Pharmacology Biochemistry & Behavior, Vol. 28, pp. 7–14. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

Effects of a Subanesthetic Concentration of Nitrous Oxide on Establishment, Elicitation, and Semantic and Phonemic Generalization of Classically Conditioned Skin Conductance Responses

ROBERT I. BLOCK,* M. M. GHONEIM,* DON C. FOWLES,†
VINEY KUMAR* AND DHIRENDRA PATHAK*

*Departments of *Anesthesia and †Psychology*
University of Iowa, Iowa City, IA 52242

Received 11 December 1986

BLOCK, R. I., M. M. GHONEIM, D. C. FOWLES, V. KUMAR AND D. PATHAK. *Effects of a subanesthetic concentration of nitrous oxide on establishment, elicitation, and semantic and phonemic generalization of classically conditioned skin conductance responses.* PHARMACOL BIOCHEM BEHAV **28**(1) 7–14, 1987.—Classical conditioning of skin conductance responses was studied in 16 men and 16 women breathing 30% nitrous oxide or 100% oxygen to see how nitrous oxide affected establishment, elicitation, and generalization of conditioned responses (CRs). For CRs that had been established before gas inhalation, nitrous oxide blocked elicitation of "anticipatory" (long latency) but not "orienting" (short latency) CRs. Nitrous oxide appeared to prevent new CRs from being established during its inhalation, but learning evidently took place since anticipatory CRs could be elicited after nitrous oxide inhalation had ceased. Words were used as the conditioned stimuli and nitrous oxide altered generalization of CRs to other words related in meaning or sound, though generalization effects were limited. Nitrous oxide also seemed to reduce the efficacy of the unconditioned stimulus. The results were interpreted in terms of Rescorla's theory of classical conditioning.

Nitrous oxide Anesthesia Conditioning Classical conditioning Semantic conditioning
Generalization Skin conductance Electrodermal response Galvanic skin response Memory Recall

CASE reports and surveys suggest that a small percentage of patients receiving nitrous oxide and other agents for general anesthesia remember some intraoperative events, but prospective studies using overt recall tests in which patients are read some information during surgery and later asked to recall that information have produced no evidence of recall [16,34]. Testing memory of intraoperative events after recovery may not be an optimal way of detecting learning during anesthesia, since information might be learned but subsequently be forgotten or inaccessible for recall. The present study assessed the feasibility of using a conditioning technique to study learning and responsiveness during anesthesia. Before testing surgical patients, it seemed prudent to examine effects of a subanesthetic concentration of nitrous oxide on conditioning under controlled laboratory conditions. A concentration (30%) that produces conscious sedation and is commonly used in dental and medical practice was administered and classical conditioning of palmar skin conductance responses was examined.

In essence, a classical conditioning procedure involves establishing a conditioned response ("CR") by pairing a conditioned stimulus ("CS") with an unconditioned stimulus ("US") that innately evokes some unconditioned response ("UR"). If conditioning is effective, subsequent presentation of the CS alone elicits a CR resembling the UR. A classical conditioning procedure was used because animal studies using this or related procedures have suggested that it may be possible to establish and/or elicit conditioning during general anesthesia, at least under certain favorable conditions. Using electrical stimulation of the brain as the US, conditioning has been established and a cortical slow potential CR has been elicited during general anesthesia [20]. An earlier study obtained similar results with an autonomic CR, though in this study anesthesia was not deep enough to abolish the corneal reflex [14]. Recently, Pavlovian fear conditioning has been established using an external stimulus (shock) as the US and a noise as the CS during deep barbiturate/chloral hydrate anesthesia with concurrent administration of epinephrine [36]. Although behavioral and physiological responses to the CS and US were minimal during anesthesia, a post-anesthesia test showed that learning had occurred, i.e., the CS had become an effective conditioned suppressor of water drinking.

In the present study, the US was a loud noise that in-

nately evoked a skin conductance response, the UR. The noise was paired with a word as the CS. Conditioning was manifested if that word came to elicit larger skin conductance responses than other, unrelated "filler" words. We tried to establish a CR before gas inhalation and to elicit it during inhalation. Then, using a different word as CS, we tried to establish a new CR during inhalation and to elicit it after inhalation had ceased.

The anecdotal literature concerned with patients' recall of intraoperative events implies that language is sometimes comprehended during general anesthesia. In testing responsiveness during anesthesia in humans, it would be desirable to assess whether words are processed for meaning or just as sounds. Therefore, in addition to testing whether the word used as CS during conditioning (e.g., "Light") subsequently elicited the CR, we examined whether the CR generalized to other words related to the CS in meaning (e.g., "Dark") or in sound (e.g., "Line"). Such "semantic" and "phonemic" generalization have been reported under nondrug conditions in a number of studies, many measuring skin conductance responses [2,22]. Chloral hydrate has been claimed to produce a "lower level" of processing, i.e., to produce a greater magnitude of phonemic generalization relative to semantic generalization ([26]; see also [22]). Similar effects have been suggested with alcohol [13] and might also be produced by nitrous oxide.

METHOD

Subjects

Thirty-two paid, healthy volunteers, 16 men and 16 women, participated. They ranged from 18 to 30 years old (mean age 21.4 years). Most were college students recruited by newspaper advertisements. They provided a medical history and information about drug use during a preliminary screening visit. Individuals were excluded if they were taking any medications which could influence the effects of nitrous oxide; if they had used 3 or more illicit drugs; or if they were heavy users of alcohol or marijuana. Three additional subjects were replaced because of equipment problems and one other subject quit because of nausea during gas inhalation.

