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KETAMINE AS A POSSIBLE MODERATOR OF HYPNOTIZABILITY: A FEASIBILITY STUDY

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Abstract

This pilot study explored the feasibility of using ketamine to increase hypnotizability scores. Ketamine, classified as a dissociative hallucinogen, is used clinically as an anesthetic in high doses and as a treatment for chronic pain and depression in lower doses. Low dose ketamine can contribute to dissociation and heightened perceptions and feelings of detachment, arguably hypnotic-like states. The authors predicted that a low dose of ketamine in healthy volunteers who scored in the low hypnotizable range on the Stanford Clinical Hypnotizability Scale would (1) report an increase in subjective ratings of dissociation and (2) demonstrate an increase in hypnotizability. The findings were in the predicted direction, warranting further investigation into the use of this agent to increase hypnotizability.

Abstract

Diese Pilotstudie erforschte die Machbarkeit der Verwendung von Ketamin, um Hypnotisierbarkeit meßbar zu erhöhen. Ketamin, das als dissoziativ wirkendes Halluzinogen klassifiziert wird, wird in der Klinik in hohen Dosen als Anästhetikum und in niedrigeren Dosen in der Behandlung chronischer Schmerzen und Depressionen angewandt. Niedrig dosiertes Ketamin kann zu Dissoziationen und erweiterter Wahrnehmung und einem Gefühl der Losgelöstheit, also tranceähnlichen Zuständen, beitragen. Die Autoren sagten voraus, daß niedrig dosiertes Ketamin, bei gesunden Probanden, die laut Stanford Clinical Hypnotizability Scale im niedrig-hypnotisierbaren Bereich anzusiedeln waren, angewandt, erstens (1) von einer Zunahme der subjektiven Bewertungen von Dissoziation und zweitens (2) eine Zunahme der Hypnotisierbarkeit zeigen würden. Die Forschungsergebnisse lagen in der vorausgesagten Weise, sodaß weitere Untersuchungen in Bezug auf die Anwendung dieser Substanz zur Anhebung der Hypnotisierbarkeit gerechtfertigt sind.

Résumé:

Les auteurs de cette étude pilote ont étudié la faisabilité de l'utilisation de la kétamine pour augmenter les scores de sensibilité à l'hypnose. La kétamine, classée comme hallucinogène dissociatif, est utilisée cliniquement à fortes doses comme anesthésique, et à faible dose dans le traitement de la douleur chronique et de la dépression. De faibles doses de kétamine peuvent favoriser la dissociation ainsi qu'une perception plus nette et un sentiment de détachement, soit

des états qui pourraient ressembler à l'état hypnotique. Les auteurs ont prédit qu'une faible dose de kétamine chez des volontaires en bonne santé, classés comme peu sensibles à l'hypnose selon le questionnaire de susceptibilité hypnotique de Stanford, 1) augmenterait les taux subjectifs de dissociation, et 2) augmenterait leur sensibilité à l'hypnose. Les résultats ont pointé dans la direction prévue, justifiant d'autres recherches sur l'utilisation de cet agent pour augmenter la sensibilité à l'hypnose.

Resumen:

Este estudio piloto exploró la viabilidad del uso de la ketamina para incrementar las puntuaciones de hipnotizabilidad. La ketamina, clasificada como un alucinógeno disociativo, se usa clínicamente como un anestésico en altas dosis y como tratamiento para el dolor crónico y la depresión en dosis menores. La ketamina en dosis bajas puede contribuir a la disociación y a agudizar sentimientos y percepciones de desprendimiento, discutiblemente estados parecidos a la hipnosis. Los autores predijeron que los voluntarios sanos, que habían puntuado en el rango bajo de hipnotizabilidad en la Escala Stanford de Hipnosis Clínica y que habían sido expuestos a una dosis baja de ketamina (1) reportarían un incremento en las evaluaciones subjetivas de disociación y (2) demostrarían un incremento en hipnotizabilidad. Los hallazgos siguieron la dirección predicha, justificando más investigación sobre el uso de este agente para incrementar la hipnotizabilidad.

