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The Role of Substance Use, Smoking, and Inflammation in Risk for Suicidal Behavior

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Abstract

Background.—Alcohol and substance use disorders are important predictors for suicidal behavior. However, the role of individual substances as proximal risk factors for suicidal behavior and the mechanisms through which substance use affect risk are not entirely clear. We examine whether the frequency of substance use and whether biological markers in the HPA axis and inflammatory pathways are associated with clinical risk factors of suicidal behavior of aggression, impulsivity, hopelessness, and poor sleep.

Methods.—The sample consisted of psychiatric inpatients, aged 15–30 years, admitted for suicide attempt (n=38), suicidal ideation (n=40); and healthy controls (n=37). We measured hair cortisol concentrations, glucocorticoid receptor (GR) sensitivity, stimulated production of interleukin- or IL-6, C-Reactive Protein, and mRNA expression of *GR*, *SKA2*, *FKBP5*, *TNF-α*, and *IL-1β*.

Results.—Smoking was associated with increased aggression [β= 2.9, 95% CI (−0.03, 6), p=0.05], impulsivity [β= 3.1, 95% CI (1.6, 4.6), p<0.001], and poor sleep [β= 0.5, 95% CI (0.03, 0.95), p=0.04] even after controlling for demographics and group. Similarly, *TNF-α* mRNA was associated with impulsivity [β= 0.07, 95% CI (0.01, 0.1), p=0.02] and hopelessness [β= 0.03, 95%

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CI (0.004, 0.05), p=0.03]. Smoking tobacco (r=0.32, p<0.001) was positively associated with *TNF-α* mRNA.

Limitations.—Study limitations include the cross-sectional design, retrospective assessment, and relatively small sample size.

Conclusions.—Future longitudinal studies are needed to test whether inflammatory markers mediate the relationships between smoking, clinical risk factors, and suicidal behavior; and to examine whether smoking cessation could reduce the risk for suicidal behavior in at-risk patients.

Keywords

Substance Use; Smoking; Inflammation; HPA Axis; Imminent Risk; Suicidal Behavior

INTRODUCTION

Alcohol and substance use disorders are important risk factors for suicidal behavior (Darvishi et al., 2015; Poorolajal et al., 2015; Schneider, 2009). However, the role of individual substances as proximal risk factors for suicidal behavior and the mechanisms through which substance use affect risk are not entirely clear.

There are several studies that have shown the link between various substances of use and abuse with suicidal ideation and behavior. Alcohol use disorder and acute alcohol use have been demonstrated to increase the risk for suicidal behavior (Boenisch et al., 2010; Darvishi et al., 2015; Flensborg-Madsen et al., 2009; Sher et al., 2009; Wilcox et al., 2004). Smoking tobacco is also associated with increased risk for suicidal behavior and suicide (Berlin et al., 2015; Boden et al., 2008; Bohnert et al., 2014; Korhonen et al., 2017; Miller et al., 2000a, 2000b; Poorolajal and Darvishi, 2016). Similarly, stimulants, specifically cocaine/crack (Artenie et al., 2015); amphetamines (Artenie et al., 2015; Marshall et al., 2011; Youssef et al., 2016); and opioids, such as heroin and prescription opioid misuse, have been associated with suicidal ideation and behavior (Ashrafioun et al., 2017; Darke and Ross, 2002; Kazour et al., 2016; Roy, 2010; Wilcox et al., 2004). For example, heroin users are 14 times more likely to die by suicide compared to peers matched by age and sex (Darke and Ross, 2002).

The relationship between suicidal behavior and other substances is less clear. Some studies report marijuana use to be associated with increased risk for suicide attempts (Borowsky et al., 2001; Kung et al., 2003; Pedersen, 2008), whereas other studies did not find a significant association (Rylander et al., 2014). Two large population-based studies reported that lifetime use of psychedelics or hallucinogens is not linked to suicidal thoughts, plans, or attempts (Johansen and Krebs, 2015; Krebs and Johansen 2013); and a study showed that past month psychological distress, past year suicidal ideation, planning, and attempts were actually decreased in adults with a history of lifetime psychedelic use (Hendricks et al., 2015). LSD and other psychedelics have been reported to have protective effects by ways of increasing optimism, openness, positive mood, and sense of well-being beyond the acute drug-use period (Carhart-Harris et al., 2016; Griffiths et al., 2008). In the National Household Survey on Drug Abuse, adolescents with lifetime history of 3,4-Methylenedioxymethamphetamine (MDMA) use, commonly known as ecstasy, had twice the rates of suicide attempt in the past

year compared to those who used other drugs and 9 times compared to those without a history of illicit drug use (Kim et al., 2011). On the other hand, MDMA has been shown to have clinically therapeutic benefits in the treatment of PTSD (Amoroso and Workman, 2016); and the US Food and Drug Administration has recently designated MDMA as a breakthrough therapy for the treatment of PTSD, leading the way for phase 3 trials (Knopf, 2016). However, there are drastic differences between therapeutic use in controlled studies *vs.* recreational use where the drug might be adulterated. Recreational drug users also typically use higher doses of the drug at a higher frequency and often show the concomitant use of other drugs (Sessa and Nutt, 2015).

The extant literature is limited in the retrospective assessment of lifetime use of drugs and in examining their association with lifetime or past 12 months suicidal ideation and attempts. In a meta-analysis of studies looking at proximal risk factors for suicide deaths, mood disorders and drug use disorders were associated with 7–9 times increased risk (Conner et al., 2017). In addition, substance use disorders were found to be important predictors of suicide attempts in the days and months preceding the attempt (Walsh, et al. 2017). Thus, these studies highlight the importance of examining the relationship of individual substances as proximal risk factors for suicidal behavior.

