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Neuropsychological correlates of PTSD and substance use

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NEUROPSYCHOLOGICAL CORRELATES OF PTSD AND SUBSTANCE USE

by

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DEDICATION

To my Grandfather, whose legacy of hard work and perseverance I strive to keep alive.

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To my parents: Thank you for the lifetime of sacrifices you've made that have allowed me to get to this place. Without you, this would not have been possible.

To my best friends – Owen and Gina: Thank you for standing by me and believing in me all these years. Not a day goes by where I don't remind myself how lucky I am to have you.

To my roommate, Kayla – Thank you for your friendship and support. I can't imagine having done this without you.

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ABSTRACT

Substance use disorder is a serious mental health condition that affects a vast number of Americans every year. Substance use disorder frequently co-occurs with other psychological conditions and may impact cognitive functioning. Substance use affects a variety of populations, with nearly 60% of individuals older than 12 reporting the use of a substance within the past month (National Survey on Drug Use and Health, 2019). However, a large gap of knowledge exists in this field among older veteran populations. Using a correlation analysis, we found there to be a significant relationship between substance use risk and PTSD in an elderly veteran population. Using multiple hierarchical regression analyses, we found that substance use risk is a significant predictor of cognitive functioning as measured by category fluency tests. Our findings indicate a growing need to examine substance use risk, comorbid conditions, and cognitive impairment in older veterans.

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LIST OF ABBREVIATIONS

AAP……. Antemortem Assessment Protocol

AFRH…….. Armed Forces Retirement Home

ASSIST……... Alcohol, Smoking, and Substance Involvement Screening Test

AUD…… Alcohol Use Disorder

CAPS-5……... Clinician Administered PTSD Scale for DSM-5

CDC…… Center for Disease Control

DSM…… Diagnostic and Statistical Manual of Mental Disorders

HPA……. Hypothalamic-pituitary-adrenal

ICD…….. Informed Consent Document

LEC-5…….. Life Events Checklist for DSM-5

MDD……... Major Depressive Disorder

MINI…… Mini International Neuropsychiatric Interview

MRI……. Magnetic resonance imaging

NCPTSD……. National Center for PTSD

NOK……	Next-of-kin
OFC…….	Orbitofrontal cortex
OUD……	Opioid use Disorder
PFC……..	Prefrontal cortex
PHQ…….	Patient Health Questionnaire
PRIME-MD	Primary Care Evaluation of Mental Health Disorders
PHQ…….	Questionnaire
PSQI……	Pittsburgh Sleep Quality Index
PTC…….	Permission to Contact
PTSD……...	Posttraumatic Stress Disorder
SUD…….	Substance Use Disorder
SUR ……	Substance use risk
TBI……..	Traumatic brain injury
USUHS……	Uniformed Services University of the Health Sciences
VABBB……...	VA Biorepository Brain Bank
VETR……..	Vietnam Era Twin Registry
VR-12……..	Veterans Rand 12 Item Health Survey

WHO…….... World Health Organization

INTRODUCTION

Substance use disorders (SUD) are serious mental health disorders characterized by inability to control the use of substances (National Institute of Mental Health). Substance use disorders affect individuals in stages of life, with almost 60% of individuals older than 12 reporting the use of tobacco, alcohol, or an illicit substance within the past month (National Survey on Drug Use and Health, 2019). Substance use disorders often co-occur with other mental health disorders such as posttraumatic stress disorder (PTSD), major depressive disorder (MDD), anxiety, and schizophrenia, among others (Swimmer and Sandelich, 2024). With substance use and dependence being so widespread, it is incredibly important to appropriately disentangle the effects of SUD and other comorbid psychopathologies. Understanding the individual effects of SUD and how it interacts with comorbid conditions will aid in the development of more effective treatment interventions, as well as the ability to prevent SUD in those who are engaged in risky substance use and have a comorbid psychological condition.

Trauma- and stress-related disorders, including PTSD, are often comorbid with SUD (Swimmer and Sandelich, 2024). Physical and psychological trauma, like combat, sexual assault, and natural disaster (National Institute of Mental Health, n.d.) leads to PTSD in around 10% of those exposed to similar traumatic events (Yehuda et al., 2015). Symptoms of PTSD are associated with a variety of neuroendocrine, neurochemical, and neuroanatomical changes in the brain (Sherin and Nemeroff, 2011). Similar to SUD, PTSD can develop in individuals of any age (National Institute of Mental Health, n.d.). Accurate diagnosis and treatment are crucial to helping individuals cope with trauma.

The comorbid nature of PTSD and SUD is well established; however, patients tend to have poorer outcomes compared to those who do not have the comorbid conditions (Berenz and Coffey, 2012, Flanagan et al., 2016). The incidence of comorbid SUD and PTSD is approximately 40% in veterans and the general population and can increase the risk of developing other mental health conditions (Flanagan et al., 2016). Despite the severity of these co-occurring disorders, effective treatment options are still lacking (Flanagan et al., 2016), prolonging the suffering of those affected. In order to better treat these conditions, clinicians need to have a solid understanding of how symptoms of each disorder manifest and more importantly, how symptoms of one disorder can affect the other.

SUD in Older Populations

Currently, the prevalence rate of substance use in adults over the age of 65 is 4% (Jaqua et al., 2022). While men have higher rates of SUD, namely Alcohol use disorder (AUD), women tend to abuse prescription medications at a higher rate (Jaqua et al., 2022). Substance use disorders in older populations are often misdiagnosed or underdiagnosed and have been for decades (Atkinson 1990). This may be in part due to overlapping symptoms or attributing symptoms to disorders more commonly seen in older adults, such as dementia or depression (Han et al., 2008). Use of certain substances, such as cannabis, may cause or exacerbate memory problems (Kuerbis et al., 2014), making a disordered use significantly more difficult to diagnose. Older adults are also less likely to receive or engage in treatment for SUD (Blanco et al., 2015), which may also contribute to underdiagnosis. Older populations face unique risk factors such as

chronic pain, reduced mobility, bereavement, and social isolation (Kuerbis et al., 2014). Comorbid conditions, specifically comorbid mental illness, greatly increase the chance of an individual experiencing a SUD (National Institute of Drug Abuse 2020). Post-traumatic stress disorder is a common comorbid condition, with nearly 45% of those with a SUD having current PTSD symptoms (Dore et al., 2011). It is also common for individuals with SUD to be using more than one type of substance (Jones and McCance-Katz 2019).

There are many theories for the rise in substance use and high-risk substance use among older adults, one being that life expectancy is higher than it was several generations ago and individuals remain healthier for longer (Yarnell et al., 2020). Unhealthy drinking habits in older populations is more common in healthy individuals than those in poor health (Kuerbis et al., 2014). Alcohol use disorder or high-risk alcohol use remains the most common substance misused by older populations (Kuerbis et al., 2014), with rates of high-risk drinking increasing 29.9% and AUD as determined by the Diagnostic and Statistical Manual of Mental Disorders-4 (DSM-IV) increasing 49.4% between 2001-2002 and 2012-2013 (Grant et al., 2017). Changes in rates of high-risk drinking were notable among adults 65 and older as well as adults that were previously married but were currently widowed, divorced, or separated (Grant et al., 2017).