Stimuli

Two sets of three words each ("Light/Dark/Line" and "Slow/Fast/Slope") were selected from word association norms [8]. Each set consisted of a stimulus word from the norms, the word which was its most common response, and a word which sounded like the stimulus word (i.e., differed in only one phoneme) but did not occur as a response to it. These were used as the CS, semantic generalization word, and phonemic generalization word, respectively. No two words in different sets were closely related to one another associatively, semantically, or phonemically and all words were neutral in pleasantness according to normative ratings [33].

For each CS ("Light," "Slow"), a list of trials was prepared for four successive phases of the assessment: habituation; conditioning; elicitation/generalization; and extinction. Each trial consisted of presentation of a single word. The habituation trials involved presentation of eight filler words and were included to attenuate any responding to words in general. The 30 conditioning trials consisted of 10 repetitions of the CS interspersed with 20 filler words. There were from one to three filler words before each occurrence of the CS. The elicitation/generalization trials consisted of four blocks of six trials each. Each block included one trial with the CS, one with the semantic generalization word, one with the phonemic generalization word, and three with other words (none used as filler words in the conditioning or habituation trials). These other words included one filler word designated the "repeated filler" which was repeated once in each block (the same word each time). The remaining words were never repeated and one in each block was designated the "nonrepeated filler" for comparison with the repeated filler; since the CS and generalization words were repeated in each block, both repeated and nonrepeated fillers were included to see if repetition per se had any effect. The extinction trials consisted of seven repeated presentations of the CS (without the US) and were expected to attenuate the CR.

The filler words were not closely related to any of the CS or generalization words but were comparable to these words in mean frequency [10] and rated pleasantness. The filler words were separated into two sets approximately balanced on frequency and rated pleasantness. One set was used in the list for the CS "Light" and the other in the list for the CS "Slow." Except for the repeated filler during the elicitation/generalization phase, no filler word occurred more than once.

The two lists of trials were tape-recorded for presentation by a loudspeaker to the left of the subject. Within each phase, the interval between the onset of successive words varied from 12 to 15 sec (averaging 13.5 sec) except for trials during the conditioning phase on which the US was presented; similar intervals, e.g., 10 to 16 sec, have been used in prior studies under nondrug conditions [18]. On trials involving US presentation, onset of the US occurred 10 sec after onset of the CS and was followed 12 to 15 sec later by the next word. The US, which was presented only during the conditioning phase, was a 1 sec white noise amplified to 110 dB (re 0.0002 dynes/square cm, calibrated at the position of the subject's left ear). The words, which were recorded on a separate channel of the tape, were presented at normal speaking volume.

TABLE 1

SCHEDULE OF EXPERIMENTAL PROCEDURES

Procedure	Time (min)
Initial Instructions	−34
Preparation and Rest	−29
Habituation and Conditioning 1	−19
Additional Instructions and Calibration of Equipment	−8
Inhalation of 30% Nitrous Oxide in Oxygen or 100% Oxygen Begins	0
Elicitation/Generalization and Extinction 1; and Habituation and Conditioning 2	10
Inhalation Ends and Rest Period Begins	30
Elicitation/Generalization and Extinction 2	55
Recall, Recognition, and Noise Ratings	66

Note: There was a 30 second pause between the Habituation and Conditioning phases and between the Elicitation/Generalization and Extinction phases.

Procedure

Subjects were tested individually. They were instructed not to use caffeine for 4 hr before the session or alcohol, marijuana, or other drugs for 24 hr before. They were asked to sleep at least 8 hr on the night before the session and to skip the meal immediately before.

During the session, subjects reclined in a lounge chair. They were told that they would hear a number of words interspersed with occasional loud noises and were asked to listen carefully, but no information about the relationships among the words and noises was given. Table 1 shows a time schedule of the testing. Before gas inhalation, the habituation and conditioning trials from one recording were played. Half the men and women then inhaled 30% nitrous oxide in oxygen while the remainder inhaled 100% oxygen as a placebo. Ten min after gas inhalation started, the remaining parts of this recording, i.e., the elicitation/generalization trials and extinction trials, were played. Immediately afterward, the habituation and conditioning trials from a second recording (which consisted of entirely different words) were played. The remaining parts of the second recording, i.e., the elicitation/generalization and extinction trials, were played 25 min after the end of gas inhalation. Each subject thus heard both lists of trials (one for each CS) during the session. The order in which the two lists were presented was counterbalanced over subjects.

Gas Administration

Neither the subjects nor the research assistant who administered the tests and scored the results knew which gas was inhaled, though the anesthesiologist who administered the gas did know. Gases were delivered through a semiclosed circuit from an anesthesia machine (Foregger 705) situated behind the subject and conducted by double regular length corrugated tubings. The latter were connected to a Rahn endtidal sampler which collected endexpired air. The sampler was attached to a mouth piece used by the subject. A clip was fastened to the subject's nose to prevent contamination of the administered gases with atmospheric air. The concentration of nitrous oxide in endexpired gases was monitored by the anesthesiologist using an infrared meter (Beckman medical gas analyzer LB-2) shielded from the subject and research assistant. After gas inhalation started, testing was not begun for 10 min, by which time an endtidal concentration of 30% nitrous oxide was achieved and the subject became used to breathing through the mouth piece and tubings. The same concentration was continuously maintained throughout the subsequent testing during gas inhalation. After gas inhalation ceased, testing was not begun for 25 min to insure that any residual effects of nitrous oxide had become negligible [9].

