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EFFECTS OF CARBON DIOXIDE ON THE ELECTROENCEPHALOGRAM AND REACTION TIME IN HUMANS

by

Melvin Russell Harter

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For the Degree of

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GRADUATE COLLEGE

I hereby recommend that this dissertation prepared under my direction by Melvin Russell Harter

entitled Effects of Carbon Dioxide on the Electroencephalogram and Reaction Time in Humans

be accepted as fulfilling the dissertation requirement of the degree of Doctor of Philosophy

Robert W. Lansing — May 17, 1966

Dissertation Director — Date

After inspection of the dissertation, the following members of the Final Examination Committee concur in its approval and recommend its acceptance:*

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*This approval and acceptance is contingent on the candidate's adequate performance and defense of this dissertation at the final oral examination. The inclusion of this sheet bound into the library copy of the dissertation is evidence of satisfactory performance at the final examination.

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SIGNED: M. Russell Hatter

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ABSTRACT

The purpose of the present study was to test the tri-phasic hypothesis that (1) low levels of CO_2 cause direct depression of cortical neural activity, (2) moderate levels of CO_2 cause generalized reticulo-cortical activation which overcomes the initial direct cortical depression, and (3) high levels of CO_2 cause narcosis and depression of reticulo-cortical activity.

The effects of acute exposures (5-min.) to carbon dioxide (0-7.9%) on the EEG, respiration rate, and reaction time of humans were investigated. Alpha frequency and amplitude were recorded from the central and occipital-parietal areas of the scalp while Ss reacted with their finger to flashes of light. Arterial CO_2 tension ($PaCO_2$) was estimated on the basis of alveolar CO_2 which was measured by a Beckman infrared analyzer. Respiration rate was measured from the expired CO_2 record.

Variance analyses indicated that the percentage CO_2 inhaled significantly affected alpha frequency (occipital-parietal and central), reaction time, and respiration rate. Alpha frequency progressively increased with CO_2 concentrations from 0 to 5.5% and decreased with higher concentrations. A frequency spectrum analysis of one subject indicated that the shift in percentage fast and slow EEG

activity under the various CO_2 conditions was highly correlated with corresponding shifts in alpha frequency. Reaction time increased from 0 to 1.5% CO_2, decreased from 1.5 to 3.5% CO_2, and increased from 3.5 to 7.9% CO_2. An orthogonal comparison indicated that the increase during the 1.5% CO_2 condition did not approach statistical significance. The fastest and slowest reaction times were obtained under the 3.5 and 7.9% CO_2 conditions respectively. Respiration rate increased linearly with increases in CO_2 concentration. Alpha amplitude was not significantly affected by CO_2 concentration in either the occipital-parietal or central records.

Significant within-trial-by-CO_2 concentration interactions in occipital-parietal alpha frequency and central alpha amplitude indicated that the effect of CO_2 on these measures changed over time. With alpha frequency, the administration of all CO_2 concentrations resulted in a temporary excitatory effect followed by an inhibitory one (increased and decreased frequency respectively)--the higher the CO_2 concentration the shorter the latency and duration of the excitatory effect. With alpha amplitude, a greater decrease in amplitude occurred under the higher CO_2 conditions (5.5 and 7.9%) than under the lower CO_2 conditions. The CO_2 concentration by within-trial interaction for RT did not approach significance, RT generally increased within trials under all the CO_2 conditions.

Inspection of records for individual subjects revealed two findings: (1) that within-subject variations in alpha frequency and reaction time were highly correlated; and (2) that the Ss could be classified into two groups as to their CO_2 sensitivity--the CO_2 insensitive group tending to have higher ventilation thresholds, higher base $PaCO_2$ levels, show little response to 1.5% CO_2, and show less excitability to higher CO_2 concentrations than the CO_2 sensitive group.

The results partially supported the tri-phasic hypothesis in that the excitatory and depressive phases during moderate and high CO_2 concentrations were evident assuming that changes in reaction time and alpha frequency reflect changes in central excitability. However, due to the complexity of factors which contributed to the effect of CO_2 on central excitability, further investigation appeared warranted before the results of the present study may be generalized to other situations.

INTRODUCTION

Increasing interest has been directed toward interpreting the significance of the electroencephalogram (EEG) in relationship to behavior. The frequency and amplitude of the EEG has been used both as a gross measure of cortical excitability reflecting the general state of arousal or alertness of the organism and, in terms of alpha activity, as indicating an excitability cycle limiting neural conduction and processing time (Gastaut, 1953; Gastaut, Roger, Corriol, & Naquet, 1951; Lindsley, 1952). A major problem in this area has been to identify means whereby excitability level and the EEG can be varied experimentally, apart from the effects of the behavioral task being employed. Usually such investigation has employed correlational techniques relating changes in performance or task difficulty with changes in the EEG. A method whereby excitability could be manipulated experimentally while holding task variables constant, thus enabling the effect of these manipulations on performance to be measured, would be a valuable tool for further investigation in this area.

A possible means for manipulating central excitability is the administration of different concentrations of carbon dioxide (CO_2). This has been found to influence

central or cortical excitability with little effect on peripheral and receptor processes (Dell & Bonvallet, 1954, 1956; Gellhorn, 1953a, p. 454; King, Garrey, & Bryan, 1932; Stokes, Chapman, & Smith, 1948). Gellhorn (1953a; 1953b), on the basis of animal experiments, proposed that CO_2 has a dissociative effect on the central nervous system: low levels of CO_2 (10 to 20%) appeared to increase the excitability of the hypothalamic-cortical nervous system and decrease the excitability of the specific cortical sensory projection systems; higher CO_2 concentrations (20-35%) appeared to inhibit hypothalamic-cortical activity while having only slight additional effects on the cortical sensory projection systems.

Wyke (1963, p. 162) expanded Gellhorn's hypothesis suggesting that increasing concentration of CO_2 causes: (1) direct depression of cortical neural activity only (3 to 7% CO_2), (2) generalized reticulo-cortical activation which overcomes the initial direct cortical depression (5 to 20% CO_2), and (3) narcosis or anesthesia and depression of reticulo-cortical activity (excess of 25% CO_2).

A considerable amount of evidence may be cited in support of the above hypotheses. The suppressive effects of low levels of CO_2 have been demonstrated primarily by sensory threshold studies. King, Garrey, and Bryan (1932) found that the knee jerk reflex may be abolished in dogs by the inhalation of 10% CO_2 and reduced considerably by lesser

concentrations. This inhibition was attributed to central causes since, after a spinal transection, CO_2 concentrations up to 40% failed to affect the knee jerk reflex.

Auditory, visual, and pain threshold were similarly depressed. Stokes, Chapman, and Smith (1948) found that inhalation of 5 and 7.5% CO_2 resulted in a respective 13 and 28% increase in pain threshold. Gellhorn and Spiesman (1935a) demonstrated that auditory threshold was significantly increased by inhaling CO_2 concentrations between 3.5 and 7%. Also, inhalation of 4 and 10% CO_2 prolonged the latency of negative after-image development (Gellhorn & Spiesman, 1935b) and impaired visual function as indicated by increased threshold and decreased brightness discrimination (Wyke, 1963, p. 58).

The few studies utilizing central measures of excitability show conflicting results as to the effect of low CO_2 concentrations on cortical excitability. An increase in $PaCO_2$ resulted in an increase in brain wave frequency (Gibbs, Williams, & Gibbs, 1940), whereas in another study, inhalation of 3% CO_2 resulted in a decrease in frequency and increase in occurrence of the alpha rhythm (Schaefer, 1949). Two measures identified with central excitability, alpha blocking time and critical flicker fusion (CFF), were suppressed by inhalation of low concentrations of CO_2 (Schaefer & Carey, 1954). These measures were obtained while subjects (Ss) inhaled 1.5, 3.3, 5.4,

and 7.5% CO_2 mixed with air. Both measures indicated a decrease in central excitability as the percentage CO_2 increased: critical flicker fusion decreased and alpha blocking time increased.

In comparison with the above studies which demonstrated the effects of low levels of CO_2 (0-7%) primarily in humans, studies demonstrating the effect of higher concentrations of CO_2 (10-35%) were based primarily on electrophysiological measures of central excitability in animals. Administration of 10-20% CO_2 to cats resulted in depressed localized cortical responses to visual stimulation while it enhanced the responses in the hypothalamic area of the brain stem and the hypothalamic-cortical tracts (Gellhorn, 1952; 1953a, p. 453; 1953b). This action of CO_2 on the hypothalamic-cortical system was demonstrated through the application of proprioceptive and nociceptive stimuli to the leg. When administering 10% CO_2, subthreshold proprioceptive stimuli became effective in evoking a cortical response. The excitatory effects were further isolated to the hypothalamus in that when the hypothalamus was surgically isolated from the cortex such effects were terminated (Gellhorn, 1953a, p. 454). Dell and Bonvallet (1954) also found EEG activation effects of low CO_2 concentrations and related this to the ascending reticular formation and respiratory drive.

At high levels of CO_2 (35%), there was a reversal in the manner in which the diffuse and specific sensory systems were effected. Hypothalamic-cortical activity was eliminated in terms of both spontaneous and evoked activity while the specific projection systems retained their excitability although at a somewhat reduced level (Gellhorn, 1953a, p. 460).

The effects of CO_2 (0-40%) on central excitability in rats and mice have been investigated as reflected by electro-shock seizure threshold (EST), spontaneous seizures, and EEGs (Woodbury & Karler, 1960; Woodbury, Rollings, Gardner, Hirschi, Hogan, Rallison, Tanner, & Brodie, 1958). With low levels of CO_2 (5-20%) EST increased, with moderate levels (25-40%) EST decreased and spontaneous seizures increased, and with high levels (40% and above) anesthesia occurred. Although somewhat less clear, the EEG records reflected similar changes in excitability. This study lends direct support to the tri-phasic effects of CO_2 cited above by Wyke.

A review of the studies cited above shows little consistent support for the excitatory phase under the influence of 5 to 20% CO_2 as proposed by Wyke. Excitatory effects were found as a result of small increases in $PaCO_2$ (Gibbs, Williams, & Gibbs, 1940), inhalation of 10-20% CO_2 (Gellhorn, 1953b), and inhalation of 25-40% CO_2 (Woodbury &

Karler, 1960; Woodbury et al., 1958). Suppression was also found for these same CO_2 values in other studies.

A number of factors were evident which may, in part, account for these inconsistencies. First, the effects of length of inhalation period have not been systematically investigated across a broad range of CO_2 concentrations in humans. Therefore it is difficult to equate studies utilizing different lengths of administration times.

