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# Associations of agression and use of caffeine, alcohol and nicotine in healthy and aggressive individuals

Carolyn Shima [a], Royce Lee [a], Emil F. Coccaro [b,*]

[a] Clinical Neuroscience Research Unit, Department of Psychiatry and Behavioral, Neuroscience, Pritzker School of Medicine, University of Chicago, Chicago, IL, USA
[b] Department of Psychiatry and Behavioral Health, The Ohio State University Wexner, Medical Center, Columbus, OH, USA

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ABSTRACT

*Background:* Caffeine, alcohol, and nicotine are the three most commonly used psychoactive substances in the world. Given the known propensity of these substances to influence behavior, the relationship between these substances and aggressive and impulsive behaviors, in particular is of interest.
*Methods:* 1062 adult individuals participated in this study including those with Intermittent Explosive Disorder (IED) and non-aggressive healthy (HC) and psychiatric (PC) controls. Data regarding current and life use of caffeine, alcohol, and nicotine were recorded as were responses on measures of aggression, anger, and impulsivity. Results. Dimensional measures of aggression, anger, and impulsiveness were variably but significantly related to the consumption of these commonly used psychoactive substances. These findings were generally mirrored when using the categorical construct of IED. Finally, these findings were not due to comorbidity with other psychiatric disorders.
*Conclusions:* These data confirm a link between these externalizing behaviors and these three legal and commonly consumed psychoactive substances in clinically relevant individuals.

## 1. Introduction

Caffeine, alcohol, and nicotine are the three most commonly used psychoactive substances in the world (Meredith et al., 2013; Carrigan et al., 2015) Given the known propensity of these substances to influence the user's behavior, the various and complex relationships between these drugs and psychiatric and behavioral disorders have long been of interest and continues to be investigated. Of particular importance is the relationship between these substances and aggressive and impulsive behaviors. The association between alcohol use and aggressive behaviors has been well-studied (Sheehan et al., 2016). Some studies also suggest an association between caffeine use and aggression/conduct issues (Martin et al., 2008) while others suggest that people with affective disorders may use nicotine to self-medicate the symptoms of their illness, such as aggression and irritability (Picciotto et al., 2015) Thus, the role of these three substances in problematic aggression warrants further study.

An important consideration in the study of aggression is Intermittent Explosive Disorder (IED), characterized by verbal and/or physical aggression and outbursts of anger (Coccaro et al., 2016). Little work to date has been done studying the relationship between substance use and IED. While aggression, anger, and impulsivity are core features of IED, they are also commonly experienced to varying degrees by those with other psychiatric disorders and by those without any psychiatric diagnosis. Whether the relationship between substance use and the experience of aggression, anger, and impulsivity differ between those with certain psychiatric disorders and those without is of particular interest. More specifically, do these substances interact with aggression, anger, and impulsivity differently depending on whether they are expressed in the context of IED as opposed to another psychiatric disorder or in the absence of a psychiatric diagnosis?

This study investigates the relationship between current and lifetime use of caffeine, tobacco, and alcohol (both rate and quantity of consumption) and aggression, anger, and impulsivity in a group of research participants overall and in those with IED. We. hypothesized that there is a positive relationship between the use of caffeine, alcohol, and nicotine, and aggression, anger, and impulsivity overall and specifically in those with IED.

* Corresponding author.
*E-mail address:* emil.coccaro@osumc.edu (E.F. Coccaro).

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## 2. Methods

### 2.1. Participants

1062 adult individuals participated in this study. All participants were physically healthy. They were systematically evaluated as part of a larger program designed to study correlates of impulsive-aggression and other pathological behaviors. Subjects were recruited through public service announcements, newspaper adverts, electronic media, and posted flyers seeking out individuals who reported psychosocial difficulty related to one or more psychiatric conditions as well as healthy controls. All subjects gave informed consent and signed the informed consent document approved by our Institutional Review Board.

