PHILIP MORRIS U. S. A.

INTER-OFFICE CORRESPONDENCE

RICHMOND, VIRGINIA

CONFIDENTIAL

To: Dr. T. S. Osdene

Date: November 26. 1980

From: W. L. Dunn

Subject: Plans and Objectives - 1981

CONFIDENTIAL

INTRODUCTORY NOTES

The Behavioral Research Laboratory effort is organized into programs which reflect to a large degree the subdisciplines of the responsible psychologists. On the one extreme of the psychological spectrum is the social psychology program of Dr. Sandra Dunn. On the other extreme is the behavioral pharmacology program of Dr. DeNoble. Ranging between are the experimental psychology program of Mr. Ryan, the electrophysiology program of Dr. Gullotta and the smoke inhalation program of Miss Jan Jones. Each of these programs is but a varied attack upon the overall objective of the Behavioral Research program: To contribute useful knowledge about the response of the smoker to the cigarette and its smoke. The results may prove useful in developing a new product, or improving an existing product, or in the defense of the company from legislative or litigative harassment.

ELECTROPHYSIOLOGY PROGRAM : . . Gullotta and Shultz

Objectives: It is our belief that the reinforcing properties of cigarette smoking are directly relatable to the effects that smoking has on electrical and chemical events within the central nervous system. Therefore, the goals of the electrophysiology program are to: (I) Determine how cigarette smoking affects the electrical activity of the brain, and (II) Identify, as far as possible, the neural elements which mediate cigarette smoking's reinforcing actions.

Planned Studies

I. Spectral Analysis of the Electroencephalogram

We have proposed this study in the past but, due to technical problems, we have been unable to undertake it. We are finally in a position to begin.

Numerous studies have investigated the effects of cigarette smoking and nicotine administration on the electroencephalogram (EEG) of man and other animals. Although there is some degree of concordance among the results of these studies, many points are yet to be resolved. For example, with regard to the human literature, an early study showed that cigarette smoking produced low amplitude, fast EEG activity. Another study, however, found that smoking did not increase low amplitude fast activity and, indeed, slowed certain EEG frequencies. A number of other examples of this type can be found in the literature.

ARCHIVED

It seems likely that most of the controversies could be resolved by a more systematic analysis and quantification of the EEG. Therefore, we plan to spectrally analyze EEG data from a variety of electrode locations under varying smoking and deprivation conditions.

II. Animal Electrophysiology

We have discussed with Dr. DeNoble the possibility of a collaberative effort to study the effects of nicotine and nicotine-like compounds on the electrical activity of the rat brain. This would involve EEG recordings from surface and deep structures within several experimental paradigms. It would also involve the use of evoked potential technology. Some technical problems must be solved before such a program can be initiated. Our early efforts will be aimed at addressing these technical considerations.

III. The Effects of Cigarette Smoking on Pattern Reversal Evoked Potentials

This study is well under way and will be completed in early 1981.

We have previously demonstrated that cigarette smoking increases the amplitude of the late components of the visual evoked potential to flash stimulation. However, since flash stimulation activates nonspecific brain structures (e.g., reticular formation, association cortex, etc.) as well as specific structures (e.g., primary visual cortex), we were unable to determine with certainty whether the enhancement we observed was due specifically to increased receptivity to visual information.

Pattern stimulation avoids the problems associated with flash by activating primarily visual structures. Therefore, we are using pattern reversal evoked potentials to checkerboard stimulation to study the effects of cigarette smoking on visual information processing.

IV. Cigarette Smoking and the Habituation of Pattern Reversal Evoked Potentials

It is commonly reported that cigarette smoking facilitates one's ability to concentrate. Concentration implies sustained attention to stimulation. We are interested in the possibility that we might gain insight into the processes involved by employing evoked potential techniques.

When, within a given session, sensory evoked potentials are repeatedly measured, there is a decrement in the response over trials. We interpret this decrement as a decrease in the sensitivity of the system to incoming sensory information. We can then ask whether cigarette smoking alters the rate at which this decrement occurs. If smoking retards the rate at which the evoked potential decreases in amplitude over trials, we will have demonstrated one manner in which concentration might be facilitated by cigarette smoking.

We have recently been gathering pilot data on this subject employing pattern reversal evoked potentials. If our data look encouraging we will mount a full-scale investigation in early 1981.

V. Cigarette Smoking and the Brainstem Auditory Evoked Potential

Recently, a new class of evoked potentials have been described. These are the acoustic and somatosensory brainstem (far-field) evoked potentials. One of the advantages of these brainstem potentials relative to the more traditional forms of recording is that the neural generators of the components are better known. For example, it has been shown that Peak I of the auditory brainstem response is due to VIIIth nerve activity, Peak II to activity of the cochlear nucleus, etc..

