INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI

A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700 800/521-0600

The Effects of Smoking on the Continuous and Time-Locked EEG

Michael Sasha John
Department of Psychiatry
McGill University, Montreal.
Submitted 1/97

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements of the degree of Master of Sciences

Abstract

In a group of predominantly light smokers (N=10), EEG was recorded before and after cigarette smoking both during rest, and while engaged by two cognitive/ perceptual tasks i) the video game Tetris, and ii) a computerized reverse mirror drawing task. Increases in beta2 power occured 0-2 minutes after smoking, which were significant in half the subjects. Significant decreases in peak alpha power and an increase of 0.7 Hz in peak alpha frequency existed 1-2 minutes after smoking. Alpha frequency and power were examined again 11 minutes post-smoking and were found to still be altered, although this did not reach signficance. Frontal midline theta (FMT), recorded during cognitive load, increased 0.6 Hz after smoking. Delta power, also recorded during cognitive load, decreased in all subjects after smoking. Auditory evoked potentials (AEP), presented in an "oddball" paradigm, and visual evoked potentials (VEP), elicited by a reversing checkerboard stimulus, were collected. Increases in amplitude, and small, but significant, decreases in latency were found in the VEP and the auditory P300 after smoking. Taken together, results suggest that, in light smokers, a general increase in arousal and an enhancement of cognitive processing is obtained from smoking.

Résumé

Dans un groupe composé majoritairement de fumeurs modérés, (N=10), l'activité EEG a été enregistrée avant et après avoir fumé une cigarette au repos et durant deux tâches cognitives et sensorielles: d'abord, le jeu vidéo "Tetris" et ensuite, une tâche informatisée de dessin en miroir inversé. Une augmentation significative de la puissance spectrale de la bande passante beta2 a été observée entre 0 et 2 minutes après avoir fumé chez environ la moitie des sujets. Une diminuation significative de la puissance spectrale du pic alpha et une augmentation de 0.7 Hz de sa fréquence ont été observées au cours des deux premières minutes après avoir fumé. L' examen de la ligne médiale frontale thêta (FMT) enregistrée durant la tâche cognitive a mis en évidence une augmentation de fréquence de 0.6 Hz, après avoir fumé. Une baisse significative de la puissance spectrale "delta" a aussi été observée chez tous les sujets également au cours de la tâche cognitive. Les potentiels auditifs évoqués (AEP) utilsés dans une modéle "oddball" et les potentiels visuels évoqués (VEP) par un stimulus d' échiquier se renversant, out aussi été obtenus. Des augmentations significatives d'amplitude et des diminutions, minimes mais significantives de la latence du VEP et du P300 auditifs ont été observés après avoir fumé. Dans l' ensemble, ces résultats suggèrent que, chez les fumeurs modérés, le fait de fumer provoque une augmentation générale du niveau d' éveil et une amélioration des facultés cogntives.

Acknowledgments

I would like to thank the following people for the contributions and support they offered while the topic of this thesis changed from an exploration of consciousness under anesthesia, to pharmaco-EEG profiles of novel CCK antagonists, to short segment spectral analysis of normal and impaired linguistic processing, and to tryptophan depletion effects on the augmentation/reduction of the N1/P2 response, before finally ending up as the current experiment.

Dr. Frank "Zeus" Ervin and Dr. Roberta Palmour, for giving me the freedom and confidence to explore my limits, for enhancing my understanding of science and the brain, and thereby improving my approach to this thesis and to the fundamental challenges in neurophysiology that lay ahead, and for some of the best food and wine that I have ever had the pleasure of experiencing.

I would especially like to thank Trishia Jandu, for her undying support, humor, love, and patience. She was as intrinsic to the success of this project as she was to my personal development and happiness outside of the laboratory. WHJ!

Caroline Desbiolles, for her wonderful non-verbal cues, her friendship, and constant intellectual and philosophical stimulation.

Dr. E.R. John and Dr. L.S. Prichep, for kindly making the time to prooofread this thesis on such short notice.

Pablo Navarro, for all the help he provided in a laboratory which experienced many equipment failures, general "computer strangeness", and the small inconvenience of a theft of our recording system, and for having the desire, persistence, and ability to evolve from a research assistant into a valuable collaborator and friend.

My family and friends who became adept at pretending to listen while I discussed the issues of this thesis and nodded encouragingly even when it was probably not how they would have preferred to spend their time.

This work was partially supported by FRSQ.

Table Of Contents

Section 1: General Overview of Smoking Related EEG Changes

The effects of smoking on brain electrical activity, cognitive processing, and behavior appear to be bi-phasic in nature. When the dose of nicotine obtained by the smoker is functionally low, in relation to the smoker's tolerance level, arousing effects are produced (Knott, 1986; Golding, 1988). Alternatively, functionally higher doses result in sedation. Evidence of these changes, and the conceptual models which have been suggested by these data, come from numerous studies. In order to provide a foundation by which both the motives and the findings of this study can be meaningfully understood, several illustrative investigations will now be reviewed.

1.1 Smoking, Arousal, and EEG Acceleration

There is wide agreement that under non-aroused conditions, smoking produces a stimulant effect in the central nervous system (CNS) as reflected in a shift of power of the electroencephalogram (EEG) from lower to higher frequencies (Pritchard, 1991; Pritchard et al., 1995; Knott, 1988; Gilbert et al., 1989). These EEG changes have a rapid onset and can be seen as early as the fourth puff on a cigarette (Knott, 1988). Reciprically, during smoking deprivation the EEG is characterized by an increase in the slower frequencies, a change which has been associated with increased drowsiness (Itil et al., 1971). The effect of smoking on cortical arousal seems to depend on the dose and rate of administration, time since last smoking, environmental stress, and where an individual is located along the extroversion/ introversion dimension (Golding, 1988; Knott, 1989; Conrin, 1980; Hori et al., 1994). When smoking, or exposure to equivalent doses of nicotine, occurs in a low-arousal environment, an increase in arousal generally occurs. In moderately arousing conditions, the effects of smoking on the EEG are more heterogeneous and tend to show increasing dependence upon individual factors. In contrast to low arousal situations, when smoking occurs under more stressful conditions less of an increase in arousal is produced in response to stressful stimuli, suggesting that smoking acts to protect the smoker from increased stress (Golding et al., 1982); in terms of the EEG, instead of decreased alpha power (arousal), a relative increase in the amount of alpha power (relaxation) is found when smoking occurs in stressful situations. For

example, during viewing of a stressful movie, smoking related decreases in both EEG activation and lateralisation (Gilbert et al., 1989) were found. Decreases in activation during exposure to noxious auditory stimuli (Golding et al., 1982) have also been reported after smoking. Additionally, during a recording session including such stressful events as the drawing of blood and a math task, alpha amplitude was shown to increase after smoking (Golding, 1988). Since smoking aids in coping with stressful environments, these latter findings are instructive, as they provide a practical model within which smoking aids the smoker by producing relaxation or arousal according to the situation. Smoking therefore produces changes that are similar to those reported in investigations of various pharmacological agents (e.g., caffeine) which also alter the EEG differently, depending upon various environmental conditions (Dimpfel et al., 1993).

1.2 Beta and Anxiety Reduction

Studies which have examined the effects of smoking on the EEG have often reported an increase in beta power that is similar to that found with anxiolytics such as the benzodiazapines (Hori et al., 1994; Philips, 1971; Hasenfratz et al., 1993; Golding, 1988). Pritchard (1991) found increased beta2 power (using a definition of beta2 which spanned from 18 to 28 Hz) to be largest at the vertex (Cz) and most evident in deeply inhaling smokers. In a subsequent study, Pritchard et al. (1995) examined the time course of this effect and found that this beta2 increase leveled off by about 7 minutes post smoking. In this latter study, evidence which further suggests a relationship between increases in beta2 and a state of anxiety relief was obtained during a relatively stressful event: the taking of a blood sample, which occurred between puffs 4 and 5 of the cigarette, was accompanied by a concurrent decrease in beta2 power and an increase in muscle tension.

Failure of various other investigators to find an increase in beta power may be attributed to the lack of a recording electrode at the Cz site (Norton et al., 1992), or an examination restricted to beta1, which generally extends from roughly 13 to 20 Hz (Knott, 1989). However, small but significant increases can be noted even without recording at

the Cz[1] site. For example, Hasenfratz et al. (1990), using only Pz, found increases in beta power in subjects smoking two cigarettes. Since two cigarettes were smoked in succession, subjects demonstrated a wide range of nicotine absorption and could be grouped into low nicotine (LN) and high nicotine (HN) absorbers.[2] Results indicated that the smoking-induced increases in heart rate and dominant alpha frequency were greater and lasted longer in the HN than in the LN group. The finding that increases in both the magnitude and duration of beta power, as well as increases in the dominant alpha frequency, were significantly correlated with nicotine absorption, has also been found by others (Pritchard, 1991). In contrast, Golding (1988) found that both smoking related increases in heart rate and beta2 power were related more to CO levels prior to smoking, than to the amount of nicotine that was obtained from the cigarette.

1.3 Lateralisation and Activation of "Go/No-Go" Systems

In accordance with previous reports, Norton et al. (1991) found that smoking altered ERP's in a bi-phasic manner that was related to dose; the amplitudes of the P300 and contingent negative variation which were increased, compared to baseline, after low doses of nicotine, were decreased with higher doses. Norton et al. extended these findings by relating them to the well known "Go" and "No-Go" model (Norton et al., 1992). While the Go system is relatively active during arousal, natural (trait) and pharmacologically induced (state) anxiety, and stress, the No-Go system is relatively active during periods of decreased arousal and clinical depression. Since lower doses of nicotine had previously led to increases in amplitude of ERP's in subjects with low stress levels, the activation of the neural Go system was implicated. Alternatively, at higher doses, or when low doses were given to subjects under conditions of stress, the effect was reduced, in line with the activation of the No-Go system. As would be expected by this model, Norton found that subjective reports of stress in the pre-smoking period were correlated with the amount of nicotine obtained by subjects. The "stressed" subjects

---

[1] Fz, Cz, Pz, and Oz refer to electrodes located at the frontal, central, parietal, and occipital regions and along the mid-sagittal plane.

[2] Nicotine levels were based upon respiratory CO, a putative indirect measure of plasma nicotine levels, as well as an estimate of plasma nicotine via blood gas analysis.

attempted to reduce the Go activity by obtaining higher doses of nicotine during the subsequent smoking period.

Norton provided additional evidence for this model by investigating the effects of smoking on lateralisation of EEG power. Prior evidence for lateralisation of the Go/No-Go system indicated a division between left and right hemispheres respectively (Gilbert et al., 1989). Using T3, C3, and T4, C4 leads, referenced to P3 and P4 respectively, the study found a bi-phasic and dose related lateralisation of EEG spectral power. Nine minutes after smoking, subjects who had obtained lower nicotine levels were characterized by left hemisphere activation, as evidenced by decreases in alpha and delta power and increases in beta power. This change occurred both during eyes open (EO) and eyes closed (EC) conditions and was accompanied by increases in subjective arousal. The shift towards left hemisphere activation was correlated (r=.86) with increasing nicotine until approximately the 1.1 mg. level, at which point a shift in lateralisation and subjective reports of decreased arousal began to occur.

In addition to lateralisation, changes in absolute power were examined. Smoking related decreases in the spectral power of the alpha band were compatible with the changes seen in ERP's and lateralisation since all these changes were in directions that have been associated with increased arousal. It is worth noting that, in contrast to the majority of previous studies, these data indicated that subjects who obtained a low amount of nicotine produced increases in delta and theta power, just after finishing the cigarette, while higher doses produced decreases. An analysis between power in the lower bands and the amount of nicotine subjects obtained from smoking indicated an inverse relationship, with correlation coefficients demonstrating a mean value of -.73.

The evidence suggests that smokers who desire arousal will attenuate their smoking before higher nicotine levels are reached, while those seeking to relieve stress will continue to smoke until the higher levels are reached and a decrease in arousal is obtained. Further, as described in Norton's conclusion, the dynamics of lateralisation and power offer insights into the smoking behavior itself. The shifts in hemispheric activation can be related to the behavioral effects of smoking. Nicotine obtained through cigarette smoking initially activates the Go system, resulting in the continued maintenance of repetitive tasks

("puffing"). Towards the end of the cigarette, the steadily increasing nicotine dose will eventually inhibit the GO system, reducing stress levels and discontinuing the urge for more puffing. This implies that smoking itself can be self-motivating, because smoking produces an initial increase in the Go system which it then reduces after a sufficient dose of nicotine has been obtained.

1.4 Smoking and Enhancement of Cognitive & Perceptual Processing

While the majority of EEG studies have focused on a change in the smoker's general state of arousal, ERP studies attempt to provide insight into the changes in information processing that accompany smoking. Before entering into a review of the ERP literature, one characteristic of the EEG that is related to information processing (rather than arousal state) should be discussed.

An increase in peak alpha frequency has often been reported in EEG studies concerned with smoking related changes in information processing. The concept that processing speed is related to the peak frequency of a rhythm is based upon studies such as that of Varela et al. (1981), who demonstrated that the frequency of a subject's alpha rhythm was relevant to the processing of incoming stimuli. The faster the peak frequency of the alpha rhythm, the more likely that two visual stimuli occurring in rapid succession were perceived as two separate events. Additional evidence that peak frequency is important in information processing comes from studies involving psychostimulants, which have produced both quicker reaction times and increases in alpha frequency (Dimpfel et al., 1993).

Increases in peak alpha frequency of 0.5 Hz (Hasenfratz et al., 1990; Knott, 1988) and 0.6 Hz (Kadoya et al., 1994a; Golding, 1988a) have been found in smokers during real compared to sham smoking, and with nicotine gum (Cohen et al., 1994). While an increase in the mean frequency of the alpha band is one of the most reliable changes related to smoking, it may not occur in smokers who fail to obtain a large enough dose (Kadoya et al., 1994b; Hasenfratz et al., 1993b). The increase in peak alpha is not merely due to a reversal of the general EEG slowing that is often present during the baseline conditions in studies which impose pre-experimental periods of smoking

deprivation. For example, Foulds (1994) found that when 2 subcutaneous injections of nicotine (0.6 mg spaced 40 min apart, since 0.8 dose occasionally induced vomiting) were given to non-smokers, an increase in dominant alpha frequency of 2 Hz was observed as compared to a placebo.

1.5 Visual Evoked Potential (VEP)

Woodson et. al. (1982) investigated the effects both of cigarette smoking and of smoking deprivation (2 hour) on visual evoked potentials obtained under quiescent conditions. Peak-to-peak amplitudes, for the VEP peaks that occurred between 100 to 200 msec. in response to a diffuse flash stimulus, were significantly enhanced by smoking, while only flash intensity altered peak latencies. Since these peaks are thought to be related to the non-specific, diffuse activation of pathways related to the perception of a stimulus, increased amplitudes suggested a general increase in arousal. However, citing both his own results and those of previous studies, which found that an increase in general arousal was not itself sufficient to produce increases in amplitude, Woodson argues that the amplitude augmentation reflected an attention specific enhancement of visual processes.

Hall et al. (1973) found decreases in amplitude of flash elicited VEP components, in the 100 to 125 msec post-stimulus period, after 12 and 36 hours of deprivation. In the four intensities that were presented, decreases were significant only in response to the 2 dimmest flashes, suggesting that smoking related changes may be more important in the processing of stimuli which occur near sensory thresholds. These decreases were reversed (and extended beyond pre-deprivation baseline levels) by smoking. While both these studies imposed a period of pre-experimental deprivation of at least 2 hours, when smokers were deprived for only 1 hour, no significant changes occurred in either absolute measures of latency or amplitude of VEPs recorded shortly after smoking (Golding, 1988). However, even with longer periods of abstinence, some studies have failed to find smoking related changes in the amplitude and latency of any VEP component (Knott, 1985).

1.6 P300

In the evaluation of a stimulus, the brain must sufficiently process the physical attributes of the stimulus in order to enable the subsequent determination of the significance of the stimulus within a given context. The term 'exogenous component' refers to regions of the ERP (usually in the earlier post-stimulus period, e.g., 0-120 msec.) that are affected by the changing physical parameters of the stimulus, while 'endogenous components' vary in accordance with the processing of meaningful information which a stimulus provides in relation to a given task (Donchin, 1981). The P300 is a late component characterized by a positive shift which usually occurs between 300 and 400 milliseconds post-stimulus and is related to endogenous attributes of the stimulus (Sutton et al., 1965). The amplitude of the P300 increases as a function of the relevance of the stimulus and its latency is related to the time required for the subject to process incoming information. Thus, shorter P300 latencies are normally accompanied by quicker reaction times.

The literature concerning the effects of smoking on P300 is mixed, with reports of increases, decreases, and no change in amplitude (Hasenfratz et al., 1989). These conflicting reports may, in part, be explained by findings that low doses increase the amplitude of the P300 while high doses produce the opposite effect (Norton et al., 1992). This finding is consistent with a model in which lower nicotine levels produce arousing effects while larger amounts lead to decreased arousal. In terms of smoking related increases in cognitive efficiency, Norton et al. (1991), and others (Hasenfratz et al., 1989) did not find any smoking related differences in P300 latency. Additionally, Michel (1989) found no change in P300 amplitude or latency to visual stimuli after administration of nicotine chewing gum (4 mg.). However, Edwards et al. (1985) found smoking related decreases in P300 latency and improved performance on a visual discrimination task. This latter study may have obtained it unique results because its discrimination task required more effort than the more simple tasks used in other studies. This explanation is supported by behavioral studies that often fail to show improvements in cognitive performance or reaction times when the tasks are not difficult enough to produce a

sufficiently broad range of performance, such that the beneficial effects of smoking can be detected (Knott, 1985; Edwards, 1985; Hasenfratz, 1989; Lorist, 1994) .

1.7 Contingent Negative Variation (CNV)

The CNV is a central response that may be elicited in paradigms in which the subjects are exposed to a warning stimulus (S1), which indicates that a subsequent imperative stimulus (S2) is about to occur to which subjects are required to respond. The CNV appears as a negative shift in the EEG that occurs during the S1-S2 interval and is thought to represent the expectant or "readiness" state of the organism. Ashton et al. (1980) found that small intravenous doses of nicotine increased the amplitude of the event related CNV potential, a result usually interpreted as an increase in CNS readiness. On the other hand, larger doses decreased CNV amplitude, a change consistent with the bi-phasic dose effects of nicotine on the EEG.

Knott extended these findings and proffered that smoking offers "protection against disruptive stressors", by looking at the CNV in subjects during both normal conditions and during concurrent exposure to distracting stimuli (Knott, 1985). Results indicated that subjects demonstrated reductions in the amplitude of the CNV during the distraction condition, which were reversed by smoking.

1.8 Duration of Central Effects

While the central effects of smoking clearly occurs almost immediately, the duration of these changes is less straightforward. Some evidence suggests that changes in alpha and delta power return to baseline levels by 10 minutes post smoking (Norton et al., 1992). Others have reported both a slightly shorter time course of 7 minutes (Pritchard et al., 1995), as well as considerably longer time courses on the order of 20 minutes (Philips, 1971; James et al., 1995).

One study by Hasenfratz et al. (1990) explored the time course of both central and peripheral effects of smoking. After 10 hours of overnight deprivation, subjects smoked the first cigarette of the day during a morning recording session. Levels of exhaled CO and plasma nicotine absorption, as well as EEG and peripheral arousal measures, were

obtained over a 90 minute period. While smoking related EEG changes in alpha frequency and beta power were still evident at 10 and 20 minutes respectively, peripheral effects lasted somewhat longer with heart rate changes enduring even 40 minutes later and respiratory measures still being affected after 90 minutes. Although this component of the study must be interpreted with caution, because subjects were required to smoke two cigarettes in rapid succession, the relatively long duration of this effect is noteworthy. In a second segment of the study, subjects smoked three cigarettes at 30-minute intervals and physiological recordings were made both 10 minutes prior to smoking and 10 minutes after smoking had ended. Smoking one cigarette, after each of the three 30-minute intervals, produced qualitatively similar but generally smaller effects. While all central measures had returned to pre-smoking levels by the 20 minute mark, the peripheral changes had a tendency to add cumulatively over subsequent smoking periods, showing slower returns to baseline values, as had previously been found for cardiovascular measures (Benowitz et al., 1982).

Section 2: Experimental Considerations

The literature reviewed aids in providing a better understanding of how smoking modulates the EEG, but there are several concerns that should be addressed. Both a lack of diversity of the methods utilized, as well as the consistent bias towards choosing heavy smokers as subjects, may have contributed to the picture of smoking which is presently accepted. The present study was undertaken in an effort to provide a broader understanding of the smoking related changes in the EEG by serving as a complement to the reports described above. Therefore, this thesis diverged from previous studies in several important respects which will now be described.

I) Pharmacological Issues.

2.1 Subject Population

Many studies examining smoking related changes in the EEG utilized subjects who were heavy smokers often ranging from 10 (Knott, 1985) or 16 cigarettes a day (Golding, 1988), up to a pack a day (Pritchard, 1991; Pritchard et al., 1995), or even three packs a day (Herning et al., 1983; Hall et al., 1973). The present study favored an alternative approach which followed two lines of reasoning. First, in order to obtain an understanding of central nervous system changes which occur across the full spectrum of the smoking population, more studies on lighter smokers are needed. For example, do individuals who smoke only three or four cigarettes a week, or who only smoke during weekends, demonstrate smoking related changes that are similar to those found in heavy smokers? People who smoke fewer than five cigarettes, at least four days per week, have been termed "chippers" (Pomerleau et al., 1993). While there is an increasing amount of literature concerning lighter smokers, the effects of smoking on EEG have not been examined in this population. Secondly, from a pharmacological perspective, while heavy smokers may need to smoke two cigarettes consecutively for satiation, lighter smokers are more likely to be affected after one cigarette (Arcavi et al., 1994). Since this study only required subjects to smoke one cigarette, any EEG changes related to smoking might have been more evident in individuals who were less likely to have built up tolerance.

2.2 *Smoking Procedure*

The literature contains a considerable number of instances in which controlled smoking procedures were used, such as smoking four puffs at 30 second or 1 minute intervals (Pritchard et al., 1995; Knott, 1989; Knott, 1985), while estimating nicotine absorption by concurrently measuring plasma levels or exhaled CO_2. The reliance on this type of formalized exposure to nicotine offers the security of a standardized procedure at the expense of failing to represent the patterns of smoking which normally occur during typical smoking. While studies concerned with the pharmacokinetics or pharmacodynamics of smoking must rely on rigorous experimental procedures of this type, the question of how the EEG is altered by smoking may be hindered by standardized methods because these ignore issues of individual tolerance. Ironically, the same authors who have used standardized puff procedures have suggested that a lack of significant findings may have been due to the unnatural exposure to tobacco smoke that was imposed by the experiment (Knott, 1985). Following this line of reasoning, regulation of intake might cause heavy smokers to obtain insufficient amounts of nicotine while lighter smokers experience overexposure, producing arousing or no effect in the first case and depressant effects in the latter. Further, not only the amount of smoke exposure, but also the rate of intake, has been shown to contribute to the type of result that is obtained. Some smokers like to increase the rate of smoking towards the end or at the very beginning of cigarette, take deeper breaths and exhale more rapidly, or sometimes take shallow breaths and retain the smoke longer (Haire-Joshu et al., 1991). When smokers are made to diverge from their normal pattern of smoking, they seem to compensate to obtain the desired effect of the cigarette which they typically experience, although whether this compensatory mechanism is due to tar or nicotine based cues is still under debate (Hasenfratz et al., 1993a). As some investigators have already elected to do by enabling the smoker to smoke in a natural manner (Pritchard, 1991; Hasenfratz et al., 1993; Norton et al., 1992), factors such as tolerance can be overcome by the smoker who is supposedly quite adept at regulating intake to achieve a desired optimum state, according to the currently accepted model.

