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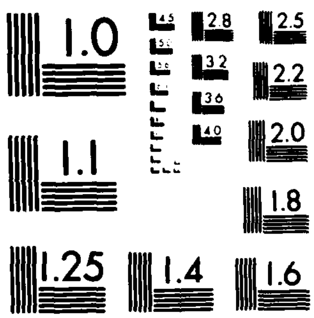

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NEUROBEHAVIORAL EFFECTS OF CARBON MONOXIDE (CO) EXPOSURE IN HUMANS
PROTOCOL 1, FINAL REPORT

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Carbon monoxide (CO) is the byproduct of incomplete combustion. As such it occurs in many military and industrial settings. The neural and behavioral effects of acute low level CO exposure are not well known but have been reported to produce sensory and vigilance deficits.

This final report of the first year of work in a five year research program designed to study the neural and behavioral effects of CO. This program has three distinct stages. Stage one is to establish a reliable paradigm for the measurement of CO effects. During stage two concentration-effects functions are to be established. -

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ABSTRACT (continued)

Stage three is concerned with the evaluation of the concentration effects functions in an actual field (army training) setting.

A total of 92 subjects were used in this double-blind study, 47 air-exposed controls and 45 subjects exposed to 200 ppm CO for 1.5 hours. After having been trained, subjects performed a foreground task consisting of tone judgments and a background task consisting of light flash detection. Tone judgment behavior consisted of reading a 10-second description of three tones in terms of loudness and pitch. Tones were then presented and subjects were required to judge the accuracy of the tones with respect to the just-read description. While reading the tone description, the subject was required to detect the infrequent occurrence of dim light flashes around the periphery of the cathode ray tube on which the tone description was displayed. Light flash detection was considered a vigilance task. Electroencephalograms (EEGs) were collected from left and right parietal sites during task performance. Power and cross spectra were used to analyze EEG data.

Subjects' data were divided into two subsamples, the exploratory sample and the confirmatory sample. Exhaustive statistical analyses were conducted on the exploratory sample, resulting in anticonservative tests of significance. Based on these tests, many variables not affected by CO were eliminated from further consideration. Variables were also eliminated based upon uninterpretable effects but only if p values were marginally small. The surviving dependent variables were used to construct formal a priori hypotheses. These hypotheses were then tested with the confirmatory sample data, which had not previously been seen.

In the confirmatory analyses CO did not affect any behavioral measure. Alpha-band EEG power may have been affected by this level and duration of CO exposure. Although the trends were subjectively reliable for each of two tasks on both EEG sites in both halves of the sample and in the total group, the effect did not reach statistical significance. Vigilance, alpha-band EEG power and theta-band EEG power had significant trends across time.

These data and the CO literature were compared with the effects of hypoxic hypoxia. Apparently unless CO has some non-hypoxic effect, no consistent vigilance decrement should occur until COHb reaches about 13%. There might be specific but minor effects as low as 7% COHb. Since these figures were based upon extrapolations, they are subject to considerable error.

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EXECUTIVE SUMMARY

Carbon monoxide (CO) is the byproduct of incomplete combustion. As such it occurs in many military and industrial settings. The neural and behavioral effects of acute low-level CO exposure are not well known but have been reported to produce sensory and vigilance deficits.

This is the final report of the first year of work in a five year research program designed to study the neural and behavioral effects of CO. This program has three distinct stages. Stage one is to establish a reliable paradigm for the measurement of CO effects. During stage two concentration-effects functions are to be established. Stage three is concerned with the evaluation of the concentration effects functions in an actual field (army training) setting.

A total of 92 subjects were used in this study, 47 air-exposed controls and an independent group of 45 subjects exposed (double blind) to 200 ppm CO for 1.5 hours. After having been trained, subjects performed a foreground task consisting of tone judgments and a background task consisting of light flash detection. Tone judgment behavior consisted of reading a 10-second description of three tones in terms of loudness and pitch. Tones were then presented and subjects were required to judge the accuracy of the tone with respect to the just-read description. While reading the tone description, the subject was required to detect the infrequent occurrence of dim light flashes around the periphery of the cathode ray tube on which the tone description was displayed. Light flash detection was considered a vigilance task. Electroencephalograms (EEGs) were collected from left and right parietal sites during task performance. Power and cross spectra were used to analyze EEG data. Before and after the exposure period subjects were given a test of speech articulation consisting of the reading of banal sentences.

Subjects were divided into two subsamples, the exploratory sample and the confirmatory sample. Exhaustive statistical analyses were carried out on the exploratory sample, resulting in anticonservative tests of significance. Based on these tests, many variables which were not affected by CO, were eliminated from further consideration. Variables were also eliminated based upon uninterpretable effects but only when p values were marginally small. The surviving dependent variables were used to construct formal <u>a priori</u> hypotheses. These hypotheses were then tested with the confirmatory sample, the data from which had not previously been seen.

In the confirmatory analyses CO did not affect any behavioral measure. Alpha-band EEG power may have been affected by this level and duration of CO exposure. Although the trends were subjectively reliable for each of two tasks on both EEG sites in both halves of the sample and in the total group, the effect did not reach statistical significance. Vigilance, alpha-band EEG power and theta-band EEG power had significant trends across time. Speech articulation was not affected by CO. In the Introduction it was argued that if CO has no nonhypoxic effects, there should be no vigilance decrement due to CO until COHb reaches 13%. The mean COHb of the subjects at the end of exposure was about 6.24%. On the

other hand, the corresponding COHb for the CO-exposed subjects in Putz et al. (1976, 1979) was only 5% and for Horvath et al. (1971) was 6.6%. Small differences in task sensitivity could account for the nonsignificant findings in this study, but the comparison to hypoxic hypoxia implies that no vigilance decrement should have occurred.

CONCLUSIONS

1. Vigilance, tone judgment and speech were not affected by 1.5 hours of exposure to 200 ppm CO.

2. Alpha-band EEG power in 200 ppm CO-exposed subjects may not increase as much as in air-exposed subjects. This difference was not statistically significant.

3. No other EEG measure was related to CO.

4. Time on task significantly affected vigilance, alpha-band EEG power and theta-band EEG power. Vigilance (d') was decremented, EEG powers were increased.

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TABLE OF ABBREVIATIONS

A to D	analog to digital conversion, the conversion of an analog signal to numeric data for further statistical processing
ANCOVA	Analysis of CO variance; a statistical technique
CNS	central nervous system
COHb	carboxyhemoglobin, a measure of the level of carbon monoxide in the blood
CRT	cathode ray tube, a video screen
dB	decibel, a measure of sound intensity
EEG	electroencephalogram, the electrical signal recorded from the brain of an organism
EOG	electrooculogram, the electrical signal generated by eyeball or eyelid movement
Hz	cycles per second
MANOVA	multivariate analysis of variance, a statistical analysis technique
N	number of subjects
p	probability
P1/N1	in evoked potential analysis the value of the span from the first positive peak to the first negative peak
P3, P4	location of the EEG electrodes on the parietal area of the scalp according to the international 10/20 system
ppm	parts per million, used to express the level of CO in the air
SPL	sound pressure level
TJ	tone judgment, evaluation of the accuracy of the played tones
TR	tone reading, the reading of the description of tones prior to hearing them played
μV	microvolts
Vol%	volume percent

GLOSSARY

a priori	an experimental hypothesis made before conducting the experiment
alpha	EEG activity in the frequency range of 8 to 12 Hertz
analog to digital	the conversion of an analog signal to numeric data for further statistical processing
A-weight	The weighting of a sound a frequency weighting network which approximates human loudness of sounds of different frequency compositions
β	in signal detection theory a measure of the subjects' willingness to risk a false alarm
background task	a task that is not done continuously but is concurrent with an ongoing foreground task
beta	EEG activity in the frequency range of 13 to 20 Hertz
bolus	a brief higher than ambient level of pollutant exposure
Bonferroni Correction	a statistical technique employed to adjust the calculated p values for the number of statistical tests carried out upon the data to arrive at a more accurate estimate. This reduces the probability of committing a type I error (see)
coherence	a multiple squared correlation spectrum giving the strength of relationship between synchronized activity between the hemispheres
d'	in signal detection theory a measure of the subjects' sensitivity
delta	EEG activity in the 1 to 4 Hertz range
double blind	an experimental strategy wherein the subject nor the experimenter in contact with the subject is aware of the exposure condition. This strategy is used to minimize experimenter and subject bias
electroencephalogram (EEG)	the recorded electrical activity of the brain of an organism
electrooculogram (EOG)	the recorded electrical activity of the muscles of eye movement and eye closure

evoked potential — electrical activity in the central nervous system occassioned by a sensory stimulus

flicker fusion — the point at which a flashing light when increased in frequency of flashing appears to be a constant light

flutter fusion — the analog to flicker fusion in the auditory system

foreground task — a task that demands constant attention and processing to perform well (see background task)

gain — a multiple coefficient of regression between hemispheres and yields information about the ratio of amplitude of the synchronized activity

hypoxia — reduced oxygen carriage by the blood

hypoxic hypoxia — reduced oxygen carriage by the blood due to the reduction of available oxygen

lateralization — the concept that certain mental functions are confined primarily to one hemisphere

parietal — that area of the brain found under the parietal bone of the skull, the parietal lobe of the brain

phase — time lag of the EEG activity between two electrode sites

post hoc — here refers to analyses done after the conclusion of the experiment that were not done to satisfy a priori hypotheses

power — is a measure of electrical energy in microvolts squared for each of the frequency bands evaluated

pseudorandom — random except for certain constraints, e.g. no strings of repeated number longer than some fixed number

SAS — statistical analysis system

signal detection — in psychophysics the identification of a target stimulus embedded in a background of noise

single blind — that experimental paradigm where the experimenter but not the subject is aware of the experimental condition

theta — EEG activity in the range of 5 to 7 Hertz

threshold — in psychophysics the arbitrarily defined point (usually 50%) above which perception of a stimulus is regarded as reliably occurring

<u>type I error</u> — in hypothesis testing, falsely rejectng the null hypothesis and concluding that there was a significant difference due to the experimental manipulation

<u>white noise</u> — acoustical noise of the same amplitude containing all frequencies equally within a specified band

INTRODUCTION

Carbon monoxide (CO) is the byproduct of incomplete combustion. As such it occurs in many military and industrial settings. The neural and behavioral effects of acute low-level CO exposure are not well known but have been reported to produce sensory and vigilance deficits.

This is the final report of the first year of work in a five year research program designed to study the neural and behavioral effects of CO. This program has three distinct stages. Stage one is to establish a reliable paradigm for the measurement of CO effects. During stage two concentration-effects functions are to be established. Stage three is concerned with the evaluation of the concentration effects functions in an actual field (army training) setting.

Before beginning a literature review of the behavioral effects of carbon monoxide (CO) exposure, it will be convenient to discuss the possible mechanisms by which such effects are produced. Such a theoretical context will permit comparison to other bodies of literature and will facilitate prediction of CO effects.

MECHANISMS OF CO EFFECTS

CO and Hypoxic Hypoxia

Blood O_2 Levels. Many investigators have explicitly assumed that the effects of CO accrue because of the reduced oxygen (O_2) carrying capacity of the blood, *e.g.* Horvath et al. (1971), Putz et al. (1976). If this were the case the effects of CO ought to be similar to those of hypoxic hypoxia (hypoxia due to reduced O_2 content in inhaled air) when similar levels of central nervous system (CNS) hypoxia were reached. Since hypoxic hypoxia is a well-studied phenomenon, it might be profitable to pursue this line of reasoning.

Traystman et al. (1978), using anesthetized dogs, produced arterial O_2 content levels of 4-19 volume percent (vol%) by either CO hypoxia or by hypoxic hypoxia. Cerebral blood flow and central nervous system (CNS) O_2 utilization were functions of arterial O_2 content, regardless of whether the reduced O_2 levels were produced by hypoxic or CO hypoxia. These results were also reported to hold for very low levels of CO hypoxia (Traystman 1978). From these data it would seem that (a) if CO produces its effects via hypoxia and (b) if arterial O_2 contents were known for each kind of hypoxia, the effects of CO exposure could be predicted from hypoxic hypoxia. Matters are not as simple as this, as will presently be discussed, but the comparison of CO and hypoxic hypoxia might be useful.

In order to make comparisons of arterial O_2 content for hypoxic and CO hypoxia, Figure 1 was constructed from hypoxic hypoxia data (Dripps and Comroe 1947) and from O_2 disassociation curves for various COHb levels (Roughton and Darling 1944). The following steps were followed in a construction of the curve shown in figure 1: (a) using least squares methods, a line was fitted to hypoxic hypoxia data, predicting arterial O_2 (b) similarly, a line was fitted predicting arterial O_2 contents from COHb and (c) points were plotted for equal arterial O_2 contents. By reference to Figure 1, levels at which hypoxic hypoxia produces various behavioral effects can be used to estimate the COHb levels at which similar effects ought to occur.

Behavioral Effects of Hypoxic Hypoxia. Reduction to about 13% or less O_2 in inspired air produce concentration-related decrements in vigilance (Finan et al. 1949, Cahoon 1973, Fiorica et al. 1971, O'Hanlon and Horvath 1973). Visual threshold increases were noted when inspired air O_2 content was reduced below 13-15% (Halperin et al. 1959, Kobrick 1976). Reduction to 11% O_2 in inspired air was required to increase color thresholds (Franten and Iusfin 1958, Schmidt and Bingle 1953) but Kobrick (1970) demonstrated a reduced color field diameter at 13% O_2 in inspired air. Reported effects of hypoxic hypoxia on flicker fusion have been inconsistent (Tune 1964). Auditory sensitivity appears to be unaffected until O_2 concentrations in inspired air are reduced to below 10% (Klein et al. 1961, Klein 1961, Tonndorf 1953) although these findings are not consistently reported (Curry and Boys 1956). Tracking behavior was affected by O_2 levels in inspired air below 10-11% (Shephard 1956, Scow et al. 1950). Studies of cognitive function have produced mixed results (Tune 1964) but some effects were reported on short-term memory at 15% O_2 in inspired air (Denison 1966).

The above brief review of hypoxic hypoxia effects upon behavior has concentrated upon most sensitive effects. From this review it appears that there are only rarely reported effects at O_2 concentrations above about 13% in inspired air and none above 15%. Reference to Figure 1 reveals that 13% O_2 content is equivalent to about 13% COHb. Fifteen percent O_2 in inspired air corresponds to about 7% COHb. It is reasonable to conjecture that no CO exposure effects ought to occur below about 7% COHb and no widespread effects until about 13% COHb.

Problems and Caveats. As was previously mentioned, the above comparison of hypoxic and CO hypoxias is not without risk. Unlike CO hypoxia, hypoxic hypoxia produces cardiopulmonary compensation (Dripps and Comroe 1947) beginning at about 16-18% O_2 in inspired air. Such cardiopulmonary changes produce readily perceivable introceptive stimuli in the subject which might well act as distraction and activation in behavioral tasks. Similarly such introceptive stimuli might act to alter performance in a state-dependent learning sense. If the effect of hypoxic hypoxia is augumented by this non-hypoxic effect then it follows that even greater hypoxia would be required in CO hypoxia to produce an equivalent effect.

Hypoxic atmospheres produce reductions in arterial O_2 content which approach asymptotic levels in a few minutes (Dripps and Comroe 1947) whereas CO hypoxia does not produce near-asymptotic reductions in arterial O_2 content for several hours. Sudden onset of hypoxic hypoxia leaves the subject with little time to adjust behavioral strategy or increase effort, whereas CO hypoxia permits quite a while for a subject to compensate for behavioral decrements. Whether such compensation actually occurs is, of course, a matter of conjecture. If it does, the subjects exposed to hypoxic hypoxia would have an added decrement to their hypoxia. Again, this implies that CO hypoxia would have to be more extreme than hypoxic hypoxia to produce equivalent effects. For short duration, high level CO exposure, the compensatory question raises quite different issues.

The argument about the equivalence of hypoxic and CO hypoxias in Figure 1 is based upon the assumption of no difference in the CNS effects of hypoxic and CO hypoxias (Traystman 1978, Traystman et al. 1978). In fact, in both of the above studies, while there were no significant differences in O_2 utilization in the CNS, CO hypoxia produced an almost consistently lower mean CNS O_2 utilization. If such a small effect were shown to be reliable by a study with a larger number of subjects or more precise control, then the effect of CO hypoxia would be more extreme than hypoxic hypoxia for a given arterial O_2 content. Hence, CO hypoxia would have to produce less arterial hypoxia than hypoxic hypoxia to get the same behavioral effect.

Before the comparison data set of hypoxic hypoxia is taken too seriously it must be pointed out that these studies, too, have problems. Not all investigators agree as to the threshold for effects. For the above brief review of hypoxic hypoxia effects, however, the highest reported O_2 levels were used. If in fact the reported threshold for effects of hypoxic hypoxia were higher than can be demonstrated, then threshold for CO effects, as estimated from Figure 1, would be too low.

Non-Hypoxic CO Effects

From time to time in the history of CO research, evidence is reported which can be construed to mean that CO has some effects other than hypoxic ones. This body of literature was recently reviewed by Coburn (1979). His general conclusions were that non-hypoxic effects perhaps existed but that they were small compared to the hypoxic ones.

