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A randomised, double-blind study investigating the relationship between early childhood trauma and the rewarding effects of morphine

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Abstract

Experiences of childhood trauma (abuse and neglect) are disproportionately higher in those with opioid use disorder (OUD). Childhood trauma may affect the reinforcing and rewarding properties of opioid drugs and responses to pain, potentially via developmental changes to the endogenous opioid system. This has been supported by preclinical research, yet this has not been investigated in non-addicted humans. Physically healthy participants with either a history of severe childhood trauma or no previous history of childhood trauma attended two sessions where they received either an intramuscular active dose of morphine (0.15 mg/kg) or a very low dose control (0.01 mg/kg) in a randomised, double-blind crossover design. Sessions were held 1 week apart. Participants' physical pain threshold and tolerance were measured pre- and post-drug administration using the cold water pressor test, alongside acute subjective and behavioural responses over 2.5 h. The trauma group reported liking the effects of morphine, feeling more euphoric and wanting more of the drug over the session, as well as feeling less nauseous, dizzy, and dislike of the effects of morphine compared to the non-trauma comparison group. Morphine increased pain threshold and tolerance, yet this did not differ between the groups. Childhood trauma may therefore sensitise individuals to the pleasurable and motivational effects of opioids and reduce sensitivity to the negative effects, providing compelling evidence for individual differences in opioid reward sensitivity. This may explain the link between childhood trauma and vulnerability to OUD, with consequent implications on interventions for OUD, the prescribing of opioids, and reducing stigmas surrounding OUD.

KEYWORDS
childhood adversity, childhood trauma, morphine, opioids, pain, reward

1 | INTRODUCTION

Exposure to childhood adversity and early life trauma such as abuse and neglect is strongly associated with the development of opioid addiction.[1,2] Rates of childhood abuse and neglect are disproportionately higher in those with opioid use disorder (OUD) compared with non-addicted individuals,[3] and greater severity of childhood adversity is linked to earlier onset of opioid use,[4] poly-drug use[5] and poorer treatment retention.[6] The link between childhood trauma and later substance use disorders is mediated by poor emotion regulation,[7–9] where individuals may use substances to reduce symptoms of hyperarousal[10] and to cope with internalised problems.[11] Childhood trauma may also sensitise individuals to the rewarding effects of opioids, however the biological mechanisms that underpin this vulnerability are not fully understood. Developmental changes to the endogenous opioid system, the primary target of opioid drugs, following trauma could underlie differences in reward sensitivity and responses to opioid drugs.

The endogenous opioid system is involved in pain processing and pleasure, particularly the μ-opioid receptor.[12] Subjective pleasure (or 'liking') is one component of reward, which is both behaviourally and neurally dissociable from motivational 'wanting'.[13] Activation of this neurobiological system via opioid agonists is associated with increased subjective pleasure in both animals[14] and humans,[15] as well as increasing the motivational qualities or incentive salience[15] which is also associated with downstream effects on increasing dopamine.[16] This incentive-sensitisation model of addiction stipulates increased 'wanting' occurs following repeated substance use via an amplified sensitivity to reward-related associations that easily trigger the neural signatures responsible for craving.[16] However, initial subjective pleasure induced by substances such as opioids are predictive of future use and dependency.[17] Childhood trauma may disrupt sensitivity to pain and pleasure via changes in endogenous opioid functioning. Maternal separation (a model of early trauma in animals) can heighten pain sensitivity in rats,[18] attenuate the analgesic effects of morphine (a μ-opioid receptor agonist), and intensify opioid-induced withdrawal, due to permanent changes to the endogenous opioid system.[19] Maternally separated rats also show increased morphine self-administration in adulthood, increased place-preference for morphine-paired areas, and slower extinction of conditioned place preference.[20,21] Self-administration is greater for morphine than other rewards (such as sucrose and amphetamines), thus suggesting a specific susceptibility to opioid addiction. Basal opioid activity is reduced as a consequence of maternal separation and is suggested to underpin the heightened rewarding effects of opioids.[20]

In human studies, childhood trauma is associated with a hypersensitivity to acute physical pain in adulthood, as demonstrated by lower pain threshold and tolerance, and increased secondary allodynia and temporal summation of second pain, via pressure, thermal, ischaemic, and capsicum-induced pain stimulations.[22–26] However, it is not known if pain processing differs following opioid administration in people with histories of childhood trauma. It is also not known if childhood trauma alters endogenous opioid functioning in humans. Existing evidence using positron-emission tomography has demonstrated a link between avoidant attachment styles—often associated with interpersonal trauma[27]—and reduced μ-opioid receptor availability.[28] Reduced opioid receptor availability has been linked to a heightened sensitivity to rewards in humans.[29]

If endogenous opioid functioning is altered as a consequence of childhood trauma, this may affect the pleasurable and adverse effects of opioid drugs. In-vivo microdialysis studies have linked receptor tone with drug reinforcement, where greater endogenous dopamine activity is associated with more adverse effects of cocaine—a dopamine reuptake inhibitor.[30] Greater activity in the medial pre-frontal cortex was found when responding to aversive images in people with a history of childhood adversity after receiving naltrexone,[31] although this study was confined to those with histories of drug and/or alcohol abuse. The authors suggest this may reflect greater effort to exert emotion regulation. To our knowledge, the link between childhood adversity and responses to opioid agonists has not been investigated in humans, despite the strong association between childhood trauma and OUD.

The current study aimed to assess the impact of childhood trauma on responses to morphine and pain processing. We set out to compare people with histories of severe childhood trauma to those without, and investigate the impact of a dose of morphine on the reinforcing, pleasurable, and adverse effects of the drug, along with analgesia. We measured subjective 'liking' and 'wanting', as well as implicit wanting using a behavioural progressive ratio task (PRT). We probed endogenous opioid functioning using pain threshold; a proxy of endogenous μ-opioid activity where receptor binding potential at resting state is positively related to pain threshold,[32] and has been frequently used in previous research for this purpose.[33–37] We firstly hypothesised that individuals with childhood trauma would have (i) a lower physical pain threshold and tolerance at baseline than individuals without trauma, indicating reduced sensitivity of the endogenous μ-opioid receptor system, and (ii) would experience less analgesic effects of morphine. We secondly hypothesised that those with childhood trauma history will (i) report more subjectively pleasant drug effects, as well as report wanting more (in line with preclinical findings and potentially due to reduced activation of the endogenous μ-opioid system), whilst the control group will report more unpleasant drug effects, and (ii) would expend greater effort to work for the drug during the PRT.