2.3 Deprivation Requirements

In many of the previous EEG and ERP studies, relatively long periods of tobacco deprivation have been utilized. The question arises as to whether such findings can be generalized to more natural smoking conditions. While some studies have found significant smoking related effects using only a 2 hour pre-experimental deprivation period (Norton et al., 1992), as little as 1 hour of pre-experimental smoking and caffeine abstinence was sufficient for the detection of differences in EEG during the post-smoking interval (Golding, 1988). Hasenfratz (1993b) found that even this duration may be excessive by having subjects smoke cigarettes at 30-minute intervals. Using this short interval, it was found that alpha power and frequency, and beta and theta power had all returned to baseline levels by 20 minutes post-smoking. Further, over these consecutive smoking periods, tachyphylaxis was found for peripheral but not central measures. In conclusion, excessive periods of pre-experimental withdrawal may make the interpretation of the data difficult due to the interaction between the effects of smoking and the reversal of withdrawal symptoms.

II) Electrophysiological Issues.

2.4 A Re-Examination of Slow Waves

A simple model which associates the smoking related enhancement of cognitive processing with a shifting of the EEG into higher frequency ranges, is attractive. However, it ignores an extensive literature which reports that, while increases in the power of delta and theta bands are found during periods of drowsiness and sleep, these increases have similarly been found over a large assortment of challenging cognitive tasks. For example, augmentation of delta power has been found during both reading and mental arithmetic tasks (Schacter, 1977; Fernandez, 1993).

Since graduated increases in delta power have been found with increasing task demand, some have speculated that there might be a relationship between delta and attention (for references and discussion see Appendix 1). If delta and theta are increased by cognitive demand, and smoking enhances the attentional mechanisms that have been

associated with these bands, it seems likely that the power in these slower frequency bands would be increased by smoking. Increases in theta have been reported during conditions of mental load (compared to a subjects baseline), but not during resting conditions, following the oral administration of caffeine (Dimpfel et al., 1993). Additionally, increases in delta power have been found during both rest and mental load, after caffeine (Pritchard et al., 1995; Clubley et al., 1979). However, rather than increases, decreases are reported in the power of slower frequency bands after smoking frequencies (Pritchard, 1991; Gilbert et al., 1989).

Studies which have reported smoking related decreases in delta and theta power, as well as changes in peak frequency, have ignored several potentially important considerations. From a cognitive and electrophysiological point of view, the post-smoking increase in the peak frequency of theta that was found during the eyes closed condition may have reflected theta related to drowsiness rather than mental load (Michel et al., 1989). As in the case of caffeine, theta might be differentially affected by smoking during conditions of rest and mental load. This has already been found to be the case for the alpha band. For example, Golding (1982) found that alpha power increased rather than decreased after smoking when it was measured under conditions of mental load rather than while a subject was merely resting. Additionally, smoking has also affected the power of the alpha rhythm differently between EO (eyes open) and EC (eyes closed) conditions, which are minimally different states (Golding, 1988).

Further, while the delta and alpha bands often manifest clear spectral maxima that have enabled researchers to make a relatively accurate analysis of their respective peak frequencies and amplitudes, the power in the theta range is often more elusive and forms a "spectral valley" between the peaks of these other two frequency bands. In the spontaneous human EEG, distinct spectral peaks in the theta band are not easily detected and may often be masked by slower alpha components impinging into the theta range (Basar-Eroglu et al., 1992). This can be seen in the top half of Figure 1, in which clear peaks in the alpha and delta range exist, while intrusion of power from the alpha band into the slower theta range accounts for activity that would often be reported as theta.

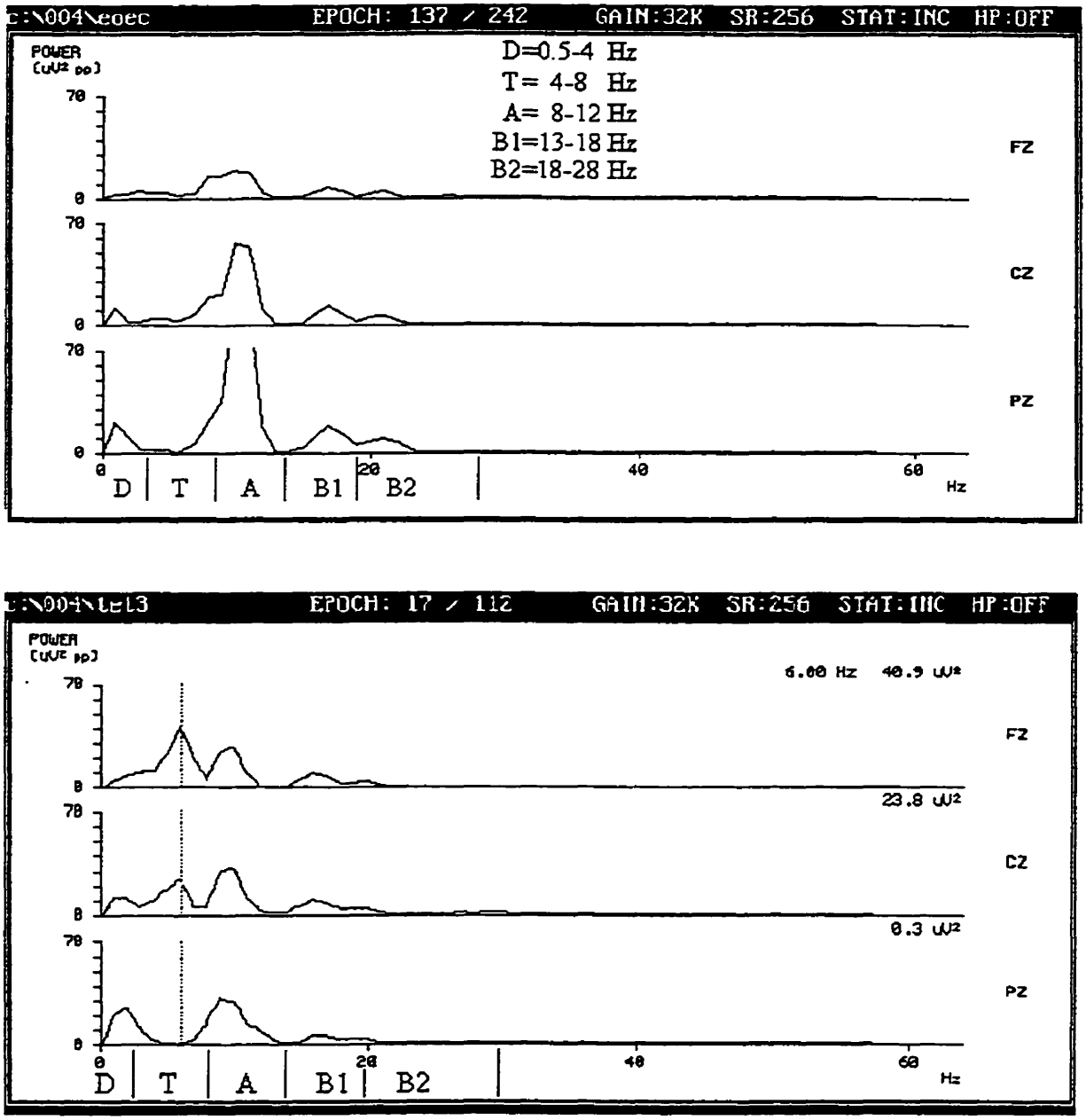


Figure 1: The top panel shows the power spectra that were computed using 1 second of EEG collected from the frontal (Fz), central (Cz), and parietal (Pz) leads. The EEG was recorded during a resting, eyes-open condition. The slower activity in the alpha (A) band, which might be measured as theta (T) activity, is apparent in all three leads. Consequently, if the alpha band power moves into a higher frequency range, as it does after smoking, the **mean frequency** of the theta band would be characterized by a corresponding shift. In the lower panel, under conditions of cognitive load, there is an emergence of a clear peak of frontal midline theta which enables proper measurement of a dominant rhythm of the band or the "**peak frequency.**" Both recordings are from the same subject.

The lower panel, on the other hand, shows the power spectrum of the same subject engaged in playing the computer game Tetris®. A clear peak, which may be accurately measured for power and peak frequency, appears clearly at Fz, and to a lesser extent, at Cz . Previous reports of a smoking related increase in peak theta frequency during an EC condition could therefore be due to a change in the power distribution of the neighboring alpha band rather than a true shift in the frequency of the theta rhythm. This consideration is relevant because even though theta power may be evident in the power spectrum of only a portion of the population, investigators have reported changes in the amplitude (Herning et al., 1983; Pickworth et al., 1986; Knott, 1988; Knott, 1989) and peak frequency (Michel et al., 1989) of theta after smoking while including all their subjects in the computation of this result.

In responding to these issues, the present study has differed from previous studies in several regards. In order to investigate changes in theta that are relevant to mental activity, and to more accurately measure the peak frequency of the theta band, frontal midline theta (FMT) rather than traditional theta was investigated. An analysis of changes in the peak frequency of FMT is more appropriate than an examination of the changes which occur in traditional theta, because FMT produces a large discrete peak in the power spectrum which enables a more accurate estimate of the peak frequency. While FMT presents a clear peak that offers improved measurement, several important differences that distinguish FMT from traditional theta must be considered in a study which aims to provide a meaningful analysis of this phenomenon. Although a detailed discussion of both theta and FMT appears in Appendix 2, a quick review of the characteristics of FMT is provided here.

FMT usually manifests itself in one to seven second rhythmic bursts which tend to be isolated to the upper range (6-7 Hz) of the theta band, and which have a relatively large amplitude with a maximum distribution over the frontal sites. Traditional theta usually occurs as a low voltage rhythm having a distribution in the slower theta frequencies (4-5 Hz) and occurring diffusely throughout the cortex. FMT occurs only in approximately half of the population during cognitive tasks (Schnider et al., 1995; Mizuki et al., 1980; Yamamoto et al., 1990) . Within the population of "FMT producers", close to one-third

show FMT continuously, while the remaining two-thirds usually produce FMT only during one-fifth of the recording period (Takii, 1986). In these latter cases, FMT appears semi-periodically at intervals of roughly 40 seconds, and lasts for only one to five seconds, where one second is often the minimum duration for an occurrence to be registered (Mizuki et al., 1980). Due to these characteristics, it should be apparent that in an investigation of smoking related changes in FMT, only a subset of the subjects will be used in the analysis and, for each subject, only a portion of the EEG, that recorded from the frontal sites, will be utilized in a comparison of FMT before and after smoking.

Studies that previously examined smoking related changes of traditional theta would not have been able to offer an adequate picture of FMT changes due to the special characteristics of this rhythm. Aside from the fact that a large amount of the data must be excluded when looking at FMT, since the time course of the FMT varies from 1 to 7 seconds, studies using signal analysis techniques which analyzed data segments spanning periods of 4 (Dimpfel et al., 1993), 5 (Knott, 1988; Domino et al., 1996), or 8 (Norton et al., 1992) seconds must have violated assumptions of the stationarity of the signal. When the window of analyzed data persists longer than the time over which the signal existed, the submitted data may contain lapses in amplitude or shifts of phase. By analyzing an EEG record using data windows of one second duration the probability that the signal is stationary across the data window is increased. However, when high frequency resolution is desired, relatively longer segments of time are required by the Fast Fourrier Transform (FFT). In order to counter this problem, techniques such as wavelet analysis and auto regressive spectral analysis have emerged. This thesis utilized an alternative technique known as "zero padding", which is a method that enables the FFT to give a more specific estimate of peak frequency while only 1 second of actual data is required. A more detailed description of this method can be found in Appendix 3.

2.5 Alpha Frequency and Amplitude

Changes in alpha power have often been related to changes in the arousal state of the subject, while alpha frequency has been shown to be correlated with the speed of information processing (Varela et al,.1981). Further, while alpha band power displays a

bi-phasic increase/decrease with increasing nicotine doses, changes in the dominant alpha frequency are more reliably elicited at higher nicotine levels and have been reported to increase in relation to increasing nicotine dose (Hasenfratz et al., 1993b). Since smoking seems to produce separate effects on EEG attributes related to information processing (alpha frequency) and arousal (alpha power), the time course of each was considered separately. In the analysis, alpha parameters were measured according to the characteristics of the dominant spectral peak of the alpha band, as has been done by others (Philips, 1971).

2.6 Beta and Narrow Band Analysis

The often reported smoking related increase in beta power has only been examined using a relatively wide frequency band (Hasenfratz et al., 1989; Pickworth et al., 1986; Knott, 1990; Roth et al, 1992; Pritchard et al, 1992). Some studies have defined the beta band as encompassing a range as large as 14-30 Hz. Others have divided this range into beta1 and beta2 which may be defined, for example, from 12-18 and 18-28 Hz respectively. Only a few studies have looked for changes in the peak frequency within the higher bands (Pickworth et al., 1986; Michel et al., 1989) and these investigated only the beta1 (13-20 Hz.) range. Further, the increase in beta power may have a shorter time course than the duration of the recording periods analyzed by some investigators (Hasenfratz et al., 1989). In order to investigate narrow band changes related to smoking which may occur, the frequencies between 15 and 28 Hz (which will be termed as the "beta2" band) was examined in this study in 1 Hz frequency increments.

2.7 EEG Record Length

Studies concerned with smoking related EEG changes have sometimes relied on 2 minute EEG records in order to obtain an estimate of the power spectrum (Hasenfratz et al., 1993b), while others have shown that a 1 minute sample of EEG is adequate to detect statistically significant changes due to smoking (Cohen et al., 1994; Golding, 1988). In accordance with these previous studies, at least 1 minute of EEG was obtained during both conditions of mental load and of rest.

2.8 Summary Notes

The fact that smoking can be characterized by a bi-phasic response, which alters the effects of smoking based upon such factors as tolerance and dosage, has important implications for the design of this thesis. The available evidence suggests clear advantages may be obtained 1) pharmacologically, by using lighter smokers, and by using natural rather than formalized smoking procedures, 2) cognitively, by incorporating low intensity stimuli that place greater demands on perceptual resources, and 3) physiologically, by examining the EEG power spectrum with narrow band analysis as well as signal processing methods that are more appropriate for the biological rhythms being measured.

The Effects of Smoking on the Continuous and Time-Locked EEG

Michael S. John and Frank R. Ervin

Department of Psychiatry
McGill University

Address Correspondences to:
Sasha John
Department of Psychiatry, McGill University
Montreal PQ, H3A-1A1
Canada.

Telephone: (514)-398-5981; FAX: (514) 398-4370; EMAIL: mjohn@PO-BOX.MCGILL.CA
sasha @BRL4.MED.NYU.EDU

Abbreviations: Electroencephalogram (EEG); Event Related Potential (ERP);
Frontal midline theta (FMT); Reverse Mirror Drawing (RMD).

Introduction

Previous studies investigating the EEG changes related to smoking have normally relied on subjects who smoke between three-quarters and three packs per day (Herning et al., 1983; Golding, 1988; Hall et al., 1973, Knott, 1996). The subjects used in the present study varied in their smoking behavior but tended to be lighter smokers (four/day) than those who have been chosen in previous studies. Since lighter smokers may have developed less tolerance to the effects of smoking and are more likely to be affected by one cigarette (Arcavi et al., 1994), it was predicted that the single cigarette smoked during this study would produce greater smoking related changes than those reported by previous studies. Further, because lighter smokers comprise a substantial proportion of the total smoking population at any given time, it seemed important to investigate the effects of smoking in these subjects in order to obtain a better understanding of the full spectrum of the smoking population. The present study thus aimed to help provide a general picture of smoking by using the full 10-20 system to explore the effects of smoking during rest, under different mental loads, and during both auditory and visual stimulation.

Another purpose of this study was to investigate the effect of smoking on the frontal midline theta (FMT) rhythm. FMT is an EEG rhythm of relatively large amplitude which may occur within the general theta frequency band (4-8 Hz.), but tends to occupy the higher frequencies of this range (6-7 Hz.) and demonstrate a maximum distribution over the frontal midline region. As discussed by Takii (1986), FMT is thought to be related to focused attention and has been shown to be elicited by tasks such as reverse mirror drawing (Takii, 1986) and mental calculation (Mizuki et al., 1980), as well as other tasks which involve moderate demands on attention or cognition (Schober et al., 1995; Yamamoto et al., 1990). Although the modulation of theta activity due to smoking has previously been explored, this experiment specifically investigated FMT for two reasons. Firstly, even under mental load, traditional theta activity is often relatively hard to detect in the eyes open power spectrum of the EEG, making an accurate measurement of the peak frequency of this rhythm difficult. FMT, on the other hand, produces a clear peak which is distinct from background spectral power and is easily measured. Secondly, although reports have already shown a significant shift in the peak frequency of theta rhythm during

the eyes closed condition (Michel et al., 1989), the EEG may be affected differently by smoking during conditions of rest and during mental load. For example, Golding (1982) has already demonstrated that alpha power shows an increase rather than decrease after smoking, when examined under conditions of stress rather than under resting conditions. Accordingly, the theta that appears during EC, which is often representative of drowsiness, may be distinct from the theta that appears under mental load (Schacter, 1977).

This study also investigated the changes which occur in both frequency and power of the alpha band after smoking. While the alpha band displays a bi-phasic increase/decrease in power with increasing nicotine amounts, the increase in the peak frequency of alpha band is larger and more reliably elicited at higher nicotine levels (Pritchard, 1991; Hasenfratz et al., 1990; Hasenfratz et al., 1993). Because smoking seems to produce separate effects on EEG attributes related to information processing (alpha frequency) and arousal (alpha amplitude), each parameter was examined at two intervals subsequent to smoking.

A further objective was to investigate smoking-induced increases in beta power which have been associated with smoking's anxiolytic properties. Recent studies (Pritchard, 1991; Pritchard et al., 1995) have extended the picture of increased beta, by examining the topographic and dose-related nature of the beta2 response. Increases in beta2 power around the Cz site were found to be larger in heavy compared to light smokers. In the present study, the time course of this change is examined. Additionally, while previous studies have coarsely examined beta2 power by combining eight or sixteen separate frequencies into a single broad band(e.g., 13-20 Hz), the present study will examine the higher frequency range for narrow band (1 Hz) changes in spectral power.

Lastly, in the aim of obtaining a more thorough understanding of the changes produced by smoking, in addition to obtaining EEG under conditions of rest and mental load, both visual evoked potential (VEP) and auditory evoked potential (AEP) tasks were incorporated into the experimental design. Since Hall et al.(1973) and others (Philips, 1971) have offered evidence that smoking produces relatively greater effects in the processing of peri-threshold stimuli, studies using easily perceived stimuli would be less

likely to detect more subtle effects of smoking. If smoking is capable of producing decreases in latencies of the VEP, these would be more likely to occur using a dimmer stimulus which does not enable the visual system to process the incoming information with maximum efficiency. For this reason, a relatively dim, reversing checkerboard stimulus, rather than a flash stimulus, was incorporated into the experimental design.

Methods

Subjects

Volunteers included ten right handed subjects (7 female, 3 male) with a mean age of 26 (range 22-36), who smoked at least three cigarettes per week (three subjects had smoked 15/day, seven subjects smoked < 3/day). The three heavier smokers were included in this study because two subjects only smoked to that extent on weekends, while the remaining subject had just started smoking again (3-4 cigarettes a day) after several months of abstinence. These subjects were still relatively light smokers compared to those used in many other studies which have, for example, relied on subjects who smoked at least 15 cigarettes as day for a minimum of 5 years (Knott et al.1996). All subjects were volunteers who agreed to participate without pay in return for printouts of topographic maps of their EEG. Subjects were asked to abstain from alcohol for 12 hours prior to participation in the study and from tea, coffee, and cigarettes during the prior two hours. When subjects arrived at the laboratory they were asked if they had abstained accordingly. Two subjects had forgotten about the coffee requirement and were rescheduled.

Studies have shown that smoking early in the morning produces performance deficits in smokers who normally begin to smoke later in the day (Roth et al., 1992). Therefore, subjects were either scheduled in the morning (11 a.m.-12 a.m.) or in the early evening (5-7 p.m.) according to their normal smoking patterns. An effort was originally made to obtain morning smokers, since FMT had been reported to occur more reliably between 10 am and noon (Takii, 1986).[3] However, subjects were often unavailable for testing during this period. In order to compensate for the inability of subjects to be scheduled in the morning, and to increase the likelihood that FMT would appear during the recording session, extra time was made available in order to practice the tasks before

[3]In an extensive study entailing both a screening phase and a test phase, Takii (1986) used a serial addition task to examine diurnal fluctuations in the appearance of FMT. A screening procedure accepted 18 of 40 subjects (about 50%), who demonstrated FMT on 3 separate days when engaged by the task. The experiment ensured that these subjects were scheduled so that at least 4 subjects were tested at each of the 9 intervals which spanned from 8 am to midnight, at 2 hour increments. A divergence was found between appearance of FMT, which was found to occur most frequently from 10 to 12 a.m., and the greatest performance scores on the task, which occurred near midnight.

the EEG recording: exposure to a task during practice sessions has also been shown to significantly increase both the chance and the duration of FMT occurrence (Takii, 1986).

Experimental Conditions

The experiment consisted of 14 separate conditions, and included seven conditions which occurred prior to smoking and which were repeated afterwards (Table 1). Aside from eyes open (EO) and eyes closed (EC) conditions, which were recorded sequentially without a break, the pre-smoking conditions were separated by two minute breaks during which subjects relaxed with the lights on. The post-smoking conditions were each separated by a break of 30 seconds.

-INSERT TABLE 1 HERE-

Smoking Procedure

Subjects were instructed to smoke a cigarette in a comfortable manner, with only one restriction. Subjects were required to inhale what they believed to be the equivalent of at least five large inhalations before reaching the end of the cigarette. Subjects were able to choose their test cigarette from between DuMaurier (1.3 mg. nicotine, 15 mg. tar, 16 mg. CO_2) or Player's Lights (1.1 mg. nicotine, 12 mg. tar, 13 mg. CO_2), two very popular brands in Montreal. Immediately after the last puff, the cigarette was extinguished in a cup of water, and recording of the post-smoking EO data was started.