Extant studies are also limited in shedding light on the mechanisms through which various substances affect risk for suicidal behavior. Impulsivity, aggression, hopelessness, and poor sleep are well-established clinical risk factors for suicidal behavior (Beck et al., 1990; Bernert et al., 2015; Garrison et al., 1993; Giegling et al., 2009; Goldstein et al., 2008; Liu et al., 2017; Wolfe et al., 2017). Substances such as alcohol, smoking, MDMA, heroin, and cocaine have also been associated with an increase in these clinical risk factors. Marijuana has also been associated with increased impulsivity (Dougherty et al., 2013; Gruber et al., 2014; McDonald et al., 2003) and poor sleep (Bolla et al., 2008; Johnson and Breslau, 2001; Pacek et al., 2017). Paradoxically, marijuana might also be a useful treatment for insomnia (Babson et al., 2017). However, withdrawal from marijuana has been linked to aggression (Smith et al., 2013).

Substance use also affect biological markers in the HPA axis and inflammatory pathways. Alcohol, nicotine, and other substances have been linked to blunted or no cortisol responses to stress (Dai et al., 2007; Gianoulakis et al., 2003; Lovallo et al., 2000; Morris et al., 2016; Neves et al., 2017). However, other studies showed higher basal cortisol levels in heavy alcohol drinkers and those with alcohol dependence, cocaine and MDMA users, and patients with heroin dependence and are on long-term methadone maintenance treatment (Dai et al., 2007; Gianoulakis et al, 2003; Manetti et al., 2014; Parrott et al., 2014; Yang et al., 2016;). Alcohol use and abuse have been reported to be significantly and positively associated with interleukin- or IL-6 and C-Reactive Protein (CRP) whereas marijuana was negatively associated with IL-1β (Karoly et al., 2017; Ransome et al., 2017). Patients with cocaine use disorder, seeking treatment and abstinent, showed lower levels of several inflammatory markers (Mazaquiroga et al., 2017). Heroin injection drug users who are negative for HIV and Hepatitis C infections were found to display elevated levels of an array of inflammatory markers including Tumor Necrosis Factor- or TNF-α (Piepenbrink et al., 2016). We previously reported that suicide attempters, at the time of their admission for an attempt, are

indistinguishable from inpatients admitted for suicidal ideation on clinical risk factors (Melhem et al., 2017). However, attempters were significantly different on several biological markers in the HPA axis and inflammatory pathways, specifically, hair cortisol concentrations, Glucocorticoid Receptor or *GR* mRNA, CRP, and *TNF-α* mRNA (Melhem et al., 2017).

In this study, we examine the relationships of various substances used by psychiatric inpatients with clinical risk factors of suicidal behavior of impulsivity, aggression, hopelessness, and poor sleep during an acute risk period for suicidal behavior; and with biological markers that differentiated attempters from those with ideation and other markers in the HPA axis and inflammatory pathways that have been previously implicated in suicidal behavior. We also examine whether the frequency of use of various substances in the 12 months preceding hospitalization and biological markers are associated clinical risk factors for suicidal behavior above and beyond suicide attempt status.

METHODS

Sample.

The sample consists of psychiatric inpatients, aged 15–30 years, admitted for suicide attempt (SA, n=38) and those admitted for suicidal ideation with no prior history of attempts (SI, n=40). Inpatients were recruited from Western Psychiatric Institute and Clinic (WPIC), University of Pittsburgh Medical Center (UPMC) and informed consent was obtained prior to participating in accordance with the University of Pittsburgh Institutional Review Board (IRB). Patients with impaired cognitive abilities to provide consent were excluded from the study. Healthy controls (n=37) with no personal or family history of psychiatric disorders or suicidal behavior were recruited from the University of Pittsburgh Clinical and Translational Science Institute (CTSI) Research Participant registry, which includes participants at points of routine clinical care at UPMC and from community outreach events. Inpatients and controls were excluded if they had no hair, had a chronic disease affecting HPA axis or inflammatory pathways, or received oral corticosteroid medication in the past year. Inpatients and controls were screened for symptoms of infection. Those who had an acute infection or received antibiotics in the past two weeks were screened again at least two weeks later, as long as inpatients were not discharged.

Assessment.

Suicidal behavior was measured using the Columbia-Suicide Severity Rating Scale (C-SSRS) with well-established psychometric properties to assesss suicidal ideation and behavior (Posner et al., 2011). Psychiatric diagnoses were obtained using the Family History-Research Diagnostic Criteria (Andreasen et al., 1986). The participants' self-reported history of substance use over the past year was obtained using the Drug Use Screening Inventory-Revised (DUSI-R), which has been found to have high test-retest reliability (0.88–0.95) and to correctly identify adolescents and adults with substance use disorders (80%) (Kirisci et al., 1995; Siewert et al., 2004; Tarter and Kirisci, 1997). In our analyses, we examined substances that were used by at least 10% of the sample. The frequency of substance use *per month* over the past year was collected for each substance on