2 | METHODS

2.1 | Participants and design

Two-hundred and eighty individuals were screened for the study, 152 were eligible, and 52 participants aged 18–65 with a mean age of 30.91 ± 14.89 years were randomised into the study (35 females; 17 males). Participants were selected based on their score on the Childhood Trauma Questionnaire (CTQ[38]), and then allocated into either Trauma ($n = 27$) or Control group ($n = 25$). Individuals were required to score in the severe range for any CTQ subscale for the

Trauma group, or show no evidence of childhood trauma for the Control group. Individuals were ineligible for the study if they scored between these ranges of the CTQ. The groups were matched for age and gender. Recruitment was completed using convenience and snowball sampling via participant databases, poster advertisements, and word of mouth. The study was advertised as looking at 'how people with different experiences in childhood respond to painful events, and respond to morphine' to reduce expectations.

The study was a double-blind, placebo-controlled cross-over design. Participants underwent two study sessions approximately 7 days apart (±1 day) where they either received a physiologically active dose of morphine (0.15 mg/kg) or a very-low dose control condition (0.01 mg/kg). The low-dose control was preferred over a pure placebo to better conceal the randomisation, in line with suggestions for analgesic administration studies[39] where the risk of bias from unblinding is high.[40] Participants were told they would receive two different morphine doses, but were not told the exact dosage for the two sessions to better conceal the treatment allocation and reduce effects of expectation. Drug administration order was randomised and counterbalanced between groups.

Inclusion criteria were: aged 18–65 years; 18.5 < BMI < 35. Exclusion criteria were: any physical health problems or taking medications known to be contraindicated with morphine; past or current history of alcohol or drug use disorder (measured by using a drug use history interview); recent drug or alcohol use (negative urine drug test and breathalyser BAC level of 0.00); severe mental health problems (asking whether they have been diagnosed with any mental health problems, or been in treatment for any psychological problems); known allergy to morphine; pregnancy (negative pregnancy test) or breastfeeding. Participants were asked to fast for 2 h prior to the study session, and abstain from alcohol or any pain medications for 24 h prior to the session. The study was reviewed by the NHS Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki, and all participants gave written, witnessed, informed consent.

2.2 | Drug administration

In each session, participants received one intramuscular injection of morphine in saline in a counterbalanced order via a 2ml syringe administered instantaneously to the antero-lateral thigh muscle. In the high dose morphine session, participants received one 0.15 mg/kg dose of morphine with a maximum dose of 10 mg. In the control session, participants were given saline containing a negligible amount of morphine (0.01 mg/kg).

2.2.1 | Subjective and physiological effects

Participants completed the Drug Effect Questionnaire (DEQ[41]), a widely used measure in acute drug administration studies.[42–47] The DEQ was collected at eight time points (pre-drug, 15-, 30-, 45-, 60-, 90-, 120- and 150-min post-drug) per session. This measured: 'feeling the effect', 'feeling high', liking and disliking the effects, and wanting more of the drug using 100-cm visual analogue scales (VAS). Opioid-specific items were also rated on 100-cm VAS and included: euphoria, nausea, dizziness and sedation. Blood pressure, heart rate and pulse oximetry were monitored and recorded at regular intervals. Participants were also cannulated prior to drug administration and blood samples were taken from a cannula prior to drug administration, and again at 30- and 60 - min post-drug administration to assess morphine levels in plasma. Further details are in supplementary material (SM1).

2.3 | Assessments

2.3.1 | Physical pain

Pain threshold was used as a proxy to assess endogenous opioid activity, in line with previous research.[32–37] The cold water pressor method was used to assess physical pain due being a highly controlled and reliable pain inducer, and prior evidence validating this technique with analgesic drug administration.[48] Participants were first asked to submerge their hand in warm water controlled at 35 ± 1°C for two minutes to ensure hand temperature equilibrium. Following this, they were asked to submerge the same hand into a cold thermostatically controlled water tank controlled at 5°C with their fingers spread apart and not touching the sides of the tank. A pump continuously circulated the water to minimise local warming from the hand. Pain threshold was measured as seconds from onset until participants indicated when the sensation felt painful by raising their opposite hand, and pain tolerance was measured as how long in seconds they could withstand the cold water before withdrawing their hand.

2.3.2 | Reward sensitivity

Using a progressive ratio task (PRT), participants were given seven opportunities to button press for either the drug dose they received earlier in the session or for money (£3.50) in a forced choice task. Button presses for each choice were on an independent progressive ratio schedule, where the number of button presses increased in the following order: 10, 20, 40, 80, 160, 320 and 640. Maximum number of button presses for either reinforcer were 1270. This task was adapted from Babalonis and colleagues[49] and measured implicit 'wanting'. Percentage of morphine choices and the maximum number of button presses completed for morphine was calculated.

2.3.3 | Questionnaires

The Childhood Trauma Questionnaire (CTQ[50]) measured emotional, physical, and sexual abuse, and emotional and physical neglect to identify eligible participants. Other baseline measures were the

Potentially Traumatic Events scale (PTE[51]), which assessed traumatic interpersonal and non-interpersonal events over a lifetime; Adverse Child Experience Questionnaire (ACE[52]) which assessed experiences of household dysfunction whilst growing up; Pain Catastrophising Scale (PCS[53]) measured catastrophic thinking surrounding pain; UCLA Loneliness Scale (UCLA LS[54]) assessed feelings of social isolation and loneliness; Multidimensional Scale of Perceived Social Support (MSPSS[55]) assessed ratings of support from family, friends and significant others; Depression, Anxiety, and Stress Scale (DASS[56]) measured depression, anxiety and stress over the past 2 weeks; Self-Compassion Scale (SCS[57]) measured self-compassion towards oneself (see SM2 for further details of each psychometric measure).

2.4 | Procedure

Prior to the study, individuals who expressed an interest in taking part were screened over the phone or via a secure online link. If they met initial eligibility criteria they were allocated a unique study ID and provided written consent before completing the CTQ. If they scored in the 'none' (scoring 25–40) or 'severe' (≥73) categories of childhood trauma on the CTQ, they were invited to the Clinical Research Facility at the Royal Devon & Exeter hospital for the testing sessions which lasted approximately 3.5–4.5 h separated by 7 days. In the first session, participants underwent a screening with a medical professional to ensure they were fit to take part. Once screened, participants gave written, witnessed informed consent and then completed all study procedures (Figure 1).

