

¹ Carbon Monoxide;

² Smoking Consequences Questionnaire (Copeland et al., 1995);

³ Withdrawal Symptoms Checklist (adapted from Hughes & Hatsukami, 1986).

⁴ Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991),

⁵ Based on DIS-IV; DSM-IV Criteria.