According to the Center for Disease Control (CDC), 21.1% of adults aged 45-64 and 11.0% of adults aged 65 and older currently use tobacco products, with cigarettes accounting for 14.9% and 8.3% respectively (Cornelius et al 2023). Using a Kessler K6 non-specific distress scale study to measure mental distress, it was found that 37.6% of

tobacco users had serious psychological distress (Cornelius et al., 2023), further supporting the theory that comorbid mental illness can impact the use of substances. Although cigarette smoking rates have decreased in the general population over the last decade, smoking rates have not decreased in adults over 65 years of age. While older women have decreased smoking behavior over the past decade, this decrease has been slow, older men, on the other hand, have increased smoking (Kalousová 2020).

Both medical and nonmedical cannabis use among older adults has increased significantly in recent years, likely due to decriminalization and legalization of use across the nation (Khoury et al., 2022). Between 2006-2007 and 2012-2013, there was a 57.8% increase in cannabis use in 50–64-year-olds and a 250% increase in use in adults 65 and older (Khoury et al., 2022). In older adults who reported cannabis use in the past year, there was a greater increase of use among those who also reported consuming alcohol (Satre et al., 2020). Those who use cannabis for medical reasons are more likely to have cannabis use disorder than those who use recreationally (Khoury et al., 2022).

Opioid use has reached epidemic proportions and older adults are becoming increasingly affected. As of 2017, 39.5% of adults over 50 years of age used a prescription opioid with 5.3% and 1% having misuse and an opioid use disorder (OUD) respectively (Han et al., 2019). Among all adults, those who reported their health are "fair/poor" had higher rates of OUD than those who considered themselves to be in "excellent" health (Han et al., 2019). Consequently, 4.4% of adults with OUD had three or more visits to the emergency department in the past year (Han et al., 2019). For older cohorts specifically, problematic opioid use in those presenting to the emergency

department increased 220% from 2006-2014 (Dufort and Samaan 2021). This dramatic increase in problematic use among older populations could be attributed to their high exposure to prescription opioids (Huhn et al., 2019), which may be a result of chronic pain, further explaining why that is an important risk factor for older adults.

Amphetamines, whether prescribed or used illicitly, also pose a risk for misuse or development of amphetamine use disorder. While first time-amphetamine prescriptions often start at a young age, there is still a risk of older adults developing amphetamine use disorder (Westover et al., 2018). Compared to individuals aged 18-44, adults between the ages of 45-64 and 65+ have a hazard risk ratio of 0.553 and 0.118 respectively (Westover et al., 2018), indicating that individuals 65 years and older are at an increased risk for developing amphetamine use disorder. As seen with most problematic or hazardous use, risk ratios increase drastically in individuals with co-occurring SUDs compared to those who do not have another SUD (Westover et al., 2018).

While there is limited research on rates of illicit drug use in older populations, heroin and cocaine are the most reported illicit substances used by older adults (Yarnell 2015). Use of these illicit substances have been reported to be on the rise as early as 1992 (Lofwall et al 2008). From 1992 to 2005, use of heroin in adults 55 years of age and older increased 8.2% and cocaine use in the same population increased 6.5% (Lofwall et al., 2008). The aging Baby Boomer population (those born between 1946 and 1964) may provide an explanation as to why we see this increase in illicit substance use and may further provide an explanation as to why these numbers may still be increasing (Lofwall et al., 2008). This population of individuals had more exposure to illicit substances than

other generations, making them more likely to have engaged in substance use at a younger age (Specht et al., 2021).

PTSD in Older Populations

According to the American Psychiatric Association, approximately one in eleven individuals in the general population will be diagnosed with PTSD in their lifetime, and around 3.5% of adults will be affected every year (American Psychiatric Association 2022). Among older adults (aged 60 years and older), prevalence of PTSD varies from 1.5-4% (National Center for PTSD, n.d). The lifetime rate of PTSD is 7% among veterans (National Center for PTSD, n.d). Lifetime risk of PTSD in female veterans is much higher than their male counterparts, with 13% being diagnosed with PTSD at some point in their life (National Center for PTSD, n.d). Service era also affects lifetime PTSD rates (National Center for PTSD, n.d). Lifetime rates of PTSD are highest in Iraq and Afghanistan veterans at 29% and were lowest in Korean war and World War II veterans at 3% (National Center for PTSD, n.d).

Risk factors for PTSD can be discussed in terms of pre-trauma, peri-trauma, and post-trauma (Sayed et al., 2015), all affecting the development and continuation of PTSD symptoms. Some factors like gender, socioeconomic status, race or ethnicity, and education level may make an individual more susceptible to developing PTSD after trauma (Carlson et al., 2016). Women are two times as likely as men to develop PTSD at some point in their life (Kessler et al 1995, Christiansen and Berke 2020). Current research suggests that anxiety sensitivity, or the belief that experiencing anxiety or anxiety symptoms may cause harm (Mantar et al., 2011), possibly explaining why

women are at an increased risk for PTSD (Norr et al., 2016). Biological factors, such as genetics, have also been shown to make individuals more susceptible to experiencing symptoms related to PTSD (Bomyea et al., 2012). Exposure to multiple traumatic events or chronic stress like, childhood maltreatment is associated with an increased risk for developingPTSD and other psychiatric diagnoses (Breslau et al., 2013). Severe childhood maltreatment may alter the stress response system, causing an inappropriate response to successive traumas (Breslau et al., 2013). The association between child abuse and PTSD may be in part due to epigenetics, a change in gene expression without DNA alteration (Weinhold, 2006). There is evidence of gene alterations being influenced by child abuse (Yehuda et al., 2010). One study found that individuals that experienced child abuse had lower levels of the GR gene in the hippocampus than suicide victims who didn't experience child abuse (Yehuda et al., 2010), indicating that there was some sort of epigenetic modification.

Peri-trauma factors can include how the trauma is perceived, how the body responds to the trauma, as well as trauma type (Sayed et al 2015). Interpersonal traumas like sexual trauma and non-sexual physical violence is associated with higher rates of PTSD and chronic PTSD when compared to non-interpersonal traumas like the sudden death of a loved one (Smith et al., 2016). Combat exposure is also associated with high rates of PTSD; however, sexual trauma is associated with more severe PTSD (Jakob et al., 2017). These findings suggest that interpersonal trauma types are more highly associated with PTSD.

Post-trauma factors also play a role in the development and severity of PTSD symptoms. Low levels of social support are a risk factor for PTSD (Brewin et al., 2000, Sayed et al., 2015). This effect is seen significantly more in veteran populations than civilian populations (Brewin et al., 2000). A caveat may be that social support appears to have a better effect when symptoms are clearly related to PTSD, as opposed to a short-term response to trauma (Ozer et al., 2003). This finding is attributed to the cumulative effects of social support (Ozer et al., 2003).

Neurobiological Substrates of SUD and PTSD

It is well-established that PTSD and SUD often present together (Saladin et al., 1995 and Brady et al., 2004). For example, around 26-43% of patients in SUD treatment programs present with PTSD (Hien et al., 2021). There are many theories related to this comorbidity, one being that engaging in substance use can increase the likelihood of experiencing a traumatic event (María-Ríos and Morrow 2020), for example drinking under the influence of an illicit substance. Another theory is that individuals with PTSD use substances to self-medicate (Khantzian 1997, María-Ríos and Morrow 2020). Shared biological mechanisms between these disorders may also explain the rates of comorbidity (Norman et al., 2012).