In this experiment we will be employing brainstem auditory evoked potentials in an attempt to ascertain sites and modes of action for centrally active smoke constituents. We chose the auditory potential because (1) there are nicotinic cholinergic synapses within the system and (2) it has recently been shown that, in rats, systemic nicotine administration alters certain components of the response.

THE BEHAVIORAL PHARMACOLOGY PROGRAM . . . DeNoble

Objectives

I. To develop a better understanding of the behavioral pharmacological actions of nicotine, particularly the action which reinforces smoking behavior.

II. Develop the empirical evidence which differentiates nicotine from the classical abuse substances.

III. Use behavioral pharmacological methods for evaluating the nicotine-likeness of nicotine analogues.

Planned Studies

I. Nicotine Self-administration

A successful development of the technique for establishing self-administration of nicotine in an animal has important implications for all three objectives of our behavioral pharmacology program.

We have developed that technique, making it quite clear that nicotine can function as a positive reinforcer for rats. We will use the technique (1) in studying the reinforcing action of nicotine, (2) in differentiating nicotine from the classical abuse substances, and (3) in evaluating analogues.

We will undertake as many of the following essential self-administration studies in 1981 as time permits:

1) Examine the dose-response curve under various schedules.

2) Examine the effects of cholinergic antagonists upon self-administration.

3) Determine substitutability of selected analogues.

4) Demonstrate, in pursuit of Objective III, that (a) nicotine-self-administration does not interfere with on-going behavior and (b) that termination of nicotine availability for self-administration does not produce behavioral impairment, or alter self-administration of other reinforcers (food, water, saccharine, etc.).

II. The Nicotine-Induced Prostration Syndrome

The prostration syndrome, first reported by Leo Abood as a gross behavioral response to the intraventricular infusion of nicotine, has been used routinely for several years in our program of nicotine analogue evaluation.

Although the prostration syndrome is a reliable screen for behaviorally active nicotine analogues, the rating scale developed by Dr. Abood provides only a descriptive interpretation of the compounds' effects, and does not permit a determination of possible prolonged changes in CNS activity. We have begun using scheduled controlled behavior to evaluate the effects of intraventricular injections, since measures based upon this behavior have been shown to be more sensitive than activity rating scales, and provide a more stable nicotine baseline from which to evaluate CNS recovery times for nicotine analogues.

We have recently observed in conducting these studies that there is a diminution of the effect of nicotine over repeated administrations. Diminution will occur even with a 7 day interval between the first and the second administration, an observation difficult to explain simply in terms of the development of metabolic tolerance. We may be observing instead an instance of behavioral tolerance. We are currently designing a study which should more accurately characterize the development of tolerance.

We will also be conducting studies in which the effects of the selective blockade of neural structure will be reflected in the behavioral components of prostration, anticipating that these observations can further our knowledge about the sites of action of nicotine.

III. Discrimination Studies

We will continue to use the now standardized discrimination technique to evaluate nicotine analogues. We are currently investigating a dose-response curve approach, a modest variant on the standard procedure.

THE EXPERIMENTAL PSYCHOLOGY PROGRAM . . . Ryan

Objectives

1. To gain a better understanding of the role of nicotine in smoking.

2. To study basic dimensions of the cigarette as they relate to cigarette acceptability.

Planned Studies

I. Salivary Nicotine

Speculation suggests that smokers modify smoking behavior to maintain certain levels of nicotine in the blood. Historically this has been the basis of nicotine titration hypotheses. Knowledgeable consideration of the issue suggests that the changes in level may be more important than the absolute levels -- that the input of nicotine from a cigarette creates a "spike" which is the summation of the discrete puff-induced spikes.

We now have the ability to measure via gas chromatograph the level of nicotine in saliva. Observations from previous work with salivation and smoking suggest that systemic nicotine in saliva tracks with systemic nicotine in the blood. We plan to use the g.c. measure to:

A. Monitor the appearance and decline of nicotine in saliva following smoking. This will shed light on the question "Does a low systemic level of nicotine trigger the smoking response." The question can only be answered if measures are made many times. Therefore, we will:

B. Observe changes in salivary nicotine level across time and smokings, relating the changes to the delivery of cigarettes smoked and the time since prior smokings. The data will bear upon the issue to the extent that salivary nicotine reflects tissue and blood levels of nicotine. This must be confirmed by means of:

C. A correlational study of the salivary nicotine with blood nicotine. This is awkward research to perform because the taking of blood samples is so intrusive and objectionable to participants and because it requires medical supervision. Therefore, we will postpone this segment of the research until it is evident that there are some systematic changes in the salivary nicotine data. We have made some preliminary contacts with our medical staff, and they will support us when needed.

II. There are tentative plans for one other project in which nicotine will be delivered intravenously in different sized spikes of different duration, to yield a broader picture of the role of the spike, the level, and the reinforcement characteristics of the substance. The execution of this project is contingent upon the execution of study I-C above, since both involve the dosing of numerous subjects with nicotine.