Coburn (1979) paid special attention to the work of Goldbaum et al. (1975, 1977) who reported data on survival rates in various groups of dogs whose COHb had been produced in different manners. Dogs were exposed to 130,000 ppm CO in air to produce COHb values ranging from 54-90%. All died in 15-60 min. Dogs whose COHb was raised to 57-64% by transfusion of blood from exposed dogs, did not die. Thus, it was argued, not COHb, but, some other factor accounted for CO exposure's toxicity. Goldbaum et al. (1975, 1977) argued that non-bound CO dissolved in blood was the critical toxic element. Coburn (1979) argued that: (a) the death in the CO-by-inspiration group was due to lung CO saturation which produced anoxia, (b) data exist to show that when COHb increased more slowly, dogs typically survived COHb values higher than those shown to be fatal by Goldbaum's exposure regimen, and (c) other measures of toxicity (than death) were not taken. According to Coburn's logic, the deaths were still due to hypoxic effects since the lung saturation was a consequence of high exposure levels. Experimental evidence is lacking, but these studies suggest that exposure time-by-intensity profile is an important variable.

If Coburn's logic is accepted, non-hypoxic effects of CO are of little concern. If the less likely hypothesis of Goldbaum is accepted then the possibility of non-hypoxic CO effects at lower levels becomes important.

Mechanism Conclusions

It seems that by a conservative theoretical and comparative approach, the thresholds for CO effects ought to be in the region of 7-13% COHb. Clearly, not all possibilities were exhausted. It is possible that small differences in cardiovascular or pulmonary compensatory mechanisms between hypoxic and CO hypoxias produce sufficiently reduced tissue O_2 levels in CO hypoxia to lower the thresholds below those predicted from Figure 1. The threshold estimate of 7-13% COHb is, however, a provocative prediction for comparison to the body of empirical information on CO effects.

BEHAVIORAL AND NEURAL EFFECTS OF CO

The literature on behavioral and neural effects of CO is large but internally inconsistent. Few studies have gone unchallenged by attempted replications. The following will be an attempt at an evaluative review with the objective of finding reasons for the state of disarray.

Critique

Before reviewing the CO literature it will be of use to explicate certain criticisms of some of the existing work. Many of these criticisms will be directed at the following studies. Rather than explain the problems in detail each time, it is simpler to explicate the problems once and then, simply refer to the problems by name later.

Double-Blind Experiments. Double-blind studies are possible in CO research since CO has no sensory stimulation effect. When the subject nor the experimenter is informed about the exposure condition until after the data have been collected (exposure selected by machine or by someone who has no contact with the subject) then it is not possible to accidentally prejudice the results. Since important consequences accrue from CO research in terms of future monetary and health effects, and, more immediately, in terms of research programs, such unconscious prejudice is quite likely. Unfortunately few studies of CO effects were conducted in a double-blind fashion. The potential importance of this is demonstrated in a study on which both double- and single-blind studies were run (Von Post-Lingen 1964). CO effects were seen only in the single-blind condition.

Quantitative Methods. The most commonly encountered problem in the CO literature is the application of anticonservative statistical tests of significance (Benignus and Muller 1982). Use of anticonservative statistics results in an overestimation of the likelihood of effects of a substance by falsely declaring effects to be significant. When such methods are employed, the reliability of an effect can only be judged by the consistency with which it is reported across investigators. The question of how much consistency is sufficient is not an easy one, except in the unusual cases where an effect is unanimously reported at some level of exposure. This problem is further aggravated by the fact that nonsignificant findings are frequently not published at all.

Concentration-Response Functions. A major problem in CO toxicology is the fact that most studies are done with exposure levels near what is taken to be the threshold for an effect. Very few studies employ a series of exposure levels above threshold. For this reason, effects are poorly described and difficult to demonstrate in a reliable fashion. This problem is in part due to the hesistancy to expose humans to CO levels which are otherwise taken to be harmful, even though only temporarily. Experimenters also fear accidents due to marginal, undetected health problems in subjects. Unless, however, a reliable estimate of concentration-response functions for the various behaviors of interest are available, it is distinctly possible that the dangers are being overestimated because of poor estimates of thresholds. Additionally, unless the trends are well documented, it is not possible to decide how dangerous a deleterious effect may be. Clearly, even though an effect may be deleterious on a short-term basis, it is not reasonable to prevent exposure until the "cost" is well understood.

Miscellaneous. The problems of lack of double-blind studies, anticonservative statistical tests, and near-threshold level studies, while the most frequently encountered, are certainly not the only ones. Such difficulties as inadequate reporting style, lack of control groups, poor quantification of measures and non-systematic treatment of subjects are also common. The latter list, however, will be discussed in the context of the following review.

Vigilance

Vigilance behavior is among the neural and behavioral effects of hypoxic hypoxia which is most reliably and frequently affected. There are also a number of reports of vigilance decrements at low-level CO exposures. As will be seen presently, however, the CO results are not very consistent. Since many of the following studies are related by replication attempts, they will be discussed in groups.

Horvath et al. (1971). Subjects were required to detect the occurrence of a brighter light flash in a series of light flashes. CO exposure of 111 ppm for 120 minutes produced a significantly reduced detection rate compared to air-exposed and 26 ppm CO-exposed sessions. Subjects were exposed for 60 min and then performed the task for an additional 60 minutes during continued exposure. For the 111 ppm CO exposure the mean COHb at the end of exposure was 6.6%.

Two attempts to replicate the Horvath et al. (1971) study both failed to find statistically significant effects. Christensen et al. (1977) used a slightly altered version of the Horvath task and added a number of physiological measurements and maneuvers which were performed during the test. While their CO-exposed subjects (113 ppm) also showed trends in vigilance decrements in the same direction as those of Horvath et al. (1971), their results were not statistically significant. Two other groups were exposed one to 17% O_2 in air, the other to both 17% O_2 and 113 ppm CO. Neither of these conditions had statistically significant affects.

Winneke (1974) also used the Horvath task but with a modified rest schedule and added feedback about performance. By use of a complicated exposure scheme, the highest exposure group reached a mean COHb level of 11.3% by the end of their sessions. No trends in behavioral results were due to CO in any group.

Unfortunately, both unsuccessful attempts to replicate the Horvath et al. (1971) experiment, made possibly important alterations in the way in which the studies were conducted. These alterations could have produced added stimulation, and thus possibly activation, of the subjects. It may reasonably be argued that these changes counteracted the CO decrements. If it had not been for the altered experimental designs, the above studies could be considered to be definitive results. Their statistical tests were not significant even though anticonservative tests were used. Since Horvath et al. (1971) also used anticonservative tests, it is possible that, properly analyzed, their results would have been statistically nonsignificant. The only aspect of these studies which make the data worth consideration, is, that in two of three studies (Horvath et al. 1971, Christensen et al. 1977) the trends were in the direction of CO effects.

Groll-Knapp (1972). These authors presented sparsely documented results using auditory signal detection. Tone pairs were presented where the second tone was sometimes "weaker" than the first and represented the signal. Subjects were exposed to 0, 50, 100 or 150 ppm for 2.5 hours but COHb was not measured. Detection rate dropped, in a concentration related fashion, beginning at 50 ppm.

The significance tests used by Groll-Knapp et al. (1972) were very anticonservative. Perhaps the consequences of such statistical practices are best illustrated in this case. Without publishing further data, the authors have twice mentioned failures to replicate (Groll-Knapp et al. 1979, Haider et al. 1976).

Fodor and Winneke (1972). Short bursts of white noise were used as stimuli and subjects were required to detect infrequent bursts which were slightly less intense than others. Subjects were exposed to 0 or 50 ppm CO for 80 minutes and then, during continued exposure, performed three blocks of 45 minutes vigilance tests. No COHb measurements were taken. By a anti-conservative test, a drop in signal detection rate during the first block of vigilance behavior was declared significant. The performance during the last two blocks was not statistically different and the CO group means were close to those of the control group.

Winneke (1974) used a slightly modified version of the above task, using exposures of 0, 50 and 100 ppm CO, and failed to find any effects. The fact that the earlier study (a) used anticonservative statistics (b) showed an effect early but not late in exposure and (c) used very low levels of CO makes the nonreplication more or less expected.

Beard and Grandstaff (1975). In this study subjects were exposed to tone bursts and required to detect shorter-than-normal tones while exposed to either 0, 50, 175, or 250 ppm CO for a total of 50 minutes The 50 and 175 ppm CO groups had significantly reduced performance (by a anticonservative test, but not after Bonferroni corrections were made). The 250 ppm group mean was nearly as good as the control group mean. Since results were not concentration related and anticonservative statistics were used, these data are quite suspect. No attempt at replication has been reported.

Benignus et al. (1977). Short term memory and vigilance were combined by requiring subjects to report numerals of differing parity in strings of three. Subjects were exposed to 0, 100 and 200 ppm CO for 3 hours and 20 minutes while the numerals were flashed on a display. COHb values for the three groups were 0.01, 4.6 and 12.6%. No statistically significant CO effects were found.

Putz et al. (1976, 1979). These investigators used a complex task structure involving a foreground tracking task (of which more will be said under the heading of Motor Performance, p 19) and a background light flash detection task as a vigilance probe. Subjects were exposed in a double blind manner to 0 or 70 ppm for a total of 4 hours, producing a mean COHb in the 70 ppm group of 5%. No difference was noted in detection rates but the reaction times in the CO group were reduced in a time-of-exposure related fashion. Since the results were substantially the same in both studies, the credibility is increased. This is especially true since there were substantial differences in the protocol between the two studies.

The Putz studies represent the most credible CO effects on vigilance reported. The statistics were reasonable, the results were time-of-exposure related and the effects seem robust with respect to protocol alterations. None of the other vigilance studies used reaction time. Putz el al. might have observed detection decrements if they had allowed a shorter time during which a response would be accepted. Another major difference in the Putz studies with respect to others was the use of a complex foreground-background design. It is noteworthy that the reaction time decrements due to CO exposure only occurred during the more difficult of two tracking tasks. Apparently, the subject must be taxed by additional behavioral loads to show CO effects on vigilance.

No attempt has yet been made to replicate the Putz et al. studies by independent investigators. Their high credibility would seem to be an encouragement to continue such research in order to find concentration-related data.

The fact that the effects occurred at such a low level is, from one standpoint, suspicious, but from the task-sensitivity standpoint, it is encouraging.

Summary. Only one pair of studies have produced reliable vigilance data by a number of evaluative criteria (Putz et al. 1976, 1979). Others have either failed the important test of replicability, have shown no significant effects or have had other serious credibility flaws. The only study, other than Putz et al., which has promise, is that of Horvath et al. (1971). Were it not for the Putz et al. study, it would not be unreasonable to declare that no significant vigilance effects had been demonstrated at CO exposures lower than 250 ppm. Since no data on higher levels of exposure have been reported, little else can be said.

Psychophysics

Sensory judgments appear to be among the most sensitive to hypoxic hypoxia. CO exposure, too, has been reported to produce decrements in such behaviors. As is usual in CO literature, there is much disagreement among studies.

Audition. No effects of CO exposure upon the auditory sense have been reported. Perhaps this is because only two studies have been conducted, both of them upon fairly insensitive dependent variables. Guest et al. (1970) reported that no changes in white noise flutter fusion were produced in subjects whose COHb reached 10%. Stewart et al. (1970) ran standard screening audiograms on subjects exposed to 100 ppm CO for 8 hours (12% COHb) and noted no effects. The fact that the dependent variables are fairly gross and variable unless practiced subjects are used, makes the two results of CO-auditory effects inconclusive. Hypoxic hypoxia, also seems to affect auditory processes only at fairly extreme levels, but there too only thresholds have been measured.

Vision. The visual system has been extensively studied with respect to CO effects. The literature is, unfortunately, in a state of great uncertainty. The most obvious measure of visual function, the absolute threshold to light stimulation, has been reported to be unaffected by CO exposures up to 250 ppm for one hour (Beard and Grandstaff 1970) but only four subjects were used and data were reported to be highly variable and were not reported. McFarland (1970), McFarland et al. (1944) and Halperin et al. (1959) reported an important experiment using trained subjects to reduce variability. They exposed subjects to short boluses of CO to rapidly raise COHb levels to 4.5, 9.4, 15.8 and 19.7%. At each increase in COHb, there was a small but reliable increase in visual threshold. Only four subjects were used and data were not well analyzed, nor were the studies conducted in a double-blind fashion. This study urgently requires replication since the three citations above were all reports of the same experiment. No conclusion can be drawn about visual threshold effects due to CO exposure with such a paucity of data. Since hypoxic hypoxia produces threshold alterations at levels of 13-15% O_2, the results of the early work by the McFarland group are plausible.

Visual acuity, depth perception and color judgment have been reported to be unaffected by COHb levels of 12% (Stewart et al. 1970). Glare recovery in night vision or depth perception were not affected at 4.4% COHb (Wright et al. 1973). Ramsey (1972, 1973) reported that up to 12.1% COHb did not alter the visual difference threshold for brightness or depth perception.

Critical flicker fusion has been studied widely and reported to be unaffected by CO exposure, in some cases high enough to produce 26% COHb (Fodor and Winneke 1972, Guest et al. 1970, Lilenthal and Fugitt 1946, O'Donnel et al. 1971a, Ramsey 1973, Vollmer et al. 1946, von Post-Lingen 1964). With the exception of absolute visual threshold effects, it would appear that visual function is not affected by CO exposure.

Two additional studies must be mentioned, however, which cast doubt upon the conclusion. In a poorly documented study, four subjects were exposed to 0, 50, 150 or 250 ppm CO for one hour (Beard and Grandstaff 1970). Data were selectively reported and legitimate statistical analysis was impossible. The authors reported concentration-related decrements in brightness-difference threshold, critical flicker fusion and visual acuity. If this were the only study showing such effects, there would be no problem in considering the effect of CO on vision as innocuous at low levels. Seppanen et al. (1977) used 1100 ppm transients of CO to raise the COHb of 22 subjects in steps to 13%. Beginning at 5% COHb, the critical-flicker-fusion threshold decreased in a concentration-related fashion. This latter result could have been due to the transient exposure or to the unfortunate fact that it was a single-blind study.

If visual system function is affected at all below 20% COHb, only sparse evidence for these effects can be found and even that evidence has serious problems. Auditory processes have been studied so infrequently that no conclusion is warranted. The importance of sensory processes and the sensitivity of the visual sense to decrements produced by hypoxic hypoxia makes it important to replicate and extend the few reports of CO-related decrements.

<u>Time Discrimination</u>. A study by Beard and Wertheim (1967) demonstrated concentration related decrements in time discrimination for CO exposures of 0, 50, 100, 175 and 250 ppm. Several other experimenters, using similar but not identical protocols failed to show any decrements (O'Donnell et al. 1971a, Stewart et al. 1973). An almost exact replication by Otto et al. (1979) also failed to show any CO effects. The reason for the concentration-related effects of Beard and Wertheim is not clear. Their study was run in a single-blind fashion, however, and this could, conceivably, have produced the effects.

Other studies using time estimation of different kinds, (O'Donnel et al. 1971a, Stewart 1975, Stewart et al. 1975, Mikulka et al. 1970) found no effects of CO.

Motor Performance

Coordination. Fine manual movements of various kinds were unaffected by COHb levels of less than 30% (Stewart et al. 1970, 1975) and lower levels (Wright et al. 1973, Fodor and Winneke 1972, Winneke 1974). Bender et al. (1971, 1972) reported, however, that when concurrent verbal behavior is required, Purdue Pegboard performance is affected at COHb levels of 7%. Ambulation was not affected at 6.6% COHb (O'Donnell et al. 1971).

Tracking. Compensatory tracking, a well studied motor performance in human engineering, is not affected by hypoxic hypoxia until inspired air levels of 10-11% O_2 are reached. Only a few studies have been done on this task with CO. O'Donnel et al. (1971a,b) used a task requiring subjects to keep a meter needle centered as part of a multi-task battery but saw no reliable effects of COHb levels up to 12.7%. Putz et al. (1976, 1979) in two studies using two different protocols demonstrated a time-on-task-related decrement in tracking with COHb levels of only 5%. Two levels of difficulty were used and the decrement only occcurred at the more difficult level. Their task involved keeping a vertically moving spot on a cathode ray tube (CRT) centered. Even though their statistical procedures were slightly anti-conservative, their time-on-task related results and their replication using a different protocol make their data credible.

Driving. Several investigators have either simulated or used actual driving tasks during CO exposure. Most of these studies have shown no effects of CO even for 30% COHb (Forbes et al. 1937). More recent studies used small numbers of subjects and were described in poor detail but reported no CO effects on actual automobile driving (Weir and Rockwell 1973, McFarland 1973). Wright et al. (1973) reported that transient exposure to 20,000 ppm CO to produce 4.4% COHb produced significant driving performance decrement. However, after Bonferroni corrections were made for very anti-conservative post hoc statistical analyses the effects were not significant.

In only one study (Rummo and Sarlanis 1974) was any CO related driving decrement reported. The investigators used a driving simulator and exposures of 800 ppm prior to a 2 hour test period to produce 7.6% COHb at the beginning and 6.0% COHb at the end. This semi-transient exposure to CO was reported to have increased reaction times to changes in lead-car speed. The statistics employed were anti-conservative and these results would probably not have been significant under proper analyses.

It would seem that some more sensitive measure of fine motor control should be used. Tracking is not the only such measure. An important motor behavior which has not been studied is that of speech articulation. Many neural pathologies, drugs and a number of self-administered toxic substances are known to produce slurred speech. No study of speech articulation and low level CO exposure has been found.

Electrophysiology

CO effects in the CNS might be detectable using electrophysiological measures. Some of these measures are broad screens for CNS effects and do not rely upon particulars of behavior to be detected.