Measurement of Skin Conductance

The methodology for measuring skin conductance was similar to that recommended by a recent committee studying electrodermal measurement techniques [3]. Skin conductance recordings were obtained using silver-silver chloride electrodes (Med Associates, Inc., TDE-20) and an electrode paste consisting of one part physiological saline and two parts Parke-Davis Unibase (a neutral ointment cream), the final mixture having a concentration of about 0.05 M NaCl. A constant 0.5 V potential was applied across the two recording sites and a 1000 ohm series resistor, with the subject's conductance estimated from the voltage generated across the series resistor. Tonic level control circuitry was used to increase the sensitivity of detection to 1 μsieman (formerly designated μmho) per cm of pen deflection, so that responses of 0.05 μsieman or more could be scored. The tonic level control circuitry incorporated calibration resistors which were used to check its accuracy before each subject was tested.

The two electrodes were placed on the thenar and hypothenar eminences of the palm of the subject's nondominant hand. The electrodes were attached using double-sided adhesive disks to control the area of contact with the skin at about 0.9 square cm for each electrode. Testing was not begun until 10 min after application of the electrode paste. Before starting the trials, the subject was asked to take several deep breaths to check that these elicited skin conductance responses.

The signal, after amplification, was recorded on one channel of a multichannel Beckman Type RM Dynograph recorder equipped with Type 9806A couplers, 418B preamplifiers, and 482M8 amplifiers. Event markers indicating the time of onset of the words and the US were automatically recorded on another channel. The experimenter observed the subject (who was in a separate room) on a video monitor and noted any movement artifacts on the tracing.

Post-Test

After the skin conductance assessment was completed and the electrodes removed, subjects were asked to write down the words that had been followed by loud noises and the other words from both lists that they had heard. Three min were allowed for recall. Then, in a recognition test, they were given a randomly ordered list of 12 words which included the CS and generalization words from the two lists. For each word, they indicated whether or not it had ever been followed by a loud noise and rated their confidence on a three-point scale ("Very Sure," "Likely," or "Guess"). Then subjects were asked to rate how unpleasant the loud noise had seemed before and during gas inhalation on 10-point scales where 1 represented "not at all unpleasant" and 10 represented "the most unpleasant noise you can imagine." After these ratings, four other assessments of subjective drug effects and anxiety (not germane to the present report) were administered.

Scoring and Statistical Analyses

As is customary, skin conductance responses following onset of a word were scored separately for two time intervals, one shortly after the word and one later. Responses in the first and second intervals have been labelled "orienting responses" and "anticipatory responses" [32]. While the psychological significance of CRs in the two intervals is controversial [6, 18, 30, 31], common interpretations are that CRs in the second interval reflect anticipation of the forthcoming US and CRs in the first interval are orienting responses to the CS, which during the course of conditioning come to reflect recognition of the signal value of the CS in predicting the US.

Orienting response magnitude and anticipatory response magnitude were defined as the largest conductance changes beginning within 1 to 4 sec and 4 to 11 sec after stimulus onset, respectively. (The upper limit of 11 sec was 1 sec longer than the interval between CS onset and US onset because skin conductance responses with latencies under 1

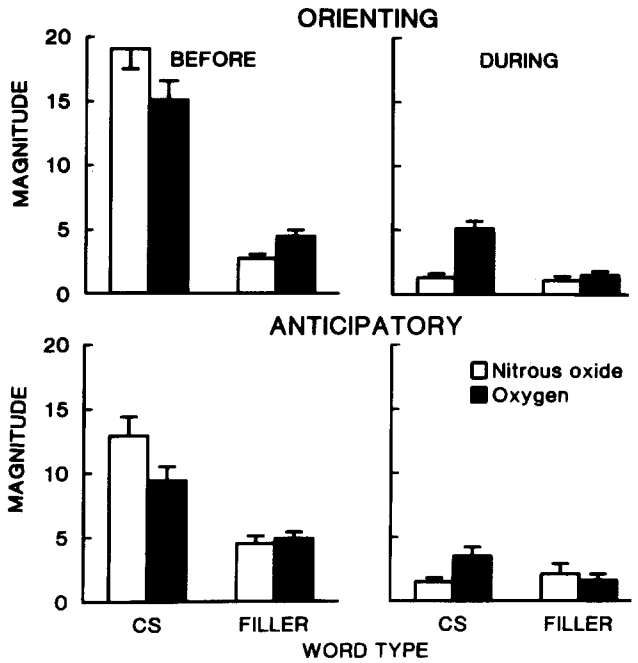

FIG. 1. Mean magnitudes (%) of the orienting and anticipatory responses for the conditioned stimulus (CS) and filler words during the conditioning phase. BEFORE=before gas inhalation, DURING=during gas inhalation. Error bars show 1 SE. Note the large conditioned responses (CRs) established before gas inhalation, the smaller CRs established during oxygen inhalation, and the *seeming* inability to establish CRs during nitrous oxide inhalation (see text).

