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A pilot study investigating cognitive impairment associated with opioid overdose

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ABSTRACT

Background: In 2021, while overdose (OD) deaths were at the highest in recorded history, it is estimated that >80% of ODs do not result in a fatality. While several case studies have indicated that opioid-related ODs can result in cognitive impairment, the possible association has not yet been systematically investigated.

Methods: 78 participants with a history of OUD who reported experiencing an OD in the past year (n=35) or denied a lifetime history of OD (n=43) completed this study. Participants completed cognitive assessments including the Test of Premorbid Functioning (TOPF) and the NIH Toolbox Cognition Battery (NIHTB-CB). Comparisons were made between those who experienced an opioid-related OD in the past year versus those who denied a lifetime OD history while controlling for factors including age, premorbid functioning, and number of prior ODs.

Results: When comparing those who experienced an opioid-related OD within the past year to those without a history of OD, uncorrected standard scores were generally comparable; however, differences emerged in the multivariable model. Specifically, compared to those without a history of OD, those who experienced a past year OD evidenced significantly lower total cognition composite scores (coef. = −7.112; *P*=0.004), lower crystalized cognition composite scores (coef. = −4.194; *P*=0.009), and lower fluid cognition composite scores (coef. = −7.879; *P*=0.031).

Conclusions: Findings revealed that opioid-related ODs may be associated with, or contribute to, reduced cognition. Extent of the impairment appears contingent upon individuals' premorbid intellectual functioning and the cumulative number of past ODs. While statistically significant, clinical significance may be limited given that performance differences (~4 – 8 points) were not particularly robust. More rigorous investigation is warranted, and future studies must also account for the many other variables possibly contributing to cognitive impairment.

1. Introduction

In 2021, an estimated 9.2 million people in the United States (U.S.) misused opioids (Substance Abuse and Mental Health Services Administration, 2022). The morbidity and mortality secondary to the opioid epidemic is arguably one of the greatest public health problems that the nation has faced. Suboptimal treatment outcomes remain elevated. For example, across a 24-week trial, individuals with opioid use disorder (OUD) treated with naltrexone and buprenorphine had exceedingly high rates (65% vs. 57%, respectively) of drug use recurrence (formerly referred to as relapse) (Lee et al., 2018). It is therefore important to consider factors that impact engagement and retention in treatment, such as cognitive impairment, which has been well-established as a risk factor for poor treatment outcomes (Aharonovich et al., 2008, 2006, 2003; Dominguez-Salas et al., 2016; McKellar et al., 2006a,b; Sofuoglu, 2010; Sofuoglu et al., 2010). Among patients receiving methadone for the treatment of OUD, cognitive impairment likewise predicted worse treatment outcomes (Acosta et al., 2012). In addition, a recent

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meta-analysis also revealed that impairments in higher order executive functions were associated with drug use recurrence in individuals with OUD (Rolland et al., 2019).

In a review of the literature which included several populations (individuals who use opioids recreationally, those with OUD, those who use opioids as prescribed for pain, and healthy controls), acute and chronic opioid use was reported to be associated with impairments across several cognitive domains including attention, concentration, memory, visuospatial skills, and psychomotor speed (Gruber et al., 2007). Long-term cognitive effects of opioid use appear to have the greatest impact on executive functions, including the ability to shift cognitive set and inhibit responses (Gruber et al., 2007). Consistent with this, in 177 patients with OUD receiving methadone treatment who were assessed using the National Institutes of Health Toolbox Cognition Battery (NIHTB-CB), impairments were noted in executive functioning and attention (Sanborn et al., 2020). Individuals with OUD have an increased risk of infectious diseases such as HIV and hepatitis C (Meade et al., 2014, 2009; Roux et al., 2013), both of which are independently associated with increased cognitive impairment secondary to disease progression. While cognitive sequelae related to OUD is well-established, it is critical to consider additional factors such as opioid-related overdose (OD) which may exacerbate, or independently contribute to, cognitive impairment in individuals with OUD (Winstanley et al., 2021).