Hosko (1970) demonstrated no electroencephalogram (EEG) or visual evoked potential changes below COHb levels of about 20%. Groll-Knapp et al. (1972) reported a reduced-amplitude slow wave potential after exposure to 150 ppm CO but the data were poorly analyzed and reported. Putz et al. (1976) reported an increased P_1/N_1 amplitude ratio of an auditory evoked potential over time in a 4 hr. exposure to 35 and 70 ppm CO. No quantitative work on EEG analysis was found.

It is logical to expect EEG measurements to be useful in the description of CO effects, especially if activation of the CNS were decreased by CO. Lindsley (1951) summarized his own and others' work by the general statement that as activation increases from sleep to full alertness there are progressively lower amplitudes and higher frequencies in the EEG. The alpha EEG band presents high amplitude sinusoidal waves when subjects are relaxed but awake (Lindsley 1957). Alertness abolishes (blocks) alpha waves. As the subject progresses from relaxed toward drowsy, the alpha activity also diminishes to be replaced by lower frequency random waves. Alpha waves are, unfortunately also correlated with eye fixations of various kinds (Mulholland and Peper 1971). It is also well known that the relationship between EEG and activation can be disrupted or "disassociated" by e.g. systemic administration of atropine (Wikler 1952). While there are interpretive problems with the use of EEG, it can, in many instances prove a valuable measure of the activity of the CNS.

Discussion

In the above review, the most outstanding conclusion is that much unreliable work has been done. Few experimenters found CO effects and few of these effects were credible. The studies by Putz et al. (1976, 1979) were perhaps the most credible. COHb levels of 5% were reported to have affected vigilance, tracking and electrophysiology. The vigilance study by Horvath et al. (1971) also is worthy of note. Visual threshold increases reported originally by McFarland et al. (1944) to COHb levels below 5% seem consistent but require replication. Other reported marginal CO effects do not form coherent patterns and/or were not replicable.

Confounded Tasks. Most of the tasks which were reported to have significant CO-related decrements were in some way related to sustained performance. Certainly vigilance behavior falls into this class. Visual threshold estimation is a long-duration, high-attention task. Tracking is a sustained, demanding task and was carried on for 4 hours (intermittently) in the studies reported by Putz et al. (1976, 1979). It may be that all of the effects which were reported were due to loss of vigilance and/or fatigue, even though different sensory or motor systems were evaluated. Whatever the source of the decrements (if real), it may to be the case that sustained performance of a task is required to produce the effects, at least at low levels of CO exposure.

Difficulty Level. In most of the studies in which statistically significant effects were reported, task difficulty level was high. Often subjects were taxed by simultaneous performance of multiple tasks. Only during more difficult task levels were CO effects seen. Perhaps, this too, points to a fatigue/CO interaction.

Exposure profile. Information about the effects of the time-concentration profile of CO exposure is scant. The large majority of investigators have used continuous exposures. In several cases where transient or semi-transient exposures were used, the effects tended to be more extreme (McFarland et al. 1944, Seppanen et al. 1977, Rummo and Sarlanis 1974). If transient exposure were directly compared to continuous exposure along some dimension and shown to be more deleterious, this would be an important finding, both practically and theoretically. A major problem in this area would be the dimension along which CO exposures would be comparable between transient and continuous profiles.

The Negative Results. Many studies showed no effects of CO exposure at low levels. In the above review, a number of the studies were cited repeatedly in different sections of the review. Authors reported studies in which many dependent variables were measured simultaneously on few subjects. Such designs tend, unless an immense number of subjects are used, to report too many significant results as noted by (Benignus and Muller 1982). When all of these anticonservative tests are not significant, however, the statement of negative results can be very compelling, depending upon the number of subjects and the size of important effects. In general, the statistically nonsignificant findings discuss above fall into the category of being more compelling than it would appear from the review since multiple dependent variables were collected but were not all reviewed in the same section for a given study.

Conclusion. CO seems to affect some aspect of continuous performance in human beings, whether it is measured in sensory or motor systems. It is not at all clear where the threshold for such effects should be set. If the results of some studies are indeed replicable, CO appears to produce effects at arterial O_2 levels higher than those produced by hypoxic hypoxia. Either (a) different mechanisms are at work or (b) the hypoxic hypoxia threshold are given at too low an O_2 level or (c) the CO results are reported at too low a COHb level. Without adequate concentration-response functions, this question will probably not be resolved.

PURPOSE OF THIS STUDY

This study was designed to construct and standardize a task which would later be used to produce concentration-response functions. The most reliable-appearing task in the literature was a foregound/background vigilance task (Putz et al. 1976, 1979). A new task was designed along those lines. In addition to this behavioral task, two other measures were included; the EEG because it is a measure of activation and a speech articulation test as a measure of fine motor coordination.

METHOD

SUBJECTS

Subjects were 92 male volunteers paid $5.00 per hour to participate. A bonus of up to $4.00 was also paid to the subjects in direct proportion to the number of correct tone judgments as an incentive. All subjects had been screened for handedness, since the foreground task involved EEG lateralization, using a modified version of Annet's (1967) test (Briggs and Nebese, 1975). Only those subjects with scores above 6.0 were accepted. A score of zero is assigned to non-lateral subjects and scores range ± 24. All subjects had also been given physical examinations by a physician and had made normal scores (± 1 SD) on the Minnesota Multiphasic Personality Inventory. The mean age of the group of subjects was 22.3 yr (SD = 4.03, Range = 18-32).

TASKS

Foreground Task

The foreground task was designed to (a) engage the subject in a difficult task and (b) alternately engage the left and right hemispheres of the CNS. One part of the foreground task involved reading tone descriptions (TR) and was expected to engage the left hemisphere (Sperry 1974, Gazaniga 1967). The other part of the foreground task required tone judgment (TJ) and was expected to engage the right hemisphere (Sperry 1974, Gazaniga 1967). Since this report will concentrate on CO effects, the issue of lateralized function of the CNS is only mentioned here to show the rationale involved in task construction.

A training session was given to subjects before CO or air exposure commenced. During this training session subjects were trained by successive approximation and then given a block of practice performance. In the practice block the TR and TJ tasks were performed in alternating trials for a 7.5 minutes period. The subject was required to read a description of a 3-tone sequence shown on a CRT. Each of the 3 tones was described as being either low, medium or high in pitch and short, medium or long in duration. After a 10 second period during which the tone description could be carefully read several times, the CRT was blanked for 1 second Three tones were then sounded via a speaker directly over the subject's head and the subject was required to judge their accuracy according to the just-read description. Tone durations were .25, .5 and 1 second and tone frequencies were 500, 1,330 and 2,160 Hz. Tones were separated by a .25 second silence and were approximately 60dB SPL (A-weight) in loudness. The TJ response was a two-switch yes-no decision made immediately after the last tone sounded. Yes-no switches were mounted on the right arm of the subjects' chair. Subjects were approximately 80% correct in their TJ behavior. The training block was conducted in a manner typical of subsequent testing.

Background Task

During the TR task the subject also watched for dim flashes of green light which he was to report by pressing a switch mounted on the left arm of his chair. Flashes were produced by 3 mm diameter green (565 nm) light-emitting diodes (Hewlett Packard HLMP-1501) driven by a current of 6.2 ma. Flash duration was 30 milleseconds. Four diodes were mounted against a black background around the CRT screen as shown in Figure 2.

Flashes occurred pseudorandomly on each of the four diodes. The flash also pseudorandomly occurred at one of four times during the TJ task, either 1, 3, 5 or 7 seconds after the tone description appeared on the CRT. Pseudorandom schedules for place and time were constructed independently. Finally a pseudorandom schedule was constructed to select the trial number on which a flash would actually occur. In each block of 50 trials 10 flashes occurred. The same schedule was repeated for each block of 50 trials.

Speech

Speech articulation was tested before and after each subject's exposure period. The speech task consisted of reading 113 banal sentences from the Templin-Darley Test of Speech Articulation (Templin and Darley 1969). Since fine motor control was being tested, only sentences testing consonant articulation were used. The same test was used before and after exposure. The subject's speech was recorded using an RCA type 77DX dynamic microphone and an Aiwa model 3600 cassette recorder with Maxell C90 tape. Scoring was performed off-line by a speech pathologist in a blind fashion.

EEG RECORDING

Silver-silver chloride electrodes were placed on left and right parietal sites, P3 and P4 (International 10-20 system), using Grass electrode cream. Reference electrodes were linked mastoids. Electrooculogram (EOG) electrodes for vertical eye movements and mastoid electrodes were attached with adhesive collars and Beckman electrode jelly.

EEG and EOG were recorded with a Beckman Dynagraph and analog-to-digital (A-D) converted on a PDP-11/34 computer using an LPA-11 A-D converter. EEG was filtered using the Beckman Dynagraph filters so as to produce a high frequency 3dB point of 22 Hz and a low frequency 3dB point of .15 Hz. A-D conversion rate was 128 Hz. A 1-second segment of EEG and EOG was collected on each of 40 trials beginning 3 second after the start of TR and another beginning with the first tone during the TJ task. Similar recordings were also collected during the practice block before exposure. EEG was not recorded during trials in which a light flash occurred.

EEG data were edited for EOG artifact by rejecting all trials with an EOG peak greater than 75 μV from baseline. Edited EEG data were stored in a Statistical Analysis System (SAS) data base (Helwig and Council, 1979). Power spectra for P4 and P3 were formed by averaging across frequency bands and averaging over all available trials of a particular kind to produce the classical frequency band spectra: delta = 1-4 Hz, theta = 5-7 Hz, alpha = 8-12 Hz and beta = 13-20 Hz. Estimates of coherence, gain and phase between P3 and P4 were also computed for each of the above frequency bands. Power spectra were common-log transformed to avoid problems with heterogeneity of variance and non-Gaussian distributions.

PROCEDURE

In order to summarize the procedure the following step-by-step outline was constructed. Details are given below.

I. Subject preparation
   A. Informed consent
   B. Electrode application
   C. Blood drawn
   D. Entry into chamber
   E. Checkout of electrodes

II. Training (no CO)*
   A. Successive approximation by piecewise introduction of parts of task (12 minutes)
   B. Practice session (24 TR-TJ trials).

III. Speech test (no CO)*

IV. Exposure testing
   A. Two groups, 0 ppm or 200 ppm CO
   B. Begin exposure immediatgely after speech test (or training*)
   C. Subject relaxation (3 min.)
   D. TR-TJ performance (80 minutes)
   E. Speech test (with CO)

V. Terminate exposure-debrief.

*Half of the subjects were trained first, then given speech test. The other half were treated vice versa.

Preparation and Chamber

Subjects who had been previously screened were informed of the nature of the study and consent was obtained. They were then prepared for EEG recording and a 5 ml sample of blood was drawn. Subjects were comfortably seated in one corner of a double-wall $2M^3$ audiometric room with light-beige walls. A 55 dB (A-weight) white noise was used as masking. Tones were clearly audible above masking noise. The video screen was placed about 1.75m from the subject, diagonally across the chamber and was masked to leave a 10 x 5 cm high message area for the tone description (see Figure 2). Each letter in the message was about 6 millemeters in height. The temperature and humidity in the chamber were regulated at 80°F and 80% respectively. Lighting was obtained from a single unshielded 25w incandescent lamp mounted over the subject's head.

Training

After the subject had been seated, preliminary EEG tests had been run and the door to the chamber shut, the training period was begun. Subjects were trained, using successive appromixation methods, to do the TR-TJ task. After a fixed-length training period (12 minute) EEG was recorded during 24 TR-TJ trials. The speech test and the TR-TJ tasks were given in randomized order across subjects.

Exposure Testing

After the practice session, the subject was allowed to relax for three min at the beginning of which CO exposure began (if a subject was to receive CO). Following the rest, the subject performed the TR-TJ task and the concurrent vigilance task for 80 min (a total of 350 trials in 7 blocks of 50). The subject was not informed about trial numbers or blocks. Subjects were exposed to CO for the entire duration of the task performance (80 minutes). CO was injected into the chambers air supply and controlled as discussed under Equipment (see below).

Subjects were pseudorandomly selected to be CO-exposed (200 ppm) or control (air only). Each subject served only once under his pseudo-randomly selected condition. Neither the subject or the technician who instructed and prepared the subject were aware of the exposure condition until after the last communication with the subject was made, at which time the technician was informed. The technician learned of the exposure condition just after the training session and just after she had asked the subject via intercom if he had any further questions. Thus the study was conducted in a double-blind fashion.

After testing was complete the subject was removed from the chamber, another 5 ml blood sample was drawn and debriefing was conducted. If the subject had been exposed to CO, he was requested to remain in the laboratory for one hour after completion of the task to permit reduction in COHb.

EQUIPMENT

All stimuli were controlled and all behaviors were measured by a Dynabyte microprocessor. The microprocessor also controlled the collection of EEG data, the CO level in the chamber, and routed all EEG signals to the PDP 11/34.

CO level in the chamber was continuously monitored by a Beckman 315 long path infrared meter. The output of the meter was continuously plotted on a stripchart recorder and was also sampled every 2 minutes by the microprocessor then computed a correction factor and adjusted an electronic flow controller to correct for drift in CO level. The air flow in the chamber was about 100 CFM, providing about 30 air exchanges per hour.

EXPERIMENTAL DESIGN AND ANALYSIS

Exploratory-Confirmatory Procedure

This study is typical of others in the area of toxicology in that many dependent variables have been measured. Legitimate statistical procedure requires the formation of hypotheses about these variables on an *a priori* basis. For each hypothesis formed, some account must be taken for the fact that other related measures are also being collected and tested on each

subject (Kirk 1968, Abt 1981, Benignus and Muller 1982). The usual consequence of testing many variables per subject is that many more subjects are required if legitimate tests are to have sufficient power.

In order to test a large number of variables per subject and still retain power for the significance tests, a strategy discussed by Muller et al. (1983) was followed. The first 40 subjects were used as exploratory subjects and all possible dependent measures were tested. This procedure obviously is anti-conservative in that the probability of a type I error is higher than would be indicated by the nominal p values. Then the most likely dependent variables were selected. This was done by selecting, as candidates for dependent variables, any variable whose estimated p value was smaller than 0.05-0.07. New tests were constructed to evaluate a reduced set of hypotheses. After several cycles a final set of hypotheses were formed. These were then used as *a priori* hypotheses and tested on the second group of 52 subjects, the confirmatory sample. In this way the full value of exploration of all possible variables was realized, legitimate tests were obtained of *a priori* hypotheses and an internal replication was performed. Since some subjects had missing data for some variables e.g. the EEG, the actual number of subjects depends on the variable being analyzed. The number of subjects is always specified for each analysis.

Statistical Tests

In general, two methods were used to control type I errors: (a) use of multivariate tests and (b) Bonferroni correction for multiple tests. The latter was used in the confirmatory sample. The multivariate approach to repeated measures (Timm 1975) was used whenever repeated measures were present. This was done due to the likelihood of violation of the homogeneity of variance assumption demanded by the univariate approach (Keselman and Rogan 1980). Rao's F approximation to Wilk's Likelihood Ratio (Rao 1973) was used throughout. The usual ANOVA and regression fixed effect F test is a special case. Note that fractional degrees of freedom can occur but that exact tests result for all data analyzed in this paper. Statistics were computed using SAS. Linear models were fitted using the LINMOD Macro package executed from SAS (Christiansen et al. 1979).

Since statistical tests and hypotheses were evolved during the exploratory work, no further description will be given here. Rather, the tests are explained in the context of their use. Where appropriate, Bonferroni corrections were used to account for the number of tests used (Abt 1981). This involves the division of the p value to be considered statistically significant (α) by the number of tests performed.

RESULTS

EXPLORATORY

In the exploratory results section not all of the exploratory analyses are presented since not all analyses were useful. Many analyses simply led to more useful ones. None of the exploratory results can be accepted without replication. The purpose of presenting exploratory results at all was to justify the selection of final hypotheses and to carefully document the serial decisions made in the data analysis.

COHb

Blood samples were collected on all subjects before and after exposure. COHb analyses were performed by the spectrophotometric method (Small et al. 1971). After the first 44 subjects' blood had been analyzed it was noted that very low COHb values were occurring in the CO-exposed group. Apparently instrumentation problems had developed. By the time accurate analysis had been re-established, the remaining samples had spoiled. Statistics for COHb values were therefore estimated from the first 44 subjects. Since the exposure control was not altered, the estimate from the first 44 subjects can be taken to be accurate. It is also the case that COHb was not a dependent variable in the study but was merely used to verify the exposure level and as a descriptive measure.

Mean values of COHb for the air exposed group were 0.53% pre-exposure and 0.59% post exposure. The CO-exposed group had a mean COHb of 0.38% pre-exposure and 6.24% post exposure. Post exposure COHb values in the CO-exposed group had a range of 5.22 - 7.58, SD = 0.66.

Vigilance

Vigilance data were analyzed using a signal detection model (Swets 1964). Both correct signal detections and false alarms are used to compute two derived parameters for each subject. The first is d', and is interpreted as the sensitivity of the observer to signals. The other, β, is related to the observer's willingness to risk a false alarm. Since the sampling distribution of β is not typically Gaussian, this parameter was log transformed and analyzed as $\log_e \beta$. For any given block of 50 trials only 10 signals were presented. Simply by normal variation some subjects occasionally either did not make a false alarm, did not miss any signal or did not detect any signal. For any one of the above conditions, d' and β cannot be computed. Rather than drop the few subjects who fell into this category, it was decided to lump two adjacent blocks of data together into 100-trial blocks. This prevented loss of subjects and also provided a more stable estimation procedure. Since seven blocks of 50 trials were observed, one of the blocks could not be included in the above procedure. It was decided that block seven, the last block would not be used. This decision was partly based upon the frequently reported finding that performance improves near the end of a session, (Warner and Heimstra 1973) probably due the subject's anticipation of the end of the task and the consequent arousal.