Second, the second phase of CO_2 effects, the excitatory phase, predominantly has been demonstrated with animals and based on central measures of excitability. These effects cannot be directly generalized to man since they occur at CO_2 concentrations which result in loss of consciousness in man. The few studies finding excitatory effects in man (Gibbs, Williams, & Gibbs, 1940; Wyke, 1963, p. 81) were difficult to interpret since levels of inspired CO_2 were not cited and the data were based on only a few subjects.

Thirdly, there is a considerable amount of confusion resulting from different use of terminology in the above studies. Concentration of CO_2 has been referred to as "low," "moderate," and "high" without referring to actual CO_2 concentration. Confusion results in that, for example, the term "low" level is used to mean subnormal CO_2 values (Wyke, 1963, p. 81), concentrations of 0 to 10% CO_2

(Schaefer & Carey, 1954) and concentrations of 10 to 20% CO_2 (Gellhorn, 1953b). In the present study these terms are used as suggested by Wyke (1963, p. 162) indicating CO_2 concentrations of approximately 0-7, 5-20, and 20-40% respectively.

The concept of "cortical excitability" has been similarly used in more than one sense. Gellhorn (1953a; 1953b) utilized the term in a relatively restricted sense. He clearly stated that EEG activation reflects the increased excitability of the hypothalamic-cortical projection system and is accompanied by increased excitation only of those sensory systems (specifically proprioceptive and nociceptive systems) directly involved with the diffuse hypothalamic-cortical system. While the effects of nocioceptive and proprioceptive stimuli were enhanced during EEG activation, there was simultaneous reduction in the responsiveness of the specific cortical projection systems. A further inconsistency in the above findings was that cutaneous pain threshold was increased (Stokes, Chapman, & Smith, 1948) during CO_2 concentrations which resulted in the increased responsiveness to nocioceptive stimuli.

The above inconsistencies are in conflict with the broader and generally more accepted meaning of "excitability" or "activation." This view was presented by Wyke as follows:

> If reticulo-cortical activation be increased for any reason, there is acceleration and desynchronization of the brain waves, augmented awareness of the environment, and increased cortical excitability--the so-called activating response. Conversely, should reticulo-cortical activation be diminished, the reverse changes occur, with slowing and increasing synchrony of the brain waves, diminished environmental awareness, and decreased cortical excitability--the deactivating response (1963, p. 160).

It should be noted that in addition to the two projection systems described by Gellhorn and Wyke (specific sensory projection systems and diffuse hypothalamic-cortical projection system) a non-specific or diffuse thalamic-cortical projection system has been described (Gastaut, 1953; Gastaut, Roger, Corriol, & Naquet, 1951; Jasper, 1949; Lindsley, 1952). This system may be identified with increased excitability of localized cortical areas and may not necessarily be reflected by EEG activation. Such a system possibly could account for the selective enhancement of proprioceptive and nocioceptive stimuli described by Gellhorn, but such localized excitability should be reflected by increased responsiveness to those specific stimuli and not by generalized cortical activation.

Finally, the evidence in support of the tri-phasic hypothesis has been based on a number of studies utilizing different kinds of Ss (man vs. animal), different concentrations of CO_2, and different measures of excitability. Past research has been deficient in human studies

investigating the effects of CO_2 over a wide range of values while simultaneously employing central and behavioral measures of cortical excitability.

The purpose of the present study was to test the tri-phasic hypothesis as to the effects of CO_2 on cortical excitability presented by Wyke, in humans, varying CO_2 concentration from 0 to 7.9%. Both central (alpha frequency and amplitude) and behavioral (reaction time) measures were utilized as indicants of central excitability. The upper limit of 7.9% was selected since it nears the maximum CO_2 concentration permissible (10%) without loss of consciousness in man (Meduna, 1950, p. 5). In addition, the effects of CO_2 on the dependent variables were evaluated in terms of duration of inhalation period.

METHOD

The experiment was conducted at the Tucson Medical Center Cardiopulmonary Laboratory, Tucson, Arizona. Medical supervision of CO_2 administration was provided by personnel from both the Cardiopulmonary Laboratory and from the University of Arizona.

Experimental Design

Five male graduate students between 21 and 30 years of age served as Ss. Each S sat for three 50-min. experimental sessions. The first session was on one day and used solely as a means of acquainting Ss with the experimental situation and for giving them experience with the reaction time task. The second and third sessions were administered on a second day separated by a 20-min. rest interval. Each session consisted of five 5-min. trials separated by 3-min. rest intervals. The Ss breathed air for the first 30 seconds of each trial prior to administration of CO_2. During each experimental session the Ss inhaled five levels of CO_2 (0, 1.5, 3.5, 5.5, and 7.9%) mixed with air. A replicated 5 X 5 balanced Latin Square (Table 1) was used to determine the trial on which the various CO_2 conditions were presented to each S for the two sessions. Six within-trial changes were obtained by sampling the data for the

Table 1

Latin Square Design for Order of Experimental Condition Presentation

Ss	Sess.	Level of CO_2				
		0	1.5	3.5	5.5	7.9
1	1	1	2	3	4	5
	2	5	4	3	2	1
2	1	2	1	5	3	4
	2	4	3	5	1	2
3	1	3	4	1	5	2
	2	2	5	1	4	3
4	1	4	5	2	1	3
	2	3	1	2	5	4
5	1	5	3	4	2	1
	2	1	2	4	3	5

first minute (the first two 30-sec. intervals) and then on alternate 30-sec. intervals for the remaining part of the trial. Therefore, the five Ss, five CO_2 concentrations, two sessions, and six 30-sec. within-trial samples resulted in a total N of 300.

Apparatus and Data Recording Procedure

Measures of EEG frequency and amplitude (central and occipital-parietal leads), and reaction time served as measures of central excitability. Arterial CO_2 tension (mmHg) was obtained by a Beckman infrared CO_2 analyzer as an estimate of changes in CO_2 concentration in the brain. Model 5P5 Grass differential input preamplifiers were used for recording EEGs. All signals were fed into a Grass Model 5 Polygraph for amplification and recording. The apparatus and a sample of the polygraph record are illustrated in Fig. 1 and Fig. 2 respectively.

Commercial silver disc electrodes (8 mm in diameter) were used for recording EEGs. In order to reduce skin resistance to less than 5,000 ohms, the S's skin was first rubbed with alcohol and then with Grass Electrode Paste. Electrodes were attached firmly in place with electrode paste.

Arterial CO_2 Tension and Respiration Rate

The fractional to- and fro-method used to obtain arterial CO_2 tension ($PaCO_2$) was described by Collier,

Fig. 1. Experimental apparatus for administering CO_2 (1.5-7.9% in air) and air and for measuring reaction time.

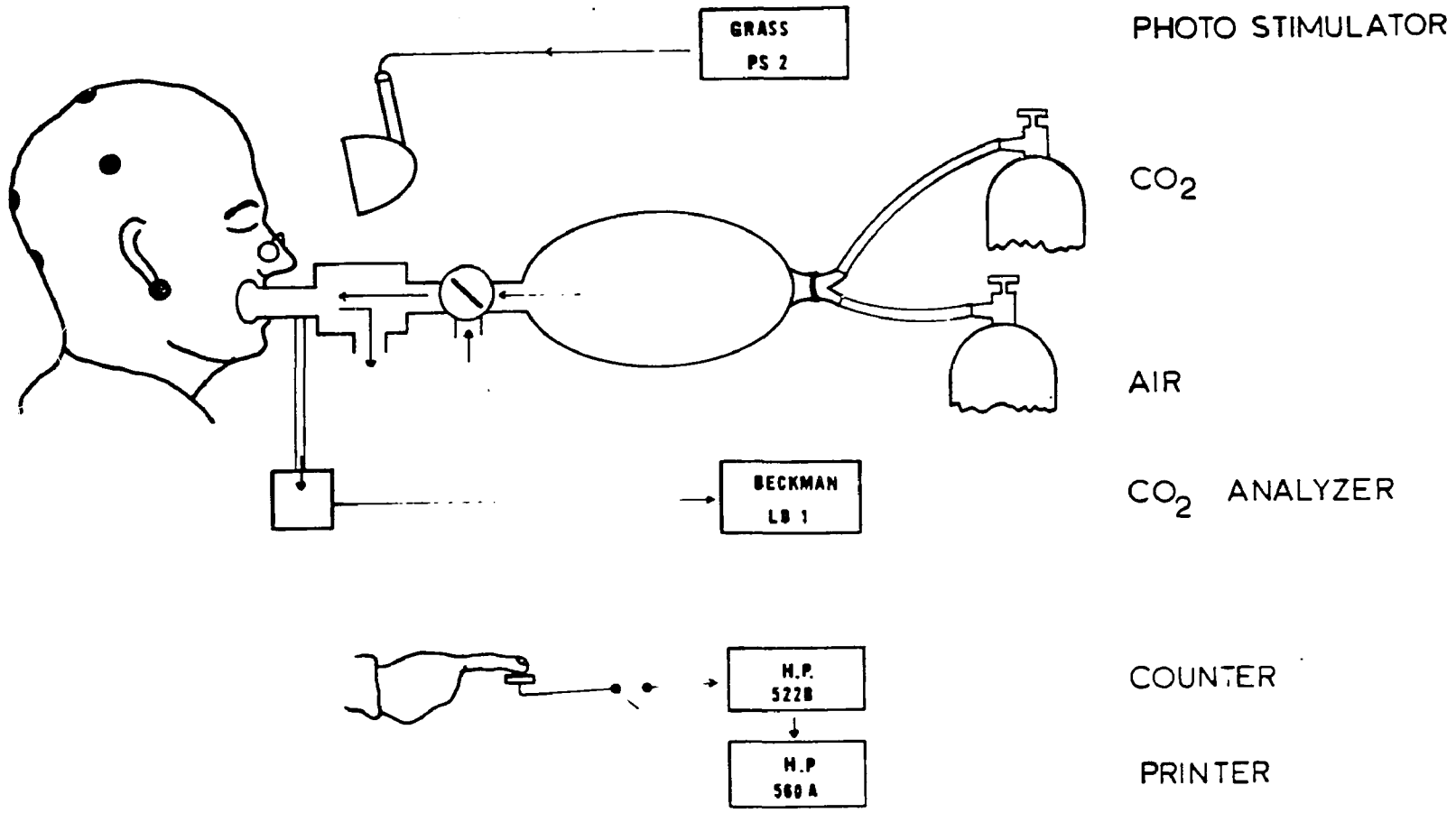

Fig. 1. Experimental apparatus for administering CO_2 (1.5-7.9% in air) and air and for measuring reaction time.