the DUSI-R as an ordinal variable with 1= 0 times, 2=1–2 times, 3=3–9 times, 4=10–20 times, and 5=more than 20 times. We also examined substances used as binary (Yes/No) variables with 0 and 1–2 times coded as No and ≥3 times coded as Yes. Aggression was assessed using the Aggression Questionnaire, which has high internal consistency (0.89) and test-retest reliability (0.72–0.80) (Buss and Perry, 1992). Impulsivity was assessed using the Barratt Impulsiveness Scale, which has high internal consistency (Chronbach's α=0.83) and test-retest reliability (0.83) (Barratt, 1965; Stanford et al., 2009). Sleep was assessed using the Pittsburgh Sleep Quality Index, which also has high internal consistency (Chronbach's α=0.83), test-retest reliability, and differentiates good from poor sleepers with 89.6% sensitivity and 86.5% specificity (Buysse et al., 1989).Feelings of hopelessness were assessed using the Beck Hopelessness Scale with well-established psychometric properties of concurrent and construct validity (Beck et al., 1974). Higher scores on these measures indicate higher impulsivity, aggression, hopelessness, and poor sleep. Household income was measured using the Hollingshead index of social status (Hollingshead, 1975).

Biological markers.

We collected hair and blood samples from participants. The details about the biological assays were previously reported (Melhem et al., 2017). Hair Cortisol Concentrations (HCC): Hair cortisol was quantified in the 3 cm segment of hair closest to the scalp from a posterior vertex position and hair samples were processed following methods described by Laudenslager et al. (Laudenslager et al., 2011). We used an enzyme immunoassay run according to manufacturer's instructions and cortisol levels are reported in pg/mg (Salimetrics, LLC, PA). All samples were run in duplicate. The average coefficient of variation (CV) was < 5% and the intra-plate CV was < 10%.

C-Reactive Protein.—CRP levels are reported in mg/dl and assays conducted using a CRPH reagent on a SYNCHRON LX System (Beckman Coulter, Inc., Brea, California).

Glucocorticoid receptor (GR) sensitivity and stimulated production of IL-6.—Whole blood samples were incubated with 50 ng/ml lipopolysaccharide from E.coli (LPS, serotype 026:B6, Sigma) with different levels of hydrocortisone and allowed to incubate for 18-h. The following hydrocortisone (H-0888, 5g, Sigma) concentrations were used: 0, 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6} M. We assessed corticosteroid suppression of cytokine (IL-6) production. GR sensitivity was determined using area under the curve, and stimulated production of IL-6 was obtained by measuring IL-6 in samples grown without hydrocortisone, which provided a measure of IL-6 derived solely from immune cells.

RNA analyses.—Blood samples using PAXgene Blood RNA Tubes were also collected and followed by RNA isolation and purification using PAXgene Blood RNA Kit. We used Illumina's Human HT-12 v4 Expression BeadChip Kit. Glucocorticoid receptor (*GR)* mRNA α-isoform, GR mRNA β-isoform, *SKA2* mRNA, *FKBP5* mRNA, *TNF-α* mRNA, and *IL-1β* mRNA were examined as these have been previously implicated in suicidal behavior and all have passed quality control analysis.

Statistical Analysis.

We compared SA, SI, and controls on demographic and clinical correlates of suicidal behavior of aggression, impulsivity, hopelessness, and poor sleep. We also compared the groups on the frequency of substance use in the past year and substance use (Yes/No) using analysis of variance (ANOVA) and chi-square tests, respectively. When the group comparison was statistically significant, we conducted post-hoc pairwise comparisons in order to determine group differences and corrected for multiple comparisons using Bonferroni correction (α=0.05/3 pairwise comparisons=0.017). We then examined the relationship of each of the clinical correlates of suicidal behavior, i.e., aggression, impulsivity, hopelessness, and poor sleep with the frequency of use of substances using Pearson's correlations. For these analyses, we also used a Bonferroni correction to correct the significance level since we are examining 4 clinical correlates as our outcomes of interest (α=0.05/4=0.01). We also examined the correlations of the frequency of each of the substances used with the biological markers using Pearson's correlations.

Hierarchical linear regression analysis was conducted for each of the clinical correlates, as dependent variables, to examine whether the frequency of each of the substances used and biological markers were associated with clinical correlates even after controlling for group status (attempt vs. ideation vs. control), age, sex, race, and household income. We introduced substances that were significantly associated with the clinical correlate in the regression in a hierarchical order where the least illicit substances were introduced first (i.e., tobacco, alcohol, and marijuana) followed by the more illicit substances (i.e, cocaine/crack, amphetamines, painkillers, heroin, LSD, and MDMA); and then followed by biological markers significantly associated with the clinical correlate. Finally, we tested for interactions between the frequency of substance use and biological markers that were significant in the final model. All analyses were conducted including SA, SI, and healthy controls and were repeated using SA and SI groups only.

RESULTS

Characteristics of the sample.

The sample had a mean age of 22.8 ± 3.4, 57% males, and 82% White. SA, SI, and controls were similar with respect to age and racial distributions; however, SA and SI were significantly different on sex and household income (Table 1). SA and controls were similar on their sex distribution; however, SI were significantly more likely to be males compared to controls. SA and SI were also similar on household income and showed significantly different and lower household income compared to controls [4.8 ± 2.6 *vs.* 5.8 ± 3.1 *vs.* 8.1 ± 1.8, F=16.4, df (1,111), p<0.001]. SA and SI groups were similar in terms of primary and comorbid psychiatric diagnoses (Table 1). They were also similar, and both significantly different compared to healthy controls, on their scores of aggression [82.7 ± 22.8 *vs.* 81.8 ± 24.6 *vs.* 46.7 ± 12.1, F=39.5, df (2,114), p<0.001], impulsivity [79.7 ± 11 *vs.* 76.9 ± 13.6 *vs.* 55.4 ± 8.1, F=57.1, df (2,114), p<0.001], hopelessness [11.6 ± 5 *vs.* 11.1 ± 5.1 *vs.* 1.8 ± 1.9, F=66.1, df (2, 114), p<0.001], and sleep [10.5 ± 3.4 *vs.* 11.6 ± 3.7 *vs.* 3.2 ±1.9, F=79.6, df (2,111), p<0.001] (Table 1).