In addition to analyzing d' and $\log_e \beta$, number of correct detections and number of misses were also tested. Each of the sets of vigilance parameters, d', $\log_e \beta$, hits and false alarms were analyzed in a separate multivariate analysis of variance (MANOVA) using a two-way CO x Blocks design. Here "Blocks" refers to blocks of trials or time on task. If vigilance were affected as COHb increased, one would expect the CO and air subjects to make similar scores early in exposure and then diverge. This would result in a significant CO x Blocks interaction. The use of several MANOVAs certainly is an anticonservative technique but, for exploratory analyses, such methods are useful.

Table 1 shows the results of the four MANOVAs. None of the effects involving CO had low estimated p values. Both d' and hits were affected by time on task (Blocks). Inspection of means indicated that performance in both CO and air groups declined, especially in the last 100-trial block. In contrast, $\log_e \beta$ and false alarms were not affected by any variable. This pattern of results is typical for time on task and is probably associated with fatigue.

Two subjects were eliminated from analysis, one from each group, due to missing d' and $\log_e \beta$, because of no false alarms, even for the 100-trial block size. If this were to occur in a verification sample, should vigilance be included in the dependent variables and if eliminated subjects were all from one group, a biased analysis would result. Data were therefore grouped into two 150-trial blocks, early exposure and late exposure, and reanalyzed. This procedure resulted in no eliminated subjects and possibly more stable estimates. In the 2-block analysis, hits and false alarms were not analyzed because in the 3-block analyses they had yielded trends which were very similar trends in d' and $\log_e \beta$. Signal detection model parameters are also more interpretable. The two signal detection parameters were also first analyzed as a multivariate measure and then stepdown tests followed. Table 2 shows the results of the reanalyzed vigilance data. In the overall tests, only time on task (Blocks) had low estimated p values. The only stepdown test in which $p < 0.00008$ was, again, the blocks effect in d'. These results are essentially the same as the 100-trial block data.

Tone Judgment

It was considered unlikely that performance of the foreground task would be affected by CO or fatigue since fatigue had not affected performance of this task during pilot studies. Tone judgment was nonetheless evaluated in exploratory analysis. With 50 trials per block, Tone Judgment could be stably evaluated for each block. Therefore, all seven 50-trial blocks were used. Occasionally some subjects did not respond on a few trials in some blocks. Accuracy of TJ was therefore expressed as proportion correct judgments in each of seven blocks.

MANOVA was used to analyze the TJ data. Table 3 shows that the CO x Blocks interaction had $p < 0.021$. Figure 3 shows a plot of tone judgment data for the CO and air groups across blocks. While the interaction of CO x Blocks was "statistically significant" (as long as no correction for multiple testing was done) the trends are not interpretable. The estimated p values for the interaction term was not very small and would not be significant by a Bonferroni-corrected test even if only the three behavioral variables were used. If no confirmatory sample were available this would be considered non-significant. In the context of an exploratory analysis, it was considered suggestive for the confirmatory sample.

Speech Articulation

Speech articulation tests were given before and after CO or air exposure. These tests were scored by (a) counting articulation errors, (b) counting perceptual errors (wrong words) and (c) measuring the time required for the subject to read the test. MANOVA was used to test the effects of CO on the two error scores and a t test was used to test the effects of CO on the time variable. Difference scores (post-pre) were used to account for variation among subjects on pre-exposure performance. The tests, then, were of the significance of the differences between post-exposure CO group means and air group means, corrected for pre-exposure individual performance.

Table 4 shows the results of the tests. The multivariate test had a p value of .041. Stepdown tests indicated that articulation might have been affected by CO ($p < .021$) but perception was not ($p > .29$). Figure 4 shows a plot of pre- and post-exposure mean articulation scores for the CO and air groups. It would, from Figure 3, appear that CO improved articulation performance. The CO group was apparently unmatched by chance assignment and made more pre-exposure articulation errors than did the air groups. The CO group, however, improved and the air group did not change. These would not be considered statistically significant results by appropriate statistical procedures.

Electrophysiology

EEGs were analyzed into four-band spectra: delta, theta, alpha and beta as described in the Methods section. This resulted in one power spectrum for each parietal site and one of each: coherence, gain and phase spectra. Power spectra are measures of electrical energy (microvolts squared) at each site, left and right parietal. Coherence, gain and phase are least-squares estimates of measures of relationship between sites (Benignus and Muller 1982), in this case, relationships between hemispheres. Coherence is a multiple squared correlation spectrum giving the strength of relationship between synchronized activity in the two hemispheres in each of the four frequency bands. Gain is a multiple coefficient of regression between hemispheres and gives information about the ratio of amplitude of the synchronized activity in the two hemispheres in each of four frequency bands. Phase is related to time lag or lead between activity in the two hemispheres in each of four frequency bands.

The above five spectra were computed for the two tasks performed during exposure, TR and TJ. One set of five spectra were computed for two tasks on each of seven blocks. The two channels of power spectra were log transformed (base 10) and analyzed as $\log_{10}(P3_f)$ or $\log_{10}(P4_f)$ where P3 and P4 are left and right parietal and the subscripts f indicates the frequency bands.

Since EEG data were collected during the training block, before CO exposure was started, these data could be used to account for any pre-existing differences between groups as well as individual differences. This was done by simply subtracting pre-exposure values from all spectra before significance tests. Analysis of covariance was precluded in this case due to a multiple design matrix problem. For plots of spectra, the grand means of the pre-exposure data were added back into the data to illustrate actual values corrected for pre-exposure.

Log Power Spectra. The two log power spectra were analyzed by MANOVA using a CO x Task x Site x Blocks design. Table 5 shows the results of this analysis. Only p values are given to avoid complexity. All of the four-way interactions had $p > 0.05$ and only the delta band had $p < 0.023$ for a three-way interaction (CO x Site x Blocks). Only the alpha band had $p \approx 0.061$ for CO x Blocks interaction without a difference between sites. The main effects showed no CO effects, no site effects, a delta-band effect of task and theta-, alpha- and beta-band effect of Blocks.

This rather simple pattern of results implied that the two measurement sites P3 and P4 could be averaged together in all but the delta band since there were no effects involving site. A CO x Site x Blocks interaction in the delta band ($p < 0.023$) possibly indicated a CO x Blocks effect in one site but not the other. A task main effect on delta ($p < 0.037$) was also suggested. Alpha band showed a suggestion of a CO x Blocks interaction ($p < 0.061$). Time-on-task (Blocks) affected theta ($p < 0.001$), alpha ($p < 0.00001$), and beta ($p < 0.016$) although alpha was apparently differentially affected across blocks in the CO group than in the air group (see CO x Blocks interaction). It is noteworthy that a CO x Blocks interaction was frequently found among the interactions. It is also noteworthy that most conditions had no effect on most variables, thus reducing the number of hypotheses to be tested in the confirmatory sample.

The simplest pattern in the above group of results was the alpha band Co x Blocks effect. Figure 5 was plotted by averaging log power in P3 and P4 together and averaging TR and TJ tasks together since no effect of these were noted. Four separate plots (not shown for simplicity) of log power in the alpha band for each site and each task verified that the trends were very similar. From Figure 5, it appeared that alpha power increased in both CO and air groups as a function of time on task. The CO group alpha power apparently did not continue to increase as much during the latter part of the task as did the air group log alpha power. This divergence between CO and air groups had a fairly low estimated p value and was certainly suggestive for exploratory purposes.

As mentioned above, a somewhat more complicated pattern of results occurred in the delta band. A three way interaction (Co x Site x Blocks) was suggested as well as a main effect of task. The pattern required eight trend plots. Figures 6 and 7 show all eight trends. Figure 6 shows the trends for both hemispheres for CO and air groups during the TR task. Figure 7 shows the corresponding data during TJ task. The CO x Site x Blocks interaction was apparently due to an inversion of the P3/P4 relationship by CO in the TR task. Careful inspection of

Figure 6 shows that for the air group P3 delta band EEG was usually of higher power than P4. For the CO group the opposite obtained. The interaction with blocks was apparently also contained in the TJ task and was due to the trend for delta band EEG amplitude to increase across Blocks in the air group but not in the CO group. It appears from Figures 6 and 7 that the main effect of task was due to the generally higher power in the delta band during the TR task.

A non-CO-related set of effects is shown in Figure 8. Here it is seen that both theta- and beta-band EEG power increased over blocks of trials. In fact, this also seemed to be true of the alpha band for the air group (see Figure 5) and for the delta band, air group on the TR task (see Figure 6). The interactions found for delta- and alpha-band EEG, however, prevented the plotting of simple main effects graphs as done in Figure 8.

Cross spectra. Each of the three cross spectrum measures, coherence, gain and phase, were analyzed with a separate MANOVA for each of four frequency bands. Each MANOVA used a CO x Task x Blocks design. In these analyses, unlike the analysis for the P3 and P4 data, site was not a factor since the cross spectrum measures are defined for the relationship between two channels. Clearly the following 12 MANOVAs yielded anticonservative results. These results were, of course, used only in an exploratory sense. They were not used for hypothesis testing but, as will be shown, for hypothesis generation.

Table 6 shows the results of the tests of the effects of three factors on coherence spectra. None of the three-way interactions had $p < 0.05$. The CO x Blocks interaction had $p < .005$ in the theta band and a possible effect was indicated in the alpha band. A Blocks main effect in the theta band cannot be interpreted in the presence of a CO x Blocks interaction.

Figures 9 and 10 show plots of the coherences in theta- and alpha-band EEGs. Data were averaged across task since no task-related effect was significant. Apparently the CO x Blocks interaction was due to the crossing of the two lines in each graph, the theta-band data between the last two blocks and the alpha-band data between the first and second blocks. Despite the p value for the theta-band interaction, the graph of the results is not easily interpretable. The air group showed the greatest change. Since the change occurred so late in the experiment, it is not clear whether it was only spurious. Inspection of the means for the air group on each of the two tasks revealed that the drop in theta band coherence occurred only during TR task performance. Similar findings obtained for the alpha-band data. These results are probably due to stochastic variation.

Table 7 shows the results of the MANOVAs on the gain spectra. Again, no three-way interaction occurred. A CO x Task interaction in the theta band and a possible CO x Blocks effect in the beta band were indicated. No main effects occurred.

Figure 11 shows that the gain in the theta-band EEG was higher in the CO group during TR task performance and higher in the air group during TJ task performance. The p value for the effect was not very small (.025) and it is difficult to conceive of a CO effect which is not a function of blocks of trials as COHb builds up. Figure 12 shows the marginal effect of CO x blocks on beta gain. Since no main effect occurred, the interaction was apparently due to the exactly opposite trends in the air and CO groups. The large p value and the fact that the opposite trends are in evidence early as well as late in CO exposure make this effect of dubious replicability.

Table 8 shows the results of the tests of the phase spectra. Here only one value of $p < 0.05$ occurred, a CO x Blocks interaction in the alpha band. Figure 13 depicts these effects. It appears that in the air group, the phase difference between hemispheres diminished whereas in the CO group it either remained constant or decreased.

Summary of Exploratory Results

Table 9 is a list of the significant findings in the exploratory sample data analyses. A total of 23 analyses were performed in addition to those preliminary tests which were peforemd but not shown. The level of probability required to declare an effect significant after Bonferroni correction, α', would be $\alpha' = \alpha/23$, if α were to be divided equally and pretending that only the analyses which were shown were in fact done. Using $\alpha = 0.05$, $\alpha' \approx 0.002$. Had these data been analyzed using only the above statistics and no confirmatory sample were to be analyzed, there would be only two statistically significant effects: a decline in vigilance performance (d') over trials and an increased log power theta-band EEG over trials. Since α' and not α would have been used to judge the interactions, however, one other main effect would have been looked at in the absence of now non-significant interaction. Specifically, the alpha-band EEG power would be declared to increase over blocks (see Table 5). The results of the Bonferroni-corrected significance tests are listed in Table 10.

Judging from Tables 9 and 10, by less anti-conservative statistical analyses, none of the CO-related effects would be declared significant. If this study were replicated with a larger sample size and the reduced set of hypotheses, specified in Table 9, a maximum of 12 significance tests would be conducted, nine of which involve CO. If 12 a priori hypotheses were formed and tested using Bonferroni-corrected tests ($\alpha' = 0.05/12 \approx 0.004$). If the data were to show the same differences, there would still be no significant CO effects unless there were a substantial increase in test power due to increased sample size or use of more powerful tests than Bonferroni corrected individual tests.

Construction of Hypotheses

EEG Hypotheses. Results listed in Table 9 were used to construct a priori hypotheses which would be tested in the confirmatory sample. Since none of the CO-related effects were very strong and since they were widely scattered among derived EEG measures, it was considered necessary to trim the number of EEG-related hypotheses. This further trimming was done on grounds other than on p values.

Both coherence measures (entries 9 and 10, Table 9) were eliminated because the CO x Blocks effect was absent throughout exposure except near one end or the other. It was feared that such results were spurious and would not replicate. Both measures of gain (entries 11 and 12, Table 9) were eliminated because interpretation was difficult. Theta gain did not vary over Blocks and the trend differences of beta gain over blocks was complex. Such results might be spurious and not replicable. Only alpha band phase remained among the cross spectrum measures listed in Table 9 (entry 13). It was decided to eliminate the entire family of cross spectrum tests and thus save another Bonferroni correction.

Elimination of EEG hypotheses had proceeded to the point where only two remained, CO x Blocks effect on alpha-band EEG power and a CO x Task x Blocks effect on delta-band EEG power (entries 4 and 5, Table 9). The delta-band EEG effects were not simple, however (see figures 6 and 7), occurring only in the TR task and involving inversion of the P3/P4 ratio and small trend differences. While these might be replicable, it was considered likely to be less so than the alpha-band effects. The latter effects were clearly interpretable. Furthermore when graphs were plotted for individual channels and individual tasks, all four graphs exhibited the same trend. It was felt that, while there might be other CO effects in the EEG data, this one was the most likely to replicate. Since effects were small, power would be low in the confirmatory sample unless few variables were chosen.

The only EEG hypothesis for the confirmatory sample would therefore be that alpha-band EEG power would not increase as much in CO-exposed subjects as in air-exposed subjects over blocks of trials. This was to be tested by a MANOVA in the same way as it was tested for the exploratory sample.

Behavioral Hypotheses. Two suggestive behavioral effects were related to CO. Neither of them were particularly easy to interpret. The predicted vigilance decrement did not eventuate in the exploratory sample. Behavioral effects, however, have face validity whereas EEG effects must be interpreted by reference to other studies where EEG was related to some behavioral change. At the risk of unwarranted reduction of power it was decided to retain two behavioral hypotheses about (a) tone judgment and (b) speech articulation for the confirmatory sample. Analyses were to be done as they had been for the exploratory sample.

Formal Hypotheses. Table 11 gives a list of the formal *a priori* hypotheses which were tested in the confirmatory sample. Also shown are the α values selected for each hypothesis. The experiment-wise probability of a type I error is seen to be $\alpha = 0.05$.

CONFIRMATORY SAMPLE

Behavioral Results

Table 12 shows the results of the analysis of the tone judgment data. No effects related to CO were significant, in contrast to the exploratory data. In the latter, trends were uninterpretable and p values were not very small. The trend of accuracy of tone judgment over time was shown to be significant only in the quadratic trend test. Figure 14 shows that performance accuracy increased during the first few blocks of trials, peaked during blocks five and six and thereafter declined.

Since only speech articulation errors showed any CO effect, during exploratory analysis a simple ANCOVA was performed using only articulation data and testing only CO effects. Articulation was not affected by CO ($p > 0.58$, $F = 0.30$, $df = 1,53$). This finding differs from the results on the exploratory sample which indicated that the CO group improved articulation more than the air group.

EEG Results

Table 13 shows that the CO x Blocks effect, which was predicted to be significant, did not reach the α criterion of 0.03. The p value was, as in the exploratory sample, close to significant. Figure 15 shows that the trends for alpha-band EEG power for the CO and air groups are quite similar to those in the exploratory group (see Figure 5). In this case also, plotting the two channels and two tasks separately revealed that all four trends conformed to the trends shown in Figures 5 and 15.

POST HOC EXPLORATION

After formal hypotheses were tested in the confirmatory sample other exploratory analyses on the whole sample (the combined exploratory and confirmatory samples) and on the confirmatory sample was undertaken. This was done in order to explore some of the low-p value results in the exploratory sample which were not included, for various reasons, in the confirmatory hypotheses. Presentation of these results will not be detailed.

Table 14 shows that, as in the exploratory sample, the p values for effects of CO on vigilance (d') were not significant in the post hoc exploration on the confirmatory sample. This was hardly surprising since the results of the exploratory study were definite. As before, d' decreased over time.

EEG Power Spectra. Table 15 shows a comparison of effects and variables which were found to have $p < 0.05$ in either the exploratory sample or in the whole sample analysis. The list of effects can be compared for consistency.

In only two cases did any effect on any variable have a $p < 0.05$ in both exploratory and whole samples as shown in Table 15. In both instances, the effects would have survived Bonferroni corrections in either sample. Both theta- and alpha-band EEG have increased power as a function of blocks of trials.

The effect which was next closest to showing $p < 0.05$ in both samples was that of the CO x Blocks interaction effect on alpha-band EEG power. While this effect was formally predicted from the exploratory results $p > 0.061$, the confirmatory results showed only $p > 0.059$. The criterion has been set at $\alpha = 0.03$. This effect would have been significant in the whole sample ($p < 0.013$).