Hypnosis has been shown to have significant benefits for managing a variety of symptoms beyond placebo or alternative active treatments in randomized, controlled trials (Patterson & Jensen, 2003). One of the most vexing challenges to the wider use of hypnosis in health care is the limitation posed by low hypnotizability. High hypnotizability has been shown to be associated with clinical success with the use of hypnosis for a variety of clinical problems (Nash & Barnier, 2008), and low hypnotizability is considered by some to be an impediment to this approach ((Hilgard & Hilgard, 1983); Spiegel & Spiegel, 1978).

In part to address this issue, a great deal of research in the field has focused on improving hypnotizability or response to suggestion. Some of this research has focused on psychological approaches, including restricted environmental stimulation (Darkjy, Barabasz, & Barabasz, 2015), magnetic brain stimulation (Dienes & Hutton, 2013) and neurofeedback to increase slow wave activity (Jensen et al., 2016). Pharmacologic approaches to enhancing hypnotizability have also been explored, with several agents showing potential benefit, including nitrous oxide (Whalley & Brooks, 2009), cannabis (Kelly, Fisher, & Kelly, 1978), low amounts of ethanol (Semmens-Wheeler, Dienes, & Duka, 2013), diazepam (Gibson, Corcoran, & Curran, 1977), oxytocin (Bryant, Hung, Dobson-Stone, & Schofield, 2013; Bryant, Hung, Guastella, & Mitchell, 2012; Bryant & Hung, 2013), and methylphenidate (Lotan, Bonne, & Abramowitz, 2015).

Ketamine, to our knowledge, is a drug that has not yet been investigated with respect to hypnosis. Ketamine is a dissociative hallucinogen that produces dose-dependent effects, including modification of mood, cognition, memory, analgesia, amnesia, and at higher doses, dissociative anesthesia, a state of insensitivity to pain (e.g., making surgery patients unconscious and/or indifferent to pain) (Chizh, 2007; Corlett, Honey, & Fletcher, 2007). At

low doses, ketamine can increase expansive mood and heighten perceptions, without hallucinations, delusions, and other concerns associated with higher doses (Bowdle et al., 1998). Low doses may also temporarily increase feelings of dissociation and produce feelings of detachment. Low dose ketamine is being used increasingly to treat a variety of psychological symptoms, particularly depression (Luckenbaugh et al., 2014) and anxiety (Castle, Gray, Neehoff, & Glue, 2017). Participants in both of these studies cited reported higher levels of dissociation when receiving ketamine and measured by the Clinician Administered Dissociative States Scale (CADSS).

Dissociation has long been regarded as an important, if not essential, component of hypnosis. Hilgard and Hilgard (1975) proposed the neodissociation theory of hypnosis, and investigators such as Bowers and Woody (Bowers, 1990; Bowers & Davidson, 1991; Woody & Sadler, 2008) more recently have proposed dissociated control theories of hypnosis. A sense that suggested behavior becomes automatic under hypnosis, with the subject feeling somewhat removed from the process, is central to these theories. Based on this body of literature it would be reasonable to examine the potential effects of pharmacologic agents that increase dissociative experiences on hypnotizability. The purpose of the present pilot study was to attempt to replicate previous findings that low-dose ketamine increases patients' subjective ratings of feeling dissociated, and to explore the possibility that low-dose ketamine could improve hypnotizability as measured by the Stanford Clinical Hypnotizability Scale (SCHS). The sample size included in this study was not large enough to provide statistical power to detect significant effects; consequently, we proposed that we would identify trends that, if present, would indicate the potential value of additional research in this area.