EEG Acquisition During Rest and Cognitive Task

EEG was recorded on a Lexicor Neurosearch®-24 EEG acquisition system. Nineteen Ag/AgCl electrodes were attached to the subjects' scalps according to the standard locations defined by the International 10-20 System, and impedances of under 10 Kohms were obtained. Linked ears were used as a reference, and a site on the center of the forehead acted as ground. EEG data were recorded with a sampling rate of 256 samples/sec, using a highpass filter set at 0.5 Hz, a notch filter of 60 Hz, and a lowpass

filter set at 64 Hz to avoid aliasing. Auditory and visual ERP data were collected at 512 samples/sec, using both a lowpass filter setting of 128 Hz, and a notch filter. ERPs were collected at a higher sampling rate to increase the accuracy of estimating the actual latencies of the elicited components.

After the electrodes were attached, subjects were asked to watch their online EEG data which was presented on a computer monitor during a five minute "training" session. During this session, subjects were shown how muscle and eye movements could influence the EEG, and instructed to practice minimizing unwanted muscle tension and eye movement. This training drastically improved the overall quality of the EEG in most subjects and should be considered as a standard procedure in any future experimental design entailing similar tasks. This training was also important because, during the mental load conditions, subjects were able to quickly improve the quality of their EEG upon warnings from the experimenter regarding too much eye movement or muscle tension.

Following the training session, two minutes of baseline EEG were recorded during both eyes EO and EC conditions. After baseline recordings were obtained, the lights were turned off and mental load data was recorded. In the first mental load condition subjects played the computer game Tetris, in which geometric forms are manipulated in order to fit into an emerging pattern. The Tetris task was under control of a 486 DX2 IBM PC which presented the game on a display terminal that was situated approximately two feet in front of the comfortably seated subject and was shielded by an anti-glare/anti-radiation grounded shield. Three steps were taken to reduce the amount of eye movement a subject might produce while engaged in the task. The Tetris game was arranged to occupy roughly the center one-third of the total screen area. Additionally, subjects were encouraged to sit back far enough from the monitor that they could see the entire relevant section without having to move their eyes. Lastly, subjects were allowed to practice for about five minutes and were instructed to choose a moderately challenging level of play (Table 1). During this practice time, subjects received additional feedback from the investigators in order to help them learn how to play Tetris while not contaminating the EEG record with excessive eye movement. Subsequent to these steps, the subjects played for 1.5 minutes while EEG was recorded.

The lights were then turned on and subjects worked on a computerized version of the reverse mirror drawing (RMD) task (Schnider et al., 1995), which was presented on a Macintosh SE.[4] The RMD task entails tracing a line within the boundary that is defined by the outline of a four pointed star. The motion of the cursor on the screen is inversely related to the direction in which the subject moves the computer mouse along the horizontal axis, but is directly related to the motion of the mouse in the vertical directions. The difficulty of the RMD ensured that no subject completed the task prior to the end of the 1.5 minute interval during which EEG was collected.

The EEG data recorded during Tetris and RMD were reviewed for overall quality and eye movement. While most subjects could consistently decrease the eye activity induced by the Tetris task to acceptable levels, two subjects displayed large levels of eye movement. In these cases the RMD, rather than the Tetris task, was used to elicit FMT after the smoking interval since less eye movement was produced by this task.

ERP Recordings

Visual evoked potentials (VEP's) were obtained during a black and white checkerboard reversal task. Checkerboard stimulation was under control of the Lexicor and consisted of six horizontal and four vertical rectangles (each 4.5 cm. vertical x 4 cm. horizontal), which were presented on a monitor located 22 inches from the subject's forehead. The monitor was adjusted so that it subtended an angle that was roughly equivalent to each subject's visual horizon and was centered within their visual field. The lights were turned off and, after 30 seconds, the subject was instructed to look at a fixation point and count the number of reversals, while 180 reversals occurred at a rate of one/second (Baseline #1). The lights were turned on for two minutes during which the subjects rested and reported their count. A second set of VEP's was then collected (Baseline #2).

---

[4]This computer task was written by Dr. Armin Schnider for testing motor activity in Parkinson's disease. The experimenter wishes to thank Dr. Schnider for kindly providing it for the experiment free of charge and for translating both the task and the 20 page instruction manual from German into English!

Auditory stimulation was under the control of a Macintosh II running PsyScope® software (Cohen et al., 1993). An oddball paradigm was presented with "common" and "rare" tones of 1000 Hz and 500 Hz (30 msec. duration, and a 10 msec. rise/fall time), respectively, occurring in a 4:1 ratio and a pseudo-random order. Tones were presented with an ISI of one second. Auditory stimuli were presented using Telephonics™ earphones, which were shown to have little effect on the recordings of electrophysiological data during recordings in pilot subjects.

Two separate pre-smoking baselines were recorded for both the visual evoked potential (VEP) and the auditory evoked potential (AEP) in order to assess the reliability of the amplitude and latency of the individual ERP components. An informal analysis of the checkerboard VEP indicated that it produced a stable estimate of the visual system's response. Both the amplitude and latency of the VEP components showed minor variability between the two baselines, relative to the post-smoking differences. In contrast, the two auditory baselines showed considerable amplitude variation, while latency of the peaks was more stable. Due to these different amounts of baseline stability, the post-smoking VEP data was compared to an average of the values obtained from the two baseline conditions, while the AEP data was only compared to the data of the first baseline as has been done traditionally.

"Signal" to "noise" ratio of the averaged ERP data tends to increase as a square root function of the number of raw ERPs that are submitted to the average. A relatively stable averaged VEP emerges after about 70 presentations of a checkerboard stimulus. Therefore, even though 180 VEPS were used in order to ensure that an adequate number of VEPs were obtained during the baseline, the 140 VEPs collected in the post-smoking condition were more than adequate. Because the time course of smoking related EEG changes has been found to be on the order of 10 minutes by some investigators (Norton et al., 1992), the number of VEPs was reduced in order to increase the likelihood that the effects of smoking would be present during the collection of the AEP data, since this was recorded after the VEP.

Data Analysis

Traditionally, EEG investigations which evaluate the peak frequency of a particular EEG band use relatively long samples of continuous data, e.g., five seconds per sample. As the amount of continuous data submitted to the FFT increases, the frequency resolution of the resulting spectral estimate also increases. In practice, submitting five seconds of EEG to spectral analysis can be inappropriate, because an assumption is made that the signal is characterized by a high degree of stationarity and also that the signal is free from phase shifts and other abrupt transitions. This assumption may not be valid for some EEG data; for example, the alpha rhythm may show jumps in phase when a subject blinks or attends to an externally or internally generated stimulus. Since this study examined not only the alpha rhythm, but also FM Theta, which is known to be a less stable rhythm, each one second sample of accepted EEG was "zero padded" with the equivalent of seven seconds of zeros (7 X 256). Zero padding enables the FFT (2048 point) to provide a spectral estimate with high frequency resolution, while segments of only one second of actual data are submitted to the algorithm.

Because FMT may exist for only a small portion of the total recording time, the data collected during the Tetris and RMD tasks were analyzed spectrally, using a 256 point FFT which yielded a spectral estimate having 1 Hz resolution for each 1 second (1 epoch) of data, before being subsequently submitted to high frequency analysis. In order for an epoch to be included in the narrow band analysis FMT it had to be characterized by a clear spectral peak in the 4 to 7 Hz range which was distributed maximally over the frontal regions. Only epochs that reached this criteria were submitted to high resolution FFT analysis.

The analysis routines provided with the Lexicor EEG collection system were used in all FFT analyses of the EEG that were limited to 1 Hz resolution as well as for the evaluation of ERP data. Matlab v4.2 was used to perform a narrow band analysis (.125 Hz) with the following definitions of band: delta, 1.0-4.0 Hz, theta, 4.125-7.5 Hz, alpha 7.625-12 Hz, and beta2, 15-28 Hz . Rather than split the alpha range into low (alpha1) and high (alpha2) bands as has been done by others (Domino et al., 1994), an estimate of alpha power was obtained by measuring the power of the peak frequency in the alpha

band. This definition was chosen over the prior method because, in the latter, a shift in the peak alpha frequency from the alpha1 to the alpha2 range produces decrease in power of the alpha1 band: this can be misleading because while a change in size of the electrical field that is oscillating at the alpha rhythm has not necessarily occurred, a decrease in alpha power appears. Alternatively, by defining alpha power in terms of the power of the dominant frequency in the alpha band, the measure may become more physiologically meaningful by acting as an indicator of the number of neurons engaged in the response. Using this latter method, changes in the peak frequency do not contribute to an estimation of the power of a band. Accordingly, power at the peak frequency rather than mean power over a band, was used for the analysis of the other spectral bands as well.

All data was submitted to an artifact rejection in which only data that was below a given threshold for muscle movement and eye-blinks was accepted. The artifact rejection process was as follows. Since a specific channel was not used to independently to monitor eye activity, one second EEG records, or "epochs", were examined by the experimenter and rejected when the spectral representation of the record indicated that power in the low delta range was distributed in a frontal to posterior fashion, and was above a threshold value. The threshold was determined individually for each subject and was based upon the EEG changes that were produced by the subject's eye movements during the "training" period described previously. Additionally, any records that contained large amplitude, high frequency components possibly due to muscle tension which were largest at the frontal (FP1, FP2) or temporal (T3,T4) were also rejected from entering into further analysis.

In regards to the VEP and AEP analysis, after all data was submitted to the artifact rejection procedure, ERPs were averaged from accepted epochs without removing linear trends or using a pre-stimulus baseline adjustment since these options are not available in the Lexicor software. AEP and VEP components were identified as a sequence of positive and negative deflections, in accordance with the methods of previous reports (Sutton et al., 1965; Plant et al., 1983; Spekreijse et al., 1973).

After the ERP and quantified EEG spectral results were obtained they were submitted to statistical analysis using GB-Stat V5.40™ software. There has been

considerable controversy concerning the appropriateness of using various statistical tests in experiments where data was obtained from multiple electrode sites. In studies which examine data from 19 or more electrodes, and investigate several frequency bands at each of these electrodes, it becomes increasingly important for the large number of comparisons (e.g.,1000) to be treated in a special manner since as the number of recording points and variables increase, the probability of finding a significant difference at one or more electrodes increases to near certainty. One solution to this problem involves data reduction. In line with previous studies, even though many electrodes were used, only the electrodes where an ERP or EEG response is maximum, are considered (Knott, 1985; Takii, 1986). Because the alpha rhythm and the VEP are usually most pronounced at the O1 and O2 sites, the statistical analysis only considered the data obtained from this occipital region. In line with this reasoning, FMT was only statistically considered at the Fz site, where it is largest, and the P300 was only measured at the Pz. The four sites were chosen because the ERPs are most clearly defined there, leading to more accurate measurement of both latency and amplitude.

Even with data reduction, multiple comparisons are often still necessary. Although specialized procedures for handling data based upon multiple channels are currently being debated and developed, investigators often rely on the Bonferroni method, which is most appropriate when the number of multiple comparisons are kept small in relation to the number of subjects tested (Karniski et al., 1994; Oken et al., 1986). In this study, the comparisons between the baseline and post-smoking conditions, which entailed more than one lead, were accomplished using a repeated measures one way analysis of variance (ANOVA) treating electrode location as a factor, while single lead comparisons, that were limited to a single post-smoking change, were accomplished using a paired t-test. Post-hoc t-tests were corrected with alpha-error adjustment using the Bonferroni method.

Results

EEG Results

1. Beta2

As can be seen in Figure 1, in 5 of the 10 subjects, a large increase [average = 550% , range 205% to 1044%] occurred in beta2 power at the Cz site during the first two minutes following smoking. While these smokers seem to be either beta2 "producers" or "non-producers", a repeated measures ANOVA indicated that the change in beta2 power by condition (pre-smoking, 2minutes post, 11 minutes post) was significant even when all subjects were included in the analysis [$F(2,18)=5.61, p<.01$]. Post-hoc *t*-tests indicated that the only beta2 increase during the first 2 minutes was significant [$t(9)=10.06$, $p<.05$]. Although the beta increase at the later interval failed to reach significance, it should be noted that in the five beta2 producers, the response was still evident, although considerably reduced, even 11 minutes after the cigarette. In the producers, a large beta2 increase was clearly evident in the first minute of the post-smoking period in 3 subjects, while in the other 2 it emerged between the first and second minute (data not shown). In the remaining subjects, two showed relatively small increases while three showed slight decreases in beta2 power.

-INSERT FIGURE 1 HERE-

In two of the ten subjects (subject 5 and 7), the beta2 increase was comparable to that subject's alpha power during the EC pre-nicotine condition, which is often the largest rhythm in the EEG. An argument may be made that the relatively large increase in beta2 power might therefore be indicative of a major change in state. However, the beta2 increase tended to be highly localized to the Cz site, and was attenuated by about 80% or more at other electrodes (Tables 2a and 2b). This topographic distribution suggested that the neuronal source of this rhythm was near the cortex under the Cz site and may have been limited to a relatively small region of the brain, as can be seen in Figure 2.

-INSERT TABLE 2a HERE-

-INSERT TABLE 2b HERE-

-INSERT FIGURE 2 HERE-

It is relevant to note that the increase in power was not due to the activity of the whole band, but rather was only 1-2 Hz wide. An examination of the power spectra of the resting EEG demonstrated that the beta2 peak existed somewhat sporadically in the EEG of several subjects prior to smoking. After smoking, the peak frequency usually occurred within 1 or 2 Hz from where it had appeared in the pre-smoking EEG (Table 3). The frequencies of the beta2 peak varied from 18 to 26 Hz among individual subjects.

-INSERT TABLE 3 HERE-

Although the maximum power was evident at the Cz rather than a more occipital site, recent articles have discussed the concern that higher frequency phenomena may be caused by power of slower frequencies, (e.g., alpha) showing up at harmonic frequencies due to the inability of spectral analysis to compensate for errors of frequency estimation which are sometimes introduced by irregularly shaped periodic activity (Juergens et al., 1995). This type of spectral artifact does not seem to be responsible for the beta2 peak since visual examination of the raw EEG demonstrated that the beta2 rhythm could be present in the absence of visible alpha (see Figure 3).

Lastly, an ANOVA, comparing beta2 increase in the 1-2 minute post-smoking period by group indicated that the occasionally moderate smokers were not significantly different from the light smokers [$F(1,8)=.38$, $p=0.5$, corrected for unequal sample size]. Because moderate subjects consistently manifested changes that failed to skew the data in a particular direction, further comparisons based upon smoking frequency were not done. Smoking related changes of the moderate subjects were indicated in tables and figures.

-INSERT FIGURE 3 HERE-

2. Alpha

The changes in alpha power which occurred during the 1-2 minute post-smoking interval (EC) can be found in the top half of Figure 4. A general decrease in the amplitude of the peak alpha response was found. A 2 (lead) X 3 (condition) repeated measures ANOVA indicated a significant main effect for alpha power by condition (factor C: baseline x post 2 minute x post 11 minute) [$F(2,36)=12.96, p<.01$], while the interaction between condition and electrode lead did not reach significance (interaction L x C) [$F(1,18)=.17, p=.68$]. Post-hoc tests indicated that alpha power was significantly decreased during the 1-2 minute interval at both O1 [$t(9)=4.55$, $p<.05$] and 02 [$t(9)=2.87$, $p<.05$] leads. In the lower half of the figure, it is evident that by the 11 minute post-smoking interval the amplitude of the peak alpha responses at both O1 and O2 have started to rebound as shown by an increase in some of the subjects, compared to their baseline levels. Figure 5 shows that soon after smoking the peak alpha frequency was generally increased by an average of 0.7 Hz at both the O1 and O2 leads. ANOVA results for this frequency increase indicated a significant main effect for condition [$F(2,36)=30.37$, $p<.001$], but not for lead. Post-hoc *t*-tests revealed that this increase was significant for both O1 and O2 leads at the 2 minute time point, [$t(9)=3.95$, $p<.01$, for O1 and ($t(9)=4.54$, $p<.01$ for O2]. Eleven minutes after the termination of the smoking period there was still a trend of a slight increase in peak frequency at both leads (average for population = 0.2 Hz) which failed to reach significance.

-INSERT FIGURE 4 HERE-

-INSERT FIGURE 5 HERE-

3. FM Theta

An FMT response appeared at Fz during pre-nicotine RMD and Tetris tasks in 6 of the 10 subjects. An analysis of the 6 subjects who had clear FMT peaks both before and after smoking indicated that the peak frequency of the FMT, measured at the Fz site, increased by an average of 0.56 Hz [$t(5)=4.53$, $p<.01$], from 6.1 Hz to 6.6 Hz. As table 4 shows, all subjects who manifested FMT demonstrated a post-smoking increase in peak

frequency of FMT. In contrast to previous investigations of traditional theta, there was no significant decrease in amplitude in the post-smoking FMT.

-INSERT TABLE 4 HERE-

4. Delta

The average delta power which appeared during the pre-smoking cognitive task condition was found to be decreased by approximately 70% during the post-smoking cognitive task. In accordance with Knott et al.(1996), who found no interaction between decreases in delta power and electrode location during a post-smoking resting condition, we examined the decrease in delta power both by region (frontal, central, parietal) and by hemisphere, and similarly found no regional differences. Therefore, the smoking related decrease in delta power which occurred during cognitive task, seems to be similar to that found previously during resting conditions (Table 5).

-INSERT TABLE 5 HERE-

AEP Results

The AEPs elicited to the rare tones were averaged across subjects in order to obtain the average P300 response. Figure 6 shows the difference between the group averaged auditory P300 which occurred during the baseline (AEP I) and that which was seen during the post-smoking (AEP III) condition. Because the P300 response in our subjects was maximal at the Pz site as expected (Sutton, 1965), only the data from this site was examined in our analysis. An examination of Figure 6 suggests that while the early regions of the auditory response (0-150 msec.) were similar between the baseline and post-smoking conditions, two later components showed smoking related changes. Although the P200 response appears larger after smoking, this peak was not submitted to a statistical analysis because, in contrast to P300, it was often characterized by complex morphology with multiple peaks. Additionally, this peak was often absent in one or both conditions, and was characterized by an inadequate morphology to merit a more formal analysis in consideration of the small number of subjects contained in this study. The P300 demonstrated a well defined peak which enabled unambiguous measurement. An

examination of P300 latency indicated that a mean decrease of 11 msec, from 341.2 to 330.2 (Table 6) in the average latency of this response was significant [$t(9)=2.37$, $p<.05$]. While a slight increase in P300 amplitude appears in the post-smoking condition, this did not reach significance. In fact, while the P300 response was larger in 6 subjects it had a smaller amplitude in the remaining 4 subjects (Table 6).

-INSERT FIGURE 6 HERE-

-INSERT TABLE 6 HERE-

VEP Results

Figure 7 shows the difference between the group averaged VEPs during the baseline (VEP I & II) and post-smoking (VEP III) conditions. A slight augmentation in the N1 peak, and clear increases in the P1 and N2 peaks, can be seen after smoking. The averaged VEPs are shown to provide a general picture of smoking related changes which occurred in the individual components. However, for a more meaningful evaluation of smoking related changes in the VEP, each subject's post-smoking averaged VEP should be compared to that subject's baseline average. For example, when the VEP data were statistically compared using the individual subject data (Appendix 4a and 4b) the N1 peak demonstrated a small but significant increase in its latency after smoking (Table 7). This increase is not evident in Figure 7, in which it actually seems as if a slight decrease occurred. This disparity sometimes emerges in the averaged VEP of a population because small, but morphologically important components in the VEP, that indicate the actual peak of a component, become lost in the smoothing of data inherent in the averaging process.

-INSERT FIGURE 7 HERE-

-INSERT TABLE 7 HERE-

The group differences which existed between the baseline and post-smoking averaged VEPs are presented in Table 7. While the amplitude of P1 demonstrated a marked increase after smoking, the change in the latency of this component was not significant. The N2 peak, on the other hand, exhibited not only an increased amplitude, but also a decrease in its latency. The latency of the N1 peak was slightly delayed while the N2 component demonstrated a more rapid onset. Although not traditionally considered, the N1 and N2 changes in the VEP, when evaluated together, represent a decrease in the total duration of the primary VEP response. The N1-N2 interval may be physiologically significant since the duration of this component is about 100 msec, which is the approximate duration of the alpha cycle.

Discussion

Pomerleau and Pomerleau (1987) review a diverse pool of evidence that smokers can regulate nicotine intake to produce a psychopharmacological response appropriate to the current needs of the smoker, causing an increase in arousal in relatively low arousal environments and a decrease of arousal in stressful situations. In our study, during a set of relatively low arousal experimental conditions which occurred in the first two minutes after smoking, subjects showed alpha power decreases and frequency increases which are EEG measures that are thought to be correlated with arousal and perceptual processing respectively (Norton et al. 1991, Varela et al. 1981, Dimpfel et al., 1993, Golding, 1988a). Additionally, all subjects who showed an FMT response, demonstrated an increase in the peak frequency of FMT. Additionally, evidence from evoked potential data supported the perceptual/cognitive enhancing properties of smoking. For example, both increases in amplitude, and decreases in latency, of the primary VEP component, as well as significantly reduced latency of the P300, appeared after smoking. Taken together, with the EEG data, these results provided additional converging evidence suggesting smokers were adept at gauging tolerance levels and obtaining the amount of nicotine that was required to produce increased arousal (increased VEP amplitude) and cognitive enhancement (decreased P300 latency). The increase in the peaks of the VEP are thought to be related to the non-specific, diffuse activation of pathways related to the perception of a stimulus as discussed by Woodson et. al. (1982). Further, P300 latency has been associated with cognitive processing partially due to studies which have found that shorter P300 latencies are normally accompanied by quicker reaction times (Donchin, 1981). In contrast to the relatively uniform changes observed in the alpha band (1-2 minutes post-smoking) and in FMT peak frequency, the heterogeneity of smoking related changes in both beta2 power, as well as the amplitude changes of the P300, demonstrated that considerable inter-subject differences also existed.

The increase in beta2 power was larger than previous reports have suggested. While this difference may be due in part to the incorporation of light smokers into the experimental design, and the measurement of the beta2 response in units of power (μV^2)

In contrast to previously reported increases of 2 Hz after smoking (Michel et al., 1989) and 3 Hz after nicotine gum (Pickworth et al., 1986) in the peak frequency of the beta1 band (13-20 Hz.), we found no consistent increase in the peak frequency after smoking. The time course of the beta2 response was also in conflict with some previous reports because in 5 subjects the beta2 response was still evident, although considerably reduced, even 11 minutes after the termination of smoking. This suggests a longer time course for the beta2 effect than the 7 minute estimate obtained by Pritchard (1995) and is more in line with the 10 to 20 minute duration reported by Hasenfratz et al. (1990).

The increase in narrow band beta2 should be investigated further, since little can be said in terms of its potential implications until the neurobiological effects of this activity are better understood. However, the fact that such a significant change occurred after smoking, and was still evident 11 minutes later, may provide insight into the addictive nature of smoking. If, during a typical day, a moderate smoker caused such an increase in the high frequency, synchronized activity of this neuronal region 15 times (once with each cigarette), then some type of compensatory response (e.g., downregulation of receptors) might occur in the region to which the afferents project. Since Pritchard has offered evidence that beta2 activation parallels the decreases in anxiety which accompany smoking, such compensatory responses might result in a chronically altered baseline state and could cause the deprived smoker to experience increased levels of anxiety. In line with this reasoning, studies have found that periods of increased stress, rather than withdrawal symptoms, are often the cause of smoking relapse (Pomerleau et al., 1991), implying that mechanisms for coping with stress may be inadequate in the smoker. Whether the proposed insufficiency of coping mechanisms was present prior to smoking, or may have been caused by a smoking induced downregulation of the beta2 system, should be addressed by future studies.