### 2.2. Diagnostic assessment

Diagnoses were made according to DSM-5 criteria (American Psychiatric Association, 2013). Assessments were completed using information from (a) the Structured Clinical Interview for DSM Diagnoses (SCID-I; First et al., 1997) (b) the Structured Interview for the Diagnosis of Personality Disorder (SIDP; Pfohl et al., 1997) (c) clinical interview by a research psychiatrist; and, (d) review of all other available clinical data. Research diagnostic interviews were conducted by individuals with a masters or doctorate in Clinical Psychology. All diagnostic raters went through a rigorous training program that included: lectures on DSM diagnoses and rating systems; videos of expert raters conducting SCID/SIDP interviews; and practice interviews/ratings until the raters were deemed reliable by the trainer. This process resulted in good to excellent inter-rater reliabilities [kappa of .84 (±) 0.05; range: 0.79 to 0.93] across the diagnosis of anxiety, mood, substance use, impulse control, and personality disorders. Final diagnoses were determined by team-based best-estimate consensus procedures involving research psychiatrists and clinical psychologists (Coccaro et al., 2012) While information for assigning syndromal (formally Axis I) diagnoses was collected through the use of the SCID-I, more than sufficient information was available to update these diagnoses from DSM-IV to those of DSM-5. DSM-5 diagnoses for personality disorders, based on the SIDP, are the same for DSM-IV. Participants with a diagnosis mutually exclusive to the diagnosis of IED were excluded from the study. Exclusion criteria included active substance use disorders (defined by no less than early remission status per DSM-5 SUD criteria), a lifetime history of bipolar disorder, schizophrenia (or other psychotic disorder), and those with an intellectual disability.

After a diagnostic assignment, 319 participants had no evidence of any psychiatric diagnosis (Healthy Controls: HC); 239 participants met criteria for a lifetime diagnosis of a syndromal psychiatric and/or a personality disorder (Psychiatric Controls: PC), and 504 met criteria for IED. Of the 743 study participants with a psychiatric disorder, most (77.5%) reported: a) a history of formal psychiatric evaluation and/or treatment (59.9%) or, b) history of behavioral disturbance during which the subject, or others, believed that they should have sought mental health services but did not (17.6%). Table 1 lists the means (±SD) for demographic, psychosocial functional/life satisfaction, and psychometric behavioral variables for the three groups; Table 2 lists the syndromal and personality disorder diagnoses for the PC and IED groups.

### 2.3. Assessment of daily use of caffeinated beverages, alcoholic beverages, and cigarette smoking

As part of the diagnostic assessment described above, participants were asked about their current (and past) use of caffeinated beverages, alcoholic beverages, and cigarettes. Caffeinated beverages were quantified by the equivalent of cups of coffee per day; alcoholic beverages (beer/wine/spirits) were quantified by the equivalent of drinks (1.5 ounces of ethanol) per week; cigarette smoking was quantified by packs of cigarettes smoked per week. Lifetime consumption was estimated as the product of daily consumption and years of consumption.

### 2.4. Assessment of aggression, impulsivity, and related behaviors

Aggression was assessed with the aggression scales of the Life History of Aggression (LHA; Coccaro et al., 1997) assessment and of the Buss-Perry Aggression (BPA) questionnaire (Buss and Perry, 1992) The LHA assesses a history of overt aggressive behavior while the BPA assesses aggressive tendencies as a personality trait. LHA Aggression is a widely used five-item measure that quantitatively assesses one's life history of overt aggressive behavior (i.e., aggressive thoughts/urges are not counted). It is conducted as a semi-structured interview. Internal consistency ($\alpha = 0.87$), inter-rater reliability ($r = 0.94$), and test-retest reliability ($r = 0.80$) is good-to-excellent. BPA Aggression is composed of the BPA's Verbal Aggression and Physical Aggression subscales and also has good to excellent psychometric properties. Trait Anger was