2.5 | Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) version 23. An a priori power calculation using an alpha criteria of 0.05, a small effect size ($f = 0.2$), and power of 0.8 was conducted using G*Power and determined a sample size of 52 for within-between interactions. For pain threshold/tolerance, three-way mixed measures ANOVA's were used with Group (trauma and control) as the between subject variable, and both Drug (morphine, placebo) and Time (pre-, post-administration) as a within subjects variables. Blood plasma was analysed using enzyme-linked immunoassay kits (procedure in SM1), and was statistically analysed using a three-way ANOVA comparing Drug and Group with Time (baseline, 30 min, 60 min). A 2×2 repeated measures ANOVA assessed differences between Group and Drug on the outcomes for the PRT. Mixed effect random intercept models were analysed using Stata version

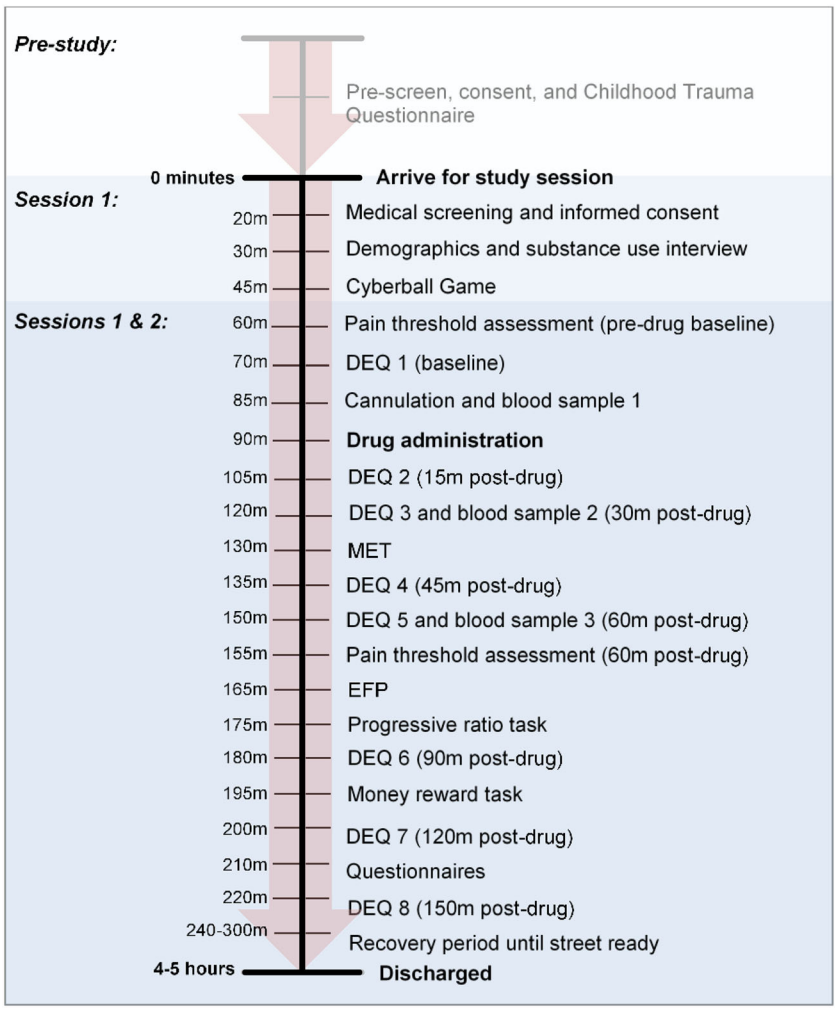

FIGURE 1 Study procedure alongside approximate timings (in cumulative order). Procedure for session two was identical to session one from pain threshold assessment (pre-drug baseline) onwards. M = minutes, DEQ = Drug Effects Questionnaire, MET = multifaceted empathy test, EFP = empathy for pain test. Although the Cyberball, MET, money reward task and EFP tasks were completed by participants, the results of these tasks are not reported in the current paper

16 developed to estimate Group × Drug × Time effect on drug effects assessed via the DEQ (primary outcomes) and opioid-specific questions (secondary outcomes) where 'Time' represents baseline, 15-, 30-, 45-, 60-, 90-, 120- and 150-min post-drug.

3 | RESULTS

3.1 | Demographics

Groups were matched on age, gender, BMI, familial histories of chronic pain, mental health and substance abuse problems (Table 1). The trauma group rated significantly higher in history of interpersonal trauma, but the groups were matched in non-interpersonal trauma history. The trauma group also reported greater loneliness, depression, anxiety and stress and lower perceived social support and self-compassion.

3.2 | Pain

Due to negative skew, both threshold and tolerance were log-transformed prior to analyses. For pain threshold, there was a significant interaction between Time and Drug (F (1,47)=21.81, $p < 0.001$, $\eta^2 = 0.10$). Holm Bonferroni-corrected t tests revealed a significant increase in pain threshold following morphine (t (50) = 4.29, $p < 0.001$, $\eta^2 = 0.27$) but no significant difference in pain threshold following the very low dose control (t (49) = 0.75, $p = 0.455$, $\eta^2 = 0.01$) (Figure 2A). There was also main effect of Time (F (1,47) = 10.76, $p = 0.002$, $\eta^2 = 0.06$), yet no main effects of Group (F (1,47) = 0.03, $p = 0.857$, $\eta^2 < 0.01$) or Drug (F (1,47) = 1.99, $p = 0.165$, $\eta^2 = 0.02$), and no interactions between Group and Time (F (1,47) = 1.41, $p = 0.242$, $\eta^2 < 0.01$) or Drug (F (1,47) = 0.36, $p = 0.550$, $\eta^2 = 0.01$), or between Time, Group and Drug (F (1,47) = 1.11, $p = 0.298$, $\eta^2 = 0.01$).

For pain tolerance, there was a significant interaction between Time and Drug (F (1,47) = 35.30, $p < 0.001$, $\eta^2 = 0.09$). Holm Bonferroni-corrected t tests revealed a significant increase in threshold in the morphine session (t (50) = 5.07, $p < 0.001$, $\eta^2 = 0.34$) but no significant difference in the placebo session (t (49) = 0.92, $p > 0.999$, $\eta^2 < 0.001$) (Figure 2B). There was a main effect of Time (F (1,47) = 19.49, $p < 0.001$, $\eta^2 = 0.10$) and Drug (F (1,47) = 14.99, $p < 0.001$, $\eta^2 = 0.11$). There were no main effects of Group (F (1,47) = 0.84, $p = 0.364$, $\eta^2 = 0.02$), and no interaction between Group and Drug (F (1,47) < 0.01, $p = 0.957$, $\eta^2 = 0.01$) or Time (F (1,47) = 1.52, $p = 0.224$, $\eta^2 < 0.01$), or interaction between Drug, Group and Time (F (1,47) = 1.50, $p = 0.227$, $\eta^2 < 0.01$).

When analysing subjective pain catastrophising, we included anxiety scores as a covariate due to being significantly correlated with pain catastrophising to assess pain-specific anxiety. When controlling for anxiety, pain catastrophising was significantly higher in the childhood trauma group ($M = 30.88$, $SD = 7.18$) than the controls ($M = 24.92$, $SD = 7.22$) (F (1,47)=7.96, $p = 0.007$, $\eta^2 = 0.15$).