One important biological system implicated in both PTSD and SUD, is the hypothalamic-pituitary-adrenal (HPA) axis (Hadad et al., 2020). The structures commonly referred to as the HPA axis are located within the paraventricular nucleus of

the hypothalamus, the adrenal gland, and the anterior lobe of the pituitary gland (Smith et al., 2006). The end product of HPA-axis activation is cortisol, a glucocorticoid (Stephan and Wand 2012). The HPA-axis is an important part of the stress response and works to counteract any circumstance threatening homeostasis (Hadad et al., 2020). Some psychiatric conditions, like depression and PTSD, are associated with dysregulated diurnal and stress-reactive HPA-axis function (Stephans and Wand 2012). After experiencing chronic stress, as psychological conditions can induce, baseline cortisol levels are elevated, and it takes longer for levels to decrease after a stressful event (Juster et al 2011, Stephans and Wand 2012). However, over time, chronic activation of the HPA-axis can lead to an attenuated response to stress as evidenced by significantly lower stress-reactive cortisol, which is often seen in individuals with PTSD (Dekel et al., 2017). Studies have shown that individuals with PTSD have lower cortisol levels than those without PTSD after being exposed to a stressor (Dekel et al., 2017).Similar findings have been shown in individuals with AUD (Chakrabarty et al., 2022 and King et al., 2006). Compared to healthy populations, those with current AUD receiving treatment had lower cortisol levels, (Chakrabarty et al., 2022). Another study found that among habitual heavy drinkers, there was a lower cortisol response compared to light social drinkers (King et al., 2006). These findings could suggest that the HPA response may become hypoactive not just in patients with trauma, but in those with substance use disorders.

Neural circuitries and neuroanatomy can also help explain manifestations of PTSD and SUD may underlie their comorbidity. Many symptoms of PTSD arise from dysfunction in communication between the prefrontal cortex (PFC), hippocampus, and

amygdala. The PFC plays a critical role in executive function like goal-planning, language, memory, and problem solving (Siddiqui et al., 2008). The hippocampus, while complex, mainly functions in memory, spatial navigation, and motor and emotional behaviors (Anand and Dhikav 2012). Lastly, the amygdala is responsible for a variety of emotional responses including emotional memory, anxiety and aggression regulation and fear conditioning (AbuHasan et al., 2023). Imaging studies of individuals with PTSD have shown dysregulation of fear learning and memory circuitry associated with the PFC, hippocampus, and amygdala may inform cognitive symptoms associated with this PTSD (Harnett et al 2020). When this system is dysregulated, it impairs the ability to regulate emotional responses (Harnett et al., 2020), which is notable for PTSD as individuals identify most stimuli as dangerous, even if they are not (Inslicht et al., 2013).

In those with SUDs, magnetic resonance imaging (MRI) has shown changes in gray and white matter in the brain; however, alterations tend to depend on the specific substance used (Pando-Naude et al., 2021). Grey matter makes up the cerebral cortex and plays an important role in a variety of different functions (Mercadante and Tadi 2023). White matter contains axon bundles and is responsible for transmitting rapid electrical impulses (Fields 2011). Damage to the white matter can impair motor, sensory, and cognitive functions (Fields 2011). Studies have shown that in individuals in early abstinence from methamphetamine use have decreases in gray matter in multiple areas of the brain, including the cingulate, limbic, and paralimbic cortices (Thompson et al., 2004), which have a role in emotion, action-outcome learning, and memory (Rolls 2019), among others. Imaging studies also show that these individuals had atrophy of the

hippocampus (Thompson et al., 2004). A study looking at those with polysubstance use found that there was both significant decreases in white matter and cortical thickness (Unterrainer et al., 2019), which may explain cognitive deficits seen in individuals with substance abuse disorders (Dean et al., 2018). Substance addiction has also been shown to have detrimental effects to the orbitofrontal cortex (OFC) which has an important role in executive function, decision making (Schoenbaum et al., 2006) and reward signaling (Moorman 2018). The OFC was found to be diminished in individuals with heavy alcohol use as well as animals with access to alcohol (Moorman 2018). Heavy alcohol use in humans was also found to hinder cognitive abilities regarding decision-making and further substance use (Moorman 2018). In an animal study, projections from the OFC to the dorsal striatum were implicated in compulsive cocaine use (Chen et al., 2022) further suggesting that the OFC has a role in inhibiting engagement in risky substance use. The insula, which has a role in interoception, cognition, motivation, awareness of self (Namkung et al., 2017) and conscious urges (Naqvi et al., 2007), has also been implicated in substance use disorders (Droutman et al., 2015). Cocaine (Gardini and Venneri 2012), cannabis, methamphetamine, and heroin users demonstrated decreased gray matter volume and thickness in the insular cortex compared to healthy controls (Droutman et al., 2015). While the literature tells us the insula plays a role in motivation (Namkung et al., 2017) and conscious urges (Naqvi et al., 2007), different regions of the insula are believed to be responsible for cue-induced craving for specific substances (Naqvi et al., 2014). For example, cocaine cues activated the right posterior insula (Kuhn and Gallinat 2011), whereas smoking cues activated the left posterior insula (Engelmann et al., 2012).

Furthermore, the insula is believed to be a key neural substrate in addiction to cigarette smoking because damage to this region disrupted the addiction, making abstinence easy (Naqvi et al., 2007). These findings further suggest the role the insula plays in having conscious urges.

Current research regarding SUD and comorbid PTSD excludes older populations, especially older veterans, which may leave them more vulnerable to developing other comorbid conditions. Our research will help to close important gaps that may aid in the treatment of these conditions and symptoms that may arise as a result.

METHODS

Participants

The sample for our study consisted of 214 participants, 71.03% (*n* = 152) were male and 84.26% (*n* = 182) of the total population were white, non-Hispanic. Participants' age ranged from 20 - 90+, with the mean age being 62.2 (SD = 13.9). The majority of participants were trauma exposed, with 94.4% having endorsed a Criterion A event on the Clinician Administered PTSD Scale (CAPS) and 43.2% of the participants endorsed a history of combat exposure. Comorbidities were common in our sample with 82.41% participants endorsing comorbid PTSD and depression or PTSD and anxiety. Similarly, 32.41% of participants self-reported a comorbid diagnosis of PTSD, anxiety, and depression. Depression was the most common psychological diagnosis in our sample with 75.95% meeting criteria for a current major depressive episode. The use of alcohol (AUD) and substance use disorder (SUD) were low within our sample, with 10.39% meeting the criteria for AUD and 6.01% meeting the criteria for SUD. When evaluating risk for substance use, 78 men and 30 women were considered to have moderate risk for use, and only 11 men and 7 women were considered to have high risk of substance use.