A possible problem in the alpha-band EEG data appeared in the whole sample *post hoc* analysis. Here the four-way interaction term, CO x Task x Site x Blocks gave $p < 0.008$. Figures 16 and 17 show the trends for each site and each task for CO and air groups. While there is a four-way interaction the general statement can be made that alpha band power rises as a function of blocks of trials for the air group but not nearly as much in the CO group.

Certain effects attained a small p value in the whole group *post hoc* exploratory analysis which were not near criterion in the exploratory sample (Table 15). The inconsistent findings, just as those from the exploratory sample analyses, would not have survived Bonferroni corrections. It must be recalled that for the *post hoc* exploratory analysis, 16 analyses were computed (see Table 16) which would have made $\alpha' = .05/16 \approx 0.003$.

Cross Spectrum Measures. The results of *post hoc* exploratory analysis of the whole sample and the exploratory sample with cross spectra are shown in Table 16. Comparisons lead to conclusions which are similar to those reached about Table 15. In only one case was any "effect" replicated in the two samples. This was the blocks effect on theta-band coherence. None of the effects listed in Table 16 would survive Bonferroni correction.

DISCUSSION

CO-RELATED FINDINGS

Behavior

There were no low level CO-related effects in any of behavioral dependent variables. Vigilance was predicted to be significantly decremented by low-level CO exposure, based upon the findings of others (Putz et al., 1976, 1979; Horvath et al. 1971). No vigilance effects were found in either exploratory or confimatory samples (see Tables 1, 2 and 12). The fact that no significant CO-related effect occurred in either sample makes this finding conclusive.

TJ was not affected by 200 ppm CO in the confirmatory sample (see Table 13). In the exploratory sample there was a suggestion of a complex and hard-to explain CO effect on trend of TJ accuracy over blocks of trials (see Table 3 and Figure 3) but the p value for this possible effect was only $p < 0.021$. This would hardly be considered significant after Bonferroni correction. The complex nature of the trends, the non-replication and the high exploratory p value make it highly likely that there were no CO-related effects in this study.

Speech articulation was not affected by 200 ppm CO in the confirmatory sample ($p > 0.58$). In the exploratory sample articulation appeared to improve more for CO- than for air-exposed subjects $p < 0.031$, but perceptual errors and reading speed were unaffected. The non-replication of exploratory results, the marginal p values and the strange direction of results makes the conclusion of no low-level CO-related effects highly likely.

Task Sensitivity

Behaviors studied in this experiment were selected on grounds of previous research or on exploratory grounds. It might be argued that the particular versions of the tasks used in this study were simply not sensitive to disruption by 200 ppm CO exposure. This argument cannot be countered for tone judgment and speech. For vigilance there is some evidence that this would be a sensitive variable. Vigilance performance, d', was decremented by time-on-task (Blocks) in both exploratory ($p < 0.00008$) and confirmatory ($p < 0.001$) samples. This can be viewed as the effect of fatigue produced by 80 minutes of task performance. The nonsignificant observed difference between groups was smaller than the significant effect of fatigue due to 80 minutes of performance. The above statement implicitly assumes that CO would affect similar aspects of CNS functioning as does fatigue. It is possible that CO would produce a CNS impairment which has nothing to do with behavioral fatigue. Hence it is still possible to argue that this version of a vigilance task is insensitive to CO.

The vigilance task used by Putz et al. (1976, 1979) showed no effects of CO on missed signals or false alarms and hence on d'. Their effect was shown upon increased mean reaction time. Reaction time was not measured in the experiment of this report. Since the response window of the flash detection task in this study was only one second it was felt that as reaction time got longer, flashes would be missed. Perhaps if reaction time had been measured, a CO effect would have been shown.

Comparison to Hypoxic Hypoxia.

In the introduction it was argued that if CO has no non-hypoxic effects, there should be no vigilance decrement due to CO until COHb until COHb reaches 13%. The mean COHb of the subjects at the end of exposure exposure was about 6.24%. On the other hand, the corresponding COHb for the CO-exposed subjects in Putz et al. (1976, 1979) was only 5% and for Horvath et al. (1971) was 6.6%. Small differences in task sensitivity could account for the nonsignificant findings in this study, but the comparison to hypoxic hypoxia implies that no vigilance decrement should have occurred. It is possible to argue that the studies of vigilance using hypoxic hypoxia were insensitive and that the effects should begin to occur at a higher O_2 level.

EEG Data

Alpha-Band Power. Although the alpha-band power was not significantly affected by the interaction of CO x Blocks in the confirmatory sample ($p > 0.059$, $\alpha = 0.03$), the trends were, in several ways, remarkably persistent. Figures 16 and 17 show that for both P3 and P4 on both tasks, the air-exposed group continued to increase the alpha-band EEG power whereas the CO-exposed groups did not. The data from Figures 16 and 17 were computed as the means of all 73 subjects. When the whole sample was analyzed in two subgroups as an exploratory sample ($n = 30$) and a confirmatory sample ($n = 43$), the p values were consistently low ($p < 0.061$ and $p < 0.059$ respectively) and the graphs which were analogous to Figures 16 and 17 showed similar relative trends. When the whole sample was analyzed in a *post hoc* exploration the effect had a value of $p < 0.013$.

Alpha-band EEG power effects might be demonstrable under circumstances of higher COHb, longer task performances, more subjects or more precise experimental control. While these trend differences were small, they were in many ways consistent although not significant. On the basis of these data it is not possible to make the binary decision that the effects were there, despite suggestions of effects from consistent trends.

Other than higher COHb values, more difficult tasks or longer task performance periods, it might be possible to reduce the variance of the observed data and so increase the reliability of the CO effects. A likely candidate for such better control is the ocular behavior of subjects. In this study the TR task demanded eye fixation while the TJ task did not. Variability in subject fixation during TJ could have produced variability in alpha-band power (Mulholland and Peper 1971). The chamber was also dimly lighted. This might have produced more alpha-band power in subjects who characteristically generate more alpha than others.

An explanation for the reduced alpha-band EEG power in CO-exposed subjects during the later blocks of trials is not easy to devise. Usually an increased alpha-band power is interpreted as decreased CNS activation (Lindsley 1957). This interpretation is consonant with the air exposed group's increased alpha-band power as a function of time-on-task. If the CNS process affected by CO were the same as that affected by fatigue, the CO-exposed subjects should have even more alpha-band power than air-exposed controls. It might be argued that the CO-exposed subjects had CNS activation decrements to such an extent that alpha rhythms began to dissappear in favor of increased power, desynchronized theta and delta activity which is characteristic of slumber (Lindsley 1951). If that were the case, however, behavior would have suffered. Possibly the increased COHb in some way affected the CNS energy supply so that the alpha rhythms did not occur and so produced another of the disassociations between EEG and behavior (Wikler 1952). These questions cannot be resolved until (a) the EEG effect can be documented (b) further concomitant behavioral data are available and (c) concentration response functions are available.

Other EEG Measures. No other EEG measure was affected by low-level CO. This includes all EEG power spectra and the three cross spectrum measures of coherence, gain and phase spectra. Several measures were suggestive during either analyses on the exploratory sample or on *post hoc* explorations of the whole sample but these were not consistent (See Tables 15 and 16).

TIME-ON-TASK

Vigilance (d'), alpha-band EEG power and delta-band EEG power exhibited blocks trends which were reliable enough to have withstood Bonferroni corrections. This was true for the exploratory sample (See Tables 1, 2 and 5) and the confirmatory sample (See Tables 12, 14 and 15).

CONCLUSIONS

1. Vigilance, tone judgment and speech were not affected by 1.5 hours. of exposure to 200 ppm CO.

2. Alpha-band EEG power in 200 ppm CO-exposed subjects may not increase as much as in air-exposed subjects. This difference was not statistically significant.

3. No other EEG measure was related to CO exposure levels in this study.

4. Time on task significantly affected vigilance, alpha-band EEG power and theta-band EEG power. Vigilance (d') was decremented, EEG powers were increased.

RECOMMENDATIONS

The findings in this study do not support the existence of a CO effect at the levels of exposure sufficient to produce 6-7% COHb. Since CO is known to produce hypoxic conditions it is recommended that higher concentrations of CO be used in future experiments in order to demonstrate its effect on behavioral or neural dependent variables. This sort of study will help in the identification of sensitive dependent variables. After a concentration-effects function has been established, the threshold can be more reasonably be defined by extrapolation.

Vigilance behavior is one of the prime candidates for further study since others have frequently reported that CO and hypoxic hypoxia both affect it. The findings of this study regarding the statistically non-significant but consistent trends in alpha-EEG power should also be investigated further.

TABLE 1. TESTS OF VIGILANCE DATA, EXPLORATORY SAMPLE, 100-TRIAL BLOCKS. N = 33 (14 air, 19 CO)

Variable	Source	df_n	df_d	F*	p
d'	CO x Blocks	2	30	1.17	0.32
	CO	1	31	0.02	0.90
	Blocks	2	30	16.11	0.00002
$\log_e \beta$	CO x Blocks	2	30	0.48	0.63
	CO	1	31	0.05	0.82
	Blocks	2	30	2.76	0.08
Hits	CO x Blocks	2	30	1.57	0.22
	CO	1	31	0.01	0.91
	Blocks	2	30	14.35	0.0004
False Alarms	CO x Blocks	2	30	0.96	0.39
	CO	1	31	0.11	0.75
	Blocks	2	30	1.10	0.10

*Exact F tests for Wilke's Likelihood Ratio (Rao, 1973, p. 555)

TABLE 2. TESTS OF VIGILANCE PARAMETERS, d' and l_n β, EXPLORATORY SAMPLE, 150-TRIAL BLOCKS. n = 35 (15 air, 20 CO).

Variable	Source	df_n	df_d	F*	p
Multivariate	CO x Blocks	2	32	0.46	0.64
	CO	2	32	0.10	0.90
	Blocks	2	32	10.64	0.0003
d'	CO x Blocks	1	33	0.87	0.36
	CO	1	33	0.04	0.85
	Blocks	1	33	20.42	0.00008
$\log_e$ β	CO x Blocks	1	33	0.04	0.84
	CO	1	33	0.06	0.81
	Blocks	1	33	2.58	0.12

*Exact F tests for Wilkes' Likelihood Ratio (Rao, 1973, p. 555)

TABLE 3. TESTS OF TONE JUDGMENT DATA (PROPORTION CORRECT), EXPLORATORY SAMPLE. N = 40 (20 air. 20 CO).

Source	df_n	df_d	F*	p
CO x Blocks	3	36	3.69	0.021
CO	1	38	0.12	0.73
Blocks	3	36	2.16	0.11

*Exact F tests for Wilkes' Likelihood Ratio (Rao, 1973, p. 555)

TABLE 4. TESTS OF CO EFFECT ON SPEECH ARTICULATION PERFORMANCE, EXPLORATORY SAMPLE. N = 38 (19 air, 19 CO)

Variable	df_n	df_d	F*	p
Multivariate Errors	2	35	3.51	0.041
Articulation	1	36	5.80	0.021
Perception	1	36	1.17	0.29
Time to Completion	1	36	0.0005	0.94

*Exact F tests for Wilkes' Likelihood Ratio (Rao, 1973, p. 555)

TABLE 5. TESTS OF POWER SPECTRUM DATA, EXPLORATORY SAMPLE. ONLY p VALUES ARE SHOWN. N = 30 (16 air, 14 CO)

Source	Delta	Theta	Alpha	Beta
CO x Task x Site x Blocks	0.27	0.45	0.08	0.16
CO x Task x Site	0.16	0.12	0.66	0.58
CO x Task x Blocks	0.30	0.79	0.65	0.13
CO x Site x Blocks	0.023	0.32	0.56	0.17
Task x Site x Blocks	0.54	0.72	0.35	0.94
CO x Task	0.84	0.27	0.36	0.061
CO x Site	0.68	0.26	0.59	0.12
CO x Blocks	0.79	0.74	0.061	0.69
Task x Site	0.60	0.17	0.94	0.14
Task x Blocks	0.36	0.49	0.66	0.93
Site x Blocks	0.73	0.36	0.43	0.33
CO	0.80	0.27	0.056	0.95
Task	0.037	0.57	0.33	0.96
Site	0.43	0.67	0.99	0.58
Blocks	0.13	0.001	0.00001	0.016

TABLE 6. TESTS OF COHERENCE SPECTRUM DATA, EXPLORATORY SAMPLE. ONLY p VALUES ARE SHOWN. N = 30 (16 air, 14 CO)

Source	Delta	Theta	Alpha	Beta
CO x Task x Blocks	0.20	0.78	0.32	0.34
CO x Task	0.21	0.17	0.32	0.81
CO x Blocks	0.31	0.005	0.09	0.69
Task x Blocks	0.07	0.25	0.12	0.91
CO	0.12	0.23	0.53	0.49
Task	0.84	0.61	0.87	0.95
Blocks	0.12	0.005	0.42	0.43

TABLE 7. TESTS OF GAIN SPECTRUM DATA, EXPLORATORY SAMPLE. ONLY p VALUES ARE SHOWN. N = 30 (16 air, 14 CO)

Source	Delta	Theta	Alpha	Beta
CO x Task x Blocks	0.12	0.30	0.11	0.33
CO x Task	0.89	0.025	0.99	0.71
CO x Blocks	0.83	0.39	0.20	0.07
Task x Blocks	0.15	0.41	0.21	0.61
CO	0.22	0.47	0.96	0.17
Task	0.45	0.11	0.83	0.16
Blocks	0.33	0.08	0.14	0.52

TABLE 8. TESTS OF PHASE SPECTRUM DATA, EXPLORATORY SAMPLE. ONLY p VALUES ARE SHOWN. N = 30 (16 air, 14 CO).

Source	Delta	Theta	Alpha	Beta
CO x Task x Blocks	0.52	0.79	0.76	0.50
CO x Task	0.19	0.36	0.68	0.71
CO x Blocks	0.17	0.29	0.024	0.40
Task x Blocks	0.48	0.38	0.31	0.79
CO	0.47	0.27	0.88	0.72
Task	0.91	0.93	0.19	0.37
Blocks	0.94	0.33	0.28	0.60

TABLE 9. LIST OF OBSERVED "SIGNIFICANT" EFFECTS IN EXPLORATORY SAMPLE.

Entry No.	Source	Variable	p	Comments	Figure No.
1	Blocks	Vigilance (d')	.00008	d' declined over blocks of trials	none
2	CO x Blocks	Tone Judgment	0.021	CO and air groups followed different but complex trends. Interpretation difficult	3
3	CO	Speech Articulation errors	0.031	CO group improved more than air group	4
4	CO x Blocks	Alpha $l_n(\mu v^2)$	0.061	Air group increased alpha-band EEG power, CO group did not	5
5	CO x Task x Blocks	Delta $l_n(\mu v^2)$	0.023	P3/P4 was inverted in CO group as compared to air group, but, only on TR task.	6,7
6	Blocks	Theta	0.001	Both groups increased theta-band EEG power over blocks of trials	8
7	Blocks	Alpha	0.00001	But Note entry No. 4	5
8	Blocks	Beta	0.016	Same result as for Theta	8
9	CO x Blocks	Theta Coherence	0.005	On last block only coherence in air group decreased, coherence in CO group decreased	9
10	CO x Blocks	Alpha Coherence	0.09	Similar to effect in theta band but occurred between first and second blocks	10
11	CO x Task	Theta Gain	0.025	CO group had higher gain during TR task, lower gain during TJ task with respect to air group	11
12	CO x Blocks	Beta Gain	0.07	CO and air groups had opposite but complex trends. Interpretation difficult	12
13	CO x Blocks	Alpha Phase	0.024	Air group decreased phase difference. CO group did not	13

TABLF 10. LIST OF "STATISTICALLY SIGNIFICANT" EFFECTS AFTER BONFERRONI CORRECTIONS. EXPLORATORY SAMPLE.

Source	Variable	p	Comment
Blocks	Vigilance (d')	.00008	d' declined over blocks of trials
Blocks	Theta $1_n(\mu v^2)$	.001	Increased theta-band EEG power over blocks of trials
Blocks	Alpha $1_n(\mu v^2)$	.00001	Increased alpha-band EEG power over blocks of trials

TABLE 11. *A PRIORI* PREDICTIONS OF VARIABLES TO BE AFFECTED BY CO AND THE α LEVEL AT WHICH THE HYPOTHESIS WILL BE TESTED IN CONFIRMATORY SAMPLE.

Variable		α
1. Tone Judgment (proportion correct)		0.01
2. Speech Articulation (no. errors)		0.01
3. Alpha-band EEG (power)		0.03
	TOTAL	0.05

TABLE 12. TEST OF TONE JUDGMENT DATA (PROPORTION CORRECT), CONFIRMATORY SAMPLE. N = 52 (27 air, 25 CO)

Source	df_n	df_d	F*	p
CO x Blocks	3	48	1.08	0.37
CO	1	50	0.12	0.73
Blocks	3	48	9.12	0.00007
linear	1	50	1.95	0.17
quadratic	1	50	24.29	0.00001
cubic	1	50	1.19	0.28

*Exact F tests for Wilkes' Likelihood Ratio (Rao, 1973, p. 555)

TABLE 13. TEST OF ALPHA-BAND EEG POWER (AVERAGED ACROSS P3 AND P4), CONFIRMATORY SAMPLE. N = 43 (22 air, 21 CO)

Source	df_n	df_d	F*	p
CO x Task x Blocks	3	39	1.16	0.34
CO x Blocks	3	39	2.70	0.059
CO x Task	1	41	0.07	0.80
Task x Blocks	3	39	2.16	0.11
CO	1	41	0.34	0.57
Task	1	41	0.84	0.37
Blocks	3	39	13.63	0.000004

*Exact F tests for Wilkes Likelihood Ratio (Rao, 1973, p. 555)

TABLE 14. TESTS OF VIGILANCE DATA, CONFIRMATORY SAMPLE. N = 49 (24 air, 25 CO).

