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Rewarding Subjective Effects of the NMDAR Antagonist Nitrous Oxide (Laughing Gas) Are Moderated by Impulsivity and Depressive Symptoms in Healthy Volunteers

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Abstract

Background: Nitrous oxide (N_2O) is an anesthetic gas with both therapeutic and abuse potential. Because N_2O is an NMDA receptor (NMDAR) antagonist, its effects are expected to resemble those of the prototypical NMDAR antagonist, ketamine. In this study, we examined the subjective rewarding effects of N_2O using measures previously employed in studies of ketamine. We also tested for moderation of these effects by bipolar phenotype, depressive symptoms, and impulsivity.
Methods: Healthy volunteers were randomly assigned to either 50% N_2O (n = 40) or medical air (n = 40). Self-reported rewarding (liking and wanting), and alcohol-like effects were assessed pre-, peri- and post inhalation.
Results: Effect sizes for the various rewarding/alcohol-like effects of N_2O were generally similar to those reported in studies of moderate-dose ketamine. Impulsivity moderated the subjective reinforcing (liking) effects of inhaled gas, while depressive symptoms moderated motivational (wanting [more]) effects. However, depression and impulsivity had opposite directional influences, such that higher impulsivity was associated with higher N_2O liking, and higher depression, with lower N_2O wanting.
Conclusion: To the extent that static (versus longitudinal) subjective rewarding effects are a reliable indicator of future problematic drug use, our findings suggests that impulsivity and depression may predispose and protect, respectively, against N_2O abuse. Future studies should examine if these moderators are relevant for other NMDAR antagonists, including ketamine, and novel ketamine-like therapeutic and recreational drugs. Similarities between moderate-dose N_2O and moderate-dose ketamine in the intensity of certain subjective effects suggest that N_2O may, at least to some extent, serve as substitute for ketamine as a safe and easily implemented experimental tool for probing reward-related NMDAR function and dysfunction in humans.

Keywords: nitrous oxide, ketamine, NMDA receptor, alcohol, reward

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Significance statement

Nitrous oxide (N2O or "laughing gas") is used extensively in medicine and dentistry as an anesthetic gas. N2O acts on the same brain receptor systems as ketamine, and like ketamine, N2O may also be a rapidly acting antidepressant, possibly with other applications in psychiatry. Some people find N2O's effects pleasurable, and therefore it is also used recreationally. One of the general challenges in psychiatry is to prospectively identify patients who will respond to a therapeutic agent and also those who will show addictive behavior toward a drug with abuse potential. In this study, we investigated the rewarding effects of N2O. We found that people who are more impulsive "like" the effects of N2O more, whereas people who are more depressed "want" N2O less. It is possible, therefore, that impulsivity and depression, respectively, predispose and protect against the addictive potential of N2O.

Introduction

Nitrous oxide (N_2O) is a simple tri-atomic gas that antagonizes the NMDA receptor (NMDAR; Jevtović-Todorović et al., 1998). Like ketamine, N_2O is a dissociative anesthetic, and may share its NMDAR-dependent rapid antidepressant effects (Nagele et al., 2015, 2018). N_2O has also been tested as a treatment for acute alcohol withdrawal (Gillman, 2019) and proposed as a memory-therapeutic agent for modulating the formulation and reconsolidation of maladaptive memories in trauma-related disorders (Das et al., 2016) and addiction (Das et al., 2018). Apart from these novel therapeutic uses, and its established role in medical and dental anesthesia, N_2O is a popular recreational drug (van Amsterdam et al., 2015; Kaar et al., 2016). Although N_2O is among the safest drugs used in medicine and surgery (Onody et al., 2006), excessive and/or chronic recreational use is linked to morbidity (neuropathies) and (rarely) mortality (Garakani et al., 2016).

Risk factors for problem use of dissociative drugs like N_2O, ketamine, phencyclidine, dextromethorphan, methoxetamine, and related novel psychoactive NMDAR antagonists are not yet well understood. However, certain subjective responses to acute drug challenges are important general determinants of future drug taking and escalating use (de Wit & Phillips, 2012). For example, nonanxiolytic drugs that have stimulating rather than sedating subjective effects tend to have greater addictive potential (Wise & Bozarth, 1987). More generally, the tendency to experience "positive" (i.e., euphoric, stimulating, etc.) effects—especially during the first (or first few) drug use occasions—may be associated with greater subsequent use of that drug (for a review, see de Wit & Phillips, 2012; see also, e.g., Agrawal et al., 2014; Duke et al., 2015; Chavarria et al., 2020). Because repeated use is a necessary step in the transition from casual drug taking to escalating use and addiction, the occurrence of enhanced self-reported rewarding drug effects can be considered a high-risk pattern of drug response. The strongest evidence for this risk comes from longitudinal studies linking the subjective response to alcohol to subsequent alcohol use disorder (AUD). Specifically, higher self-reported ratings on liking, wanting, and stimulation (relative to sedation) during an acute alcohol challenge predicted AUD up to a decade later (King et al., 2014, 2021).