3.3 | Drug effects

Results from maximum-likelihood based random intercept models for all outcomes are presented in SM3a/b. The log likelihood ratio tests showed significant model improvement ($p < 0.001$) in favour of random intercept models compared to single-level models for all outcomes. The full factorial three-way interaction coefficients represent the marginal effect of morphine for 'Trauma' group on each outcome compared to the 'Control' group with low-dose placebo at each time point. The model estimates alone are not sufficient to draw inferences about within-session-between-group effect or within-group-between-session effect, and therefore the post-model estimated means/CIs and their comparisons for each time point are presented in SM4 and plotted in Figure 3 (primary outcomes) and Figure 4 (secondary outcomes).

3.3.1 | Feeling the drug effects

When assessing primary outcomes using the DEQ, both groups rated significantly higher in feeling the drug effects in the morphine session after every time point (Figure 3A) ($p < 0.001$). There were no significant group differences in feeling the effects in the morphine or placebo session (all p values > 0.284).

3.3.2 | Feeling high

Ratings of feeling high were significantly greater for the childhood trauma group in the morphine session at 30 min than the controls (Figure 3B) (MD = 10.42, 95%CI [0.16,20.69], $p = 0.047$), alongside a trend at 15 and 45 min in the same direction (15 m: MD = 10.07, 95%CI [−0.20,20.33], $p = 0.055$; 45 m: MD = 9.82, 95%CI [−0.45,20.08], $p = 0.061$). Both groups rated feeling significantly more "high" after morphine than placebo between 15–90 min (all p values < 0.001 for the trauma group, and <0.026 for the controls).

3.3.3 | Disliking drug effects

Ratings of dislike of the drug effects were significantly higher in the control group at 90 min (MD = 16.65, 95%CI [5.40,27.91], $p = 0.004$) and 150 min (MD = 18.86, 95%CI [7.55,30.81], $p < 0.001$) compared with the trauma group after morphine, alongside a trend at 120 min (MD = 11.05, 95%CI [0.20,22.31], $p = 0.047$) (Figure 3C). The control rated greater for disliking the effects in the morphine session over the placebo session between 90 and 150 min (90 m: MD = 24.19, 95%CI [15.24,33.14], $p < 0.001$; 120 m: MD = 16.78, 95%CI [7.82,25.73], $p < 0.001$; 150 m: MD = 24.11, 95%CI [15.16,33.06], $p < 0.001$), and at 15, 120 and 150 min for the trauma group (15 m: MD = 10.42, 95%CI [2.00,18.84], $p = 0.015$; 90 m: MD = 10.00, 95%CI [1.58,18.42], $p = 0.020$; 120 m: MD = 10.00, 95%CI [1.58,18.42], $p = 0.020$).

TABLE 1 Demographic differences (M and SD's) between the trauma and control group

	Trauma ($n = 27$)	Control ($n = 25$)	t, χ^2 or U	p value
Age	28.92 (13.38)	33.04 (16.39)	1.00	0.325
Gender (male, female)	10, 17	7, 18	0.48	0.488
BMI	24.62 (4.62)	23.30 (2.71)	1.27	0.211
Age left education	23.37 (8.34)	21.56 (3.04)	1.01	0.316
Physical health problems	4	3	0.09	0.766
History of mild to moderate anxiety or depression	14	4	6.10	0.014*
Medications	5	5	0.02	0.892
Received morphine in the past	9	7	0.17	0.677
Been under general anaesthetic	15	11	0.96	0.328
Regular use of over-the-counter painkillers	8	4	1.36	0.244
Familial history of chronic pain	1	2	0.40	0.529
Familial history of mental health problems	9	9	0.01	0.918
Familial history of substance abuse problems	5	3	0.50	0.478
Inter- and intrapersonal characteristics				
Childhood trauma questionnaire (total score)	64.37 (13.58)	28.20 (2.61)	12.08	<0.001***
Physical abuse	11.56 (5.45)	5.08 (0.28)		
Emotional abuse	16.44 (4.80)	6.00 (1.04)		
Sexual abuse	9.82 (5.86)	5.08 (0.40)		
Physical neglect	9.85 (3.81)	5.32 (0.63)		
Emotional neglect	16.70 (4.05)	6.72 (1.60)		
PTE Non-interpersonal trauma[a]	0.00 (1.00)	0.00 (1.00)	284.0	0.268
PTE Non-intimate interpersonal trauma[a]	1.00 (1.00)	0.00 (0.00)	194.0	0.001**
PTE Intimate interpersonal trauma[a]	2.00 (2.00)	0.00 (0.50)	94.00	<0.001***
ACE score[a]	4.00 (3.00)	0.00 (1.00)	12.00	<0.001***
Perceived social support	2.22 (1.21)	3.74 (0.65)	5.70	<0.001***
Loneliness	50.33 (9.15)	37.16 (7.38)	5.73	<0.001***
Self-compassion	2.83 (0.75)	3.39 (0.73)	2.70	0.010*
Depression[a]	10.00 (9.00)	7.00 (2.00)	170.50	0.005**
Anxiety[a]	9.00 (6.00)	7.00 (2.00)	189.00	0.014*
Stress[a]	12.00 (9.00)	8.00 (3.00)	155.50	0.002**
Drug use history, (n = ever used)			χ^2	p
Alcohol (n = yes)	27	25	–	–
Tobacco	20	15	1.17	0.280
Ecstasy/MDMA	9	6	0.55	0.458
Cannabis	23	16	3.11	0.078
Cocaine	7	3	1.62	0.203
Illicit opioids	2	1	0.28	0.599

[a]*Note:* Non-parametric test used where data is non-normal (median and interquartile range are reported). No chi squared data is presented for 'Alcohol' in drug use history as all participants from both groups have used alcohol.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

3.3.4 | Liking drug effects

The trauma group rated liking the drug effects significantly more in the morphine session than placebo at all time points (all p values < 0.010), whilst liking the drug effects were not statistically different between sessions at any time point for the controls (all p values > 0.125) (Figure 3D). In addition, the trauma group rated liking the drug effects significantly more than controls after morphine at the following time points: 30 min (MD = 14.67, 95%CI [0.48,28.87], $p = 0.043$), 45 min (MD = 20.02, 95%CI [5.82,34.21], $p = 0.006$),