In 2021, drug-related OD deaths were at the highest in recorded history and of the documented 106,854 OD deaths, opioids accounted for, or contributed to, the majority of these fatalities (75.1%; 80,242 total deaths) (Ahmad et al., 2021). While the rates of fatal opioid-related OD remain elevated, there is a markedly higher incidence of non-fatal OD as only 4–18% of ODs treated in the pre-hospital or hospital setting result in a fatality (Chang et al., 2020; Dunn et al., 2010; Lasher et al., 2019; Lowder et al., 2020). Consistent with this, 46–92% of people who misuse opioids or have OUD have either experienced a non-fatal OD or witnessed an OD during their lifetime (Bennett et al., 2011; Doe-Simkins et al., 2009; Winstanley et al., 2020). Fortunately, given that naloxone is widely available to first responders and community members, more people are surviving OD events (Walley et al., 2013), which also highlights the need to consider the additive cognitive and neurological impact of multiple ODs, especially since repeated ODs increase the risk for eventual OD fatality (Krawczyk et al., 2020). While treatments including medications for opioid use disorder (MOUD) are effective at reducing the risk of OD death (Larochelle et al., 2018), cognitive impairment, as mentioned previously, has been well-established as a risk factor for poor treatment outcomes. Therefore, cognitive impairment secondary to OUD and/or multiple ODs may further impede treatment retention and lead to detrimental outcomes, including death.

Despite this high incidence of non-fatal ODs, the associated morbidity has not been adequately characterized by empirical research, though several case studies in humans have indicated that opioid OD can result in neuroanatomical abnormalities which in turn are associated with specific cognitive impairments. Results from a review of seventy-nine journal articles which involved opioid OD supported the association between opioid OD and brain abnormalities and/or cognitive impairments; however, few of the available studies controlled for confounding factors and methodological differences complicated direct comparisons across studies (Winstanley et al., 2021). Despite these limitations, findings have supported that opioid-related OD, if untreated, can lead to cerebral hypoxia which is the suspected mechanism of OD-related cognitive impairment (Zibbell et al., 2019). Case studies have suggested that opioid-related OD can produce acute and delayed onset of toxic leukoencephalopathy (Arciniegas et al., 2004; Beeskow et al., 2018; Carroll et al., 2012; Cheng et al., 2019; Ginsberg et al., 1976; Huisa et al., 2013; Long et al., 2013; Molloy et al., 2006), as well as damage to brain areas sensitive to hypoxic ischemia, such as the hippocampus and cerebellum (Andersen and Skullerud, 1999; Barash and Kofke, 2018; Milroy and Parai, 2011; Morales Odia et al., 2010; Salgado et al., 2010). Reduced oligodendria and myelin, with white matter damage and vacuolation have also been described following an opioid OD (Barnett et al., 2001; Huisa et al., 2013; Milroy and Parai, 2011; Salgado et al., 2010).

In addition to structural and histopathological changes in the brain, cognitive impairments have been reported following opioid OD; case studies have revealed that ODs involving methadone or heroin have resulted in a constellation of cognitive impairments that persisted for several months (Barnett et al., 2001; Huisa et al., 2013; Salgado et al., 2010). Specifically, cognitive impairments following OD include inattention (Bileviciute-Ljungar et al., 2014), confusion, forgetfulness, amnesia (Barash and Kofke, 2018; Duru et al., 2018; Haut et al., 2017), impairments in working and long-term memory (Bileviciute-Ljungar et al., 2014; Butler et al., 2019; Molloy et al., 2006), and verbal fluency (Molloy et al., 2006) along with poor emotional control (McDonald et al., 2013).

Together, existing data suggest: 1) an independent relationship between OUD and cognitive impairment 2) an increased prevalence of non-fatal opioid ODs in recent years, and 3) neuroanatomical abnormalities and cognitive sequelae following OD. As such, empirical work examining whether opioid OD exacerbates underlying cognitive impairment is warranted, especially considering the well-established relationship between cognitive impairment and poor treatment outcomes. The aim of the current case-control pilot study is to determine whether individuals with OUD who have experienced an opioid-related OD in the past year evidence greater cognitive impairment than those with OUD and no history of OD. Gaining a better understanding of OD-related cognitive impairment, especially in the context of cerebral hypoxia, is critical given the known relationship between cognitive impairment and treatment prognosis and may aid in the development of adapted treatment approaches.

2. Methods

2.1. Participants

Between September 2019 and October 2020, 88 total participants (n=65 from sites in Morgantown, WV and n=23 from sites in New York City, NY) provided written informed consent to participate. Participants were recruited from two locations: 1) a university-based hospital system in West Virginia including a 28-day residential treatment program, an acute inpatient detoxification unit, and outpatient addiction treatment programs and 2) an opioid research laboratory at the New York State Psychiatric Institute (NYSPI). Participants recruited from the WVU site were pre-screened for eligibility through a preliminary search of electronic medical records to confirm a diagnosis of OUD. After participants were provided with a definition of an opioid-related OD (see Supplementary Information for terminology used to define OD) they were asked: “In your lifetime, have you ever experienced an overdose after using heroin, prescription pain medication, or fentanyl?” Individuals who responded ‘yes’, were queried if their most recent OD occurred within the past year; those who reported an OD that occurred in the past year were eligible for the case group. Those individuals who responded ‘no’ to having a history of lifetime OD were then eligible for the control group. Participants from NYSPI/Columbia University were recruited from other ongoing research studies and pre-screened for eligibility through a brief telephone interview conducted by a research assistant. Eligible participants were scheduled for an in-person visit which included a clinical interview with a research psychologist that assessed current drug use and history of opioid OD.