III. Other smoking related research

1. Role played by Cigarette Firmness in determining cigarette acceptability. Much attention has been paid to the problem of maintaining the firmness of our cigarettes at a level consistent with the image of a high quality product. We have recently found that a trained panel's evaluations of firmness are highly correlated with the firmness data provided by the Firmness-while-smoking machine and our compacimeter procedures. However, we know neither the relative importance of firmness to the consumer (compared to other characteristics of the cigarette's appearance) nor the most desirable firmness level. We will try to find out.

IV. Support for other projects, within R & D and within behavior research, will be provided, as necessary.

SOCIAL PSYCHOLOGY PROGRAM S. Dunn

Objectives

I. To gain a better understanding of the role of social psychological factors in shaping cigarette smoking behavior.

II. To apply social psychology techniques to the study of cigarette acceptability.

Planned Studies

I. Exploratory Study on Psychosocial Determinants of Smoking Behavior

As an initial approach to the problem, we have designed a one-on-one interview including both objective questions and in-depth probes. This interview is an intensive two-hours of data gathering, ranging across a spectrum of social, personality, attitudinal and situational dimensions. The dimensions were chosen for inclusion because of their potential relevance to smoking behavior. Items included in the questionnaire/interview schedule can be subsumed under these headings:

1. Emotional state and responsivity.

2. Stress-handling mechanisms.

3. Situational determinants and cues.

4. Socio-cultural influences.

5. Health concerns and smoking.

Interviewees are being drawn from among the population of 45 year-old, white, college-educated, upper-middle class women, half of whom who smoke high-delivery cigarettes and half of whom smoke ultra-low delivery cigarettes. Focus on these groups will also provide data on women smokers and on the factors determining choice of delivery level.

The data obtained will be subjected to a statistical analysis designed to identify the underlying higher order factors. The nature of these factors, and the extent of their influence upon smoking behavior will provide the basis for further studies. The analysis is scheduled for completion by the end of the first quarter of 1981. Upon completion of this analysis we will generate hypotheses testable under rigorous, laboratory-controlled conditions.

II. The Influence of Cigarette Firmness Upon Cigarette Acceptability

Mr. Ryan has reported a study of the correlation of subjective firmness with measures obtained on the Firmness-while-smoking machine and on the compacimeter. The question has been raised as to what relevance, if any, these measures have to cigarette acceptability. We are designing a study that will address this question. The study will incorporate interview techniques of social psychology rather than rely upon conventional marketing research survey methods.

III. THE INHALATION MONITORING PROGRAM . . . Jones

Objective: To determine in what manner the smoker alters inhalation patterns in response to changes in the chemical composition of cigarette smoke.

Planned Studies

I. Instrumentation

A. Exploratory research using the new recording system.
The literature on smoke-laden inhalation research is limited, and that which does exist suffers from severe technological constraints. Our inhalation monitoring system provides us with the advanced technology necessary to acquire fundamental information about inhalation behavior. We are immediately concerned with establishing valid and reliable criteria for determining when a subject's inhalation patterns have stabilized -- at what point we are seeing a reproducible representation of the subject's inhalation behavior. In designing our experiment we must determine what would be sufficient time within each period of data collection for the smoking behavior to stabilize, before introducing a new experimental condition. Other information which is related to experimental design involves what happens to baseline behavior, established on a smoker's own cigarette, following experimental conditions. Is there a return to baseline inhalation behavior or will the baseline readjust? Carry-over effects resulting from the use of repeated measures may occur and must be taken into account.

B. Programming a dedicated minicomputer for data display and analysis.
The MINC/DECLAB minicomputer, expected to arrive early in 1981, will be used to store and display the quantities of information collected. Following our programming efforts, the computer will be customized to handle the high-speed analyses required for our specific needs.

II. Experiment #1: Does the smoker demonstrate compensatory inhalation behavior in response to changes in the nicotine content of cigarette smoke?

The experimental design is repeated measures with an ABACA format - a powerful method for examining what happens to inhalation patterns when a smoker switches between cigarettes of high, low, and ultra-low nicotine delivery. Baseline measures will be taken on the smoker's own low delivery cigarette until we observe stable behavior. The smoker will then switch to an ultra-low or high delivery experimental cigarette for two weeks, the order of presentation being balanced across subjects. Following each experimental condition, the smoker will switch back to his own cigarette to re-establish baseline behavior. Our primary interest is in comparing the inhalation parameters of Condition B with Condition C, demonstrating differences due to nicotine delivery of the cigarette smoked. The other 3 conditions will mainly serve to make this information meaningful.

We will be collecting data for approximately 2 months on each subject. The study will begin early in 1981 and is expected to continue throughout the year.