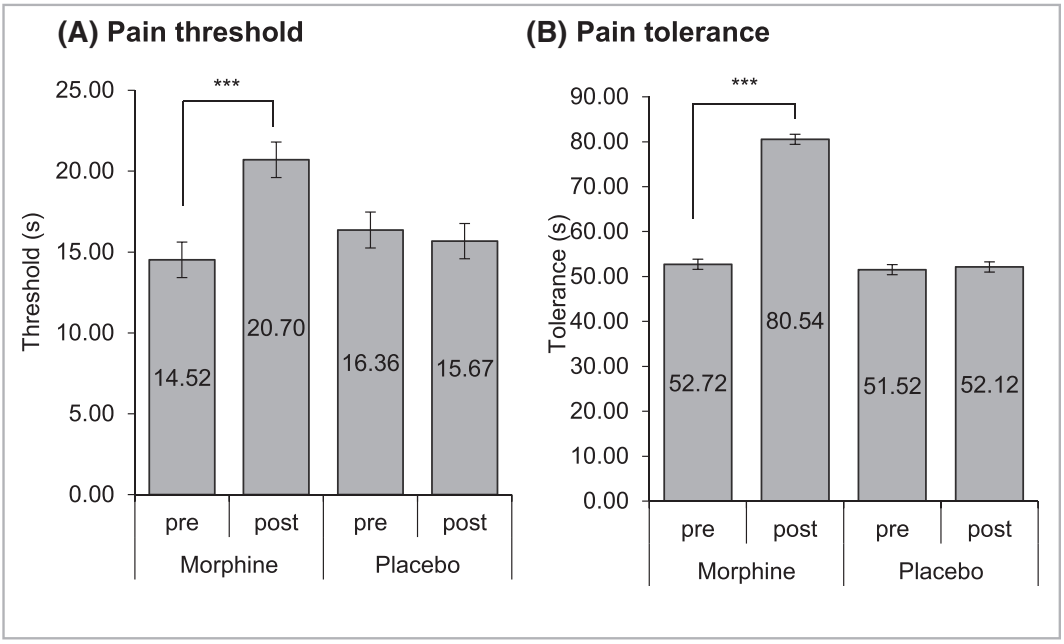

FIGURE 2 Pain threshold and tolerance pre- and post-drug administration collapsed across trauma and control groups. (A) There was a significant increase in pain threshold post-drug administration in the morphine session ($p < 0.001$) but not in the placebo session ($p = 0.455$). (B) There was a significant increase in pain tolerance post-drug administration in the morphine session ($p < 0.001$) but not in the placebo session ($p < 0.999$). (s = seconds). Means and standard error values in the figures have been back-transformed from the log-transformed data

90 min (MD = 18.20, 95%CI [4.00,32.39], $p = 0.012$), 120 min (MD = 20.14, 95%CI [5.94,34.33], $p = 0.005$), and 150 min (MD = 20.97, 95%CI [6.71,35.24], $p = 0.004$).

3.3.5 | Wanting more of the drug

The trauma group wanted more of the drug significantly greater after morphine compared with placebo at all time points (all p values < 0.001) (Figure 3E), whereas the control group did not rate significantly differently in wanting more between the two sessions (all p values > 0.307). In addition, wanting more of the drug was significantly higher in the trauma group compared with controls after morphine at every times point (15 m: MD = 23.42, 95%CI [10.55,36.29], $p < 0.001$; 30 m: MD = 24.53, 95%CI [11.66,37.40], $p < 0.001$; 45 m: MD = 29.90, 95%CI [17.03,42.77], $p < 0.001$; 60 m: MD = 38.05, 95%CI [25.10,51.01], $p < 0.001$; 90 m: MD = 35.51, 95%CI [22.65,48.38], $p < 0.001$; 120 m: MD = 31.09, 95%CI [18.23,43.96], $p < 0.001$; 150 m: MD = 25.25, 95%CI [12.31,38.19], $p < 0.001$). There was a trend for greater wanting between 30–150 min in the trauma group after placebo (30 m: MD = 12.87, 95%CI [0.00,25.74], $p = 0.050$; 45 m: MD = 12.61, 95%CI [−0.26,25.47], $p = 0.055$; 60 m: MD = 11.35, 95%CI [−1.52,24.21], $p = 0.084$; 90 m: MD = 12.06, 95%CI [−0.81,24.92], $p = 0.066$; 120 m: MD = 12.81, 95%CI [−0.06,25.67], $p = 0.051$).

For opioid-specific outcomes, the control group felt significantly more nauseous after morphine than the trauma group between 120 and 150 min (Figure 4A) (120 m: MD = 9.27, 95%CI [1.56,16.98], $p = 0.018$; 150 m: MD = 10.24, 95%CI [2.47,18.01], $p = 0.010$). Nausea was significantly greater following morphine compared with placebo between 60 and 150 min for controls (all p values < 0.005) and 90–150 min for the trauma group (all p values < 0.041). The trauma group were significantly more euphoric than controls between 15 and 60 min (Figure 4B) (15 m: MD = 17.99, 95%CI [6.69,29.30], $p = 0.002$; 30 m: MD = 13.69, 95%CI [2.39,25.00], $p = 0.018$; 45 m: MD = 14.20, 95%CI [2.89,25.50], $p = 0.014$; 60 m: MD = 14.84, 95%CI [3.45,26.22], $p = 0.011$). The trauma group also reported feeling more euphoric after morphine compared with placebo between 15 and 90 min (all p values < 0.18), whereas the controls did not feel any difference in euphoria between the morphine or placebo sessions (all p values > 0.195). Controls reported more dizziness than the trauma group after morphine between 90 (MD = 12.81, 95%CI [4.69,20.92], $p = 0.002$) and 120 min (MD = 10.64, 95%CI [2.52,18.75], $p = 0.010$), alongside a trend at 60 and 150 min (Figure 4C). Both groups reported dizziness after morphine compared with placebo between 45 and 150 min (all p values < 0.030). Both groups reported feeling more sedated after morphine compared with placebo over all time points (all p's < 0.012) (Figure 4D); however, there were no significant differences between the two groups.

Blood plasma levels of morphine confirmed greater levels of morphine at 30 and 60 min after the high dose morphine session compared with the low dose control (Table 2), as well as increases in mean arterial pressure. There were no group effects or differences in heart rate (SM5 for analyses of physiological/biological outcomes).