Relatedly, drinkers with a positive family history (FH+) for AUD—itself an independent predictor of AUD—report greater stimulating versus sedating effects of alcohol (Morean & Corbin, 2010). FH+ also moderates sensitivity to stimulating (rewarding) effects of other NMDAR antagonists, namely, ketamine (e.g., Petrakis et al., 2004; Yoon et al., 2016) and N_2O (Walsh et al., 2017). Specifically, participants with FH+ (but not those with a negative family history [FH–]) showed high stimulant-to-sedative ratios during infusion of moderate-dose ketamine or inhalation of moderate-concentration (50%) N_2O. This common pattern of subjective effects produced by NMDAR antagonists is hypothesized to reflect a heritable marker of dysregulated NMDA receptor functioning (Petrakis et al., 2004) and an endophenotype for AUD (Walsh et al., 2017). Excessive alcohol use is another potential moderator of sensitivity to the motivational and rewarding effects of NMDAR antagonists. For example, heavy drinkers selected N_2O more frequently in a drug choice procedure, and liked inhalation of N_2O more than inhalation of air relative to light drinkers (Zacny et al., 2008).

The above findings suggest the existence of a network of interacting neuropharmacological determinants of subjective responses to NMDAR antagonists and of AUD risk. Also potentially relevant to these outcomes are the influences of a number of stable traits and psychiatric risk factors, which may also reflect neurobiological maladaptations of the glutamatergic (Chitty et al., 2013) and interacting neurotransmitter systems (Schuckit et al., 2003; Levey et al., 2014). For example, based on their role in determining sensitivity to the subjective effects of alcohol (Yip et al., 2012), hypomanic symptoms are also potential moderators of N_2O's subjective effects. Given the association between AUD and bipolar disorder, and between hypomania and hypersensitivity to reward (O'Sullivan et al., 2011), an intuitive hypothesis is that a bipolar phenotype would be associated with enhanced sensitivity to the subjective effects of alcohol and other psychoactive drugs. However, in an acute challenge study with 0.8 g/kg alcohol, Yip et al. (2012) reported reduced general sensitivity to alcohol in those with a history of hypomania, a pattern that was also found following acute amphetamine administration in a different study (Schepers et al., 2019). As such, while some risk factors for AUD and substance use disorder (SUD; e.g., FH+) appear to be associated with enhanced subjective responses to certain psychoactive drugs, others (e.g., bipolar phenotype) are associated with reduced responses.

Other traits or background variables that are related to bipolarity by virtue of co-occurrence (impulsivity; Najt et al., 2007) or comorbidity (depression; Kessler et al., 1997) are also of interest as moderators of NMDAR antagonist sensitivity. Impulsivity for example, is associated with greater rewarding (stimulating) and dampened aversive (sedating) effects of high-dose intravenous alcohol in both social drinkers (Leeman et al., 2014) and alcohol-dependent individuals (Westman et al., 2017). Impulsivity may also moderate the subjective effects of NMDAR antagonists other than alcohol (Krishnan-Sarin et al., 2015). Establishing a similar pattern with N_2O would provide support for the notion that impulsivity is a common predisposition for high-risk subjective responses to NMDAR antagonists.

Apart from impulsivity, the role of depression (or depressed mood) in moderating the subjective effects of NMDAR antagonists is of particular clinical interest, especially because

NMDAR antagonism is an important therapeutic strategy in the treatment of major depressive disorder (Amidfar et al., 2019). However, depression is associated with heightened risk of SUDs (Baskin-Sommers & Foti, 2015) and AUD (Boden & Fergusson, 2011), and ketamine use disorder is therefore a potential complication of treating depression with ketamine (see Sanacora et al., 2017). Similar concerns may become relevant for N_2O if future clinical trials support its use in treating depression.

To date, laboratory studies examining the link between depression and responsivity to psychoactive drugs have tended to focus on dysfunctional reward processing and drug taking behavior in habitual drug users (e.g., Audrain-McGovern et al., 2014). With the exception of studies that have probed dysfunctional reward processing in depression using the subjective response to stimulants as an assay (e.g., Tremblay et al., 2002), few studies have examined the subjective response to other drugs in relation to depressed mood (see Pang et al., 2017 for an exception).

Furthering our understanding of the determinants of sensitivity to the subjective reinforcing/motivational effects of NMDAR antagonists may be informative in identifying risk factors for problem use of N_2O- and ketamine-like drugs, especially as novel recreational psychoactive compounds emerge that mimic the effects of ketamine and N_2O (Schifano et al., 2019). An improved understanding of these factors is also of potential value in the development of novel pharmaceuticals or repurposing of existing NMDAR antagonists. In particular, uncovering the phenotypic profiles of likely treatment responders (for example, to N_2O's antidepressant effects, e.g., Niciu et al., 2018; Mathai et al., 2020) or, alternatively identifying patients at greater risk of dysphoric reactions or potential iatrogenic harm in medical and psychiatric settings may contribute to increased understanding of effective uses of NMDAR antagonists in precision medicine.

Therefore, in the current study, we extended extensive previous research on the subjective effects of N_2O (e.g., Yajnik et al., 1994, 1996; Zacny et al., 1996a & b; Zacny et al., 2008; Zacny & Jun, 2010), by investigating the moderation of these effects by stable psychological traits or symptoms of psychopathology. We specifically tested the a priori hypothesis that past hypomania would be associated with a general reduction in sensitivity to N_2O, as has been found with alcohol (Yip et al., 2012). In addition, although no a priori (i.e., preregistered) hypotheses were proposed for impulsivity and depression, their roles as general SUD/AUD risk factors (see above) would suggest that examining the moderation by these factors of the rewarding effects of N_2O would be a valuable exploratory step in further delineating relevant determinants of NMDAR antagonist sensitivity. A separate aim of the study was to test the hypothesis that, because of properties shared with other NMDAR antagonist like ketamine, N_2O's subjective effects will resemble those of alcohol. Across a series of outcomes relevant to alcohol's effects, we therefore compared the size of our effects obtained with 50% N_2O to those reported in previous studies with moderate-dose ketamine.