Method

Participants

This report describes a peripheral study of a larger project investigating the impact of ketamine and immersive virtual reality on experimentally induced pain. A total of 11 participants were enrolled in the current study. The mean age of the participants was 30 years (range 22 to 50). Seven of the participants were women and 4 were men; in terms of ethnicity, 7 were Caucasian non-Hispanics, 1 was Caucasian Hispanic, 2 were Asian-Americans, and 1 was African American. The University of Washington Institutional Review Board approved the protocol used in this study. Healthy English-speaking subjects of all ethnic and racial origins who were able to communicate verbally were recruited from the university and surrounding community by electronic and paper notices and were screened by telephone script. Exclusion criteria included being unable to communicate verbally, conditions associated with acute or chronic pain, significant medical illness, history of substance abuse, and urine toxicology indicating opioid analgesic use. Potential participants were also excluded if they had a severe predisposition to motion sickness, or an unusual sensitivity or lack of sensitivity to pain.

Measures

The primary outcome measures assessed dissociation and hypnotizability. Dissociation was measured using the Clinician Administered Dissociative States Scale (CADSS)—a series of 19 self-report queries (each scored on a 0–4 Likert scale, yielding a 0–76 total score) assessing subjects' dissociative state based on visual and aural interpretations of their immediate physical environment; e.g., “Do things seem to be unreal for you, as if you are in a dream?” (Bremner et al., 1998). Hypnotizability was assessed using the 5 item Stanford Clinical Hypnotizability Scale (SHCS; Hilgard & Hilgard, 1975). This scale consists of a standard hypnotic induction followed by five suggestions designed to elicit specific classic hypnotic responses, including hand lowering, coughing or throat clearing, posthypnotic amnesia, age regression, and having a suggested dream. Scale scores are normally distributed and correlate strongly with other established measures of hypnotizability (e.g., $r = .72$ for the correlation with scores on the Stanford Hypnotic Susceptibility Scale: Form C (Weitzenhoffer & Hilgard, 1962).

Procedure

As mentioned previously, the assessments of hypnotizability were performed as part of a larger investigation on analgesia in a laboratory pain setting. Participants were enrolled in a 2-day, double-blind, within-subjects study design. Each of the 11 individuals who participated in the current study received a low-dose ketamine infusion (3.5 mcg/kg/min) on one day and received a placebo (saline) infusion on another day (treatment order randomized), with study days separated by at least 48 hours. The ketamine infusion protocol was designed to achieve plasma ketamine levels of 50–100 ng/ml (confirmed by plasma assay in a preliminary study). This plasma concentration typically produces only nonspecific symptoms of mild tiredness, expansive mood, and heightened perception, with no sedation, hallucinations, or significant cognitive dissociation (G. D. Honey et al., 2005; R. A. Honey et al., 2003).

On each study day, urine toxicology was performed prior to drug infusion to confirm no recent use by subjects of opioids, benzodiazepines, and other psychoactive/analgesic drugs. The SHCS was administered approximately 75 minutes after the ketamine infusion began, when plasma ketamine concentrations were within the desired target range. Cognitive dissociation was measured with the CADSS tool on each of the 2 treatment days immediately following the SHCS assessment.

Results

On the basis of Hilgard and Hilgard's (1975) classification system (for normative tables) and under the placebo condition, 5 subjects scored in the low range of hypnotizability (0–1 out of 5 on the SHCS); 6 participants scored in the medium range (2–3 out of 5). None of the participants scored in the high range of hypnotizability (4–5 out of 5).

We had predicted that low hypnotizable participants would score higher on the SHCS when receiving low-dose ketamine. The results of the effects of ketamine on hypnotic suggestibility scores are presented in Figure 1. Low hypnotizability participants did show the

predicted pattern of increased SHCS scores when receiving low-dose ketamine (effect size, Cohen's $d = 1.57$ representing a large effect). In contrast, medium hypnotizability participants did not show an increase in SCHS scores with the low-dose ketamine infusion. Rather, medium hypnotizable participants demonstrated a nonsignificant reduction in hypnotizability when receiving low-dose ketamine (effect size for hypnotizability decrease, Cohen's $d = .36$, small/medium effect); Cohen, 1988).