Group comparisons on frequency of substance use.

The frequency of use for almost all substances—amphetamines, cocaine/crack, heroin, painkillers, MDMA, and marijuana were similar between SA and SI and were significantly different compared to controls (Table 2). The only exceptions were for smoking tobacco, alcohol, and LSD. SA showed higher frequency of smoking tobacco compared to SI and controls [4.55 ± 1.2 *vs.* 3.4 ±1.92 *vs.* 1.44 ±0.85, respectively, F=47.7, df (2,114), p<0.001]. SI and controls were also significantly different on smoking. SA also showed higher frequency of alcohol use compared to SI; however, controls were not statistically different than SA and SI [3.29 ± 1.27 *vs.* 2.6 ±1.28 *vs.* 3.26 ±1.09, df (2,114), p=0.02]. SA and SI were similar on the frequency of LSD use; however, only SA were significantly different than controls [1.53 ± 0.98 *vs.* 1.25 ±0.59 *vs.* 1.08 ±0.27, F=4.4, df (2, 114), p=0.015] (Table 2) Results were almost similar when examining group differences on presence or absence of substance use (Yes/No); however, SA and SI were significantly different on use of amphetamines and no differences between groups were found regarding LSD and MDMA. When looking at polysubstance use, SA and SI (86.6% vs. 77.5%) were significantly more likely to use 2 or more substances compared to controls (20.5%, χ^2=45.5, df=4, p<0.001) (Table 2).

Relationship of the clinical correlates of suicidal behavior with the frequency of substance use.

Table 3 shows that each of aggression, impulsivity, hopelessness, and sleep were positively correlated with almost all substances, except for alcohol, when including all groups.

Correlations ranged between 0.25 and 0.68. Alcohol was not significantly associated with any of the clinical correlates of suicidal behavior. In addition, LSD was only significantly correlated with impulsivity (r=0.30, p<0.01). When looking at these correlations within the SA and SI groups only, we find the frequency of use of amphetamines, cocaine, heroin, and smoking to be significantly associated with aggression and impulsivity with correlations ranging between 0.29 and 0.41.

Relationship of frequency of substance use with biological measures.

Table 4 shows correlations between the frequency of substance use and biological measures including and excluding healthy controls. *IL-1β* mRNA was significantly and positively correlated with the frequency of almost all substances used in the past 12 months when including all groups, except for amphetamines and LSD, with correlations ranging between 0.21 and 0.27 (Table 4). Some of these correlations were no longer significant when excluding controls due to our reduced sample size. *TNF-α* mRNA was correlated with the frequency of use of cocaine/crack (r=0.22, p < 0.05), heroin (r=0.26, p < 0.01), painkillers (r=0.23, p < 0.05), MDMA (r=0.26, p < 0.01), and smoking tobacco (r=0.32, p < 0.001). However, none of these correlations were significant when excluding controls. *FKBP5* mRNA was consistently correlated with heroin, painkillers, and MDMA use. HCC and GR sensitivity were not correlated with any of the substances including and excluding controls.

Relationships of the clinical correlates of suicidal behavior with the frequency of substance use and biological markers controlling for group and demographic characteristics.

We have previously reported *TNF-α* mRNA to be significantly and positively correlated with impulsivity (r = 0.40, p < 0.001), hopelessness (r = 0.30, p < 0.01), and poor sleep (r = 0.31, p < 0.01) at α=0.01 (Melhem et al., 2017). We examined here whether the frequency of substance use in the past year and biological markers that were significantly associated with each of the clinical correlates of suicidal behavior at α=0.01 continued to be significant when controlling for group and demographic characteristics. Both SA and SI groups were significantly associated with each of aggression, impulsivity, hopelessness, and poor sleep *(Table 5)*. Smoking tobacco was significantly associated with each of aggression [β= 2.9, 95% CI (−0.05, 6), p=0.05], impulsivity [β= 2.9, 95% CI (1.4, 4.4), p<0.001], and poor sleep [β= 0.5, 95% CI (0.03, 0.9), p=0.04] even after controlling for covariates. The frequency of use of heroin was also significantly associated increased aggression [β= 3.4, 95% CI (0.8, 6.0), p=0.01] (Table 5). *TNF-α* mRNA was significantly associated with increased impulsivity [β= 0.07, 95% CI (0.01, 0.1), p=0.01] *(Figure 1)* and hopelessness [β= 0.03, 95% CI (0.003, 0.05), p=0.03]. There was no significant interaction between smoking and *TNF-α* mRNA on impulsivity. Similar results were obtained when excluding controls except that the effect of *TNF-α* mRNA on impulsivity and that of smoking on sleep did not reach statistical significance given our reduced sample size. In addition, SA and SI were similar on aggression, impulsivity, and hopelessness; however, SA showed lower scores on sleep [β= −2.3, 95% CI (−4.3, −0.4), p=0.02], which reflects better sleep, compared to SI.