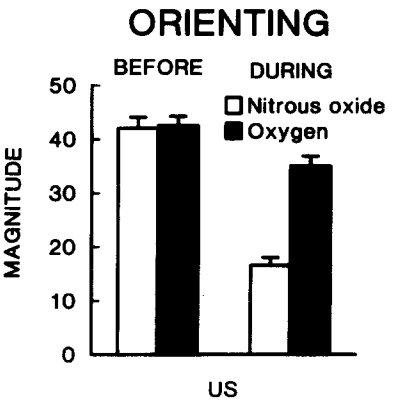

FIG. 2. Mean magnitudes (%) of the orienting responses for the unconditioned stimulus (US) during the conditioning phase. BEFORE=before gas inhalation, DURING=during gas inhalation. Error bars show 1 SE. Note the smaller responses to the US during nitrous oxide inhalation (see text).

sec would not be expected [35]; therefore, the few responses beginning less than 1 sec after US onset were considered attributable to the preceding CS.) When more than one response began in an interval, their combined magnitude was scored. Magnitudes were scored as zero for intervals not showing any response.

Subjects varied greatly in response magnitudes. The largest response to the loud noise ever shown by individual subjects ranged from 1.1 to 8.8 μsieman. To control this source of variability, the magnitude of each response by a subject was expressed as a percentage of the magnitude of that subject's largest response to the loud noise [15].

The analyses of the *conditioning phase* compared responses to the CS and to the immediately preceding filler words. The orienting and anticipatory response magnitudes were submitted to separate analyses of variance involving the factors drug group (nitrous oxide vs. oxygen), sex, order of the lists (the two counterbalanced orders), word type (CS vs. filler word), trials (the 10 trials), and time (the two times relative to gas inhalation). Similar analyses without the word type factor were done for the habituation trials, the extinction trials, and the US.

The analyses of the *elicitation/generalization phase* involved the same factors as for conditioning but there were five word types (CS, semantic and phonemic generalization words, repeated and nonrepeated fillers) and four trials for each word type (the four blocks of trials). The effect of word type was partitioned into four planned orthogonal contrasts which assessed (and are subsequently denoted) "conditioning" (CS vs. all other words), "generalization" (generalization words vs. fillers), "type of generalization word" (semantic vs. phonemic), and "type of filler word" (repeated vs. nonrepeated). The drug × word type and drug × time × word type interactions were similarly partitioned into interactions with these four orthogonal contrasts. For conciseness in presenting the results, drug effects are the focus; significant effects not involving the drug treatment and those related to sex differences or the counterbalanced orders of the lists are discussed only where essential.

RESULTS

Conditioning Phase: Establishment of CRs

Figure 1 shows the mean magnitudes of the orienting and anticipatory responses during the conditioning phase. The analyses comparing the CS and filler words indicated that both orienting CRs and anticipatory CRs were established, $F(1,24)=36.9$ and 19.9, respectively, $ps<0.001$, i.e., response magnitudes were larger for the CS than for filler words. The CRs established during gas inhalation were weaker than those established before gas inhalation, $F(1,24)=40.7$ and 32.6 for word type × time effects for orienting and anticipatory responses, respectively, $ps<0.001$. This decline in establishment of CRs during gas inhalation was greater for the nitrous oxide group than the oxygen group, $F(1,24)=6.2$, $p<0.05$ and $F(1,24)=10.2$, $p<0.01$ for drug × word type × time effects for orienting and anticipatory responses, respectively. In fact, there was no evidence that CRs had been established at all during nitrous oxide inhalation, i.e., the means for CS and filler words were essentially the same. Follow-up analyses indicated that establishment of CRs during oxygen inhalation was significant for orienting CRs and marginally significant for anticipatory CRs, $F(1,24)=7.1$, $p<0.05$ and $F(1,24)=3.5$, $p=0.08$, respectively.

Additional follow-up analyses of the CS and filler words separately indicated that the drug's effect on conditioning was due to an effect on the CS, not the filler words. There were no drug effects for the filler words, while the response magnitudes for the CS declined more during nitrous oxide inhalation than during oxygen inhalation, relative to pre-inhalation values, $F(1,24)=4.3$ and 6.1 for drug × time effects for orienting and anticipatory responses, respectively,