Fig. 2. A polygraph sample record for Ss BF showing the central-temporal (MLC-RT), occipital-parietal (MLO-MLP), temporal-ear (RT-LE), and occipital-ear (MLO-LE) EEG records, the reaction time record, and the expiration (Exp.) and inspiration (Insp.) CO_2 tension record.

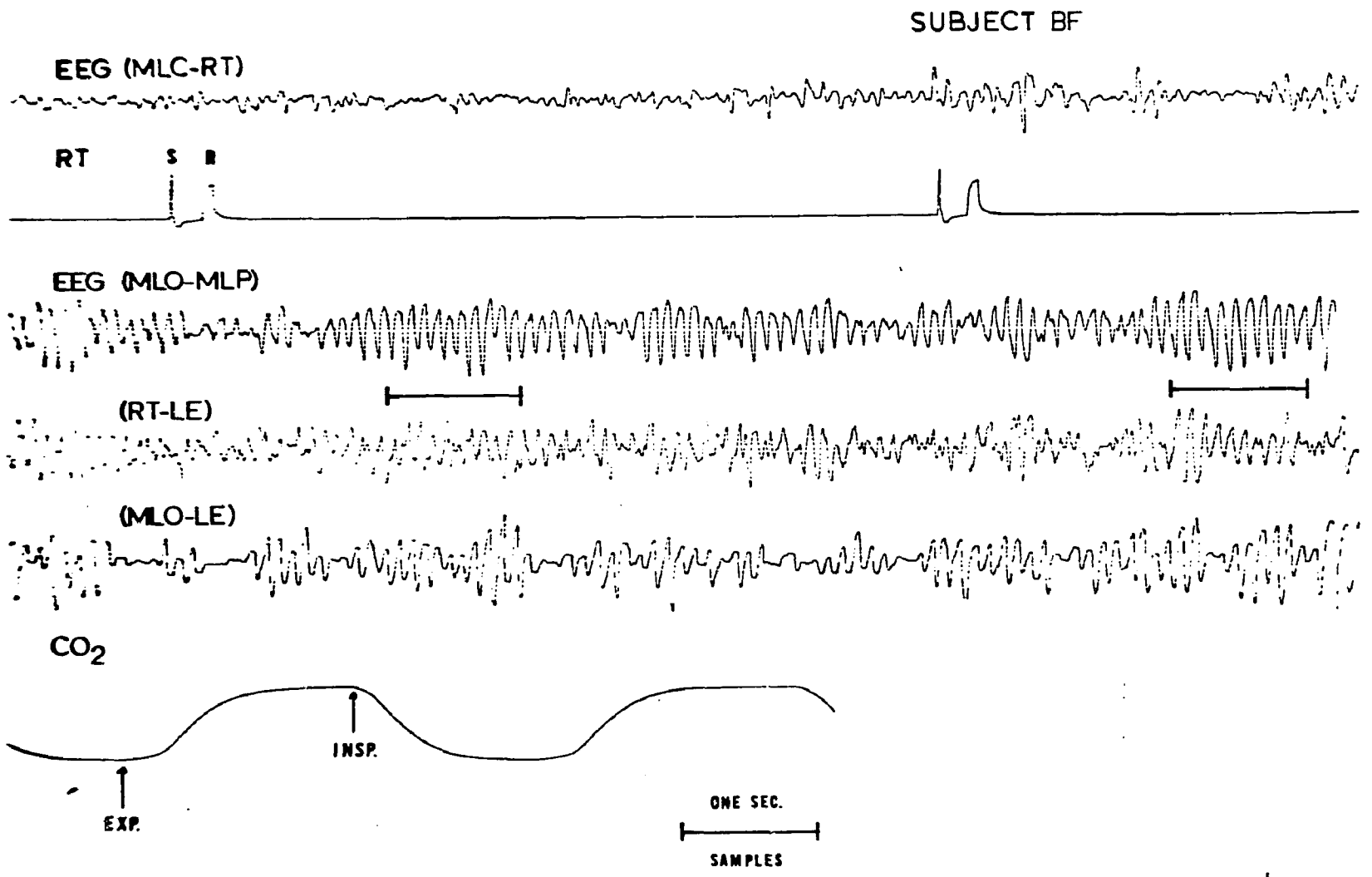

Fig. 2. A sample polygraph recording of EEG, reaction time, and expired CO_2.

Affeldt, and Farr (1955). The pen deflection reflecting the end-tidal of expired CO_2 was measured in millimeters and then converted to percentage CO_2 by the use of calibration curves. The apparatus was calibrated at the beginning and end of each experimental session by the use of known gas mixtures. The average percentage expired CO_2 for each 30-sec. interval was then converted to $PaCO_2$ by the formula:

$$PaCO_2 = \%\ \text{expired}\ CO_2/100\ (\text{barometric pressure} - 47).$$

Respiration rate was determined by counting the number of end-tidal peaks in the expired CO_2 record for the first two 30-sec. intervals and then for each following minute.

Reaction Time

RT was measured to the nearest millisecond by a Hewlett Pakard Model 522B electronic counter and Model 560A digital recorder. A Grass photo stimulator Model PS2, set on intensity 16, was used to present visual stimuli of 10 microseconds duration. A hood, attached to the flash tube, separated the S's eyes 6" from the stimulus. Stimuli were presented at intervals varying from 2 to 5 seconds, one being presented in every 5-sec. interval. A Model 220 California Technical Industries 6-channel tape reader triggered the photo-stimulator, counter, and polygraph RT monitor. Subjects reacted by pushing a micro-switch key

with their right index finger which, in turn, sent a terminating pulse to the counter and polygraph monitor. A 180 gr. force was required to move the key the 7 mm. excursion necessary to close the switch. In that modal RT values were of interest in the present study, and in order to reduce the effect of extreme RT values, RTs over 350 msec. were voided. Frequency distributions indicated that this exclusion did not differentially affect RTs obtained during the various CO_2 conditions, approximately 1.4% of the data being voided under each CO_2 condition. Reaction times obtained during movement, as indicated by muscle tension or slow frequency artifacts in the EEG records, were also voided.

Alpha Frequency and Amplitude

Bipolar and monopolar EEGs were recorded from the occipital-parietal and central regions of the scalp according to the International Standardized 10-20 system. Subjects were grounded by their right earlobe. Alpha frequency (any rhythmic discharge between 8 and 13 cps) was determined by selecting three 1-sec. samples of the highest amplitude alpha waves within each 30-sec. interval, counting the alpha waves of each sample, and dividing by their accumulated duration in seconds. Alpha amplitude was measured in microvolts from the same portion of the record used in measuring alpha frequency.

Gas Inhalation

Subjects breathed through a rubber mouth piece attached to a Hans Rudolph valve from a 60 liter Douglas Bag. The bag was emptied of gas by means of a vacuum pump during the rest intervals prior to being filled with the appropriate CO_2 mixture. A two-way valve, situated at the neck of the Douglas Bag, enabled the experimenter to switch from air to CO_2 after the first thirty seconds of each trial.

Experimental Precautions and Controls

Precautions were taken to standardize the experimental sessions and control for any placebo effects. The Ss were instructed to sit in a comfortable position, to keep body movement at a minimum, and to keep their eyes shut during the experiment. They were also told to remain alert at all times. The general experimental procedure was explained to them briefly. Care was taken not to give the Ss any cues as to the CO_2 mixture they would be inhaling. The Ss were permitted to talk and move while seated during the 3-min. rest intervals between trials and to walk around during the 20-min. rest interval between sessions.

RESULTS

Analyses of variance were performed to determine the effects of CO_2 concentration inhaled, experimental sessions, and within-trial changes on $PaCO_2$, respiration rate, RT, and alpha frequency and amplitude from central and occipital-parietal leads (Tables 4-10). The significant F-ratios for the various conditions and dependent variables are summarized in Table 11.

Effects of CO_2 Concentration

The effects of CO_2 concentration inhaled on the various dependent variables are illustrated in Fig. 3. Respiration rate and $PaCO_2$ increased approximately linearly as CO_2 concentration was increased ($P < .05$ and $P < .01$ respectively).

Reaction time and occipital-parietal (O-P) and central (C) alpha frequency varied significantly ($P < .05$ and $P < .01$ respectively) as a function of CO_2 concentration. Both measures varied curvilinearly--RT increased, decreased, and increased while alpha frequency increased and decreased as CO_2 concentration was increased from 0 to 7.9%. The fastest (232 msec.) and slowest (249 msec.) RT occurred respectively under the 3.5 and 7.9% CO_2 conditions whereas the fastest and slowest alpha frequency occurred

Fig. 3. Effects of CO_2 concentration administered on arterial CO_2 tension ($PaCO_2$), respiration rate, reaction time, and alpha EEG. Each plotted point is an average based on an N of 60 distributed evenly among 5 Ss.