Procedures

Recruitment

Participants diagnosed with PTSD and comorbid psychiatric conditions as well as those without said diagnoses were recruited to join the VA Biorespiratory Brain Bank (VABBB) via advertisements and brochures distributed to the VA Boston Outreach Task Force and the City of Boston Veterans Services. Veterans who were enrolled in other

PTSD registries were also recruited. In collaboration with the National Center for PTSD (NCPTSD), recruitment materials were sent by mail to veterans with PTSD nationwide. Agreeable VA clinics treating veterans with PTSD were also sent recruitment packets to distribute. The VABBB also utilized the VA Corporate Data Warehouse to retrieve patient information for Veterans over 65 diagnosed with PTSD and/or Major Depressive Disorder (MDD). A nonprofit focusing on brain injury in women, PINK concussions, has a webpage initiative that allows women to reach out to various programs about brain donation. If a woman is interested in joining the VABBB, she must call the toll-free number PTSD Brain Bank number. The VBBB also has a relationship with Vietnam Era Twin Registry (VETR) in which the VETR will distribute recruitment materials for the Brain Bank to eligible veterans. Veterans will complete a permission to contact (PTC) form which is then sent to VA Brain Bank staff, or interested parties may contact the Brain Bank themselves.

Enrollment

Staff from the Brain Bank contacted participants interested in the antemortem study and gave further information on the study and what it entails. Interested parties can consent in-person or via mail. In order to participate, veterans must have a legal next-of-kin (NOK) co-sign the Informed Consent Document (ICD). During an in-person consent, the veteran and their NOK both sign the ICD and the veteran signs a HIPAA form. Two copies are completed, one for the enrollee's records and one for VABBB staff. If the NOK cannot attend the in-person meeting, the consent form is mailed. Both veterans and

non-veterans have the option to do mail consent if they do not live close to the Brain Bank location in Boston, do not come to the VA Boston regularly, or have mobility issues that would significantly impact travel. If this is the case, two copies of the ICD and HIPAA forms are sent to the participants and NOK. One copy is kept by the enrollee and the other is signed and mailed. Re-consenting may be required if an assessment determines a participant is cognitively impaired. If a participant has cognitive impairment, staff will attempt to obtain surrogate consent, unless the participant does not agree to this, in which case they will be excluded from the study.

Antemortem Assessment Protocol (AAP)

There are four mailed surveys/questionnaires used in the AAP: Primary Care Evaluation of Mental Health Disorders Questionnaire (PRIME-MD PHQ), PTSD BB Health Questionnaire, PTSD Checklist for DSM-5, and Pittsburgh Sleep Quality Index (PSQI).

The psychiatric diagnostic interview is completed over the phone and is composed of five tests: Life Events (LEC-5), Clinician-Administered PTSD Scale, Mini International Neuropsychiatric Interview (MINI), Telephone Interview for Cognitive Status (TICS), and Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST).

Measures

VA Biorespiratory Brain Bank Posttraumatic Stress Disorder (PTSD) Baseline Survey

The VA Brain Bank PTSD Baseline Survey is a questionnaire that collects information on participant demographics, military and health history. Embedded in the Baseline survey are the SNAC and the Rand VR-12 (Veterans Rand 12 Item Health Survey). The survey is divided into 13 sections. Sections 1 and 2 ask about basic demographic information, like date of birth, gender, weight and height. Section 3 asks questions about athletic history. Section 4 through 7 asks about Military history and exposure to toxic chemicals. Section 8 through 13 assess the participants' health history and includes questions related to current and past health, healthcare utilization, and family health history.

Patient Health Questionnaire PRIME-MD (PHQ)

The PHQ is a questionnaire composed of sixteen questions that assesses for 8 DSM-IV diagnoses as well as subthreshold diagnoses such as other depressive disorder, alcohol abuse, and binge eating disorders (Spitzer et. al, 1999). The PHQ is scored based on symptoms experienced over the past two weeks and responses are categorized as "not at all", "several days", "more than half the days", or "nearly every day". The participant is then asked how much, if any, difficulty these symptoms have posed in their daily, work, and interpersonal lives. A PHQ score of 5 represents mild depression and can range up to 20 which represents severe depression (Kroenke et. al, 2001).

World Health Organization (WHO) Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)

ASSIST is an eight-question test created by the World Health Organization to assess an individual's current (within the past 3 months) and lifetime use of substances. The purpose of this screening test is to determine if the individual needs intervention and if so, how intense the treatment should be. The ASSIST asks if an individual has used a specific substance (e.g. alcoholic beverages) from a list of 10 substances - tobacco, alcohol, cannabis, cocaine, amphetamine-type stimulants, inhalants, sedatives or sleeping pills, hallucinogens, opioids, and 'other' drugs. The VA BBB has added an additional question that asks about the age participants began using a specific substance. Questions two through five range on a scale of zero "never" through eight "daily or almost daily." Questions six and seven ask about family or friend concern and attempts to reduce or stop using substances. These questions are scored on a scale of zero "no, never" to six, "yes, in the past three months." Question eight inquires about injecting a substance and offers scores of zero, one, and two, coinciding with the possible answers for questions six and seven. Each participant receives a risk score ranging from 0-39 for the 10 substances inquired about, with the exception of tobacco having a risk score from 0-31. A risk score of 0-3 for all substances, except alcohol in which the risk score is 0-10, demonstrates a lower risk of having negative experiences related to substance use (Humeniuk et al., 2008). Those with a risk score of 11-26 for alcohol and 4-26 for other substances are at a moderate risk of becoming dependent on substances and may already experience negative side effects related to their use. For alcohol and all other substances, a score of 27 and

greater is indicative of a serious substance abuse problem that is likely affecting everyday life and relationships.

Life Events Checklist for DSM-5 (LEC-5 Weathers et al., 2013)

The LEC-5 is a two-part questionnaire composed of 17 items that assess exposure to traumatic events over a participant's lifetime. The first section of the LEC-5 asks about exposure to specific traumatic events (e.g. Natural disaster) and how they experienced the event (e.g. "Happened to me"). The second section asks follow up questions about the events endorsed in section 1. These questions include how long ago the event occurred, how it was experienced, if someone's life was in danger, if someone was injured or killed - and if so - was it due to an accident, violence, or natural cause, if sexual violence occurred, and lastly, if the individual has experienced more than one traumatic event.

Telephone Interview for Cognitive Status (TICS)

The Telephone Interview for Cognitive Status (TICS) is a 12-question assessment conducted in-person or over the phone to assess cognitive functioning and impairments, specifically Alzheimer's disease (AD) (Fong et al. 2009). The VA BB used a modified version of the TICS test, TICSm, which additionally tests for delayed recall and verbal comprehension (Fong et al. 2009). TICSm is scored as follows: 1 point for a correct response, 0 for incorrect, DK for don't know, SR for semantically related, PP for phonemic paraphasia, and question 8 (asks interviewee to repeat phrases) has a possible score of unable. Some questions allow for 2 points to be awarded as well. The TICSm

includes supplemental tests: digit span forward, digit span backward, and animal fluency. The animal fluency supplemental item gives interviewees 60 seconds to list as many animals as possible. This is scored based on correctness, total repetitions, and total errors. Following the interview, there is a post interview de-briefing to determine if the assessment caused frustration or stress to the participant and lastly, the interviewer indicates whether hearing difficulty affected the participants performance.

Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (APA, 2013)

The CAPS-5 is a 20-item assessment used to diagnose and assess symptoms of current (within the past 30 days) or lifetime PTSD. The CAPS-5 assesses the 20 PTSD symptoms outlined in the DSM-5 (APA, 2013). Items on the CAPS-5 are scored on a scale from 0 to 4, with 0 representing "absent" or no DSM-5 criteria met and 4 representing extreme/incapacitating symptoms. Symptoms of reexperiencing (Criterion B), avoidance (Criterion C), negative alterations of in cognition and mood (Criterion D), and hyperarousal (Criterion E) are clustered into groups and scored based on severity (Weathers et. al, 2013).

PTSD Checklist for DSM-5 (PCL-5)

The PCL-5 is composed of 20 items and asks participants to self-report symptoms of PTSD as determined by the *DSM-5* (Weathers et al, 2013). The PCL-5 is used to make a provisional diagnosis of PTSD and has three possible formats: without Criterion A when trauma is being measured by another test, with a brief test for Criterion

A, or with the LEC-5 and an extended Criterion A (National Center for PTSD). Symptoms are scored on a scale of 0-4, similar to the CAPS-5. There are separate checklists for civilians and military personal.

RESULTS

Table 1

Demographic Characteristics of the Participants

Sample Characteristics	*n*	*%*	*M*	*SD*
Gender				
Men	150	69.80	-	-
Women	62	28.80	-	-
Age	-	-	62.25	13.88
Education				
Less than high school	3	1.40	-	-
High school - diploma/GED	15	7.00	-	
Some college credit but no - degree	47	21.90	-	

Associate's Degree - (e.g. AA, AS)	32	14.90	-	
Bachelor's Degree (e.g. BA, BS)	51	23.70	-	-
Master's Degree (e.g. MA, MS MBA)	53	24.70	-	-
Professional Or Doctoral - Degree	8	3.70	-	
Race/Ethnicity				
White, Non-Hispanic	182	84.30	-	-
African American, Non-Hispanic	8	3.70	-	-
Hispanic	15	6.90	-	-
Other or Unknown	11	5.10	-	-

Note. Gender missing *n* = 3, 1.4%
Education missing *n* = 6, 2.l8%
Race/ethnicity missing *n* = 12

CORRELATION RESULTS

A Pearson correlation was performed to examine the relationship between psychological conditions and substance use. There was a significant positive relationship between current PTSD severity as measured by the PCL, $r(135) = .313$, $p = < .001$, lifetime PTSD, as measured by the PCL, $r(130) = .261$, $p = .002$, depression, $r(168) = .199$, $p = .009$, and substance use risk. We also investigated the relationship between PTSD and substance use risk in a subsample of participants who were interviewed using the CAPS-5. When examining the relationship between CAPS-5 PTSD severity and substance use risk, we confirm that there is a positive correlation between current PTSD, $r(132) = .329$, $p < .001$, lifetime PTSD, $r(108) = .224$, $p = .019$, and substance use risk, such that greater PTSD severity is associated with greater risk for substance use disorder. Lastly, there was a significant moderate positive relationship between number of traumatic brain injuries (TBI) and substance use, $r(173) = .242$, $p = .001$. There was no significant relationship between substance use and trauma exposure as measured by the LEC-5.

Pearson correlations were also performed to explore which substances were most strongly associated with psychological outcomes. Current PCL PTSD severity was related to increased tobacco use, $r(124) = .197$, $p = .027$, increased alcohol use, $r(128) = .230$, $p = .008$, increased cannabis use, $r(127) = .224$, $p = .001$, increased cocaine use, $r(132) = .214$, $p = .013$, increased amphetamine use, $r(130) = .194$, $p = .026$, increased sedative use $r(133) = .184$, $p = .033$, and increased opioid use $r(134) = .216$, $p = .012$.

Similarly, current CAPS PTSD severity was associated with increased tobacco use, $r(118) = .262$, $p = .004$, increased alcohol use, $r(122) = .181$, $p = .045$, increased cannabis use, $r(122) = .255$, $p = .004$, increased cocaine use, $r(128) = .310$, $p = <.001$, increased amphetamine use, $r(126) = .260$, $p = .003$, increased sedative use, $r(130) = .192$, $p = .028$, and increased opioid use, $r(130) = .296$, $p = <.001$. Trauma exposure was not associated with increased substance use and neither inhalants nor hallucinogens were found to have a significant relationship with any of our tested psychological conditions.

Depressive symptoms were associated with increased cocaine use, $r(164) = .185$, $p = .017$ and increased opioid use, $r(166) = .209$, $p = .007$.The number of TBIs were associated with increased alcohol use, $r(160) = .228$, $p = .004$, increased cannabis use, $r(161) = .372$, $p = <.001$, increased cocaine use, $r(169) = .152$, $p = .047$, and increased opioid use, $r(171) = .305$, $p = <.001$.

REGRESSION RESULTS

Hierarchical Regression Models Predicting Cognitive Function

We performed three hierarchical regression analyses to examine the prediction of global cognitive functioning, recognition memory, and category fluency from substance use disorder risk and psychological conditions.

Psychological Conditions and Cognitive Function

Tables 6-8 display full regression model statistics. Model 1 investigated the prediction of global cognitive function from psychological conditions. The covariates

Age, sex, and education were entered into step 1 and number of TBIs, MDD, total substance use disorder risk, and PTSD (CAPS-5) symptom severity were entered into step 2. Age predicted global cognitive functioning (β = -.263, p = .008).

Model 2 investigated the prediction of recognition memory from psychological conditions after adjusting for age, sex, and education. Age predicted recognition memory (β = -.264, p = .010). No other predictors were significant in the model.

Model 3 investigated the prediction of category fluency from psychological conditions after adjusting for age, sex, and education. In step 1, sex (β = .206, p = .047) predicted category fluency. In step 2, after controlling for age, sex and education, total substance use risk (β = -.247, p = .013) significantly predicted category fluency.

Because total substance use was predictive of deficits in category fluency, we were interested in exploring how category fluency was predicted by risk for substance use disorder from individual substances. In step 1, the covariates age, sex, and education were entered. In step 2 risk for substance abuse for 13 substances were entered. In step 1, sex (β = .206, p = .047) predicted category fluency. Individual substance abuse risk did not significantly predict category fluency.

Table 2

Correlation analysis of psychological outcomes related to substance use

Psychological Outcomes	Total Substance Use
Current PCL PTSD	<.001**
Lifetime PCL PTSD	.002**
LEC-5	0.184
PHQ9	.009**
Current CAPS PTSD	<.001**
Lifetime CAPS PTSD	0.019**
TBI	.001**

Note. ** = $p < .05$
Note. PCL PTSD is measured by the PTSD Checklist for DSM-5
Note. LEC-5 is the Life events checklist
Note. PHQ-9 is the Patient health questionnaire used to test for depression
Note. CAPS PTSD is measured by the Clinician administered PTSD scale for DSM-5
Note. TBI is traumatic brain injury

Table 3

Substance	**Psychological Outcomes**						
	Current PCL PTSD	Lifetime PCL PTSD	LEC-5	PHQ9	Current CAPS PTSD	Lifetime CAPS PTSD	TBI
Tobacco	.027**	0.148	0.202	0.117	.004**	.008**	0.878
Alcohol	.008*	.012**	0.284	0.116	.045**	0.697	.004**
Cannabis	.011**	.047**	0.989	0.117	.004**	.040**	<.001**
Cocaine	.013**	0.327	0.468	.017**	<.001**	0.101	.047**
Amphetamines	.026**	0.598	0.317	0.091	.003**	0.058	0.100
Inhalants	0.337	0.533	0.581	0.597	0.141	0.088	0.067
Sedatives	.033**	0.256	0.934	0.258	.028**	0.689	0.877
Hallucinogens	0.257	0.266	0.795	0.958	0.068	0.141	0.263
Opioids	.012**	0.165	0.176	.007**	<.001**	.012**	<.001**