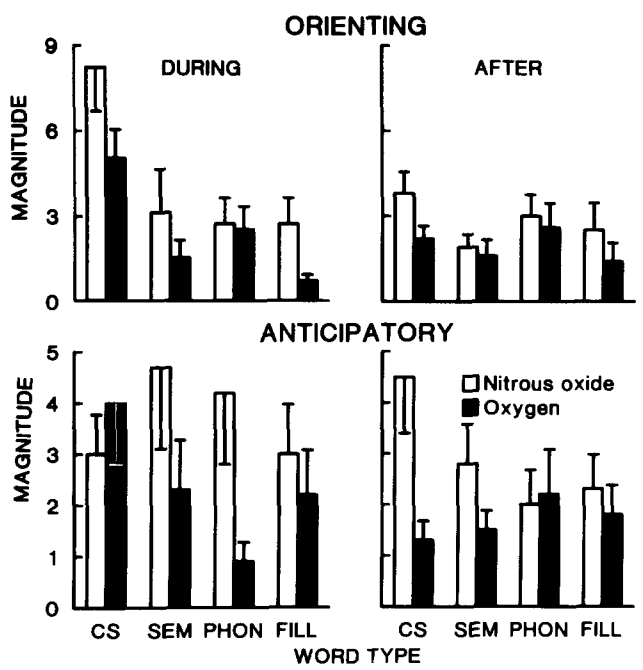

FIG. 3. Mean magnitudes (%) of the orienting and anticipatory responses for the CS, generalization, and filler words during the elicitation/generalization phase. The means over all four blocks of trials are shown. The means for repeated and nonrepeated filler words have been combined since the drug did not affect them differently. DURING=during gas inhalation, AFTER=after gas inhalation, SEM=semantic generalization word, PHON=phonemic generalization word, FILL=filler words. Error bars show 1 SE. Note the opposite effects of nitrous oxide on elicitation of *anticipatory* CRs during and after gas inhalation: during gas inhalation, these CRs were elicited for the oxygen group but not the nitrous oxide group; after gas inhalation, these CRs were elicited for the nitrous oxide group but not the oxygen group (see text).

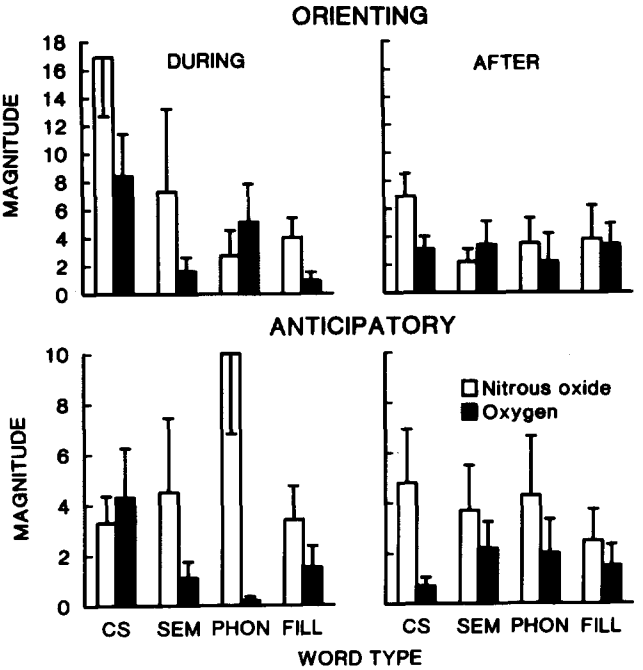

FIG. 4. Mean magnitudes (%) of the orienting and anticipatory responses for the CS, generalization, and filler words during the elicitation/generalization phase. The means for the first of the four blocks of trials are shown. The means for repeated and nonrepeated filler words have been combined since the drug did not affect them differently. The abbreviations are the same as in Fig. 3. Error bars show 1 SE. Note that during gas inhalation, the nitrous oxide group showed generalization of *anticipatory* responses while the oxygen group did not, the difference between groups being larger for phonemic generalization than semantic generalization (see text).

$ps<0.05$. During gas inhalation, the nitrous oxide and oxygen groups differed significantly in orienting response magnitudes for the CS; this difference was marginally significant for anticipatory responses, $F(1,24)=8.1$, $p<0.01$ and $F(1,24)=3.7$, $p=0.07$, respectively.

Nitrous oxide also affected responses to the US, i.e., the noise, as shown in Fig. 2. Orienting response magnitudes for the US were lower during gas inhalation than before, and this decline was greater for subjects breathing nitrous oxide than for those breathing oxygen, $F(1,24)=9.8$, $p<0.01$ for drug × time effect and $F(1,24)=7.6$, $p<0.05$ for drug effect.

Elicitation/Generalization Phase: Elicitation and Generalization of CRs

Figure 3 shows the mean magnitudes of orienting and anticipatory responses during the elicitation/generalization phase. Trials with the CS during the elicitation/generalization phase tested whether the previously established CRs could be elicited. The results were positive, i.e., the CS showed larger orienting response and anticipatory response magnitudes than the other words overall, $F(1,96)=18.9$, $p<0.001$ and $F(1,96)=4.0$, $p<0.05$, respectively, for conditioning contrast. Nitrous oxide affected elicitation of anticipatory CRs but not orienting CRs: The drug altered anticipatory response magnitudes for the different types of words, with its effects differing during vs. after gas inhalation, $F(4,96)=3.1$, $p<0.05$ for drug × time × word type effect, and being related mainly to elicitation of CRs, $F(1,96)=9.6$, $p<0.01$ for drug × time × conditioning contrast. Follow-up analyses indicated that during gas inhalation, these response magnitudes showed elicitation of anticipatory CRs for the oxygen group but not the nitrous oxide group [Fig. 3, lower left; $F(1,96)=4.3$, $p<0.05$ for drug × conditioning contrast during gas inhalation]. After gas inhalation, surprisingly, the opposite pattern prevailed, i.e., the response magnitudes showed elicitation of anticipatory CRs for the nitrous oxide group but not the oxygen group [Fig. 3, lower right; $F(1,96)=7.6$, $p<0.01$ for drug × conditioning contrast after gas inhalation].