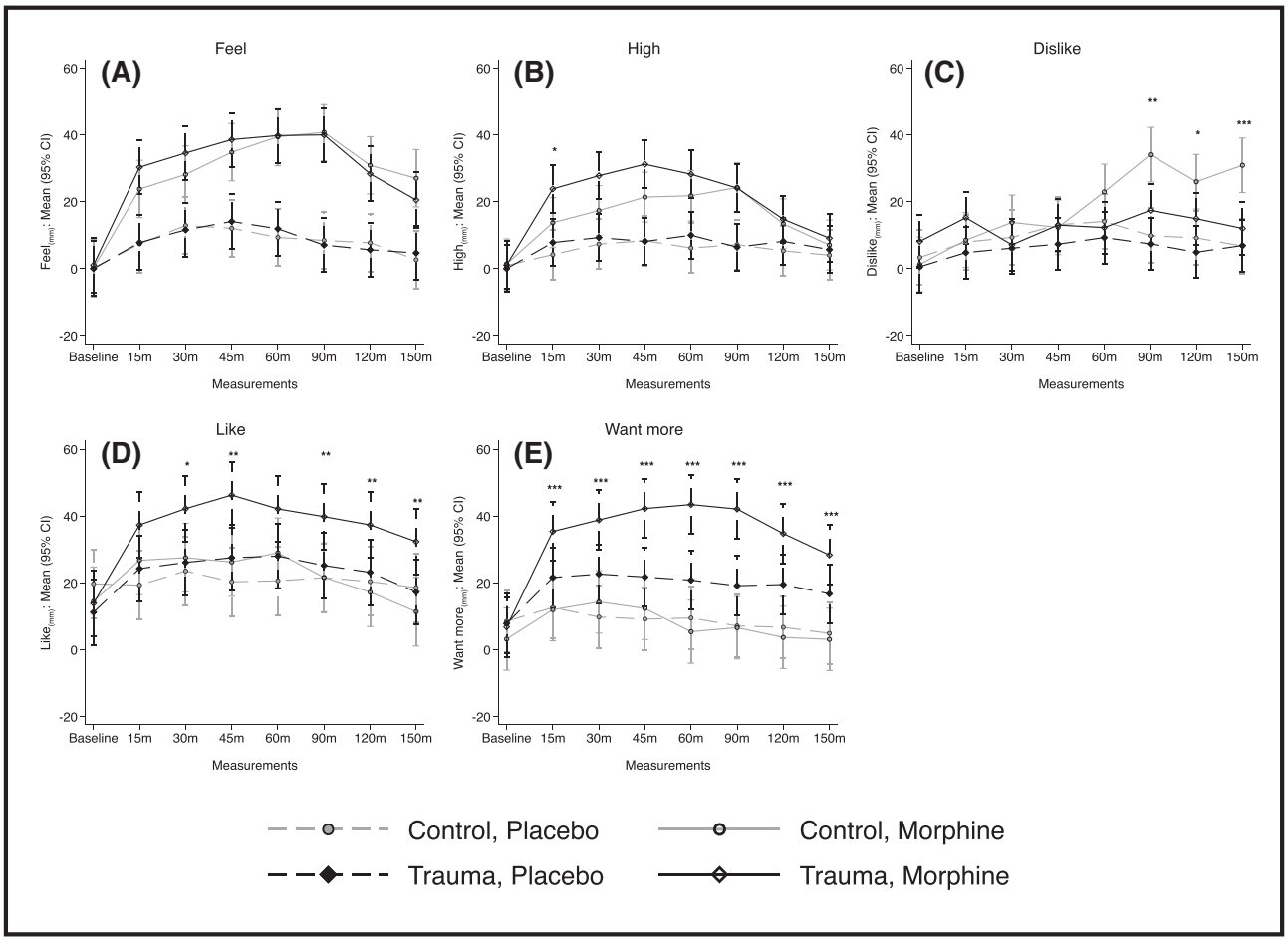

FIGURE 3 Subjective responses to morphine and placebo using the Drug Effects Questionnaire between the trauma and control groups over eight time points (baseline, 15-, 30-, 45-, 60-, 90-, 120- and 150-m post-drug administration). (A) Feeling effects. When assessing primary outcomes using the DEQ, both groups rated significantly higher in feeling the drug effects in the morphine session after every time point. There were no group differences in feeling the effects in the morphine or placebo session. (B) Feeling high. Feeling high was significantly greater for the childhood trauma group in the morphine session at 30 min than the controls, alongside a trend at 15 and 45 min in the same direction. Both groups rated feeling significantly more 'high' after morphine than placebo between 15 and 90 min. (C) Disliking effects. Disliking the drug effects were significantly higher in the control group at 90 and 150 min compared with the trauma group after morphine, alongside a trend at 120 min. The control rated greater for disliking the effects in the morphine session over the placebo session between 90 and 150 min, and at 15, 120 and 150 min for the trauma group. (D) Liking effects. The trauma group rated liking the drug effects significantly more in the morphine session than placebo at all time points, whilst liking the drug effects were not statistically different between sessions at any time point for the controls. In addition, the trauma group rated liking the drug effects significantly more than controls after morphine at 30, 45, 90, 120 and 240 min. (E) Want more. The trauma group wanted more of the drug significantly greater after morphine compared with placebo at all time points, whereas the control group did not rate any differently in wanting more between the sessions. In addition, wanting more of the drug was significantly higher in the trauma group compared with controls after morphine at all time points. There was also a trend to suggest greater wanting more between 30 and 150 min in the trauma group after placebo. Graphs reflect predicted means and 95% confidence intervals. Significant differences between trauma and control group in the morphine session are indicated by $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

3.4 | Reward sensitivity

PRT: when analysing the percentage of morphine choices made, there was no main effect of Group or interaction between Group and Drug (Table 3). When assessing the maximum number of button presses for morphine, there was no main effect of Group or interaction between Group and Drug.

3.5 | Exploratory analyses

There was a large effect size for the correlation between ACE score with liking the effects of morphine at peak effects (30 min) ($r = 0.47$, $n = 27$, $p = 0.154$) (Holm–Bonferroni corrected) within the trauma group, and no relationship with ACE score and wanting more morphine at peak effects ($r = 0.23$, $n = 27$, $p = 0.400$). Large effect sizes