DISCUSSION

Of all substances, we found smoking was associated with higher levels of aggression, impulsivity, and poor sleep even after controlling for demographics and group. Similarly, *TNF-α* mRNA was associated with impulsivity and hopelessness even after controlling for demographics, group, and substances used. Similar results were obtained when including and excluding healthy controls.

We discuss these results in the context of the study's strengths and limitations. Alcohol and substance use disorders are important predictors of suicidal behavior (Nock et al., 2010). However, most studies report on the relationship of lifetime or past 12 months substance use with lifetime or past 12 months suicidal ideation and behavior. This study examines the relationship of substance use in the past 12 months with HPA axis and inflammatory markers and clinical risk factors of suicidal behavior of aggression, impulsivity, hopelessness, and poor sleep in psychiatric inpatients at the time of their admission for suicide attempt or ideation. Another strength of our study design is the inclusion of psychiatric inpatients across the spectrum of psychopathology, which is more representative of the clinical population at risk for suicidal behavior. In addition, attempters and those with ideation were similar on primary and comorbid psychiatric diagnoses. There were several limitations including the cross-sectional design, retrospective assessment, and relatively small sample size. We relied on patient interviews to obtain information regarding the frequency of substance use in the past 12 months prior to admission rather than obtaining

toxicology results at the time of admission. Thus, our study did not include objectives measures and subjective reporting of substance use at the time of admission or in the days prior to admission. However, toxicology results would only reflect acute levels of drugs and in suicide attempters, many of whom attempted through an overdose on medications and drugs, would not represent their chronic levels of exposure to these substances. Our study is also limited with the relatively small sample size and the low frequency of use of some substances (e.g., LSD, MDMA), which limits our power to examine their effects in this population. The sample size also limits our ability to examine the combined effects of polysubstance use. The prevalence of polysubstance use in the past year among inpatients is high and as such the relationships of substance use with biological and clinical measures may not reflect the individual effects of these substances.

While almost all substances were associated with clinical risk factors for suicidal behavior, smoking was the strongest correlate of aggression, impulsivity, and poor sleep. Suicide attempters showed higher rates of smoking compared to those with ideation and controls; and those with ideation also showed significantly higher rates of smoking compared to controls. These results are consistent with findings that people with mental illness are 2–3 times more likely to smoke compared to the general population (Prochaska et al., 2017). This increased prevalence in people with mental illness is attributed to several factors including disparities in access to tobacco cessation programs, lower socioeconomic status, and increased rates of stressful life events (Prochaska et al., 2017). Our results are also consistent with prior studies showing smoking to be associated with increased risk for suicidal behavior, suicide, and with increased aggression, impulsivity, and poor sleep (Bloom et al., 2013; Dakwar et al., 2011; Miller et al., 2000a, 2000b; Mitchell, 1999; Oquendo et al., 2004; Patterson et al., 2018; Poorolajal and Darvishi, 2016). Furthermore, aggression, impulsivity, and poor sleep are risk factors for suicidal behavior (Carli et al., 2010; Goldstein et al., 2008; Melhem et al., 2007; Nock and Kessler, 2006). These results suggest that smoking *may* increase risk for suicidal behavior through these clinical correlates; although bidirectional relationships are also reported (De Witt H, 2009; Pieters et al., 2015).

We also find the frequency of heroin use to be associated with aggression even after controlling for groups and demographic characteristics. Heroin use has long been identified as a risk factor for suicidal behavior and aggression has been previously reported to be a risk factor for suicide attempt among heroin users (Darke and Ross, 2002; Roy, 2010). Surprisingly, alcohol was the only substance that was not correlated with any of the clinical correlates of suicidal behavior. This could be attributed to the frequency of alcohol use in controls, which was similar to the frequency of alcohol use in SA and SI. Our sample of controls mostly consisted of college students where 36% of them consumed alcohol at a frequency of 10–20 times per month or more. However, these results remained unchanged when excluding healthy controls.

We find *TNF-α* mRNA to predict impulsivity and hopelessness even after controlling for group, demographics, and frequency of substances used that were significant in our models, specifically, smoking. Smoking was significantly and positively correlated with *TNF-α* mRNA, which is consistent with previous studies (O'Connor et al., 2009); however, there

was no significant interaction between smoking and *TNF-α* mRNA in our sample. We have previously reported *TNF-α* mRNA to differentiate SA from SI and controls (Melhem et al., 2017). We were not able to test whether *TNF-α* mRNA mediates the relationships between substance use and clinical risk factors for suicidal behavior due to our cross-sectional design. Future longitudinal studies with large sample size are needed to test these mechanisms. These results are also consistent with several studies showing increased expression of *TNF-α* in people who died by suicide, and increased peripheral expression of inflammatory genes and markers of inflammation among subjects at risk for suicidal behavior (Hoyo-Becerra et al., 2013; Pandey et al., 2012; Tonelli et al., 2008). In a meta-analysis, TNF-α was robustly increased in patients with suicidal ideation and behavior (Black and Miller, 2015). Surprisingly, none of the substances used were correlated hair cortisol concentrations that previously differentiated suicide attempters (Melhem at al., 2017); and HCC was not associated with any of the clinical risk factors of suicidal behavior after controlling for demographics and group. However, we found *FKBP5* mRNA to be positively correlated with the frequency of use of heroin, painkillers, and MDMA. Reduced hippocampal *GR* expression has been previously reported in brains of people who died by suicide and had a history of abuse (Labonte et al., 2012; McGowan et al., 2009). FKBP5 and SKA2 proteins are co-chaperones of the GR and regulate its unfolding and trafficking; and *SKA2* and *FKBP5* mRNA have been previously implicated in suicidal ideation and behavior (Guintivano et al., 2014; Niculescu et al., 2015; Pandey et al., 2016; Perez-Ortiz et al., 2013; Yin et al., 2016).