Lastly, an interaction between smoking status (moderate or light smoker) and beta2 increase did not reach significance. While Hasenfratz et al. (1990) noted a relationship between increased beta2 response and heavy smoking based upon nicotine intake, nicotine measures were not available in the present study. In consideration of both the small subject number, as well as the fact that the moderate smokers in this study did

not necessarily smoke more than the lighter smokers during the experimental session, this result should not be interpreted as conflicting with previous findings.

The appearance of FMT in 6 of the 10 subjects was similar to previous studies which have found that FMT only occurs in about half of all subjects. In contrast to investigations which have examined smoking related changes in theta (Pritchard, 1991; Herning et al., 1983; Golding, 1988), subjects in the present study did not display a decrease in the amplitude of FMT in the post-smoking Tetris task. In fact, during the this interval, FMT emerged in two of the subjects who had failed to show FMT previously. This finding was consistent with reports of FMT augmentation after exposure to anxiolytics (Mizuki et al., 1986). Additionally, FMT in the post smoking period demonstrated sharper spectral peak, suggesting a more restricted timing of the neuronal generator responsible for this rhythm.

The smoking related change in the peak frequency of FMT, which occurred in the 6-7 Hz range during cognitive task, is different from previous reports such as those which have found increases, from 4.5 to 5.5 Hz , during EC post-smoking periods (Knott, 1988; Michel et al., 1989). Additionally the FMT data presented here differ from the non-significant increase (in the 4.0 to 5.0 Hz range) in theta frequency which had previously been found after 4.0 mg. nicotine gum, during an EC resting condition (Pickworth et al., 1986). While FMT was only measured at Fz, previous studies used an index of theta frequency which combined data from all leads or relied only on posterior leads. Therefore, changes in both amplitude and frequency were found for FMT that were unique from the changes in traditional theta power reported by previous studies.

The increases in FMT peak frequency suggest that a smoking related enhancement of cognitive processing occurs after smoking. In an excellent review (Basar-Eroglu et al., 1992), the evidence both for and against cortical-hippocampal interplay as reflected by theta activity has been examined. While coherence and phase relationships between hippocampal and cortical theta have been investigated, it is still uncertain whether or not the theta activity in the frontal regions is associated with theta activity in the hippocampus. If frontal theta is found to be associated with that of the hippocampus, then the smoking

related shift in FMT rhythm is indicative of an acceleration of a structure that is known to be central to cognitive processing, memory, and attention.

Studies previously examining delta power during post-smoking resting conditions have reported decreases that were similar to those found in this study (Kadoya et al., 1994a; Knott, 1988a; Robinson et al., 1992a; Pritchard, 1991a; Golding, 1988a), while reports of increases are rare (Norton et al., 1992). Smoking related changes in delta power have not been examined during mental tasks in prior studies.

In line with EEG changes, the evoked potential data generally suggested a smoking related enhancement of covariants of cognitive processing. The high variability between baseline I and II in the AEP recordings was not expected. Possibly this variance was due to a fluctuating baseline arousal state, which may have been caused by the requirement that subjects refrain from coffee before the experimental procedure. Additionally, subjects may have been slightly fatigued during the AEP II recording since they had already spent nine minutes attending to relatively dull stimuli, and trying not to blink, before this recording was obtained. In comparing AEP III to AEP I, the analysis reverted back to the traditional procedure of comparing the post-smoking data to only one baseline condition.

While a significant decrease in the latency of the P300 was found, mixed results were obtained for amplitude, with the population being almost equally split between an augmentation or a decrease after smoking. The failure of smoking to produce changes in P300 amplitude has been reported by others (Hasenfratz et al., 1989). Although these are the only findings which were submitted to formal analysis, it is appropriate to discuss the general features of the AEP which were present before and after smoking. The post-smoking AEP's were often characterized by a complex morphology with multiple peaks which made a comparison between the AEP's, that were elicited in response to the common tones, inappropriate. In fact, increases in the complexity and number of components of the post-nicotine AEP was so striking that it should be noted as an effect of smoking and possibly understood in relation to models of ERP's which suggest that increased complexity (shown by an increase in number of deflections over time) is associated with increased cognitive capacity (Weiss, 1992; Liberson, 1994). Additionally,

although the decrease in the latency of the P300, found at the Pz site, suggests increased processing speed, anterior regions manifested both P200 and P3a peaks that often indicated that a more complex set of smoking related changes had occurred. For example, in some subjects, anterior sites demonstrated either increases in the latencies of peaks occurring in the 200 to 400 msec interval, the emergence of new peaks, or changes in the shape and area of the previously existing peaks. While in line with reports of smoking related decreases in the latency of the VEP (Edwards et al., 1985), the decreased latency of the posterior P300 is in contrast to studies which have failed to find any smoking related changes in the auditory P300 (Norton et al.,1991; Hasenfratz et al., 1989). Thus, our results should be interpreted cautiously given the conflicting literature and the concurrent abundance of electrophysiological changes which fail to clearly support either an increase or decrease in the speed of processing stimuli.

In contrast to the AEP data, the VEP demonstrate good stability over the two baseline conditions and showed clear smoking related changes, for example, all subjects showed a smoking related decrease in the N1-N2 interval. In combination with the changes which occurred in the alpha and theta bands, the VEP data lend additional support to the finding that our subjects were characterized by an overall increase in arousal and enhancement of cognitive/perceptual processing following smoking. These results are in accordance with the increase in the amplitude of the early components of the VEP which have been found with other stimulants such as caffeine (Lorist et al., 1994; Lorist et al., 1995).

The novel measurement of the N1-N2 interval may be interpreted as representing a decrease in the total duration of the primary VEP response which may be relevant to the time it takes for the visual system to respond to an incoming stimulus. This change may also be physiologically significant since the duration of this interval is about 100 msec, which is the approximate duration of the alpha cycle. Therefore, the fact that nicotine actually increased the latency of the N1 peak, suggesting smoking related decrease in perceptual processing time, may be secondary to the observation that nicotine acts to shorten the full N1-N2 cycle.

The definitions used to describe the peaks of Table 7 diverge from the conventional nomenclature of the *flash* elicited VEP peaks, in which the N1-P1-N2 peaks are defined differently. Since previous reports of smoking related changes in the VEP have used flash, rather than checkerboard, stimuli an attempt to relate the present findings to the previous work requires a reconciliation of the distinct terminologies. Woodson et. al. (1982) reported smoking related changes in VEP components that were characterized by a similar morphology, but by an opposite polarity, and were referred to as peaks IV, V, and VI, respectively. Others have obtained smoking related changes in VEPs that were less similar in shape, but of similar polarity, as peaks V-VI-VII (Hall et al., 1973). Independent of the terms used to name these peaks, the amplitudes of the VEP peaks in this time range have been generally attributed to arousal level. These previous studies found significant increases in the amplitudes of these VEP components, but no differences in latency, suggesting that an increase in arousal but, not necessarily in processing speed, had occurred (Woodson et al., 1982; Hall et al., 1973). In contrast, Golding (1988), who defined the VEP peaks as we did, failed to find smoking related change in either the amplitude or latency of the VEP components elicited by flash stimuli.

The failure by previous studies to obtain changes in VEP latency may have been due to several factors, including a reliance on absolute rather than peak-to-peak measures (Golding, 1988). Table 7 shows that the measurement of relative rather than absolute latencies caused an increase in the statistical significance of the changes seen after smoking. Additionally, smoking has often been shown to produce its most noticeable effects during relatively difficult perceptual or cognitive tasks. For example, Hall et al. (1973) found that smoking related changes in amplitude occurred only for the weakest flash stimuli used, suggesting that smoking selectively enhances the perception of weak stimuli. Further, the VEP response to critical flicker fusion, which entails a perceptually difficult task using stimuli which appear close to threshold levels, has been reported to be modified even 20 minutes after smoking (Philips, 1971). Accordingly, while the flash stimulus is relatively intense and easily processed, the lower intensity of reversing checkerboard stimulus may have enabled more subtle changes to appear.

This study provides a much needed examination of smoking related EEG changes produced in a more moderate population of smokers than has previously been examined. While it may have clarified several reasons why previous studies did not obtain results supporting a smoking related increase in arousal and cognition, new questions have appeared. Why does smoking produce an extremely large change in the beta2 band in some smokers while not in others? What is the source of the beta2 power which manifested itself at the Cz site? The results strongly suggest that an appropriately designed PET or FMRI study, using several beta "producers" and several subjects who fail to show a large beta2 increase, might be an important component in formulating a model of smoking. Further, the incorporation of 10 subjects drawn from the heavy smoking populations traditionally relied upon should be tested in a VEP condition identical to that used in this study in order to discover whether the checkerboard VEP is better at detecting smoking related changes than the flash VEP. Data from 10 additional subjects has already been collected and is presently being analyzed in order to provide additional support for the findings reported here.

References

Arcavi, L., Jacob, P. 3., Hellerstein, M., & Benowitz, N. L. (1994). Divergent tolerance to metabolic and cardiovascular effects of nicotine in smokers with low and high levels of cigarette consumption. Clinical Pharmacology & Therapeutics, 56(1), 55-64.

Ashton, H., Marsh, V. R., Millman, J. E., Rawlins, M. D., Telford, R., & Thompson, J. W. (1980). Biphasic dose-related responses of the CNV (contingent negative variation) to I.V. nicotine in man. British Journal of Clinical Pharmacology, 10, 579-589.

Basar-Eroglu, C., Basar, E., Demiralp, T., & Schurmann, M. (1992). P300-response: possible psychophysiological correlates in delta and theta frequency channels. A review. [Review]. International Journal of Psychophysiology, 13, 161-179.

Benowitz, N. L., Jacob, P. 3., Jones, R. T., & Rosenberg, J. (1982). Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. Journal of Pharmacology & Experimental Therapeutics, 221(2), 368-372.

Brandt, M. E., Jansen, B. H., & Carbonari, J. P. (1991). Pre-stimulus spectral EEG patterns and the visual evoked response. Electroencephalography & Clinical Neurophysiology, 80, 16-20.

Bringmann, A., & Klingberg, F. (1995). Behavior-dependent and drug-induced changes of rat visual evoked potential: relation to the EEG spectral power. Neuropsychobiology, 31, 89-97.

Bruneau, N., Roux, S., Guerin, P., Garreau, B., & Lelord, G. (1993). Auditory stimulus intensity responses and frontal midline theta rhythm. Electroencephalography & Clinical Neurophysiology, 86, 213-216.

Clubley, M., Bye, C. E., Henson, T. A., Peck, A. W., & Riddington, C. J. (1979). Effects of caffeine and cyclizine alone and in combination on human performance, subjective effects and EEG activity. British Journal of Clinical Pharmacology, 7, U57-63.

Cohen, C., Pickworth, W. B., Bunker, E. B., & Henningfield, J. E. (1994). Caffeine antagonizes EEG effects of tobacco withdrawal. Pharmacology, Biochemistry & Behavior, 47, 919-936.

Cohen, J. D., MacWhinney, B., Flatt, M., & Provost, J. (1993). PsyScope: A new graphic interactive environment for designing psychology experiments. Behavioral Research Methods, Instruments & Computers, 25(2), 257-271.

Conrin, J. (1980). The EEG effects of tobacco smoking--a review. [Review]. Clinical Electroencephalography, 11, 180-187.

Dimpfel, W., Schober, F., & Spuler, M. (1993). The influence of caffeine on human EEG under resting conditions and during mental loads. Clinical Investigator, 71, 197-207.

Domino, E. F., & Matsuoka, S. (1992). Effects of tobacco smoking on the topographic EEG-II. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 16, 463-482.

Domino, E. F., & Matsuoka, S. (1994). Effects of tobacco smoking on the topographic EEG-I [published erratum appears in Prog Neuropsychopharmacol Biol Psychiatry 1994 Dec;18(8):iii]. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 18, 879-889.

Donchin, E.(1981) Surprise!....surprise? Psychophysiology,18, 493-513.

Edwards, J. A., Wesnes, K., Warburton, D. M., & Gale, A. (1985). Evidence of more rapid stimulus evaluation following cigarette smoking. Addictive Behaviors, 10, 113-126.

Fernandez, T., Harmony, T., Rodriguez, M., Reyes, A., Marosi, E., & Bernal, J. (1993). Test-retest reliability of EEG spectral parameters during cognitive tasks: I. Absolute and relative power. International Journal of Neuroscience, 68, 255-261.

Foulds, J., McSorley, K., Sneddon, J., Feyerabend, C., Jarvis, M. J., & Russell, M. A. (1994). Effect of subcutaneous nicotine injections of EEG alpha frequency in non-smokers: a placebo-controlled pilot study. Psychopharmacology, 115, 163-166.

Gilbert, D. G., Robinson, J. H., Chamberlin, C. L., & Spielberger, C. D. (1989). Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie. Psychophysiology, 26, 311-320.

Golding, J., & Mangan, G. L. (1982). Arousing and de-arousing effects of cigarette smoking under conditions of stress and mild sensory isolation. Psychophysiology, 19, 449-456.

Golding, J. F. (1988). Effects of cigarette smoking on resting EEG, visual evoked potentials and photic driving. Pharmacology, Biochemistry & Behavior, 29, 23-32.

Haire-Joshu, D., Morgan, G., & Fisher, B. (1991). Determinents of cigarette smoking. Smoking Cessation, 12(4), 711-725.

Hall, R. A., Rappaport, M., Hopkins, H. K., & Griffen, R. (1973). Tobaco and Evoked Potential. Science, 180, 212-215.

Hasenfratz, M., Michel, C., Nil, R., & Battig, K. (1989). Can smoking increase attention in rapid information processing during noise? Electrocortical, physiological and behavioral effects. Psychopharmacology, 98, 75-80.

Hasenfratz, M., Nil, R., & Battig, K. (1990). Development of central and peripheral smoking effects over time. Psychopharmacology, 101, 359-365.

Hasenfratz, M., Baldinger, B., & Battig, K. (1993a). Nicotine or tar titration in cigarette smoking behavior? Psychopharmacology, 112, 253-258.

Hasenfratz, M., Baldinger, B., & Battig, K. (1993b). Nicotine or tar titration in cigarette smoking behavior? Psychopharmacology 112(2-3):253-8,

Hashimoto, M., Mukasa, H., Yamada, S., Nakamura, J., & Inanaga, K. (1988). Frontal midline theta activity and platelet MAO in human subjects. Biological Psychiatry, 23, 31-43.

Herning, R. I., Jones, R. T., & Bachman, J. (1983). EEG changes during tobacco withdrawal. Psychophysiology, 20, 507-512.

Hori, T., Hayashi, M., Oka, M., Agari, I., Kawabe, K., & Takagi, M. (1994). Re-examination of arousing and de-arousing effects of cigarette smoking. Perceptual & Motor Skills, 78, 787-800.

Inouye, T., Shinosaki, K., Iyama, A., Matsumoto, Y., & Toi, S. (1994). Moving potential field of frontal midline theta activity during a mental task. Brain Research Cognitive Brain Research, 2, 87-92.

Itil, T. M., Ulett, G. A., Hus, W., Klingenberg, H., & Ulett, J. A. (1971). The effects of smoking widhdrawal on quantitatively analyzed EEG. Clinical Electroencephalography, 2(1), 44-51.

James, J. R., & Nordberg, A. (1995). Genetic and environmental aspects of the role of nicotinic receptors in neurodegenerative disorders: emphasis on Alzheimer's disease and Parkinson's disease. [Review]. Behavior Genetics, 25, 149-159.

John, E. R., & Easton, P. (1995). Quantitative electrophysiological studies of mental tasks. Biological Psychology, 40, 101-113.

Juergens, E., Roesler, F., Hennighausen, E., & Heil, M. (1995). Stimulus induced gamma oscillations: harmonics of alpha activity? Neuroreport, 6, 813-816.

Kadoya, C., Domino, E. F., & Matsuoka, S. (1994a). Relationship of electroencephalographic and cardiovascular changes to plasma nicotine levels in tobacco smokers. Clinical Pharmacology & Therapeutics, 55, 370-377.

Kadoya, C., Domino, E. F., & Matsuoka, S. (1994b). Relationship of electroencephalographic and cardiovascular changes to plasma nicotine levels in tobacco smokers. Clinical Pharmacology & Therapeutics, 55, 370-377.

Karniski, W., Blair, R. C., & Snider, A.D. (1994) An exact statistical method for comparing topographic maps, with any number of subjects and electrodes. Brain Topography, 6(3), 203-210.

Knott, V. J. (1985). Effects of tobacco and distraction on sensory and slow cortical evoked potentials during task performance. Neuropsychobiology, 13, 136-140.

Knott, V. J. (1986). Tobacco effects on cortical evoked potentials to task stimuli. Addictive Behaviors, 11, 219-223.

Knott, V. J. (1988). Dynamic EEG changes during cigarette smoking. Neuropsychobiology, 19, 54-60.

Knott, V. J. (1989). Brain electrical imaging the dose-response effects of cigarette smoking. Neuropsychobiology, 22, 236-242.

Knott, V. J., & Harr, A. (1996). Assessing the Topographic EEG Changes Associated with Aging and Acute/Long-Term Effects of Smoking. Neuropsychobiology, 33, 210-222.

Liberson W.T. (1994). Mapping of somato-sensory evoked potentials (SEP): new findings suggesting the role of brain waves as a "temporal analyzer of the stimulus". Electromyography & Clinical Neurophysiology, 34, 23-8 .

Lorist, M. M., Snel, J., & Kok, A. (1994). Influence of caffeine on information processing stages in well rested and fatigued subjects. Psychopharmacology, 113, 411-421.

Lorist, M. M., Snel, J., Mulder, G., & Kok, A. (1995). Aging, caffeine, and information processing: an event-related potential analysis. Electroencephalography & Clinical Neurophysiology, 96, 453-467.

Meador, K. J., Loring, D. W., Abney, O. L., Allen, M. E., Moore, E. E., Zamrini, E. Y., & King, D. W. (1993). Effects of carbamazepine and phenytoin on EEG and memory in healthy adults. Epilepsia, 34, 153-157.

Michel, C., & Battig, K. (1989). Separate and combined psychophysiological effects of cigarette smoking and alcohol consumption. Psychopharmacology, 97, 65-73.

Mizuki, Y., Tanaka, M., Isozaki, H., Nishijima, H., & Inanaga, K. (1980). Periodic appearance of theta rhythm in the frontal midline area during performance of a mental task. Electroencephalography & Clinical Neurophysiology, 49, 345-351.

Mizuki, Y., Hamasaki, J., Hirano, H., Miyoshi, A., Yamada, M., & Inanaga, K. (1986). Effects of centrally acting drugs on the frontal midline theta activity in man. Japanese Journal of Psychiatry & Neurology, 40, 647-653.

Mizuki, Y., Suetsugi, M., Imai, T., Kai, S., Kajimura, N., & Yamada, M. (1989). A physiological marker for assessing anxiety level in humans: frontal midline theta activity. Japanese Journal of Psychiatry & Neurology, 43, 619-626.

Mizuki, Y., Kajimura, N., Kai, S., Suetsugi, M., Ushijima, I., & Yamada, M. (1992). Differential responses to mental stress in high and low anxious normal humans assessed by frontal midline theta activity. International Journal of Psychophysiology, 12, 169-178.

Montgomery, L. D., Montgomery, R. W., & Guisado, R. (1995). Rheoencephalographic and electroencephalographic measures of cognitive workload: analytical procedures. Biological Psychology, 40, 143-159.

Norton, R., Howard, R., & Brown, K. (1991). Nicotine dose-dependent effects of smokng on P300 and mood. Medical Science Research, 199, 355-356.

Norton, R., Brown, K., & Howard, R. (1992). Smoking, nicotine dose and the lateralisation of electrocortical activity. Psychopharmacology 108(4):473-9,

Oken, B. S., & Chiappa, K. (1986). Statiscal Issues Concerning Computerized Analysis of Brainwave Topography. Neuroscience Letters, 19(5):493-4,

Philips, C. (1971). The EEG changes associated with smoking. Psychophysiology, 8, 64-74.

Pickworth, W. B., Herning, R. I., & Henningfield, J. E. (1986). Electroencephalographic effects of nicotine chewing gum in humans. Pharmacology, Biochemistry & Behavior, 25, 879-882.

Plant, G. T., Zimmern, R. L., & Durden, K. (1983). Transient visually evoked potentials to the pattern reversal and onset of sinusodal gratings. Electroencephalography & Clinical Neurophysiology, 56, 137-158.

Pomerleau, C. S., & Pomerleau, O. F. (1987). The effects of a psychological stressor on cigarette smoking and subsequent behavioral and physiological responses. Psychophysiology, 24, 278-285.

Pomerleau, O. F., & Pomerleau, C. S. (1991). Research on stress and smoking: progress and problems. British Journal of Addiction, 86, 599-603.

Pomerleau, O. F., Hariharan, M., Pomerleau, C. S., Cameron, O., & Guthrie, S. (1993). Differences between smokers and never-smokers in sensitivity to nicotine: a preliminary report. Addiction, 88, 113-118.

Pritchard, W. S. (1991). Electroencephalographic effects of cigarette smoking. Psychopharmacology, 104, 485-490.

Pritchard, W. S., Robinson, J. H., deBethizy, J. D., Davis, R. A., & Stiles, M. F. (1995). Caffeine and smoking: subjective, performance, and psychophysiological effects. Psychophysiology, 32, 19-27.

Robinson, J. H., Pritchard, W. S., & Davis, R. A. (1992). Psychopharmacological effects of smoking a cigarette with typical "tar". Psychopharmacology 108(4):466-72,

Roth, N., Lutiger, B., Hasenfratz, M., Battig, K., & Knye, M. (1992). Smoking deprivation in "early" and "late" smokers and memory functions. Psychopharmacology, 106, 253-260.

Rugg, M. D., & Dickens, A. M. (1982). Dissociation of alpha and theta activity as a function of verbal and visuospatial tasks. Electroencephalography & Clinical Neurophysiology, 53, 201-207.

Schacter, D. L. (1977). EEG theta waves and psychological phenomena: a review and analysis. Biological Psychology, 5, 47-82.

Schellenberg, R., Todorova, A., Dimpfel, W., & Schober, F. (1995). Pathophysiology and psychopharmacology of dementia--a new study design. I. Diagnosis comprising subjective and objective criteria. Neuropsychobiology, 32, 81-97.

Schnider, A., Gutbrod, K., & Hess, C. W. (1995). Motion imagery in Parkinson's disease. Brain, 118, 485-493.

Schober, F., Schellenberg, R., & Dimpfel, W. (1995). Reflection of mental exercise in the dynamic quantitative topographical EEG. Neuropsychobiology, 31, 98-112.