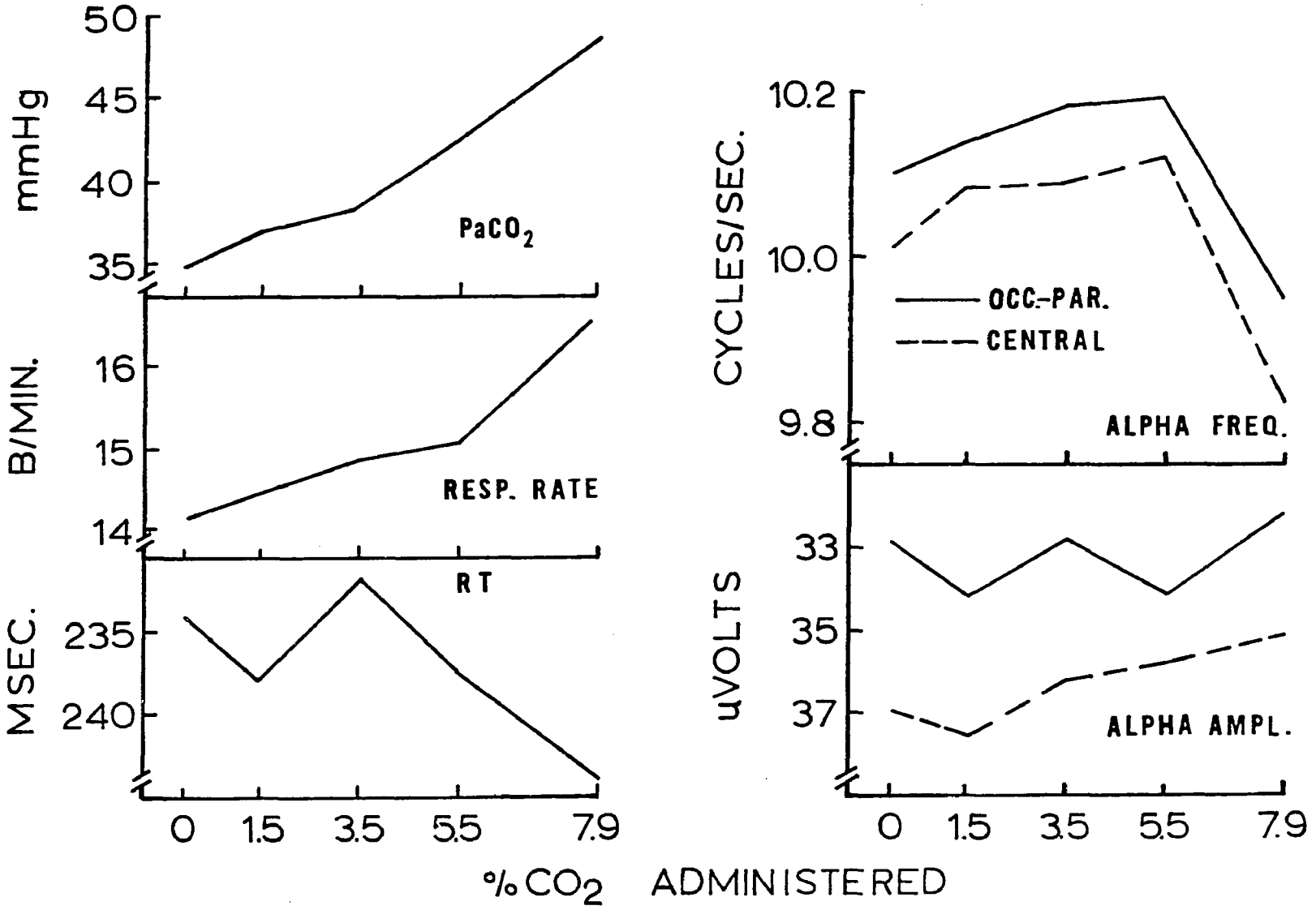

Fig. 3. Effects of CO_2 on $PaCO_2$, respiration, reaction time, and the EEG for 5 Ss.

respectively under the 5.5 and 7.9% CO_2 conditions. Orthogonal comparisons indicated that both RT and alpha frequency (O-P) were significantly faster during the O-5.5% CO_2 conditions than during the 7.9% CO_2 condition ($P < .01$). The fluctuations in RT and alpha frequency under the O, 1.5, 3.5, and 5.5% CO_2 conditions did not differ significantly.

Although alpha amplitude (O-P and C) was not significantly affected by the various CO_2 concentrations, consistent trends were evident. Alpha amplitude first increased and then decreased as CO_2 concentration increased from O-7.9%. It should be noted that this trend appears to be directly related to variations in alpha frequency--increases in alpha frequency were accompanied by increases in alpha amplitude.

Effects of Time

Changes occurring between sessions are indicated in Table 2. Significant decreases in alpha frequency (O-P and C) and increases in alpha amplitude (C) were obtained ($P < .01$ and $P < .05$ respectively). A similar change in occipital-parietal alpha amplitude was evident although not significant ($P < .07$). Between sessions changes in respiration rate, $PaCO_2$, and RT were not significant.

Within-trial changes (changes across minutes) are indicated in Fig. 4. Significant changes were obtained for $PaCO_2$ and respiration rate ($P < .01$) and for RT ($P < .05$).

Table 2

Between Session Changes

Dependent Variable	Sessions 1	Sessions 2
$PaCO_2$ (mmHg)	34.7	34.3
Respiration Rate (B/M)	14.9	15.2
Reaction Time (msec.)	238.1	237.9
O-P Alpha Frequency (cps)	10.23	9.99**
C Alpha Frequency (cps)	10.14	9.90**
O-P Alpha Amplitude (uV)	32.2	34.4
C Alpha Amplitude (uV)	34.2	38.2*

*Session 1 differed significantly from session 2 ($P < .05$)
**Session 1 differed significantly from session 2 ($P < .01$)

Fig. 4. Within-trial changes in arterial CO_2 tension ($PaCO_2$), respiration rate, reaction time, and alpha EEG. Each plotted point is an average based on an N of 50 distributed evenly among 5 Ss.

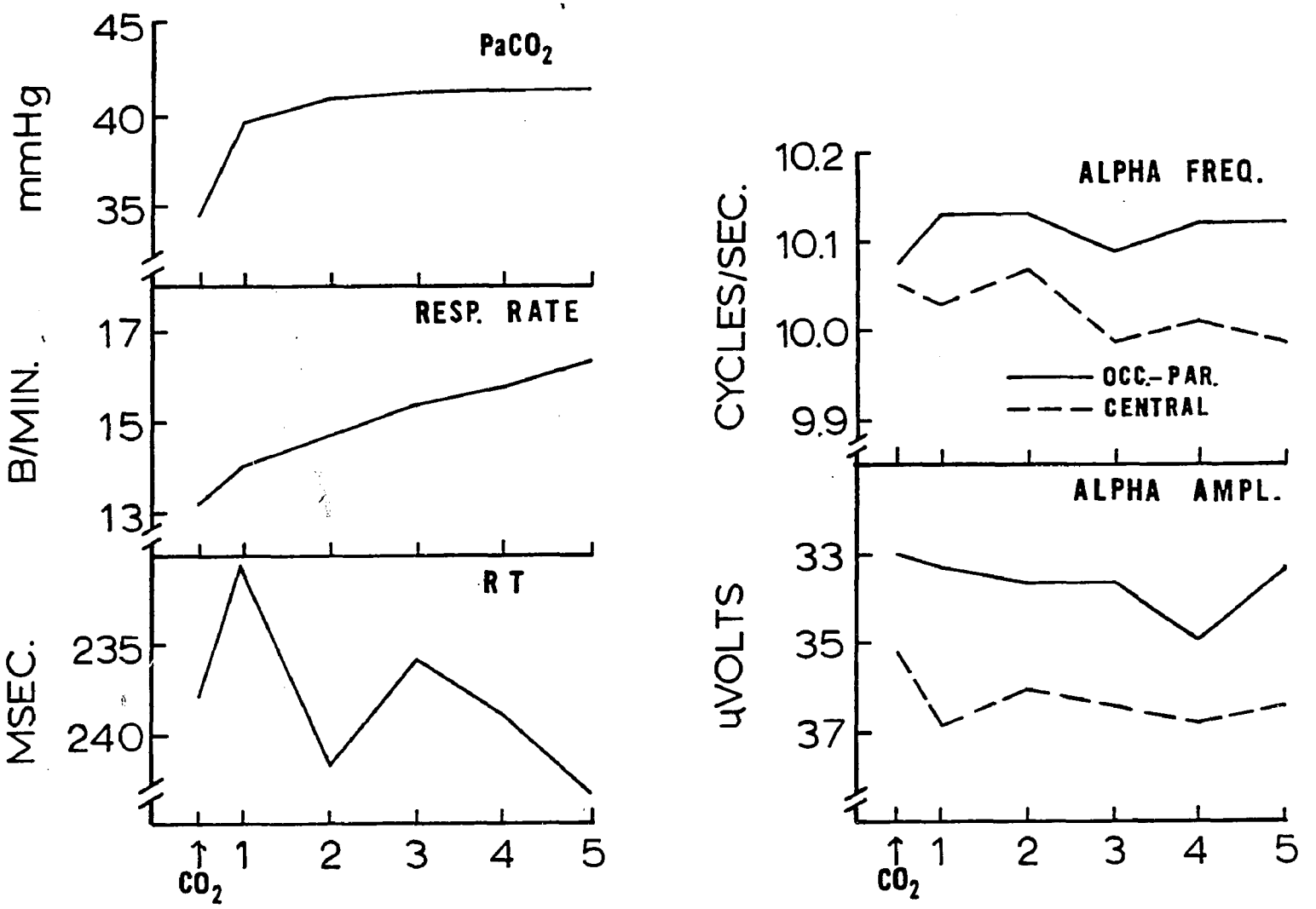

Fig. 4. Within-trial changes in arterial CO_2 tension ($PaCO_2$), respiration rate, reaction time, and alpha EEG.

Arterial CO_2 tension increased as a negatively accelerated function of CO_2 concentration. An orthogonal comparison demonstrated that $PaCO_2$ significantly increased only during the first and second minutes of CO_2 inhalation ($P < .01$), no significant changes occurring during the last three minutes of the trial.

Respiration rate increased linearly whereas RT decreased linearly within trials. An orthogonal comparison was performed in order to determine the significance of RT fluctuations during the first three minutes of the trial which indicated that the increases in RT from the first to second and fifth minute were the only significant differences obtained ($P < .05$ and $P < .01$ respectively).

The interaction effects of the various CO_2 concentrations on $PaCO_2$ and respiration rate within trials (Fig. 5) were significant ($P < .01$). The length of time required before $PaCO_2$ became stable varied as a function of CO_2 concentration inhaled--the higher the concentration the longer the time required for stability. Respiration rate did not stabilize under any of the CO_2 concentrations but increased linearly across minutes--the higher the CO_2 concentration the greater the increase in respiration rate.

The differential effects of CO_2 concentration within trials on alpha frequency and amplitude (Fig. 6) were less clear although significant ($P < .05$). The following trends may be noted with alpha frequency (O-P).

Fig. 5. Within-trial changes in arterial CO_2 tension ($PaCO_2$) and respiration rate under the different CO_2 conditions. Each plotted point is an average based on an N of 10 evenly distributed among 5 Ss.