Data from 78 out of the 88 participants were included in the analyses. Participants in the Case group (total n=35; WVU: n=31, NYSPI/CU: n=4) self-reported an opioid-related OD within the past 12-months and participants in the Control group (total n=43; WVU: n=34, NYSPI/CU: n=9) reported no lifetime history of opioid OD. Data from 10

NYSPI/CU subjects were not used: seven subjects had experienced an opioid-related OD, but not in the past year; 1 subject was falling asleep during the cognitive tasks, and information related to OD history were inadvertently not assessed for 2 subjects. A single WVU participant was missing a score for the Oral Reading Recognition Test, and therefore also had no Total Composite or Crystalized Composite scores. All participants were at least 18 years old and had a documented diagnosis of OUD. Individuals who were pregnant, met the definition of incarceration, had a history of moderate or severe traumatic brain injury, and/or had a history of a neurocognitive disorder that was not associated with OD, were determined to be ineligible and excluded from study participation. In accordance with standardized procedures at both sites, if a potential participant was unable to comprehend the procedures outlined in the consent form (e.g., unable to describe the purpose and procedures in their own words), they would not proceed with signing the consent form. Participants from WVU received a $20 gift card and participants from NYSPI/Columbia University received $25 in monetary compensation for study participation. The Institutional Review Boards of West Virginia University and NYSPI approved this study. This study was conducted in accordance with all relevant guidelines, including the 1964 Declaration of Helsinki.

2.2. Measures and assessments

2.2.1. Demographic and clinical characteristics

All participants underwent a structured clinical interview to obtain demographic information, opioid and other substance use history, and select medical history. Participants completed a semi-structured clinical interview with a research psychologist or research assistant that detailed current use of opioids and other substances, use of medications for OUD, history of opioid-related OD, a brief assessment of medical and psychiatric history, and collected demographic data. Questions pertaining to substance use focused on frequency and quantity of use, route of administration, and duration of use. Participants endorsing a history of OD were asked to provide details on the substance(s) taken prior to OD, total number of prior OD(s), estimated date(s) of OD(s), and whether naloxone was administered during the most recent OD event.

2.2.2. Test of premorbid functioning (TOPF)

The TOPF (Wechsler, 2011) provides an estimate of premorbid verbal intellect and requires examinees to pronounce a list of phonemically irregular words. A hardcopy of the instrument was provided to the participant by the research assistant who then documented whether they pronounced the word correctly. The raw number of words correct was then transformed into an age-corrected standard score.

2.2.3. NIH toolbox cognition battery (NIHTB-CB)

The NIHTB-CB (Gershon et al., 2013) consists of assessments designed to yield different measures of cognitive performance. These seven assessments take ~60 minutes to complete and measure constructs including language, executive functioning, attention, episodic memory, working memory, and processing speed and generate fluid, crystalized, and total cognition composite scores. The NIHTB-CB is administered on an iPad, available through the NIH Toolbox app; it is largely self-administered by the participant with the use of written and audio instructions and staff who provides guidance and scoring. The NIHTB-CB includes the following tasks which generate a Crystalized Cognition Composite score: 1*) Picture Vocabulary Test* which measures vocabulary, word association, and picture recognition; 2) *Oral Reading Recognition Test* which measures reading and pronunciation abilities. The NIHTB-CB also includes the following tasks which generate a Fluid Cognition Composite Score: *3) Flanker Inhibitory Control and Attention Test* which measures the ability to complete a task in an overstimulating environment; 4) *List Sorting Working Memory Test* which measures how the limits of how much memory can be stored; *5) Dimensional Change Card Sort Test* which measures the abilities involved in working towards a goal*;* 6) *Pattern Comparison Processing Speed Test* which measures the speed and quantity of information that can be cognitively processed; and *7) Picture Sequence Memory Test* which measures how information is obtained, stored, and received.