In conclusion, amongst licit and illicit substances, smoking tobacco has the strongest association with risk for suicidal behavior in psychiatric patients. Smoking may exert its effect on risk in this population through increased aggression, impulsivity, and poor sleep. Smoking is also associated with inflammatory markers and inflammatory markers are in turn associated with aggression, impulsivity, and poor sleep. Future longitudinal studies are needed to test whether inflammatory markers mediate the relationships between smoking, clinical risk factors, and suicidal behavior and to examine whether smoking cessation could reduce the risk for suicidal behavior in at-risk patients.

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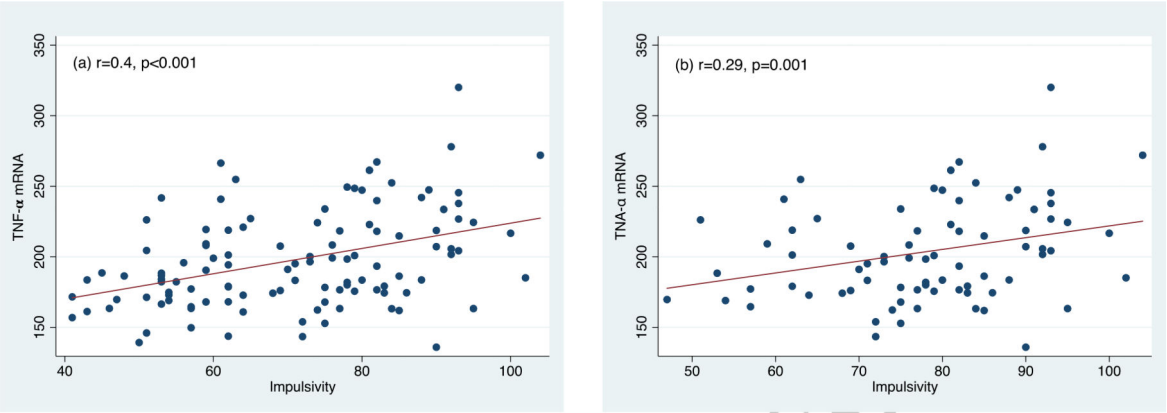

Figure 1.

Correlations between impulsivity and *TNF-??* mRNA. a) Including suicide attempters, subjects with suicidal ideation, and healthy controls; b) Including suicide attempters and subjects with suicidal ideation only

Table 1.

Demographic and clinical characteristics of suicide attempters, subjects with suicidal ideation, and healthy controls

	Suicide attempters (SA)	Subjects with suicidal ideation (SI)	Healthy controls	Test	df	P-value
	n=38	n=40	n=37			
Demographics						
Sex, % Males (n)	55.3 (21 f[a,b]	72.5 (29)[b]	43.6 (17)[a]	χ^2=6.84	2	0.03
Race, % White (n)	89.5 (34)	75.0 (30)	83.8 (31)	X^2=2.9	2	0.24
Age, Mean ± SD	22.8±3.8	23.6±3.9	22.1±2.2	F=1.8	2, 112	0.18
Household income, Mean ± SD	4.8±2.6[a]	5.8±3.1[a]	8.1±1.8[b]	F=15.8	1, 110	<0.001
Clinical correlates of suicidal behavior						
Aggression, Mean ± SD	82.7±22.8[a]	81.8±24.6[a]	46.7 (12.1)[b]	F=36.8	2, 112	<0.001
Impulsivity, Mean ± SD	79.7±11.0[a]	76.9±13.6[a]	55.4± 8.1[b]	F=53.2	2, 112	<0.001
Hopelessness, Mean ± SD	11.6± 5.0[a]	11.1±5.1[a]	1.8± 1.9[b]	F=61.9	2, 112	<0.001
Sleep, Mean ± SD	10.5± 3.4[a]	11.6±3.7[a]	3.2± 1.9[b]	F=79.6	2, 111	<0.001
Psychiatric diagnoses						
Major Depressive Disorder, N (%)	50.0 (19)	62.5 (25)	—	FET*	—	0.58
Bipolar disorder, N (%)	42.1 (16)	32.5 (13)	—			
Psychotic disorders, N (%)	0.0 (0)	7.5 (3)	—	FET*	—	0.24
Anxiety disorders, N (%)	71.1 (27)	60.0 (24)	—	X^2=1.05	1	0.31
Posttraumatic Stress Disorder (PTSD), N (%)	14 (36.8)	16 (40.0)	—	X^2=0.08	1	0.77
Attention Deficit Hyperactivity Disorder (ADHD), N (%)	8 (21.1)	3 (7.5)	—	X^2=2.95	1	0.09
Eating disorders, N (%)	2 (5.26)	2 (5.0)	—	FET*		>0.99
Alcohol dependence, N (%)	9 (23.7)	6 (15.0)	—	X^2=0.95	1	0.33
Substance dependence, N (%)	15 (39.5)	17 (42.5)	—	X^2=0.07	1	0.79
Personality disorders, N (%)	6 (15.8)	2 (5.0)	—	FET*	—	0.15

*FET = Fisher's Exact Test

Table 2.