Methods

The study was approved by the University College London Research Ethics Committee and conducted in accordance with the Declaration of Helsinki. The study was preregistered on ISRCTN (trial register number: 16259778).

Participants

Healthy volunteers (age 18–40 years; n = 80) were recruited from University College London and surrounding areas by using online advertisements. One aim of the current study was to test for moderation by bipolarity. As such, and following Yip and colleagues (2012), a proportion of participants (n = 30) were recruited based on high scores (≥7) on the Mood Disorders Questionnaire and were randomly assigned evenly to medical air (placebo) or N_2O drug conditions. All participants provided full written informed consent and were compensated for their participation. Further details on participants, recruitment, and statistical power are provided in the Supplementary methods.

Procedure

After providing baseline demographic information and completing questionnaires on stable psychological characteristics (e.g., mood, impulsivity, bipolarity; see below) participants completed baseline (preinhalation) state measures and provided a blood pressure (BP) reading. This was followed by gas inhalation and equilibration for 5 minutes, after which BP assessment was repeated. The peri-inhalation state measures were repeated within the 30-minute inhalation period. After a "recovery" period (15 minutes), participants completed state measure for a third time (postinhalation) followed by a final BP reading. After all assessments were complete, participants provided a treatment guess and completed an assessment of side effects. All participants were required to remain in the laboratory for at least 30 minutes after inhalation ended.

Due to practical constraints, the primary researcher also supervised drug administration such that drug condition could only be concealed from the researcher until just before the testing session. However, to obviate concerns about the lack of researcher blinding (and minimize session variability), researcher-participant interactions during the experimental session were limited and were largely scripted. Questionnaires were administered, and responses were recorded on a computer-based survey tool (Qualtrics). Instructions were provided onscreen and progression through the survey was controlled by the participant. Once entered, responses were "locked" until transferred to a final spreadsheet, a task performed by a researcher who was not aware of treatment allocation and was not involved in data collection. The data analysts were not involved in data collection and had no prior access to the data.

Drugs

Participants inhaled either 50% N_2O premixed with 50% oxygen (Entonox) or placebo-medical air (BOC) delivered via identical mouthpieces and controlled by a demand valve. This is the standard delivery mode for auto-analgesia in UK hospital settings. Inhalation lasted 30 minutes and acute tolerance was not expected to occur within this period (Yajnik et al., 1996). Participants were instructed to breathe at their normal pace and depth through the mouthpiece and were informed that they could stop inhalation at any time if they experienced any discomfort or distress. Cylinders were fully concealed from participants, although 89% of participants correctly guessed their drug allocation at the end of the experiment.

Measures

Baseline Measures

Baseline questionnaires assessing participant characteristics were completed prior to drug administration. The Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 2001) was used to ascertain patterns of hazardous consumption. Historical subjective responses to early alcohol use (i.e., the first few drinking occasions in the participant's life) were assessed retrospectively using the Subjective Response to Ethanol questionnaire (Schuckit, 1984; see Supplementary Methods). Previous week drinking was determined using the timeline follow-back diary method (Sobell & Sobell, 1992). The Mood Disorders Questionnaire (MDQ) was included for assessment of bipolar traits (Hirschfeld et al., 2000) (Hirschfeld et al., 2000) a primary, a priori moderator in our statistical analyses. The 21-item Depression Anxiety and Stress Scale (DASS-21; Lovibond & Lovibond, 1995) was used as a measure of common psychological disorder symptoms over the previous week (raw scores were doubled, per standard scoring instructions) and the Barratt Impulsiveness Scale-11 Brief (BIS-11; 8 items) was used to assess trait impulsivity (Steinberg et al., 2013). Other trait and state measures (e.g., psychosis proneness and dissociation) were included to address a separate set of questions and are not extensively reported here.

State Measures

Subjective effects of N_2O were assessed with the Drug Effects Questionnaire (DEQ) using recommended instructions (Morean et al., 2013). The DEQ was completed pre-, peri-, and postinhalation and consisted of the following items: "Do you feel a drug effect right now?," "Are you high right now?," "Do you dislike any of the effects you are feeling right now?," "Do you like any of the effects you are feeling right now?" The want [more] item ("Would you like more of the drug you took, right now?") was only assessed peri- and postinhalation. To allow for predrug assessment of the other DEQ items, participants were instructed as follows: "Even though you haven't taken any drug or inhaled any gas so far, please answer the questions in relation to how you feel right now." This instruction was omitted from the peri- and postinhalation assessments. Responses were made on a 0 ("not at all") to 100 ("extremely") visual analogue scale.