The NIHTB-CB was normed in a diverse population to match the U.S. demographics (Beaumont et al., 2013) and the iPad app automatically generates uncorrected standard, age-corrected standard, and fully corrected scaled scores, allowing for comparison to true "normals" (average scores from a nationally representative sample); hence eliminating the need for a non-drug using control group. Previous validation and standardization procedures have demonstrated that the NIHTB-CB shows good discriminant and convergent validity (ranging from r=0.05 to r=0.30 and r =0.48 to r =0.93, respectively) when tested against those measures considered to be the "gold standards" in cognitive assessment (Weintraub et al., 2013). The NIHTB-CB demonstrates high test-retest reliability in adults (r=0.72 to r=0.96) and is available in English and Spanish. The NIHTB-CB is becoming more frequently utilized to measure cognitive functioning in individuals with substance use disorders (Frazer et al., 2018; Meredith et al., 2020; Sanborn et al., 2020).

2.3. Data analytic strategy

The primary outcome was the NIHTB-CB Total Cognition Composite Score and secondary outcomes included the NIHTB-CB Fluid and Crystallized Cognition Composite Scores and all seven subtest scores. The NIHTB-CB data was exported from each individual tablet used to collect the data and then merged. The raw TOPF scores were converted to standardized scores based on normative data provided by the test developer. The normative Mean and Standard Deviation (SD) for the uncorrected standard scores are 100 and 15, respectively. Sociodemographic and clinical measures were summarized by case/control group, along with standardized absolute mean differences between groups. Only those demographic/drug use characteristics and historical information that were harmonized across sites were included in the analyses. Differences between groups were tested using t-tests for continuous variables and Fisher's exact tests (Clarkson et al., 1993) for categorical variables. Comparisons between sites were also performed using these same analyses and can be found in the supplementary information.

Multiple linear regression was used to test the association between uncorrected NIHTB-CB standard scores and OD in the past year. The rationale for using the uncorrected standard scores was to more accurately account for age given the wide age bands (18−30, 30−39, 40−49) used in the algorithm to calculate the NIHTB-CB fully corrected and age-corrected scaled scores. An additional reason for utilizing uncorrected rather than corrected standard scores was that previous studies have found that the NIHTB-CB fully corrected scaled scores indicate less impairment than would be expected in samples of individuals with SUDs (Frazer et al., 2018; Meredith et al., 2020). NIHTB-CB standard scores were regressed on number of past ODs and adjusted for age (as a continuous variable) and TOPF score. Days of stimulant use in the past 30 days was included in an initial model with outcome NIHTB-CB standard scores. This model term was discarded as, unlike other covariates, the coefficient was non-significant and there was no discernable impact on the coefficient for past OD. Standardized TOPF scores were included given the known relationship between premorbid intellectual functioning and cognition in healthy controls and individuals with SUD (Diaz-Asper et al., 2004; Mahoney et al., 2017). In addition to age (Mean ±SD: 36.08±8.32; range: 23–62) and TOPF (Mean±SD: 92.88±14.11; range: 66–131) being included as covariates, total number of past ODs was also included as a covariate given the wide range of prior ODs in the sample (Mean±SD: 4.03±2.92; range: 1–11 past ODs) in order to account for the potential additive impact of multiple ODs. The coefficients for the terms for total number of past ODs were significant in models where it was used as a covariate, but the coefficients for number of ODs in models without terms for past OD were not significantly different from 0 ($P \geq 0.30$).

To aid in the interpretation of the NIHTB-CB data, the NIHTB-CB total, crystallized, and fluid cognition composite and subtest scores were also presented as dichotomous variables where 'impaired' was defined as >1 standard deviation (SD) below the normative mean and 'within normal limits' was defined as within one SD below the normative mean or higher. This cut-off was utilized based on information provided in the NIHTB-CB Scoring and Interpretation Guide which states that scores <16th percentile suggest "below-average cognitive abilities" or "health-related, acquired cognitive impairment". Chi-square tests were used to identify statistically significant differences in impaired performance.

The number of total lifetime ODs was highly skewed, with over half of participants reporting none. To assess the robustness of the model results, a sensitivity analysis was run with new models fitted with a 3-level categorical variable for lifetime history of OD: no lifetime history of OD (n = 43), 1–3 overdoses during lifetime (n = 18), and 4+ overdoses (n = 17) during lifetime. The two levels with some history of OD were chosen to have near-equal sample sizes. The "no history of OD" category of this variable overlapped completely with the "no ODs in the past year" category of the corresponding binary variable, and the other two categories overlapped perfectly with the "OD in past year" category of the binary variable. Unlike the continuous total number of past ODs, this 3-level categorical variable allowed for nonlinear relationships with the outcome scores. For all significance testing, alpha was set at 0.05. Statistical analyses were performed using SPSS 26.0 and R 4.1.0.