Schober, F., Schellenberg, R., & Dimpfel, W. (1995). Reflection of Mental Exercise in the Dynamic Quantitative Topographical EEG. Pharmocoelectroencepholgrapy, 31, 98-112.

Spekreijse, H., van der Tweel, L. H., & Zuidema, T. (1973). Contrast evoked responses in man. Vision Research, 13, 1577-1601.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. Science, 150, 1187-1188.

Takii, O. (1986). Diurnal rhythm in appearance of frontal midline theta activity. Japanese Journal of Psychiatry & Neurology, 40, 609-615.

Thatcher, R. W., Krause, P. J., & Hrybyk, M. (1986). Cortico-cortical associations and EEG coherence: a two-compartmental model. Electroencephalography & Clinical Neurophysiology, 64, 123-143.

Tucker, D. M., Dawson, S. L., Roth, D. L., & Penland, J. G. (1985). Regional changes in EEG power and coherence during cognition: intensive study of two individuals. Behavioral Neuroscience, 99, 564-577.

Varela, F. J., Toro, A., John, E. R., & Schwartz, E. L. (1981). Perceptual framing and cortical alpha rhythm. Neuropsychologia, 19, 675-686.

Walter, D. O., Rhodes, J. M., Brown, D., & Adey, W. R. (1966). Comprehensive spectral analysis of human EEG generators in posterior cerebral regions. Electroencephalography & Clinical Neurophysiology, 20, 224-237.

Weiss, V. (1992). The relationship between short-term memory capacity and EEG power spectral density. Biological Cybernetics, 68, 165-172.

Woodson, P. P., Baettig, K., Etkin, M. W., Kallman, W. M., Harry, G. J., Kallman, M. J., & Rosecrans, J. A. (1982). Effects of nicotine on the visual evoked response. Pharmacology, Biochemistry & Behavior, 17, 915-920.

Yamamoto, S., & Matsuoka, S. (1990). Topographic EEG study of visual display terminal (VDT) performance with special reference to frontal midline theta waves. Brain Topography, 2, 257-267.

Table 1: Description of Experimental Conditions

Condition	Duration	Condition #	
Training Session	5.0 min		
Eyes Open/Eyes Closed	2.0 /2.0 min.	1	
Tetris*	1.5 min.	2	
Reverse Mirror Drawing (RMD)	1.5 min.	3	
VEP I (Checkerboard)	3.0 min.,180 trials,1 sec. ISI	4	
VEP II (Checkerboard)	3.0 min.,180 trials,1 sec. ISI	5	
AEP I (P300 = 1:4 probability)	3.0 min.,180 trials,1 sec. ISI	6	
AEP II (P300 = 1:4 probability)	3.0 min.,180 trials,1 sec. ISI	7	
3 minute break and then smoke cigarette			Time Post-Smoking
Eyes Open	1.0 min.	8	(0 -1 min)
Eyes Closed	1.0 min	9	(1 -2 min)
Tetris or RMD	1.5 min.	10	(2.5-4 min)
VEP III (Checkerboard)	2.3 min.,140 trials,1 sec. ISI	11	(4.5-6.8 min)
AEP III (P300 = 1:4 probability)	3.0 min.,180 trials,1 sec. ISI	12	(7.3-10.3 min)
Eyes Closed	1.0 min	13	(10.8 -11.8 min)
Eyes Open	1.0 min	14	(12.3 -13.8 min)

* Before acquiring EEG under mental load, subjects were allowed to practice playing Tetris and choose a level that they found to be challenging. Usually this took about five minutes.

Table 1: Description of experimental conditions and their times in relation to smoking. The inter-stimulus interval (ISI) was 1 second for both the VEP and AEP tasks. Additional details provided in the text.

Tables 2a and 2b: Individual Data for Beta2 Topological Distribution.

Table 2a.

Subject #	FP1	FP2	F3	F4	C3	C4	P3	P4	O1	O2	F7	F8	T3	T4	T5	T6	FZ	CZ	PZ
1	8.28	7.07	7.73	6.56	3.25	4.33	2.15	2.12	1.72	2	6.15	3.73	2.23	5.72	1.93	2.02	4.47	**24.55**	3.31
7	11.5	7.5	11.2	8.33	8.01	18.1	7.89	8.38	3.46	3.32	6.97	17.2	12.3	13.8	3.98	4.63	16.9	**48.23**	6.88
10	3.96	3.73	6.22	5.28	7.59	5	7.02	6.37	10.8	8.56	3.7	2.15	4.4	5.62	5.79	3.72	7.74	**48.7**	7.32
4	2.39	2.21	5.33	4.08	5.04	4.39	3.34	3.1	2.56	2.23	1.93	1.34	1.61	0.79	2.44	1.68	6.66	**55.65**	8.13
5	5.92	5.53	7.02	7.76	7.67	12.1	6.51	8.39	7.16	7.37	4.17	4.32	6.93	2.75	6.88	6.21	9.67	**28.19**	9.98
Average	**6.42**	**5.21**	**7.49**	**6.4**	**6.31**	**8.78**	**5.38**	**5.67**	**5.13**	**4.7**	**4.58**	**5.75**	**5.5**	**5.74**	**4.21**	**3.65**	**9.09**	**41.06**	**7.12**

Table 2b.

Subject #	FP1	FP2	F3	F4	C3	C4	P3	P4	O1	O2	F7	F8	T3	T4	T5	T6	FZ	CZ	PZ
1	33.7	28.8	31.5	26.7	13.2	17.6	8.8	8.7	7.0	8.2	25.0	15.2	9.1	23.3	7.9	8.2	18.2	**100.0**	13.5
7	23.9	15.5	23.1	17.3	16.6	37.5	16.4	17.4	7.2	6.9	14.5	35.7	25.6	28.7	8.3	9.6	35.1	**100.0**	14.3
10	8.1	7.7	12.8	10.8	15.6	10.3	14.4	13.1	22.1	17.6	7.6	4.4	9.0	11.5	11.9	7.6	15.9	**100.0**	15.0
4	4.3	4.0	9.6	7.3	9.1	7.9	6.0	5.6	4.6	4.0	3.5	2.4	2.9	1.4	4.4	3.0	12.0	**100.0**	14.6
5	21.0	19.6	24.9	27.5	27.2	42.9	23.1	29.7	25.4	26.2	14.8	15.3	24.6	9.7	24.4	22.0	34.3	**100.0**	35.4
Average	**18.2**	**15.1**	**20.4**	**17.9**	**16.3**	**23.2**	**13.7**	**14.9**	**13.3**	**12.6**	**13.1**	**14.6**	**14.2**	**14.9**	**11.4**	**10.1**	**23.1**	**100.0**	**18.6**

Tables 2a and 2b: In table 2a, beta2 power (μV^2) for all nineteen channels in the five subjects who showed large increases in the first 1-2 minutes after smoking. The distribution of beta2 power appears to be highly localized to the Cz site. In table 2b, the data is presented as percentages for all nineteen channels. Percentage was calculated by dividing the power at each electrode site by the power of the Cz site (x 100 for percentage) in the same individual. The beta2 power at the electrodes surrounding Cz is generally about 80% to 85% less than that found at the Cz site.

Table 3: Individual Data for Beta2 Power and Frequency at Cz.

Subject #	Baseline Frequency (Hz)	Post-Smoking Frequency (Hz)	Baseline Power (μV^2)	Post-Smoking Power (μV^2)	Post-Pre % Change Power (μV^2)	Post-Pre % Change Power (μV^2)
1	22	23	6.75	24.55	17.80	363.5
7	22	24	11.15	48.23	37.08	432.4
10	20	19	7.09	48.70	41.61	687.0
4	22	22	5.33	55.65	50.32	1044.4 *
5	22	22	13.73	28.19	14.45	205.2 *
6	19	20	2.07	3.22	1.16	156.2
3	18	16	11.61	8.94	-2.67	77.0
8	21	16	5.00	1.30	-3.69	26.1 *
9	17	16	3.61	2.59	-1.03	71.6
2	15	15	5.20	6.42	1.22	123.5

*=Moderate smokers

Table 3: Individual values for peak frequency in the beta2 band, both before and after smoking. A paired *t*-test (two-tailed probability) of the *frequency values* before and after smoking indicated that the values were not significantly different ($t(9)=.808$, $p=0.44$) suggesting the enhancement of a rhythm that exists during baseline rather than the emergence of a new rhythm. In subject 8 there is a 5 Hz difference between the baseline and post-smoking conditions. This subject is one of the five subjects who did not manifest a clear beta2 response after smoking.

Table 4: Individual Data for FMT Power and Frequency at Fz.

Subject #	Pre-Smoke Power (μV^2)	Pre-Smoke Frequency (Hz)	Post-Smoke Power (μV^2)	Post-Smoke Frequency (Hz)	Difference in Peak Frequency Frequency (Hz)
2	9.54	6.250	11.13	6.875	0.625
3	42.35	6.125	28.65	6.625	0.500
*4	13.42	6.500	12.94	6.875	0.375
6	51.61	6.250	59.26	7.000	0.750
7	129.93	6.500	142.07	6.625	0.125
9	10.82	5.000	13.16	6.000	1.000
Average	42.94	6.104	44.54	6.667	0.56
Std.	46.18	0.56	51.15	0.36	0.30

*=Moderate smokers.
Students-T for change in Power (*P* value at d.f.=5) = 0.34
Students-T for change in Frequency (*P* value at d.f.=5) = 0.003

Table 4: Changes in power and frequency of the FMT peak response in the six subjects who demonstrated FMT. FMT was defined as the maximum spectral peak that occurred between 4.125 and 7.50 Hz. Although the increase in FMT amplitude after smoking did not reach significance, this change is in contrast to the significant decrease in traditional theta reported previously.

Table 5: Differences in Delta Power During Cognitive Task.

Scalp Region		Baseline (μV^2)	Post-smoke(μV^2)	% of Pre-Smoke
Frontal	(F3,F4,Fz)	35.90	21.23	59 %
Central	(C3,C4,Cz)	27.70	20.23	72 %
Parietal	(P3,P4,Pz	25.97	18.16	69 %
Right	(F3,C3,P3,O1)	24.61	16.54	68 %
Left	(F4,C4,P4,O2)	24.29	16.50	70 %

Table 5: Generally about 70% of the pre-smoke delta power existed after smoking. A repeated measures ANOVA, 3 (electrode region) x 2 (pre-post) indicated that the decrease in delta power due to smoking was significant ($F(1,27) = 41.71$, $p < .001$), while the interaction between regions and delta decrease did not reach statistical significance. Post-hoc comparisons of each region (with Bonferroni correction) indicated the pre-post decrease in delta power was significant ($p < .01$) for each electrode region. Additionally, a 2 (hemisphere) x 2 (pre-post) ANOVA indicated that while the decrease for delta power was significant in each hemisphere ($F(1,18) = 29.15$, $p < .01$), the interaction between hemispheres and delta decrease did not reach significance. Post-hoc tests indicated significant decreases occurred in both hemispheres ($p < .01$).

Table 6: Individual Data for Amplitude and Latency of P300 at Pz

Subject #	P300 I (μV)	P300 II (μV)	P300 III (μV)
1	3.9	5.4	4.7
2	12	7.9	8.4
3	10.7	11.9	9.6
*4	10.5	9.5	2.8
*5	7.2	6.5	6.9
6	8.6	9.2	13.3
7	11.5	8.9	13.9
*8	11	11.5	11.3
9	11.2	7.2	17.5
10	6.5	2.7	7.5
Average	9.31	8.07	9.59
***t*-test (d.f.=9)**			0.890

Subject #	P300 I (msec.)	P300 II (msec.)	P300 III (msec.)
1	345.7	326.2	341.6
2	337.9	320.3	328.1
3	355.5	353.5	349.6
*4	345.8	349.6	328.1
*5	339.8	335.9	335.9
6	353.5	328.1	322.3
4	314.5	320.3	314.5
*8	355.5	361.3	357.4
9	355.5	359.4	314.5
10	308.6	330.1	310.3
Average	341.2	338.47	330.2
***t*-test (d.f.=9)**			0.041

*=Moderate smoker.

Table 6: Amplitude and latency data for the auditory P300 response before and after smoking. While on average there is a small increase in the amplitude of the P300, this is clearly not a uniform response in all subjects.

Table 7: Summary of Changes in VEP Before and After Smoking

	Lead	N1	P1	N2
ABSOLUTE LATENCY (msec)	O1	**3.42***	0.985	-6.285
	O2	**4.205***	-0.77	**-5.77***
ABSOLUTE AMPLITUDE (μV)	O1	-0.18	0.4	-0.31
	O2	0.085	0.935	-0.9
		N1-P1	P1-N2	N1-N2
PEAK-TO-PEAK INTERVAL (msec)	O1	**-2.435***	**-7.27***	**-9.705****
	O2	**-4.975****	**-5.0***	**-9.975****
PEAK-TO-PEAK AMPLITUDE (μV)	O1	0.58	0.71	-0.13
	O2	0.85	**1.835***	-0.985

**$p<.01$ *$p<.05$

Table 7: Difference between baseline (average VEP I & VEP II) average and post-smoking (VEP3) response to reversing checkerboard stimulus.

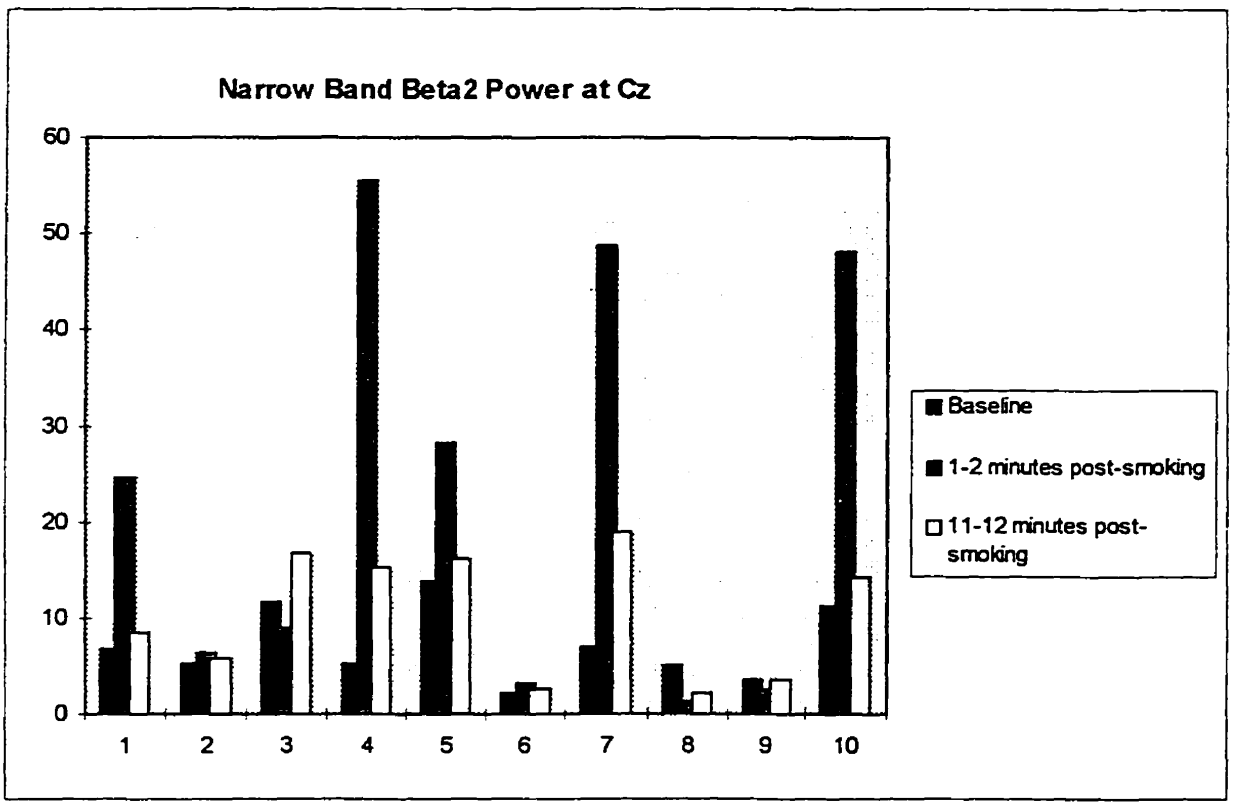


Figure 1: An increase in narrow band beta power can be seen for 7 of the 10 subjects in the first 2 minutes after smoking. In 5 of the subjects the increase is substantial. 11 minutes later this increase is still evident and has emerged in subject 3. Subjects 4, 5 and 8 were the more moderate smokers.

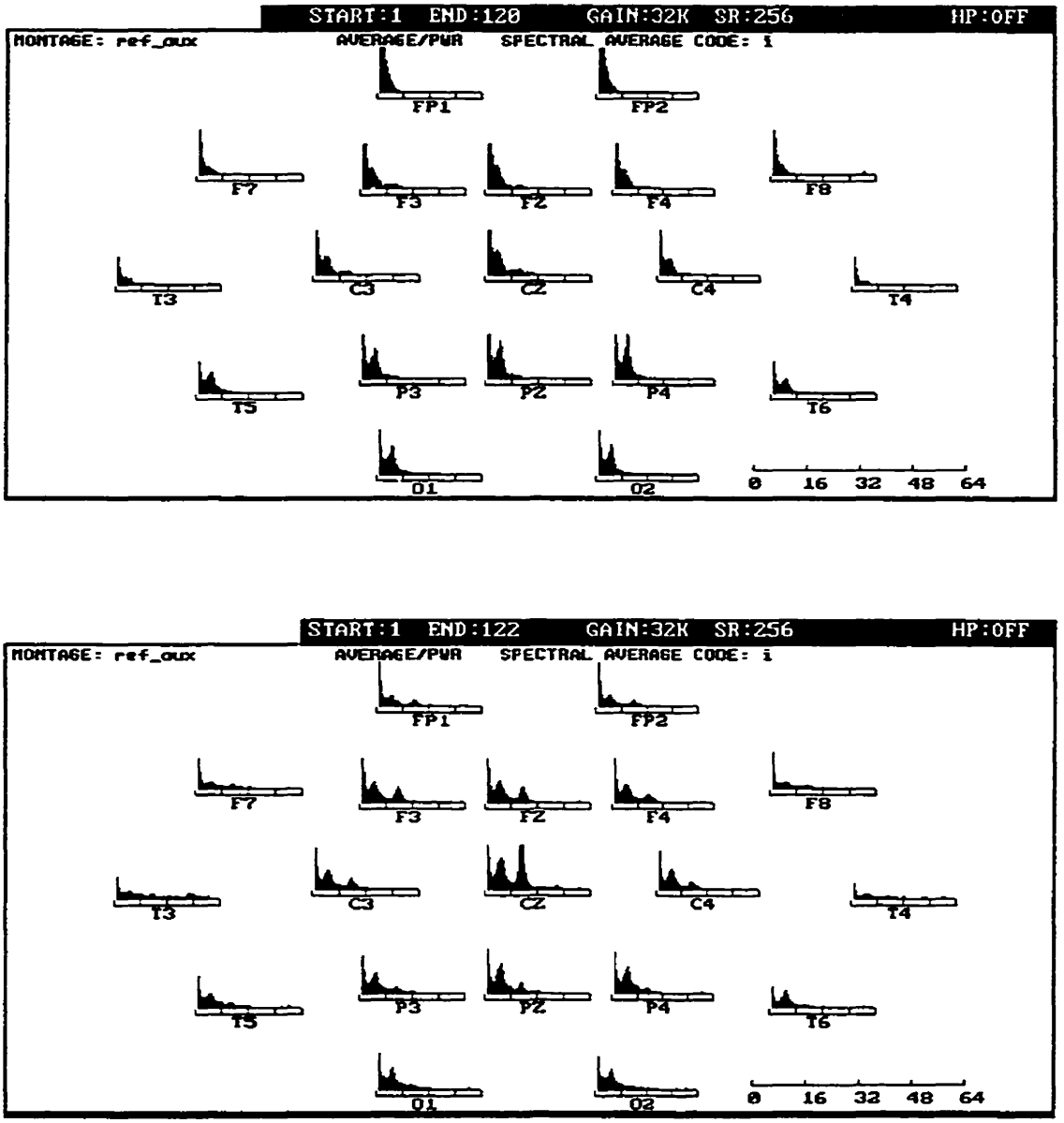
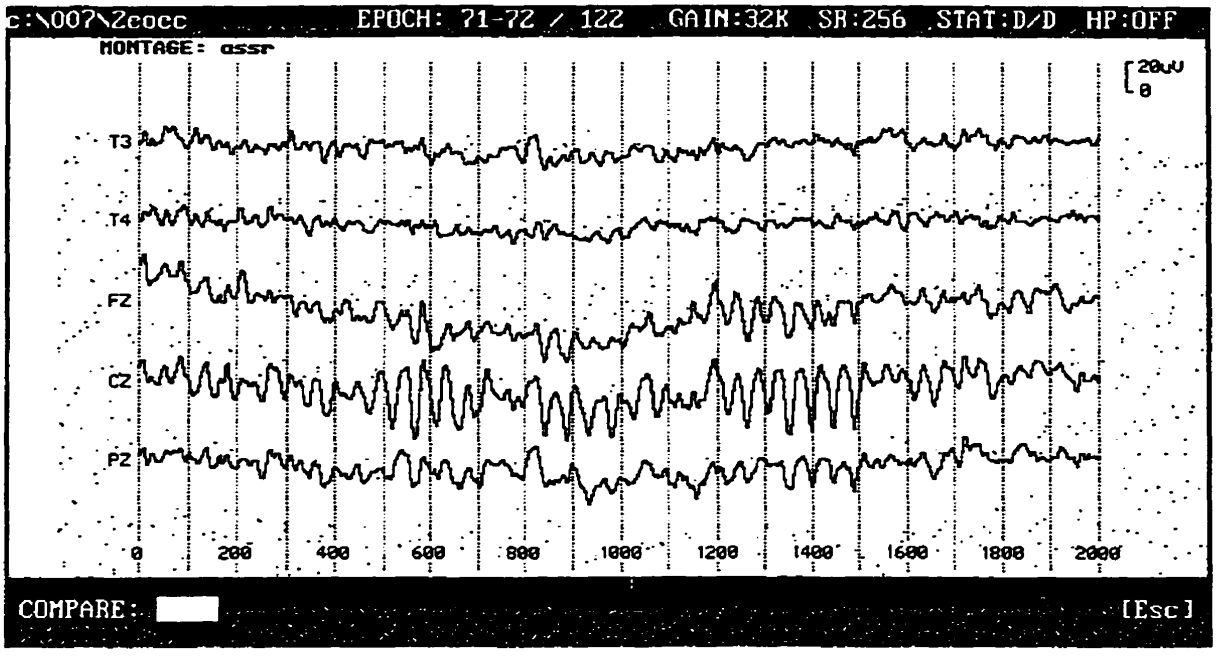


Figure 2: The top panel shows the frequency composition, at each lead, of 2 minutes of eyes open EEG that was recorded prior to smoking. The major spectral component of the EEG is the alpha rhythm which is biggest in the posterior regions. The bottom panel was derived from EEG that was recorded from the same subject during the first 2 minutes after smoking and contains the average spectral power computed from 1 minute of eyes open and 1 minute of eyes closed data. It is clear that the increased beta2 power, while demonstrating more power than the subject's alpha rhythm, is relatively restricted in its topographic distribution. Note the relatively narrow peak of the beta2 increase.