Subjective evaluation of similarity to alcohol, and if relevant, to cannabis and cocaine, was assessed using the following questions: "How similar to [alcohol/cannabis/cocaine] intoxication does your current mental and physical state feel?" (0 = not at all similar; 100 = identical, e.g., Krystal et al., 1998). While alcohol-like ratings were obtained from all participants, the results of similarity to cannabis or cocaine were only from those with any lifetime experience of using cannabis (medical air, n = 24; N_2O, n = 31; chi-square (1) = 2.851, P = 0.091) or cocaine (medical air, n = 12; N_2O, n = 10; chi-square (1) = 0.251; P = 0.617). Levels of alcohol-like intoxication were assessed by asking participants "How many alcoholic drinks does it feel like you have consumed?" on a 12-point scale, truncated at the top end (0, 1, 2, …10, >10 drinks). The brief (6-item) biphasic alcohol effects scale (BAES) was used to assess stimulant and sedative alcohol-like effects of N_2O, with the following instructions "Please rate the extent to which these words describe your feelings at the present time" (0 = Not at all; 10 = Extremely; Rueger et al., 2009). Semantically, the items on the sedation subscale correspond to dysphoric effects ("sluggish," "slow thoughts," "sedated"), whereas the stimulation items corresponded more closely to euphoria-like states ("energized," "up," "excited"). Because the BAES has only been thoroughly validated with alcohol, effects produced by other drugs using this scale (including N_2O and ketamine) should properly be referred to as "alcohol-like stimulation" and "alcohol-like sedation." This meaning is implied in our use of the terms "stimulation" and "sedation" in the results that follow. Effects on state dissociation and psychotomimesis are also briefly reported (assessed respectively using the Clinician Administered Dissociative Symptoms Scale; Bremner et al., 1998, and the Psychotomimetic States Inventory; Mason et al., 2008), but are not the focus of the current paper.

Finally, participants indicated (retrospectively) whether they experienced any common side effects of N_2O, including the following: headache, nausea, sweating, sleepiness, shivering, and dizziness. Participants were also able to add other comments about their experience in a free text box.

Statistical Analysis

Due to the skewed nature of all relevant outcomes, analyses were performed using robust 2- and 3-way repeated measures ANOVA (Wilcox, 2011), with time (pre-, peri-, postinhalation) as the within-subjects factor and drug as the main between-subjects factor. Based on purposive recruitment, an additional categorical between-subjects factor, phenotype, was included in 3-way robust ANOVAs to test for moderation by bipolarity, which was the a priori moderator of interest. Other than phenotype, additional moderators in exploratory analyses were depression and impulsivity. Because these variables were continuous, their influence was assessed using regression-based moderation analyses (Hayes, 2017).

Two-tailed tests are reported throughout. False discovery rate–adjusted P values (Benjamini-Hochberg adjustment; $P_{(BH\ adj)}$; Benjamini & Hochberg, 1995) are presented for the family of depression × drug and impulsivity × drug interactions on liking and wanting. Descriptive statistics for outcomes are presented in tables as trimmed means with SDs unless otherwise stated. Further details on statistical analyses are presented in the Supplementary Methods.

Results

Participant Characteristics

Per-group demographics, mental health, and trait variables are presented in Table 1. These data indicate that participants were, on average, psychologically healthy young adults, with high levels of education and low levels of problematic alcohol use.

Dissociation and Psychotomimesis

The expected pattern of dissociation was found for N_2O, reflected in a time × drug interaction [$F(2, 32.6) = 15.72$, $P < .001$; See Table 2]. Similarly, N_2O produced robust psychotomimesis [$F(2,42.1) = 8.641$, $P < .001$ Table 2]. As the focus of the current paper is on rewarding and alcohol-like effects of N_2O, these effects should be viewed as positive controls for N_2O and will not be discussed further, except to comment that they were consistent with predictions.

Stimulant and Sedative Effects Of N_2O

A significant time × drug interaction was found for BAES stimulation [$F(2, 40.5) = 4.629$, $P = .015$]. The peri-inhalation N_2O versus placebo (medical air) difference on BAES stimulation indicated a medium effect size (Hedges' g). BAES sedation showed

Table 1. Sample Demographic and Baseline Mental Health Characteristics

	Medical air (n = 40)	Nitrous oxide (n = 40)
Sex (male:female)	19:21	17:23
Ethnicity (Caucasian:other)	19:21	23:17
Previous N_2O (Y:N)	10:30	9:31
Age	26.09 (4.92)	23.88 (3.66)
Education (years)	16.75 (2.46)	16.53 (2.23)
DASS-21 (Depression)	5.95 (6.61)	4.95 (4.77)
DASS-21 (Anxiety)	4.80 (5.56)	4.85 (4.59)
MDQ (bipolarity)	4.10 (3.69)	3.90 (3.81)
BIS-11-brief (impulsivity)	18.43 (2.24)	19.93 (2.16)
AUDIT (alcohol use)	5.13 (5.17)	3.58 (2.38)
Number of drinks (previous week)	4.44 (6.07)	5.59 (8.00)

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BIS-11, Barratt Impulsiveness Scale-11; DASS, Clinician Administered Dissociative Symptoms Scale; MDQ, Mood Disorders Questionnaire; PSI, Psychotomimetic States Inventory.
Values are counts (ethnicity, sex) or means (SDs). Age is based on n = 64 (because of a documentation error, age was not recorded for n = 6 medical air and n = 8 N_2O participants).

a similar 2-way interaction [F(2, 44.4) = 7.54, *P* = .002] and the periinhalation N_2O versus placebo effect size was, by convention, large. Despite overlapping 95% CIs for the estimated effect sizes, in absolute terms, the N_2O versus medical air effect sizes on both BAES subscales were considerably smaller than those previously reported with ketamine (Table 3).

Although both stimulation and sedation increased during N_2O inhalation, these effects appeared separable. In particular, participants who indicated high levels of stimulation during N_2O inhalation reported low levels of sedation [and vice versa; r(38) = -0.538, *P* < .001; Supplementary Figure 1].

