FAILURE TO REPPLICATE NEGATIVE EFFECTS OF TRACE ANAESTHETICS ON MENTAL PERFORMANCE

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SUMMARY
Twenty-four male subjects individually undertook a selection of cognitive tasks during each of two different 2-h sessions in a climatic chamber. Twelve subjects breathed a mixture of air, nitrous oxide 1600 p.p.m. (v/v) and halothane 16 p.p.m. (v/v) during the first session, and air alone during the second session 1 week later. For the other 12 subjects the order was reversed. The tests comprised learning a list of word-number pairs, solving a set of anagram problems, recognizing words and numbers, recalling word-number pairs and performing a four-choice audiovisual reaction time task. Testing was commenced after 45 min of exposure to the atmospheric conditions. A strong learning effect both within and between sessions was observed on the audiovisual task. None of the tasks, however, reflected any adverse effect of the trace anaesthetics.

In recent studies, Bruce and his colleagues have presented evidence for significant decrements in cognitive functioning of volunteer subjects who had been exposed to as little as 500 p.p.m. of nitrous oxide, or 50 p.p.m. of nitrous oxide plus 1 p.p.m. of halothane in the laboratory (Bruce, Bach and Arbit, 1974; Bruce and Bach, 1976). However, no effects were observed by Gamberale and Svensson (1974), who studied perceptual accuracy and reaction times in a group of anaesthetic nurses and a comparable group of intensive care nurses (not exposed to trace anaesthetics) at the beginning and the end of a working day. In addition, Smith and Shirley (1977) exposed subjects to as much as 100–150 p.p.m. of halothane in air, or nitrous oxide 500 p.p.m. plus halothane 15 p.p.m. in air and failed to detect any decrement in performance. Close examination of the reports of these investigations reveals differences in type of subjects studied, duration of exposure to the anaesthetic, type of test administered, experimental programme, and uncontrolled factors such as the subject’s level of fatigue or his prior consumption of stimulants or depressants, or both.

In the present study we have attempted to duplicate the results of one of Bruce’s highly sensitive tasks, namely the audiovisual four-choice reaction time task. This task subjects have to react as quickly as possible to changes in a continuously presented signal comprising a visual and an auditory component. Because the required duration of exposure exceeded the time needed to perform this test, a few “paper-and-pencil” tests of cognitive function were incorporated in the study.

SUBJECTS AND METHODS

Subjects
Twenty-four male university students served as paid subjects. All were in good health and none had been exposed to anaesthetic gases during the 3-month period preceding the study. This was checked by obtaining a blood sample. Every subject was tested twice, once in an atmosphere containing air alone and once whilst breathing a mixture of nitrous oxide and halothane in air. The subjects were tested individually and during morning hours only. Approximately 1 week separated the two sessions for each subject.

Experimental chamber
Depending upon the programme, either air or a mixture of nitrous oxide and halothane in air was vented into a climatic chamber, measuring approximately \(3 \times 2 \times 2 \text{ m}\), in which temperature and relative humidity were maintained at average values of 20°C and 45% respectively. The trace anaesthetics were administered by passing nitrous oxide from a cylinder through a calibrated vaporizer (Dräger Vapor) containing halothane, and introducing the mixture into the fresh air stream. A fan was used to mix thoroughly the anaesthetics with room air in the chamber. An experimental session lasted for about 105–120 min, and during the last 60–75 min the fan was turned off to prevent any possible disturbance of the subject’s test performance by noise. Switching off
the fan did not affect the homogeneity of the distribution of nitrous oxide and halothane in the chamber. Nitrous oxide concentration was measured continuously using a Miran I infra-red gas analyser and halothane concentrations were measured by taking samples of the chamber's atmosphere immediately before and towards the end of experimental testing. These samples, taken in glass syringes, were analysed by gas chromatography.

The measured concentrations of nitrous oxide were $1600 \pm 100$ p.p.m. (v/v), and of halothane $16 \pm 2$ p.p.m. (v/v). These values are of the same order of magnitude as the concentrations measured in "non-ventilated" operating theatres (Burm, Spierdijk and Reiger, 1976). Inflow of fresh air into the chamber amounted to approximately $60$ m$^3$ h$^{-1}$. The ambient conditions of the chamber were stabilized thoroughly before any subject was introduced.

Procedure and experimental tasks

Every session followed the same sequence of:

(A) a 45-min introductory period of free reading from newspapers, books or a textbook;

(B) 10-min performance of an audiovisual multiple-choice reaction time (RT) task modelled on the one studied by Bruce, Bach and Arbit (1974);

(C) 20 min of learning a list of word-number combinations;

(D) 20 min of solving anagram problems;

(E) 10 min of recognizing the words and numbers and recalling the appropriate word-number combinations from task (C);

(F) a second 10-min run of task (B).