3. Results

3.1. Baseline socio-demographics and substance use

Demographic, clinical, and drug use characteristics for the entire sample and subgroups (past year OD versus no history of OD) can be found in Table 1. There were no differences on any of the measured demographic or drug use variables between those with an opioid-related OD within the past year and those with no history of OD. When comparing the NY (n=13) and WV (n=65) sites, differences were noted on demographic characteristics as participants in NY were significantly older (48.31±9.73 vs. 33.63±5.39; P=0.0001) and more likely to be Black or African American (69.2% vs. 4.6%; P<0.0001) and Hispanic (30.8% vs. 7.7%; P=0.0376). There were also site differences in stimulant use in the past 30 days as participants recruited in WV were more likely to report methamphetamine use (51% vs. 0%; P<0.0001) **(**Supplementary Table 1**).**

3.2. Cognitive differences between those with an opioid-related OD in the past year and those with no OD history

When comparing those who experienced an opioid-related OD within the past year to those without a history of OD, uncorrected NIHTB-CB standard scores were generally comparable (Table 2); however, differences emerged in the multivariable model when age, TOPF, and total number of ODs were included as covariates (detailed regression statistics for NIHTB-CB standard scores and covariates can be found in Supplementary Table 2). Specifically, in comparison to those without a history of OD, those who experienced an OD in the prior year evidenced significantly lower total cognition composite scores (coef. (SE) = −7.11 (2.38); P=0.004), lower crystalized cognition composite scores (coef. (SE) = −4.19 (1.55); P=0.008), and lower fluid composite scores (coef. (SE) = −7.88 (3.58); P=0.031). NIHTB-CB subtest models found that participants who experienced an OD in the past year evidenced significantly lower scores on tasks of picture vocabulary (coef. (SE) = −4.71 (2.04); P=0.024) and list sorting (coef. (SE) = −7.73 (3.79); P=0.045) with trends towards significance on tasks of picture sequencing (coef. (SE) = −7.49 (3.79); P=0.052) and oral reading (coef. (SE) = −3.25 (1.65); P=0.052) compared to those with no OD history.

For the entire sample and separated by case and control groups, percentages of individuals who had composite and subtest scores which were "impaired" (defined as >1 SD below the mean or <16th percentile)

Table 1
Demographic and characteristics of the sample (N=78).

	Overall (N=78)		No OD (N=43)		OD (N=35)		SMD[a]	*t*-statistic (df)	*P*[b]
	n	% or Mean (SD)	n	% or Mean (SD)	n	% or Mean (SD)			
Site									0.363
NYSPI/CU	13	16.7%	9	20.9%	4	11.4%	0.684		
WVU	65	83.3%	34	79.1%	31	88.6%	0.684		
Age	78	36.08 (8.32)	43	37.44 (8.09)	35	34.40 (8.41)	0.366	$t(71.6) = 1.616$	0.110
Gender									>0.999
Male	72	92.3%	40	93%	32	91.4%	0.225		
Female	6	7.7%	3	7.0%	3	8.6%	0.225		
Education	78	12.08 (2.02)	43	12.30 (1.96)	35	11.80 (2.08)	0.249	$t(70.8) = 1.088$	0.280
TOPF	76[c]	92.88 (14.11)	41	91.76 (14.85)	35	94.20 (13.28)	0.173	$t(73.8) = -0.757$	0.451
Race									0.588
White	60	76.9%	33	76.7%	27	77.1%	0.022		
Black or AfricanAmerican	12	15.4%	8	18.6%	4	11.4%	0.551		
American Indian or Alaska Native	2	2.6%	1	2.3%	1	2.9%	0.213		
Other	4	5.1%	1	2.3%	3	8.6%	1.284		
Ethnicity									>0.999
Not Hispanic or Latino	69	88.5%	38	88.4%	31	88.6%	0.020		
Hispanic or Latino	9	11.5%	5	11.6%	4	11.4%	0.020		
Opioid Use									
Days used in last 30[d]	64[c]	1.28 (3.58)	33	0.67 (1.87)	31	1.94 (4.73)	0.354	$t(38.6) = -1.394$	0.171
Age of First Opioid Use	64[c]	18.53 (5.59)	33	18.88 (6.52)	31	18.16 (4.48)	0.128	$t(56.9) = 0.516$	0.608
Total Number of OD's	35	4.03 (2.92)	0	0.0 (0.0)	35	4.03 (2.92)			
Stimulant Use									
Methamphetamine (last 30 days)	33[e]	6.94 (5.80)	17	7.47 (6.60)	16	6.38 (4.98)	0.189	$t(75.9) = 0.034$	0.593
Cocaine (last 30 days)	15[e]	4.13 (7.38)	8	2.88 (2.10)	7	5.57 (10.83)	0.366	$t(38.3) = -0.654$	0.539