Similarity of N_2O to Alcohol, Cannabis, and Cocaine

Time × drug interactions were significant for N_2O's alcohol-like effects (ratings of "similarity-to-alcohol"; F(2, 29.5) = 20.33, *P* < .001) and cannabis-like effects [similarity-to-cannabis; F(2, 23.1) = 26.20, *P* < .001]. The effect size for N_2O's alcohol-like effects was large and very similar to that previously reported for moderate-dose ketamine (Dickerson et al., 2010). However, N_2O's cannabis-like effects were considerably larger than previously found with ketamine, and the effect size CIs for N_2O and ketamine did not overlap (Table 3). In contrast, N_2O's cocaine-like effects were small, and the time × drug interaction was nonsignificant [F(2, 11.8) = 3.19, *P* = .078; we are not aware of a study of moderate-dose ketamine in healthy volunteers that has examined its cocaine-like subjective effects for comparison].

The level of alcohol-like intoxication (number of alcoholic drinks equivalence) produced during inhalation also showed a drug × time interaction [F(2, 31.0) = 23.935, *P* < .001]. During N_2O inhalation, participants indicated a level of intoxication equivalent to 3.44 alcoholic drinks, reflecting a large effect size, which was not dissimilar to the effects observed with moderate-dose ketamine (Table 3).

General Drug Effects of N_2O

Based on responses to the Drug Effects Questionnaire (DEQ) liking and disliking scales, participants in the N_2O group varied in the extent to which they found drug inhalation reinforcing rather than aversive. The majority (n = 26/40) indicated greater liking than disliking of N_2O (liking > disliking by ≥10 points), with the remainder finding N_2O either predominantly aversive (disliking > liking by ≥10 points: n = 6/40), or were indifferent (liking-disliking difference ≤ 9 points: n = 8). In contrast, participants in the placebo-medical air group were modally indifferent (n = 19/40), with only 14/40 indicating liking > disliking [drug effect:chi-square(2) = 8.152, *P* = .017].

Table 2. Dissociation (Clinician Administered Dissociative Symptoms Scale) and Psychosis-Like Effects (Psychotomimetic States Inventory).

CADSS	Mean pre- (SD)	Mean peri- (SD)	Mean post- (SD)
Medical air	2.25 (4.09)	2.47 (4.31)	1.59 (3.52)
N_2O	1.25 (3.48)	14.19 (15.34)	8.13 (10.67)
PSI			
Medical air	16.44 (7.39)	16.97 (6.94)	14.56 (5.15)
N_2O	12.34 (3.21)	22.34 (9.53)	19.16 (7.14)

Abbreviations: CADSS, Clinician Administered Dissociative Symptoms Scale; PSI, Psychotomimetic States Inventory.
Values are trimmed means (SD).

As can be seen in Table 4, there were pronounced time effects in the N_2O group, reflected in significant 3 × 2 (time × drug) interactions on the DEQ "feel" [F(2, 33.3) = 56.331, *P* < .001], "high" [F(2, 29.8) = 32.77, *P* < .001], and "like" [F(2, 44.8) = 9.12, *P* < .001] items. For the "want [more]" item, there was no time (peri, post-) by drug interaction [F(1, 35.9) = 0.593, *P* > .1], although the main effect of drug was significant [F(1,35.6) = 22.32, *P* < .001], suggesting a sustained effect of N_2O on wanting between peri- and postinhalation. For the other DEQ items, there also seemed to be some continued effects at 15 minutes postinhalation (i.e., scores had not returned to baseline), as was also the case for the outcomes reported in Table 3. The effect sizes for liking and wanting in particular appeared to be very similar to those reported previously with moderate-dose ketamine (Morgan et al., 2004).

Moderators of Sensitivity to N_2O's Rewarding Effects

Moderation by phenotype (high versus low scorers on the MDQ) of general drug effects (on DEQ items) were prespecified. However, we found no evidence of a phenotype effect (3-way time × drug × phenotype interactions) on any of these items assessed at the peri-inhalation time-point (all F values ≤ 1.30, *P* values > .1).

Alternatively, as shown in Figure 1, peri-inhalation motivational (wanting more) effects of N_2O were dependent on levels of depression (drug × depression interaction β = 3.01, SE = 1.00, t = 3.01, $P_{(BH\ adj)}$ = .016). Low (–1 SD) levels of depression were associated with greater wanting in response to N_2O relative to medical air (conditional effect β = 37.52, SE = 7.58, t = 4.95, *P* < .001), as were mean levels of depression (β = 21.12, SE = 5.43, t = 3.89, *P* < .001). Elevated (+1 SD) depressive symptoms however, were associated with lower levels of wanting more, which were equivalent in the N_2O and medical air groups (β = 3.80, SE = 8.02, t = 0.47, *P* > .1).

In addition, moderation of drug effects by Impulsivity was indicated by a drug × impulsivity interaction predicting periinhalation liking (β = 6.89, SE = 2.88, t = 2.39, $P_{(BH\ adj)}$ = .0386; Figure 2). At low (–1 SD) levels of impulsivity, conditional effects indicated a relatively small (and nonsignificant) difference in liking between N_2O and medical air (β = 15.05, SE = 9.45, t = 1.59, *P* > .1). However, compared to low impulsivity, the difference between drug groups was twice as large at the mean of impulsivity

Table 3. Stimulating and Sedating Effects and Similarity of N_2O to Alcohol, Cannabis, and Cocaine