These tasks were always administered in a fixed order, as the primary aim of the study was to attempt to replicate the results obtained with the most sensitive (audiovisual RT) task of the studies by Bruce and colleagues. The time schedule described above is approximate and incorporates the times required to give part instructions before each task. During the session the observer remained in a separate control room, from where he could watch the subject on a video monitor and communicate with him via an intercom system. Total duration of each session varied between 105 and 120 min.

(A) Free reading. The 45-min period of free reading was designed to allow the subject to reach equilibrium with the ambient atmosphere and accommodate to the experimental conditions.

(B) Audiovisual RT task. The stimulus–response device for this task consisted of a panel containing an upper and a lower red light source below which a green signal light may flash. A high (1000 Hz) or a low (500 Hz) tone auditory signal was presented to the subject via earphones simultaneously with one of the red lights. The subject was required to identify each stimulus combination as follows: 1 = upper light, high tone; 2 = upper light, low tone; 3 = lower light, high tone; 4 = lower light, low tone—by pressing the appropriate button at the bottom of the panel (fig. 1). One hundred and twenty-five such signal combinations were presented in random order for a maximum of 4 s each, without a pause between stimuli. During these 4 s the subject had to react as quickly as possible and the time needed to hit the correct button was measured. The green light signalled such a correct response during the remainder of the 4-s period. The total sequence of 125 stimuli was divided in blocks of 25 and designed such that each type of stimulus occurred approximately equally often within each block. Only the last four blocks of responses were analysed. The number of error responses, made before the correct response, was treated as a second dependent variable. The stimulus sequences were generated by and the responses were recorded with appropriate electronic equipment.

(C) Learning word–number pairs. Using the anticipation method each subject had to learn a list of 10 word–number pairs (e.g. table–36, cycle–91) to a criterion of eight correct pairs in two successive tests of the list. In each presentation of the list the pairs occurred in a different random order. Of each pair, the word was presented first, whereupon the subject was given 5 s to produce the correct number. The dependent variable was the number of times
the subject had to go through the list before the
criterion was reached. Parallel lists were used in
balanced order in the first and second session for
each subject. Dutch two-syllable words of approx-
imately the same frequency class and numbers
between 10 and 100 (excluding multiples of 11) were
used as stimulus materials. No two words or numbers
started with the same letter or digit, respectively.
The instruction and the word number pairs were
recorded on tape and presented via a loudspeaker.

(D) Anagram problem solving. Two parallel lists
each of 38 anagram problems were composed for use
in the two sessions for each subject. The dependent
variable was the total number of anagrams solved in
a period of 15 min. Word frequency of the solutions
and total bigramfrequencies of both anagram and
solution-word were controlled. Every anagram had
only five letters and one solution, which was always a
noun. The instruction and list of anagrams were
presented on paper and the subject had to write each
solution word next to the anagram problem. Subjects
were encouraged to work as quickly as possible, and
were allowed to work through the anagram list in
any order they wished.

(E) Recognition and recall of words, numbers and
word-number pairs. This memory task consisted of
three parts and was performed approximately 30 min
after the learning task (C). The 10 words from this
task were mixed together with 10 similar, but new
words, and each subject was required to indicate,
within 5 s, which words were “old” and which were
“new” when these words were presented success-
ively to him. A similar recognition task was
performed for 10 “old” and 10 “new” numbers.
Finally, the original 10 stimulus-words from the
learning task were presented randomly for a response
with the appropriate numbers. The instruction and
stimulus presentations were recorded on tape and
presented via a loudspeaker.

(F) Towards the end of each session, after
approximately 100 min of exposure in the chamber,
the audiovisual RT task was repeated with a different
random selection of 125 stimulus occurrences.

Experimental design
The 24 subjects were allocated to two groups of 12.
Group 1 was exposed to air plus the anaesthetics
(experimental) in the first session, and to air alone
(control) in the second session, 1 week later. For
group 2 this order was reversed. For those tasks
requiring parallel lists (a and b) of stimulus materials
in the two sessions, each group was again divided
into two, so that the presentation of these lists could
be balanced, as illustrated in table I. A double-blind
procedure was followed and neither the observer nor
the subject knew at any time during the experiment
if the latter was breathing low concentrations of
anaesthetics or air alone. These conditions were
monitored by an independent technician. The
experimental design permits analysis of the variance
in the observed data according to a 12-times repeated
2 x 2 Latin square design, with order-of-sessions as
the between-subjects variable, and all other experi-
mental manipulations being treated as within-
subjects variables. A Latin square design does not
permit meaningful interpretations of possible inter-
actions among any two or all three of the groups-,sessions-, and atmospheric conditions-variables.