**Table 1**
Demographic, functional, and psychometric characteristics of study participants.

| | Healthy Controls (N = 319) | Psychiatric Controls (N = 239) | Intermittent Explosive Disorder (N = 504) | p* | Group Differences |
|---|---|---|---|---|---|
| Demographic Variables | | | | | |
| Age | 31.1 ± 9.5 | 32.5 ± 10.0 | 35.7 ± 10.2 | <0.001[a] | HC < PC = IED |
| Gender (% Male) | 53.0% | 48.1% | 46.0% | = 0.150[b] | HC = PC = IED |
| Race (% White) | 54.5% | 55.6% | 42.3% | <0.001[b] | HC = PC < IED |
| SES Score | 44.9 ± 12.3 | 39.3 ± 15.0 | 37.9 ± 13.5 | <0.001[a] | HC > PC = IED |
| ***Psychosocial Function*** | | | | | |
| GAF Score | 82.9 ± 5.4 | 64.4 ± 11.1 | 55.9 ± 8.0 | <0.001[a] | HC > PC > IED |
| Q-LES-Q Score | 52.2 ± 7.9 | 45.5 ± 10.1 | 39.0 ± 10.3 | <0.001[a] | HC > PC > IED |
| *Psychometric Variables* | Healthy Controls (N = 319) | Psychiatric Controls (N = 239) | Intermittent Explosive Disorder (N = 504) | p[a] | Group Differences |
| Aggression: LHA | 4.5 ± 3.3 | 7.9 ± 5.3 | 18.3 ± 4.1 | <.001 | HC < PC < IED |
| Aggression: BPA | 27.9 ± 9.0 | 32.0 ± 9.6 | 46.7 ± 12.0 | <.001 | HC < PC < IED |
| Anger: BPA | 12.2 ± 4.7 | 15.0 ± 6.2 | 24.5 ± 6.5 | <.001 | HC < PC < IED |
| Anger: STAXI-2 | 13.1 ± 3.1 | 16.2 ± 5.5 | 26.2 ± 7.1 | <.001 | HC < PC < IED |
| Impulsivity: LHIB | 22.6 ± 15.6 | 35.3 ± 20.4 | 52.6 ± 20.0 | <.001 | HC < PC < IED |
| Impulsivity: BIS-11 | 54.3 ± 9.1 | 63.1 ± 11.3 | 68.6 ± 11.6 | <.001 | HC < PC < IED |
| State Depression | 3.0 ± 8.7 | 11.5 ± 12.5 | 16.6 ± 12.4 | <.001 | HC < PC < IED |
| State Anxiety | 22.5 ± 2.2 | 27.2 ± 7.8 | 29.9 ± 8.2 | <.001 | HC < PC < IED |

[a] Means ± SD based on raw data; statistics based on one-way ANCOVA (age, sex, ethnicity, and SES score as covariates).

**Table 2**
Syndromal and personality disorder diagnoses among study participants.

| | Psychiatric Controls (N = 239) | Intermittent Explosive Disorder (N = 504) | p | Group Differences* |
|---|---|---|---|---|
| Current Syndromal Disorders: | | | | |
| Any Depressive Disorder | 38 (15.9%) | 105 (20.8%) | = 0.111 | PC = IED |
| Any Anxiety Disorder | 67 (28.0%) | 130 (25.8%) | = 0.518 | PC = IED |
| Stress and Trauma Disorders | 19 (7.9%) | 81 (16.1%) | = 0.002 | PC < IED* |
| Obsessive-Compulsive Disorders | 4 (1.7%) | 24 (4.8%) | = 0.039 | PC = IED |
| Eating Disorders | 10 (4.2%) | 35 (6.9%) | = 0.141 | PC = IED |
| Somatoform Disorders | 3 (1.3%) | 8 (1.6%) | = 0.726 | PC = IED |
| Non-IED Impulse Control Disorders | 1 (0.4%) | 7 (1.4%) | = 0.231 | PC = IED |
| **Lifetime Syndromal Disorders:** | | | | |
| Any Depressive Disorder | 117 (49.0%) | 303 (60.1%) | = 0.004 | PC = IED |
| Any Anxiety Disorder | 80 (33.5%) | 163 (32.3%) | = 0.759 | PC = IED |
| Any Substance Use Disorder | 90 (37.7%) | 267 (53.0%) | <0.001 | PC < IED* |
| Stress and Trauma Disorders | 40 (16.7%) | 134 (26.6%) | = 0.003 | PC = IED |
| Obsessive-Compulsive Disorders | 8 (3.3%) | 30 (6.0%) | = 0.132 | PC = IED |
| Eating Disorders | 26 (10.9%) | 68 (13.5%) | = 0.317 | PC = IED |
| Somatoform Disorders | 3 (1.3%) | 9 (1.8%) | = 0.592 | PC = IED |
| Non-IED Impulse Control Disorders | 3 (1.3%) | 20 (4.0%) | = 0.046 | PC = IED |
| **Personality Disorders:** | | | | |
| Cluster A (Odd) | 14 (5.9%) | 81 (16.1%) | <0.001 | PC < IED* |
| Cluster B (Dramatic) | 52 (21.8%) | 248 (49.2%) | <0.001 | PC < IED* |
| Cluster C (Anxious) | 75 (31.4%) | 128 (25.4%) | = 0.087 | PC = IED |
| PD-NOS | 51 (21.3%) | 154 (30.6%) | = 0.009 | PC = IED |