				Effect size (95% CI)	
	Mean Pre (SD)	Mean Peri (SD)	Mean Post (SD)	N2O (current study)	Ketamine (Dickerson et al., 2010)
BAES Stimulation (0–30)					
Medical air	13.63 (4.65)	9.66 (4.88)	10.03 (5.58)		
N_2O	13.78 (4.65)	14.94 (10.66)	11.47 (7.45)	0.63 (0.13, 1.14)	1.19 (0.63, 1.77)
BAES Sedation (0–30)					
Medical air	5.50 (4.07)	5.75 (5.63)	5.41 (5.05)		
N_2O	4.22 (4.57)	11.09 (7.14)	10.47 (6.27)	0.82 (0.32, 1.34)	1.68 (1.10, 2.31)
# Drinks equivalence					
Medical air	0.00(0.00)	0.22 (0.42)	0.06 (0.25)		
N_2O	0.00(0.00)	3.44 (2.05)	1.41 (1.24)	2.15 (1.55, 2.79)	1.38 (0.81, 1.98)
Similar to Alcohol (0–100)					
Medical air	0.16 (0.37)	2.88 (5.81)	0.53 (1.68)		
N_2O	0.19 (0.47)	40.53 (26.58)	18.91 (16.95)	1.93 (1.35, 2.55)	1.82 (1.21, 2.47)
Similar to cannabis (0–100)*					
Medical air	0.90 (2.49)	5.35 (9.01)	2.60 (7.32)		
N_2O	0.00 (0.00)	47.20 (20.24)	23.12 (22.51)	2.64 (1.99, 3.34)	1.19 (0.64, 1.78)
Similar to cocaine (0–100)**					
Medical air	0.00 (0.00)	0.50 (1.08)	0.60 (1.90)		
N_2O	0.63 (1.77)	9.00 (11.03)	0.63 (1.77)	1.07 (0.56, 1.61)	NR

Abbreviations: BAES, Biphasic Alcohol Effects Scale.
Pre-, peri-, and postsubjective ratings for alcohol-, cannabis, and cocaine-like effects. Effect sizes are Hedges' g based on peri-inhalation (trimmed) means and SDs for medical air and N_2O. For comparison, the right-most column displays effect sizes for the same outcomes (where available) for ketamine (0.23 mg/kg bolus + 58 µg/kg/min) versus medical air at 15 minutes postbolus in Dickerson et al (2010). * Based on n = 24 in medical air; n = 31 in N_2O group
** Based on n = 12 in medical air; n = 10 in N_2O group
NR = Outcome not reported.

Table 4. Drug Effect Questionnaire Responses for N_2O and Ketamine

				Effect size (95% CI)	
				N2O	Ketamine
	Mean Pre (SD)	Mean Peri (SD)	Mean Post (SD)	(current study)	(Morgan et al., 2004)
Like					
Medical air	18.34 (26.03)	14.72 (18.69)	6.72 (14.07)		
N_2O	15.34 (24.64)	50.06 (28.29)	27.44 (24.70)	1.46 (0.92, 2.02)	1.44 (0.73, 2.21)
Want more					
Medical air	-	4.03 (7.51)	0.69 (1.86)		
N_2O	-	25.03 (23.34)	17.44 (17.87)	1.20 (0.67, 1.74)	1.06 (0.37, 1.78)
Feel					
Medical air	0.09 (0.30)	3.47 (4.68)	1.44 (3.67)		
N_2O	0.00 (0.00)	63.38 (23.21)	20.84 (12.38)	3.53 (2.78, 4.37)	2.23 (1.42, 3.11)
High					
Medical air	0.09 (0.30)	1.16 (2.24)	1.13 (2.66)		
N_2O	0.00 (0.00)	53.31 (27.51)	14.16 (14.03)	2.65 (2.00, 3.36)	NR
Dislike					
Medical air	0.97 (2.61)	5.53 (9.83)	0.84 (2.53)		
N_2O	0.06 (0.25)	18.53 (15.90)	12.31 (16.95)	0.97 (0.46, 1.50)	NR

Abbreviations: Med, medical; NR, outcome not reported.
Pre, peri and post subjective ratings for "liking," "wanting more," "feeling [the effect]," "[feeling] high," "disliking," for medical air and N_2O. Effect sizes are Hedges' *g* based on peri-inhalation (trimmed) means (SDs) for medical air and N_2O. For comparison, the right-hand column displays effect sizes for the same outcomes (where available) for ketamine (0.4 mg/kg) versus medical air, obtained 10 minutes after infusion began based on data extracted from graphs presented in Morgan et al (2004).

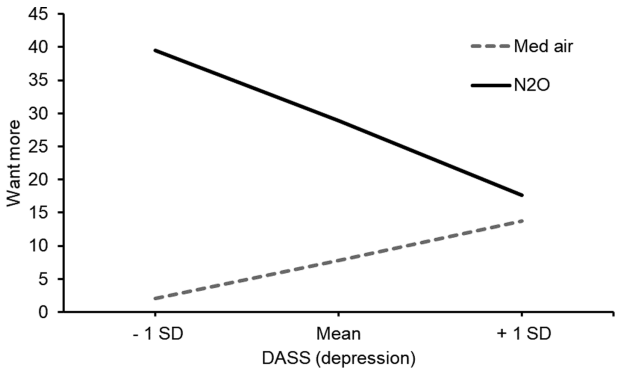

Figure 1: Effects of different levels of depression (mean ± 1 SD) on periinhalation "wanting [more]" for N_2O (sold black line) and medical air (dashed line).