Correlation analysis of psychological outcomes related to individual substances

Note. ** = $p < .05$
Note. PCL PTSD is measured by the PTSD Checklist for DSM-5
Note. LEC-5 is the Life events checklist
Note. PHQ-9 is the Patient health questionnaire used to test for depression
Note. CAPS PTSD is measured by the Clinician administered PTSD scale for DSM-5
Note. TBI is traumatic brain injury

Table 4

Hierarchical regression analysis to examine prediction of global cognitive function from substance use disorder risk and psychological conditions

		TICS	
	Adj. R^2	R^2	*p*
Predictor			
Step 1: Education, sex, age	0.113	0.137	.001**
Step 2: TBI, MDD, Total substance use, CAPS PTSD	0.122	0.176	.004**

Note. ** = p< .005

Table 5

Hierarchical regression analysis to examine prediction of recognition memory from substance use disorder risk and psychological conditions

		TICS RECOGNITION	
	Adj. R^2	R^2	*p*
Predictor			
Step 1: Education, sex, age	0.033	0.059	0.082
Step 2: TBI, MDD, Total substance use, CAPS PTSD	0.084	0.141	.021**

Note. ** = p< .005

Table 6

Hierarchical regression analysis to examine prediction of category fluency from substance use disorder risk and psychological conditions

	Category Fluency		
Predictor	Adj. R^2	R^2	*p*
Step 1: Education, sex, age	0.067	0.092	.014**
Step 2: TBI, MDD, Total substance use, CAPS PTSD	0.079	0.137	.027**

Note. ** = p< .05

Table 7

Exploratory regression analysis to examine prediction of category fluency from individual substances

	Beta	Category Fluency *p*
Predictor		
Tobacco	-.162	.084
Alcohol	.093	.382
Cannabis	-.007	.955
Cocaine	-.034	.890
Amphetamines	.033	.780
Inhalants	.493	.236
Sedatives	-.099	.291
Hallucinogens	-.084	.573
Opioids	-.462	.279

DISCUSSION

Relationship between Substance Use Risk and Psychological outcomes - Correlation

When examining the relationship between substance use risk (SUR) and psychological comorbidities, we found that SUR was positively and significantly related to depression severity, PTSD symptom severity, and number of lifetime TBIs.

SUR and depression

When examining the relationship between SUR and depression, significance was found for total substance use. It is well established that depression and SUD are often comorbid in adults, with lifetime prevalence rates falling between approximately 9-30% (Mackie et al., 2012). Veterans serving during the Iraq and Afghanistan wars were found to have significantly increased risk of having both SUD and depression (Shen et al., 2012), although more research should be done looking at all veterans. When looking more closely at the relationship between risk for specific substances and depression, we found significance for cocaine and opioids.

SUR and TBI

We also examined the relationship between risk for SUD and number of TBIs in which there was a significant correlation. When examining the risk for specific substances and number of TBIs, we found significance for alcohol, cannabis, cocaine, and opioids. Much of the existing research surrounding the relationship between SUD

and TBIs supports the belief that risky substance use can increase the likelihood of a TBI (Olsen and Corrigan, 2022), and pre-injury substance use can make an individual with a TBI more likely to misuse or form a SUD post-injury (Adams et al., 2019). However, there isn't as much data to support the hypothesis that TBI acts as a direct risk factor for SUD (Merkel et al., 2017). One notable factor that can increase the risk for developing SUD after TBI is age at the time of injury (Merkel et al., 2017). Evidence shows that early-life TBI can predict onset and severity of substance use (Fishbein et al., 2016). These findings are especially relevant because young adults are at a high risk of sustaining a TBI, as are adults 65 and older (Georges and Das, 2023). Our participants only reported how many TBIs they've had over their lifespan, not age sustained, so it is difficult to know if this had any effect on onset or severity of substance use. Sex, severity of injury, and repetitive injury can also increase the risk for developing SUD after TBI (Merkel et al., 2017).

SUR and PTSD

Lastly, we examined the relationship between risk of SUD and PTSD using participant self-report (current and lifetime PCL severity) and the gold standard test for PTSD (current and lifetime CAPS-5 severity). We used both the PCL and CAPS in our population due to having more participants in the PCL category, however we also wanted to use the CAPS-5 because it is the gold standard for diagnosing PTSD. In doing so, we found varying degrees of significance for both these measures and total substance use. Current PCL PTSD and current CAPS PTSD were significantly associated with the same substances, tobacco, alcohol, cannabis, cocaine, amphetamines, sedatives, and opioids.

However, lifetime CAPS PTSD found significance for tobacco use and lifetime PCL PTSD did not. This discrepancy may be due to the self-report nature of the PCL. The comorbidity of PTSD and SUD has been extensively researched with multiple theories surrounding this relationship. Some researchers believe PTSD symptoms inform the use of substances while others believe trauma related to substance use results in PTSD, but there is more evidence supporting the former (Van den Brink, 2015). It is believed that patients use substances as a form of self-medication (Van den Brink, 2015, Jacobsen et al., 2001), with patients reporting that certain substances like alcohol, cannabis, and opioids help to ease PTSD symptoms (Jacobsen et al., 2001). The self-medication hypothesis, while popular, is noted to have flaws (Hawn et al., 2020). The reporting of use of certain substances is consistent with the findings of many of our PTSD measures. Despite the PCL and CAPS-5 both assessing for PTSD, there are some inconsistencies in our findings. Multiple studies have shown that participants frequently score higher on the PCL than the CAPS-5 (Resick et al., 2023). This may be due to patients feeling more comfortable self-reporting symptoms than they are reporting symptoms to an interviewer. We also assessed for current PTSD and lifetime severity with both the CAPS-5 and PCL, however, assessing for lifetime PTSD requires participants to reflect across decades, which may have affected accuracy in our findings.

Individual Substances and Depression

Opioids

Risk for OUD could possibly be attributed to chronic pain in our elderly population, as 66% of adults over 65 experience chronic pain (Corsi et al., 2018). There is also evidence that chronic pain can contribute to symptoms or worsening symptoms of depression, with approximately 40-60% of chronic pain patients also having depression (Surah et al., 2013). Furthermore, rates of depression increase more than 20% after an older adult experiences a serious hospitalization (Taylor, 2014). Chronic pain may lead to surgeries or hospitalizations, which could further explain the significant relationship between risk for OUD and depression.

Cocaine

With the baby boomer generation becoming older, there has been an increased need to look at the use of illicit substances due to their likelihood of using these substances (Gfroerer et al., 2003). While there is limited research estimating the exact relationship between cocaine use and depression, there is evidence that cocaine users suffer with depression (Falck et al., 2002, Connor et al., 2008). Among crack-cocaine users, 55% had moderate to severe depression, with there being a positive association because frequency of use and higher depression scores (Falck et al., 2002).