*$p < 0.05$ after correction for multiple comparisons (uncorrected $p < 0.003$).

assessed with the anger scale of the BPA and with the trait anger sale of the Spielberger State-Trait Anger and Expression of Anger (STAXI-2; Spielberger, 1999) assessment. The BPA anger scale has seven items (i.e., "when frustrated, I let my irritation show") scored on a five-point Likert scale (1 = extremely uncharacteristic, 5 = extremely characteristic) with a published internal consistency of $\alpha = 0.83$. The STAXI Anger scale has fifteen items and has an internal consistency of 0.82. Impulsivity was assessed with the Life History of Impulsive Behavior (LHIB; Coccaro and Schmidt-Kaplan, 2012) and with the Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995). The LHIB assesses history of actual impulsive behavior and is conceptually similar to the LHA. It includes 20 items regarding impulsive behavior and is scored on a five point ordinal scale (as is the LHA). The LHIB demonstrates good internal consistency ($\alpha = 0.96$) and test-retest reliability ($r = 0.88$). State depression and state anxiety were assessed with the Beck Depression Inventory-2 (BDI-2; Beck et al., 1996) and the Beck Anxiety Inventory (BAI; Beck and Steer, 1993). Psychosocial function was assessed with the Global Assessment of Function (GAF) scale. Satisfaction of life experience was assessed by the Quality of Life Experience and Satisfaction Questionnaire (Q-LES-Q; Endicott et al., 1993).

### 2.5. Statistical analysis and data reduction

Statistical procedures included Chi-square, binary logistic regression and analysis of covariance (ANCOVA) as appropriate. All reported odds ratios were adjusted for age, sex, ethnicity, and socio-economic status. A two-tailed alpha value of 0.05 was used to denote statistical significance for all analyses except in cases where a correction for multiple comparisons was more appropriate. Data reduction involved the creation of composite variables for trait aggression, trait anger, and trait impulsivity. Since each of the variables related to these dimensions was highly correlated with each other, composite variables were created by z-transforming each individual variable and taking the mean z-score of each of the related variables.

## 3. Results

### 3.1. Demographic and psychometric characteristics of the sample (Table 1)

The three groups differed modestly but significantly in age, socio-economic score, and in the distribution of ethnicity by not as a function of sex. Accordingly, all relevant analyses factored in these demographic differences. The groups differed in each variable related to psychosocial function/satisfaction and clinical behavior, as expected. Finally, PC and IED study participants were similar in terms of psychiatric comorbidity with the exception of lifetime substance use disorder (IED > PC). While non-significant after correction for multiple comparisons, IED participants were more likely to have lifetime depressive disorder and current/lifetime stress/trauma disorder compared with PC participants.

### 3.2. Caffeine use and IED, aggression, anger, and impulsivity

The proportion of participants reporting current and lifetime use of caffeine did not differ among the diagnostic groups (Table 3). However, the reported quantity of current (Fig. 1a) and lifetime (Fig. 1b) caffeine consumption did differ significantly by group (current: $F[2,1061] = 14.76$, $p < 0.001$; lifetime: $F[2,1061] = 13.53$, $p < 0.001$). Post-hoc analysis revealed that current/lifetime caffeine consumption was significantly greater among IED and PC compared with HC participants. aWhile caffeine consumption was higher among IED participants when compared with PC participants, this difference was non-significant. Multiple regression analysis with composite aggression as the dependent variable (and age, sex, ethnicity, and SES score as independent covariates) on Step 1 and quantity of caffeine consumption on Step 2 revealed a significant relationship between composite aggression score and both current and lifetime caffeine consumption (Table 4). Adding lifetime syndromal disorders that tended to be more frequently comorbid in IED vs. PC participants (i.e., depressive, anxiety, substance use, and stress/trauma disorders) to the regression model did not change these results. Similar regression analyses with the anger and impulsivity variables revealed significant relationships between current and lifetime caffeine consumption, composite anger, and composite impulsivity scores (Table 4). Adding the lifetime syndromal disorders, described above, to the regression model did not change these results except for composite impulsivity scores, specifically for lifetime caffeine consumption, which was no longer statistically significant.