Statistical analyses were also done for the first block of trials separately because effects had generally been largest during the first block and declined on subsequent blocks in a preliminary study under nondrug conditions [1]. The results for anticipatory response magnitudes on the first block of trials alone were consistent with the results over all blocks concerning the drug's effect on elicitation of CRs (Fig. 4, bottom). In addition, anticipatory response magnitudes on the first block of trials during gas inhalation showed some drug effects on generalization (Fig. 4, lower left). In contrast to the results for elicitation of CRs, there was more generalization for the nitrous oxide group than for the oxygen group, which showed no evidence of generalization,

$F(1,96)=4.2, p<0.05$ for drug × generalization contrast. This difference was larger for phonemic generalization than for semantic generalization, $F(1,96)=4.2$, $p<0.05$ for drug × type of generalization word contrast. These contrasts pertaining to generalization were not significant over all four blocks of trials, however; and orienting response magnitudes on the first block of trials alone showed a different, nonsignificant pattern (Fig. 4, upper left).

Other Drug Effects

Anticipatory response magnitudes on the first block of trials during the elicitation/generalization phase were larger overall for the nitrous oxide group than the oxygen group, $F(1,24)=7.3$, $p<0.05$ for drug effect (Fig. 4, bottom). The only drug effects during habituation and extinction were of little interest since they involved interactions with sex or the counterbalanced orders of the lists of words.

Response Frequencies

If skin conductance were to be used during anesthesia and surgery, it would be considerably simpler for practical purposes to use response frequencies rather than magnitudes, i.e., to score responses as present or absent instead of measuring their size. To see how this would affect the results, the analyses were repeated for response frequencies. The response frequencies, like the magnitudes, showed that CRs were established and elicited, that new CRs apparently could not be established during nitrous oxide inhalation, and that the drug decreased responses to the US. With respect to drug effects on elicitation of previously established CRs, the effects on anticipatory response magnitudes were not significant for response frequencies. With respect to drug effects on generalization on the first block of trials during the elicitation/generalization phase, response frequencies showed an effect for anticipatory responses that was consistent with the effects on response magnitude, but an opposite pattern for orienting responses. Generally response frequencies, though sensitive to drug effects, were less sensitive than response magnitudes.

Post-Test

Noise ratings. The post-test ratings of the unpleasantness of the noise before and during gas inhalation agreed with the observed changes in response magnitudes. The ratings indicated less unpleasantness during nitrous oxide inhalation than before, but little difference before and during oxygen inhalation, $F(1,24)=24.2$, $p<0.001$ for drug × time effect and $F(1,24)=11.9$, $p<0.01$ for drug effect. The mean ratings for nitrous oxide were 8.1 before gas inhalation and 3.7 during gas inhalation. The corresponding ratings for oxygen were 7.9 and 7.0, respectively.

Recall and recognition. Subjects receiving nitrous oxide recalled fewer of the filler words than subjects receiving oxygen [means of 6% and 9%, respectively; $F(1,24)=5.2$, $p<0.05$]. Nitrous oxide did not affect recall of the CS or generalization words or recognition of which words had been followed by noise. Recall and recognition means for the CS words were 97% and 100%, respectively, for subjects receiving nitrous oxide and 84% and 97%, respectively, for subjects receiving oxygen.

DISCUSSION

The results from the conditioning phase indicated that the CRs established during gas inhalation were weaker than those established before gas inhalation. Even subjects breathing oxygen showed this pattern. It was probably not an effect of oxygen inhalation per se, since a similar (though somewhat milder) pattern occurred in a preliminary study under nondrug conditions [1]. The CR that was established first may have interfered with establishing the second, new CR. However, the pattern was more dramatic in the nitrous oxide group; there was no evidence that CRs were established at all during nitrous oxide inhalation. Since nitrous oxide also reduced skin conductance responses to the US, i.e., the noise, this drug effect on conditioning might be explained by a drug-induced decrease in the efficacy of the US, analogous to the effect of objective variations in US loudness [17]. Decreased efficacy of the US is consistent with its decreased evoked unpleasantness as was revealed in the subjective ratings of the nitrous oxide group and could be related to drug-induced decreases in auditory evoked potentials [12] and/or in sensitivity to painful stimuli.

The results from the elicitation/generalization phase complicate this picture, however. Though nitrous oxide seemed to prevent new conditioning from being established during its inhalation, learning evidently took place, since anticipatory CRs could be elicited after gas inhalation more for subjects receiving nitrous oxide than for those receiving oxygen. This pattern—no evidence of conditioning during drug action but elicitation of conditioning afterward—was observed in early animal studies of conditioning of skeletal muscle responses during anesthetic [29] and subanesthetic [27] doses of barbiturates and during neuromuscular blockade [28]. The finding that anticipatory CRs could not be elicited after oxygen inhalation was unexpected. It might be explained by the weakness of the CRs established during oxygen inhalation; but the pattern observed with nitrous oxide requires some additional explanation.

Nitrous oxide also reduced the elicitation during gas inhalation of CRs established before gas inhalation. This effect, like the drug's effect after gas inhalation, was significant only for anticipatory responses, not orienting responses. Orienting CRs could be elicited during nitrous oxide inhalation, as during oxygen inhalation. This specificity suggests that the findings cannot be attributed to drug effects on efferent mechanisms subserving skin conductance. Our interpretation is that nitrous oxide decreased anticipatory responding to the US rather than decreasing the efficacy of the CS as a signal for the US. This seems consistent with the notion that nitrous oxide reduced the efficacy of the US.