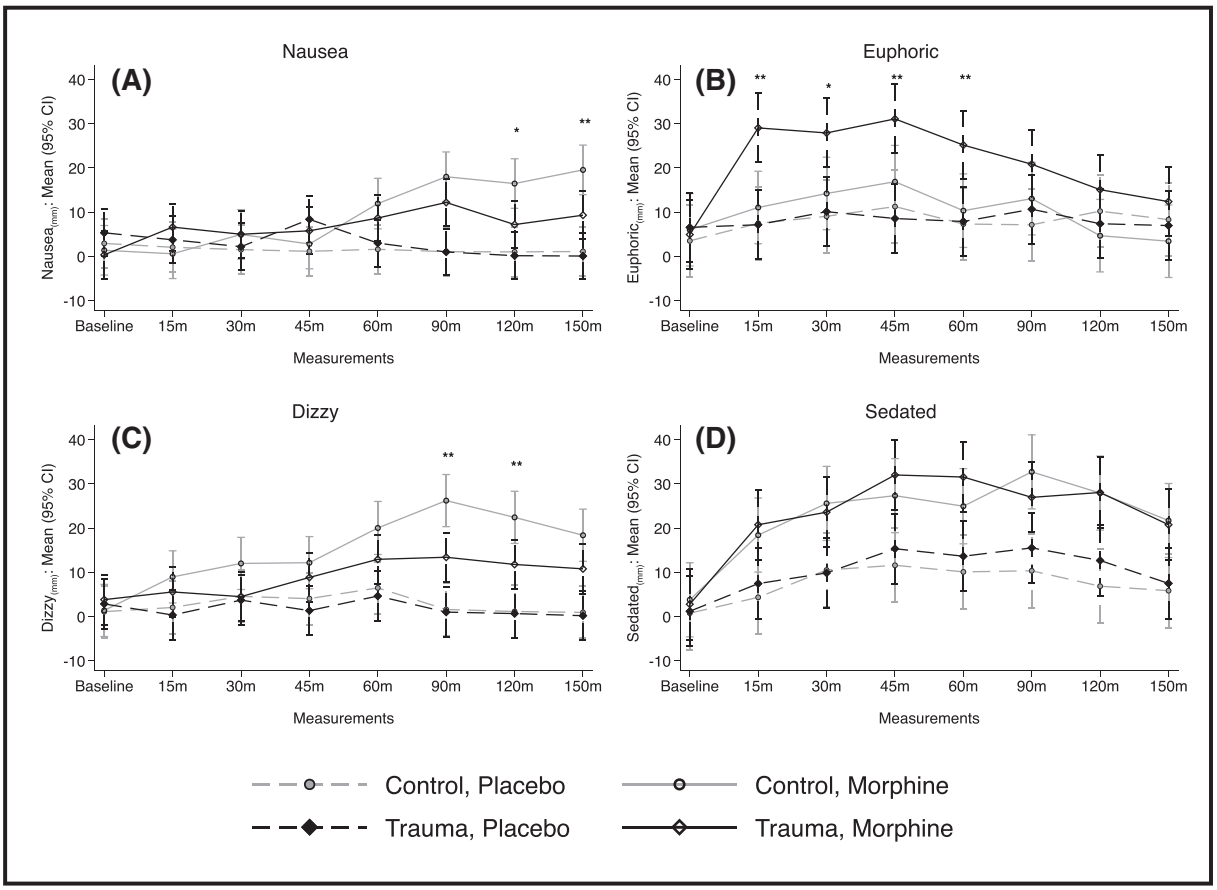

FIGURE 4 Subjective responses to opioid-specific effects in the morphine and placebo sessions between the trauma and control groups over eight time points (baseline, 15-, 30-, 45-, 60-, 90-, 120- and 150-m post-drug administration). (A) Nausea. The control group felt more nauseous after morphine than the trauma group between 120–150 min. Nausea was greater following morphine compared with placebo between 60 and 150 min for controls and 90–150 min for the trauma group. (B) Euphoria. The trauma group were significantly more euphoric than controls between 15–60 min. The trauma group also reported feeling more euphoric after morphine compared with placebo between 15 and 90 min, whereas the controls did not feel any difference in euphoria between the morphine or placebo sessions. (C) Dizziness. Controls reported feeling more dizzy than the trauma group after morphine between 90 and 120 min, alongside a trend in the same direction at 60 and 150 min. Both groups reported feeling more dizzy after morphine compared with placebo between 45 and 150 min. (D) Sedation. Both groups reported feeling more sedated after morphine compared with placebo at every time point; however, there were no differences between the two groups after morphine or placebo. Graphs reflect predicted means and 95% confidence intervals. Significant differences between trauma and control group in the morphine session are indicated by $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

also indicated stress as associated with wanting more morphine at peak effects in the childhood trauma group, and anxiety with wanting more in the control group (these and other correlations with depression, anxiety and stress are available in SM6). Prior exposure to analgesics such as morphine and general anaesthetics were not associated with differences in the subjective effects or responses to pain (analyses available in SM7).

4 | DISCUSSION

In the current study, we aimed to investigate the impact of childhood trauma on acute response to morphine and pain. We found that individuals with childhood trauma consistently reported liking the effects of morphine more than those without a history of childhood trauma, as well as reporting wanting more of the drug compared with controls over the duration of the session. Compared to those with a history of childhood trauma, the control group had a greater dislike of the effects of morphine towards the end of the session, and experienced more nausea and dizziness. Euphoria was also significantly greater in the trauma group, as well as feeling 'high' at peak effects, whereas euphoria in the control group was low and did not differ between the active and very low dose morphine sessions. We did not find any differences in the tendency to work for morphine over money between the two groups using the progressive ratio task. Morphine increased pain threshold and tolerance, in line with its known analgesic effects; however, this did not differ between the trauma and control group. Nonetheless, pain catastrophising was greater in the childhood trauma group. The two groups were well matched on gender, age, BMI alcohol and drug use. Those who had experienced childhood trauma showed greater depression, anxiety, stress, loneliness and lower perceived social support and self-compassion.

TABLE 2 Plasma morphine and physiological outcomes (Ms and SDs)

		Trauma ($n = 27$)	Control ($n = 25$)
Plasma Morphine			
High dose morphine	Baseline	0.14 (0.46)	0.34 (1.34)
	30 min	22.65 (11.34)	22.61 (16.17)
	60 min	20.88 (10.31)	22.17 (15.87)
Low dose control	Baseline	0.05 (0.10)	0.24 (0.56)
	30 min	2.54 (2.09)	2.26 (2.47)
	60 min	2.46 (1.71)	2.47 (2.18)
Heart rate			
High dose morphine	Baseline	68.63 (9.32)	64.26 (17.68)
	30 min	71.74 (11.48)	67.13 (10.82)
	60 min	66.33 (9.93)	60.39 (16.68)
Low dose control	Baseline	67.85 (9.67)	63.57 (9.17)
	30 min	64.44 (12.03)	62.13 (7.93)
	60 min	66.85 (11.46)	61.74 (8.76)
Mean arterial pressure			
High dose morphine	Baseline	85.48 (10.37)	82.97 (9.00)
	30 min	85.73 (10.26)	81.37 (11.42)
	60 min	87.01 (9.90)	83.63 (20.10)
Low dose control	Baseline	86.21 (9.35)	78.21 (15.97)
	30 min	86.10 (10.27)	86.00 (9.55)
	60 min	86.00 (10.59)	80.89 (11.06)

Note. Mean arterial pressure (MAP) was calculated from systolic and diastolic blood pressure recordings as MAP $= {}^{1}/_{3}$ (SBP + (2[DBP]).

TABLE 3 Analyses of the progressive ratio task choices (M and SD's)

		Trauma	Control		F	p	η^2
% morphine choices	High dose morphine	31.32 (20.61)	28.57 (18.70)	Drug	1.22	0.276	0.03
	Low dose control	30.21 (18.66)	25.33 (17.60)	Group	0.55	0.461	0.01
				Drug*Group	0.30	0.588	0.01
Max. morphine button presses	High dose morphine	34.62 (29.43)	26.36 (20.60)	Drug	2.53	0.119	0.05
	Low dose control	30.77 (27.41)	21.36 (16.42)	Group	1.84	0.182	0.04
				Drug*Group	0.04	0.837	<0.01

Liking the effects of morphine, feeling euphoria, and wanting more of the drug was greater in those with a history of childhood trauma. This supports our hypotheses that those with a history of childhood abuse and neglect would find the drug more pleasurable and rewarding, and is in line with the preclinical research where early trauma is associated with greater reinforcing effects of morphine (shown by more rapid rates of self-administration and stronger conditioned place-preference).[20,21] In addition, the non-traumatised control group reported disliking the effects more than the childhood trauma group, alongside increased rates of aversive effects such as nausea and dizziness. We also found a large effect that failed to reach statistical significance which suggested severity of childhood adversity in the trauma group may be positively associated with how much they liked the morphine at the time of peak blood concentration. To our knowledge, this is the first study to link history of childhood trauma with the experiential effects of opioids in non-addicted individuals, suggesting that childhood trauma may produce a greater sensitivity to the positive and pleasurable effects of opioids.