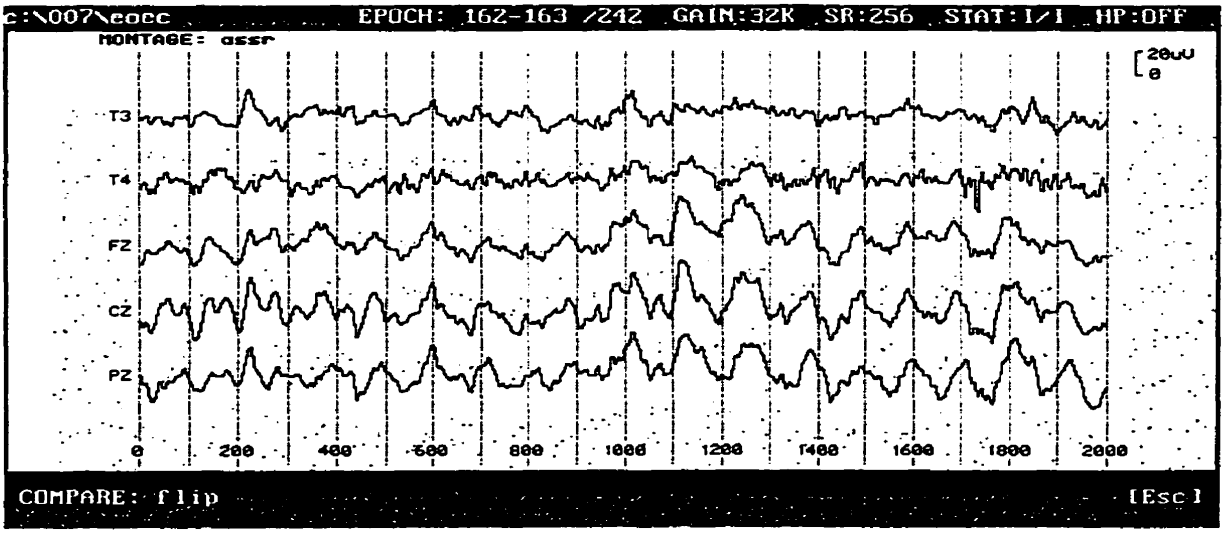
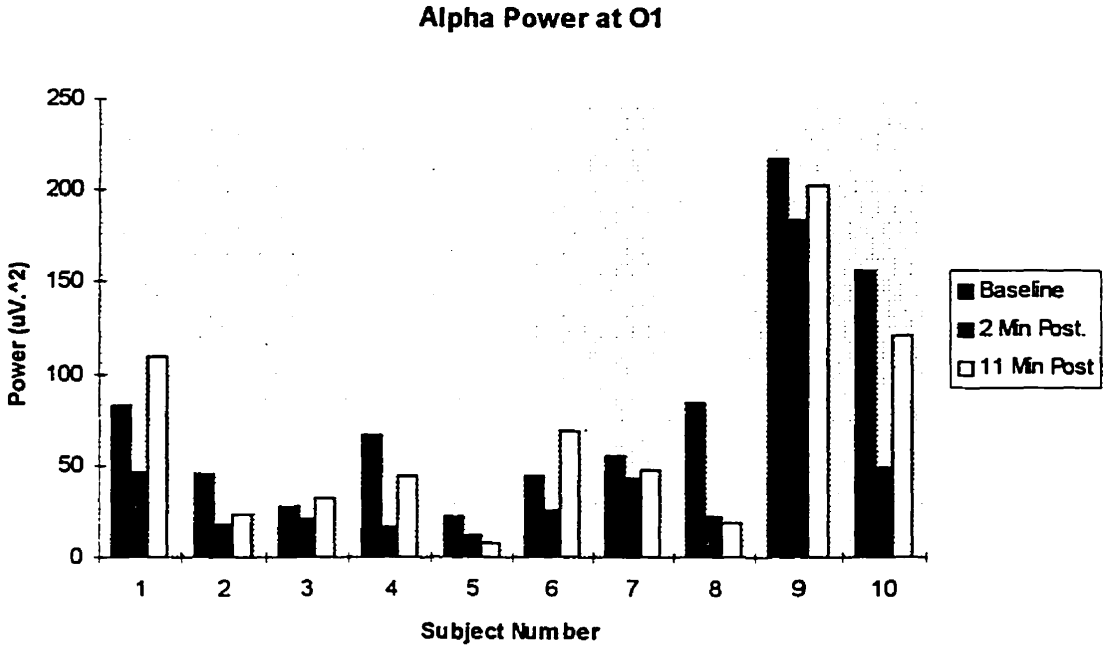


Figure 3: In the top panel, a large amplitude rhythm of about 25 Hz is clearly evident and highly localized to the Cz site, in the EEG of the EO condition collected 1-2 minutes after smoking. The bottom panel shows the same subject during the pre-smoking EC condition. Note that the magnitude of the beta2 rhythm in the top panel actually surpasses that of the alpha rhythm, during eyes closed, shown in the bottom panel.



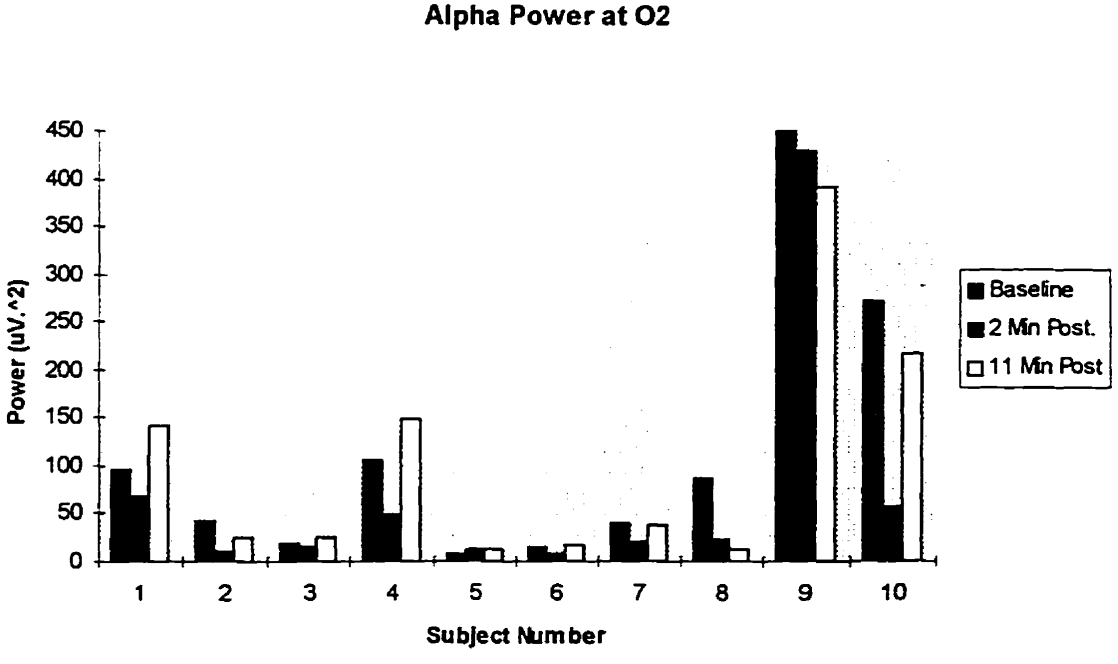


Figure 4: **Top**-Compared to pre-smoking baseline levels, almost every subject shows a decrease in alpha power at O1 during the first 2 minutes after smoking. By 11 minutes the alpha shows some rebound which in 3 subjects exceeds the baseline level. **Bottom**-. Data for O2. In subjects 4 and 6 the O1 and O2 leads suggest different levels of alpha decrease at the 11 minute timepoint. Subjects 4, 5 and 8 were the more moderate smokers.

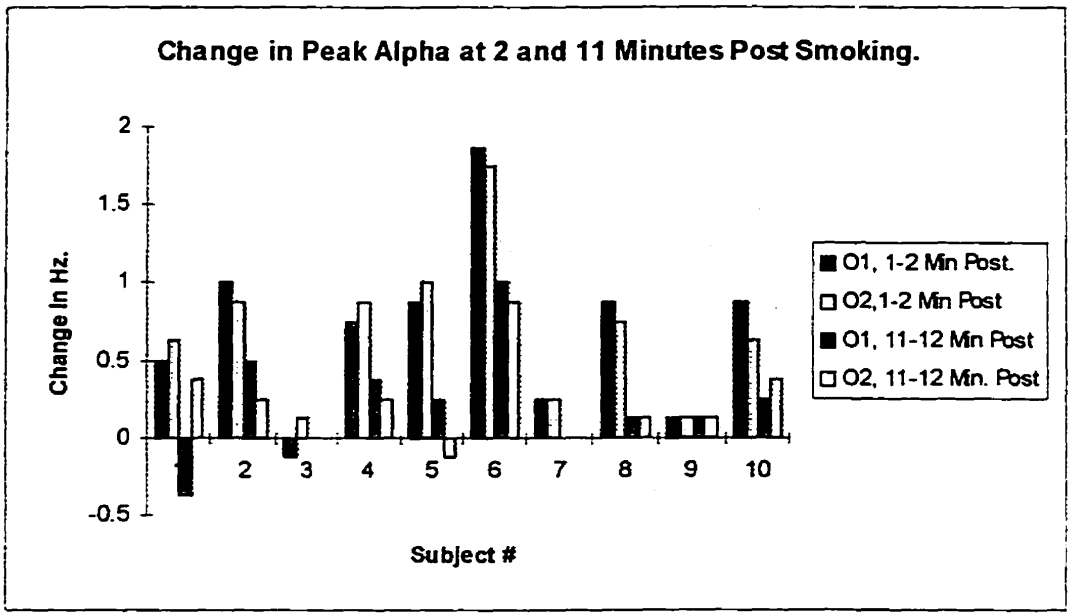


Figure 5: The increase in peak frequency of the alpha rhythm can be found in almost every subject, during the 1-2 minute interval with eyes closed. Eleven minutes later, when the amplitude of the peak alpha response has begun its rebound, frequency still appears to be increased, supporting separate time-courses for amplitude and frequency.(note: missing bars = no difference from baseline values). Subjects 4, 5 and 8 were the more moderate smokers.

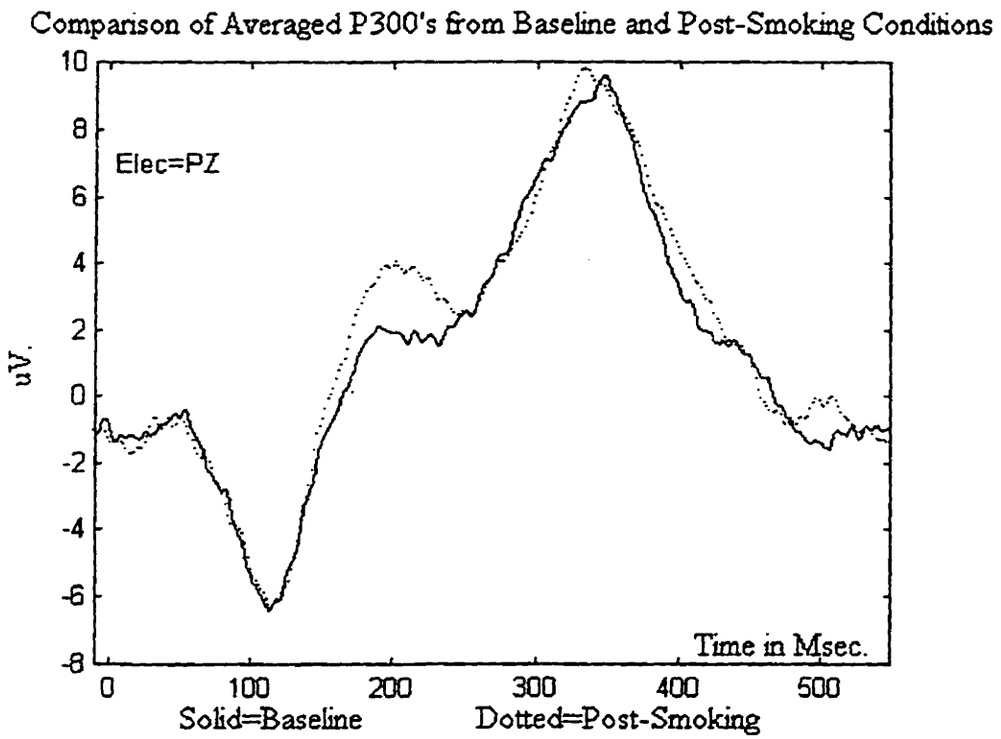


Figure 6: Mean smoking related changes in the auditory P300 response at the Pz site across 10 subjects. The baseline AEP average was calculated from baselines I, while the post-smoking average was collected during roughly the 7-10 minute interval which followed the end of the cigarette. Amplitude units are in μV., with positive up.

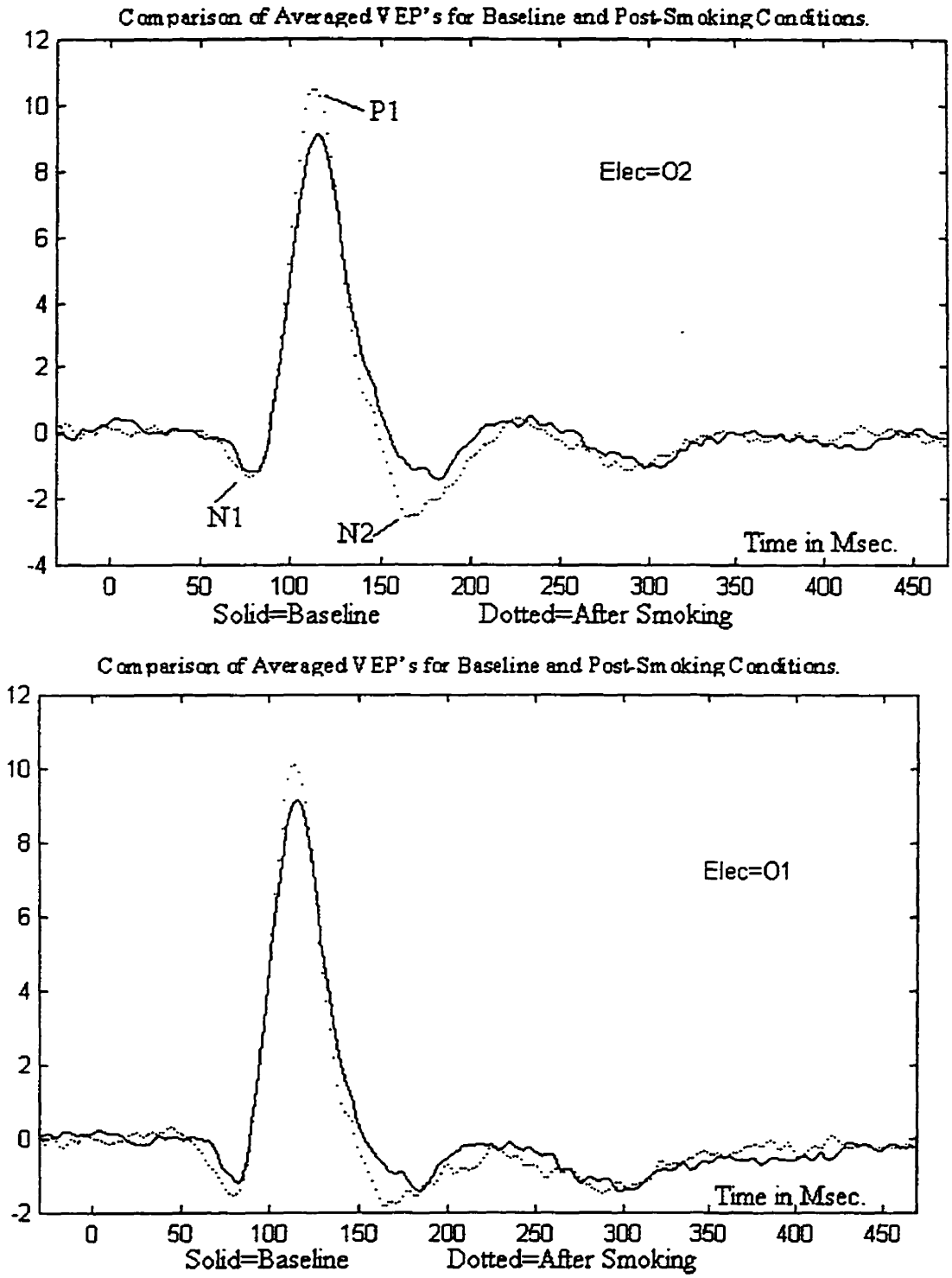


Figure 7: Mean smoking related changes in the checkerboard VEP for O1 and O2 sites across 10 subjects. The baseline VEP average of the VEP's collected during baselines I and II, while the post-smoking average was collected roughly during the 4-7 minute interval which followed the end of the cigarette. Amplitude units are in μV., with positive up.

Appendix 1: Delta Activity and Cognition.

When delta power is present during the *resting state* it is often related to brain damage (when it is focal), eye activity (when it has a front to back distribution), drowsiness, or disorders such as Alzheimer's (Schellenberg et al., 1995). However, increases in delta also seem to be an attribute of healthy cognitive processing (Tucker et al., 1985; Meador et al., 1993). Unlike the delta which is produced by eye movement, increased delta power during cognitive tasks may show an asymmetry of power (task minus baseline) and may not be localized to frontal areas (Tucker et al., 1985; Fernandez et al., 1993). Schober et al. (1995) found graduated increases, both in amount of absolute delta and theta power and in the cortical area manifesting activity in these bands, that corresponded to the increasing demands of 4 cognitive tasks. These task related increases have been noted by others (Schacter, 1977). A considerable discussion of the neurobiological origins and functional roles of task induced delta activity is provided by Fernandez et al. (1993) who draw upon several lines of evidence suggesting that delta acts as a focusing mechanism, but this goes beyond the scope of this thesis.

Task induced increases in delta power have been found to be diminished in cognitively impaired individuals. Schellenberg et al. (1995) compared the QEEG responses of normal subjects and those suffering from dementia and noted that while an increase in delta power was evident during various mental tasks, this increase was smaller in the latter group. Interestingly, the increase was found in the frontal and posterior leads while the central leads were relatively unchanged, suggesting that the delta activity was not propagating, via the cortex, between the two regions. Other investigators have also found this topographical distribution in normal subjects under a variety of cognitive tasks (Schober et al., 1995). Neuroanatomical structures that might mediate these results are the various neuronal pathways which have previously been shown to cause posterior and anterior regions of the head to manifest a greater degree of coherence while central-midline areas, which do not show the associated changes in delta activity, may be separately engaged by sub-cortical structures such as the thalamus (Thatcher et al., 1986). Therefore, coherent delta power may serve a role in the communication between the frontal cortex and posterior regions.

Appendix 2: Theta, Frontal Midline Theta (FMT), and Posterior Theta

Theta

In an often cited review, Schacter (1977) discusses the paradoxical findings concerning the nature of the theta rhythm. The initial report of theta waves was made by Walter and Dovey in 1944, who noted the activity in patients with sub-cortical tumors. During the period between 1950 and 1970, considerable research by two schools of investigators furthered our understanding of this rhythm. One line of investigation provided ample evidence that theta was linked to a decrease in the vigilance state, while another set of experiments demonstrated a strong connection between theta and cognitive, as well as perceptual, processing.

Evidence linking theta to drowsiness came from studies showing that a low voltage theta occurred diffusely throughout the cortex during periods of drowsiness, and in the hypnogogic state. This "theta-drowsiness" was accompanied by increased reaction times and was thought to signify a decrease in awareness of the environment. Additionally, sleep deprivation studies showed both that theta prevalence increased with the length of deprivation and, during intervals of increased theta, subjects were more likely to produce incorrect responses in "detection" type tasks.

Alternatively, it was also demonstrated that theta was increased during problem-solving, perceptual processing, learning, and memory tasks. The earliest reports of cognitive induced theta has been attributed to research done in the early 1950's by Arelano and Schwab, and Mundy-Castle who reported increased theta during mental arithmetic. An increasing amount of evidence has recently suggested that theta abundance is related to task performance, as long as the task is relatively challenging. As Schacter notes, an interesting distinction between alpha and theta activity has been made by several authors. While alpha becomes reduced in a stepwise fashion as soon as a subject is engaged by a cognitive task, the amount of theta that appears is related to the difficulty of the task and increases as the amount of selective attention required by the subject is increased. In addition to studies examining problem solving, a link between theta and selective attention has also been support by studies involving solely perceptual processing. Shacter reviews this latter issue and provides evidence from several studies that have

shown increases in the abundance of frontal-central theta which were related to the complexity of a stimulus.

FMT

In the early 1970's Ishiharan and Yoshii began to expand upon the early evidence provided by Arellano and Schwab, and investigated a type of theta that was induced during mental tasks such as serial addition and intelligence tests. They reported an activity that tended to occur in the higher theta range, between six and seven hertz, and was clearly separate from background EEG activity, demonstrating a magnitude of between 30-69 μV. They termed this activity frontal midline theta due to its topological distribution.

Over the years, several differences between theta and FMT have been uncovered which support a model in which these rhythms are considered as two separate phenomena. For example, "traditional" theta may often be smaller than FMT and has been found to occur in only one-third of subjects during rest while FMT can be elicited in about half the population during mental load (Mizuki et al., 1980). While both theta and FMT may occur in the frontal-central midline region just anterior to the vertex, theta often occurs diffusely throughout the cortex during resting conditions and may span from 3.5 to 7 Hz. FMT can be elicited in subjects that normally do not show theta under resting conditions and often includes activity, that is primarily in the 6-7 Hz range. Lastly, while the theta often occurs during rest in a semi-continuous fashion, FMT may occur in bursts as short as 1 second in duration.

Much of the work on FMT has been accomplished by Japanese investigators who have clarified many of its characteristics (Mizuki et al., 1989; Mizuki et al., 1992; Mizuki et al., 1986; Hashimoto et al., 1988). While EEG is increasingly analyzed using the power spectrum in current literature, research on the FMT has often maintained a reliance on the measures used early on in the Japanese studies and, consequently, the data are often quantified in terms the amount of time that the FMT was present (percent occurrence or "abundance"). Due to the different methods of quantifying the EEG, some of the inconsistency of results concerning the relationship between theta activity and cognition

are caused by what different investigators mean as "theta increase." The current tendency of EEG investigators is to rely heavily upon the power spectrum as a means of obtaining a quantifiable description of electrophysiological activity. The power spectrum yields an estimate of the power over a set of frequencies for each electrode. While *theta power* measures the size of an electrical field that oscillates at particular frequency, *percentage theta* concerns the total amount of time in which theta was the dominant frequency of the EEG. While theta power may yield a large estimate, even when only several epochs contain theta, percentage theta does not distinguish between a 50 and 100 μV signal, and only measures the duration of the signal's presence. Each of these measures has its own advantages. In the following review of the FMT literature the reader is reminded that the studies often examine percent occurrence of the FMT rather than theta power.