[a] Standardized absolute mean difference (SMD) is calculated as the average absolute difference between groups divided by the overall standard deviation
[b] *P*-values for two-tailed t-tests of continuous variables and Fisher's exact tests of categorical variables
[c] TOPF was not completed with 2 participants; opioid use in the last 30 days and age of first opioid use was not obtained from 14 participants
[d] Lower recent opioid use reflects current enrollment in inpatient/residential treatment and/or MOUD treatment
[e] Only participants who reported using methamphetamine and/or cocaine in the last 30 days were included, n reflects numbers responding in the affirmative

Table 2
NIHTB-CB performance of the sample (N=78).

NIHTB-CB Uncorrected Standard Scores	Overall (N=78)		No OD (N=43)		OD (N=35)			
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	Coef. (SE)[a]	*P*[b]
Total Cognition Composite	77[c]	100.00 (10.36)	42	100.07 (10.23)	35	99.91 (10.66)	-7.11 (2.38)	0.004
Crystalized Cognition Composite	77[c]	99.79 (8.55)	42	100.21 (9.68)	35	99.29 (7.06)	-4.19 (1.55)	0.008
Picture Vocabulary	78	98.90 (8.85)	43	99.74 (9.77)	35	97.86 (7.59)	-4.71 (2.04)	0.024
Oral Reading	77	101.70 (8.44)	42	101.67 (8.99)	35	101.74 (7.87)	-3.25 (1.65)	0.052
Fluid Cognition Composite	78	101.15 (13.11)	43	100.95 (12.74)	35	101.40 (13.72)	-7.88 (3.58)	0.031
Flanker	78	102.79 (8.77)	43	102.14 (8.98)	35	103.60 (8.57)	-1.25 (2.77)	0.653
List Sorting	78	99.05 (12.35)	43	99.16 (10.46)	35	98.91 (14.49)	-7.73 (3.79)	0.045
Dimensional Change Card Sort	78	104.08 (16.68)	43	104.12 (17.04)	35	104.03 (16.47)	-3.18 (5.29)	0.550
Pattern Comparison	78	106.97 (18.85)	43	106.98 (18.33)	35	106.97 (19.74)	-8.24 (5.65)	0.149
Picture Sequence Memory	78	95.95 (12.08)	43	95.70 (11.50)	35	96.26 (12.93)	-7.49 (3.79)	0.052

Normative Mean (Standard Deviation (SD)) for the uncorrected standard scores = 100 (15).
[a] Coefficient Value (Standard Error).
[b] *P*-values are from t-tests of terms in multivariable models representing differences in uncorrected standard scores between case and control groups with age, TOPF, and total number of ODs set as covariates.
[c] The oral reading subtest crashed during administration on one occasion, therefore total and crystalized cognition composite scores could not be calculated for one participant.

or were "within normal limits" can be found in Table 3. Across the entire sample, 55.1% (n=43) scored within normal limits across all of the subtests, while 29.5% (n=23) evidenced 1 impaired subtest score, 10.3% (n=8) evidenced 2 impaired subtest scores, 2.6% (n=2) evidenced 3 impaired subtest scores and 2.6% (n=2) evidenced >3 impaired subtest scores. When comparing those who experienced an OD in the past year to those without a history of OD, there were no differences in the rates of impairment on any of the composite scores nor any of the subtest scores (Table 3). The sensitivity analysis showed that participants reporting 1–3 ODs during their lifetime had significantly lower total scores (coef. (SE) = −5.24 (2.05), *P*=0.013), crystalized composite scores (coef. (SE) = −2.88 (1.34), *P*=0.035), and picture vocabulary scores (coef. (SE) = −3.69 (1.75), *P*=0.038) compared to controls (no lifetime history of OD). Participants reporting 1–3 ODs during their lifetime had statistically higher total scores (estimate (SE) = −5.23 (2.46), *P*=0.037), list sorting scores (estimate (SE) = −7.95 (3.90), *P*=0.045), and picture sequence scores (estimate (SE) = −7.87 (3.91); *P*=0.048) compared to participants reporting 4+ ODs. There were no statistically significant differences between participants reporting 4+ ODs compared to controls (*P*≥0.36).

Table 3
Prevalence of Impaired[a] NIHTB-CB performances.