With all 11 participants combined, CADSS scores of dissociation were significantly higher on the day they received ketamine. The average CADSS score with placebo was 0.91, ($SD = 1.81$), and the average CADSS score with ketamine was 7.09, $SD = 5.41$; $t(10) = 3.71$, $p < .005$. Both low and medium hypnotizable participants showed increases on their CADSS scores on the day they received ketamine. For low hypnotizables, dissociation during placebo was zero and dissociation during Ketamine was 5.80, (Cohen's $d = 1.16$, representing a large effect). For medium hypnotizables, dissociation during placebo was 1.67, and dissociation during Ketamine was 8.17, (Cohen's $d = 1.02$, representing a large effect).

Discussion

Hypnotizability was measured in 11 healthy volunteers under conditions of low-dose ketamine or saline placebo. Although the sample was too small to analyze using inferential tests, the 5 participants with low hypnotizable scores during the placebo showed the predicted pattern of increased hypnotizability when receiving this pharmacologic agent ketamine. In contrast, the 6 participants with medium hypnotizability during placebo showed hypnotizability scores that did not increase when receiving ketamine. In fact, the pattern of results from the medium hypnotizables showed a reduction in hypnotizability during ketamine, as discussed in more detail below. As shown in previous studies (Castle et al., 2017; Luckenbaugh et al., 2014), low-dose ketamine increased levels of dissociation as measured by the CADSS.

The current study has several limitations. First, this was a preliminary study that used a small sample size of 11 subjects total ($N = 5$ low hypnotizable subjects and 6 medium hypnotizable subjects). A study with an adequate sample of participants for detecting the effects of low-dose ketamine on hypnotizability will be necessary for definitive results; however, the current findings suggest this to be a worthy endeavor. Another limitation is that the participants were enrolled in a larger thermal pain study during the 75 minutes before the current hypnosis study began. This may have resulted in potential demand characteristics that could have influenced the findings. However, our use of a within-subjects design measuring hypnotizability before and after each infusion helped control for demand characteristics, and a double blind design (neither participant nor researcher was aware of drug condition) was used to test the study hypothesis. Finally, the primary study outcome—hypnotizability—was measured by the SCHS, which contains only 5 items. Although this measure has evidence supporting its reliability and validity, a measure of hypnotizability with a greater number of items may have resulted in greater sensitivity and larger effects than identified here. However, for low hypnotizable participants, we still found the predicted

pattern of effects of ketamine on hypnotizability as measured by the SCHS, providing some support for the validity of this measure in the current context.

Although low hypnotizable subject showed the predicted response, medium hypnotizable subjects did not show greater hypnotizability during ketamine. An interesting question to consider in further studies on the effects of ketamine on hypnotizability is whether it is useful to do a formal hypnotic induction before measuring response to the items on the scale. It may be the case that the cognitive effort necessary to go through formal hypnosis while the patients were chemically dissociated may have interfered with hypnotic response (especially for medium hypnotizable subjects). It would be of interest to study hypnotic response in subjects under the effects of ketamine both with and without a formal hypnotic induction (i.e., some subjects would receive only the suggestions that are part of a hypnotic scale without the formal induction).

Despite the study's limitations, the findings provide important preliminary support that ketamine may increase hypnotizability, based on replicated evidence that low-dose ketamine temporarily increases participants' subjective ratings of dissociation. Dissociation has long been regarded to be an important component of hypnosis. Our findings suggest that it is worth investigating further whether ketamine might be an efficient pharmacologic technique to increase hypnotizability, particularly in participants who scored low on measures of this variable.

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Figure 1.
Pattern of results: Ketamine increased hypnotizability scores of low hypnotizable subjects more than medium hypnotizable subjects.