Individual Substances and TBI

Alcohol

The relationship between alcohol and TBIs is well researched, and alcohol is a major risk factor for TBI (Horner et al., 2005), with nearly half of TBIs being related to alcohol use (Savola et al., 2005). A study examining alcohol misuse in Iraq and Afghanistan veterans found that there were higher rates of TBI in those who sought treatment for their substance use compared to those without TBI (Grossbard et al., 2016). Another study looking at veterans found similar results with those experiencing TBI having increased risk of AUD (Johnson et al., 2015). These findings, specifically those in veterans, support our findings.

Cannabis

Research regarding the relationship between cannabis use and TBI is less clear, however. The consensus among researchers appears to be that those without TBI are less likely to engage in cannabis use than those with TBI, however these studies have limitations (Jacotte-Simancas et al., 2021). One possibility for significance in our cohort is the use of cannabis to ease symptoms of TBI, such as pain or insomnia, as some case studies have found this in other cohorts (Hergert et al., 2021). Cannabis use after mild TBI is also very common among veterans (Utter et al., 2023), which further supports our findings. The legalization of cannabis across the United States may also explain why there was a strong relationship between cannabis and TBI in our cohort, however further

research is needed to determine if cannabis is a reasonable treatment for TBI (Jacotte-Simancas et al., 2021).

Cocaine

The relationship between illicit substances and TBI is well established, although there aren't many studies focusing specifically on cocaine use. A previous study found that when compared to controls, those with TBI are more likely to use illicit substances, including cocaine (Allen et al., 2016). Animal studies may play an important role in explaining this relationship, as it was found that adolescent brain injury enhanced the cocaine reward mechanism (Cannella et al., 2019) making the adult brain more sensitive to stimulants like cocaine (Merkel et al., 2017). It is unclear, however, if the same is true in adult brain injury when the brain is fully developed.

Opioids

It is not uncommon for physicians to prescribe opioids for pain (Nafziger and Barkin, 2018) especially in those who have sustained a TBI due to their likelihood of having persistent pain compared to healthy controls (Kumar et al., 2021). In veteran populations, TBI is common and in those with moderate to severe TBI, there is an increased likelihood for pain (Kumar et al., 2021), often resulting in an opioid prescription. For veterans with TBI, there is increased concern of opioid prescription due to the likelihood of having comorbid psychiatric conditions like depression or PTSD (Fonda et al., 2020), which are risk factors for OUD (Webster, 2017). Having older participants may mean that there is a large number that are prescribed opioids for chronic

pain, which may help explain our significant findings. In the era of an opioid epidemic and strong evidence of chronic pain in individuals who experienced a TBI (Adams et al., 2019), it is increasingly important for studies to look specifically at the relationship between opioids and TBIs.

Individual Substances and PTSD

Tobacco

As of 2021, it was reported that almost 19% of adults in the United States use some sort of tobacco product (Cornelius et al., 2023). Among those with PTSD; however, the prevalence of tobacco use is nearly 45% (Pericot-Valverde et al., 2018), indicating a comorbid relationship. Supporting the theory that PTSD informs substance use, tobacco use has also been reported as a way to cope with PTSD symptomology (Kearns et al., 2018). In our veteran population, there may be unique explanations for our significant findings. For those in older war eras like the Vietnam War, cigarettes were given out as rations and dangerous effects of tobacco was not advertised the way it is today (Kirby et al., 2008). This is important to consider because smoking while deployed increases lifelong consumption of cigarettes (Kirby et al., 2008).

Alcohol

The comorbid relationship between alcohol misuse and PTSD is well-documented and ranges between 30-50% (Hawn et al., 2020); however, these ranges often vary dramatically. Being diagnosed with PTSD or having symptoms of PTSD also puts individuals at a higher risk of developing AUD compared to the general population

(Gilpin and Weiner, 2016). In veterans, comorbid PTSD and AUD is even more common (Gilpin and Weiner, 2016), with those who have experienced combat having higher rates of problem drinking than non-combat veterans (Jacobson et al., 2008). It has been noted that AUD follows the development of PTSD (Gilpin and Weiner, 2016), which may point to the self-medication hypothesis. It is difficult to know if that hypothesis holds up in our population. Men are also more likely to develop AUD or drink problematically (Erol and Karpyak, 2015), which may help to explain our significant findings, as our population is mostly men (69.8% male vs. 28.8% female).

Cannabis

Interestingly, cannabis was the only substance we found to have a significant relationship with all measures of PTSD – current and lifetime. Cannabis use is common in those with PTSD, particularly in those who have high score high for PTSD (Bonn-Miller et al., 2014). Both cannabis and synthetic cannabinoids (not screened for in our population) were found to be therapeutic in easing symptoms of PTSD (Orsolini et al., 2019). One common symptom cannabis is used to ease is insomnia (Bonn-Miller et al., 2014, Orsolini et al., 2019). A possible explanation supporting the popularity of cannabis is the reduction in side effects compared to traditional pharmacological treatments for PTSD (Orsolini et al., 2019). One study of veterans in a focus group found that all patients (n = 7) started using cannabis because of negative experiences with traditional medication such as inefficiency, side effects, and overmedication (Krediet et al., 2020). In this same cohort, patients reported increased relaxation, better sleep, and reduction in headache (Krediet et al., 2020). It is likely our participants found the same benefits to be

true. Full legalization of cannabis, both medicinal and recreational, may help explain our significant findings, as it is widely available. Although cannabis use is popular amongst many, there is limited evidence regarding efficacy and safety of use for PTSD symptoms (Krediet et al., 2020), and with use comes risk for misuse and developing a use disorder. Rates of cannabis use disorder among veterans are rising, especially among those with PTSD (Bryan et al., 2021). This finding is especially true for veterans in the post – 9/11 era, with 72.3% having both cannabis use disorder and PTSD (Bryan et al., 2021). Future research is necessary to determine safety and efficacy of cannabis for PTSD compared to traditional pharmacotherapy.

Cocaine

Lifetime PTSD is common in individuals with cocaine use disorder, with over 40% meeting PTSD criteria (Back et al., 1999). Among cocaine dependent individuals, current PTSD was found in a higher rate of women compared to men (Najavits et al., 2003). Among female veterans 55 and younger, cocaine use disorder was present 0.8% and 3.6%, depending on war era (Hoggart et al., 2015). A pilot study found that with an increase in cocaine use came worsening PTSD symptoms (Back et al., 2006). Over 95% of subjects in the aforementioned study believed that their cocaine use and PTSD were related, also noting that their cocaine use decreased if their PTSD symptoms improved (Back et al., 2006). These findings help to support the self-medication hypothesis.

Amphetamines

Research into the use and effects is relatively new and may become more common as amphetamine use, particularly methamphetamine use, is increasing globally (Stoneberg et al., 2017) and causing concern for the effect they may have on mental health (Thoradeniya et al., 2020). In a study looking at young adults in Australia, rates of PTSD were significantly higher in those who used amphetamine-type stimulants compared to those who didn't (Thoradeniya et al., 2020). Research regarding amphetamine use and veterans is limited, however, stimulants are often used in military aircrew during combat to decrease fatigue (Gore et al., 2010). It is unclear if this contributed to our finding in any way, as the duration of use is unclear. One study examining active duty military members found that as stimulant prescriptions increased in their population, so did risk for PTSD (Crum-Cinaflone et al., 2015). Similarly, the same study found that those who used stimulants had a higher risk for PTSD compared to those who didn't (Crum-Cinaflone et al., 2015). The use of amphetamines in our population may be independent of PTSD, and instead contributed to a separate diagnosis. Further research is needed to accurately determine the relationship between amphetamine use and PTSD.