Cumulative # of Impaired Scores Across 7 Subtests	**Overall (N=78)**	**No OD (N=43)**	**OD (N=35)**	***P*[b]**
	N (%)	**N (%)**	**N (%)**	
No Impaired Scores	43 (55.1%)	26 (60.5%)	17 (48.6%)	0.362
At Least 1 Impaired Score	35 (44.9%)	17 (39.5%)	18 (51.4%)	0.362
1 Impaired Score	23 (29.5%)	7 (16.3%)	16 (45.7%)	0.006
2 Impaired Scores	8 (10.3%)	8 (18.6%)	0	0.007
3 Impaired Scores	2 (2.6%)	2 (4.7%)	0	0.499
>3 Impaired Scores	2 (2.6%)	0	2 (5.7%)	0.198
Impaired NIHTB-CB Performances	**Overall (N=78)**	**No OD (N=43)**	**OD (N=35)**	**P[b]**
	N (%) Impaired	**N (%) Impaired**	**N (%) Impaired**	
Total Cognition Composite	7 (9.1%)	5 (11.9%)	2 (5.7%)	0.450
Crystalized Cognition Composite	2 (2.6%)	2 (4.8%)	0	0.499
Picture Vocabulary	4 (5.1%)	2 (4.7%)	2 (5.7%)	0.999
Oral Reading	0	0	0	0.999
Fluid Cognition Composite	10 (12.8%)	7 (16.3%)	3 (8.6%)	0.498
Flanker	2 (2.6%)	2 (4.7%)	0	0.499
List Sorting	8 (10.3%)	4 (9.3%)	4 (11.4%)	0.999
Dimensional Change Card Sort	9 (11.5%)	5 (11.6%)	4 (11.4%)	0.999
Pattern Comparison	14 (17.9%)	8 (18.6%)	6 (17.1%)	0.999
Picture Sequence Memory	16 (20.5%)	8 (18.6%)	8 (22.9%)	0.780

[a] Impaired is defined as >1 Standard Deviation below the normative mean (Uncorrected Standard Scores < 85).
[b] *P*-values for Fisher's exact tests of categorical variables.

4. Discussion

The findings from the current study revealed differences in cognitive functioning, assessed via the NIHTB-CB, when comparing individuals with OUD who experienced an opioid OD in the prior year to those without any history of an opioid OD. The sensitivity analysis supported these findings; however, it is unclear whether the effects of multiple ODs are cumulative across the life span. Also, when controlling for age, premorbid intellectual functioning, and total number of past ODs, while the differences between groups were statistically significant, the clinical significance of these findings is not entirely clear. For example, the total cognition composite scores were significantly lower in those who experienced an OD in the prior year; however, the estimate (coef. = −7.11) which indicates an approximate 7-point reduction in the standard score (equating to approximately 18 percentile points) may not be clinically meaningful. Given that the mean composite score of our sample was ~100 (or the 50th percentile) a 7-point reduction would mean that the individual would fall at the 32nd percentile, a score which is still well within normal limits. While there is variability across classification systems and how clinicians define cognitive performance falling within normal limits versus impairment, a recent consensus statement published by the American Academy of Clinical Neuropsychology concluded that scores <24th percentile should be considered below expectations (Guilmette, 2020). Specifically, performance within the 9th to 24th percentile is considered low average, 2nd to 8th percentile considered below average, and <2nd percentile considered exceptionally low. As such, the clinical significance of our findings is not entirely clear given that, while there was a reduction, the overall findings do not suggest a significant level of impairment.

In comparison to prior studies which included the NIHTB-CB data in SUD populations, our results were relatively comparable (falling within one SD) to the findings in individuals with alcohol use disorder (Meredith et al., 2020) and OUD (Sanborn et al., 2020) with the exception of flanker task performance in the latter study (participants in the current study evidenced improved performance (>1 SD) in comparison to Sanborn et al., 2020). The prevalence of cognitive impairment, generally, noted in the current sample based on composite and subtest scores was lower than what has been reported in the previous literature. For example, when examining fully corrected scaled scores in the current sample, ~20% of the sample evidenced impairment (defined as <1 SD below the normative mean) on the total cognition composite score and

only ~22% of the sample scored in the impaired range on more than 2 of the 7 subtests. For comparison, one study reported that ~60% of their OUD sample showed impairments (≥2 SDs from the published norms) on ≥2 neuropsychological tests (Davis et al., 2002). Regardless, differences between groups in our sample were observed; those with a history of OD in the past year were less likely to have a fully intact profile in comparison to those with no OD history (~23% versus ~47%, respectively, had profiles which were entirely within normal limits).