**Table 3**
Current/past use rates of caffeinated and alcoholic beverages and of smoking cigarettes.

| | Healthy Controls (N = 319) | Psychiatric Controls (N = 239) | Intermittent Explosive Disorder (N = 504) | p* | Group Differences |
|---|---|---|---|---|---|
| Current Use | | | | | |
| Caffeinated Beverages (%) | 75.2% | 80.3% | 75.6% | = 0.291 | HC = PC = IED |
| Alcoholic Beverages (%) | 31.7% | 31.2% | 26.4% | = 0.142 | HC = PC = IED |
| Cigarette Smoking (%) | 10.7% | 16.3% | 27.4% | <0.001 | HC < PC < IED |
| ***Lifetime Use*** | | | | | |
| Caffeinated Beverages (%) | 82.1% | 86.2% | 82.7% | = 0.393 | HC = PC = IED |
| Alcoholic Beverages (%) | 67.7% | 62.8% | 65.3% | = 0.474 | HC = PC = IED |
| Cigarette Smoking (%) | 19.4% | 30.1% | 42.1% | <0.001 | HC < PC < IED |

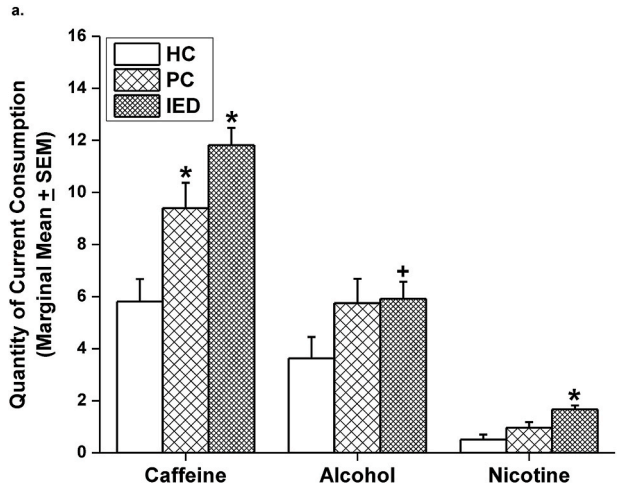


**Fig. 1a.** Marginal Means (+/- SEM), as a function of diagnostic group, for current consumption of caffeine (standard cups / day), alcohol (standard drinks / day), and nicotine (packs of cigarettes / week). *: p < 0.05; +: p < 0.10.

### 3.3. Alcohol use and aggression, anger, and impulsivity in IED

Likewise, the proportion of participants reporting current and lifetime use of alcohol did not differ among the diagnostic groups (Table 3). However, the reported quantity of alcohol consumption differed as a function of group at a trend level of statistical significance for both current (Fig. 1a) and lifetime (Fig. 1b) consumption (current: F[2,1061] = 2.55, p = 0.076; lifetime: F[2,1061] = 2.42, p = 0.089) with IED participants having higher levels of current and lifetime alcohol consumption compared with HC participants. PC participants had consumption levels equal to those of IED but not significantly higher than those of HC participants. Multiple regression analysis with composite aggression as dependent variable, described above, on Step 1 and quantity of alcohol consumption on Step 2 revealed a significant relationship between composite aggression score and both current and lifetime alcohol consumption (Table 4). Adding the lifetime syndromal disorders, described above, to the regression model, however, reduced the finding for lifetime alcohol consumption to a trend level of statistical significance (β = 0.05, t = 1.76, p = 0.078) and the finding for current alcohol consumption to non-significance (β = 0.04, t = 1.39, p = 0.166). Regression analyses with the anger and impulsivity variables revealed significant relationships between current and lifetime alcohol consumption and composite anger (Table 4) and composite impulsivity (Table 4), scores. Adding the syndromal disorders, described above, to the regression model did not change these results for composite impulsivity scores, but did reduce the results for composite anger scores to non-significance.