RESULTS
There were no significant differences between
experimental conditions in (C) the learning of word-
number pairs, (D) the anagram problem solving and
(E) the recognition of words, numbers and word-
number pairs. Therefore these will not be discussed
further.

The audiovisual reaction time task
These data consist of a response time and number
of errors (from 0 to 3) incurred before pressing the
correct response button, for each of 125 consecutive
stimulus combinations, both at the beginning and at
the end of the period of testing. For each run of 125
stimuli, the first block of 25 was discarded, and the
remainder divided up into four blocks of 25 response
occurrences. The average response time and the
total number of error responses were computed for
each block, and the results served as basic data for
further analysis.
As the average number of errors amounted to only little more than one in 25 responses, and differences in error scores were extremely small and not related systematically to the independent variables, error scores will not be discussed further.

Each cell of the experimental design in table I contains eight measurements per subject (mean RT or total number of errors for the trial blocks 2–5 in both the first and second performances of the audiovisual RT task). This adds two within-subject variables to the design (trial blocks, and first v. second performance).

An analysis of variance was performed on response times. The main significant effects are represented in figure 2. The following statistical conclusions were obtained:

1. Response times are significantly shorter as a function of the trial block number ($P < 0.001$) and from the first to the second performance within each session ($P < 0.001$).

2. The rate of improvement in response speed within a session is greater during the first than during the second performance ($P < 0.01$) and the improvement from first to second performance is greater in the first session than in the second session ($P < 0.001$).

3. When breathing air alone subjects seem to perform a little slower (average 35 ms) than when breathing air plus anaesthetic agents ($P < 0.05$); this result obtains when data are averaged over sessions (fig. 2). However, the difference between

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**Fig. 2.** Average response time (ms) (ordinate) as a function of trial blocks in first and second performance across sessions. The solid line represents the “air + anaesthetic” condition. The dashed line represents the “air alone” condition. Note that group assignment to atmospheric conditions is reversed to the left and right of the perpendicular broken line.

**Fig. 3.** Average response time (ms) (ordinate) as a function of session, performance and trial block number, separated for groups 1 and 2. The solid line represents the “air + anaesthetic” condition. The dashed line represents the “air alone” condition.
“air alone” and “air + anaesthetic” is opposite for the two sessions as figure 3 shows; the effect depends on which group is in which atmospheric condition. Figure 3 presents, for each group separately, the effects of atmospheric conditions separated for sessions, first- and second performances and trial blocks.

It would seem that group 1 has responded faster overall, irrespective of the atmospheric condition. As the group difference in session 1 is stronger and in favour of the air + anaesthetic condition, this difference dominates what happens in session 2, where group 1 received “air alone”. The end result is a just-significant overall effect of atmospheric conditions. These latter conclusions are based on a pictorial representation of average reaction time data. The relevant interactions to be considered for statistical significance testing are confounded with other factors and cannot be separated from the total variance in the $2 \times 2$ Latin square design (the “sessions x atmospheric conditions” interaction, for instance, is confounded by the groups factor).

The most sensible conclusion, therefore, seems to be that the overall effect of atmospheric condition arises from chance fluctuations, or from a complex interaction of several independent variables.

(4) The “atmospheric conditions x first/second performance” interaction is insignificant: the effect of atmospheric condition does not depend on duration of exposure.

**DISCUSSION**

In this study we have found that 1600 p.p.m. of nitrous oxide and 16 p.p.m. of halothane in air inspired for approximately 2 h by student subjects working in an otherwise comfortable climatic chamber did not appear to have any adverse effects on performance in several cognitive tasks. One could postulate that the learning and anagram problem solving tasks did not permit the measurement of any subtle effects, and that the recognition and recall tasks were too insensitive. However, the audiovisual reaction time task has proved to be strongly sensitive to familiarity factors, and therefore presumably sufficiently sensitive for detecting effects of trace anaesthetics.

The average response times from the audiovisual task in this study (table II) may be compared to those observed by Bruce, Bach and Arbit (1974) (table III) and, more recently, by Bruce and Bach (1976) (table IV).

<table>
<thead>
<tr>
<th>Session 1</th>
<th>Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>1.06 (1)</td>
</tr>
<tr>
<td>Control</td>
<td>1.16 (2)</td>
</tr>
</tbody>
</table>

**TABLE III. Average response times (s) for the 7-min audiovisual task in the study of Bruce, Bach and Arbit (1974). Group numbers (20 subjects per group) are given in parentheses. Experimental dosage was nitrous oxide 500 p.p.m. plus halothane 15 p.p.m. in air.**

<table>
<thead>
<tr>
<th>Session 1</th>
<th>Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>1.81 (1)</td>
</tr>
<tr>
<td>Control</td>
<td>1.48 (2)</td>
</tr>
</tbody>
</table>