Despite these informative findings, some important limitations warrant discussion. First, opioid ODs were self-reported and thus the circumstances and/or details surrounding these events may be subject to recall bias. Individuals who have experienced an OD may not be able to accurately report details of the event, particularly regarding how long they had inadequate respiration or how quickly life-saving interventions (such as naloxone) were initiated. The suspected mechanism by which opioid-related ODs may cause cognitive impairment is prolonged inadequate respiration which causes cerebral hypoxia. In order to address this limitation in future studies, objective clinical data on the OD event is needed to establish or more accurately estimate the period of time without adequate respiration and the severity of the event. For example, clinical records from a prehospital setting and/or emergency department may have information on the duration of loss of consciousness, Glasgow Coma Scale scores, timing of naloxone administration, or neuroimaging results that would help to determine the extent of hypoxia or structural brain changes that would be critical in determining the severity of the event.

A common limitation with most studies investigating cognitive sequelae related to a diagnosis, event, or injury is the absence of a baseline assessment of cognitive functioning. In the absence of such data, it can be difficult to determine whether reductions in cognitive functioning are attributable to the event of interest. While premorbid functioning (assessed via the TOPF in the current study) provides an estimate of premorbid functioning, it will be useful for future investigations to utilize a longitudinal approach, acquiring data related to cognitive functioning prior to and following an OD. For example, in the current sample, there were 43 individuals who had not experienced an OD at the time of participation and completion of the NIHTB-CB. Following up with these individuals to assess whether they experienced an OD in the time since their initial enrollment would provide an opportunity to re-evaluate their cognitive functioning so that a one-to-one, within-subject, pre-post OD comparison can be made.

A third limitation is the number of potential confounding variables which were not accounted for in the current pilot study, however, a more complex model, accounting for multiple covariates (in addition to those already included: age, premorbid functioning, number of prior ODs), would require a much larger sample. Additional confounding variables include comorbid medical diagnoses (e.g. vascular diagnoses such as hypertension, hyperlipidemia, and diabetes) as these are known to independently contribute to cognitive impairment (Dichgans and Leys, 2017); potential history of hypoxia/anoxia secondary to sleep apnea or toxin exposure; prescribed medication, such as those with higher anticholinergic burden which are also known to contribute to cognitive compromise (Fox et al., 2014); and co-occurring substance use which may also contribute to and/or exacerbate cognitive impairment. In addition, future studies should investigate the temporal relationship between the occurrence of OD and cognitive functioning in order to better characterize the acute impact of OD versus the residual sequelae and possible cognitive recovery following an OD event. Further investigations utilizing the NIHTB-CB in SUD populations are needed to determine whether this battery provides a valid assessment and accurate detection of the presence of cognitive impairment. Future studies should be developed where individuals with SUD are administered both the NIHTB-CB along with a battery of standardized, well-validated, and accepted cognitive measures assessing the same domains, so that conclusive decisions about the validity and subsequent utility of the NIHTB-CB in SUD populations can be made. In addition, while not sufficiently powered to investigate geographical differences (e.g., rural versus urban settings) in relation to cognitive impairment secondary to OD in the current study, future studies may want to consider geographic differences when calculating sample size in order to ensure that such comparisons can be made. This will also provide the opportunity to determine how other factors, such as differences in drug use characteristics, may be associated with cognitive functioning in relation to OD. For example, in the current study, over half of the participants enrolled at the WV site reported methamphetamine use whereas no participants at the NY site reported methamphetamine use. In addition, as is the case with all multi-site trials, using a standardized definition/description of key terminology will be important for standardization and data harmonization (in the current study, each site utilized their respective definition/description of opioid-related overdose; exact definitions for each site can be found in the supplementary information). Finally, longitudinal studies are needed to determine the relationship between NIHTB-CB performances over time in relation to treatment adherence and attrition.

We found in the current pilot study that opioid-related ODs may be associated with or contribute to reduced cognition, and the extent of the impairment appears to be contingent upon individuals' premorbid intellectual functioning and the cumulative number of past ODs. While these pilot findings may not be robust, given the prevalence of non-fatal ODs and that individuals frequently experience multiple ODs, these findings warrant more rigorous investigation. Future studies must account for many other possible variables besides history of OD which may also be contributing to cognitive impairment given the instability of the findings detected during the sensitivity analysis in the current analyses. By accounting for these additional variables, along with addressing the limitations noted above, more substantive conclusions regarding the impact of OD on cognition can be made.

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CRediT authorship contribution statement

JJM, ELW, and SDC conceptualized the study. JJM, ELW, SDC, and FC developed study methodology. RL oversaw data collection at CU/NYSPI. JLM oversaw data collection at WVU and maintained cumulative database across sites. DMA and YL verified the data and conducted statistical analyses. All co-authors had full access to the study data, edited and agreed upon the final manuscript, and shared the final responsibility for the decision to submit for publication.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose/declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the

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