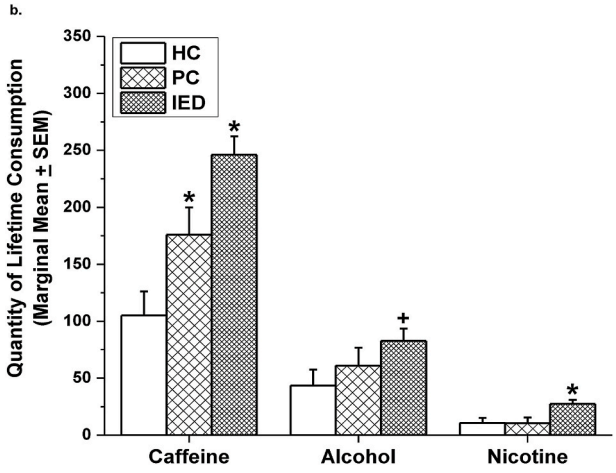


**Fig. 1b.** Marginal Means (+/- SEM), as a function of diagnostic group, for lifetime consumption of caffeine (standard cups / life), alcohol (standard drinks / life), and nicotine (packs of cigarettes / life). *: p < 0.05; +: p < 0.10.

**Table 4**
Relationship (β) between caffeine, alcohol, and nicotine consumption. And composite aggression, anger, and impulsivity scores.

| | β Current Consumption | t | P | β Lifetime Consumption | t | p |
|---|---|---|---|---|---|---|
| Caffeine | | | | | | |
| Composite Aggression | 0.14 | 4.62 | <0.001 | 0.14 | 4.40 | <0.001 |
| Composite Anger | 0.13 | 3.59 | <0.001 | 0.13 | 3.59 | = 0.001 |
| Composite Impulsivity | 0.13 | 3.20 | = 0.001 | 0.10 | 2.28 | = 0.023 |
| **Alcohol** | | | | | | |
| Composite Aggression | 0.10 | 3.23 | = 0.001 | 0.10 | 3.09 | = 0.002 |
| Composite Anger | 0.09 | 2.39 | = 0.017 | 0.08 | 2.05 | = 0.041 |
| Composite Impulsivity | 0.13 | 3.11 | = 0.002 | 0.11 | 2.59 | = 0.010 |
| **Nicotine** | | | | | | |
| Composite Aggression | 0.14 | 4.12 | <0.001 | 0.12 | 3.68 | <0.001 |
| Composite Anger | 0.11 | 2.94 | = 0.003 | 0.11 | 2.72 | = 0.007 |
| Composite Impulsivity | 0.10 | 2.38 | = 0.018 | 0.09 | 2.13 | = 0.033 |

### 3.4. Nicotine use and IED, aggression, anger, and impulsivity

Unlike caffeine and alcohol, the proportion of participants with current and lifetime use of nicotine did differ among the diagnostic groups (Table 2). IED participants were more likely to report current use of nicotine than HC and PC participants. For lifetime use, IED participants were more likely to use nicotine compared with PC participants, who, in turn, were more likely to use nicotine than HC participants. Like caffeine and alcohol, the quantity of current (Fig. 1a) and lifetime (Fig. 1b) nicotine consumption differed by group (current: $F[2,1061] = 11.01$, $p < 0.001$; lifetime: $F[2,1061] = 6.33$, $p = 0.002$). Nicotine consumption was significantly greater among IED compared with HC and PC participants who were not significantly different from each other in this regard. Multiple regression analysis with composite aggression as the dependent variable, described above, on Step 1 and quantity of nicotine consumption on Step 2 revealed a significant relationship between composite aggression score and both current and lifetime nicotine consumption. Adding the lifetime syndromal disorders described above to the regression model did not change these results. Subsequent regression analyses with the anger and impulsivity variables revealed significant relationships between current and lifetime nicotine consumption and composite anger and composite impulsivity scores (Table 4). Adding the lifetime syndromal disorders to the regression model did not change these results except for composite anger scores but reduced the effects for composite impulsivity scores to non-significance.