Frequency distributions of substance use in the past year in suicide attempters, subjects with suicidal ideation, and healthy controls

	Suicide attempters (SA)	Subjects with suicidal ideation (SI)	Healthy controls	Test	df	p-value
	n=38	n=40	n=39			
Frequency of substance use in the past year						
	Mean±SD	Mean±SD	Mean±SD			
Alcohol	3.29±1.27[a]	2.60±1.28[b]	3.22±1.11[a,b]	F= 3.7	2, 112	0.027
Amphetamines	2.39±1.53[a]	1.93±1.35[a]	1.10±0.39[b]	F=10.9	2, 112	<0.001
Cocaine/crack	2.11±1.33[a]	2.03±1.56[a]	1.0 ±0.0[b]	F=10	2, 112	<0.001
Heroin	2.55±1.83[a]	2.70±1.96[a]	1.0 ±0.0[b]	F=13.7	2, 112	<0.001
Painkillers	2.32±1.42[a]	2.38±1.66[a]	1.18±0.51[b]	F= 9.9	2, 112	<0.001
LSD	1.53±0.98[a]	1.25±0.59 [a,b]	1.08±0.28[b]	F= 4.1	2, 112	0.019
MDMA	1.53±0.83[a]	1.50±0.75[a]	1.03±0.16[b]	F= 6.9	2, 112	0.002
Marijuana	3.47±1.54[a]	3.38±1.65[a]	1.68±1.08[b]	F=18.3	2, 112	<0.001
Smoking tobacco	4.55±1.20[a]	3.4±1.92[b]	1.43±0.87[c]	F=46.6	2, 112	<0.001
Substance use in the past year (Yes/No) *						
	% (n)	% (n)	% (n)			
Alcohol	68.4 (26)[a]	45.0 (18)[a,b]	73 (29)[a]	X^2= 7.4	2	0.024
Amphetamines	42.1 (16)[a]	17.5 (7)[b]	2.7 (1)[b]	X^2=18.0	2	<0.001
Cocaine/crack	31.6 (12)[a]	27.5 (11)[a]	0.0 (0)[b]	χ^2=13.8	2	0.001
Heroin	39.5 (15)[a]	42.5 (17)[a]	0.0 (0)[b]	χ^2=22.1	2	<0.001
Painkillers	44.7 (17)[a]	42.5 (17)[a]	5.1 (2)[b]	χ^2=17.1	2	<0.001
LSD	7.9 (3)	7.5 (3)	0.0 (0)	FET **	2	0.24
MDMA	10.5 (4)[a]	15.0 (6)[a]	0.0 (0)[a]	FET **	2	0.06
Marijuana	68.4 (26)[a]	65.0 (26)[a]	13.5 (5)[b]	χ^2=28.5	2	<0.001
Smoking tobacco	89.5 (34)[a]	62.5 (25)[b]	5.4 (2)[c]	χ^2=55.4	2	<0.001
Polysubstance use in the past year						
0	5.3 (2)	15.0 (6)	27.0 (10)	χ^2=42.6	4	<0.001
1	7.9 (3)	7.5 (3)	51.4 (19)			
2 or more	86.8 (33)	77.5 (31)	21.6 (8)			

* No=0 or 1–2 times; Yes > 3 times

** FET = Fisher's Exact Test

Table 3.

Pearson correlations (r) between clinical correlates of suicidal behavior of aggression, impulsivity, hopelessness, and sleep with the frequency of substance use in the past year

	Aggression	Impulsivity	Hopelessness	Sleep
Including suicide attempters, subjects with suicidal ideation, and healthy controls				
Alcohol	0.04	0.05	−0.01	−0.12
Amphetamines	0.45**	0.45**	0.24*	0.35**
Crack/cocaine	0.47**	0.46**	0.25*	0.33**
Heroin	0.51**	0.48**	0.30**	0.37**
Painkillers	0.41**	0.42**	0.29*	0.41**
LSD	0.19	0.29*	0.14	0.18
MDMA	0.38**	0.37**	0.32**	0.29*
Marijuana	0.43**	0.44**	0.27*	0.39**
Tobacco	0.59**	0.68**	0.48**	0.53**
Including suicide attempters and subjects with suicidal ideation only				
Alcohol	0.19	0.18	0.14	− 0.07
Amphetamines	0.31*	0.30*	−0.05	0.12
Crack/cocaine	0.33*	0.32*	−0.05	0.07
Heroin	0.35*	0.29*	−0.04	0.16
Painkillers	0.25	0.22	0.02	0.21
LSD	0.09	0.23	−0.01	0.05
MDMA	0.25	0.22	0.14	0.07
Marijuana	0.15	0.16	−0.15	0.03
Tobacco	0.32*	0.41**	0.04	0.11

* $p<0.01$

** $p<0.001$

Table 4.

Pearson correlations (r) between biological markers and the frequency of substance use in the past year