These drug effects seem interpretable within Rescorla's theory of classical conditioning [7, 23–25], according to which elicitation of a CR depends on the status of the internal representations of both the US and the association between the CS and the US. Part of the evidence for this theory is that manipulations *following* conditioning which increase or decrease the noxious or rewarding qualities of the US (e.g., habituation of a noise US) produce corresponding increases or decreases in the magnitude of conditioning that can subsequently be elicited. Breathing nitrous oxide can be interpreted as such a manipulation, and so can recovery from the drug's effects. The drug reduced elicitation of CRs established before gas inhalation because the transition from the undrugged state to the nitrous oxide state reduced the potential efficacy of the US. After gas inhalation ended, the transition from the nitrous oxide state to the undrugged state correspondingly increased the potential efficacy of the US, accounting for the increased elicitation of CRs following

nitrous oxide compared to oxygen. (Since the latter finding is the opposite of a state-dependent effect, state-dependency cannot account for the results.)

In the first block of elicitation/generalization trials during gas inhalation, nitrous oxide increased generalization of anticipatory responses, particularly phonemic generalization, relative to oxygen. This pattern seems consistent with previous suggestions that CNS depressants encourage "lower-level" phonemic relative to "higher-level" semantic generalization [13,26]. However, the drug's effect on generalization must be interpreted very cautiously since it was restricted to the first of the four blocks of elicitation/generalization trials; generalization extinguished rapidly and neither generalization itself nor the drug's effect on it was significant over all four blocks. Moreover, generalization was observed on the first block of trials only for anticipatory responses; the pattern for orienting responses was different and neither generalization itself nor the drug's effect on it was significant.

While nitrous oxide increased generalization of anticipatory responses on the first block of elicitation/generalization trials during gas inhalation, it simultaneously abolished anticipatory CRs (though not orienting CRs). Generalization without elicitation of the CR is unusual though not completely unprecedented [11] in studies of semantic conditioning under nondrug conditions. This unusual finding may be instructively compared to Rescorla's [7, 23, 24] findings for second-order conditioning. In second-order conditioning, conditioning of a second-order CS is established by pairing it with a previously established CS rather than with the US itself. The effects Rescorla observed for basic conditioning did not occur for second-order conditioning, i.e., manipulations following conditioning which altered the efficacy of the US did not produce corresponding alterations in the magnitude of second-order conditioning that could subsequently be elicited. Rescorla suggested that elicitation of a second-order CR (in contrast to elicitation of a basic CR) did not depend on the status of the internal representation of the US.

While the leap from second-order conditioning in animals to generalization of a verbal CR in humans is a long one, this suggests a partial interpretation of our unusual finding for generalization. If semantic and phonemic generalization (in contrast to elicitation of the CR) do not depend on the status of the internal representation of the US, this may help explain how nitrous oxide could produce different effects on generalization and on elicitation of the CR.

Two caveats concerning this speculation should be noted. First, it does not explain why nitrous oxide should have different effects on generalization of orienting and anticipatory responses, i.e., why subjects breathing nitrous oxide showed no generalization of orienting responses, considering that they showed elicitation of orienting CRs and generalization without elicitation of anticipatory CRs. Second, results inconsistent with Rescorla's theory of second-order conditioning have been observed in some studies [5,21].

Since the present study used a subanesthetic concentration of nitrous oxide, it does not establish whether general anesthesia would produce similar effects. This subanesthetic concentration of nitrous oxide did not impair subjects' memory of the contingency between the CS and the US; in the post-test, subjects receiving nitrous oxide, despite their impairment in recalling the filler words, showed almost perfect recall of the words that had been paired with noise. Such overt recall would not be expected in fully anesthetized subjects.

Repeating the experiment during general anesthesia could help clarify the capacity for learning and responsiveness that remains despite the depression of much brain function [36]. The limited information available about effects of general anesthesia on electrodermal responsiveness in humans does not clearly indicate whether some responsiveness remains [4] or not [19]. The present study found that establishment, elicitation, and generalization of verbal CRs were altered in several ways but not abolished by a subanesthetic concentration of nitrous oxide; if similar effects occurred during general anesthesia, this would provide evidence of learning and responsiveness in the anesthetized brain.

ACKNOWLEDGEMENTS

Thanks are due to Mrs. Kristen Rickey for assisting with the research and to Dr. Isidore Gormezano, Department of Psychology, University of Iowa for commenting on the manuscript.

REFERENCES

1. Block, R. I., D. Fowles and M. M. Ghoneim. Semantic conditioning of skin conductance responses: Effects of electrode size and sex. In preparation, 1987.
2. Feather, B. W. Semantic generalization of classically conditioned responses: A review. *Psychol Bull* **63:** 425–441, 1965.
3. Fowles, D. C., M. J. Christie, R. Edelberg, W. W. Grings, D. T. Lykken and P. H. Venables. Publication recommendations for electrodermal measurements. *Psychophysiology* **18:** 232–239, 1981.
4. Goddard, G. F. A pilot study of the changes of skin electrical conductance in patients undergoing general anaesthesia and surgery. *Anaesthesia* **37:** 408–415, 1982.
5. Green, L. and L. Schweitzer. Second-order conditioning of the pigeon's key-peck using an autoshaping procedure. *Am J Psychol* **93:** 25–39, 1980.
6. Grings, W. W. Orientation, conditioning, and learning. *Psychophysiology* **14:** 343–350, 1977.
7. Holland, P. C. and R. A. Rescorla. The effect of two ways of devaluing the unconditioned stimulus after first- and second-order appetitive conditioning. *J Exp Psychol [Anim Behav]* **1:** 355–363, 1975.
8. Jenkins, J. J. The 1952 Minnesota word association norms. In: *Norms of Word Association,* edited by L. Postman and G. Keppel. New York: Academic, 1970, pp. 1–38.
9. Korttila, K., M. M. Ghoneim, L. Jacobs, S. P. Mewaldt and R. C. Petersen. Time course of mental and psychomotor effects of 30 per cent nitrous oxide during inhalation and recovery. *Anesthesiology* **54:** 220–226, 1981.
10. Kučera, H. and W. Francis. *Computational Analysis of Present-Day American English.* Providence, RI: Brown University Press, 1967.
11. Lacey, J. I. and R. L. Smith. Conditioning and generalization of unconscious anxiety. *Science* **120:** 1045–1052, 1954.
12. Lader, M. and H. Norris. The effects of nitrous oxide on the human auditory evoked response. *Psychopharmacologia* **16:** 115–127, 1969.