### 3.5. Aggression, anger, impulsivity and caffeine, alcohol, and nicotine

When considered simultaneously, composite aggression scores were significantly related to the quantity of current caffeine ($\beta = 0.11$, $t = 3.34$, $p = 0.001$) and nicotine ($\beta = 0.10$, $t = 3.12$, $p = 0.002$) consumption. The relationship with quantity of alcohol consumption was observed at only a trend level of significance ($\beta = 0.05$, $t = 1.78$, $p = 0.076$). For lifetime consumption, composite aggression scores were significantly related to quantity of caffeine ($\beta = 0.12$, $t = 3.35$, $p = 0.001$) and alcohol ($\beta = 0.07$, $t = 1.97$, $p = 0.049$), but not for quantity of nicotine ($\beta = 0.05$, $t = 1.24$, $p = 0.216$) consumption. Composite anger scores were significantly related to current caffeine consumption ($\beta = 0.11$, $t = 2.75$, $p = 0.006$), to current nicotine consumption at a trend level ($\beta = 0.07$, $t = 1.73$, $p = 0.085$), but not significant for current alcohol consumption ($\beta = 0.06$, $t = 1.44$, $p = 0.151$). For lifetime consumption, composite anger scores were significantly related only to lifetime caffeine ($\beta = 0.11$, $t = 2.95$, $p = 0.003$), but not to lifetime alcohol ($\beta = 0.05$, $t = 1.09$, $p = 0.275$), or nicotine ($\beta = 0.05$, $t = 1.02$, $p = 0.310$), consumption. Composite impulsivity scores were significantly related to current caffeine ($\beta = 0.11$, $t = 2.53$, $p = 0.012$) and alcohol ($\beta = 0.10$, $t = 2.31$, $p = 0.021$), but not with current nicotine ($\beta = 0.03$, $t = 0.64$, $p = 0.524$) consumption. For lifetime consumption, composite impulsivity scores related to lifetime caffeine ($\beta = 0.08$, $t = 2.53$, $p = 0.091$) and alcohol ($\beta = 0.09$, $t = 1.93$, $p = 0.055$) at only a trend level of significance; composite impulsivity scores did not relate to lifetime nicotine consumption ($\beta = 0.02$, $t = 0.37$, $p = 0.714$).

## 4. Discussion

The primary finding in this study was that dimensional measures of aggression, anger, and impulsiveness were variably but significantly related to the commonly consumed psychoactive substances in the US and other western cultures. This finding was mirrored when comparing the categorical construct of IED: IED was associated with higher rates of current and lifetime caffeine and nicotine compared to their non-aggressive counterparts. The same was true for rate/consumption of alcohol, but only at a trend level of statistical significance. These data are consistent with a study in adolescents finding that aggressive behavior associated with high daily consumption of caffeine (Martin et al., 2008) and a large community survey reporting that current smokers are more likely than never and former smokers to have increased incidence of other- and self-directed aggressive behavior (Lewis et al., 2016).

These analyses cannot speak to cause and effect because the data are cross-sectional, rather than experimental, in nature. That said, results from experimental studies indicate that each of these substances is associated with increased aggressive behavior in intoxicated and/or withdrawal states.

The relationship of nicotine to aggressiveness is complex. Some data indicates that nicotinic agonists reduce aggression (Lewis and Picciotto, 2020) (Cherek, 1981). These effects may be dependent on contextual factors like gender and stress exposure (File et al., 2001) or personality traits of hostility (Jamner et al., 1999; Parrott and Zeichner 2001).

Others research finds that nicotinic agonists increase aggression Berntson et al. (1976), or find non-linear relationships between dose and aggressive behavior (Roliński and Herbut, 1981). However, withdrawal reliably increases aggression, which would support studies finding that acute administration largely reduces it (Cherek et al., 1989; Parrott and Zeichner 2001). The effect of nicotine on aggression may be mediated in part through the serotonergic system, which is implicated in human aggression (Coccaro et al., 2009). Emprical data suggest that smoking disturbs erotonergic function (Malone et al., 2003) (Anthenelli and Maxwell 2000) (Patkar et al., 2003). The active use of nicotine may be associated with reduced 5-HT function in smokers. To what extent these effects are enduring is unclear. A study of a large community cohort reported that former smokers looked like non-smokers in terms of aggression (Lewis et al., 2016), but this remains incompletely understood. It may be that some aggressive individuals use nicotine to regulate aggression. Given that we found that IED individuals were more likely to be either current or past smokers, smoking cession programs could benefit if they were accompanied by interventions addressing irritability and aggression for aggressive individuals.