	HCC	GR mRNA α-isoform	GR mRNA ß-isoform	SKA2 mRNA	FKBP5 mRNA	GR-Sensitivity	CRP	TNF- α mRNA	IL1ß mRNA	Stimulated production of IL-6
Including suicide attempters, subjects with suicidal ideation, and healthy controls										
Alcohol	0.08	0.01	−0.07	−0.15	0.12	0.06	0.08	0.08	0.22*	−0.05
Amphetamines	−0.06	−0.17	−0.01	0.06	0.06	−0.004	0.18*	0.17	0.13	−0.12
Cocaine/crack	−0.05	−0.15	0.14	0.22*	0.12	−0.005	0.14	0.22*	0.23*	−0.05
Heroin	0.15	0.01	0.18*	0.21*	0.19*	0.07	0.09	0.26**	0.26**	0.005
Painkillers	0.03	0.07	0.12	0.12	0.23**	0.12	−0.05	0.23*	0.27**	0.01
LSD	−0.01	−0.01	0.03	0.04	−0.002	0.16	0.16	0.17	0.11	0.08
MDMA	−0.03	−0.16	0.17	0.19*	0.29**	0.18	0.04	0.26**	0.22*	0.16
Marijuana	−0.01	−0.0003	0.10	0.002	0.08	0.09	0.02	0.12	0.21*	−0.05
Smoking Tobacco	0.09	−0.09	0.03	0.18	0.10	0.07	0.11	0.32***	0.24**	0.04
Including suicide attempters and subjects with suicidal ideation only										
Alcohol	0.10	0.08	−0.13	−0.12	0.07	0.10	0.08	0.12	0.26*	0.03
Amphetamines	−0.07	−0.22*	−0.12	−0.04	0.15	−0.10	0.21	0.05	0.08	−0.23*
Cocaine/crack	−0.03	−0.18	0.09	0.18	0.25*	−0.05	0.13	0.15	0.20	−0.10
Heroin	0.21	0.03	0.14	0.16	0.26*	0.05	0.07	0.18	0.24*	−0.04
Painkillers	0.04	0.09	0.01	0.02	0.26*	0.07	−0.10	0.13	0.25*	−0.04
LSD	−0.03	−0.03	−0.04	−0.02	−0.04	0.11	0.19	0.10	0.09	0.04
MDMA	−0.02	−0.20	0.12	0.13	0.36**	0.15	0.01	0.21	0.20	0.16
Marijuana	−0.04	−0.03	−0.05	−0.11	0.06	0.01	0.03	−0.03	0.18	−0.15
Smoking Tobacco	0.16	−0.16	−0.13	0.09	0.18	−0.0004	0.19	0.19	0.19	−0.06

* p<0.05

** p<0.01

*** p<0.001

Table 5.

Regression analyses examining the relationships of the frequency of substance use and biological markers with clinical correlates of suicidal behavior controlling for age, sex, race, socioeconomic status, and group

	Aggression		Impulsivity		Hopelessness		Sleep	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Including suicide attempters, subjects with suicidal ideation, and healthy controls								
Age	0.7 (−0.4, 1.9)	0.23	0.07 (−0.5, 0.7)	0.82	−0.08 (−0.3, 0.2)	0.57	−0.13 (−0.32, 0.06)	0.17
Sex	6.2 (−1.1, 13.6)	***0.09***	1.8 (−2.1, 5.7)	0.36	−0.9 (−2.6, 0.8)	0.29	−1.2 (−2.4, 0.05)	**0.01**
Race	8.5 (−1.6, 18.6)	0.10	−3.2 (−8.4, 1.9)	0.22	−0.4 (−2.6, 1.9)	0.74	−1.1 (−2.7, 0.54)	***0.07***
Household income	−1.1 (−2.6, 0.4)	0.17	−0.4 (−1.2, 0.4)	0.30	0.4 (0.04, 0.7)	**0.03**	−0.1 (−0.4, 0.12)	0.33
Group*								
SA	16.7 (4.0, 29.5)	**0.01**	11.3 (4.6, 18)	**0.001**	10.6 (8.3, 12.9)	<**0.001**	5.3 (3.2, 7.4)	<**0.001**
SI	18.0 (7.6, 28.4)	**0.001**	13.5 (8.1, 19)	<**0.001**	10.0 (7.8, 12.1)	<**0.001**	7.6 (6.0, 9.3)	<**0.001**
Smoking	2.9 (−0.03, 6.0)	**0.05**	3.1 (1.6, 4.6)	<**0.001**	-		0.5 (0.03, 0.95)	**0.04**
Heroin	3.4 (0.8, 6.0)	**0.01**	-		-		-	
TNF- α mRNA	-		0.07 (0.01, 0.1)	**0.02**	0.03 (0.004, 0.05)	**0.03**	-	
Including suicide attempters and subjects with suicidal ideation only								
Age	0.8 (−0.7, 2.3)	0.31	0.3 (−0.5, 1.1)	0.43	−0.04 (−0.4, 0.3)	0.82	−0.12 (−0.4, 0.13)	0.33
Sex	4.3 (−6.7, 15.2)	0.44	0.1 (−5.3, 5.5)	0.97	−2.1 (−4.5, 0.3)	***0.09***	−1.1 (−2.9, 0.6)	0.20
Race	3.2 (−11.3, 17.7)	0.66	−5.0 (−12.2, 2.2)	0.17	−0.7 (−3.9, 2.5)	0.65	−1.1 (−3.5, 1.2)	0.33
Household income	−1.6 (−3.6, 0.4)	0.11	−0.3 (−1.3, 0.6)	0.49	0.5 (0.04, 0.9)	**0.03**	−0.12 (−0.4, 0.2)	0.45
Group*								
SA vs. SI	−4.8 (−16.9, 7.3)	0.43	−2.2 (−8.2, 3.7)	0.46	0.5 (−2, 3)	0.69	−2.3 (−4.3, −0.4)	**0.02**
Smoking	4.3 (0.7, 8)	**0.02**	2.9 (1.0, 4.7)	**0.003**	−		0.5 (−0.09, 1.1)	***0.09***
TNF- α mRNA	-		0.07 (−0.01, 0.1)	***0.08***	0.04 (0.005, 0.07)	**0.03**	-	

*SA and SI are compared to Controls