**TABLE IV. Average response times for the 7-min audiovisual task in the study of Bruce and Bach (1976; courtesy of Dr D. L. Bruce). Group numbers (10 subjects per group) are given in parentheses. Experimental dosage was nitrous oxide 500 p.p.m. plus halothane 10 p.p.m. in air. The row effect is significant at 0.1%**

<table>
<thead>
<tr>
<th>Session 1</th>
<th>Session 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental</td>
<td>1.30 (1)</td>
</tr>
<tr>
<td>Control</td>
<td>1.08 (2)</td>
</tr>
</tbody>
</table>

The experimental designs of the three studies are exactly the same. The difference in effect of atmospheric conditions between this study and those of Bruce are, first, differences in manner of drug administration (oxygen tent and mask in the Bruce, 1974 and 1976 studies, respectively), second, a longer duration of exposure (4 h) adhered to by Bruce and colleagues, and third, a small difference in the RT task. In the Chicago studies, subjects were requested to judge whether there was a high or low frequency of clicks presented over earphones simultaneously with one of two visual signals. As it takes longer to judge “click frequency” (cf. tables III and IV) than to judge pitch (cf. table II), the former task might be supposed to be slightly more difficult, thus leading to somewhat longer response times. Also, the American studies used a pattern of ventricular fibrillation from an electrocardiographic stimulator appearing either on the top or on the bottom channel (1974), or appearing in contrast with a horizontal flat line on a single channel (1976) of an oscilloscope screen. In both instances the discriminability of the two visual signals cannot be thought to
have been any more difficult than that of the upper and lower signal lights used in the present experiment. A fourth difference was the double blind procedure followed in this study.

However, none of these minor differences in experimental technique seems to offer a satisfactory explanation for the differences in the results of the present study and those of Bruce and his colleagues.

ACKNOWLEDGEMENTS

This study was carried out with the support of a grant from the “Preventie Fonds” to the Department of Anaesthesiology. The authors wish to thank Professor Joh. Spierdijk, Miss H. v. Meeverden, and Mr A. Högeling of the Department of Anaesthesiology and the staff of the Netherlands Institute of Preventive Medicine TNO, whose generous help and hospitality were indispensable in designing and running the experiment.

REFERENCES


MANQUE DE REPRODUCTION DES EFFETS NEGATIFS DES TRACES D'AGENTS ANESTHESIANTS SUR LES PERFORMANCES MENTALES

RESUME

Vingt-quatre sujets mâles ont chacun entrepris une sélection de tâches apparentées, pendant chacune des deux différentes sessions d'une durée de 2 h, dans une chambre climatique. Douze sujets ont respiré un mélange d'air, de protoxyde d'azote à raison de 1600 p.p.m. (v/v) et d'halothane à raison de 16 p.p.m. (v/v) pendant la première session, et seulement de l'air pendant la seconde session, tenue une semaine plus tard. En ce qui concerne les 12 autres sujets, cet ordre a été inversé. Les tests consistaient à apprendre une liste de paires de mots et de chiffres, à résoudre une série de problèmes d'anagrammes, à reconnaître les mots et les chiffres, à se souvenir des paires de mots et de chiffres et à exécuter une tâche minutée, comportant un choix de quatre réactions audiovisuelles. Les tests ont commencé après 45 min d'exposition à ces conditions atmosphériques. On a observé au cours de la tâche audiovisuelle un fort désir de vouloir apprendre aussi bien pendant les sessions, qu'entre les sessions. Aucune de ces tâches n'a, toutefois, reflété d'effet adverse des traces d'agents anesthésiants.

ERFOLGLOSER VERSUCH DER UMBIEGUNG NEGATIVER WIRKUNGEN VON SPUREN-ANÄSTHETIKA AUF GEISTIGE LEISTUNGSFÄHIGKEIT

SUMMARY

Twenty-four male subjects undertook a selection of similar tasks, each lasting two different sessions of 2 h, in a climatic chamber. Twelve subjects inhaled a mixture of air, 1600 ppm nitrous oxide (v/v) and 16 ppm halothane during the first session, while the remaining subjects inhaled pure air during the second session, a week later. Neither of these two groups showed any signs of adverse effects of the small concentrations of nitrous oxide and halothane used on their psychomotor or perceptual performance, nor did they develop any memory disturbances or suffer any delays in reaction time.

ACKNOWLEDGEMENTS

This study was carried out with the support of a grant from the “Preventie Fonds” to the Department of Anaesthesiology, and the authors wish to thank Professor Joh. Spierdijk, Miss H. v. Meeverden, and Mr A. Högeling of the Department of Anaesthesiology and the staff of the Netherlands Institute of Preventive Medicine TNO, whose generous help and hospitality were indispensable in designing and running the experiment.

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