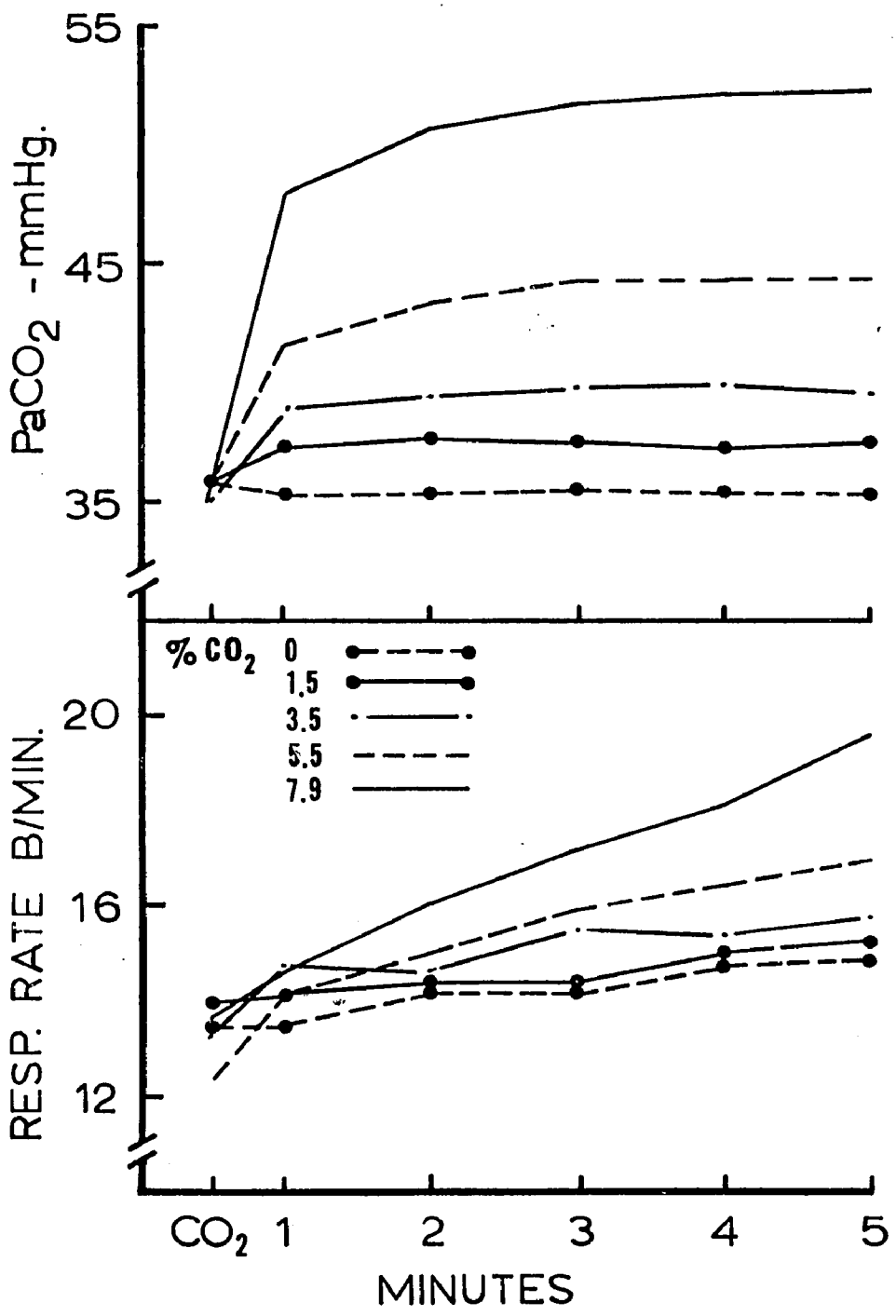

Fig. 5. Within-trial changes in arterial CO_2 tension ($PaCO_2$) and respiration rate under the different CO_2 conditions.

Fig. 6. Within-trial changes in occipital-parietal alpha frequency and central alpha amplitude under the different CO_2 conditions. Each plotted point is an average based on an N of 10 evenly distributed among 5 Ss.

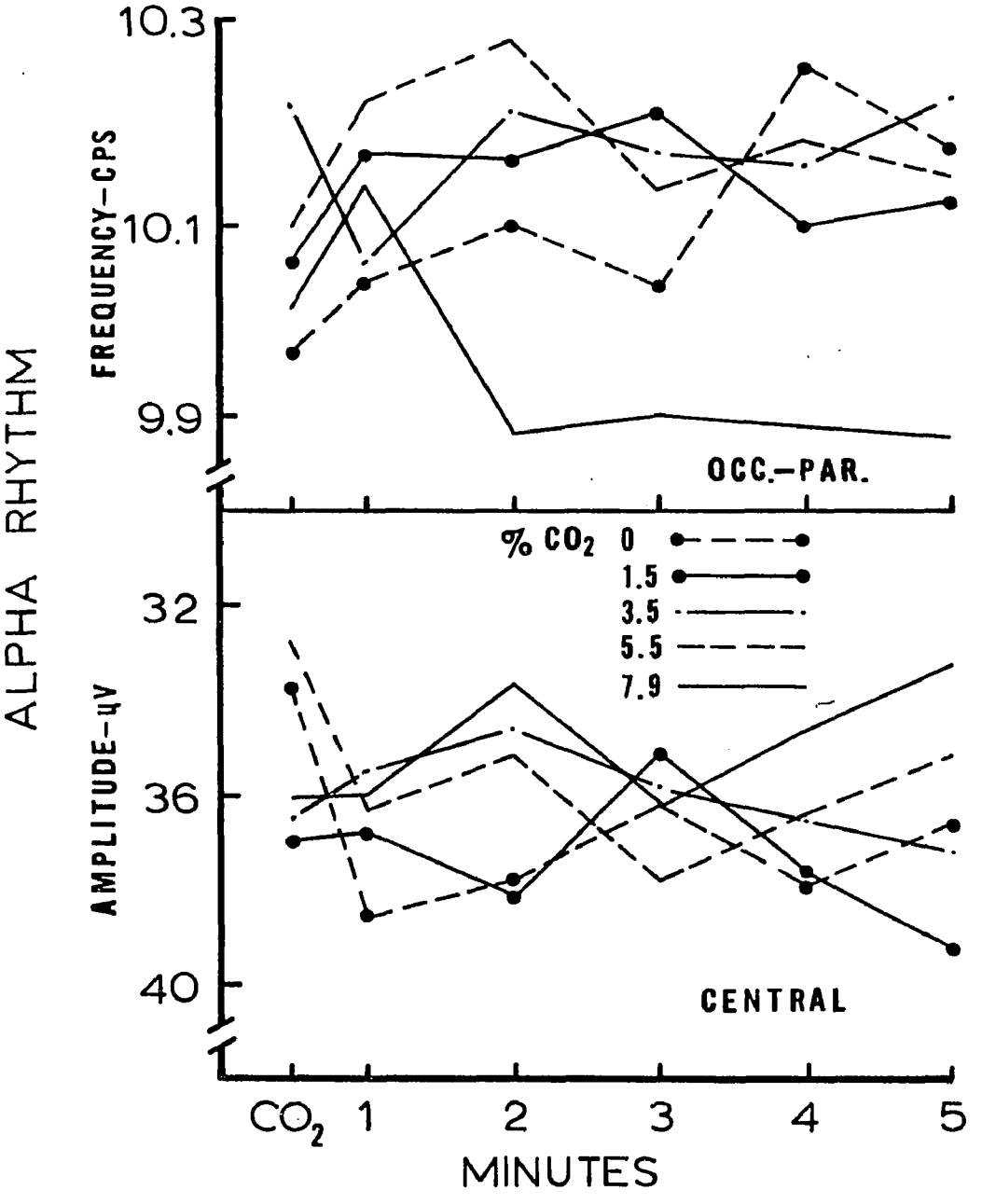

Fig. 6. Within-trial changes in occipital-parietal alpha frequency and central alpha amplitude under the different CO_2 conditions.

First, with the exception of 7.9% CO_2 the longer the inhalation period the less the differential effect of the various CO_2 concentrations. The differential CO_2 effects were greatest during the second minute of inhalation and least during the fifth minute of inhalation. Second, the fastest alpha frequency for each CO_2 concentration was obtained earlier within the trial the higher the CO_2 concentration--with air during the fifth minute, with 1.5% CO_2 during the third minute, with 3.5 and 5.5% CO_2 during the second minute, and with 7.9% CO_2 during the first minute. Thirdly, the direction of within-trial change in alpha frequency appears to be a function of CO_2 concentration inhaled--with air alpha frequency increased, with low concentrations (1.5, 3.5, and 5.5%) alpha frequency increased and then decreased, and with high concentrations (7.9%) alpha frequency decreased. Similar trends were evident with central alpha frequency although not significant. The variability of points during the 0% CO_2 conditions, which should be minimal since each point reflects a replication of the same condition, may be noted as reflecting the magnitude of chance variation.

The significant CO_2-by-minute interaction in central alpha amplitude may be attributed to changes occurring at the end of the trial. With the higher CO_2 concentrations (5.5 and 7.9%), amplitude decreased during the last two minutes whereas with the lower concentrations

(1.5 and 3.5%) amplitude increased. With the air condition, no consistent changes were evident. The CO_2-by-sessions, sessions-by-minutes, and CO_2-by-sessions-by-minutes interactions did not approach significance for any of the dependent variables.

Additional Analyses

A number of supplementary analyses were performed in order to pursue questions raised by the grouped data and in order to present a number of informal observations. In that these analyses did not involve all the Ss and all the experimental conditions, they are not included in the main body of the results.

To further investigate alpha frequency changes in specific cortical areas and to observe if monopolar vs. bipolar recording would give different results, the monopolar (central and occipital) and bipolar (occipital-parietal and central-temporal) records were compared in two Ss (BF and GH) during the last minute interval of each trial. An analysis of variance (Table 12) indicated that the difference between these four measures and how they were affected by CO_2 did not approach significance.

In order to compare changes in alpha frequency with changes in EEG activity over a wide frequency range and in order to compare the results of the present study with studies using EEG measures of excitability other than alpha

frequency, a frequency spectrum analysis was performed on the central EEG record of one S (BF). The manual method used for obtaining the EEG frequency spectrum was described in detail by Kaufman and Hoagland (1946) which consisted in determining the frequency of all waves (5-30 cps), as a function of wave length, for waves over 5 micro-volts in amplitude. Each frequency band was then expressed in terms of the percentage time it occupied in the EEG record sampled.

The obtained frequency spectrum (Table 13) indicated that the greatest percentage of EEG activity occurred in the 11 and 24 cps frequency ranges. The relationship between the percentage time of these frequency bands and alpha frequency is illustrated in Fig. 7. An increase in alpha frequency was clearly accompanied by a shift toward greater activity in the higher frequency range and a decrease in activity in the lower frequency range. Alpha frequency was directly related to the percentage fast activity (24 cps) and inversely related to the percentage alpha activity (11 cps) in the EEG record.

In order to assess more accurately the relationship between RT and alpha frequency and to observe individual differences, these variables were plotted across the various CO_2 conditions for individual Ss (Fig. 8). Although the between Ss CO_2 effects were considerable, the within Ss relationship between RT and alpha frequency was

Fig. 7. The effects of CO_2 concentration on alpha frequency and percentage time of 11 and 24 cps EEG activity. The data were obtained from the central EEG record of one S (BF) during the last minute interval of each trial.