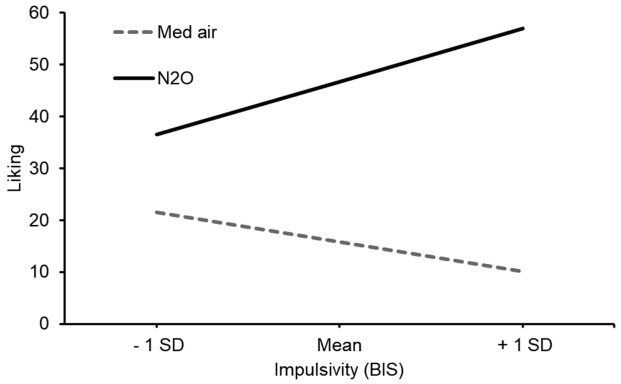

Figure 2: Moderation of drug effects (periinhalation) on liking by levels of impulsivity (BIS-11-brief: mean ± 1 SD). BIS-11, Barratt Impulsiveness Scale-11.

(β = 31.00, SE = 6.63, t = 4.68, P < .001), and 3 times as large at high impulsivity levels (β = 46.95, SE = 9.35, t = 5.02, P < .001).

The drug × depression interaction on liking was not significant (t = 1.79, $P_{(BH\ adj)}$ = .101); similarly, the drug × impulsivity interaction on wanting was not significant (t = 1.63, $P_{(BH\ adj)}$ = .108). Despite the lack of significance, it should be noted that descriptively, the pattern of effects on liking and wanting for the 2 drug conditions across levels of depression and impulsivity, respectively, resembled those shown in Figures 1 and 2 respectively.

Side Effects

No adverse blood pressure responses were recorded, and on average, neither group showed ≥2.5 mm Hg pre- to periinhalation change in systolic or diastolic BP (F values < 2.5, P values ≤ .087). The frequencies of most side effects were not substantially different between groups (P values ≥ .1 Fisher exact test): headache (medical air: n = 3; N_2O: n = 5, P = .712), nausea (medical air: n = 4; N_2O: n = 6, P = .737), sweating (medical air: n = 1; N_2O: n = 6, P = .102), or sleepiness (medical air: 13; N_2O: n = 21; P = .113). There did, however, appear to be a higher frequency of shivering in the N_2O group, although this was still relatively uncommon (n = 5 versus n = 0 in the medical air group; P = .055). However, frequency of dizziness clearly differentiated the groups with n = 24 participants in the N_2O group and only n = 9 in the medical air group experiencing this effect (P = .001). No other negative side effects were noted in these participants. In contrast to popular belief, laughter/urge to laugh but was mentioned by only 2 participants, 1 of whom was in the medical air group (verbatim: "uncontrollable laughter at the beginning"). The other participant (N_2O group) noted "[I] felt like I wanted to laugh."

Discussion

In the current study we examined the alcohol- and ketamine-like subjective effects of the NMDAR antagonist N_2O, along with moderators of these effects. An understanding of the conditions that determine sensitivity to such effects may provide insights into susceptibility to the therapeutic effects, as well as vulnerability to excessive consumption of N_2O and related drugs in recreational users. Because ketamine is an unwieldy experimental tool (it is a scheduled drug, requiring intravenous infusion which can only be performed in medical facilities by specialist medical personnel), it is of interest to determine whether N_2O might substitute for ketamine in human psychopharmacological studies, especially those probing the role of NMDARs in maladaptive reward processes (e.g., Yoon et al., 2016; Walsh et al., 2017). We therefore also compared a range of our observations against previously published findings with ketamine.

We found broad qualitative and quantitative (effect size) parallels between our findings with N_2O and effects previously reported with moderate-dose ketamine on measures of alcohol-like intoxication and general drug effects. We also found considerable individual variation in the hedonic response to N_2O, with 65% of participants liking its effects and only 15% disliking them (the remainder were indifferent; see Dohrn et al., 1992 for similar findings). Contrary to our hypothesis regarding a moderating role for bipolar phenotype, which we predicted would be associated with reduced sensitivity to N_2O—as previously observed following an acute dose of alcohol—we found no evidence of moderation by phenotype. The absence of such an effect might suggest that the previously reported modulation of alcohol's effects by bipolar phenotype (Yip et al., 2012) was dependent on neurotransmitter/neuromodulatory systems that are not shared by N_2O and alcohol (i.e., the effect was not NMDAR dependent). Alternatively, our assessment of bipolar phenotype was based only on a measure of past hypomanic episodes (using the MDQ); we were therefore unable to determine the contribution of current levels of hypomania. It is possible, for example, that while average MDQ scores were similar in the current study (8.23 ± 0.26) and Yip et al (2012; 9.45 ± 0.37), unassessed state hypomania differed between the studies and might have played a more determinative role than trait hypomania in the subjective drug response.

In contrast to the lack of moderation by bipolar phenotype, post hoc analysis showed that ratings of liking of N_2O were positively correlated with impulsivity, a finding that complements a larger body of research on the relation between impulsivity and problem drug use (Verdejo-García et al., 2008). Because our participants consisted of low-risk drinkers (i.e., possessing low AUDIT scores and low FH+ prevalence; see Supplementary methods), sustained excessive alcohol exposure—which can increase glutamatergic function and hence alter the systemic response to NMDAR antagonists—is unlikely to be an important explanatory factor in the positive association between impulsivity and N_2O-liking.

An association between impulsivity and "high-risk" patterns of subjective responding have also been found in previous studies of acute alcohol intoxication in participants with

a light-drinking profile similar to that of the participants in the current study (Leeman et al., 2014; Berey et al., 2017, 2019). In particular, impulsivity predicted increased sensitivity to stimulating—but not sedating—alcohol effects, a pattern which is itself longitudinally predictive of AUD (King et al., 2014). Given our related findings on N_2O liking, high levels of impulsivity may identify individuals who are simultaneously at risk of problem use of a variety of NMDAR antagonists. It is worth noting that while additional exploratory analysis revealed that the impulsivity × drug effect was not significant for stimulation, the pattern of effects was broadly similar to that shown with liking (see Supplementary Figure 2), and descriptively mirrored effects found in alcohol clamp experiments (e.g., Leeman et al., 2014).