Childhood trauma increased the subjective pleasurable effects of morphine (via greater liking and euphoria), intensified the motivational qualities of morphine (via wanting more), and reduced the likelihood of negative effects (such as nausea and dizziness). One potential explanation for these differences may be via alterations in the endogenous opioid system through childhood adversity. Prior research has linked childhood trauma to altered neural responses to naltrexone, potentially via existing differences in endogenous opioids.[31] Preclinical research has also reported that maternal separation results in hyposensitive endogenous opioid functioning, which is suggested as responsible for the heightened sensitivity to the rewarding effects of opioid drugs.[20] A hyposensitive endogenous opioid system could

therefore potentially underlie the increased pleasurable effects and reduced aversive effects of morphine in the trauma group in the current study. This combination of not only increased pleasurable effects but also blunted adverse effects suggests enhanced risk of susceptibility to the addictive properties of the drug, providing evidence for individual differences in subjective opioid effects that could be a major vulnerability factor for addiction.

Although subjective wanting was higher, there was an absence of effect for the implicit behavioural measure of wanting using the PRT task. This could support a stronger effect for opioid 'liking' (pleasure) over behavioural 'wanting' (incentive salience) in those with childhood trauma, a dissociation outlined by Robinson and Berridge's theory of incentive sensitisation.[16] Incentive salience occurs following repeated exposure of a substance, therefore it is plausible that sensitisation may not be observed in the current sample with a single psychoactive dose. This conclusion should be interpreted with caution, however, as subjective reports of 'wanting more' were high, and the specific task used money as a comparator reward in a non-dependent population. Money may be a greater incentive than morphine in this group, where investigating effort to work for other rewards (such as food) or nothing may be better comparisons in non-addicted populations.

The current study found no group differences in pain threshold, unlike previous studies.[22–26] Neither did we report a reduced analgesic effect of morphine in those with childhood trauma, unlike similar preclinical studies.[19] Higher levels of pain catastrophising were observed in the trauma group suggesting some differences in pain interpretation, as well as greater depression and anxiety. This is relevant not only for addiction but also for chronic pain, where there are similarly high rates of childhood trauma.[58]

Given the absence of differences in pain threshold, the findings of the current study may not support the notion that greater opioid-induced pleasure and wanting of morphine is due to impaired endogenous opioid functioning, as suggested by preclinical studies.[20,21] However other explanations may be that increased liking of opioids is not specific to this drug, as a similar pattern has been observed with amphetamines,[59] where 'perceived stress' (an index of stress reactivity) was associated with both amphetamine-induced dopamine release and pleasure. Permanent alterations in the hypothalamic–pituitary–adrenal (HPA) axis caused by chronic stress in childhood[60] could therefore affect subjective responses to drugs. We also observed greater stress in adulthood in the form of lower social support and higher loneliness in the trauma group. Preclinical research has shown that plasma corticosterone is greater in rats exposed to early life stress,[61] and mice exposed to social stress that show greater corticosterone have higher alcohol consumption, where it is suggested that corticosterone interacts with dopamine to promote alcohol intake.[62] Neurobiological differences in HPA functioning, as well as its effects on other neurotransmitters such as dopamine, could underlie the heightened pleasurable effects in the childhood trauma group. Although cardiovascular measures did not differ between groups, a continuous or biological measure of these outcomes using ECG or salivary cortisol may have provided greater precision for measuring HPA activity. However, there may also be psychological explanations: Childhood trauma is related to heightened vigilance and preparedness for threats in both childhood[63] and adulthood,[64] where opioids may be rewarding because they offer relief from a chronic hypervigilant state. The findings also suggest differences in the interpretation of the drug effects, opposed to pharmacological differences between the groups. Anxiety and depression were also greater in the childhood trauma group although largely not significantly related to the subjective effects, however given that childhood trauma chronologically predates and predicts these, the observed relationship is likely primary and not secondary to symptoms.

Clinical implications of this study are wide-ranging. The suggestion that people who have experienced childhood trauma feel more positive and less negative effects of morphine may go some way towards starting to reduce the stigma associated with OUD. Evidence suggests that it is still widely believed that addiction is a choice, which is a major barrier for seeking help[65] and reduces the public's willingness to support policies for helping people with addictions.[66] The findings also highlight the importance of introducing preventative measures aimed at high-risk children and adolescents to reduce the initiation of opioid use. Such preventative measures could include introducing other rewarding activities in order to reduce the motivational strength of opioids, and training in emotion regulation to reduce hyperarousal.

The current study has several strengths and limitations. The exclusion of severe mental health problems or addiction history which could indicate the trauma group as particularly resilient, therefore potentially reducing ecological validity. Yet there were greater rates of social stressors such as loneliness and reduced social support, and greater depression and anxiety in those with childhood trauma, thus it is difficult to disentangle the influence of trauma and these other factors. A measure of socio-economic status would have also provided an index of other psychosocial life stressors that may be associated with subjective effects. Female menstrual cycle should also be measured and considered when evaluating pain due to variation in pain perception.[67] Furthermore, in the progressive ratio task we assessed behavioural responses to wanting more morphine via asking them to work towards another dose hypothetically, yet future studies could build on this by assessing self-administration of morphine using patient-controlled analgesia pumps as an objective measure of motivation for more of the drug.

In summary, the current findings suggest that experiences of childhood trauma can sensitise individuals to opioid-induced pleasure and increase the desire for more of the drug. The trauma group reported greater catastrophising of pain, but did not respond differently to a painful stimulus in terms of threshold or tolerance. The findings of this study are a stepping stone in highlighting the role of childhood trauma in OUD, emphasising the need to address trauma symptoms in this vulnerable group, and targeting early interventions at traumatised young people. These findings have many clinical and social implications including reducing the guilt and shame common amongst those with OUD about the reasons behind the development of this damaging addiction.

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CONFLICT OF INTEREST

C.J.A.M has consulted for Janssen, GlaxoSmithKline and Beckley canopy therapeutics. All other authors report no biomedical financial interests or potential conflicts of interest.

AUTHOR CONTRIBUTIONS

M.C., R.B., G.S. and C.J.A.M. conceptualised the study and design. M.C. collected and analysed the data, and wrote the manuscript. C.J.A.M., G.S. and R.B. also assisted in writing and editing the manuscript. R.H., L.F., M.M. and J.D. also collected the data, and R.B. and G.S. administered the drug dose, collected biological samples and provided medical oversight. M.M. assisted in analysed the data and interpreting the results.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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