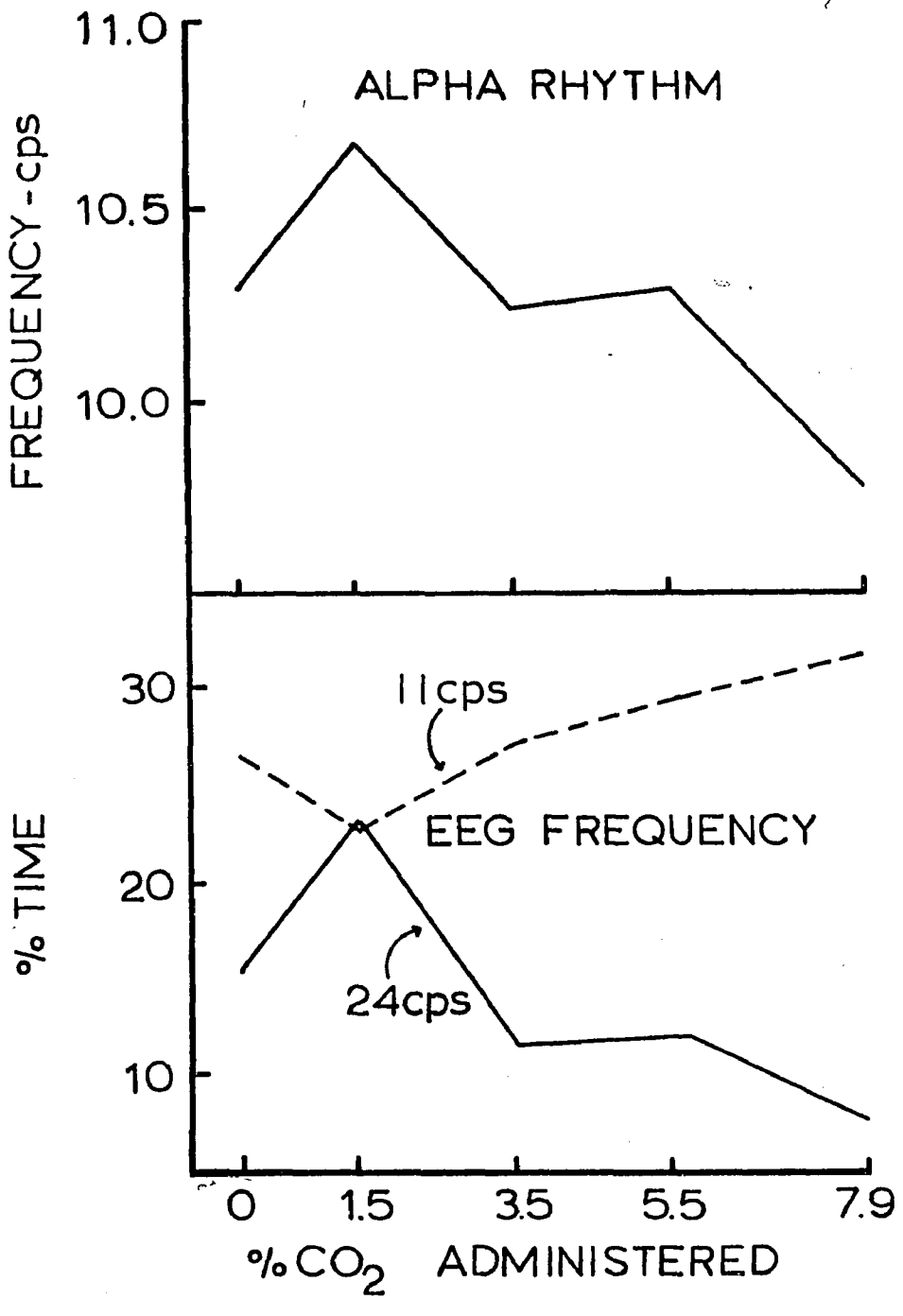

Fig. 7. The effects of CO_2 concentration on alpha frequency and percentage time of 11 and 24 cps EEG activity.

Fig. 8. The effects of CO_2 on reaction time (RT) and occipital-parietal alpha frequency (AF) in individual Ss. Each plotted point is an average based on an N of 12.

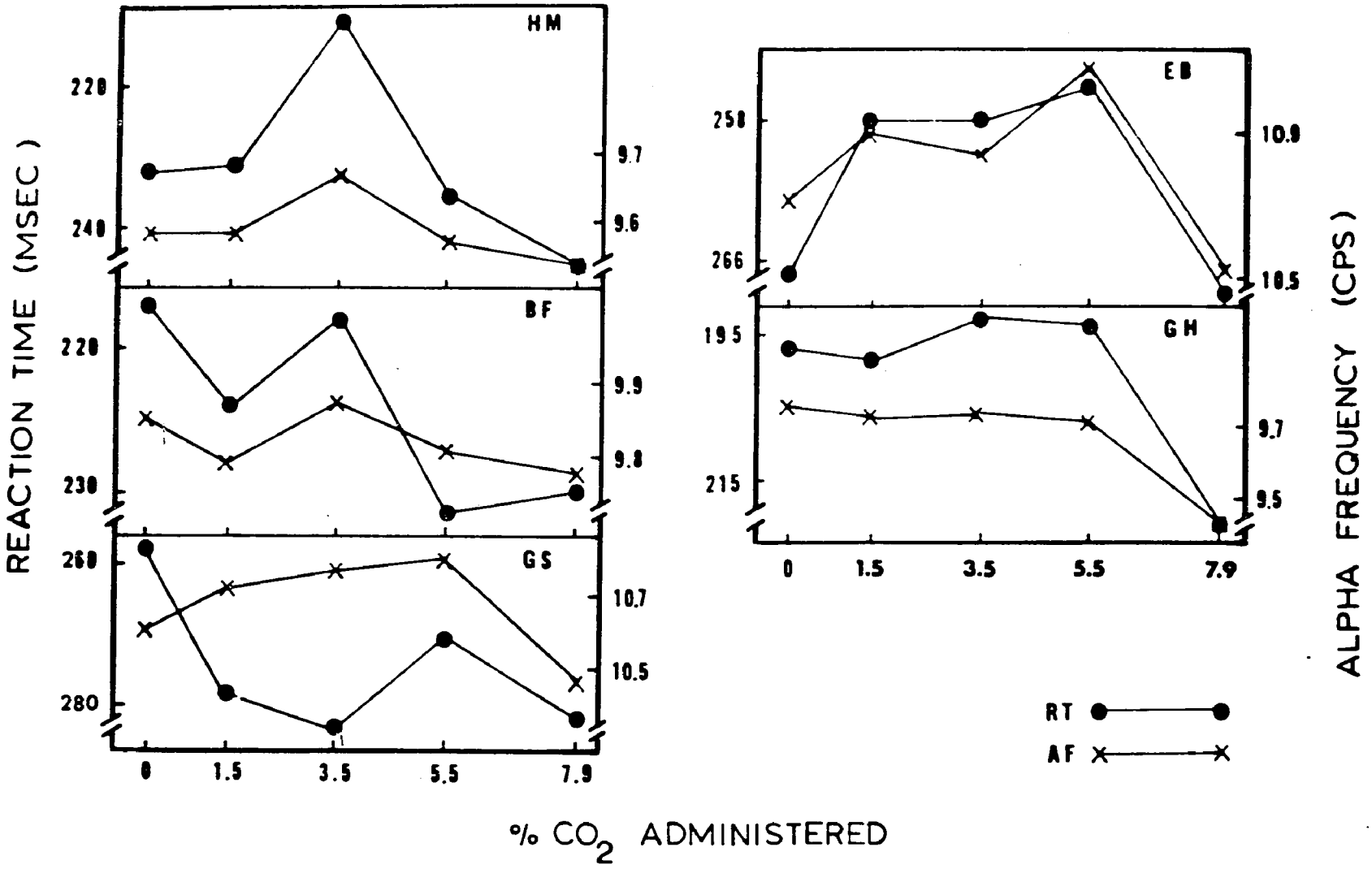

Fig. 8. The effects of CO_2 on reaction time (RT) and occipital-parietal alpha frequency (AF) in individual Ss.

apparent in four of the five Ss. The respective rank order correlation coefficients for Ss EB, GH, HM, BF, and GS were +.50, +.60, +.90, +.90, and .00 ($r = .90$ significant $P < .025$).

In light of the differences between Ss as to the effect of CO_2 on the various dependent measures, individual records were inspected for differences in sensitivity to CO_2. The Ss were compared on the bases of ventilation threshold (increase in respiration rate), base $PaCO_2$ level, excitatory effects of 1.5% CO_2, and CO_2 concentration causing maximum excitability (Table 3). The Ss appeared to fall into two groups in terms of their sensitivity to CO_2. The CO_2 insensitive group tended to have higher ventilation thresholds, higher base $PaCO_2$ levels, show no change or decreased excitability to 1.5% CO_2, and showed less excitability to higher CO_2 concentrations than the CO_2 sensitive group. It may be noted that both the RT and alpha frequency measures indicated similar changes in excitability.

Table 3

Individual Differences in CO_2 Effects

Ss		Vent. Thresh.	Base $PaCO_2$	Excit. 1.5% CO_2	Max. Excit.
CO_2 Insensitive	GH	none	31	none	3.5%
	BF	5.5%	29	Decr.	0.0%
	HM	3.5%	32	none	3.5%
CO_2 Sensitive	EB	1.5%	30	Incre.	5.5%
	GS	1.5%	30	Incre.	5.5%

DISCUSSION

In the introduction, three phases were proposed in relation to the effects of increasing CO_2 concentrations on cortical excitability: direct depression of cortical neural activity, generalized reticulo-cortical activation which overcomes the initial direct cortical depression, and direct depression of reticulo-cortical activity. For the purposes of the present study, central excitability was inferred on the bases of changes in alpha frequency and amplitude, RT, and respiration rate--increased excitability assumed to be accompanied by increased alpha frequency and decreased alpha amplitude, decreased RT, and increased respiration rate. The second and third phases were clearly evident in the present study as indicated by changes in RT and alpha frequency but not by changes in alpha amplitude which were relatively insensitive to changes in CO_2 concentration. Phase two was evident in the increase in respiration rate and alpha frequency and decrease in RT during low CO_2 concentrations (1.5-5.5%). Phase three was evident in the decrease in alpha frequency and increase in RT during the high CO_2 concentration (7.9%).