The link between alcohol use and aggressive behavior is established (Chermack and Blow 2002) (Coccaro et al. 2016, 2017). At least some of this effect is pharmacological, as acute administration of alcohol increases aggressive behavior, particularly in those who are high in trait aggression use (Giancola, 2002; Parrott and Zeichner 2002; Miller et al., 2009). It is also well known that individuals in varying degrees of alcohol withdrawal will be irritable and aggressive (Morgan, 2015). As with nicotine, the effects of alcohol on aggression may be through disturbed serotonergic function (Farren et al., 1995). Alcohol's effect on the function of brain regions regulating behavior, such as the orbitofrontal cortex, are also important (Sachs and Dodson 2017) (Dom et al., 2005).

Less is known about the association between caffeine with aggression. Animal studies suggest an inverse U curve regarding caffeine dose and aggressive behavior (Holloway and Thor 1984; Wilson et al., 2000). Human studies provide some confirmation of non-linear effects of caffeine on aggression (Cherek et al., 1983) (Martin et al., 2008). As with niconine and alcohol, caffeine may affect aggression through disturbances in 5-HT function (Arnolda et al., 2019). Caffine may also directly affect aggression through antagonistic effects on adenosine 2a receptors (Daly et al., 1994) (Ledent et al., 1997).

The effects of these common psychoactive substances on our outcome variables were relatively modest, pointing to the importance of other factors in the etiology of aggression. Stronger relationships were found between substance use and aggression measured dimensionally as opposed to categorically. This is mostly due to either the greater statistical power of dimensional factors, or perhaps due to their greater validity, or both. While modest in size, these effects may be greater in different individuals (especially aggressive ones) and these findings do warrant attention to comorbid aggression and psychoactive substance use in the clinic. This may be especially true when it comes to the consumption of caffeine and nicotine use, which may be more likely to be overlooked in the treatment of aggressive individuals.

This study has several strengths and limitations. Its greatest strength

is a large clinical research sample diagnostically ascertained with semi-structured interviews and with psychometrically validated measures of aggression, anger, and impulsivity. The primary limitation is the cross-sectional nature of this study, which prevents causal inference. Exclusion of psychotic and bipolar psychopathology, and the fact that the clinical research participants were not recruited from treatment facilities, reduce the degree to which the results may generalize to clinical populations. That said, three-quarters of the PC/IED participants history of formal psychiatric evaluation and/or treatment or history of behavioral disturbance during which the subject, or others, believed they should have sought mental health services but did not, suggesting this group resembles those recruited from clinical contexts. Indeed, recruitment of subjects occurred in the Department of Psychiatry, albeit via local advertisements rather than medical record review. Because both the IED and psychiatric control group are more impulsive than the health control group, the results of this study are not able to disentangle how impulsivity and aggression may be related to substance use. Finally, we note that all assessments regarding the consumption of caffeine, alcohol, and nicotine were conducted by participant self-report to diagnostic interviewers as opposed to other methods. Despite this, our results are consistent with several studies in the literature.

## 5. Conclusion

There is a modest relationship between increased consumption rates of caffeine, alcohol, and nicotine (smoking) and adult, human aggression measured dimensionally and categorically through the IED diagnosis. This confirms a link between these externalizing behaviors and these three legal and commonly consumed psychoactive substances. We did not see a strong relationship between IED and the lifetime or current use of alcohol and caffeine, probably because these are commonly used in all three groups. However, current and past smoking appears to be more commmon in IED, pointing to the need for more research about the overlap of IED and smoking. It is advisable for clinicians to assess the potential effect of these substances in individuals who present with problems with aggression, anger, and/or impulsivity.

## CRediT authorship contribution statement

**Carolyn Shima:** Writing – review & editing, and, Conceptualization. **Royce Lee:** Writing – review & editing, and, Conceptualization. **Emil F. Coccaro:** Conceptualization, Formal analysis, and writing.

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