Variable	Source	df_n	df_d	F*	p
	CO x Blocks	1	47	0.001	0.97
d'	CO	1	47	0.13	0.72
	Blocks	1	47	11.69	0.001

*Exact F test for Wilkes' Likelihood Ratio (Rao, 1973, p. 555)

TABLE 15. LIST OF RESULTS WHERE $p < 0.05$ IN EITHER EXPLORATORY SAMPLE ($N = 30$)** OR IN *POST HOC* EXPLORATION OF WHOLE SAMPLE ($N = 73$).** DEPENDENT VARIABLE IS POWER SPECTRUM IN 1_{10} (μv^2).

Source	Frequency Band	p values: Exploratory $n = 30$	p values: Whole $n = 73$
CO x Task x Site x Blocks	Alpha	0.08	0.008*
CO x Task x Blocks	Beta	0.13	0.013*
CO x Site x Blocks	Delta	0.023*	0.23
CO x Blocks	Alpha	0.061	0.013*
Task x Site	Delta	0.60	0.036*
CO	Delta	0.80	0.027*
Task	Delta	0.037*	0.11
Blocks	Delta	0.13	0.019*
Blocks	Theta	0.001*	1×10^{-6}*
Blocks	Alpha	1×10^{-5}*	1×10^{-10}*
Blocks	Beta	0.016*	0.10

*Results in which $p < 0.05$.

**In exploratory analyses there were 16 air exposed and 14 CO exposed subjects. In whole sample analyses there were 38 air exposed and 35 CO exposed subjects. Some subjects were dropped from the sample due to missing data.

TABLE 16. LIST OF RESULTS WHERE $p \leq 0.05$ IN EITHER EXPLORATORY SAMPLE (N = 30)** OR IN *POST HOC* EXPLORATION OF WHOLE SAMPLE (N = 73).** DEPENDENT VARIABLES ARE VARIOUS CROSS SPECTRUM MEASURES.

Source	Variable	p values: Exploratory n = 30	p values: Whole n = 73
CO x Blocks	Theta Coherence	0.005*	0.37
Task x Blocks	Delta Coherence	0.07	0.021*
Blocks	Delta Coherence	0.12	0.022*
Blocks	Theta Coherence	0.005*	0.004*
CO x Blocks	Theta Gain	0.039*	0.35
CO x Task	Theta Gain	0.025*	0.07
CO x Block	Alpha Phase	0.024*	0.09

*Results in which $p < 0.05$

**In exploratory analyses there were 16 air exposed and 14 CO exposed subjects. In whole sample analyses there were 38 air exposed and 35 CO exposed subjects. Some subjects were dropped from the sample due to missing data.

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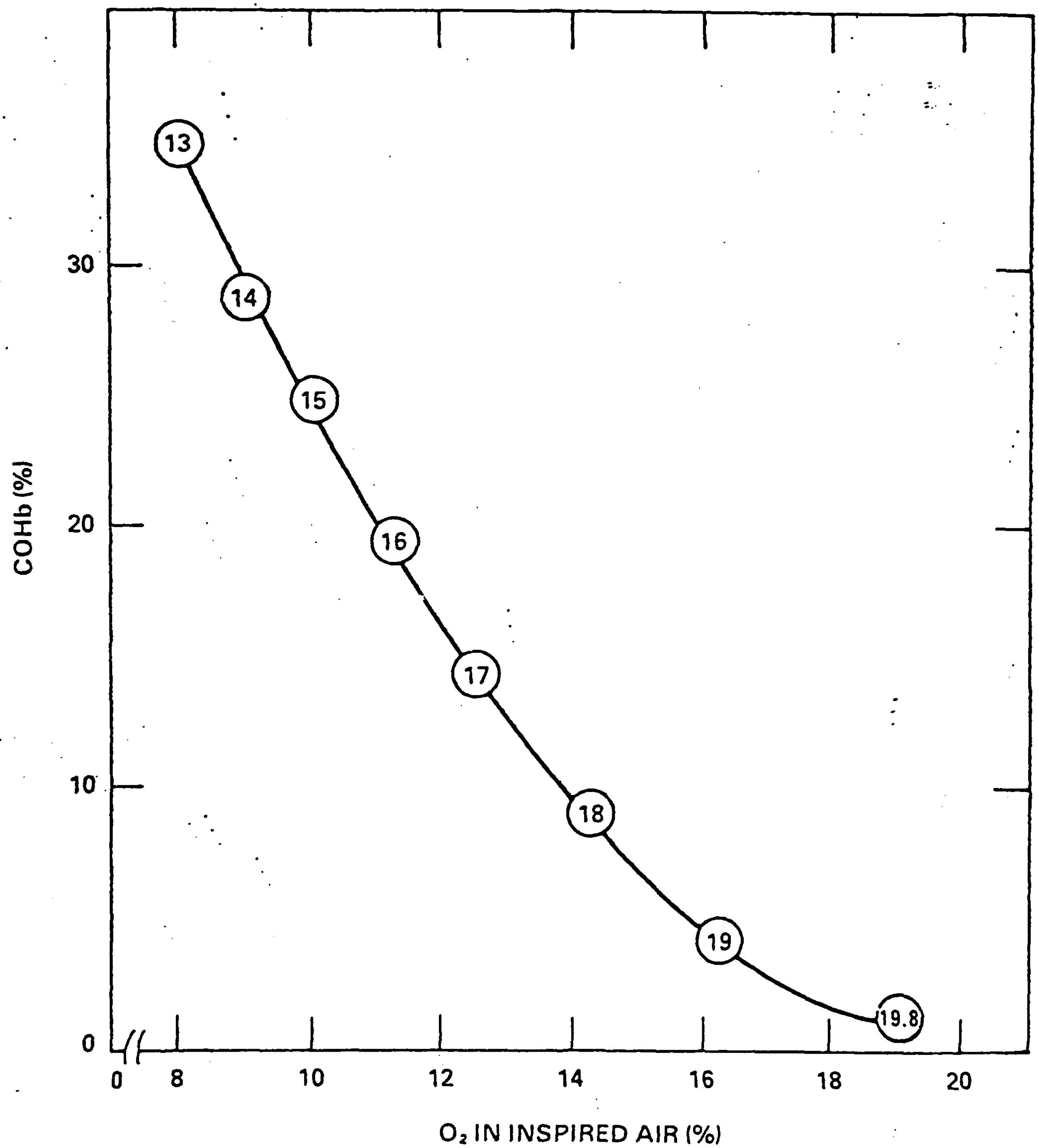


Figure 1. Comparison of hypoxic hypoxia and CO hypoxia via arterial O_2 content (Vol. %). Numbers in circles on graph are arterial O_2 valves (Vol. %).

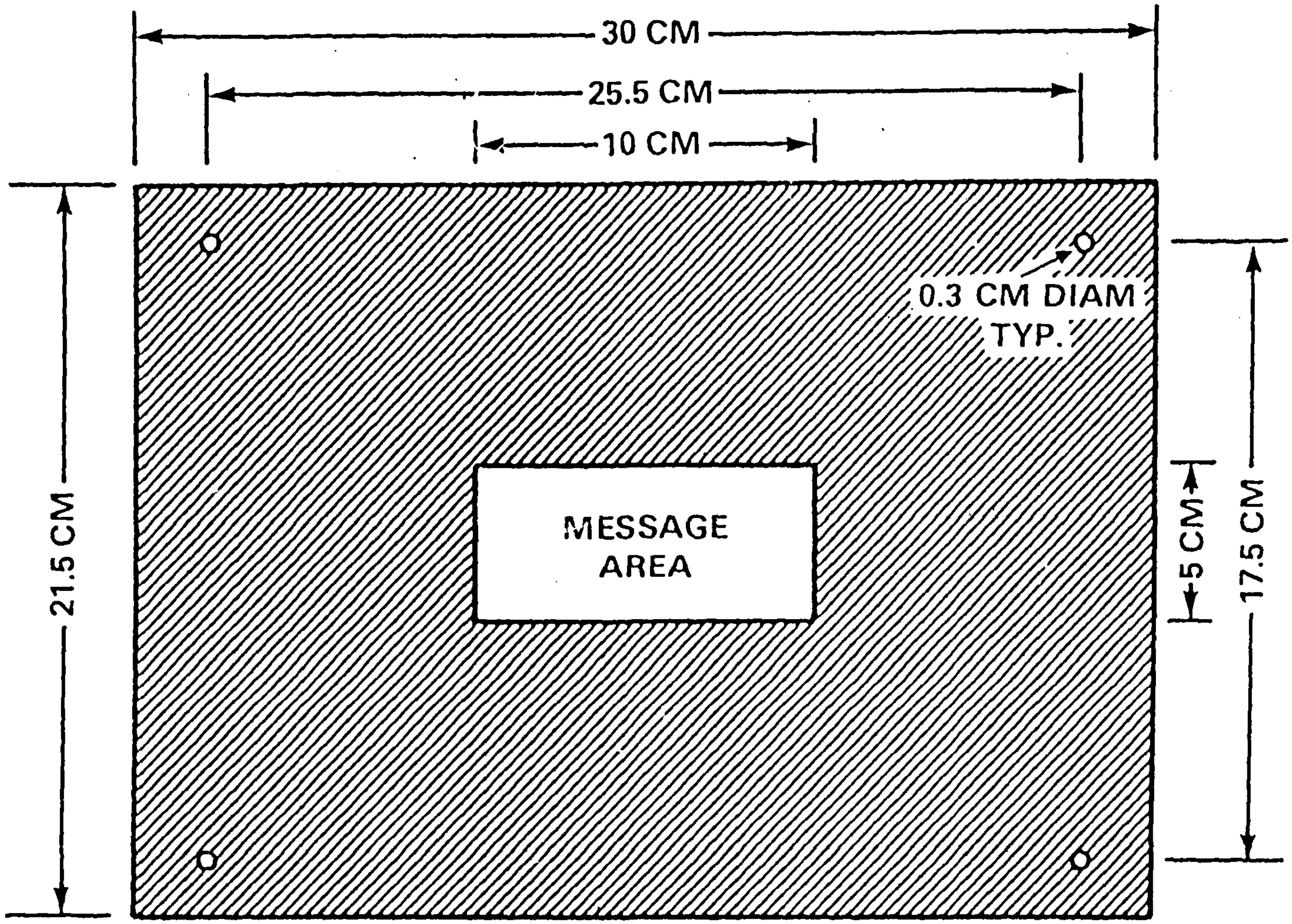


Figure 2. Sketch of CRT message area and stimulus lights. Cross-hatched area represents flat-black surface.

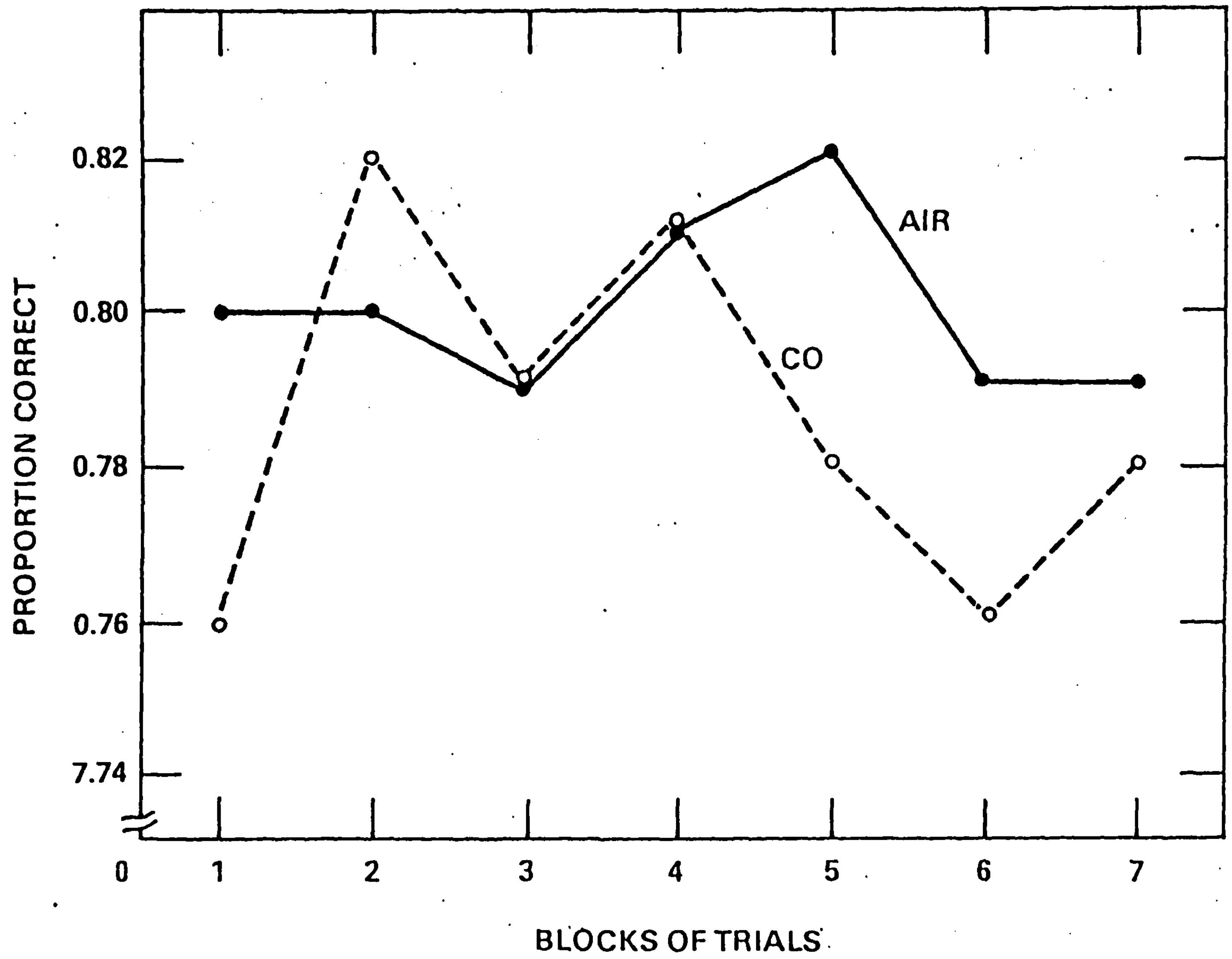


Figure 3. Trends in tone judgement, proportion correct, as a function of blocks of trials. Exploratory sample.

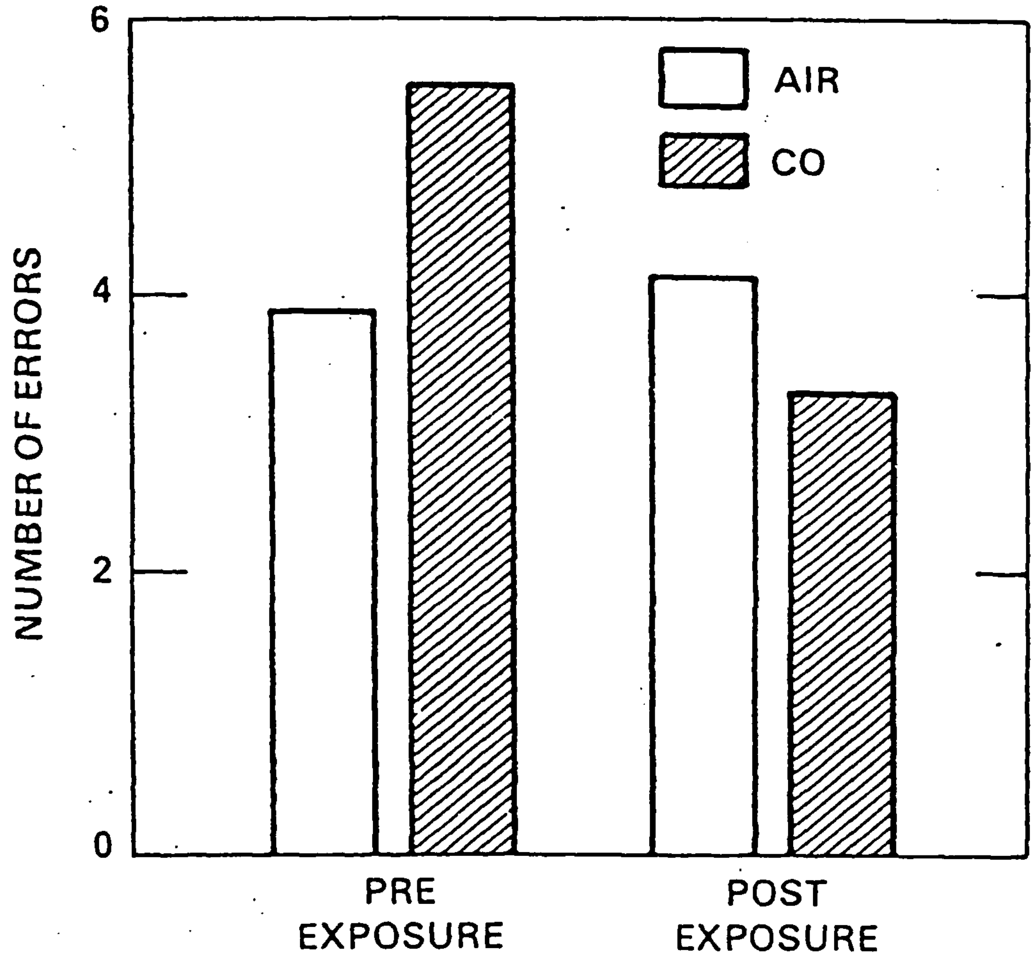


Figure 4. Speech articulation errors before and after exposure to CO.