Phase one, direct depression of cortical activity during low CO_2 concentrations, was only slightly evident as reflected by the increase in RT during 1.5% CO_2. In that

this increase in RT did not approach statistical significance and since a corresponding depressive effect was not evident in any of the other measures, it must be interpreted with caution.

The concept of cortical activation, as described by Wyke (1963), appears to be favored by the above findings. It was noted in the introduction that Gellhorn (1953a, p. 453; 1953b) proposed that EEG activation (as reflected by the asynchrony and reduced voltage of the EEG record) was accompanied by increased responsiveness in the proprioceptive and nocioceptive systems and decreased responsiveness in the visual system. In contrast, Wyke proposed that EEG activation was accompanied by increased responsiveness in all the sensory systems. The data were consistent with the latter proposal since the excitability of the visual system (as reflected by the visual reaction time task) and cortical excitability (as reflected by alpha frequency) were both enhanced by low concentrations of CO_2. In that the RT task involved both sensory and motor systems, it should be noted that the lack of depressive effects on RT may have been due to the excitation of the motor system by the reticular activating system which would be confounded with any depressive effects on the visual sensory system.

The apparent similarity of the occipital-parietal and central cortical activity in response to CO_2 lends additional support to the proposal that CO_2 effects

generalized cortical excitability. The lack of regional differences may have been due to derivations selected. For instance, monopolar central recordings may have yielded changes similar to those of occipital-parietal recordings because the ear electrode (used as ground in monopolar recording) was acting as a low occipital-temporal electrode. Therefore, occipital and central activity would have been confounded in the central EEG recording. This explanation does not appear plausible since the monopolar (central and occipital) and bipolar (occipital-parietal and central-temporal) records were compared in two Ss and did not differ significantly.

In light of the above discussion, the question may be raised if changes in alpha frequency utilized in the present study are comparable to the EEG activation response (increase in fast activity) utilized in past studies as a measure of central excitability. This relationship between these two measures was investigated in one S and both alpha frequency and percentage fast activity reflected similar changes in cortical excitability, in other words, CO_2 did not have a selective effect on alpha mechanisms alone. This conforms with other studies which have shown a shift to higher frequencies in EEG activity under conditions of increased excitability.

It should be noted that the CO_2 concentrations at which phase two and three were evident in the present study

(1.5-5.5% and 7.9% respectively) were considerably lower than the concentrations proposed by Wyke. Three explanations for this discrepancy appear plausible. First, the tri-phasic hypothesis was generated on the basis of data obtained primarily from animal studies. Possibly animals have a higher tolerance for CO_2 than humans. Second, the animals were usually under anesthetics in order to allow electrode implants which were used for EEG measurement. Therefore, higher concentrations of CO_2 may have been required to overcome the cortical depression resulting from the anesthetic before the excitatory phase was evident. Finally, the inhalation periods were longer and the CO_2 concentrations higher in past studies than those used in the present one. It is possible that as $PaCO_2$ increases above the values obtained in the present experiment--either due to increased length of inhalation period or concentration of CO_2--a second excitatory phase may occur following the depression observed in the present study during the 7.9% CO_2 condition.

The factor of duration of inhalation period may also serve as an explanation of the discrepancy between the excitatory effects and threshold values found in the present study and those found by Schaefer and Carey (1954). In contrast to the present study where within-trial changes were observed over a 5-min. trial, Schaefer and Carey reported data only from the last five minutes of a 15-min.

trial and did not observe within-trial changes. In observing the within-trial effects of CO_2 concentration in Fig. 6, a trend was evident indicating that had the trial been longer, alpha frequency might have been highest during the air condition with all the CO_2 conditions resulting in depressed alpha frequency. Therefore, alpha frequency possibly would have indicated cortical depression during all CO_2 concentrations as did the CFF and alpha blocking time measures utilized by Schaefer and Carey.

The within-trial changes in alpha frequency suggest that all the CO_2 concentrations had an initial brief excitatory effect during the 1- or 2-min. interval prior to the depressive effect. It may be noted that the higher the CO_2 concentration, the shorter the latency and duration of the excitatory effect. This initial excitatory effect was evident in both RT and alpha frequency (Fig. 4) and has been observed in previous studies (Necheles & Gerard, 1930; Schaefer, 1949). In that Schaefer and Carey (1954) did not report data obtained during this initial period of time, the excitatory effect may have been overlooked.

Since the greatest change in $PaCO_2$ occurred within this same period of excitability, cortical excitability may partially have resulted from rapid changes in CO_2 concentration within the blood in addition to the absolute $PaCO_2$ level. A finding in the Schaefer and Carey study lends support to this suggestion. In comparing alpha blocking

time before and after the 1.5 and 3.3% CO_2 conditions (concentrations found to have excitatory effects in the present study), alpha blocking time was faster during the recovery period after CO_2 inhalation than during the air breathing period prior to CO_2 inhalation. This excitatory effect following periods of CO_2 inhalation has been observed in a number of other studies (Gellhorn & Spiesman, 1935a; Necheles & Gerard, 1930).

The increase in alpha frequency obtained during the 0% CO_2 condition within trials (Fig. 6) may be explained partially by the excitatory effect after breathing CO_2 noted above. The 0% CO_2 condition was preceded by a 1.5-7.9% CO_2 condition in eight of its ten replications and therefore may have been serving as a recovery period. The within-trial increase in alpha frequency also may be attributed to increased effort or motivation directed toward the RT task in order to compensate for increasing task difficulty due to fatigue and other inhibiting factors accumulating across time. This explanation has been presented to account for within-trial increases in heart-rate and muscle tension during pursuit rotary tracking (Harter, Eason, & White, 1964).

When comparing the results of the present study with those of studies measuring sensory threshold, two observations may be made: (1) the threshold CO_2 concentrations for decreased cortical excitability as indicated by

RT and alpha frequency (3.5-5.5%) were similar to those for increased auditory threshold (Gellhorn & Spiesman, 1935a), longer latency of after image formation (Gellhorn & Spiesman, 1935b), and higher cutaneous pain threshold (Stokes, Chapman, & Smith, 1948); and (2) that RT decreased and alpha frequency increased during CO_2 concentrations (1.5-5.5%) which had little effect on these same sensory thresholds. The latter discrepancy may be attributed to the effects of low CO_2 concentrations (less than 5%) on the individual neurons in the neural systems involved in RT and the alpha frequency. Such concentrations have been found to increase the threshold, amplitude and duration of the action potential, and spontaneous firing of the neuron while simultaneously decreasing conduction time (Davis, Pascual, & Rice, 1928; Necheles & Gerard, 1930).

A secondary finding of the present study which warrants particular notice was the relationship between a number of the dependent measures obtained across CO_2 conditions and time. The linear increase in $PaCO_2$ and respiration rate with increases in CO_2 concentration (Fig. 3), which has been observed previously (White, Humm, Armstrong, & Lundgren, 1952), suggests that respiration rate could serve as a rough estimate of relative $PaCO_2$ level. In some situations, such substitution would be advantageous due to the difference in difficulty in obtaining these two measures. It should be noted that this relationship did

not hold when measuring changes across time since $PaCO_2$ stabilized relatively rapidly whereas respiration rate increased linearly throughout the trial.

The relationship between respiration rate and RT is also of interest in that fluctuations in RT possibly could result directly from changes in respiratory pattern rather than changes in central excitability. Reaction time might vary as a function of the excitatory effect of proprioceptive feedback from the muscles involved in respiration. Upon inspection of the data, this proposal appears implausible for two reasons: (1) RT and respiration rate were not correlated in the grouped or individual data for changes across CO_2 conditions or time; and (2) RT variability did not vary as a function of respiration rate or CO_2 concentration. Therefore, it may be concluded that changes in RT were not causally related to changes in respiration rate.

In past studies increased central excitability has been identified with an increase in alpha frequency and a decrease in alpha amplitude whereas decreased central excitability has been identified with a decrease in alpha frequency and increase in alpha amplitude (Ellingson, 1956; Lindsley, 1952). In the present study, this relationship was found only for changes across time, both measures indicating decreased excitability within trials and between sessions. This may be assumed to reflect a general

decrease in arousal resulting from adaption to the experimental situation. The fact that this relationship was not obtained across the various CO_2 conditions--alpha frequency increased and then decreased while alpha amplitude generally decreased--further illustrates the problem of using any one measure to assess central excitability. As noted previously (Schaefer, 1949; Wyke, 1963, p. 85), EEG amplitude appears to decrease with increases in CO_2 relatively independent of changes in EEG frequency.

The degree of correlation observed between RT and alpha frequency (Fig. 8) was sufficiently great to suggest a causal relationship between these measures or a common underlying cause. The possibility of the alpha rhythm reflecting an excitability cycle which limits the conduction and processing time of sensory information was noted in the introduction of the present paper. This concept has been supported in that RT has been shown to be related (1) to the phase of the alpha rhythm during stimulus presentation (Lansing, 1957), and (2) to alpha frequency in different S (Surwillo, 1963). The present results lend further support to this concept in that RT was related to fluctuations in alpha frequency within Ss.

The individual differences observed in the present study were similar to those found by Schaefer (1958). He classified Ss into CO_2 sensitivity groups on the basis of individual differences in reaction to CO_2 in terms of

respiration minute volume, base respiration rate, and base $PaCO_2$ level. He found that CO_2 sensitive Ss showed greater reaction to CO_2, had higher base $PaCO_2$ levels, and had higher respiration rates than the CO_2 insensitive Ss. In the present study, Ss could be similarly classified in terms of respiration rate reaction and base $PaCO_2$ level but no relationship was evident between base respiration rate and the other measures. The importance of these individual differences should be noted, especially when considering grouped data.

In conclusion, the original problem of the present paper--the feasibility of manipulating activation or arousal level by administering various concentrations of CO_2--may be re-evaluated. In the present and past studies the effects of CO_2 on central excitability were shown to be a function of the following variables: (1) concentration of CO_2 administered; (2) length of inhalation period; (3) sensory modality under investigation; (4) measure employed to assess central excitability; and (5) individual differences in sensitivity to CO_2. Under the conditions of the present experiment, central excitability was manipulated, as indicated by both behavioral and EEG measures, by administering different concentrations of CO_2.