FMT has been elicited under a variety of cognitive tasks such as serial addition or subtraction, or tasks which often have a strong sensory-motor component such as reverse mirror drawing, or the detection of targets (Yamamoto et al., 1990). Yasushi et al. (Mizuki et al., 1980) examined FMT during various mental tasks, such as a five minute serial addition task. FMT did not appear in any of the subjects during a five minute baseline that occurred prior to the task. Additionally, three types of subjects were identified. In 11 of the 30 subjects examined, bursts of FMT that lasted for more than one second could not be found (non-FMT responders). Of the remaining subjects, seven exhibited a large amount of FMT (LFMT) on a semi-continuos basis, while 12 manifested only periodic (PFMT) bursts that were 1-7 seconds in duration. The PFMT was found to occur at approximately 40 second intervals over the five minute testing period with a peculiar absence during 120-190 seconds after the start of the task. The amount of EEG characterized by PFMT accounted for about one-fifth of the entire recording period. No correlation was found between the amount of FMT that was induced by the arithmetic task and either the amount of task performed or number of errors. The authors reconcile the lack of correspondence between performance and performance induced FMT by suggesting that the simplicity of the addition task produced too small a range of performance differences for any underlying correlation to emerge. In line with Yasushi,

the ease of the task has been suggested by others as being responsible for their failure to find a correlation between FMT and task performance measures (Takii, 1986).

FMT, Personality, and Emotional State

Several studies have found that differences in personality and emotional state are involved in the characteristics of the FMT in individuals. FMT was more likely to be markedly evident in subjects who were extroverted, less neurotic and less anxious (Mizuki et al., 1986). Accordingly, studies have also shown that within the individual, pharmacologically induced graduated decreases in anxiety (as measured by anxiety questionnaires), are associated with similar increases in appearance of the FMT (Mizuki et al., 1989; Mizuki et al., 1986). FMT increases have also been shown following the ingestion of alcohol, presumably due to its anxiolytic properties. Although these studies found that FMT was related to anxiety level rather than task performance, it should be obvious that the design of this study suffers from the fact that the drugs used to reduce anxiety (e.g., alcohol) may have also impaired cognitive ability, thereby requiring the subject to concentrate harder to achieve the same level of performance.

Further evidence which relates FMT to emotion and the underlying physiological traits responsible for the general emotional state of subjects was found when, FMT, induced by a mental arithmetic task, was shown to vary as a function of platelet monoamine oxidase (MAO) activity (Hashimoto et al., 1988). Subjects EEG and personality/emotion trait and state profiles were obtained on 3 occasions that were separated by 2 week intervals. At the end of the third session blood was drawn for MAO analysis. Both FMT and extroversion showed evident decreases as platelet MAO activity increased. In the context prior evidence, supporting a positive correlation between MAO activity and anxiety, Hashimoto suggests his results provide further evidence of relationship between anxiety and FMT appearance.

Posterior Theta

More recently, Yamamoto et al. (1990) explored FMT using both a lexical search task presented visually, and a point and click operation entailing the rapid detection of a

target via a computer mouse. Each task consisted of 8 repetitions 15 minutes each. In each repetition, EEG was recorded during the 3-5 and 12-15 minute interval and both the power and the percentage time of EEG in the 3.4 to 7.8 Hz range was assessed. This study was different from the two just described in that it utilized a measure of FMT which included power recorded across the entire head, rather than just at Fz, in its calculation of FMT correlation with performance. The novel analysis provided by this study, which ignored the traditional definition of FMT, included a posterior FMT and measured power from 3.4 to 7.8 rather than merely 6-7 Hz activity. Some of the findings were based on measurements relating to activity in the posterior regions, where the FMT is traditionally not examined (possibly because most investigators feel there is some validity to the term FMT). Because posterior leads were considered and because the band utilized included activity up to 7.8 Hz, the contribution of the slower components of the alpha rhythm, which have been shown to increase with some types of cognitive tasks (Schober et al., 1995), may have contributed to the findings of this study.

Although it may not be particularly relevant to FMT, Yamamoto's report of a correlation between posterior theta and task difficulty has been supported by the findings of several other authors. Using only the left and right parietal locations (P3, P4), Rugg et al. (1982) found that while alpha merely showed a decrease in amplitude during a verbal task and a visuospatial task, theta (especially at P4) showed an increase in power with increased task difficulty and performance. Additionally, Montgomery et al. (1995) found that the strongest relationship between theta power and mental arithmetic performance occurred at the P3 and P4 sites. John et al. (1995) found a strong relationship between coherence of Pz-P4 narrow band theta (3.8-4.2) and task difficulty. Others have also found a similar increase in coherence (Walter et al., 1966)

Summary

It is important to remind ourselves of the paradoxical nature of the theta rhythm reviewed by Shacter and to attempt to distinguish between the different types of activity presently classified under the term theta since researchers are still somewhat confused as to the limits of the current definitions. Yamamoto's discussion of a type of frontal midline

theta, which was related to the difficulty of a cognitive task, but only in the posterior regions of the head, should properly raise a red flag. The data reviewed lend support to a model in which theta abundance (% occurrence) in the frontal and central regions of the head, and theta power and coherence in the posterior regions, show a relation to the demands on selective attention imposed by various tasks. Diffuse cortical theta, on the other hand, seems to be increased either by cognitive task or drowsiness. Thus, while the percentage time occupied by FMT is increased by, but not necessarily correlated with, increasing mental load, theta power in posterior regions seems to be related to task difficulty. A classification of theta might rely on the division of theta into 3 different classes based upon specific topological differences: diffuse cortical theta, FMT, and posterior theta. While exceptions to this model will certainly emerge, it may serve as a useful framework for interpreting the various findings reported in the literature.

Appendix 3: Issues of Spectral Analysis

The FFT algorithm describes a times series in the frequency domain by decomposing it into set of continuous frequencies that are the components of the original signal. The FFT provides an estimate of the frequency composition of time series data with a frequency resolution that is inversely proportional to the number of seconds of data submitted for analysis, e.g., an 8 second window of data yields a spectral estimate with a frequency resolution of 0.125 Hz. (1/8 of a second). When the original signal consists of EEG rather than a set of ideal periodic data (e.g., sine waves), the success of the FFT in accurately transforming the data from the time into the frequency domain is influenced by the degree of stability (or "stationarity") of the component signals.

Knott (1988) examined changes in the peak frequency of the alpha band by performing FFT's on several 5 second recordings and was able to show that the peak alpha rhythm increased by 0.5 Hz after smoking. Although Knott successfully measured an increase in peak alpha frequency, using 5 continuous seconds of data can decrease the accuracy of the spectral analysis when the signal is unstable over the analyzed time period. Although the alpha rhythm is a relatively stable signal, it can reset its phase in response to blinking, changes in arousal, or due to internally or externally occurring events. This issue becomes more significant in the case of FMT (which often lasts for only 1 to 5 seconds) where using an 8 second data window for analysis almost certainly violates assumptions of stationarity.

Figures 1a and 1b show what may occur when non-stationary signals are submitted to the traditional FFT techniques. Figure 1a shows 6 signals that increase from 4.2 to 5.2 Hz in 0.2 Hz steps. Each signal lasts for 8 seconds and contains a jump of phase every second (2 seconds shown). Several characteristics of the corresponding frequency spectrum should be

noted. While each signal consists of a pure sine wave with an amplitude of 2 μV, which oscillates at a single frequency, the result of spectral analysis is comprised of multiple peaks. Not only is there no clear peak frequency, but the amplitudes of the spectral peaks are all below 2 μV, since the energy has been spread out over neighboring frequencies. Although a subject's alpha rhythm is usually not characterized by jumps in phase which occur as often as these model signals, other frequencies such as FMT frequently have a time course of only 1 or 2 seconds (Mizuki et al., 1992) and approximate the behavior of these illustrative signals. Failure by previous investigators to find consistent changes in amplitude or peak frequency of a particular EEG band could be explained by their failure to adjust their investigative approach to compensate for the brevity of the signal's occurrence. It should be evident from the spectral plots that a decrease in the power of the peak frequency of a band may be due to an increase in the number of phase jumps or reversals that occur over time, rather than necessarily representing an actual decrease in power.

Figure 1b shows the effects of a multiplying the signal by a Hanning window. By windowing the original signal, the effects of the phase jumps are smoothed because both the beginning and end of each 1-second signal is multiplied so that these regions approximate zero. Although the estimate of a mean frequency might be slightly more accurate than when no window is used, the underestimate of the original signal's power is still evident.

In order to increase the probability that the signal will be stationary over the period being analyzed, an eight second record can be broken into 8 one-second segments of the EEG which can separately be submitted to the FFT analysis. However, since the frequency resolution decreases in relation to the length of the data submitted, an FFT performed on one-second of EEG yields a spectral result with 1 Hz resolution. If an estimate of the

changes in peak frequency that might occur in FMT after smoking is based upon the size of the shifts which have been previously detected in the alpha band (0.5 Hz), then 1 Hz resolution is not specific enough to detect the changes in FMT peak frequency. In order to regain higher spectral resolution each one-second signal can be "padded" with seven seconds of zeros.

In this thesis, a method known as "zero padding" was used, as shown in Figure 1c. In zero padding, a one second signal is attached to or "padded" by a series of zeros. Since a resolution of .125 Hz was desired, 7 seconds worth of zeros were appended to the end of the signal. Because the additional zeros cause the FFT to underestimate the power of the actual frequencies that are present in the 1 second of signal, the spectral result is usually multiplied by a coefficient that is the reciprocal of the fraction of time occupied by actual non-zero data. Although the resulting spectral peak is wider than a spectral result that used 8 seconds of actual data (see 1d), the maximum value occurs at the signal's true frequency with no loss of power (i.e. the amplitude of the peak accurately registers 2 μV).

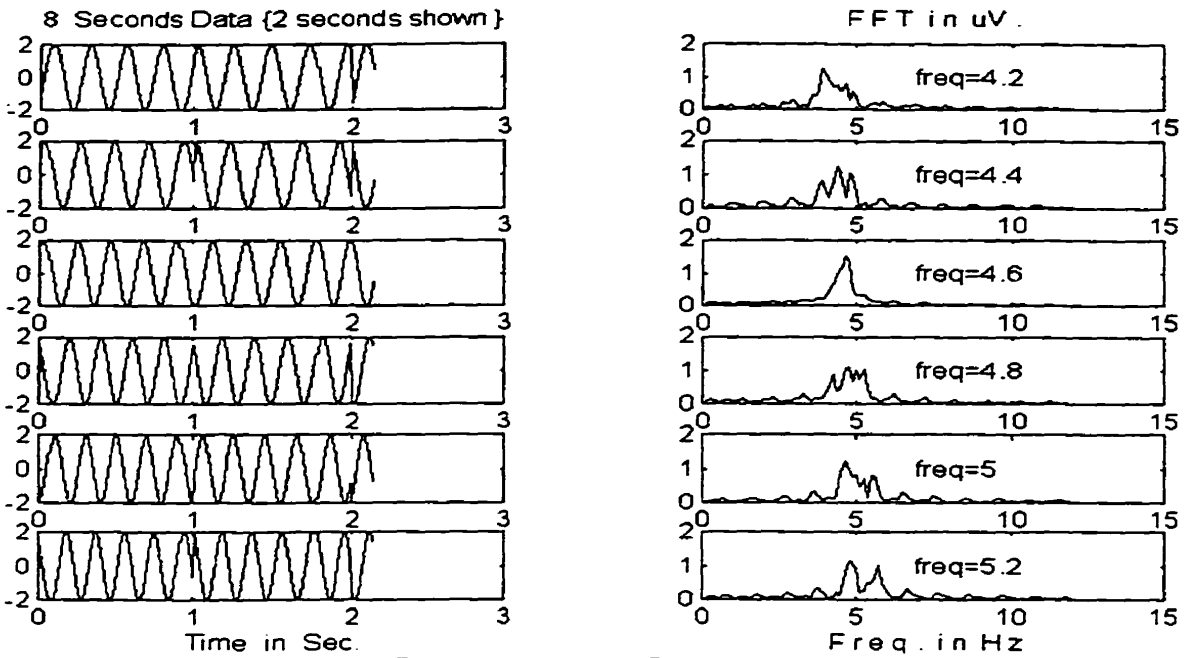


Figure 1a. Jumps in Phase

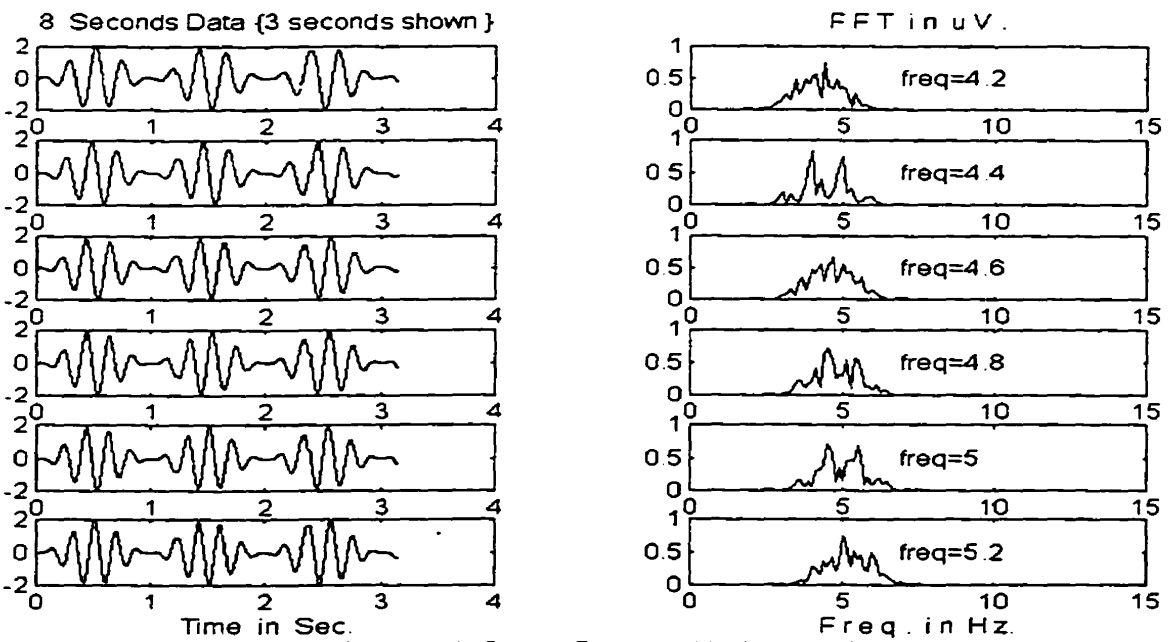


Figure 1b: Jumps in Phase Smoothed by Hanning Window

Figure 1a and 1b: The effect of phase shifting on the result of an FFT can be seen in 1a. Such jumps of phase can occur when a subject blinks and the alpha rhythm becomes temporarily blocked before resetting itself. Notice that when the frequency is 4.6, the spectral peak occurs close to 5 Hz. Additionally, the estimate of peak frequency is not very accurate due to multiple peaks. In 1b, the jumps of phase have each been smoothed by a Hanning window. Even with this aid in the transition between various phases, the FFT does not produce a reliable estimate of the signal's "true frequency."

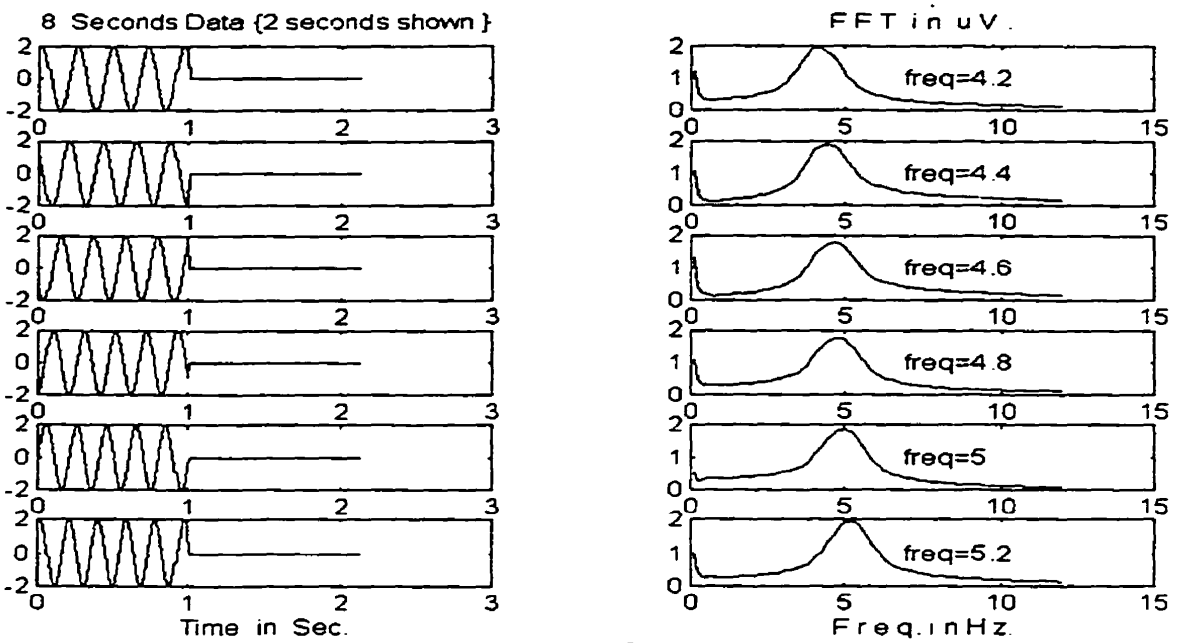


Figure 1c: 1 Sec. Data with 7 Sec. Zero Taper

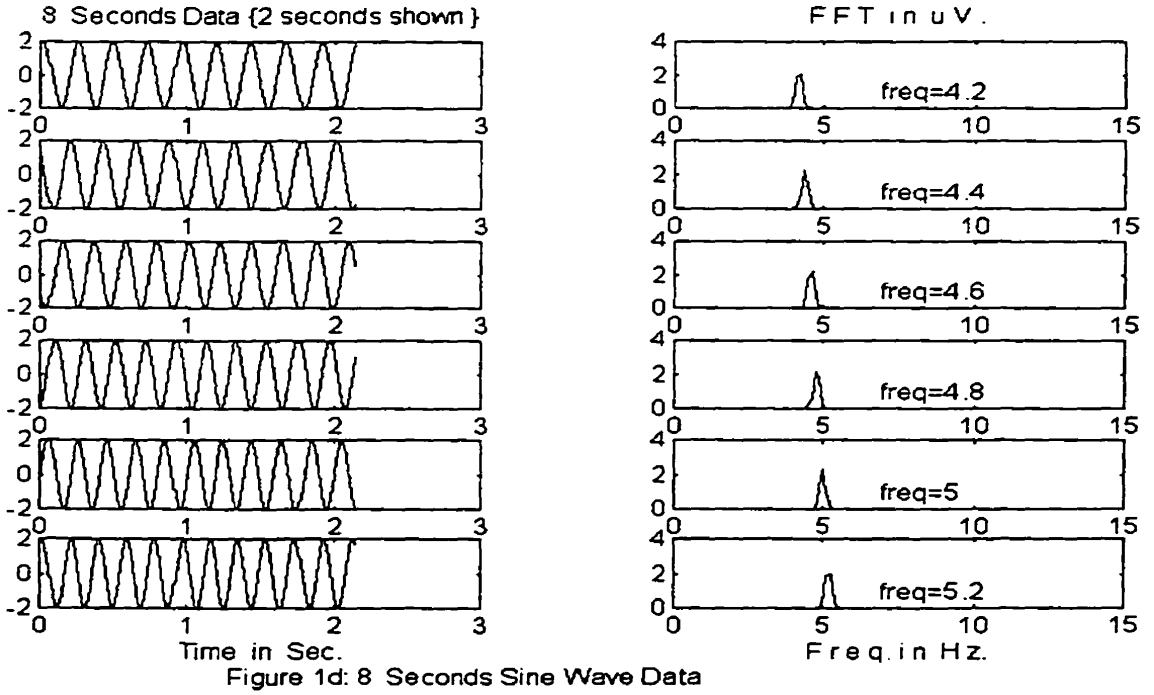


Figure 1d: 8 Seconds Sine Wave Data

Figures 1c and 1d: A technique known as "zero padding" is shown in 1c. The signal is padded with a series (e.g., 7 seconds) of zeros. This method forces the FFT to give its best estimate of peak frequency based on the data available. While the spectral peak is wide, its maximum reliably occurs at the true frequency. In 1d, the ideal case is shown, in which a full 8 seconds of the signal occurs in a pure, uninterrupted episode. The FFT produces the best results with this signal, showing a narrow peak centered about the signal's true frequency.

Introduction to Appendix 4a and 4b.

The following appendices give the individual data for the visual evoked potentials obtained during the two baseline conditions (VEP I, VEP II) and during the post-smoking period (VEP III). The average values for each electrode and each peak are given in order to demonstrate the variability of the measure both over time and between electrodes O1 and O2. The results of VEP III were compared to the average of the values obtained during the baseline conditions (VEPI+VEPII)/2. The results of paired *t*-tests (Bonferroni corrected) are found in the text of the thesis in Table 8. Appendix 4a includes the absolute values for amplitude and latency, while appendix 4b includes the relative amplitudes, and peak-to-peak (P-P) intervals. All latency data is in milliseconds and all amplitude is in microvolts. Subjects 4, 5 and 8 were the more moderate smokers.

Appendix 4a: Individual Data for Amplitude and Latency of VEP (Absolute).