Sedatives

Sleep problems and insomnia are common symptoms associated with PTSD (Inman et al., 1990), and may result in a sedative prescription. In veteran populations, almost 70% suffer from some sort of sleep dysfunction (Bernardy et al., 2014). The significant findings in our cohort may be enhanced because our participants are veterans

and most are older, with our mean age being 62.5 (SD = 13.9). With sleep dysfunction being a common problem in those with PTSD, and sedatives being disproportionately prescribed in the elderly (Vitiello, 1997), it is likely that many have prescriptions. A 2004 study estimated that approximately 75% of veterans with PTSD had a prescription for a sedative, with many being prescribed more than one (Bernardy et al., 2014). One study showed that in veterans wounded in combat, nearly 22% reported misusing sedatives (Kelley et al., 2019). More research is needed to accurately estimate the percent of veterans misusing sedatives.

Opioids

It is well established that we are in the midst of an opioid epidemic stemming from both prescription opioids and synthetic opioids like fentanyl (Dahlby and Kerr, 2020). PTSD is a known risk factor for OUD, especially in cases of chronic pain (Lopez-Martinez et al., 2019). Among veterans, rates of OUD have skyrocketed, nearly tripling between 2003 and 2017 (Wyse et al., 2021). One possible explanation to explain the increase in opioid use and OUD in veteran populations is chronic pain, with nearly 50% of male and 80% of female veterans reporting chronic pain (Jomy and Hapidou, 2019). Similarly, 50% of veterans with chronic pain also have PTSD (Jomy and Hapidou, 2019), highlighting the severe comorbid nature of these diagnoses. Veterans are also at high risk for overdose, with mortality rates jumping over 50% from 2010-2019 (Bennett et al., 2022). However, chronic pain may only be a small portion of why veterans may seek out opioids. The biopsychosocial model, an approach looking at physical pain, mental health, and relationships and environment, may be able to better predict an individual's risk for

overdose based on behaviors (Bennett et al., 2022). Mental health disorders, military sexual trauma, lack of social support, and homelessness can increase the risk of OUD (Bennett et al., 2022).

Relationship between Psychological conditions and cognitive function - Regression

When predicting the relationship between various psychological conditions and cognitive function, we found that SUR predicted category fluency, but not global cognitive functioning or recognition memory. Based on this finding, we performed an exploratory analysis to see if individual substance use risk predicted category fluency; however, it did not significantly predict this measure of cognitive function.

Cognitive decline is a relatively normal hallmark of aging and is often caused by dysfunction in neuronal networks, loss of synapses, and structural changes of the brain (Murman, 2015). However, based on our findings, we can infer that our population may have suffered some cognitive decline due to substance use. While one specific substance did not significantly predict a cognitive deficit, it's important to know how different substances may affect verbal and category fluency. For example, one study found that patients with alcohol dependence had significant dysfunctions in the frontal cerebral cortex that affected verbal fluency (Nowakowska-Domagala et al., 2017). These deficits in verbal fluency persisted even in long periods of abstinence (Nowakowska-Domagala et al., 2017), indicating that risky alcohol use can have negative long-term effects on the brain. Other studies have reported similar deficits in verbal fluency among former and current opioid users (Arias et al., 2016). Future research should continue to look at overall SUR and cognitive deficits.

Neurobiology and Category Fluency

Category fluency is a measure of verbal fluency and is associated with dementia and Alzheimer's disease (Cooper et al., 2004). Semantic, or category fluency, is mainly mediated by the temporal cortex (Baldo et al., 2006), specifically the left temporal regions (Vonk et al., 2019), including the left fusiform and left middle frontal gyrus (Birn et al., 2009).

The left hippocampus and medial frontal cortex also play a role in category fluency (Baldo et al., 2006). The fusiform gyrus is responsible for face and object recognition (Weiner and Zilles, 2015). The left fusiform gyrus recognizes faces and objects through shape configuration (Starrfelt and Gerlach, 2007). One possible explanation for the left fusiform gyrus being associated with category fluency is its proximity to the occipital lobe, as memory involved with category fluency (listing animals) is associated with semantic processing, which partially occurs in the occipital lobe (Biesbroek et al., 2021). The left middle frontal gyrus is associated with literacy, whereas the right middle frontal gyrus which is associated with numeracy (El-Baba and Schury, 2023). This is significant because literacy plays a key role in accessing information (Kolinsky et al., 2014), which in the case of category fluency in our study is names of animals. The left hippocampus mediates episodic verbal memory (Ezzati et al., 2016), which could be why it is implicated in category fluency.

Cortical Thickness and Category Fluency

In normal aging, there is a widespread decrease in gray matter cortical thickness, however, rates of decline vary by brain region (Thambisetty et al., 2010). In patients with dementia or AD, the rate of decline of cortical tissue differs with dementia severity, with less cortical volume present in more severe cases (Im et al., 2008). Cortical thickness is also positively correlated with category fluency (Jones et al., 2019). In memory disorder patients, there was found to be significant correlation between category fluency and left temporal lobe thickness (Jones et al., 2019). This is significant because the findings of our study indicate that SUR predicts category fluency, which may suggest that SUR speeds up aging. Further research into SUR and category fluency is necessary to fully understand how aging is affected.

Clinical Outcomes and Treatment

A decrease in cortical thickness is strongly indicative of cognitive impairment, even in preclinical stages of dementia (Hilal et al., 2015). Because cognitive deficits are commonly seen in late life depression (Weisenbach et al., 2012) and we know that SUR and depression often present together, it is important to prevent or slow cognitive decline. One way to do this is through follow a Mediterranean diet (Kouvari et al., 2022), which includes eating plant foods, olive oil, cheese, fish, poultry, and red meat among others (McManus 2023). Eating a Mediterranean diet has been found to lower the risk of developing mild cognitive impairment (MCI) and dementia (Kouvari et al., 2022 and Solfrizzi et al., 2003). Some vitamin deficiencies such as B_1 , B_2 , B_6 ,B_{12} and vitamin C have been associated with cognitive impairments (Solfrizzi et al., 2003). Cognitive

impairments in some vitamin deficit individuals may improve after supplementation (Solfrizzi et al., 2003).

Exercise can also be beneficial for cognitive functioning in both healthy individuals and those with MCI and dementia (Öhman et al., 2014). In individuals with MCI, especially females, high intensity aerobic exercise was found to favorably impact tasks of executive functioning, like category fluency (Öhman et al., 2014). Exercise has also been shown to increase global cognitive functioning in individuals with dementia or MCI (Vengegas-Sanabria et al., 2022).

These findings are important because they indicate that there are ways to either prevent or result in improvement of cognitive impairments (George and Reddy, 2019). In individuals with SUR, it is important to encourage healthy diet and exercise to help prevent cognitive impairments that may result from their substance use. Further research should examine if diet and exercise can impact or prevent a decline in category fluency in those with SUR and SUD.

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