In addition to the association between hedonic effects and impulsivity, we found that depression × drug predicted wanting more. Unlike the positive association between impulsivity and liking, higher depressive symptoms in the N_2O group were associated with lower wanting (a smaller difference between medical air and N_2O at higher levels of depression). Because N_2O is ostensibly a rapidly acting antidepressant (Nagele et al., 2015), and depression is often comorbid with (and precedes the onset of) AUD and SUDs (Swendsen et al., 2010), there may be a potential for iatrogenic harm of N_2O treatment in depression (i.e., increased risk of N_2O misuse). However, to the extent that an initial rewarding response to psychoactive drugs is associated with future risk of maladaptive use of that drug (de Wit & Phillips, 2012), our findings do not support this concern in relation to N_2O in people with high levels of depressive symptoms. It would be interesting to determine whether a similar relationship between depression and drug wanting exists for ketamine. Indeed, concerns about misuse were the basis for tamper proofing the new intranasal formulation of ketamine for depression.

The choice of subjective outcomes in this study was guided by their extensive use in previously published reports of ketamine's subjective effects. We compared our results with those of 2 studies in particular, which, despite using different infusion protocols, likely achieved similar plasma ketamine levels in the early phases of treatment (0.23 mg/kg bolus + 58 μg/kg/min assessed at 15 minutes in Dickerson et al., 2010 and 0.4 mg/kg assessed at 10 minutes in Morgan et al., 2004). Broadly speaking, both ketamine and N_2O produced large to very large effects on these measures. However, BAES sedation and stimulation effects reported by Dickerson et al (2010) with ketamine seemed considerably large than our N_2O-induced effects. Whether this reflects a reliable difference between the 2 drugs is unclear (e.g., the CIs around the respective effect sizes were overlapping), although a 2-fold difference in magnitude is noteworthy. This divergence might reflect the use of the brief (6-item) BAES in our study versus the full (14-item) version in Dickerson et al (2010). For example, the additional items in the 14-item version of the BAES might be more sensitive to NMDAR antagonist effects. Alternatively, because the measure of equivalent alcoholic drinks was administered first in the battery of assessments in Dickerson et al (2010), whereas BAES was one of the last (I. Petrakis, personal communication), it is possible that plasma ketamine levels may have been somewhat higher when the BAES was assessed, potentially giving rise to a relatively larger effect on this measure. Despite this divergence in effect sizes between ketamine and N_2O on the BAES, the overall pattern of subjective effects seems to suggest broadly similar responses between the 2 drugs on the measures examined here.

A number of limitations of the current study must be acknowledged. First, although attempts were made to ensure participant blinding, treatment concealment did not survive the gas inhalation period, during which nearly all participants correctly guessed their assigned condition. As such, the size and direction (i.e., liking versus disliking) of N_2O effects may have been influenced by prior beliefs about N_2O's effects (e.g., Kirk et al., 1998). On the other hand, we are not aware of plausible mechanisms through which such beliefs could account for the different (opposite) patterns of moderation seen with depression and impulsivity.

While steps were taken to limit experimenter effect, experimenters were not blinded during inhalation. In any case, double blinding is difficult to achieve when there are only 2 conditions and the active drug produces highly discriminable effects relative to placebo. To improve concealment, future studies might consider using an additional minimal dose condition (e.g., 10% N_2O).

An additional limitation is that the moderating effects of impulsivity and depression were not predicted a priori and as such these findings should be considered provisional, pending replication. It would have been interesting to examine moderation by AUD risk. In a previous study we demonstrated that the stimulation-to-sedation ratio in response to N_2O was determined by family history of problem alcohol use (Walsh et al., 2017). We could not replicate that finding here, or extend it by examining, for example, the statistical interaction between impulsivity, drug, and AUD risk status because the recruited sample had an unusually low level of AUD risk characteristics. Future studies should aim to delineate such interactions in relation to N_2O's subjective effects, as has been examined in studies of the effects of acute alcohol administration in participants with varying levels of impulsivity and AUD risk (e.g., Leeman et al., 2014).

Finally, we should reiterate that our participants were healthy volunteers. This can be viewed as a strength and a limitation. Specifically, because our participants were not receiving any form of treatment, our findings cannot be attributed to concurrent effects of psychiatric medication. On the other hand, our findings on the link between depression and the rewarding effects of N_2O in particular should not yet be assumed to extend to patients with major depressive disorder. Replication of our results beyond healthy individuals is essential before the clinical implications of these findings can be properly understood.

To conclude, we found that, unlike the subjective effects of alcohol, those of N_2O did not depend on a bipolar phenotype. Instead, exploratory analysis showed that N_2O's rewarding effects depended on impulsivity and depression, which may respectively predispose or protect against N_2O's abuse potential. Future studies could examine if these moderators are relevant for other NMDAR antagonists, including ketamine, as well as novel ketamine-like therapeutic and recreational drugs. We also found a number of qualitative and quantitative similarities between N_2O and ketamine. Although firm conclusions about the extent of these similarities would ideally be tested in a within-subject crossover study, with varying concentrations of each drug, the current study at least provisionally suggests that N_2O as an experimental tool might be a convenient alternative to ketamine for probing reward-related NMDAR function and dysfunction in humans.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Statement of Interest

None

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