N1 Latency Subject #	VEP I O1	VEP II O1	VEP I O2	VEP II O2	VEP (II - I) O1	VEP (II - I) O2	VEP III O1	VEP III O2	VEP III-((bI+bII)/2) O1	VEP III-((bI+bII)/2) O2
1	76.2	76.2	76.2	76.2	0.0	0.0	76.2	76.2	0	0
2	66.4	62.5	66.4	60.5	0.0	-2.0	64.5	64.5	0.05	1.05
3	68.4	70.3	66.4	68.4	-2.0	-1.9	74.2	74.2	4.85	6.8
4	64.5	64.5	64.5	68.4	0.0	3.9	68.4	68.4	3.9	1.95
5	74.2	74.2	64.5	74.2	-9.7	0.0	82	82	7.8	12.65
6	74.2	76.2	74.2	72.3	0.0	-3.9	76.2	76.2	1	2.95
7	74.2	76.2	74.2	74.2	0.0	-2.0	80.1	74.2	4.9	0
8	76.2	76.2	76.2	70.3	0.0	-5.9	76.2	76.2	0	2.95
9	64.5	62.5	68.4	62.5	3.9	0.0	74.2	76.2	10.7	10.75
10	78.1	80.1	76.2	78.1	-1.9	-2.0	80.1	80.1	1	2.95
Average	**71.7**	**71.9**	**70.7**	**70.5**	**-1.0**	**-1.4**	**75.2**	**74.8**	**3.420**	**4.205**
		Standard Dev. =			**3.5**	**2.6**	**Standard Dev. =**		**3.70**	**4.42**

P1 Latency Subject #	VEP I O1	VEP II O1	VEP I O2	VEP II O2	VEP (II - I) O1	VEP (II - I) O2	VEP III O1	VEP III O2	VEP III-((bI+bII)/2) O1	VEP III-((bI+bII)/2) O2
1	111.3	113.3	111.3	113.3	0.0	0.0	111.3	109.4	-1	-2.9
2	107.4	105.5	105.5	107.4	-1.9	1.9	103.5	103.5	-2.95	-2.95
3	99.6	109.4	101.6	107.4	2.0	-2.0	109.4	107.4	4.9	2.9
4	103.5	101.6	101.6	101.6	-1.9	0.0	103.5	99.6	0.95	-2
5	103.5	109.4	103.5	107.4	0.0	-2.0	107.4	105	0.95	-0.45
6	107.4	103.5	105.5	105.5	-1.9	2.0	107.4	107.15	1.95	1.65
7	115.2	119.1	115.2	121.1	0.0	2.0	117.2	117.2	0.05	-0.95
8	107.4	107.4	105.5	105.5	-1.9	-1.9	107.4	103.5	0	-2
9	93.8	95.5	97.7	97.7	3.9	2.2	101.6	99.6	6.95	1.9
10	107.4	111.3	107.4	109.4	0.0	-1.9	107.4	105.5	-1.95	-2.9
Average	**105.7**	**107.6**	**105.5**	**107.6**	**-0.2**	**0.0**	**107.6**	**105.8**	**0.985**	**-0.770**
		Standard Dev. =			**1.9**	**1.9**	**Standard Dev. =**		**3.01**	**2.20**

N2 Latency Subject #	VEP I O1	VEP II O1	VEP I O2	VEP II O2	VEP (II - I) O1	VEP (II - I) O2	VEP III O1	VEP III O2	VEP III-((bI+bII)/2) O1	VEP III-((bI+bII)/2) O2
1	193.4	195.3	191.4	193.4	-2.0	-1.9	179.7	179.7	-14.65	-12.7
2	185.5	175.8	187.5	173.8	2.0	-2.0	168	166	-12.65	-14.65
3	144.5	154.3	146.5	154.3	2.0	0.0	154.3	152.3	4.9	1.9
4	162.1	160.2	160.2	158.2	-1.9	-2.0	162.1	158.2	0.95	-1
5	152.3	164.1	152.3	164.1	0.0	0.0	144.5	152.3	-13.7	-5.9
6	160.2	175.8	160.2	173.8	0.0	-2.0	168	166	0	-1
7	162.1	162.1	162.1	160.2	0.0	-1.9	154.3	154.3	-7.8	-6.85
8	144.5	140.6	146.5	138.7	2.0	-1.9	140.6	142.6	-1.95	0
9	127.9	132.8	127	132.8	-0.9	0.0	130.9	130.9	0.55	1
10	177.7	171.9	177.7	171.9	0.0	0.0	156.3	156.3	-18.5	-18.5
Average	**161.0**	**163.3**	**161.1**	**162.1**	**0.1**	**-1.2**	**155.9**	**155.9**	**-6.285**	**-5.770**
		Standard Dev. =			**1.5**	**1.0**	**Standard Dev. =**		**8.16**	**7.25**

Appendix 4a: (continued).

N1 Amplitude					VEP	VEP			VEP III-	VEP III-
Subject #	VEP I	VEP II	VEP I	VEP II	(II - I)	(II - I)	VEP III	VEP III	((bI+bII)/2)	((bI+bII)/2)
	O1	O1	O2	O2	O1	O2	O1	O2	O1	O2
1	-2.6	-2.8	-3.4	-3.5	-0.2	-0.1	-2.8	-3.7	-0.1	-0.25
2	-1.2	-1.5	-0.9	-1.5	-0.3	-0.6	-1.1	-1.1	0.25	0.1
3	-1.2	-1.4	-0.2	-0.8	-0.2	-0.6	-1.7	-0.8	-0.4	-0.3
4	-1.1	-0.3	-0.7	-0.1	0.8	0.6	-0.4	0.2	0.3	0.6
5	-2.5	-1.4	-1.5	-0.4	1.1	1.1	-0.8	0.8	1.15	1.75
6	-4.5	-2.1	-7.1	-3.8	2.4	3.3	-6	-6	-2.7	-0.55
7	-3.8	-1.5	-3.2	-1.5	2.3	1.7	-2	-2	0.65	0.35
8	-2.8	-2.1	-1.3	-1.5	0.7	-0.2	-1.8	0	0.65	1.4
9	-0.7	-1.4	0.2	-0.4	-0.7	-0.6	0.3	0.9	1.35	1
10	-1.7	-2.8	-1.1	-2.6	-1.1	-1.5	-5.2	-5.1	-2.95	-3.25
Average	**-2.2**	**-1.7**	**-1.9**	**-1.6**	**0.3**	**0.1**	**-2.2**	**-1.7**	**-0.180**	**0.085**
		Standard Dev. =			**1.2**	**1.4**	**Standard Dev. =**		**1.49**	**1.39**

P1 Amplitude					VEP	VEP			VEP III-	VEP III-
Subject #	VEP I	VEP II	VEP I	VEP II	(II - I)	(II - I)	VEP III	VEP III	((bI+bII)/2)	((bI+bII)/2)
	O1	O1	O2	O2	O1	O2	O1	O2	O1	O2
1	16.9	14	14.4	13.4	-2.9	-1.0	16	15.2	0.55	1.3
2	13.2	11.6	13.8	12.3	-1.6	-1.5	12	12.9	-0.4	-0.15
3	8.7	8.8	7.6	7.9	0.1	0.3	9.6	8.9	0.85	1.15
4	11.9	12.1	12.8	13.4	0.2	0.6	13.5	15.4	1.5	2.3
5	8.5	8.7	8	9.3	0.2	1.3	8.3	7.7	-0.3	-0.95
6	13.8	13.5	15.1	16	-0.3	0.9	16.1	19.4	2.45	3.85
7	8.3	6.9	7.7	6.8	-1.4	-0.9	6.7	6	-0.9	-1.25
8	10.4	11.9	9.5	10.9	1.5	1.4	11.5	11.3	0.35	1.1
9	8.2	7.3	6.9	6.2	-0.9	-0.7	7.5	8.2	-0.25	1.65
10	3.4	5.3	3.4	4.9	1.9	1.5	4.5	4.5	0.15	0.35
Average	**10.3**	**10.0**	**9.9**	**10.1**	**-0.4**	**0.1**	**10.6**	**11.0**	**0.400**	**0.935**
		Standard Dev. =			**1.4**	**1.1**	**Standard Dev. =**		**1.00**	**1.52**

N2 Amplitude					VEP	VEP			VEP III-	VEP III-
Subject #	VEP I	VEP II	VEP I	VEP II	(II - I)	(II - I)	VEP III	VEP III	((bI+bII)/2)	((bI+bII)/2)
	O1	O1	O2	O2	O1	O2	O1	O2	O1	O2
1	-5.4	-9.2	-4.6	-7.9	-3.8	-3.3	-5.9	-7.5	1.4	-1.25
2	-2.5	-3.2	-1.5	-2.9	-0.7	-1.4	-5.1	-4.7	-2.25	-2.5
3	-3.5	-4	-3	-3.5	-0.5	-0.5	-5.1	-4.7	-1.35	-1.45
4	-2.8	-3.8	-3.5	-4.7	-1.0	-1.2	-3.4	-3.6	-0.1	0.5
5	-1.5	-1.5	-1	-0.8	0.0	0.2	-2.2	-0.7	-0.7	0.2
6	-6.2	-8.2	-6.9	-8.8	-2.0	-1.9	-4.4	-6.5	2.8	1.35
7	0.1	-0.9	0.3	0.1	-1.0	-0.2	-0.5	-0.5	-0.1	-0.7
8	-1.9	-0.7	-2.2	-0.6	1.2	1.6	-1.1	-1.7	0.2	-0.3
9	-1.9	-3.5	-1.1	-2.3	-1.6	-1.2	-1.7	-1.8	1	-0.1
10	-2.2	-2.6	-1.3	-2.2	-0.4	-0.9	-6.4	-6.5	-4	-4.75
Average	**-2.8**	**-3.8**	**-2.5**	**-3.4**	**0.3**	**0.4**	**-3.6**	**-3.8**	**-0.310**	**-0.900**
		Standard Dev. =			**1.3**	**1.3**	**Standard Dev. =**		**1.92**	**1.73**

Appendix 4b: Individual Data for Amplitude and P-P Interval.

N1-P1 Interval Subject #	VEP I O1	VEP II O1	VEP I O2	VEP II O2	VEP (II - I) O1	VEP (II - I) O2	VEP III O1	VEP III O2	VEP III-((bI+bII)/2) O1	VEP III-((bI+bII)/2) O2
1	35.1	37.1	35.1	37.1	0.0	0.0	35.1	33.2	-0.67	-2.90
2	41.0	43.0	39.1	46.9	-1.9	3.9	39.0	39.0	-2.03	-4.00
3	31.2	39.1	35.2	39.0	4.0	-0.1	35.2	33.2	0.03	-3.90
4	39.0	37.1	37.1	33.2	-1.9	-3.9	35.1	31.2	-2.63	-3.95
5	29.3	35.2	39.0	33.2	9.7	-2.0	25.4	23.0	-9.10	-13.10
6	33.2	27.3	31.3	33.2	-1.9	5.9	31.2	31.0	0.60	-1.30
7	41.0	42.9	41.0	46.9	0.0	4.0	37.1	43.0	-4.53	-0.95
8	31.2	31.2	29.3	35.2	-1.9	4.0	31.2	27.3	0.63	-4.95
9	29.3	33.0	29.3	35.2	0.0	2.2	27.4	23.4	-3.13	-8.85
10	29.3	31.2	31.2	31.3	1.9	0.1	27.3	25.4	-3.27	-5.85
Average	**34.0**	**35.7**	**34.8**	**37.1**	**0.8**	**1.4**	**32.4**	**31.0**	**-2.41**	**-4.98**
		Standard Dev. =			**3.7**	**3.1**	**Standard Dev. =**		**2.94**	**3.64**

P1-N2 Interval Subject #	VEP I O1	VEP II O1	VEP I O2	VEP II O2	VEP (II - I) O1	VEP (II - I) O2	VEP III O1	VEP III O2	VEP III-((bI+bII)/2) O1	VEP III-((bI+bII)/2) O2
1	82.1	82	80.1	80.1	-2.0	-1.9	68.4	70.3	-13.00	-9.80
2	78.1	70.3	82	66.4	3.9	-3.9	64.5	62.5	-12.30	-11.70
3	44.9	44.9	44.9	46.9	0.0	2.0	44.9	44.9	0.00	-1.00
4	58.6	58.6	58.6	56.6	0.0	-2.0	58.6	58.6	0.00	1.00
5	48.8	54.7	48.8	56.7	0.0	2.0	37.1	47.3	-13.67	-5.45
6	52.8	72.3	54.7	68.3	1.9	-4.0	60.6	58.85	0.67	-2.65
7	46.9	43	46.9	39.1	0.0	-3.9	37.1	37.1	-8.50	-5.90
8	37.1	33.2	41	33.2	3.9	0.0	33.2	39.1	-3.90	2.00
9	34.1	37.3	29.3	35.1	-4.8	-2.2	29.3	31.3	-4.27	-0.90
10	70.3	60.6	70.3	62.5	0.0	1.9	48.9	50.8	-18.17	-15.60
Average	**55.4**	**55.7**	**55.7**	**54.5**	**0.3**	**-1.2**	**48.3**	**50.1**	**-7.31**	**-5.00**
		Standard Dev. =			**2.6**	**2.5**	**Standard Dev. =**		**6.74**	**5.82**

N1-N2 Interval Subject #	VEP I O1	VEP II O1	VEP I O2	VEP II O2	VEP (II - I) O1	VEP (II - I) O2	VEP III O1	VEP III O2	VEP III-((bI+bII)/2) O1	VEP III-((bI+bII)/2) O2
1	117.2	119.1	115.2	117.2	-2.0	-1.9	103.5	103.5	-14.65	-12.7
2	119.1	113.3	121.1	113.3	2.0	0.0	103.5	101.5	-12.7	-15.7
3	76.1	84	80.1	85.9	4.0	1.9	80.1	78.1	0.05	-4.9
4	97.6	95.7	95.7	89.8	-1.9	-5.9	93.7	89.8	-2.95	-2.95
5	78.1	89.9	87.8	89.9	9.7	0.0	62.5	70.3	-21.5	-18.55
6	86	99.6	86	101.5	0.0	1.9	91.8	89.8	-1	-3.95
7	87.9	85.9	87.9	86	0.0	0.1	74.2	80.1	-12.7	-6.85
8	68.3	64.4	70.3	68.4	2.0	4.0	64.4	66.4	-1.95	-2.95
9	63.4	70.3	58.6	70.3	-4.8	0.0	56.7	54.7	-10.15	-9.75
10	99.6	91.8	101.5	93.8	1.9	2.0	76.2	76.2	-19.5	-21.45
Average	**89.3**	**91.4**	**90.4**	**91.6**	**1.1**	**0.2**	**80.7**	**81.0**	**-9.705**	**-9.975**
		Standard Dev. =			**4.0**	**2.7**	**Standard Dev. =**		**7.85**	**6.80**

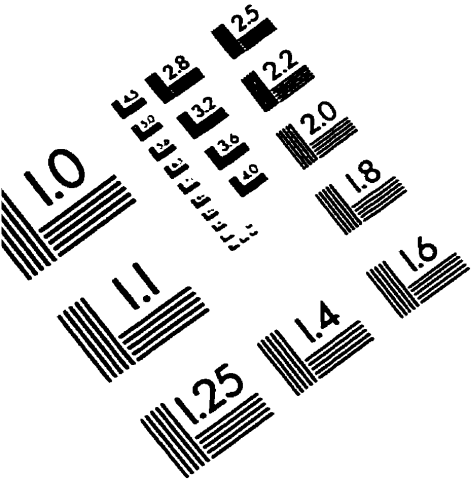
Appendix 4b: (Continued)

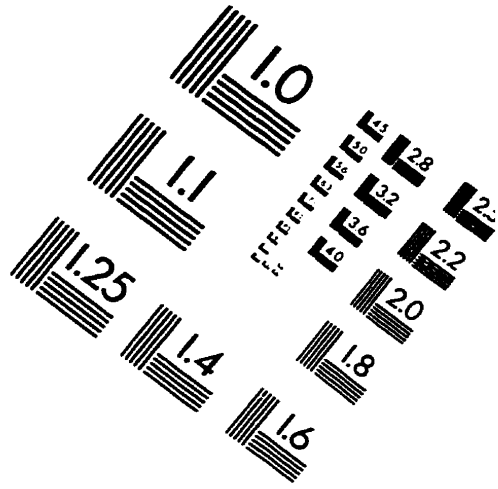
N1-P1 Amplitude Subject #	VEP I O1	VEP II O1	VEP I O2	VEP II O2	VEP (II - I) O1	VEP (II - I) O2	VEP III O1	VEP III O2	VEP III-((bI+bII)/2) O1	VEP III-((bI+bII)/2) O2
1	19.5	16.8	17.8	16.9	-2.7	-0.9	18.8	18.9	0.65	1.55
2	14.4	13.1	14.7	13.8	-1.3	-0.9	13.1	14	-0.65	-0.25
3	9.9	10.2	7.8	8.7	0.3	0.9	11.3	9.7	1.25	1.45
4	13	12.4	13.5	13.5	-0.6	0.0	13.9	15.2	1.2	1.7
5	11	10.1	9.5	9.7	-0.9	0.2	9.1	6.9	-1.45	-2.7
6	18.3	15.6	22.2	19.8	-2.7	-2.4	22.1	25.4	5.15	4.4
7	12.1	8.4	10.9	8.3	-3.7	-2.6	8.7	8	-1.55	-1.6
8	13.2	14	10.8	12.4	0.8	1.6	13.3	11.3	-0.3	-0.3
9	8.9	8.7	6.7	6.6	-0.2	-0.1	7.2	7.3	-1.6	0.65
10	5.1	8.1	4.5	7.5	3.0	3.0	9.7	9.6	3.1	3.6
Average	**12.5**	**11.7**	**11.8**	**11.7**	**-0.7**	**0.0**	**12.7**	**12.6**	**0.580**	**0.850**
		Standard Dev. =			**2.0**	**1.7**	**Standard Dev. =**		**2.21**	**2.18**

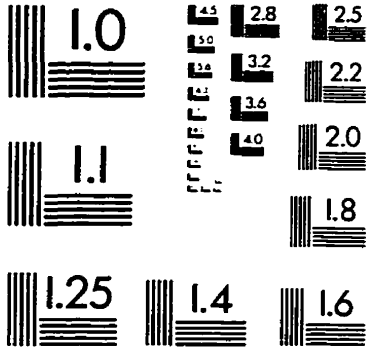
P1-N2 Amplitude Subject #	VEP I O1	VEP II O1	VEP I O2	VEP II O2	VEP (II - I) O1	VEP (II - I) O2	VEP III O1	VEP III O2	VEP III-((bI+bII)/2) O1	VEP III-((bI+bII)/2) O2
1	22.3	23.2	19	21.3	0.9	2.3	21.9	22.7	-0.85	2.55
2	15.7	14.8	15.3	15.2	-0.9	-0.1	17.1	17.6	1.85	2.35
3	12.2	12.8	10.6	11.4	0.6	0.8	14.7	13.6	2.2	2.6
4	14.7	15.9	16.3	18.1	1.2	1.8	16.9	19	1.6	1.8
5	10	10.2	9	10.1	0.2	1.1	10.5	8.4	0.4	-1.15
6	20	21.7	22	24.8	1.7	2.8	20.5	25.9	-0.35	2.5
7	8.2	7.8	7.4	6.7	-0.4	-0.7	7.2	6.5	-0.8	-0.55
8	12.3	12.6	11.7	11.5	0.3	-0.2	12.6	13	0.15	1.4
9	10.1	10.8	8	8.5	0.7	0.5	9.2	10	-1.25	1.75
10	5.6	7.9	4.7	7.1	2.3	2.4	10.9	11	4.15	5.1
Average	**13.1**	**13.8**	**12.4**	**13.5**	**-0.7**	**-0.3**	**14.2**	**14.8**	**0.710**	**1.835**
		Standard Dev. =			**0.9**	**1.2**	**Standard Dev. =**		**1.71**	**1.74**

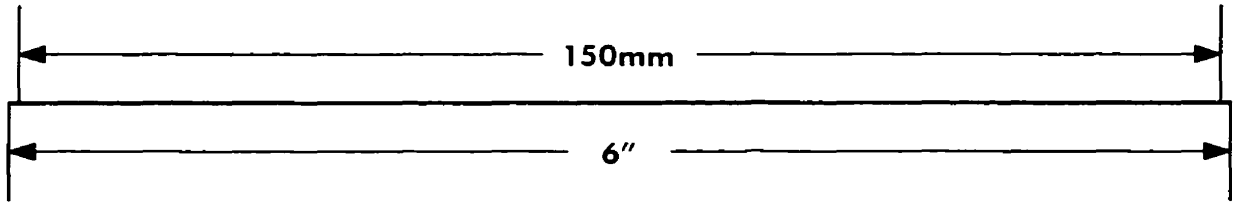
N1-N2 Amplitude Subject #	VEP I O1	VEP II O1	VEP I O2	VEP II O2	VEP (II - I) O1	VEP (II - I) O2	VEP III O1	VEP III O2	VEP III-((bI+bII)/2) O1	VEP III-((bI+bII)/2) O2
1	-2.8	-6.4	-1.2	-4.4	-3.6	-3.2	-3.1	-3.8	1.5	-1
2	-1.3	-1.7	-0.6	-1.4	-0.4	-0.8	-4	-3.6	-2.5	-2.6
3	-2.3	-2.6	-2.8	-2.7	-0.3	0.1	-3.4	-3.9	-0.95	-1.15
4	-1.7	-3.5	-2.8	-4.6	-1.8	-1.8	-3	-3.8	-0.4	-0.1
5	1	-0.1	0.5	-0.4	-1.1	-0.9	-1.4	-1.5	-1.85	-1.55
6	-1.7	-6.1	0.2	-5	-4.4	-5.2	1.6	-0.5	5.5	1.9
7	3.9	0.6	3.5	1.6	-3.3	-1.9	1.5	1.5	-0.75	-1.05
8	0.9	1.4	-0.9	0.9	0.5	1.8	0.7	-1.7	-0.45	-1.7
9	-1.2	-2.1	-1.3	-1.9	-0.9	-0.6	-2	-2.7	-0.35	-1.1
10	-0.5	0.2	-0.2	0.4	0.7	0.6	-1.2	-1.4	-1.05	-1.5
Average	**-0.6**	**-2.0**	**-0.6**	**-1.8**	**0.0**	**0.3**	**-1.4**	**-2.1**	**-0.130**	**-0.985**
		Standard Dev. =			**1.8**	**2.0**	**Standard Dev. =**		**2.24**	**1.20**

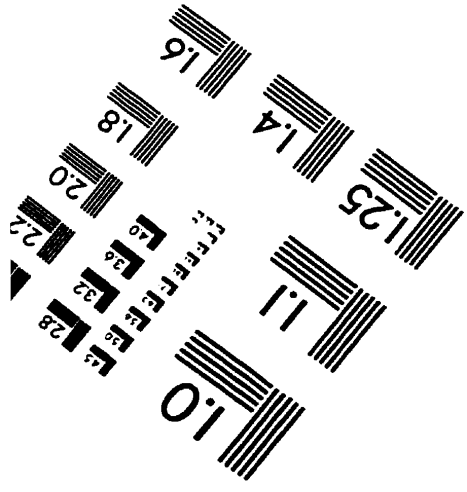
IMAGE EVALUATION
TEST TARGET (QA-3)

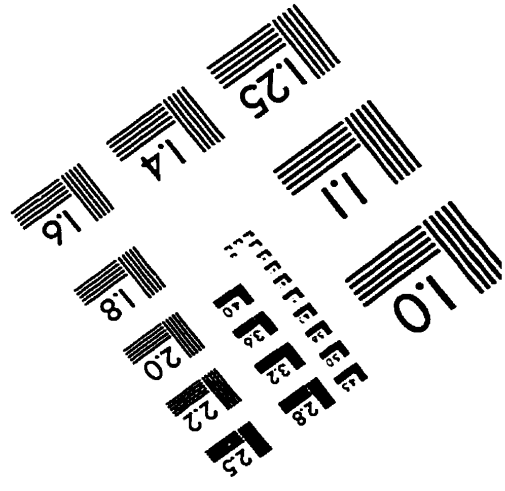












APPLIED IMAGE . Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989