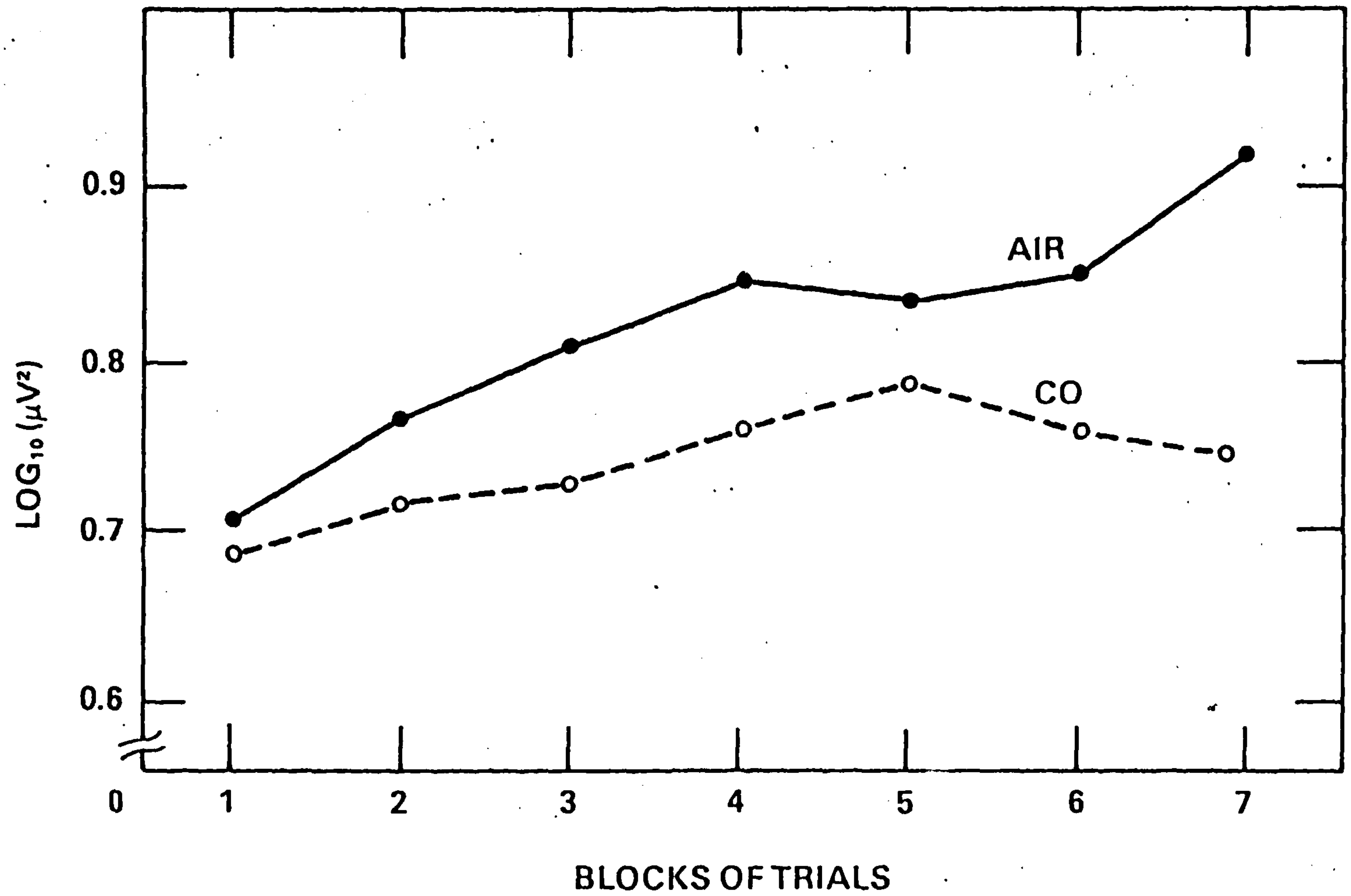
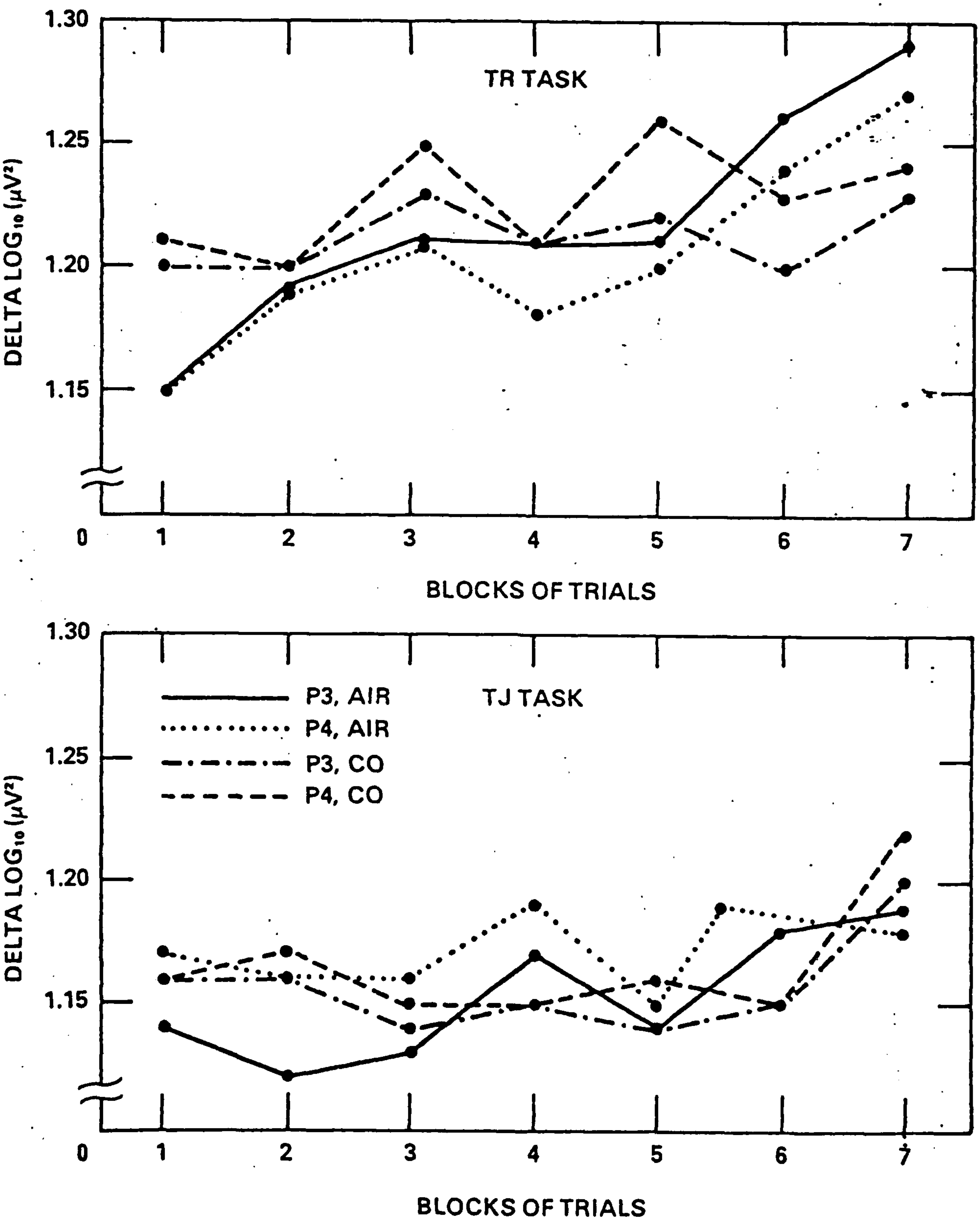


Figure 5. Trends of alpha-band power over blocks of trials for air and CO groups. Exploratory sample.



Figures 6 and 7. Log power trends over blocks of trials, delta band EEG. Figure 6 (top) is for TR task, Figure 7 (bottom) is for TJ task. Exploratory sample.

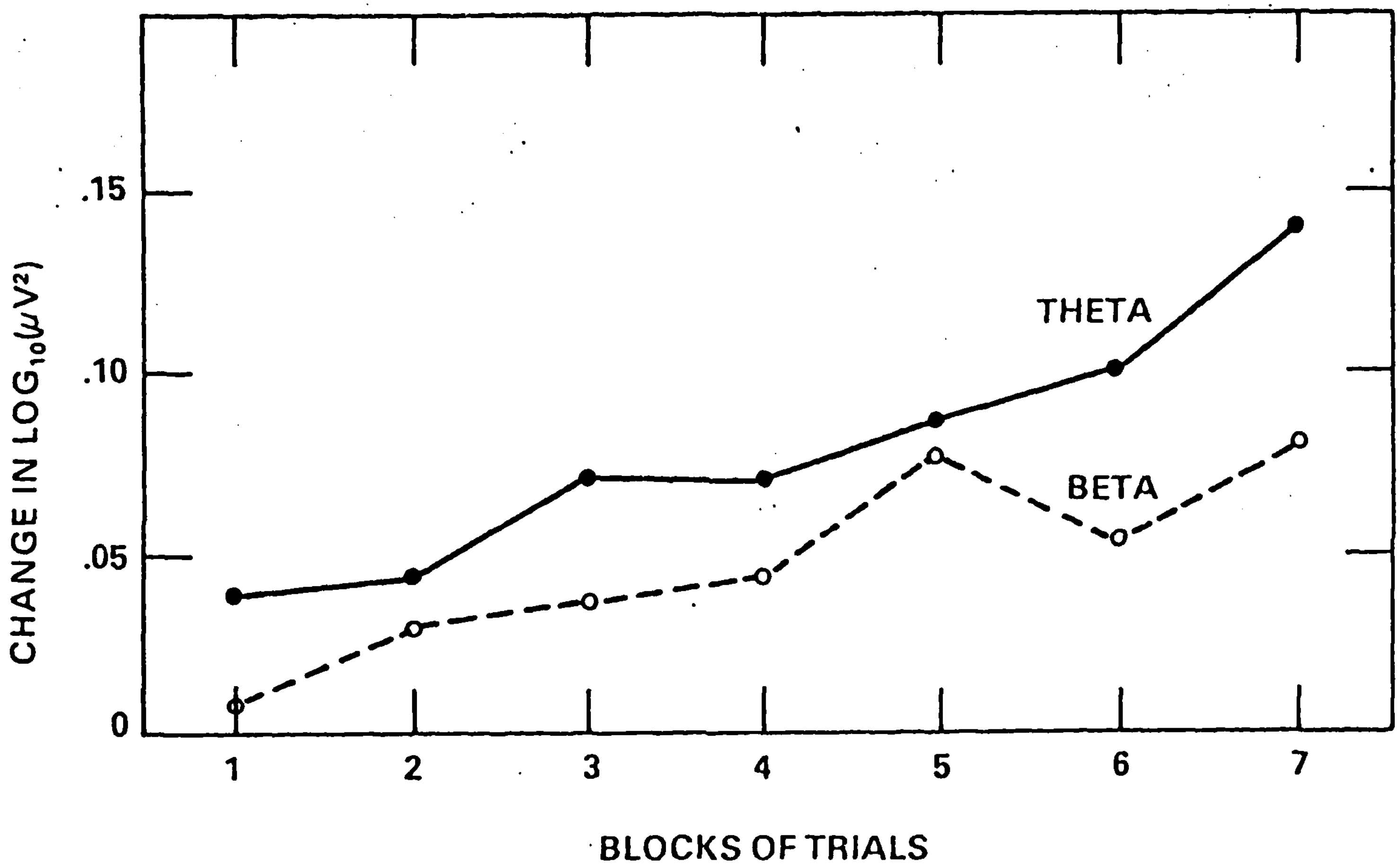
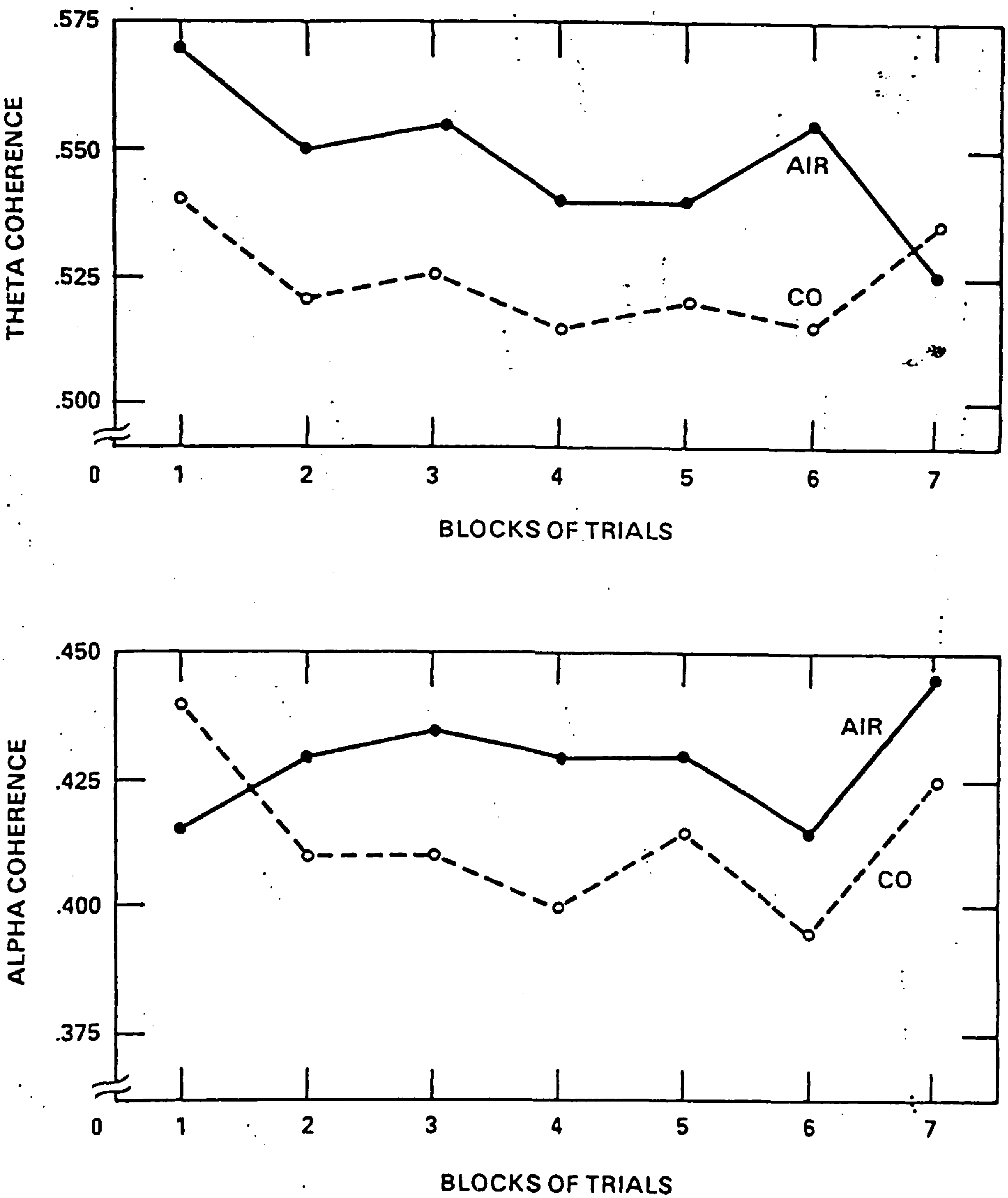


Figure 8. Log power trends over blocks of trials for theta- and beta-band EEG. Note: increases in power were plotted in order to put both graphs on the same scale.



Figures 9 and 10. Coherence as a function of blocks of trials for the theta band EEG in Figure 8 (top) and alpha band EEG Figure 9 (bottom). Exploratory sample.

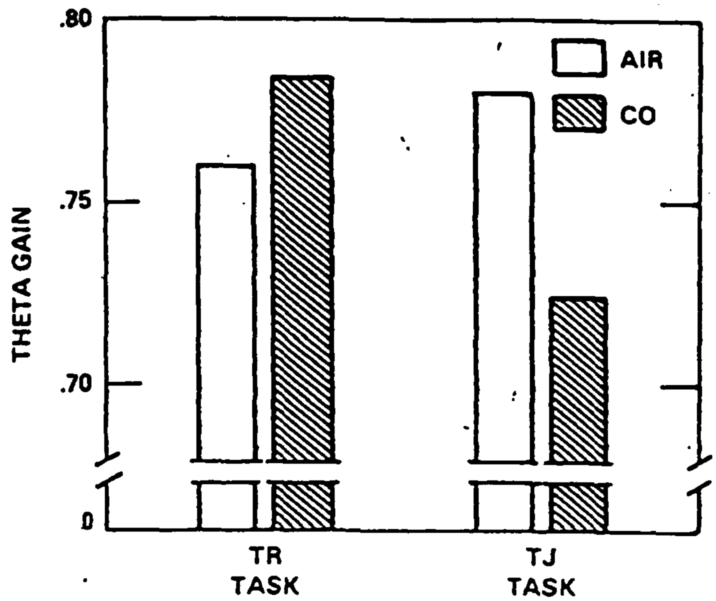


Figure 11. Effects of CO and task on gain in the theta-band EEG. Exploratory sample.