APPENDIX

Table 4

$PaCO_2$ Analysis of Variance for CO_2, Sessions, and Minutes

Source	SS	df	MS	F
Within Ss	9652.03	59		
CO_2	6606.94	4	1651.74	317.03*
Sessions	10.30	1	10.30	.45
Minutes	1620.67	5	324.13	410.29*
CO_2 X Sessions	19.95	4	4.99	.61
Sessions X Minutes	6.71	5	1.34	2.31
CO_2 X Minutes	1374.40	20	68.72	49.80*
CO_2 X Sessions X Min.	13.06	20	.65	1.07
Between Ss	528.36	4		
Within X Between Ss	503.29	236		
Ss X CO_2	83.35	16	5.21	8.54*
Ss X Sessions	91.15	4	22.79	37.36*
Ss X Minutes	29.88	20	1.49	2.44
Ss X CO_2 X Sessions	130.55	16	8.16	13.38*
Ss X CO_2 X Minutes	110.12	80	1.38	2.26*
Ss X Sessions X Min.	9.39	20	.47	.77
Ss X CO_2 X Sessions X Min.	48.85	80	.61	
Total	10683.68	299		

*Significant $P < .01$

Table 5

Respiration Rate Analysis of Variance for CO_2, Sessions, and Minutes

Source	SS	df	MS	F
Within Ss	741.54	59		
CO_2	197.49	4	49.37	3.57*
Sessions	4.64	1	4.64	--
Minutes	338.03	5	67.61	20.49**
CO_2 X Sessions	27.81	4	6.95	1.78
CO_2 X Minutes	132.26	20	6.61	2.73**
Sessions X Minutes	7.21	5	1.44	--
CO_2 X Sessions X Min.	34.10	20	1.71	1.26
Between Ss	1642.10	4		
Within X Between Ss	726.39	236		
Ss X CO_2	221.36	16	13.84	11.34**
Ss X Sessions	46.60	4	11.65	9.55**
Ss X Minutes	65.99	20	3.30	2.70**
Ss X CO_2 X Sessions	62.39	16	3.90	3.20**
Ss X CO_2 X Minutes	193.72	80	2.42	1.98**
Ss X Sessions X Minutes	38.92	20	1.95	1.60
Ss X CO_2 X Sessions X Min.	97.41	80	1.22	
Total	3110.03	299		

*Significant $P < .05$
**Significant $P < .01$

Table 6

Reaction Time Analysis of Variance for CO_2, Sessions, and Minutes

Source	SS	df	MS	F
Within Ss	30172.73	59		
CO_2	10483.51	4	2620.88	3.02*
Sessions	12.40	1	12.40	--
Minutes	5058.47	5	1011.69	2.51*
CO_2 X Sessions	796.99	4	199.25	--
CO_2 X Minutes	4907.05	20	245.35	--
Sessions X Minutes	1567.66	5	313.53	--
CO_2 X Sessions X Min.	7345.65	20	367.38	--
Between Ss	208192.01	4		
Within X Between Ss	118476.79	236		
Ss X CO_2	13892.26	16	868.27	2.21*
Ss X Sessions	3515.42	4	878.86	2.24
Ss X Minutes	8863.95	20	443.20	1.13
Ss X CO_2 X Sessions	13713.44	16	857.09	2.18*
Ss X CO_2 X Minutes	38013.78	80	475.17	1.21
Ss X Sessions X Minutes	9082.62	20	454.13	1.16
Ss X CO_2 X Sessions X Min.	31395.32	80	392.44	
Total	356841.53	299		

*Significant .05 level

Table 7

Alpha Frequency (O-P) Analysis of Variance for CO_2, Sessions, and Minutes

Source	SS	df	MS	F
Within Ss	9.4857	59		
CO_2	2.2297	4	.5574	5.98**
Sessions	4.4907	1	4.4907	78.65**
Minutes	.1326	5	.0265	--
CO_2 X Sessions	.1033	4	.0258	--
CO_2 X Minutes	1.7119	20	.0856	1.81*
Sessions X Minutes	.1109	5	.0222	--
CO_2 X Sessions X Min.	.7003	20	.0350	--
Between Ss	81.8660	4		
Within X Between Ss	14.6516	236		
Ss X CO_2	1.4904	16	.0932	1.70
Ss X Sessions	.4089	4	.1022	1.87
Ss X Minutes	1.1718	20	.0586	1.07
Ss X CO_2 X Sessions	3.3410	16	.2088	3.81**
Ss X CO_2 X Minutes	3.1693	80	.0396	--
Ss X Sessions X Min.	.6866	20	.0343	--
Ss X CO_2 X Sess. X Min.	4.3836	80	.0548	
Total	106.0033	299		

*Significant $P < .05$
**Significant $P < .01$

Table 8

Alpha Frequency (C) Analysis of Variance for CO_2, Sessions, and Minutes

Source	SS	df	MS	F
Within Ss	10.122	59		
CO_2	3.494	4	.8735	11.59**
Sessions	4.144	1	4.1440	27.94**
Minutes	.313	5	.0626	--
CO_2 X Sessions	.121	4	.0303	--
CO_2 X Minutes	1.067	20	.0534	--
Sessions X Minutes	.048	5	.0096	--
CO_2 X Sessions X Min.	.035	20	.0468	--
Between Ss	80.244	4		
Within X Between Ss	19.088	236		
Ss X CO_2	1.760	16	.1100	1.61
Ss X Sessions	.593	4	.1483	2.75*
Ss X Minutes	2.118	20	.1059	1.55
Ss X Sessions X Min.	.620	20	.0310	--
Ss X CO_2 X Minutes	5.651	80	.0706	1.03
Ss X CO_2 X Session	2.870	16	.1794	2.62**
Ss X CO_2 X Sess. X Min.	5.476	80	.0685	
Total	109.454	299		

*Significant $P < .05$
**Significant $P < .01$

Table 9

Alpha Amplitude (O-P) Analysis of Variance for CO_2, Sessions, and Minutes

Source	SS	df	MS	F
Within Ss	1469.93	59		
CO_2	208.54	4	52.14	1.06
Sessions	365.64	1	365.64	7.55
Minutes	106.82	5	21.36	--
CO_2 X Sessions	91.75	4	22.94	--
CO_2 X Minutes	336.50	20	16.83	--
Sessions X Minutes	128.64	5	25.73	2.24
CO_2 X Sessions X Min.	232.04	20	11.60	1.09
Between Ss	28552.34	4		
Within X Between Ss	4434.94	236		
Ss X CO_2	784.18	16	49.01	4.59**
Ss X Sessions	193.83	4	48.46	4.54**
Ss X Minutes	435.83	20	21.79	2.04*
Ss X CO_2 X Sessions	533.20	16	33.33	3.12**
Ss X CO_2 X Minutes	1358.68	80	16.98	1.59*
Ss X Sessions X Min.	293.78	20	14.69	1.38
Ss X CO_2 X Sess. X Min.	853.44	80	10.67	
Total	34457.21	299		

*Significant $P < .05$
**Significant $P < .01$

Table 10

Alpha Amplitude (C) Analysis of Variance for CO_2, Sessions, and Minutes

Source	SS	df	MS	F
Within Ss	2195.16	59		
CO_2	206.64	4	51.66	1.19
Sessions	1215.73	1	1215.73	10.54*
Minutes	77.48	5	15.50	1.31
CO_2 X Sessions	86.00	4	21.50	--
CO_2 X Minutes	441.76	20	22.09	1.88*
Sessions X Minutes	9.80	5	1.96	--
CO_2 X Sessions X Minutes	157.75	20	7.89	--
Between Ss	9758.44	4		
Within X Between Ss	4992.16	236		
Ss X CO_2	692.08	16	43.26	4.16**
Ss X Sessions	461.53	4	115.38	11.11**
Ss X Minutes	347.83	20	17.39	1.67
Ss X CO_2 X Sessions	1252.91	16	78.31	7.54**
Ss X CO_2 X Minutes	1049.41	80	13.12	1.26
Ss X Sessions X Minutes	357.23	20	17.86	1.72*
Ss X CO_2 X Sess. X Min.	831.07	80	10.39	
Total	16945.76	299		

*Significant $P < .05$
**Significant $P < .01$

Table 11

F-ratio Significance Summary for Dependent Variables

Source	Dependent Variable						
	$PaCO_2$	Resp. Rate	Reaction Time	Alpha Freq. (O-P)	Alpha Freq. (C)	Alpha Ampl. (O-P)	Alpha Ampl. (C)
Within Ss							
CO_2	.01	.05	.05	.01	.01	--	--
Sessions	--	--	--	.01	.01	.07	.05
Minutes	.01	.01	.05	--	--	--	--
CO_2 X Sessions	--	--	--	--	--	--	--
CO_2 X Minutes	.01	.01	--	.05	--	--	.05
Sessions X Minutes	--	--	--	--	--	--	--
CO_2 X Sessions X Min.	--	--	--	--	--	--	--
Between Ss							
Within X Between Ss							
Ss X CO_2	.01	.01	.025	.07	--	.01	.01
Ss X Sessions	.01	.01	--	--	.05	.01	.01
Ss X Minutes	--	.01	--	--	--	.025	.07
Ss X CO_2 X Sessions	.01	.01	.025	.01	.01	.01	.01
Ss X CO_2 X Minutes	.01	.01	--	--	--	.05	--
Ss X Sessions X Min.	--	--	--	--	--	--	.05

Table 12

Alpha Frequency Analysis of Variance CO_2 and Leads, for Ss BF and GH (last minute interval)

Source	SS	df	MS	F
Within Ss	8.613	19		
CO_2	5.100	4	1.275	7.04*
Leads	1.646	3	.549	--
CO_2 X Leads	1.867	12	.156	1.63
Between Ss	5.798	1		
Within X Between Ss	5.031	19		
Ss X CO_2	.722	4	.181	1.88**
Ss X Leads	3.158	3	1.053	10.96**
Ss X CO_2 X Leads	1.151	12	.096	
Total	19.442	39		

*Significant $P < .05$
**Significant $P < .01$

Table 13

Percentage Time EEG Frequency
CO_2 Conditions for Ss BF

EEG Frequency (cps)	% CO_2 Administered				
	0	1.5	3.5	5.5	7.9
30	8.8	10.7	11.1	9.6	4.7
24	15.3	23.3	11.5	11.9	7.8
17	16.5	14.0	15.0	6.5	10.0
13	13.7	16.6	15.5	18.6	14.9
11	26.5	22.9	27.1	29.7	32.0
9.2	8.0	21.7	13.9	18.5	10.4
8.0	5.6	7.3	11.7	6.5	4.2
7.1	2.0	6.8	7.2	5.2	1.5
6.3	2.2	4.6	7.2	1.2	1.6
5.7	4.0	7.8	7.9	8.6	3.2
5.2	8.7	8.1	7.7	13.9	13.9

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