13. Levy, C. M. and P. H. Murphy, III. The effects of alcohol on semantic and phonetographic generalization. *Psychon Sci* **4:** 205–206, 1966.
14. Lico, M. C., A. Hoffmann and M. R. Covian. Autonomic conditioning in the anesthetized rabbit. *Physiol Behav* **3:** 673–675, 1968.
15. Lykken, D. T. and P. H. Venables. Direct measurement of skin conductance: A proposal for standardization. *Psychophysiology* **8:** 656–672, 1971.
16. McIntyre, J. W. R. Awareness during general anaesthesia: Preliminary observations. *Can Anaesth Soc J* **13:** 495–499, 1966.
17. Maltzman, I., B. Langdon, M. Pendery and C. Wolff. Galvanic skin response-orienting reflex and semantic conditioning and generalization with different unconditioned stimuli. *J Exp Psychol [Gen]* **106:** 141–171, 1977.
18. Maltzman, I., S. Weissbluth and C. Wolff. Habituation of orienting reflexes in repeated GSR semantic conditioning sessions. *J Exp Psychol [Gen]* **107:** 309–333, 1978.
19. Perez-Reyes, M. and C. Cochrane. Differences in sodium thiopental susceptibility of depressed patients as evidenced by the galvanic skin reflex inhibition threshold. *J Psychiatr Res* **5:** 335–347, 1967.
20. Pirch, J. H., M. J. Corbus and I. Ebenezer. Conditioned cortical slow potential responses in urethane anesthetized rats. *Int J Neurosci* **25:** 207–218, 1985.
21. Rashotte, M. E., R. W. Griffin and C. L. Sisk. Second-order conditioning of the pigeon's keypeck. *Anim Learn Behav* **5:** 25–38, 1977.
22. Razran, G. The observable unconscious and the inferable conscious in current Soviet psychophysiology: Interoceptive conditioning, semantic conditioning, and the orienting reflex. *Psychol Rev* **68:** 81–147, 1961.
23. Rescorla, R. A. Effect of US habituation following conditioning. *J Comp Physiol Psychol* **82:** 137–143, 1973.
24. Rescorla, R. A. Effect of inflation of the unconditioned stimulus value following conditioning. *J Comp Physiol Psychol* **86:** 101–106, 1974.
25. Rescorla, R. A. and C. D. Heth. Reinstatement of fear to an extinguished conditioned stimulus. *J Exp Psychol [Anim Behav]* **104:** 88–96, 1975.
26. Schwartz, L. A. Conditioned reflexes to verbal stimuli. In: *Problems of Psychology, 1960,* edited by N. O'Connor. Oxford: Pergamon, 1962, pp. 36–49.
27. Settlage, P. The effect of sodium amytal on the formation and elicitation of conditioned reflexes. *J Comp Psychol* **22:** 339–343, 1936.
28. Solomon, R. L. and L. H. Turner. Discriminative classical conditioning in dogs paralyzed by curare can later control discriminative avoidance responses in the normal state. *Psychol Rev* **69:** 202–219, 1962.
29. Sterling, K. and J. G. Miller. Conditioning under anesthesia. *Am J Psychol* **54:** 92–101, 1941.
30. Stern, J. A. Physiological response measures during classical conditioning. In: *Handbook of Psychophysiology,* edited by N. S. Greenfield and R. A. Sternbach. New York: Holt, 1972, pp. 197–227.
31. Stern, J. A. and L. C. Walrath. Orienting responses and conditioning of electrodermal responses. *Psychophysiology* **14:** 334–342, 1977.
32. Stewart, M. A., J. A. Stern, G. Winokur and S. Fredman. An analysis of GSR conditioning. *Psychol Rev* **68:** 60–67, 1961.
33. Toglia, M. P. and W. F. Battig. *Handbook of Semantic Word Norms.* Hillsdale, NJ: Lawrence Erlbaum, 1978.
34. Trustman, R., S. Dubovsky and R. Titley. Auditory perception during general anesthesia—Myth or fact? *Int J Clin Exp Hypn* **25:** 88–105, 1977.
35. Venables, P. H. and M. J. Christie. Electrodermal activity. In: *Techniques in Psychophysiology,* edited by I. Martin and P. H. Venables. Chichester: John Wiley and Sons, 1980, pp. 3–67.
36. Weinberger, N. M., P. E. Gold and D. B. Sternberg. Epinephrine enables Pavlovian fear conditioning under anesthesia. *Science* **223:** 605–607, 1984.