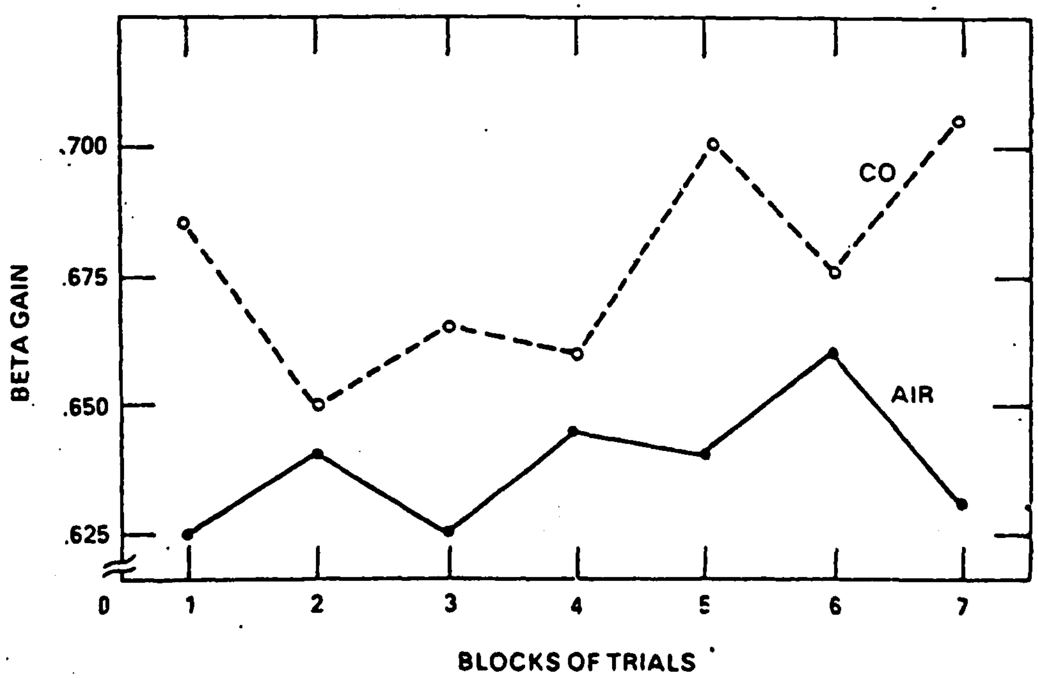


Figure 12. Gain as a function of blocks of trials for beta-band EEG. Exploratory sample.

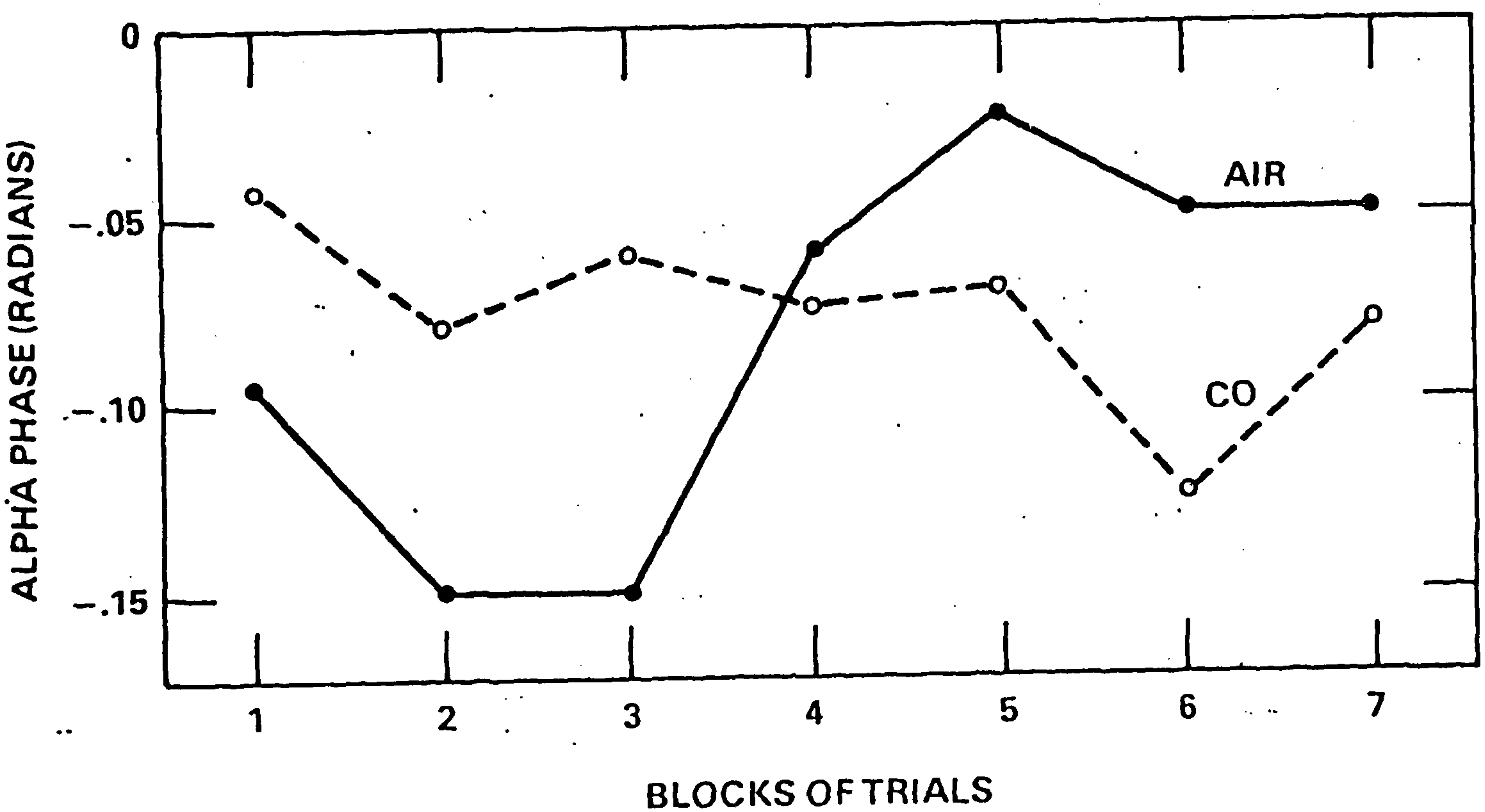


Figure 13. Phase as a function of blocks of trials for alpha-based EEG. Exploratory sample.

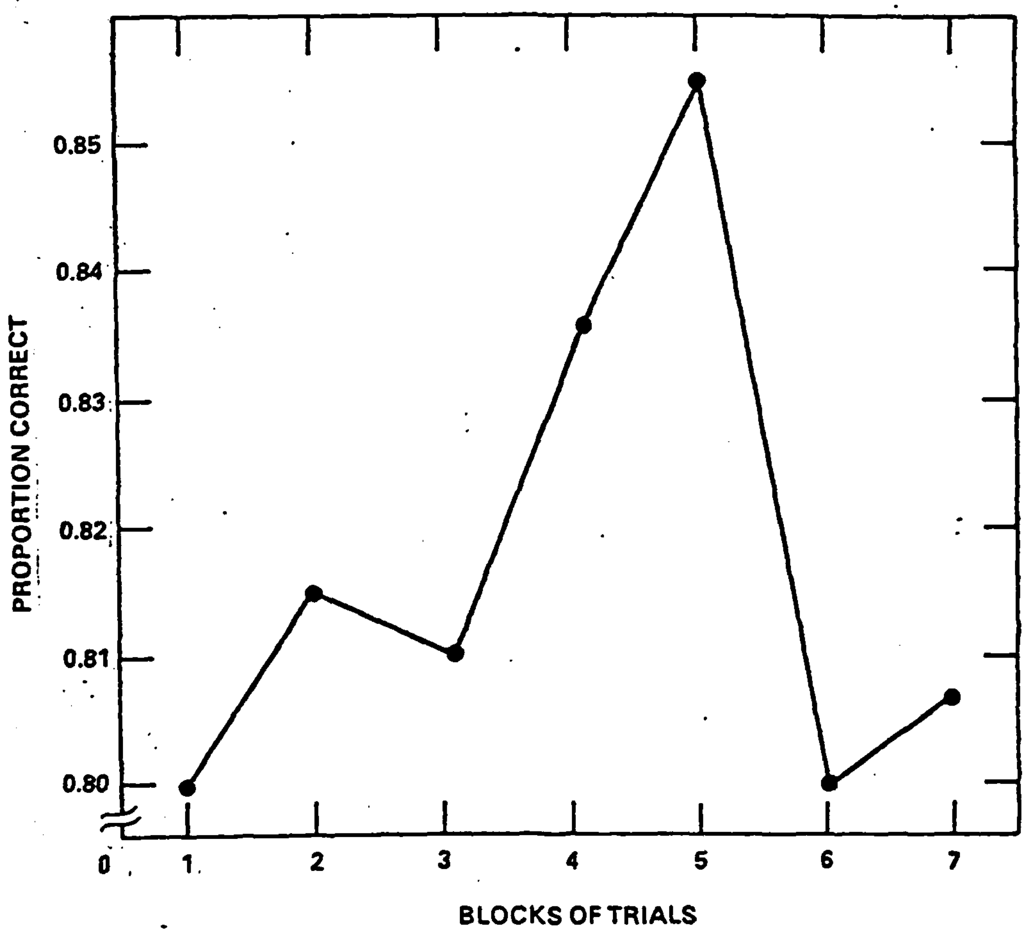


Figure 14. Accuracy of tone judgements as a function of time. Confirmatory sample.

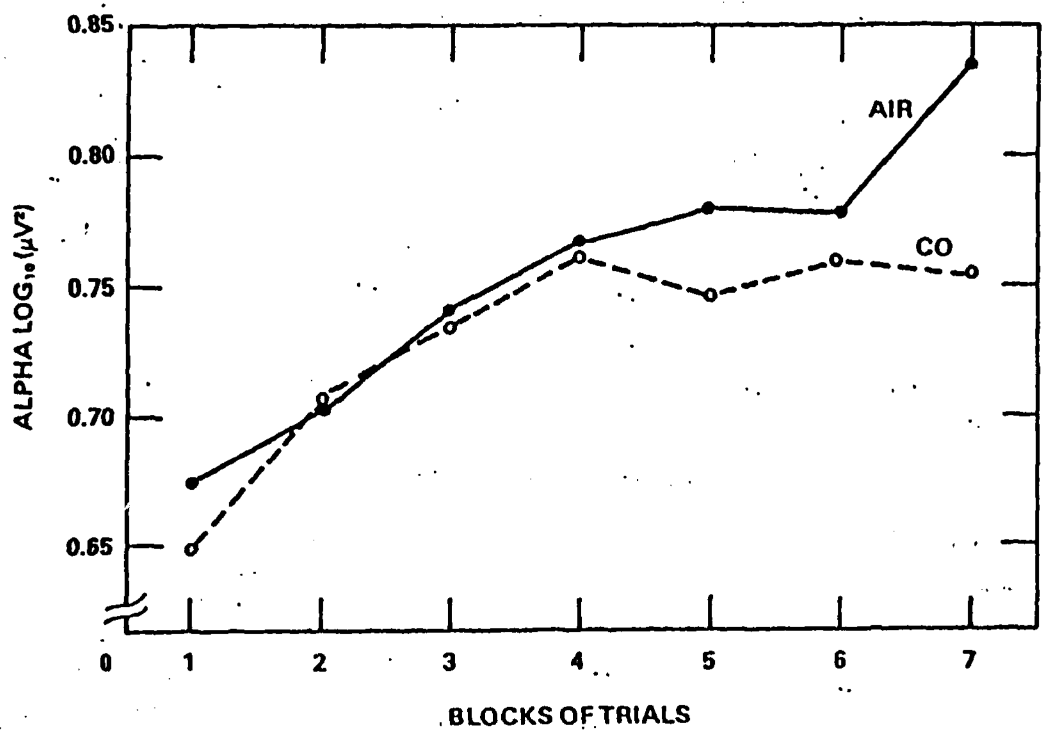
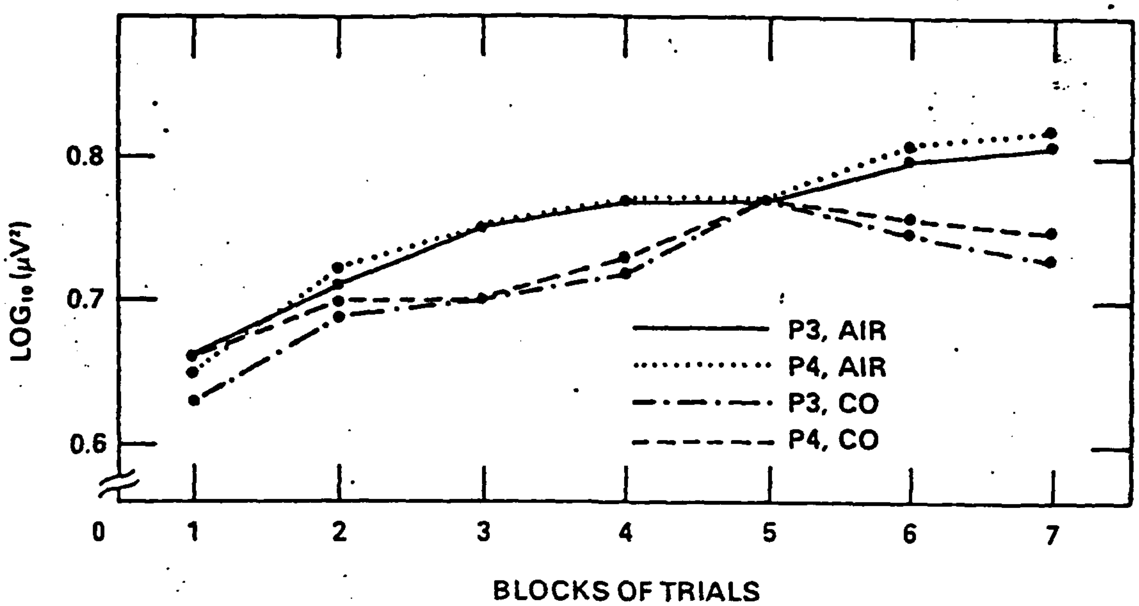
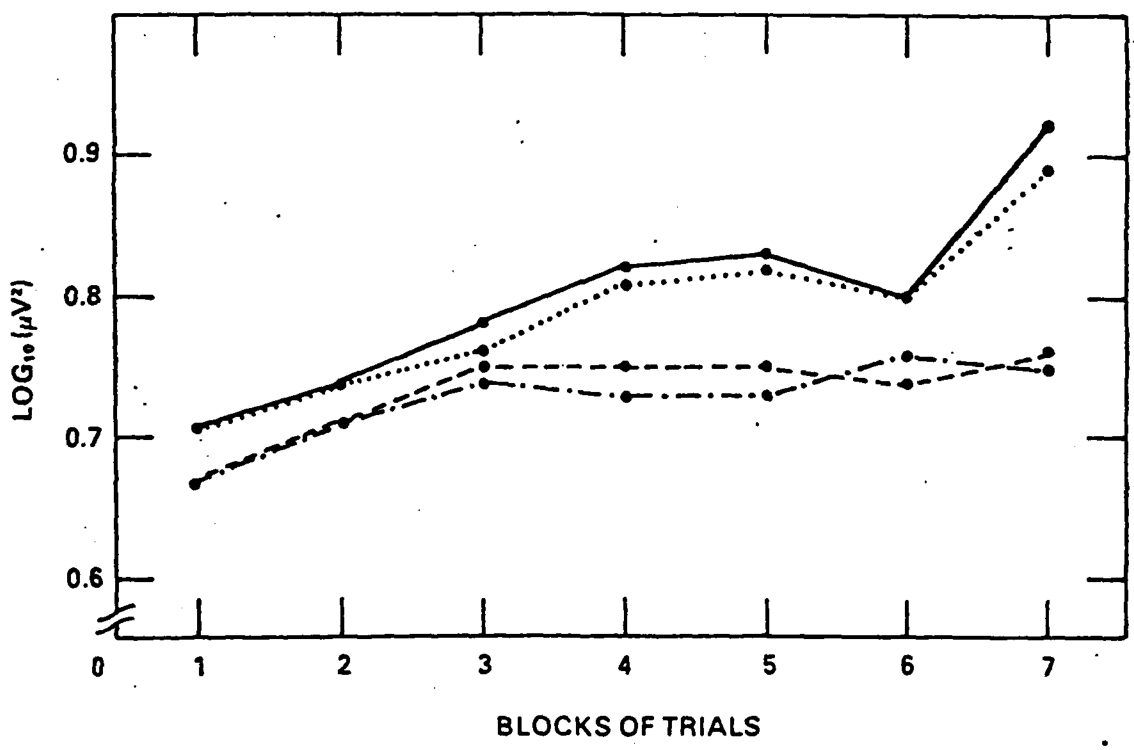


Figure 15. Alpha-band EEG power trends over blocks of trials. Confirmatory sample.





Figures 16 and 17. Alpha-based EEG power trends over blocks of trials. Figure 16 (top) is for TR task. Figure 17 (bottom) is for TJ task. Whole sample post-hoc exploration.

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